Diagnosis and Management of Castleman Disease  
Jacob D. Soumerai, MD, Aliyah R. Sohani, MD, and Jeremy S. Abramson, MD

Blastic Plasmacytoid Dendritic Cell Neoplasm: Update on Molecular Biology, Diagnosis, and Therapy  
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Langerhans Cell Histiocytosis  
Nanette Grana, MD

Transplantation in Rare Lymphoproliferative and Histiocytic Disorders  
Alexis Cruz-Chacon, MD, John Mathews, MD, and Ernesto Ayala, MD
Advances in the Management of Multiple Myeloma

March 6–7, 2015
Loews Don Cesar Hotel
St. Petersburg Beach, Florida

Course Directors:
Melissa Alsina, MD, Rachid Baz, MD,
and Kenneth H. Shain, MD, PhD
Moffitt Cancer Center, Tampa, Florida

Conference Overview:
Advances in the Management of Multiple Myeloma conference is designed to foster the exchange of the most recent advances in the biology and treatment of multiple myeloma. National and international leading experts in the field will present in a format promoting discussion and interaction with participants.

Target Audience:
This educational program is directed toward hematologists, medical and surgical oncologists, and BMT physicians who diagnose, treat, and manage multiple myeloma. Other health care professionals who are interested in the diagnosis, treatment, and care of patients with multiple myeloma are also invited to attend.

To be added to the conference mailing list, contact:
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Ten Best Readings Relating to Rare Lymphoproliferative and Histiocytic Diseases

Index for 2014, Volume 21

Peer Reviewers, 2014

About the art in this issue:
Sherri Damlo has been a professional medical editor for nearly a decade. Currently, she runs Damlo Edits, a small editing business, and is the medical copy editor for Cancer Control. She became interested in photography as a hobby when she moved to the Pacific Northwest in 2008. Ever since she was a young girl she has always had her nose pointed toward the ground to discover the specimens of nature that many people tend to overlook. Her collection in this issue reflects this same ecological obsession, including photographs of fungi, gastropods, and insects. She also is intrigued about the way in which nature reclaims objects, so she has always been attracted to ruins and places lost to time. Sherri loves to travel, and she never leaves home without her camera. More of her work can be seen at www.flickr.com/sdamlo, www.damloshots.com, and on the stock image site, Getty Images.

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Eye of a Dandelion
Mushroom Biome
Snail on Moss
Net-Wing Beetle
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White Butterfly
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Hope for Orphan Lymphoproliferative and Histiocytic Diseases on the Horizon?

Orphan diseases are conditions with low prevalences in the population, and the rarity of these diseases has been a major obstacle for experimental and clinical investigations. The recent advent of new high-throughput molecular biology techniques (eg, next-generation sequencing) has accelerated our understanding of these diseases as well as the identification of new target molecules, which have substantially facilitated drug discovery. Although our understanding of the pathobiology of these rare diseases is far from satisfactory, progress has been made in the diagnosis and management of several rare lymphoproliferative and histiocytic disorders discussed in this issue of *Cancer Control*.

The first article in this issue is by Dr Soumerai and colleagues and is devoted to Castleman disease. The majority of patients with the unicentric, hyaline-vascular subtype of Castleman disease can be cured with complete surgical resection of the enlarged lymph nodes; by contrast, the multicentric plasma cell variant of Castleman disease typically has a more aggressive course of disease. Results from a recent, randomized phase 3 study of an anti-interleukin 6 monoclonal antibody led the US Food and Drug Administration to approve the agent as a therapeutic option for the multicentric plasma cell variant of Castleman disease in patients negative for both HIV and human herpesvirus 8 infections.

Dr Riaz and others discuss a rare aggressive malignancy called blastic plasmacytoid dendritic cell neoplasm, a disease initially believed to arise from immature natural killer cells; however, more recently, a plasmacytoid dendritic cell origin has been suggested. Whole genome sequencing revealed somatic gene mutations similar to those identified in myelodysplastic syndrome, acute myeloid leukemia, and some lymphoproliferative disorders. The strong expression of interleukin 3α receptor (CD123) on blastic plasmacytoid dendritic cell neoplasm cells became a target for novel biological therapy. Recent data from an early phase 1/2 study of an anti-CD123 antibody conjugate are very promising.

Dr Dalia and coauthors review rare dendritic and histiocytic cell sarcomas, which make up a clinically and histopathologically heterogeneous group of malignant diseases derived from mature dendritic cells or histiocytes. Patients with localized disease can benefit from a complete resection of the tumor mass. However, the standard of care has not been established for patients with disseminated disease; therefore, such patients should be referred to tertiary centers for diagnostic confirmation and for the design of a therapeutic plan.

Dr Zhang and colleagues review hemophagocytic lymphohistiocytosis in the next article. Within the last decade significant progress has been made in the diagnosis and management of familial hemophagocytic lymphohistiocytosis. Several causative germinal mutations have been identified in families with this disorder. Patient outcomes have improved following the introduction of allogeneic stem cell transplantation; however, patients with secondary hemophagocytic lymphohistiocytosis due to malignancies, viral infection, or autoimmune diseases have a worse prognosis. The mortality rate is high, particularly in patients who develop multiple organ failure; therefore, early diagnosis is essential for better outcomes.

Dr Deaver and others discuss Kikuchi–Fujimoto disease, which is a rare histiocytic disorder. This idiopathic condition frequently manifests with the rapid and painful enlargement of cervical lymph nodes and systemic B symptoms in young women of Asian descent. Clinical symptomatology and high fluoro-deoxyglucose uptake using positron emission tomography/computed tomography may clinically mimic malignant lymphoma. Typically, excisional or core needle biopsy of the enlarged lymph nodes and a careful histology and immunohistochemistry evaluation by an experienced hematopathologist are sufficient for diagnosis. The disease is self-limiting and rarely requires treatment.

In their article, Dr Dalia and colleagues describe Rosai–Dorfman disease, a rare histiocytic disorder that involves various organs and systems (eg, central nervous system, skin, lymph nodes). Surgical resection of the tumor mass in patients with localized disease is considered the most effective frontline therapy, although some patients with more advanced or unresectable disease can benefit from radiation therapy. The use of systemic chemotherapy or immunotherapy is based on case reports alone.

Dr Grana reviews the diagnosis and management of Langerhans cell histiocytosis in children and adults. This disease can aggressively manifest in infants and young children as Letter–Siwe disease or Hand–Schüller–Christian disease, respectively, and
may require intensive systemic therapy. A less acute course of the disease is often observed in adults who present with localized eosinophilic granuloma that commonly involves the bones and the lungs. Smoking has been implicated in the pathogenesis of Langerhans cell histiocytosis when the lungs are involved. Smoking cessation can result in the spontaneous regression of the disease. The discovery of the \textit{BRAF} V600E gene mutation in patients with Langerhans cell histiocytosis has offered the possibility of novel targeted therapy using BRAF inhibitors.

Dr Cruz-Chacon and coauthors provide a comprehensive review about the utility of hematopoietic stem cell transplantation in patients with rare lymphoproliferative and histiocytic disorders. Some of these diseases are aggressive and have short-lived responses to conventional chemotherapy regimens. Consolidation with high-dose chemotherapy followed by hematopoietic stem cell transplantation during the first remission or in patients with chemosensitive disease can be curative in selected patients.

In 2 \textit{Special Reports} included in this issue, Dr Harvey and coauthors review the medical literature dealing with the social determinants of racial and ethnic disparities in cutaneous melanoma outcomes, and Dr Tayyem and colleagues compare fruit and vegetable intake between 2 groups of Jordanians in a case-control study of colorectal cancer.

I hope that our series of articles dealing with rare lymphoproliferative and histiocytic disorders as well as the \textit{Special Reports} in this issue will be useful for busy hematology practitioners and other medical professionals interested in this field.

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Head, Section of Lymphoma
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H. Lee Moffitt Cancer Center & Research Institute
Tampa, Florida
Lubomir.Sokol@Moffitt.org
The Department of Malignant Hematology specializes in the evaluation, treatment, and comprehensive care of patients with lymphoma, leukemia, multiple myeloma, myelodysplastic syndrome (MDS), and myeloproliferative syndrome. The department is recognized as a Center of Excellence by the Myelodysplasia Foundation and is 1 of 4 founding institutions of the Bone Marrow Failure (BMF) Consortium funded by the National Institutes of Health. All patients with MDS, large granular lymphocytic leukemia, aplastic anemia, or other rare causes of bone marrow failure are registered in the Consortium's national database, which was developed and is maintained at the H. Lee Moffitt Cancer Center & Research Institute. The BMF Consortium is the first and only co-operative network developed by the National Institutes of Health for the study of the biology and development of novel therapeutics for these disorders.

Although chemotherapy remains an integral component of the treatment for most hematological malignancies, the development of disease-specific or targeted therapeutics represents the research goal of Moffitt investigators who treat patients with lymphoma, leukemias, and multiple myeloma. Marrow or stem cell transplantation often is indicated for the treatment of hematological malignancies. The treatment protocols of the Department of Malignant Hematology are integrated with those of the Blood and Marrow Transplant Program. The Cancer Center has state-of-the-art facilities for both inpatient and outpatient administration of chemotherapy.

These specialists are complemented by physician extenders, nurses, dietitians, social workers, data managers, and administrative support. Education and training are also heavily emphasized, with programs ranging from medical student courses to fellowship training and international education.
### Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Trial Code</th>
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<tr>
<td>MCC 15625</td>
<td>Phase 1/2 Study of Sequential Idarubicin + Cytarabine, Followed by Lenalidomide, in Patients With Myelodysplastic Syndrome (RAEB-2) or With Previously Untreated Acute Myeloid Leukemia</td>
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<tr>
<td>MCC 16434</td>
<td>Study of the Anti-EphA3 Monoclonal Antibody KB004 in Subjects With EphA3-Expressing Hematologic Malignancies</td>
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<tr>
<td>MCC 16548</td>
<td>Phase 3, Randomized, Controlled, Double-Blind, Multinational Clinical Study of the Efficacy and Safety of Vosaroxin and Cytarabine Versus Placebo and Cytarabine in Patients With First Relapsed or Refractory Acute Myeloid Leukemia (VALOR)</td>
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<td>MCC 17208</td>
<td>Phase 1, Open-Label, Dose-Escalation Study of SGN-CD19A in Patients With B-Lineage Acute Lymphoblastic Leukemia and Highly Aggressive Lymphomas</td>
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<td>MCC 17409</td>
<td>Open-Label, Randomized Phase 3 Study of Inotuzumab Ozogamicin Compared to a Defined Investigators Choice in Adult Patients With Relapsed or Refractory CD22-Positive Acute Lymphoblastic Leukemia (ALL)</td>
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### Acute Myelogenous Leukemia

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<tr>
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<td>Phase 1B/2 Study to Evaluate the Safety and Efficacy of PF-04449913, an Oral Hedgehog Inhibitor, in Combination With Intensive Chemotherapy, Low Dose ARA-C or Decitabine in Patients With Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome</td>
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<tr>
<td>MCC 17088</td>
<td>Phase 1 Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients With Advanced Hematological Malignancies</td>
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<tr>
<td>MCC 17234</td>
<td>Phase 3, Multicenter, Randomized, Trial of CPX-351 (Cytarabine:Daunorubicin) Liposome Injection Versus Cytarabine and Daunorubicin in Patients 60-75 Years of Age With Untreated High Risk (Secondary) AML</td>
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<tr>
<td>MCC 17576</td>
<td>Phase 1 Trial of SGN-CD33A in Patients With CD33-Positive Acute Myeloid Leukemia</td>
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### Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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<th>Trial Code</th>
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<tr>
<td>MCC 16002</td>
<td>Phase 1/2 Study of MEDI-551, a Humanized Monoclonal Antibody-Directed Against CD19, in Adult Subjects With Relapsed or Refractory Advanced B-Cell Malignancies</td>
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<tr>
<td>MCC 16622</td>
<td>Phase 2 Study of Ofatumumab in Combination With High Dose Methylprednisolone Followed by Ofatumumab and Lenalidomide Consolidative Therapy for the Treatment of Untreated CLL/SLL: The HiLOG Trial</td>
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<td>MCC 16631</td>
<td>Phase 2 Study of Ofatumumab in Combination With High Dose Methylprednisolone Followed by Ofatumumab and Lenalidomide Consolidative Therapy for the Treatment of Relapsed or Refractory CLL/SLL: The HiLOG Trial</td>
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<td>MCC 17180</td>
<td>Brentuximab Vedotin Plus AVD in Non-Bulky Limited Stage Hodgkin Lymphoma</td>
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### Chronic Myeloid Leukemia

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<th>Trial Code</th>
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<tr>
<td>MCC 17114</td>
<td>Phase 1/2 Study of Ruxolitinib in Combination With Nilotinib in CML Patients With Evidence of Molecular Disease</td>
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<td>MCC 17396</td>
<td>Single-Arm, Multicenter, Nilotinib Treatment-Free Remission Study in Patients With BCR-ABL1 Positive Chronic Myelogenous Leukemia in Chronic Phase Who Have Achieved Durable Minimal Residual Disease (MRD) Status on First Line Nilotinib Treatment</td>
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<tr>
<td>MCC 17577</td>
<td>Phase 2 Randomized, Multicenter Study of Treatment-Free Remission in Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Patients Who Achieve and Sustain MR4.5 After Switching to Nilotinib</td>
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# Selected Active Clinical Trials Relating to Malignant Hematology at Moffitt Cancer Center

## Chronic Myelomonocytic Leukemia

**MCC 17182**  
Open-Label, Randomized Phase 2, Parallel, Dose-Ranging, Multicenter Study of Sotatercept for the Treatment of Patients With Anemia and Low or Intermediate-1 Risk Myelodysplastic Syndromes or Non-Proliferative Chronic Myelomonocytic Leukemia (CMML)

**MCC 17259**  
Sequential Two-Stage Dose Escalation Study to Evaluate the Safety and Efficacy of Ruxolitinib for the Treatment of Chronic Myelomonocytic Leukemia (CMML)

## Lymphoma

**MCC 16434**  
Study of the Anti-EphA3 Monoclonal Antibody KB004 in Subjects With EphA3-Expressing Hematologic Malignancies

**MCC 17088**  
Phase 1 Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients With Advanced Hematological Malignancies

## Mantle Cell Lymphoma

**MCC 16002**  
Phase 1/2 Study of MEDI-551, a Humanized Monoclonal Antibody-Directed Against CD19, in Adult Subjects With Relapsed or Refractory Advanced B-Cell Malignancies

**MCC 17303**  
A Phase 1, Open-Label, Dose-Escalation Study of SGN-CD19A in Patients With Relapsed or Refractory B-Lineage Non-Hodgkin Lymphoma

## Multiple Myeloma

**MCC 16434**  
Study of the Anti-EphA3 Monoclonal Antibody KB004 in Subjects With EphA3-Expressing Hematologic Malignancies

**MCC 16659**  
Phase 1b, Open-Label, Multicenter Study of BMS-936564 in Combination With Lenalidomide (Revlimid®) Plus Low-Dose Dexamethasone, or With Bortezomib (Velcade®) Plus Dexamethasone in Subjects With Lapsed or Refractory Multiple Myeloma

**MCC 17088**  
Phase 1 Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients With Advanced Hematological Malignancies

**MCC 17155**  
Phase 1/2 Trial of Combination Plerixafor (AMD3100), Bortezomib and Dexamethasone in Relapsed or Relapsed/Refractory Multiple Myeloma

**MCC 17223**  
Phase 1/2 Open-Label Study to Assess the Safety, Tolerability and Preliminary Efficacy of TH-302, a Hypoxia-Activated Prodrug, and Dexamethasone With or Without Bortezomib in Subjects With Relapsed/Refractory Multiple Myeloma

**MCC 17419**  
Phase 1b/2, Multicenter, Open-Label Study of Oprozomib and Dexamethasone in Patients With Relapsed and/or Refractory Multiple Myeloma

## Myelodysplastic Syndrome

**MCC 15445**  
Randomized Phase 3 Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment With Lenalidomide (Revlimid) Alone and in Combination With Epoetin Alfa (Procrit) in Subjects With Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

**MCC 15625**  
Phase 1/2 Study of Sequential Idarubicin + Cytarabine, Followed by Lenalidomide, in Patients With Myelodysplastic Syndrome (RAEB-2) or With Previously Untreated Acute Myeloid Leukemia

**MCC 16434**  
Study of the Anti-EphA3 Monoclonal Antibody KB004 in Subjects With EphA3-Expressing Hematologic Malignancies

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**Selected Active Clinical Trials Relating to Malignant Hematology at Moffitt Cancer Center**

**Myelodysplastic Syndrome (continued)**

**MCC 16523**  
Sequential Two-Stage Dose Escalation Study to Evaluate the Safety and Efficacy of Eltrombopag in Myelodysplastic Syndrome (MDS) Patients With Thrombocytopenia Who Progressed or Are Resistant to Hypomethylating Agents

**MCC 17061**  
Phase 1B/2 Study to Evaluate the Safety and Efficacy of PF-04449913, an Oral Hedgehog Inhibitor, in Combination With Intensive Chemotherapy, Low Dose ARA-C or Decitabine in Patients With Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome

**MCC 17182**  
Open-Label, Randomized Phase 2, Parallel, Dose-Ranging, Multicenter Study of Sotatercept for the Treatment of Patients With Anemia and Low- or Intermediate-1 Risk Myelodysplastic Syndromes or Non-Proliferative Chronic Myelomonocytic Leukemia (CMML)

**MCC 17382**  
Phase 2 Study Evaluating the Oral Smoothened Inhibitor PF-04449913 in Patients With Myelodysplastic Syndrome

**Non-Hodgkin Lymphoma**

**MCC 16002**  
Phase 1/2 Study of MEDI-551, a Humanized Monoclonal Antibody-Directed Against CD19, in Adult Subjects With Relapsed or Refractory Advanced B-Cell Malignancies

**MCC 17303**  
Phase 1, Open-Label, Dose-Escalation Study of SGN-CD19A in Patients With Relapsed or Refractory B-Lineage Non-Hodgkin Lymphoma

**MCC 17344**  
Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas

**MCC 17682**  
Phase 1B, Multi-Center, Open-Label Study of Novel Combinations of CC-122, CC-223, CC-292, and Rituximab in Diffuse Large B-Cell Lymphoma

**T-Cell Lymphoma**

**MCC 17006**  
Phase 3 Randomized Two-Arm Open-Label Multicenter International Trial of Alisertib (MLN8237) or Investigators Choice (Selected Single Agent) in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma

**MCC 17215**  
Open-Label, Multi-Center, Randomized Study of Anti-CCR4 Monoclonal Antibody KW-0761 (Mogamulizumab) Versus Vorinostat in Subjects With Previously Treated Cutaneous T-Cell Lymphoma

**MCC 17343**  
Pilot Study of Brentuximab Vedotin in Relapsed/Refractory Peripheral T-Cell Lymphoma Expressing CD30 Receptor

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To schedule a patient appointment with a physician in the Department of Malignant Hematology, call the New Patient Appointment Center at (813) 745-3980 or 1-888-860-2778 (during normal business hours).

For information about clinical trials, please call Cheryl Maker in the Clinical Research Department at (813) 745-4106 or e-mail Cheryl.Maker@moffitt.org or check the Department of Malignant Hematology’s Web page at www.MOFFITT.org.
Castleman disease is an uncommon and heterogeneous lymphoproliferative disorder for which management is rapidly evolving.

Diagnosis and Management of Castleman Disease

Jacob D. Soumerai, MD, Aliyah R. Sohani, MD, and Jeremy S. Abramson, MD

Background: Castleman disease is an uncommon lymphoproliferative disorder characterized as either unicentric or multicentric. Unicentric Castleman disease (UCD) is localized and carries an excellent prognosis, whereas multicentric Castleman disease (MCD) is a systemic disease occurring most commonly in the setting of HIV infection and is associated with human herpesvirus 8. MCD has been associated with considerable morbidity and mortality, and the therapeutic landscape for its management continues to evolve.

Methods: The available medical literature on UCD and MCD was reviewed. The clinical presentation and pathological diagnosis of Castleman disease was reviewed, along with associated disorders such as certain malignancies and autoimmune complications.

Results: Surgical resection remains the standard therapy for UCD, while systemic therapies are required for the management of MCD. Rituximab monotherapy is the mainstay of therapy; however, novel therapies targeting interleukin 6 may represent a treatment option in the near future. Antiviral strategies as well as single-agent and combination chemotherapy with glucocorticoids are established systemic therapies. The management of Castleman disease also requires careful attention to potential concomitant infections, malignancies, and associated syndromes.

Conclusions: UCD and MCD constitute uncommon but well-defined clinicopathologic entities. Although UCD is typically well controlled with local therapy, MCD continues to pose formidable challenges in management. We address historical chemotherapy-based approaches to this disease as well as recently developed targeted therapies, including rituximab and siltuximab, that have improved the outcome for newly diagnosed patients. Ongoing research into the management of MCD is needed.

Introduction

Castleman disease, also known as angiofollicular lymph node hyperplasia, is an uncommon lymphoproliferative disorder originally described in a case published in 1954. The patient from that case was a man aged 42 years who presented with high fevers, sweats, fatigue, and a nonproductive cough. He was found to have an anterior mediastinal mass with anemia and an elevated sedimentation rate. The treating physician suspected tuberculosis and empirical streptomycin was administered prior to complete surgical resection. The discussants favored a diagnosis of teratoma or dermoid cyst, also considering
mediastinal tuberculosis, thymoma, and Hodgkin disease. Castleman presented the surgical pathology and described a new syndrome characterized by hyperplasia of mediastinal lymph nodes with regressed germinal centers. The disease did not recur in this patient following surgical resection. This case, followed 2 years later by a case series, described what is now known as unicentric Castleman disease (UCD), which is distinct from multicentric Castleman disease (MCD), a condition with unique clinical and pathological features.

Histologically, Castleman disease may be classified as either the hyaline-vascular or plasma cell variant, with occasional cases demonstrating mixed features. The hyaline-vascular histology accounts for most UCD cases and the plasma cell type characterizes most cases of MCD. UCD is typically localized, associated with minimal symptoms, and treated with local therapy alone. However, MCD is a systemic disease that commonly occurs in the setting of HIV infection and is clinically characterized by diffuse lymphadenopathy, splenomegaly, anemia, and systemic inflammatory symptoms. Accordingly, MCD is primarily treated with systemic therapies.

Although Castleman disease is not a malignant condition, the condition has been associated with an increased risk of developing certain malignancies and other diseases, most notably large B-cell lymphomas, along with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormality (POEMS) syndrome, follicular dendritic cell sarcomas, and paraneoplastic pemphigus. Kaposis sarcoma is also commonly diagnosed concurrently or sequentially with MCD because the 2 entities share a common viral pathogenesis.

**Pathogenesis**

The pathogenesis of Castleman disease is not fully understood; however, the central roles of interleukin (IL) 6 in UCD and both IL-6 and human herpesvirus (HHV) 8 in MCD have been well described. Dysregulated and overproduced IL-6, particularly in patients with MCD, stimulates the production of acute phase reactants in the liver, resulting in constitutional symptoms, including fever, sweats, and fatigue, and laboratory abnormalities, such as anemia, elevated inflammatory markers, hypergammaglobulinemia, and hypoalbuminemia. IL-6 also stimulates B-cell proliferation and induces the expression of vascular endothelial growth factor and increased angiogenesis. The activation of the IL-6 receptor further results in the activation of the Janus kinase–mediated activation of the signal transducers and the activation of transcription pathway and the mitogen-activated protein kinase cascade, which enhances B-cell proliferation and survival. IL-6 has emerged as a therapeutic target in Castleman disease based on its critical role in pathogenesis and driving of symptomatology.

HIV-associated MCD is uniformly associated with HHV-8 infection, although its prevalence in HIV-negative MCD varies by the local prevalence rate of HHV-8. Plasma levels of HHV-8 DNA correlate with clinical symptoms and predict relapse rates in HIV-associated MCD. In patients with HHV-8-positive MCD, HHV-8-infected vascular and lymphoid cells express a viral analog of IL-6 (vIL-6), which likely contributes to the pathogenesis of this significant subset of Castleman disease. Both human IL-6 and vIL-6 are sufficient to induce disease flares in HIV-associated MCD and promote the expression of proinflammatory cytokines during disease flares.

**Pathological Diagnosis**

Castleman disease is a pathological diagnosis made by excisional biopsy of affected lymph node tissue. In cases of deeper or less accessible disease, core needle biopsy is preferred to fine needle aspiration, because fine needle aspirations are insensitive for both UCD and MCD.

Most cases of UCD are histologically classified as the hyaline-vascular variant, which is characterized by increased numbers of small, hyalinized blood vessels within and between follicles with obliteration of the medullary sinuses. Lymphoid follicles are increased in number and exhibit features of “regression,” a term referring to a predominance of dendritic cells within germinal centers with a relative paucity of lymphocytes and a consequent broadening of mantle zones. The small lymphocytes of the mantle zones are frequently arranged in concentric rings around the germinal center (“onion-skinning”), and follicles may be radially penetrated by a blood vessel (“lollipop” follicle; Fig 1). Plasma cells may be found in the interfollicular region, but they are typically few and present in small clusters. Cases with abundant plasma cells likely reflect examples of UCD with “mixed” or “transitional” features between the hyaline-vascular and plasma cell histological variants.

By contrast to hyaline-vascular Castleman disease, cases of plasma cell variant Castleman disease typically show greater retention of the nodal architecture with hyperplastic follicles of varying sizes and focally patent medullary sinuses. The interfollicular region may be mildly hypervascular and characteristically contains sheets of mature-appearing plasma cells, which show monotypic immunoglobulin (Ig) G or IgA restriction in up to 50% of cases (Fig 2). Cases positive for HHV-8 show distinctive histological features with greater interfollicular vascularity, blurring of the germinal center-mantle zone boundary, and scattered plasmacytoid immunoblasts, or plasmablasts present within the mantle zones (Fig 3), giving rise.
Fig 1. — Hyaline-vascular Castleman disease. (A) Low power view of an involved lymph node shows increased numbers of lymphoid follicles with small, regressed germinal centers and broad mantle zones. The interfollicular areas demonstrate increased vascularity with obliteration of medullary sinuses (H & E, × 40). (B–D) Higher magnification reveals typical features of the follicles, including an increased proportion of follicular dendritic cells relative to lymphocytes within germinal centers, known as follicle regression; concentric arrangement of mantle zone lymphocytes in an “onion skin” pattern; and hypervascularity of follicles, some of which are radially penetrated by a hyalinized blood vessel, resembling a lollipop (B–C: H & E, × 200; D: H & E, × 400). Note the sharp demarcation between the germinal center and mantle zone in images B to D, a feature unlike that seen in HIV-associated multicentric Castleman disease. H & E = hematoxylin and eosin.

Fig 2. — Plasma cell variant of Castleman disease negative for human herpesvirus 8. (A) Low power view shows hyperplastic follicles of varying sizes with mildly increased interfollicular vascularity and focally patent medullary sinuses; they are best seen in the lower right-hand portion of the image. Some follicles contain more than 1 germinal center, a feature that may also be seen in the hyaline-vascular variant (H & E, × 25). (B) Higher magnification of the interfollicular areas shows sheets of mature plasma cells with eccentric nuclei and clumped chromatin (H & E, × 400). H & E = hematoxylin and eosin.
Fig 3. — HIV-associated plasmablastic Castleman disease with concurrent nodal involvement by Kaposi sarcoma. (A) Follicles are regressed with a paucity of lymphocytes, hypervascularity, and an indistinct border between the germinal center and surrounding mantle zone, which contains scattered, large, atypical plasmablasts (arrows) with vesicular chromatin, prominent nucleoli, and scant to moderate pink cytoplasm (H & E, ×400). (B) In this case, further examination revealed an atypical spindled cell proliferation consisting of plump endothelial cells with small nucleoli and prominent red blood cell extravasation extending from the lymph node capsule to the subcapsular region, consistent with nodal involvement by Kaposi sarcoma (H & E, ×400). (C) Plasmablasts within the mantle zones showed λ light-chain restriction (λ-mRNA in situ hybridization, ×400). (D) K-mRNA in situ hybridization showed staining of mature polyclonal plasma cells outside of follicles (×200). (E) Plasmablasts were also positive for immunoglobulin M heavy chain (anti-μ immunohistochemical stain, ×400). (F) Immunohistochemistry with an antibody specific for human herpesvirus 8 latency-associated nuclear antigen 1 showed finely stippled nuclear staining of the plasmablasts (×1000); a similar staining pattern with this antibody was seen in the endothelial cells of the vascular proliferation (not shown), confirming the concurrent diagnoses of Castleman disease and Kaposi sarcoma involving the same lymph node. H & E = hematoxylin and eosin.
to the term “plasmablastic variant” of Castleman disease.\textsuperscript{18} Immunohistochemistry demonstrates positivity of plasmablasts for HHV-8 latency-associated nuclear antigen 1; these cells express monotypic IgM $\lambda$, but they have been shown to be polyclonal. In some cases, the atypical plasmablasts coalesce to form microscopic nodules adjacent to or replacing some follicles, an early stage of large B-cell lymphoma arising in HHV-8-associated MCD; cases of frank lymphoma are characterized by complete effacement of the lymph node architecture by sheets of atypical plasmablasts expressing HHV-8 latency-associated nuclear antigen 1.\textsuperscript{19} Foci of Kaposi sarcoma may be present in some cases, and a diagnosis of Kaposi sarcoma must also be excluded in cases positive for HHV-8; in such cases, the atypical endothelial cells also show staining for HHV-8 latency-associated nuclear antigen 1 (see Fig 3).

From a pathological standpoint, Castleman disease is a diagnosis of exclusion and its varied histological features give rise to a broad differential diagnosis that includes both benign and neoplastic entities, most of which can be excluded on the basis of careful histological examination, immunohistochemical, or other ancillary studies (eg, flow cytometry, molecular genetics) and correlation with clinical, laboratory, and radiological findings. Angioimmunoblastic T-cell lymphoma and rare cases of early interfollicular Hodgkin lymphoma may be associated with Castleman disease–like changes, including the regression of residual germinal centers and hypervascularity. However, Castleman disease lacks an atypical interfollicular population of neoplastic T cells or Reed–Sternberg cells. The appearance of the follicles in hyaline-vascular Castleman disease may raise the possibility of early nodal involvement by follicular lymphoma in which atypical follicles can show variable degrees of hyalinization. The prominence of the mantle zones in hyaline-vascular Castleman disease may also raise the possibility of early mantle cell lymphoma. Finally, the plasma cell variant of Castleman disease may mimic lymphoplasmacytic lymphoma (Waldenström macroglobulinemia) due to the large number of interfollicular plasma cells; this distinction may be particularly challenging in cases showing $\lambda$ light chain restriction. In all of these scenarios, the diagnosis of Castleman disease can be made based on the lack of additional histological features supporting a diagnosis of lymphoma and the absence of a clonal B-cell population with a characteristic immunophenotype. In addition, lymphoplasmacytic lymphoma commonly expresses IgM heavy chain and may not show $\lambda$ light chain restriction, unlike IgG or IgA $\lambda$-restricted plasma cell variant Castleman disease.\textsuperscript{17}

Among non-neoplastic conditions, the plasma cell variant of Castleman disease may mimic lymph nodes biopsied in the setting of rheumatoid arthritis or syphilitic (luetec) lymphadenitis due to overlapping features of follicular hyperplasia and increased interfollicular plasma cells. In addition, lymphadenopathy associated with IgG4-related disease may show features that overlap with Castleman disease. The diagnosis of rheumatoid arthritis, syphilis, or IgG4-related disease can be readily established based on clinical and laboratory features. In addition, Castleman disease lacks the histiocytic inflammation and inflamed vasculature seen in syphilis in which spirochetes can be identified using special histochemical stains or antitreponemal immunohistochemistry.\textsuperscript{17,20-22} Perhaps the most challenging histological distinction in the pathological diagnosis of MCD is with that of HIV-related generalized lymphadenopathy, which is characterized by plasmacytosis, vascular prominence, and hyperplastic or regressive changes in the follicles of involved lymph nodes depending on their stage of evolution. However, HIV-related lymphadenopathy should not contain plasmablasts positive for HHV-8 that characterize HIV-associated MCD. For the diagnosis of other subtypes of Castleman disease in the setting of HIV infection, one should adhere to strict morphological criteria given the known histological overlap between these entities.\textsuperscript{17}

\section*{Staging}

Once Castleman disease is confirmed and the histological subtype has been identified, clinical staging guides treatment decisions and prognosis. The goals of the staging and pretreatment evaluation in Castleman disease are to (1) determine whether the patient has unicentric or multicentric disease, (2) identify patients with systemic inflammatory manifestations of Castleman disease, and (3) assess for the presence of HIV, as well as associated conditions and malignancies.

The initial laboratory evaluation of patients with Castleman disease includes a complete blood count, inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), complete metabolic panel, and albumin. HIV testing should be performed in all patients. Plasma HHV-8 DNA levels should be obtained, because these levels correlate with symptomatic disease and may serve as a helpful biomarker, both to support the diagnosis of MCD and to monitor disease activity and response to therapy. Although levels of cytokines, most notably IL-6 and IL-10, are important in the pathogenesis of Castleman disease and have been used as surrogate markers of disease activity in clinical studies, we do not recommend routinely measuring them. Serum protein electrophoresis with immunofixation should be obtained when POEMS syndrome is suspected. In patients with HIV-associated MCD, a thorough skin examination should be performed to assess for previously undiagnosed Kaposi sarcoma given the common concurrent presentation of these entities.
Computed tomography of the chest, abdomen, and pelvis should be obtained at the time of diagnosis to assess for adenopathy and splenomegaly. This imaging modality also helps inform the question of resectability in patients with UCD. A role for routine positron emission tomography has not been established in the setting of Castleman disease, although involvement of nodes in MCD are quite fludeoxyglucose-avid.

**Unicentric Castleman Disease**

**Epidemiology**
UCD most commonly presents in the third and fourth decade of life, with the mean age of diagnosis being 34 years (range, 2–84 years); UCD also has a slight female predominance (1.4:1). No association with HIV or HHV-8 infection exists and epidemiological risk factors have not been established.

**Clinical Presentation**
UCD may be asymptomatic at diagnosis and be incidentally discovered on chest or abdominal imaging performed for other reasons. Other patients may present with painless lymphadenopathy or local anatomical symptoms varying by location. Common sites of presentation in UCD include the chest (30%), neck (23%), abdomen (20%), retroperitoneum (17%), and, rarely, the axilla (5%), groin (3%), or pelvis (2%). Intrathoracic disease is frequently found along the tracheobronchial tree or lung hila. Thoracic disease may present with cough, hemoptysis, dyspnea, or chest discomfort. Abdominal, retroperitoneal, and pelvic disease may present with abdominal or back discomfort. Disease confined to the peripheral lymph node chains, including the neck, axilla, or groin, may present with nontender lymphadenopathy. Systemic manifestations, including B symptoms (fevers, drenching night sweats, and weight loss) and laboratory abnormalities (anemia, elevated inflammatory markers, hypergammaglobulinemia, and hypoalbuminemia) are uncommon in unicentric disease, but such symptoms are observed frequently among patients with the plasma cell variant.

**Management**
The optimal therapy for UCD is surgical resection, which is usually curative if the disease is amenable to complete resection. For disease that cannot be completely excised, radiation therapy is an option due to its high rates of objective response, including complete responses in nearly one-half of reported cases.

For select patients who are not candidates for surgical excision, but who are also not candidates for radiation therapy based on the location of the disease, partial resection followed by clinical observation alone may result in lengthy remissions; however, such treatment warrants careful attention to local progression. Select patients who are asymptomatic with a low disease burden who cannot be treated with either surgery or radiation may be closely followed, given the often indolent nature of the disease. Systemic options for MCD, as necessary, should be considered for patients with symptomatic local disease who cannot be treated with surgery or radiation or for those whose disease fails to respond to such treatment.

**Multicentric Castleman Disease**

**Epidemiology**
MCD commonly presents in the sixth decade of life, although patients with HIV infection tend to present at a younger age. A slight male predominance is seen in MCD. HIV infection is an important risk factor for MCD, and all patients with HIV-associated MCD are coinfected with HHV-8. HHV-8 infection is present in approximately 50% of HIV-negative cases of MCD and varies with the HHV-8 seroprevalence of the population.

Large population studies have revealed an increased incidence of HIV-associated MCD since the introduction of antiretroviral therapy, which is in contrast to the marked decline in incidence of HIV-associated Kaposi sarcoma. The mechanism of this increase is unclear, but such an increase may reflect improved survival rates, longstanding immune dysregulation associated with long-term HIV infection, or an increased awareness of the disease among health care professionals.

**Clinical Presentation**
Systemic inflammatory manifestations characterize the vast majority of patients with MCD who present with fevers, night sweats, weight loss, and fatigue. Physical examination is typically notable for generalized lymphadenopathy and hepatosplenomegaly, and many patients have evidence of fluid retention with lower extremity edema, pleural and pericardial effusions, and abdominal ascites. Common hematological abnormalities include anemia, elevated inflammatory markers, hypergammaglobulinemia, and hypoalbuminemia. Systemic symptoms and hematological abnormalities have been shown to correspond to elevated inflammatory markers and cytokine levels, particularly IL-6 and IL-10.

The natural history of MCD is variable. Some patients may present with indolent disease and very slow progression over months to years, while others will experience a relapsing-remitting course or an acute and fulminating disease that can be fatal within weeks; the latter courses are more common in patients with HIV-associated MCD. HIV-associated
MCD may also concurrently or sequentially present with other concomitant malignancies, including Kaposi sarcoma or primary effusion lymphoma, each of which share an HHV-8–mediated pathogenesis. Kaposi sarcoma may be identified in 72% of HIV-related MCD cases at diagnosis and may be seen in HIV-negative MCD, although at a far lower rate. Patients are also at significant risk for diffuse large B-cell lymphoma, which may arise directly out of HHV-8–positive MCD; therefore, one must consider the possibility of a second malignancy at the time of diagnosis and perform a thorough skin examination for cutaneous Kaposi sarcoma, as well as consider biopsying bulky or visceral locations seen on imaging studies for staging that may constitute a distinct histology from Castleman disease. Repeat biopsy should also be considered at progression or relapse to evaluate for lymphomatous transformation. Patients with HIV-associated MCD will often present with a low CD4 count, so concomitant opportunistic infections must also be considered at diagnosis and during the course of illness, including Pneumocystis jiroveci, Toxoplasma gondii, cytomegalovirus, and mycobacterial infections, among others.

**Treatment**

Treatment options for MCD are based on few nonrandomized prospective studies, small case series, and expert opinion; therefore, the body of evidence must be interpreted with caution. Available treatments include glucocorticoids, single-agent and combination chemotherapy, antiviral strategies, and monoclonal antibody therapies targeting CD20 or IL-6.

**Antiretroviral Therapy:** All patients with HIV infection and MCD should be initiated on combination antiretroviral therapy if they are not already taking it, although antiretroviral therapy alone is unlikely to independently result in a Castleman disease response. The risk of developing MCD is not influenced by the use of combination antiretroviral therapy or by the CD4 count at the time of diagnosis. However, independent of MCD, the initiation of combination antiretroviral therapy can prevent further consequences of poorly controlled HIV, including opportunistic infections and malignancies, and allows for the safe administration of chemotherapy due to immune reconstitution. Patients should be monitored for immune reconstitution inflammatory syndrome, including an exacerbation of MCD and concurrent Kaposi sarcoma.

**Glucocorticoids:** Glucocorticoids have activity as monotherapy in MCD and may offer short-term control of symptoms, but complete remissions are rare and are generally short-lived. Twenty-one cases of MCD treated with glucocorticoids alone have been described in case reports and small case series, and responses were observed in approximately 80% of patients. None of these reported cases were known to be positive for HIV. Given the delayed response to rituximab monotherapy, glucocorticoid pulses may be helpful as an initial adjunct for acutely symptomatic disease. In these patients, prednisone 1 mg/kg daily or its equivalent may be added to rituximab until systemic inflammatory symptoms are adequately controlled and then tapered off.

**Cytotoxic Chemotherapy:** Various agents have been used as single-agent chemotherapy in the treatment of MCD, although data are limited to few case reports and small case series. These include oral etoposide, vinblastine, cyclophosphamide, cladribine, chlorambucil, and liposomal doxorubicin. Responses following these agents are often short-lived and symptoms may rapidly recur following the completion of therapy. Single-agent chemotherapies are often administered at doses and schedules routinely used to treat patients with lymphoma. Etoposide may be administered at a dose of 50 or 100 mg by mouth daily on days 1 through 7 of a 1/4-day cycle until maximal response, or 100 mg/m² intravenously once weekly for 4 weeks, and can be used with a maintenance schedule to prolong remission duration. Vinblastine may be administered at a dose of 4 to 6 mg/m² every 2 weeks until maximal response, and it can be used with a maintenance schedule in the absence of significant toxicity.

Combination chemotherapy with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or cyclophosphamide/vincristine/prednisone (CVP) without rituximab have produced durable remissions in small case series of patients with MCD, although many patients will progress or experience infectious toxicities. These data are primarily from before the introduction of rituximab, and the impact of rituximab in combination with chemotherapy in these patients is unknown. Our practice is to include rituximab for most patients and to administer chemotherapy at doses and schedules typical for patients with lymphoma, but infectious risk is increased; therefore, caution and attention to supportive care are required, particularly in patients with low CD4 counts.

Dose reductions may be necessary on the basis of interactions with antiretroviral therapy; because protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolized by the CYP450 system, which is either induced or inhibited by many chemotherapeutic agents, including cyclophosphamide, doxorubicin, etoposide, vinblastine, and vincristine. **Rituximab:** Rituximab is highly active as monotherapy in MCD. Its role in HIV-associated MCD is supported by prospective and retrospective trials demonstrating sustained remissions. Small case series have also demonstrated activity in patients with MCD who are HIV negative.
A prospective study enrolled 24 patients with chemotherapy-dependent, HIV-associated MCD. Patients had received single-agent chemotherapy (etoposide, vinblastine, or liposomal doxorubicin) for a median of 13 months and all patients had failed at least 1 attempt to discontinue chemotherapy. All patients received concurrent combination antiretroviral therapy. After 4 weekly infusions of rituximab at a dose of 375 mg/m², 22 of 24 patients (92%) achieved the primary endpoint of sustained remission at 60 days off treatment, and 17 patients (71%) were alive and in remission at 1 year. A second prospective trial enrolled 21 patients with previously untreated HIV-associated MCD and treated with 4 weekly rituximab infusions. Clinical and radiological responses occurred in 20 (95%) and 14 (67%) patients, respectively, and the 2-year progression-free survival rate was 79%.

These small prospective studies are also supported by a retrospective analysis of 49 patients naive to treatment with HIV-associated MCD who were given rituximab with or without etoposide. Combination therapy with rituximab/etoposide was reserved for patients with a poor performance status or evidence of end-organ involvement. For the entire cohort, 5-year progression-free and overall survival rates were 61% and 90%, respectively. No difference was seen in outcomes between the 2 treatment arms; however, the 2 arms included distinct patient populations by design, and it is unknown whether patients treated with combination therapy would have performed as well if treated with rituximab alone. This does add to a body of literature demonstrating favorable progression-free and overall survival rates in patients treated with rituximab therapy.

Patients with concomitant MCD and Kaposi sarcoma require vigilance for Kaposi sarcoma flareups during rituximab therapy. Exacerbations of Kaposi sarcoma during rituximab treatment was observed in all trials of rituximab in HIV-associated MCD, occurring in 36% to 67% of reported patients.

**Anti-Interleukin 6 Therapy: Siltuximab and tocilizumab are monoclonal antibodies targeting IL-6 and its receptor (IL-6R), respectively. The US Food and Drug Administration (FDA) has approved siltuximab for the treatment of patients with HIV negative, HHV-8 negative MCD, where it shows significant clinical activity, resulting in control of IL-6–dependent systemic symptoms and laboratory abnormalities.** A phase 2 study that included 19 patients with HIV negative and HHV-8 negative MCD reported 8 radiological responses, including 1 complete response. At a median follow-up of 5.1 years (range, 3.4–7.2 years), all 19 patients taking siltuximab therapy were still alive.

The data from those studies prompted a multicenter, randomized, double-blind, placebo-controlled trial of siltuximab in patients with HIV negative, HHV-8 negative MCD. Patients were randomized 2:1 to siltuximab or placebo administered once every 3 weeks. Patients receiving placebo were permitted to cross over to open-label siltuximab at progression. Of the 79 randomized patients, 53 received siltuximab and 26 received placebo. The median age was 48 years and a 2:1 male predominance was seen. Hyaline-vascular, plasma cell, and mixed pathologies were observed in 33%, 23%, and 44% of patients, respectively. A total of 58% had received prior therapy and 30% were on corticosteroids at enrollment. The primary endpoint was durable radiological and symptomatic responses (improvement or stabilization of symptoms) lasting at least 18 weeks. Treatment with siltuximab was associated with a higher rate of achieving the primary endpoint (34% vs 0%). Radiographic tumor response rates were seen in 38% and 4% of patients, favoring the siltuximab arm, and symptomatic response rates were 57% and 19%. Complete symptom resolution was observed in those receiving siltuximab (25% vs 0%). Patients receiving siltuximab also had improvements in anemia and hypoalbuminemia, and a decrease in inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, and fibrinogen) relative to patients receiving placebo. These data demonstrate that siltuximab is highly active in MCD with durable disease control and improvement in clinically relevant outcomes. However, an important caveat is that patients with HIV and HHV-8-associated MCD were excluded from this study. Siltuximab was also compared against a placebo rather than rituximab.

The anti-IL-6R humanized monoclonal antibody tocilizumab is also active in MCD. Twenty-eight patients with symptomatic MCD were enrolled in a phase 2 trial, all of whom were HIV negative and only 2 of whom were positive for HHV-8. All patients had pathological findings consistent with the plasma cell variant. Patients received tocilizumab every 2 weeks for 16 weeks and the study drug was continued thereafter at the discretion of the treating investigator. The alleviation of systemic inflammatory symptoms was universal and weight gain occurred in all patients. Laboratory abnormalities, including anemia, hypoalbuminemia, and elevated C-reactive protein, all improved with therapy, as did lymphadenopathy. Eleven of the 15 (73%) patients receiving corticosteroids at enrollment were able to decrease or discontinue concomitant corticosteroid therapy. It is worth noting, however, that tocilizumab is currently FDA approved only for rheumatoid arthritis and systemic or polyarticular juvenile idiopathic arthritis.

Monoclonal antibodies targeting IL-6 remain largely unevaled in patients with HIV and HHV-8-associated MCD. It is not known whether targeting IL-6 is similarly effective in this population, yet several
features make these patients appealing candidates for therapies targeting IL-6. Although vIL-6 is implicated in the pathogenesis of HHV-8-associated MCD and is not targeted by the current monoclonal antibodies, human IL-6 is also elevated in the majority of patients with HIV-associated MCD and likely remains a significant contributor to disease activity and symptomatology.\(^3\) Three cases in the literature have demonstrated activity of IL-6 targeted therapy in HIV and HHV-8-associated MCD,\(^61,65\) speaking to the need for prospective clinical trials in these patients.

**Antiviral Therapy:** Antiviral agents have been explored as therapy for HIV-associated MCD given the pathogenetic link with HHV-8.\(^66-68\) Lytic replication of HHV-8 is common in MCD and may be important in its pathogenesis, as opposed to Kaposi sarcoma in which HHV-8 infection most often remains latent. Many HHV-8–derived gene products, including vIL-6, are expressed during the lytic cycle of HHV-8 replication.\(^69\) Therefore, MCD is potentially targetable with antiviral therapy, particularly in patients with detectable HHV-8 viral loads. An early report of 3 patients with MCD treated with intravenous or oral ganciclovir was promising.\(^70\) Two patients experienced flares of symptomatic disease less frequently and a third patient had prolonged remission.\(^70\) This report prompted a prospective study evaluating the use of high-dose zidovudine (600 mg orally every 6 hours) and valganciclovir (900 mg orally every 12 hours) given for 1 out of every 3 weeks.\(^57,68\) Fourteen patients with symptomatic HIV-associated, HHV-8 positive MCD were enrolled and demonstrated overall clinical and complete response rates of 86% and 50%, respectively. The overall radiographic response rate was lower at 36%, with 29% of patients experiencing a complete radiographic response. Three patients who achieved a complete clinical and radiographic response remained in sustained remission at a median of 29 months after the completion of therapy.\(^68\) Antiviral agents have not been studied in patients who were HIV negative in whom HHV-8 is often present but whose role in pathogenesis is less clearly defined. Among small reports, success has not been observed with cidofovir.\(^71\)

**Bortezomib:** Bortezomib is a proteasome inhibitor active in plasma cell neoplasms by multiple mechanisms; it also decreases the production of IL-6 via the NFκB blockade.\(^72\) Anecdotal reports of durable clinical and radiographic responses in MCD warrant further study in the context of clinical trials.\(^73-76\)

**Summary of Treatment Approaches:** For initial systemic therapy, rituximab monotherapy has been recommended based on encouraging efficacy and safety results, with a high likelihood of initial response and associated long-term, progression-free survival rates reported to be between 60% and 79%.\(^34,50,57,59,77,78\) Treatment involves 4 weekly doses at 375 mg/m\(^2\) that can be repeated as necessary for subsequent flareups in patients who previously responded favorably to therapy.\(^55,77\)

In patients who are negative for HIV but who have failed to respond to, or relapse rapidly following rituximab monotherapy, siltuximab monotherapy is recommended. For patients who progress following treatment with siltuximab, single-agent chemotherapy can be utilized with etoposide,\(^5\) vinblase,\(^43\) or liposomal doxorubicin\(^47\) with or without rituximab. Combination chemotherapy regimens such as rituximab plus CHOP (R-CHOP) and rituximab plus CVp (R-CVP) are options for patients with resistant or rapidly progressive disease. In patients with HIV-associated MCD who fail to respond to or relapse rapidly following rituximab monotherapy, the use of either single-agent chemotherapy with or without rituximab or antiviral therapy with high-dose zidovudine and valganciclovir is recommended.\(^67\) Given the increased toxicity in patients with HIV infection and MCD, combination therapy with R-CHOP or R-CVP should be reserved for select patients with treatment-resistant, rapidly progressive, or fulminant disease.

In cases of progression following second-line therapy, the use of alternative single-agent or combination chemotherapies with or without rituximab, bortezomib, antiviral therapies, or IL-6-directed therapy is recommended. For patients who progress following rituximab monotherapy, single-agent chemotherapy with or without rituximab or antiviral therapy with high-dose zidovudine and valganciclovir is recommended.\(^67\) Given the increased toxicity in patients with HIV infection and MCD, combination therapy with R-CHOP or R-CVP should be reserved for select patients with treatment-resistant, rapidly progressive, or fulminant disease.

**Associated Conditions and Malignancy Risk**

**Kaposi Sarcoma**

HHV-8 plays a critical role in the pathogenesis of both MCD and Kaposi sarcoma, and the clinical association of these diseases was noted prior to the identification of HHV-8 as a common underlying viral pathogen. Patients with HIV-associated MCD have a 72% risk of being diagnosed with Kaposi sarcoma, either concurrently or sequentially, and the 2 diseases may coexist in the same pathological specimen (see Fig 3).\(^55\) The association is lower with Kaposi sarcoma negative for HIV, where the dual incidence is reported at 0% to 13%.\(^33,81\) Exacerbations of Kaposi sarcoma have been observed with rituximab therapy,\(^34,50,51\) therefore, vigilance for flareups of Kaposi sarcoma is necessary.
when using treatments containing rituximab in a patient with both diseases.

**Lymphoma**

Patients with Castleman disease are at increased risk for lymphoma. Non-Hodgkin lymphoma has been reported in approximately 20% of patients with MCD, as well as in patients with UCD. Among these, large B-cell lymphoma arising in HHV-8-associated MCD is the most common lymphoma subtype. Patients with MCD are also at increased risk for primary effusion lymphoma, which shares a common HHV-8-mediated pathogenesis. Patients infected with HIV may also develop other HIV-associated lymphomas not directly related to MCD, including plasmablastic lymphoma, Hodgkin lymphoma, and primary lymphoma of the central nervous system. Amyloidosis has also been reported in association with both UCD and MCD.

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**Fig 4.** Recommended treatment algorithm for Castleman disease. IV = intravenous, MCD = multicentric Castleman disease, R-CHOP = rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, R-CVP = rituximab/cyclophosphamide/vincristine/prednisone, UCD = unicentric Castleman disease.
Although most cases of lymphoma arising in MCD occur in patients with HIV or HHV-8 infection, patients with MCD in the absence of HIV or HHV-8 infection are also at increased risk of lymphoma to a lesser degree.92,93

**POEMS Syndrome**

POEMS syndrome is characterized by a light chain monoclonal gammopathy and a progressive polyneuropathy with early sensory symptoms and later more severe motor symptoms, resembling a chronic inflammatory demyelinating polyneuropathy.90,91 MCD is present in 15% to 25% of patients with POEMS syndrome and is included as a major criterion for the diagnosis of POEMS syndrome.7,92 Other common features include osteosclerotic bone lesions, elevated levels of vascular endothelial growth factor, hepatosplenomegaly, lymphadenopathy, endocrinopathy, skin changes, and elevated protein in the cerebrospinal fluid. Treatment is directed at the plasma cell clone and includes dexamethasone, lenalidomide, and alkylator-based therapy, with high-dose chemotherapy and autologous stem cell transplantation reserved for select cases.

**Follicular Dendritic Cell Sarcoma**

Follicular dendritic cell sarcoma is a rare malignancy that frequently occurs in lymph nodes, although it may also involve extranodal sites. Follicular dendritic cell sarcoma has been associated with UCD; in such cases, follicular dendritic cell sarcoma is diagnosed either concurrently with or following the diagnosis of UCD.93-100 Optimal therapy is surgical resection, with or without adjuvant radiation therapy or chemotherapy, although data to guide chemotherapy in this population are scant given the rarity of the disease.

**Paraneoplastic Pemphigus**

Paraneoplastic pemphigus is an autoimmune mucocutaneous blistering disease associated with localized Castleman disease in 18% of cases and can be a devastating disease with a high mortality rate.101 Approximately two-thirds of patients with paraneoplastic pemphigus have either UCD or an associated malignancy (eg, B-cell lymphoma, lymphoplasmacytic lymphoma, chronic lymphocytic leukemia) at the time of diagnosis.102 The disease precedes the diagnosis of UCD or cancer in the remaining cases. UCD should be suspected in any young patient with paraneoplastic pemphigus. Complete resection of UCD results in clinical improvement or complete remission in most patients.

**Conclusions**

Castleman disease is an uncommon lymphoproliferative disorder that continues to pose clinical challenges.

Although surgical resection remains the standard therapy for unicentric disease, the landscape for the management of multicentric disease continues to evolve. Rituximab monotherapy is the current mainstay of therapy, and novel agents targeting interleukin 6 represent exciting new additions to the treatment armamentarium. Single-agent and combination chemotherapies as well as antiviral therapy provide adjunctive support, particularly in the setting of relapsed or refractory disease. The ongoing exploration of antiviral and novel strategies, such as proteasome inhibition, is warranted.

The management of Castleman disease also requires careful attention to potential concomitant infections, malignancies, and associated syndromes.

**References**


Blastic Plasmacytoid Dendritic Cell Neoplasm: Update on Molecular Biology, Diagnosis, and Therapy
Wasif Riaz, MD, Ling Zhang, MD, Pedro Homa, MD, and Lubomir Sokol, MD, PhD

Background: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy with an aggressive clinical course. Most patients with BPDCN have skin lesions and simultaneous involvement of the peripheral blood, bone marrow, and lymph nodes.

Methods: A search of PubMed and Medline was conducted for English-written articles relating to BPDCN, CD4+CD56+ hematodermic neoplasm, and blastic natural killer cell lymphoma. Data regarding diagnosis, prognosis, and treatment were analyzed.

Results: BPDCN is derived from precursor plasmacytoid dendritic cells. The diagnosis of BPDCN is based on the characteristic cytology and immunophenotype of malignant cells coexpressing CD4, CD56, CD123, blood dendritic cell antigens 2 and 4, and CD2AP markers. Multiple chromosomal abnormalities and gene mutations previously reported in patients with myeloid and selected lymphoid neoplasms were identified in approximately 60% of patients with BPDCN. Prospectively controlled studies to guide treatment decisions are lacking. The overall response rate with aggressive acute lymphoblastic leukemia–type induction regimens was as high as 90%, but the durability of response was short. Median survival rates ranged between 12 and 16 months. Patients with relapsed disease may respond to L-asparaginase–containing regimens. Allogeneic hematopoietic stem cell transplantation, particularly when performed during the first remission, may produce durable remissions in selected adults.

Conclusions: BPDCN is a rare aggressive disease that typically affects elderly patients. The most commonly affected nonhematopoietic organ is the skin. Although BPDCN is initially sensitive to conventional chemotherapy regimens, this response is relatively short and long-term prognosis is poor. In the near future, novel targeted therapies may improve outcomes for patients with BPDCN.
Introduction
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematological neoplasm derived from the precursor of plasmacytoid dendritic cells (pDCs).\(^1\) The nomenclature of BPDCN has evolved over the last 20 years; the disease is classified under acute myeloid leukemia (AML) and related precursor neoplasms in the 2008 World Health Organization classification of tumors of hematopoietic and lymphoid tissues.\(^1\) It was initially described in the mid-1990s as agranular CD4\(^+\) natural killer (NK) cell leukemia due to its unique agranular morphology and phenotype (CD4\(^+\), CD56\(^+\), CD15\(^-\), and CD3\(^-\))\(^2\).\(^3\) It has also been termed blastic NK cell lymphoma\(^4\)\(^5\) due to its expression of NK-cell marker CD56, blastic NK cell leukemia/lymphoma, as well as CD4\(^+\) CD56\(^+\) hematodermic neoplasm/tumor based on morphology, immunophenotype, and tropism for the skin.\(^5\)\(^6\)

Epidemiology
BPDCN can occur at any age and any geographical area; however, most patients are older adults with a median age of 67 years (range, 8–105 years), and the male:female ratio is 2.2–3.0:1.0.\(^7\)\(^8\) Although the exact incidence of BPDCN is unknown, it represents 0.44% of all hematological malignancies, less than 1% of acute leukemias, 0.7% of cutaneous lymphoma cases, and 6.3% of the NK-cell lineage malignancies in Japan.\(^5\)\(^9\)-\(^12\) In 2005, an estimated 100 cases were reported since its first description,\(^13\) and, since then, more than 100 new cases have been described in the literature.

Etiology
The etiology of BPDCN is unknown, with no evidence suggesting an association with Epstein-Barr virus.\(^1\) A single case of BPDCN has been reported in a carrier of human T-cell lymphotropic virus 1, favoring a random coincidence over causative relation.\(^14\) In a series of 43 patients with BPDCN, 10 patients (23%) were diagnosed with secondary leukemia.\(^8\) In 4 patients (9%), myelodysplastic syndrome (MDS) preceded BPDCN and had a median latency time of 3.5 years (range, 1–4 years); 6 patients (14%) presented with therapy-related leukemia following chemotherapy for the first neoplasm. The median time of latency between chemotherapy exposure and diagnosis of BPDCN was 5 years (range, 1–15 years).\(^8\) These observations support a hypothesis that exposure to prior chemotherapy is an important pathogenic factor, and the association with myeloid neoplasms suggests that a putative initiating mutation might reside in hematopoietic stem cells or a common myeloid/lymphoid progenitor.\(^15\)

Cell of Origin
Normal pDCs can originate from common myeloid or common lymphoid progenitors.\(^16\) Due to a lack of lineage-specific markers and CD56 expression, BPDCN was initially believed to have arisen from immature NK cells;\(^6\) however, subsequent studies identified a malignant cell counterpart in plasmacytoid monocytes.\(^5\)\(^7\)\(^8\) It is believed that BPDCN arises from precursor pDCs, with normal pDCs accounting for fewer than 0.4% of peripheral blood mononuclear cells.\(^1\) A small proportion of these cells reside in primary and secondary lymphoid organs.\(^10\)\(^18\) Nonmalignant pDCs can accumulate in various pathological conditions such as autoimmune diseases, classical Hodgkin lymphoma, and carcinomas.\(^19\)

pDCs are characterized by a lineage (Lin) negative human leukocyte antigen (HLA)-DR\(^+\) CD56\(^+\) CD123\(^+\) CD11c\(^-\) immunophenotype, which is distinct from the immunophenotype seen in malignant cells of BPDCN. Functionally, pDCs belong to a group of type I interferon–producing cells implicated in innate adaptive immune responses such as sensing nucleic acids of viruses and bacteria via the Toll-like receptors 7 and 9 expressed on the surface of pDCs.\(^19\)\(^21\)

An analysis of subsets of dendritic cells in normal healthy individuals identified a potential normal counterpart of BPDCN.\(^22\)\(^23\) A search for cells with the Lin\(^-\) HLA-DR\(^+\) CD56\(^+\) immunophenotype revealed a minor cell population comprising 0.03% of peripheral blood mononuclear cells among the healthy volunteers. These plasmacytoid dendritic-like cells (pDLCs) were functionally distinct from more abundant normal pDCs expressing the Lin HLA-DR\(^-\) CD56\(^-\) CD123\(^-\) CD11c\(^-\) immunophenotype.\(^23\) The ratio of pDLC:pDC was higher in bone marrow than in peripheral blood, and pDLC also expressed BDCA2, BDCA4, myeloid antigens, and Toll-like receptors, yet produced less interferon \(\alpha\) after stimulation. These data demonstrate that pDLCs are a distinct subpopulation with an immunophenotype similar to BPDCNs.

Molecular Biology
Approximately two-thirds of patients with BPDCN have multiple karyotypic abnormalities (Table).\(^1\)\(^24\)-\(^32\) Leroux et al\(^24\) reported 6 recurrent cytogenetic abnormalities, including chromosomes 5q (72%), 12p (64%), 13q (64%), 6q (50%), 15q (43%), and monosomy 9 (28%) in 21 patients; however, none were specific or diagnostic. Lucioni et al\(^25\) employed array-based comparative genomic hybridization and found the 4 most commonly deleted regions involved 9p21.3 (CDKN2A/CDKN2B), 13q13.1-q14.3 (RB1), 12p13.2-p13.1 (CDKN1B), and 13q11-q12 (LAT52), with biallelic loss or multiple heterozygous deletions of these genes in more than 90% of cases. The biallelic loss of 9p21.3 was associated with poor prognosis.

Wiesner et al\(^26\) analyzed skin samples from 14 patients using high-resolution, array-based comparative genomic hybridization and immunostaining.
and found that the most frequent chromosomal aberrations were the losses of chromosomes 9, 12, 13, and 15. A loss of the CDKN1B locus was identified in 64% of tumors, and the cell-cycle inhibitor p27 (KIP1), which is encoded by CDKN1B, was weakly expressed in the nuclei of tumor cells. A loss of the CDKN2A/ARF/CDKN2B locus occurred in 50% of patients. The cell-cycle inhibitor p16 (INK4a), which is encoded by CDKN2A, was not expressed in tumor cells, suggesting a complete loss of function. The loss of chromosome 13, including RB1, was observed in 43% of tumors.

The results of this study suggested that the loss of multiple cell-cycle checkpoints that control proteins might play a role in the malignant transformation and the aggressive biological behavior of BPDCN.

Tokuda et al27 reported on an infant with congenital BPDCN with clinically manifested hemophagocytic lymphohistiocytosis. An analysis of the peripheral blood leukocytes revealed a t(2;17;8)(p23;q23;p23) translocation with a CLTC-ALK fusion gene. This translocated fusion gene was identified in cells of myeloid and T-cell lineages, suggesting that the chromosomal defect occurred in a common myeloid/lymphoid progenitor.

Sapienza et al28 studied gene expression profiling in 27 samples of BPDCN and 8 samples of non-neoplastic resting pDCs. The up regulation of the nuclear factor (NF)-κB pathway concurrently with the upregulation of 2 NF-κB targets (BCL2 and IRF4) was detected and confirmed by immunohistochemistry. Both the proteasome inhibitor bortezomib and a selective inhibitor of IkB kinase-β induced cell cycle arrest and apoptosis in BPDCN cells.

Dijkman et al29 identified the overexpression of the oncogenes HES6, RUNX2, and FLT3 without the associated genomic amplification as well as the high expression of various pDC-related genes. Aleyed et al30 also studied 16 patients with BPDCN, 5 of whom (31%) had myelodysplastic changes in their marrow. Conventional cytogenetics revealed the abnormal karyotype in 6 of the 13 (46%) patients. Targeted next-generation sequencing was performed on 5 patient samples and showed TET2 mutations but no other MDS/AML-associated mutations.

Menezes et al31 performed whole-exome sequencing on samples of BPDCN. Based on these data, the researchers designed a custom panel of 38 genes for a targeted resequencing of 25 samples. Their data revealed mutations in TET2 (36%), ASXL1 (32%), NPM1 (20%), NRAS (20%), IKZF1 (20%), IKZF1-3 (20%), ZEB2 (16%), HOXB9 (4%), and UBE2G2 (4%). A total of 48% of patients with gene mutations in the methylation pathways had significantly worse overall survival rates than patients without these gene mutations (11 months vs 79 months).

Taylor et al32 reported on the next-generation sequencing of all exons of 219 genes known to be

Table. — Genetic Abnormalities in Blastic Plasmacytoid Dendritic Cell Neoplasm

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Methods</th>
<th>Chromosome Abnormality</th>
<th>Gene Defect</th>
<th>GEP</th>
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<tr>
<td>Leroux et al24</td>
<td>21</td>
<td>Cytogenetics</td>
<td>5q, 12p, 13q, 6q, 15q, monosomy 9</td>
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<td>14</td>
<td>aCGH</td>
<td>Losses of chromosomes 9, 12, 13, 15</td>
<td>CDKN1B, CDKN2A/ARF/CDKN2B, RB1</td>
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<tr>
<td>Tokuda et al27</td>
<td>1</td>
<td>Cytogenetics</td>
<td>t(2; 17; 8) (p23; q23; p23)</td>
<td>Fusion protein CLTC-ALK</td>
<td>IRF4, NFκB, BCL2</td>
</tr>
<tr>
<td>Sapienza et al28</td>
<td>27</td>
<td>GEP</td>
<td>NA</td>
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<td>GEP</td>
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<td>16</td>
<td>NGS</td>
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<td>NA</td>
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<tr>
<td>Menezes et al31</td>
<td>3</td>
<td>WES/TS</td>
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<td>TET2, ASXL1 NPM1, NRAS, IKZF1, IKZF1-3, ZEB2, HOXB9, UBE2G2</td>
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</tr>
<tr>
<td>Taylor et al32</td>
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<td>NGS</td>
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<td>TET2, TP53, ASXL1, IDH2, KRAS, ABL1, ARID1A, GNA13, U2AF1, SRSF2, IRAF, ZRSR2</td>
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</tr>
</tbody>
</table>

aCGH = array-based comparative genomic hybridization, GEP = gene expression profiling, NA = not applicable, NGS = next-generation sequencing, TS = target sequencing, WES = whole-exome sequencing.
recurrently mutated in hematological malignancies. A discovery gene cohort was sequenced in 7 patients with BPDCN. Many mutations in genes previously described in various hematological malignancies, such as TET2 (57%), TP53 (14%), and ASXL1 (28%), were confirmed, along with multiple loss-of-function mutations in the splicing factor ZRSR2 (57% of patients).32 The mutations were also more frequently present in older men. Altogether, these molecular data demonstrate that BPDCN cells can carry multiple mutations that overlap with the genetic abnormalities of myeloid and lymphoid neoplasms, leading to the dysregulation of multiple pathways that may serve as targets for agents (eg, proteasome and anaplastic lymphoma kinase inhibitors).

**Clinical Manifestations**

Most patients present with nonpruritic cutaneous lesions, blood, bone marrow, and lymph node involvement,1,8 although patients with cutaneous disease alone have also been described.35-35 Cutaneous lesions are variable in size, shape, and color and can present as tumors, nodules, bruise-like infiltrates, or plaques (Fig 1).1,7 In a large registry study, the majority of patients manifested with skin nodules (73%) and, less frequently, with bruise-like lesions (12%).7 Splenomegaly, hepatomegaly, and cytopenias due to bone marrow involvement can be present at diagnosis or may occur with disease progression.1 Involvement of other sites, including soft tissues, the lungs, and the central nervous system, has been also reported.1,25 Less frequently, patients with BPDCN can present with in the leukemic phase without skin involvement.8,36

**Diagnosis**

The diagnosis of BPDCN is pathological (Fig 2). BPDCN should be suspected in older patients with non-specific persistent skin lesions refractory to treatment; these patients should undergo skin biopsy. In addition to characteristic morphology, a demonstration of a specific immunophenotype either by immunohistochemistry or flow cytometry is required for diagnosis.

Skin biopsy typically demonstrates a diffuse, monomorphic infiltrate of medium-sized blast cells with irregular nuclei, fine chromatin, and at least 1 small nucleolus. Typically, malignant cells do not infiltrate the epidermis (Fig 3). The cytoplasm is scant and agranular. Mitoses are variable in number and angioinvasion and coagulative necrosis are absent.1 Bone marrow is involved in the majority of patients. Findings on bone marrow biopsy may range from small interstitial infiltrates detectable by immunohistochemistry or flow cytometry to diffuse bone marrow involvement (Fig 4). Dysplastic changes may also be present in residual hematopoietic tissue, particu-

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**Fig 1.** — Skin involvement with bruise-like infiltrate of blastic plasmacytoid dendritic cell neoplasm.

**Fig 2.** — Diagnostic algorithm for BPDCN. BPDCN = blastic plasmacytoid dendritic cell neoplasm.
BPDCN exhibits a specific immunophenotype and coexpresses CD4, CD43, CD45RA, and CD56 as well as pDC-related antigens, including CD123 (interleukin 3α chain receptor), T-cell leukemia 1 (TCL1), cutaneous lymphocyte-associated antigen, blood dendritic cell antigen (BDCA) 2 (CD303), BDCA4/CD304, CD2AP, Spi-B transcription factor, and platelet endothelial cell adhesion molecule (CD31). Terminal deoxynucleotidyl transferase (TdT) is expressed in approximately one-third of cases. Stem cell markers, including CD34 and CD117, and Epstein–Barr virus-encoded small RNAs are negative. The immunophenotype of BPDCN overlaps with pDC, occurring in reactive lymph nodes except the expression of CD56 and TdT. CD7 and CD33 expression is common. T-cell markers (CD3, CD5) and B-cell markers (CD19, CD20, CD79a) are not expressed. Typically, lysozyme and myeloperoxidase are negative. Rarely, CD56 can be negative; in such cases, BPDCN can be diagnosed based on morphology and complete immunophenotypic profile.

Garnache-Ottou et al proposed a diagnostic algorithm for BPDCN. They determined that the coexpressions of CD4+, CD56−/−, CD123+, BDCA2+, and/or BDCA4+ and an absence of CD3−, CD11c−, MPO−, and CD79a− are diagnostic for BPDCN. If CD123 expression is negative or dim, or when CD123 is positive but cells do not express BDCA2 or BDCA4, then a diagnosis of BPDCN should not be considered. Julia et al analyzed 91 patients with BPDCN and identified that the 5 most characteristic immunophenotypic markers are CD4, CD56, CD123, CD303, and TCL1.

Fig 3. — (A) Punch biopsy of a skin lesion showing blastic plasmacytoid dendritic cell neoplasm (H & E, × 40) and (inset) medium-sized malignant cells spare the epidermis (H & E, × 1000). (B) Immunohistochemical staining demonstrates the coexpression of CD4, CD56, CD123, and (immunoperoxidase, × 200). (C) Flow cytometry identified an atypical lymphoid population (areas in red) expressing CD45 and CD56 that was negative for T-cell markers (CD3, CD8). H & E = hematoxylin and eosin, TdT = terminal deoxynucleotidyl transferase.
Simultaneous expression of all markers was observed in 46% of patients, but the expression of 4 markers was sufficient for a reliable diagnosis.7

**Differential Diagnosis**

BPDCN must be differentiated from several distinct myeloid and dendritic cell neoplasms and from cutaneous involvement with T-cell and NK-cell malignancies exhibiting the CD4+ or CD56+ immunophenotype.1 Extramedullary myeloid sarcoma (EMS) may be difficult to differentiate from BPDCN because immunophenotypic overlap exists among these 2 diseases and both diseases frequently manifest with skin infiltration.

Sangle et al45 studied the clinical utility of 3 novel markers previously described in BPDCN (myxovirus A, CD162/cutaneous lymphocyte-associated antigen, and CD303/BDC2) on 23 paraffin samples of EMS and 17 samples with BPDCN. The results of this study suggested that BPDCN is associated with the positive coexpression of CD56, TdT, or TCL1 or negative staining for lysozyme. The EMS samples also showed positive staining for lysozyme or myeloperoxidase or negative staining for CD56, CD123, myxovirus, or TCL1. Two of the 3 novel markers (CD162 and CD303) showed a poor predictive value for differentiating BPDCN from EMS.45

Patients with cutaneous T-cell lymphoma frequently present with skin lesions and blood involvement, but the disease can be differentiated from BPDCN based on morphology, disproportionate epidermotropism, and mature T-cell immunophenotype with a lack of CD56 expression.46 Extranodal NK/T-cell lymphoma can manifest with skin lesions and the expression of the CD4+/CD56+ immunophenotype. This rare aggressive malignancy can be differentiated from BPDCN by demonstrating Epstein–Barr virus positivity via in situ hybridization using Epstein–Barr virus-encoded small ribonucleic acids.1,47

Vitte et al48 identified 42 patients from a French database who had cutaneous involvement of malignant myeloid and dendritic cell neoplasms. Four distinct clinicopathologic groups were identified, the first of which included myelomonocytic cell tumors (n = 18) positive for CD68, myeloperoxidase, or both but negative for dendritic cell markers. The second group consisted of mature pDC tumors (n = 16) coexpressing CD123, TCL1, and CD303 but missing CD56,
CD1a, and S100 markers. The third group was composed of blastic pDC tumors (n = 4) consisting of medium-sized blasts positive for CD4, CD56, CD123, and TCL1 but negative for CD1a and S100. The fourth group included blastic indeterminate dendritic cell tumors (n = 4) that coexpressed monocytic and dendritic cell markers. A different prognosis was observed among these disease entities. A minimal diagnostic panel for stratification of all 4 entities included CD68, CD1a, S100, langerin, and CD123.

Assaf et al studied a heterogeneous group of cutaneous malignancies expressing the CD56 marker, including hematodermic neoplasm, AML, NK/T-cell lymphoma, and cutaneous T-cell lymphoma. Patients without a diagnosis of cutaneous T-cell lymphoma had a poor prognosis and a median survival rate of 11 months. Altogether, these data underline the complexity and difficulty of diagnosing cutaneous myeloid and dendritic cell neoplasms, which frequently require the expertise of dermatopathology and hematopathology consultants at a tertiary center.

**Therapy**

Typically, patients with BPDCN have poor outcomes. Prospective data are lacking, with retrospective case reports, case series, and disease registry reviews alone available to guide treatment decisions. Reported median overall survival rates in most of the studies reviewed ranged from 12 to 16 months.7,15,50

**Induction Therapy**

BPDCN can be initially limited to skin without obvious systemic involvement. Skin-directed therapies with focal radiation therapy, systemic glucocorticosteroids, or nonintensive chemotherapy regimens can be initially effective and may lead to the complete resolution of cutaneous lesions, but such approaches do not appear to provide a long-term benefit.33-35 Nearly all patients relapse within several months after such treatment; however, because patients with isolated cutaneous lesions may have better prognoses, the skin-directed therapeutic approach can be a reasonable palliative option for patients who have a poor performance status due to underlying comorbidities and who are unable to tolerate systemic intensive chemotherapy.35

Standard frontline therapy has not been established for patients with advanced-stage BPDCN; thus, participation in a clinical trial should be encouraged (Fig 5). Clinical practice varies based on institutional preference. Patients with BPDCN may have been treated with regimens derived from the management of more common hematological malignancies, including non-Hodgkin lymphoma (cyclophosphamide/hydroxydaunomycin/vincristine/prednisone [CHOP] or CHOP-like), acute lymphoblastic leukemia (ALL; hyperfractionated/cyclophosphamide/vincristine/doxorubicin/dexamethasone [hyper-CVAD] alternating with methotrexate and cytarabine), and AML.51-55

Feuillard et al treated 23 patients with CHOP-like regimens and reported a complete response (CR) rate of 86%; however, responses were short lived, with a median time to relapse of 9 months. Three patients had isolated cutaneous lesions at diagnosis and demonstrated bone marrow involvement at relapse, and 5 patients had central nervous system relapse. Overall survival was 25% after 24 months of follow-up.51 More intensive, ALL-like treatment regimes (eg, hyper-CVAD) yielded higher response rates. Pemmaraju et al reported a CR of 90% in 10 patients treated with hyper-CVAD, reporting a median duration of response of 20 months and a median overall survival rate of 29 months.

AML-like treatment regimens have also been used as initial therapy. Dietrich et al reported a CR rate of 83% in 6 patients treated with an AML-like regimen. An et al54 reported a single institutional experience with 6 patients treated with multiagent chemotherapy as first-line treatment and 1 patient treated with radiation therapy. The median progression-free survival rate was 8.6 months (range, 2.6–28.9 months) and the overall survival rate was 15 months (range, 4.4–60.0 months), with a median follow-up of 13.8 months (range, 1.9–29.9).54 Four patients with cutaneous involvement survived, which is in contrast to the patient without skin involvement who died of disease.54 Gills et al6 treated 11 patients with BPDCN, with 6 receiving high-dose methotrexate followed by L-asparaginase. All 6 patients (55%) who received the combination therapy achieved CR, while 5 patients treated with an alkylating agent as frontline therapy achieved only a partial response (PR). Nine patients (82%) died of disease progression (median survival, 9 months).51

Pagano et al reported the outcomes of 43 patients with BPDCN who were diagnosed in Italy between 2005 and 2011. Forty-one of these patients received induction therapy, with 26 and 15 receiving AML-like and ALL-like regimens, respectively. Seventeen (41%) patients achieved a CR (7 in the AML-like group and 10 in the ALL-like group), with a statistically significant advantage for ALL-like chemotherapy (P = .02). Of the 17 patients who achieved a CR, 6 (35%) subsequently relapsed. Three patients had a central nervous system relapse. None received central nervous system prophylaxis.8 Although prospective, randomized studies have not compared ALL-like with AML-like induction regimens, data from retrospective studies have suggested a higher response rate with ALL-like regimens.8,55 Due to a high risk of central nervous system involvement, particularly among patients who have relapsed, central nervous system prophylaxis should be considered, as the incidence of central nervous system involvement is between 9% and 26%.8
**Relapse Management and Maintenance Therapy**

Gruson et al\textsuperscript{56} treated 7 patients with an L-asparaginase–containing regimen (L-asparaginase/methotrexate/dexamethasone) and reported good tolerance in both the untreated and relapsed patients. The objective response rate was 71% (4 CR and 1 PR), and overall survival rates ranged from 6 to 34 months.\textsuperscript{56} However, only patients who received consolidation with allogeneic stem cell transplantation were alive at the time of the report. Leitenberger et al\textsuperscript{57} reported on a patient with relapsed BPDCN following 2 cycles of CHOP who demonstrated a regression of skin tumors after being treated with weekly pralatrexate. Using low-dose etoposide therapy, Hatano et al\textsuperscript{58} maintained a long-term remission in a patient with relapsed BPDCN. These data suggest that less intensive regimens containing L-asparaginase and monochemotherapy may be used in relapsed disease or as maintenance in patients not eligible for hematopoietic stem cell transplantation (HSCT).

**Hematopoietic Stem Cell Transplantation**

Despite a favorable response to initial induction therapy in most patients, responses are typically short-
lived, suggesting that induction therapy alone is not sufficient to maintain durable remissions. The role of maintenance or consolidative therapy has not been well defined, and no randomized controlled trials define the role of HSCT. In most HSCT reports, because of the small number of patients, statistical power could not be shown regarding whether a difference could be seen among patients undergoing transplantation and those who did not. In a literature review of HSCT in patients with BPDCN, 76 patients were identified who underwent consolidation with allogeneic HSCT and 13 patients with autologous HSCT. Because younger patients typically have a better performance status and a good response to induction chemotherapy than older patients, younger people are typically selected for HSCT; therefore, the better outcomes seen in some reports among patients undergoing HSCT could be due to a selection bias.

Autologous HSCT has been utilized as consolidative therapy in patients with BPDCN. Suzuki et al reported on the outcomes of 6 patients who received high-dose chemotherapy followed by autologous HSCT. Two patients had a CR, 1 patient had a PR, another patient had a second PR, 1 patient was treated at the time of the first relapse, and 1 patient had primary refractory disease. Three patients died after disease progression and 3 patients were alive at 11, 22, and 37 months following autologous HSCT. Reimer et al reported disease relapse in 3 of 4 patients studied following autologous HSCT; the median survival rate was 13 months. Due to limited data and a high relapse rate, only selected patients with chemosensitive disease and no available donor for allogeneic HSCT should be referred for autologous HSCT.

Allogeneic HSCT offers durable disease control and possible cure, particularly if it is performed during the first complete remission. Roos-Weil et al analyzed 34 patients (median age, 41 years) in the European Group for Blood and Marrow Transplantation registry who underwent allogeneic HSCT between 2003 and 2009. Eleven patients received a transplant from siblings, 23 patients received a transplant from unrelated donors, and 19 (56%) patients underwent transplantation during their first remission. The 3-year cumulative incidences of relapse, disease-free survival, and overall survival rates were 32%, 33%, and 41%, respectively. In a univariate analysis, allogeneic HSCT at first remission was associated with improved survival rates. In a single institutional report, 6 of the 19 patients (32%) studied underwent consolidation with autologous (3 patients), allogeneic (2 patients), and cord blood (1 patient) transplantation. The median overall survival rate for patients undergoing transplantation was 31 months vs 29 months for those not receiving transplantation (n = 13; P = .82). The results of this study suggested no statistically significant improvement in survival among patients treated with HSCT compared with conventional therapy. However, the numbers of patients were too small to draw any definitive conclusions. Unteregger et al treated 5 patients with allogeneic HSCT during the first or subsequent remission. Four patients received reduced intensity conditioning and 2 umbilical cord blood transplantations. No graft-vs-host disease was observed in patients who received umbilical cord blood transplantation, but both of these patients developed post-transplantation lymphoproliferative disease.

Jegalian et al retrospectively reviewed the cases of 25 pediatric patients with BPDCN who underwent induction therapy with intensive high-risk, ALL-type chemotherapy regimens. The event-free survival rate was 64%, and 9 of the 25 patients (36%) were alive 5 years after diagnosis. Three patients underwent HSCT. Among those who did not manifest cutaneous involvement, the survival rate was 100%; by contrast, the survival rate was 61% in patients with cutaneous disease. The overall survival rate was 72% with a median follow-up of 30 months. This study suggested that a prognosis of BPDCN might be better in pediatric patients; thus, consolidation with HSCT should be reserved for pediatric patients in cases of relapse during complete remission.

**Targeted Therapy**

No specifically targeted agents are currently approved for patients with BPDCN. However, advances in the understanding of the pathobiology of BPDCN, as well as the results of early clinical studies, have revealed novel targets and potentially effective agents. FLT3-ITD mutations were detected in 3 patients among 14 examined cases of BPDCN; none of these 3 patients had previous MDS or myeloproliferative neoplasm. If these results are confirmed in a larger cohort of patients, then these findings could lead to a potential novel therapy with FMS-like tyrosine kinase-3 inhibitors.

Agliano et al demonstrated the ex vivo efficacy of lenalidomide against BPDCN cells in a xenograft mouse model; thus, the activity of lenalidomide should be further explored in clinical studies of patients with BPDCN. Laribi et al reported on 2 patients with BPDCN who underwent frontline therapy with 5-azacytidine and achieved a resolution of their skin lesions and a stabilization of their hematological parameters. This therapy could be effective, particularly among patients with BPDCN and concurrent myelodysplastic changes or myeloid malignancy (eg, MDS, AML).

Several groups of investigators have reported the results of preclinical and early clinical data with SL-401, a recombinant human interleukin 3α protein.
conjugated with truncated diphtheria α-toxin, a potent inhibitor of protein synthesis. In a preclinical study, SL-401 revealed antitumor activity against BPDCN cell lines with the half maximal inhibitory concentration in the femtomolar range. Frankel et al reported on data from a phase 1/2 study in which 11 patients with BPDCN received a single daily course of SL-401 at 12.5 mcg/kg for 5 days. Of those patients, 2 were not evaluable for a response; however, 7 patients (78%) achieved major responses (5 CRs, 2 PRs). Complete remissions included the elimination of malignant cells from all compartments, including skin, bone marrow, peripheral blood, spleen, and lymph nodes. The median duration of response was 5 months (range, 1–20+ months). The most common adverse events seen in these patients were fever, chills, hypotension, hypoalbuminemia, peripheral edema, thrombocytopenia, and the transient elevation of liver transaminases. These encouraging results suggest that targeted therapy has the potential for improving patient outcomes.

Prognosis
The long-term prognosis of patients with BPDCN is poor due to the aggressive behavior of the disease, the advanced age of most patients, and an absence of effective targeted therapy with low toxicity rates. Due to the limited number of patients in retrospective reports, validated prognostic and predictive markers are lacking. Analyses of small case series suggest that adult patients with skin involvement at presentation have better prognoses than their counterparts. By contrast, in 1 study, patients with the leukemic form of BPDCN had a median survival rate of 8.7 months, which is shorter than the 12 months reported for all patients together.

In a large, retrospective, national registry study, the expression levels of CD303 and high Ki-67 proliferative index were significantly associated with longer survival rates. The biallelic loss of 9p21.3 and the mutation in the methylation pathway genes have been associated with an unfavorable prognosis. Pediatric patients with BPDCN treated with high-risk, ALL-like induction regimens had better prognoses than their adult counterparts, and most of these patients did not require consolidation with allogeneic HSCT during their first remission.

Conclusions
Blastic plasmacytoid dendritic cell neoplasm is a rare but aggressive hematological malignancy with a poor prognosis. Prognosis for pediatric patients appears to be better than for adults. No established standard frontline treatment regimen exists for patients with blastic plasmacytoid dendritic cell neoplasm. Acute lymphoblastic leukemia–like and acute myeloid leukemia–like induction chemotherapy regimens are associated with relatively high response rates, although with a short duration in adult patients. Available data suggest that allogeneic hematopoietic stem cell transplantation, particularly if performed during the first complete response, offers the best chance of durable remission. Although it is difficult to conduct randomized trials in this rare disease entity, prospective studies using novel targeted agents could establish more effective and tolerable therapies in the near future.

References


Immunohistochemistry remains the mainstay of diagnosing rare dendritic cell and histiocytic neoplasms. Collaborative efforts are needed to better treat patients with these rare disorders.


Dendritic Cell and Histiocytic Neoplasms: Biology, Diagnosis, and Treatment

Samir Dalia, MD, Haipeng Shao, MD, PhD, Elizabeth Sagatys, MD, Hernani Cualing, MD, and Lubomir Sokol, MD, PhD

Background: Dendritic and histiocytic cell neoplasms are rare malignancies that make up less than 1% of all neoplasms arising in lymph nodes or soft tissues. These disorders have distinctive disease biology, clinical presentations, pathology, and unique treatment options. Morphology and immunohistochemistry evaluation by a hematopathologist remains key for differentiating between these neoplasms. In this review, we describe tumor biology, clinical features, pathology, and treatment of follicular dendritic cell sarcoma, interdigitating dendritic cell sarcoma, indeterminate dendritic cell sarcoma, histiocytic sarcoma, fibroblastic reticular cell tumors, and disseminated juvenile xanthogranuloma.

Methods: A literature search for articles published between 1990 and 2013 was undertaken. Articles are reviewed and salient findings are systematically described.

Results: Patients with dendritic cell and histiocytic neoplasms have distinct but variable clinical presentations; however, because many tumors have recently been recognized, their true incidence is uncertain. Although the clinical features can present in many organs, most occur in the lymph nodes or skin. Most cases are unifocal and solitary presentations have good prognoses with surgical resection. The role of adjuvant therapy in these disorders remains unclear. In cases with disseminated disease, prognosis is poor and data on treatment options are limited, although chemotherapy and referral to a tertiary care center should be considered. Excisional biopsy is the preferred method of specimen collection for tissue diagnosis, and immunohistochemistry is the most important diagnostic method for differentiating these disorders from other entities.

Conclusions: Dendritic cell and histiocytic cell neoplasms are rare hematological disorders with variable clinical presentations and prognoses. Immunohistochemistry remains important for diagnosis. Larger pooled analyses or clinical trials are needed to better understand optimal treatment options in these rare disorders. Whenever possible, patients should be referred to a tertiary care center for disease management.

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Submitted December 20, 2013; accepted May 1, 2014.

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No significant relationships exist between the authors and the companies/organizations whose products or services may be referenced in this article.
Introduction
Dendritic and histiocytic neoplasms are rare hematological malignancies that involve common immune accessory or mesenchymal cells. These tumors are typically placed into 2 main groups based on their derivation from either bone marrow precursors or mesenchymal cells. Histiocytic sarcoma (HS), Langhans cell histiocytosis (LCH), and interdigitating dendritic cell sarcoma (IDCS) are derived from bone marrow precursors, while follicular dendritic cell sarcoma (FDCS), indeterminate dendritic cell sarcoma (INDCS), fibroblastic reticular cell tumors (FRCTs), and disseminated juvenile xanthogranuloma (DJX) are histogenetically of stromal-derived dendritic cells or mesenchymal in origin.1,2 Divergent differentiation from marrow precursors is the normal histogenesis, although hybrid or transdifferentiation from neoplastic lymphoid clones has also been proposed in IDCS, HS, or FDCS.2-4 Together, dendritic and histiocytic neoplasms make up less than 1% of neoplasms presenting in the lymph nodes or soft tissues.

The rarity of these tumors makes them difficult to accurately diagnose and treat, and they are often mistaken as non-Hodgkin lymphoma or other lymphoproliferative disorders. Patients with suspected dendritic and histiocytic neoplasms require hematopathology consultation and should be referred to a tertiary care cancer center when possible. The diagnosis of these rare disorders is based on differential features in morphology and immunohistochemistry. Recent advances in immunohistochemistry have helped in a better classification of dendritic cell and histiocytic neoplasms and have improved our knowledge of their tumor biology and histogenesis, which may be helpful in the management of these rare diseases. The aim of this review is to provide clinicians with the current scientific framework to better understand the tumor biology, clinical features, pathology, and treatment of FDCS, IDCS, INDCS, HS, FRCT, and DJX.

We performed a literature search for articles published between January 1, 1990, and December 1, 2013, to find research related to tumor biology, clinical features, pathology, and treatments for each of these rare disorders. We referred to the text and references of the fourth edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues4 as a basis to comprehensively cover these disorders. Although LCH is integral in understanding these entities, it has been separately reviewed by Dr Grana on page 328 of this issue and will not be covered here.

Follicular Dendritic Cell Sarcoma
Tumor Biology
FDCS is a very rare clonal neoplasm of follicular dendritic cells (FDCs). FDCs are stromal-derived cells normally found in the germinal centers of lymph nodes or the extranodal ectopic lymphoid tissue, including lymphoid nodules in the bone marrow. Through the formation of immune complexes, these cells store and retain antigens and serve as a nidus for B-cell proliferation and differentiation, along with help from T cells.5,6 FDCs are mesenchymal in origin and similar to myofibroblasts. Although FDCs are not derived from bone marrow progenitors, they express antigens related to bone marrow stroma. Hence, these cells typically express markers of FDC differentiation, including CD21, CD23, and CD35.8

Although FDCS is mesenchymal in origin, it is clonally related to follicular lymphoma, possibly through transdifferentiation of the follicular lymphoma clone.3 The disease has also been associated with Castleman disease, paraneoplastic pemphigus, and myasthenia gravis.9,10 FDCS may arise in lymph nodes that harbor dysplastic FDCs in Castleman disease, with some studies reporting clonal expansion of FDCs in these patients.14,15 FDCS and non-neoplastic FDCs of Castleman disease express epidermal growth factor receptor, which may promote FDC persistence and allow for mutations that may result in FDCS.16 In addition, a correlation exists between FDCS and the presence of Epstein–Barr virus (EBV).17 Because FDCs express CD21 (acting as a receptor for EBV), the virus could gain entry into these cells.18,19 The differential diagnosis of FDCS remains broad and includes B- and T-cell lymphomas, myeloid sarcomas, melanoma, carcinomas, and other dendritic and histiocytic disorders, such as blastic plasmacytoid dendritic cell neoplasms and LCH (Table 1). Rarely, peripheral nerve sheath tumors and malignant fibrous histiocytoma are mistaken for FDCS; immunohistochemistry might help in the diagnosis of these entities.21,22

Clinical Features
FDCS presents in a wide range of ages, but it shows adult predominance (mean age, 44 years).23,24 Localized FDCS has a benign course, a median survival rate of 168 months (range, 2–360 months), and risks of local recurrence and distant metastasis of 27% to 28%, respectively.10 Larger tumor size (≥ 6 cm), the presence of coagulative necrosis, high mitotic count (≥ 5 per 10 HPF), and cytological atypia are associated with a poor prognosis.8,10,25 Stage did not significantly impact overall survival rates in patients with FDCS.10 Saygin et al10 reported that 2-year survival rates for early, locally advanced, and distant metastatic disease were 84.2%, 80%, and 42.8%, respectively.

In the majority of cases, FDCS presents as a slow-growing mass, usually with the most frequent location in the head and neck or abdominal lymph nodes. Approximately one-half of patients will present with a local cervical and intra-abdominal mass.10,26 Although rare, most extranodal involvement occurs
in the liver, lungs, tonsils, or spleen. Workup for patients with FDCS should include computed tomography (CT) scans with contrast from the neck to the pelvis to evaluate other sites of disease, complete blood counts, bone marrow aspiration, and biopsy. In certain patients, HIV, EBV, and hepatitis testing can be considered to exclude concurrent viral infection. Core needle biopsy or excisional biopsy (preferred) of the tumor mass is necessary for an accurate diagnosis of FDCS. Fine needle aspiration biopsy should be avoided.

Pathology
Cytomorphology of a biopsied/resected lesion is characterized as spindled to ovoid cells that form fascicles, whorls, diffuse sheets, or nodules (Fig 1). Individual cells generally show indistinct cell borders and a moderate amount of eosinophilic cytoplasm. Nuclear pseudoinclusions are common and binucleated, and multinucleated tumor cells are seen. Long cytoplasmic projections and desmosomal junctions are seen on electron microscopy; Birbeck granules and numerous lysosomes are not present. Lymphoplasmacytic infiltration is present in more than 90% of cases. Rarely, Reed-Sternberg-like cells can lead to a mistaken diagnosis of Hodgkin disease.

Immunohistochemistry is the most important work-up to help differentiate FDCS from other histiocytic tumors. In FDCS, CD21, CD23, CD35, R4/23, Ki-FDC1p, and KiM4 are positive and a variable expression of CD68 can be seen. Clusterin is strongly positive in FDCS and is negative or weakly positive in other dendritic cell tumors. Desmoplakin, vimentin, epidermal growth factor receptor, CD45, and HLA-DR can be variably positive. Immunoglobulin and T-cell receptor genes are in a germline configuration. Cytogenetic data in patients with FDCS are limited and do not aid in diagnosis.

The major clinical and pathological findings for FDCS are outlined in Table 2.

Treatment
Surgical resection remains the mainstay of treatment in FDCS. A Surveillance, Epidemiology, and End Results database study reported that 94% of patients with localized disease had surgical resection as the initial treatment.
The benefit of adjuvant therapy for fully resected lesions in patients with limited stage disease is debatable. Two large analyses both reported no benefit for adjuvant radiation therapy in patients with localized FDSC.\textsuperscript{10,36} Soriano et al\textsuperscript{10} reported in a series of 14 cases with FDSC that 3 patients treated with surgery followed by adjuvant chemotherapy and radiotherapy had complete remission, while 3 patients given chemotherapy alone showed no complete response. The role of adjuvant chemotherapy or radiation therapy in localized FDSC remains controversial and should be considered on a case-by-case basis.

In patients with extensive disease, Saygin et al\textsuperscript{10} reported that 23 patients treated with combined chemotherapy and radiotherapy had excellent survival rates, with only 2 deaths due to disease. These data suggest the importance of combined modality in advanced FDSC, although no prospective randomized trial data exist. Regimens designed to manage aggressive lymphomas, such as cyclophosphamide/vincristine/dacarbazine (ABVD), have been used.\textsuperscript{5,10,32,33} Currently, lymphoma-type chemotherapy remains the mainstay of treatment for disseminated FDSC. The role of allogeneic transplantation for FDSC is unclear. One study reported relapses within 1 year in 2 patients treated with allogeneic transplantation for FDSC.\textsuperscript{32}

**Interdigitating Dendritic Cell Sarcoma Tumor Biology**

Normal interdigitating dendritic cells (IDCs) are antigen-processing cells usually located in the lymph node paracortex, a major T-cell region. These cells present antigens to T cells and regulate cellular immune response.\textsuperscript{10,34-38} IDCS originate from narrow hematopoietic precursors through the conversion of Langerhans cells as they travel to the lymph node.\textsuperscript{10,34,39-41} Malignant IDCS result in IDCS and are usually positive for S100 and vimentin and negative for CD1a and langerin.\textsuperscript{1}

Unlike FDSC, they do not express CD21 or CD35.

IDCS have been reported in association with other hematological and solid tumor malignancies, including B-cell neoplasms, mycosis fungoides, and neoplasms of the skin, liver, stomach, colon, breast, and brain.\textsuperscript{10} A clonal relationship between IDCS and low-grade B-cell lymphomas has been reported and may be due to the transdifferentiation of the lymphoma clones.\textsuperscript{1,4} In one series of 7 patients with chronic lymphocytic leukemia/small lymphocytic leukemia, 4 patients had features suggestive of IDCS. In these

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**Table 2. — Clinical and Pathological Findings of Dendritic Cell Sarcomas**

<table>
<thead>
<tr>
<th>Clinical Findings (usual presentation)</th>
<th>FDSC</th>
<th>IDCS</th>
<th>INDCS</th>
<th>HS</th>
<th>FRCT</th>
<th>JXG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow growing mass, usually a lymph node</td>
<td>Asymptomatic solitary lymph node mass</td>
<td>Papules, nodules, or plaques on the skin</td>
<td>Solitary mass with systemic symptoms Can have skin lesions (rash-like)</td>
<td>Asymptomatic mass</td>
<td>Small solitary papule</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytomorphology</th>
<th>FDCS</th>
<th>IDCS</th>
<th>INDCS</th>
<th>HS</th>
<th>FRCT</th>
<th>JXG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spindle to ovoid cells with whorls</td>
<td>Spindle to ovoid cells with whorls</td>
<td>Resembles Langerhans cells with irregular nuclear grooves and clefts</td>
<td>Large and round to oval shape with focal areas of spindling</td>
<td>Spindle to ovoid cells with whorls in paracortical areas</td>
<td>Small and oval with a bland round to oval nucleus without grooves</td>
<td></td>
</tr>
</tbody>
</table>

| Immunophenotypical Markers | CD4 (+) | CD21 (+) | CD34 (-) | CD35 (--) | CD68 (+) | Fascin (+) | S100 (+) | CD1a (-) | CD4 (+) | CD45 (+/-) | CD68 (+) | Fascin (+) | S100 (+) | CD1a (-) | CD63 (+) | CD68 (+) | Lysozyme (+) | CD1a (-) | CD21 (+) | CD35 (-) | CD33 (-) | Vimentin (+) | Desmin (+) | Smooth muscle actin (+) | Factor XIIIa (+) | CD21 (-) | CD35 (-) | S100 (-) | CD1a (-) | Vimentin (+) | sCD14 (+) | CD68 (+) | Stabilin-1 (+) | CD163 (+) | Factor XIIIa (+) | CD1a (-) |

| Treatment for Limited Disease | Surgical resection ± adjuvant chemotherapy or RT | Surgical resection or RT | Surgical excision | Surgical resection ± RT | Surgical resection ± RT | None needed for localized asymptomatic lesion |

| Treatment for Disseminated Disease | Lymphoma-type chemotherapy | Lymphoma-type chemotherapy | Multimodality | Lymphoma-type chemotherapy | Participation in a clinical trial | Langerhans histiocytosis–based treatment |

FDSC = follicular dendritic cell sarcoma, FRCT = fibroblastic reticular cell tumor, HS = histiocytic sarcoma, IDCS = interdigitating dendritic cell sarcoma, INDCS = indeterminate dendritic cell sarcoma, JXG = juvenile xanthogranuloma, RT = radiation therapy.
cases, identical clonal IGH or IGK was found, along with chromosome 17p deletion by fluorescence in situ hybridization, suggesting a common clonal origin.\(^2\) Another series of 3 cases showed an identical V-J junction sequences and trisomy 12 in both chronic lymphocytic leukemia and IDCS tumors, suggesting transdifferentiation of the lymphoma clones.\(^4\)

Unlike FDGS, a viral etiology for IDCS has not been demonstrated. Most cases of IDCS are negative for EBV and the human herpesvirus 8 genome.\(^10\) IDCS has also been reported following the use of calcineurin inhibitors, which may be due to their effect by dampening the responses of T cells to which IDCs present antigens.\(^10,42,43\) The differential diagnosis for IDCS is presented in Table 1. With advances in immunohistochemistry and molecular diagnosis, IDCs has become less difficult to diagnose; however, a recent report reclassified malignant fibrous histiocytoma as IDCS, highlighting the importance of accurate diagnosis in these rare neoplasms.\(^44\)

**Clinical Features**

IDCS is an extremely rare disease with a pooled analysis of 462 cases of dendritic cell sarcomas, of which 100 were cases of IDCS. Another Surveillance, Epidemiology, and End Results database study of 74 IDC cases included 20 IDCS cases.\(^10,26\) Median age at diagnosis is 56.5 years (range, 21 months to 88 years), and the disease has a male-female ratio of 1.38:1.\(^10\) Prognosis varies in patients with IDCS, from a benign course to rapidly progressive lethal disease in patients with disseminated disease. Patients who are younger and those who have a higher stage as well as intra-abdominal involvement have a worse prognosis than their counterparts.\(^10,26\) Median survival rates for patients with disseminated disease are between 9 and 10 months; according to 2 reported series, those with localized disease did not reach median survival.\(^10,26\) Saygin et al\(^10\) reported 1- and 2-year survival rates of 84.8% and 68.1%, respectively, while patients with metastatic disease had 1- and 2-year survival rates that dropped to 38.5% and 15.8%, respectively.

Patients normally present with a solitary lymph node mass, but cases with skin and soft-tissue involvement have been described.\(^1,28,35,45,47\) Patients are usually asymptomatic, but fatigue, fever, and night sweats may be present. Similar to FDGS, staging includes CT scans with contrast from the neck to the pelvis to evaluate other sites of disease, complete blood counts, bone marrow aspiration, and biopsy. Because viral etiology has not been implicated in patients with IDCS, testing for HIV infection and hepatitis is not indicated in most cases. Core needle biopsy or excisional biopsy (preferred) of the tumor mass is necessary for an accurate diagnosis; fine needle aspiration biopsy should be avoided.

**Pathology**

Cytomorphology typically reveals large spindle to ovoid cells with the formation of whorls. Cells may have coarse nuclear chromatin with moderate to abundant cytoplasm resembling histiocytes.\(^28\) The presence of small lymphocytes intermingling with the large histiocytic cell population is a key diagnostic feature less typical of carcinomas and sarcomas (Fig 2A).\(^28\)

Immunophenotype will show cells negative for CD1a, positive for S100 and CD45, and have variable positivity for CD68 (Fig 2B).\(^42,45\) Some cases of IDCs are positive for vimentin, HLA-DR, and fascin.\(^45\) Lysozyme can also be positive, although this is uncommon.\(^45\) B-cell markers such as CD20 and T-cell markers such as CD3 and CD5 are usually negative. Cytokeratin, myeloperoxidase, CD1a, CD21, CD23, CD30, CD35, clusterin, langerin, CD34, CD79a, BCL2, and BCL6 are negative.\(^1,24,45,46\) A distinguishing feature of IDCS is the absence of Birbeck granules on electron microscopy.\(^24,45\) Immunoglobulin and T-cell receptor genes are in a germline configuration.\(^48\) Table 2 illustrates the clinical and pathological findings associated with IDCs.

**Treatment**

Historically, the mainstay of treatment of IDCS has been surgical resection. One report suggests that surgical resection is associated with improved overall survival rates ($P = .04$).\(^26\) Conversely, another study reported no difference in overall survival rates between surgery and nonsurgical modalities of treatment such as radiation treatment for localized IDCS.\(^10\) Until further conclusive evidence is available, either surgical resection or radiation therapy is recommended as initial therapy for localized IDCS. In disseminated disease, chemotherapy such as CHOP, ICE, and ABVD has been used with variable success.\(^10,43,46\) Although chemotherapy is usually considered for patients with disseminated IDCS, surgical resection may still play a role, with 1 study reporting a trend toward improved overall survival in patients who underwent surgery followed by chemotherapy.\(^10\) Currently, no consensus exists on optimal treatment in patients with disseminated disease; participation in a clinical trial or referral to a tertiary care center is optimal. No data have been published on hematopoietic stem-cell transplantation in IDCS; therefore, the procedure cannot be recommended.

**Indeterminate Dendritic Cell Sarcoma**

**Tumor Biology**

INDCS, also known as indeterminate cell histiocytosis, is a rare neoplastic proliferation of normal dendritic accessory cells, which are usually found in the dermis. Because indeterminate cells share morphological and immunophenotypical features with Langerhans cells (except the presence of Birbeck granules on electron microscopy), some authors speculate that
indeterminate cells may represent a mature form of Langerhans cells. Neoplasms of indeterminate cells are extremely rare and little is known of the natural history of INDCS. Associations between the proliferation of indeterminate cells and nodular scabies, pityriasis rosea, and low-grade B-cell lymphomas have been reported. Immunophenotypical markers are similar to IDCS, which show cells positive for S100 and CD1a; on an ultrastructural examination, Birbeck granules will be absent. The differential diagnosis for INDCS is presented in Table 1.

**Clinical Features**

INDCS has been reported in case reports alone; thus, no data exist on median age, sex, or race predilection among those with INDCS. Most patients present with 1 or more papules, nodules, or plaques on the trunk, face, neck, or extremities. Generalized distribution has rarely been reported. Diagnosis is usually made by skin biopsy and systemic workup, including CT scans and bone marrow biopsy. Other testing is typically not indicated in localized cases.

**Pathology**

Microscopy evaluation shows that these dermal lesions are diffusely infiltrating and are composed of cells with irregular nuclear grooves and clefts that resemble Langerhans cells. Cytoplasm is abundant, pale, and eosinophilic. Multinucleated giant cells may be seen and the spindling or dendritic formation of some cells may be present (Fig 3A, B). These cells lack Birbeck granules on electron microscopy and desmosomes are lacking; however, interdigitating cell processes may be present.

Immunophenotype shows that INDCS cells are positive for S100 and CD1a (Fig 3C–E). These cells are negative for specific B- and T-cell markers, CD30, CD163, CD21, CD23, CD35, and langerin. Factor XIIIa and CD34 are both negative, unlike xanthogranulomas and dermatofibrosarcoma protuberance, respectively. Variable positivity is seen for CD45, CD68, lysozyme, and CD4. One case report indicates that INDCS may be clonal by the human androgen receptor gene assay. The clinical and pathological characteristics for INDCS are summarized in Table 2.

**Treatment**

Due to the rarity of INDCS, little is known about the natural history or treatment of this disease. Most lesions are indolent or self-limited. New lesions may develop, and the spontaneous regression of lesions has been reported. Currently, the resection of lesions, if present, remains the therapy of choice. The roles of chemotherapy and radiation therapy remain unclear in INDCS. In rare cases of disseminated disease, multimodality treatment can be considered.

**Histiocytic Sarcoma**

**Tumor Biology**

HS is a rare non-Langerhans histocyte disorder of mature tissue histiocytes. The etiology of this disorder remains unknown, but some cases have occurred in patients with mediastinal germ cell tumor, suggesting that HS may arise from pluripotential germ cells. Associations between HS and follicular lymphoma, myelodysplastic syndrome, and acute lymphoblastic leukemia have also been made. A study has reported transdifferentiation in patients with HS and follicular lymphoma and reported the presence of t(14;18) and IGH gene rearrangements in all of the patients, suggesting a common clonal origin of follicular lymphoma and HS. Another study reported that 2 patients with HS had a clonal immunoglobulin rearrangement, suggesting a clonal evolution of HS from chronic lymphocytic leukemia/small lymphocytic leukemia. Further research is needed to confirm these findings.

![Fig 2. — Interdigitating dendritic cell sarcoma. (A) Paracortical infiltrate by large neoplastic cells with oval to elongated nuclei, abundant eosinophilic cytoplasm, and indistinct cell border. (B) Neoplastic cells positive for S100 and negative for CD21, clusterin, and langerin. Note the positive stain for CD21 and cluster on follicular dendritic cells in the residual germinal centers.](image-url)
Expert morphology review and immunohistochemistry remain important in the diagnosis of HS. Immunohistochemical markers in patients with HS include positivity for CD163, CD68, and lysozyme. The differential diagnosis for HS is presented in Table 1.

**Clinical Features**

HS has been reported in all age groups but is more commonly seen in adults (median age, 46–55 years). Male predilection has been found in 2 reports but has not been confirmed in others. The disease usually presents with single or multifocal extranodal tumors, most commonly in the intestines, skin, or soft tissue. Rarely, cases have been described with diffuse lymphadenopathy and multiple sites of involvement, and those with multifocal disease have a worse outcome. Systemic symptoms such as fever and weight loss are common, and symptoms from the compression of a vital organ (eg, small bowel obstruction) can occur. Skin involvement can include rash to innumerable tumors in multiple areas of the body. Cytopenias are seen in 30% of cases. Because patients with unifocal disease have better outcomes, we recommend that patients receive full staging, including CT scans and bone marrow biopsy, to rule out multifocal disease. Excisional biopsy is the preferred diagnostic method in these cases.

**Pathology**

Microscopic evaluation can show a noncohesive proliferation of large cells twice the size of small lymphocytes that may have focal spindling. The eosinophilic cytoplasm can contain vacuoles. Nuclei are pleomorphic and can be eccentric and have 1 or more nucleoli (Fig 4A). On occasion, the cells may have a xanthomatous appearance.

Immunohistochemistry is positive for histiocytic markers, including CD163, CD68, and lysozyme. CD1a, CD21, CD35, and CD33 markers are all negative. S100 can be positive but is usually weak or focal (Fig 4B). Ki67 is variable (see Table 2).

**Treatment**

The rarity of HS makes it difficult to assess the benefits of multimodality treatment in these patients. In unifocal extranodal disease, a study of 14 patients gave insights into different treatment modalities. In this series, 5 patients were treated with surgical resection alone, 3 patients with surgical resection and adjuvant radiation therapy, and 6 patients were treated with surgical resection followed by adjuvant chemotherapy. The 2 patients treated with surgery alone went on to develop distant disease within 6 months, while 1 recurred at 6 months and was alive 11 years after repeat resection and adjuvant radiation therapy. Two patients treated with surgery alone did not have evidence of recurrence. In the 3 patients initially treated with surgical resection and adjuvant radiation therapy, no local recurrences were seen; however, 1 patient had distal recurrence and was treated with repeat resection. The most common chemotherapy regimen in the 6 patients receiving adjuvant chemotherapy was CHOP. Two patients had distant spread within weeks and received salvage chemotherapy, and 2 patients were alive and disease free at a median follow-up of 16 months. From this series we can conclude that the mainstay of treatment in patients with HS re-
maintains surgical resection. Adjuvant radiation therapy may help reduce local recurrence rates, but the role of adjuvant chemotherapy remains unclear and should only be used in cases of disseminated disease in which surgical resection is not possible. The optimal chemotherapy regimen remains unclear, and patients should be referred for clinical trials or treatment at tertiary care centers.

**Fibroblastic Reticular Cell Tumor**

**Tumor Biology**

FRCT is a rare neoplasm of fibroblastic reticular cells. Fibroblastic reticular cells are stromal support cells located in the parafollicular areas and the deep cortex of lymph nodes where they are associated with the nodal reticular network. These cells are also thought to be crucial to the interaction between IDCs and T cells in the primary immune response. The entity previously reported as cytokeratin-positive interstitial reticulum cell tumor is likely the same as FRCT, and both entities usually present together in a series. In general, FRCT presents in the lymph nodes but can occur in the spleen, lung, liver, and soft tissue. Although smoking, drug abuse, and viral illnesses have been reported with FRCT, these associations are controversial. FRCT is differentiated from IDCS and FDCS based on immunohistochemistry. FRCTs are immunoreactive with vimentin, smooth-muscle actin, factor XIIIa, and desmin, but they are negative for CD21, CD35, and CD1a. The differential diagnosis for FRCT is presented in Table 1.

**Clinical Features**

Clinical information about FRCT generally comes from a pooled analysis of 19 cases. In this analysis, Saygin et al reported the median age of patients to be 61 years with a male predominance. Sixteen of the 19 patients presented with nodal disease, with the cervical and mediastinal lymph nodes being the most commonly involved. Extranodal sites included the liver, spleen, lung, kidney, adrenal, bone, and soft tissue. Univariate analysis of the prognostic variable did not show a statistically significant prognostic marker in patients with FRCT but did show that patients with higher-stage disease have a significantly shorter survival rate than their counterparts. Patients with local disease had a 2-year survival rate of 85.7%; median survival was not reached. Patients with distant disease died in 2 years and had a median survival rate of 13 months.

Most patients present with a newly diagnosed asymptomatic mass that is surgically excised. The value of CT scans, bone marrow biopsy, and other staging work in single nodal disease is unknown and should be considered in patients with multiple en-
larged lymph nodes. Excisional biopsy is the preferred diagnostic method for FRCT.

**Pathology**
Morphologically, FBRC presents as spindle to ovoid cells with whorls in the paracortical areas associated with abundant reticulin staining fibers. Immunohistochemistry is positive for vimentin, desmin factor XIIIa, and smooth muscle actin. CD45RB, CD21, CD35, S100, CD65, and CD1a are negative. Ultrastructural evaluation reveals peripherally located fusiform densities, long cytoplasmic extensions, and desmosomal-like intercellular attachments.

**Treatment**
Surgery is the treatment of choice for patients with localized disease. Limited data exist on the role of adjuvant radiation therapy, and chemotherapy has no role in localized disease. Not enough data exist to offer treatment recommendations for distal FRCT. Patients should be encouraged to participate in clinical trials, referred to tertiary care centers for treatment recommendations, or both.

**Disseminated Juvenile Xanthogranuloma**

**Tumor Biology**
DJX is a proliferation of histiocytes similar to that seen in dermal juvenile xanthogranuloma (JXG). Solitary dermal JXG is common and does not progress to more disseminated forms. Skin lesions normally regress, but lesions have been reported in the brain, soft tissue, or, rarely, with disseminated disease.

These disorders have been associated with type 1 neurofibromatosis and juvenile myelomonocytic leukemia. Patients with both LCH and JXG have also been reported, suggesting a clonal relationship of these disorders. The differential diagnosis for DJX is presented in Table 1.

**Clinical Features**
DJX usually occurs by 10 years of age, with one-half of reported cases occurring in the first year of life. Skin and soft-tissue presentations are the most common sites of involvement and can include the mucosal surfaces of the upper airway. These lesions are commonly solitary, papular, and small, and multiple lesions can be present. Although rare, the central nervous system, eyes, liver, lungs, lymph nodes, and bone marrow can all be involved. Lesions of the central nervous system can cause diabetes insipidus, seizures, hydrocephalus, and changes in mental status. The workup in patients with suspected DJX should include excisional biopsy of the lesion with an immunopathological review. The role of staging CT scans and bone marrow biopsy remains unclear.

**Pathology**
Morphologically, the JXG cell is small and oval with a bland, round to oval nucleus and pink cytoplasm (Fig 5A). Touton cells are seen at dermal sites but are less common in nondermal sites. The cells become xanthomatous and inflammatory components can be seen. Immunohistochemistry reveals cells that express vimentin, lysozyme, CD14, CD68, CD163, and CD1a. Vascular and myofibroblastic markers for dermatofibrosarcoma, such as CD34, are negative. Note the inflammatory component of eosinophils, lymphocytes, and few plasma cells. Touton giant cells are usually transient and not present in all cases.

![Figure 5](image-url)
stabilin-1, and factor XIIIa (Fig 5B–D). CD1a is negative and S100 is usually negative but can be variably weak and focally positive in some cases (Fig 5E; see Table 2). Despite this multifocal presentation, which simulates lymphoma in some cases, immunoglobulin and T-cell receptor genes are present in a germline configuration.

Treatment

In patients with cutaneous, subcutaneous, and soft-tissue JXG, no treatment is indicated because many of the lesions may spontaneously regress. Patients with symptomatic DJX or central nervous system involvement require referral to a tertiary care center and chemotherapy. Variable responses have been seen with LCH-based treatments with agents such as vinblastine, prednisone, and methotrexate; when possible, the patients should be encouraged to participate in a clinical trial.

Conclusions

Dendritic and histiocytic neoplasms are rare neoplasms that represent less than 1% of all the neoplasms seen in the lymph nodes or soft tissues. An accurate diagnosis, with the help of an experienced hematopathologist, a morphology review, and immunohistochemistry studies, will help differentiate these disorders from other malignancies. When possible, patients should be referred to a tertiary care center for diagnosis and treatment. The mainstay of treatment of localized disease continues to be surgery. The role of adjuvant therapies remains controversial and must be studied in larger pooled analyses or in the context of a clinical trial. In patients with disseminated disease, the mainstay of treatment remains chemotherapy, although participation in a clinical trial is preferred. The role of bone marrow transplantation remains unclear in this group of disorders. Collaborative efforts are needed to better understand tumor biology, clinical features, associations with other malignancies, and treatments in these rare diseases.

References

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is clinical syndrome characterized by a hyperinflammatory condition caused by increased levels of circulating inflammatory cytokines due to a highly stimulated but ineffective immune process, and it is uniformly manifested by an abnormal proliferation of histiocytes throughout the reticuloendothelial system with the engulfment of hematopoietic cells (hemophagocytosis).\textsuperscript{1-3} The first case of HLH was described by Scott and Robb-Smith\textsuperscript{4} in 1939 as histiocytic medullary reticulosis in light of poorly controlled histiocytic proliferation; later, the term was changed to HLH and macrophage activation...
Immune Deficiency Syndrome

Parasitic

Approximately 16,17

Fungal

12

Table. — Classification of Hemophagocytic Syndrome

<table>
<thead>
<tr>
<th>Primary or Genetic Hemophagocytic Syndrome</th>
<th>Immune Deficiency Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hemophagocytic Lymphohistiocytosis</td>
<td>Chédiak–Higashi syndrome (LYST) (1q42.1 – q42.2)</td>
</tr>
<tr>
<td>Type 1 HPLH, 9q21.3-q22</td>
<td>Griscelli syndrome (15q21)</td>
</tr>
<tr>
<td>Type 2 PRF1, 10q21-22</td>
<td>X-linked lymphoproliferative syndrome</td>
</tr>
<tr>
<td>Type 3 Munc13-4, 17q25</td>
<td>Type 1: SH2D1A (SAP) (Xq25)</td>
</tr>
<tr>
<td>Type 4 STX11, 6q24.1</td>
<td>Type 2: BIRC4 (XIAP) (Xq25)</td>
</tr>
<tr>
<td>Type 5 STXBP2, 19p13.3-13.2</td>
<td>Wiskott–Aldrich syndrome (WAS, Xp11.4-p11.21)</td>
</tr>
</tbody>
</table>

Secondary or Reactive Hemophagocytic Syndrome

Infection-Associated Hemophagocytic Syndrome

Virus-associated hemophagocytic syndrome

Herpesvirus

HIV

Other viruses

Adenovirus | Mumps

Hepatitis (A, B, C) | Enterovirus

Parvovirus B19 | Human T-lymphotropic virus

Influenza | Flavivirus (dengue fever)

Measles | H1N1

Other infections associated with hemophagocytic syndrome

Bacterial

Staphylococcus aureus | Salmonella typhi sp

Campylobacter sp | Rickettsia sp

Fusobacterium sp | Brucella sp

Mycoplasma sp | Ehrlichia sp

Chlamydia sp | Borrelia burgdorferi

Legionella sp | Mycobacterium tuberculosis

Parasitic

Leishmania sp | Plasmodium sp

Ehrlichia sp | (vivax, falciparum)

Toxoplasma sp | Strongyloides sp

Sapronema sp | Spirochetes sp

Fungal

Candida sp | Cryptococcus sp

Cryptococcus sp | Pneumocystis sp

Histoplasma sp | Aspergillus sp

Fusarium sp

Malignancy-associated hemophagocytic syndrome

Hematopoietic malignancies

T-cell/NK-cell lymphoma/leukemia

Peripheral T-cell lymphoma (not otherwise specified)

Anaplastic T-cell lymphoma

Acute leukemia

Classical Hodgkin lymphoma

Non-Hodgkin B-cell lymphoma

Solid tumors

Hepatocellular carcinoma

Prostatic carcinoma

Lung carcinoma

Macrophage activation syndrome (association with autoimmune disease)

Systemic juvenile idiopathic arthritis

Still disease

Systemic lupus erythematosus

Kawasaki disease

Rheumatoid arthritis

NK = natural killer.


Epidemiology

The incident rate of HLH is variable, occurring in 1 out of every 3,000 persons in North America,3,14 whereas the annual incidence of adult and pediatric cases of HLH in Japan was 1 per 800,000 persons.15 Approximately 25% of pediatric cases are PHLH, whereas nearly all adult cases are SHLH; the annual incidence rate of PHLH is 1.2 per 1 million children, whereas the incidence of SHLH among adults is uncertain.16,17 Approximately 80% of patients with FHLH are young children (< 1 year of age).16 One report showed that, for approximately every
2,000 inpatient admissions, there was approximately 1 diagnosis of HLH.\textsuperscript{17} HLH can occur in all age groups without predilection for race or sex.\textsuperscript{10,16} However, a higher incidence has been observed in Turkey, which is most likely due to increased consanguinity and a higher prevalence of genetic defects in the cytotoxic pathway.\textsuperscript{18}

**Pathoetiology**

Natural killer (NK) cells comprise a subset of lymphocytes engaged in immune surveillance and host defense against cancer and primary or secondary viral infections. The steps for killing target cells via NK cells are complex, multistage processes (Fig 1A).\textsuperscript{19} When NK cells are activated, they secrete lytic or cytotoxic granules that contain perforin and granzymes at the immunological synapse to eliminate abnormal cells. As soon as these granules are delivered to a target cell, perforin permeabilizes the cell membranes of the target cell so that granzymes can enter the cytoplasm and induce caspase-dependent and caspase-independent apoptosis.\textsuperscript{20,21} Thus, any defect of the normal NK cell cytolytic pathway will impair this function, resulting in the disruption of immune surveillance and host defense systems.

Cytotoxic T lymphocytes (CTLs) play a role similar to NK cells. CTLs express T-cell receptors that can recognize a specific antigen in the context of class I major histocompatibility complex molecules. When the immune response is triggered in a healthy individual, NK cells, CTLs, and histiocytes are activated to kill the infected or malignant cells. This process is followed by the elimination of the stimulating antigen and termination of the immune response via a feedback loop. All activated cells involved in this process interact with each other via normal receptors and secrete proinflammatory cytokines and chemokines (Fig 1).\textsuperscript{19,22,23}

![Fig 1A-B](https://example.com/fig1.png)

**Fig 1A-B.** — (A) The normal pathway goes through granule activation, polarization, docking, priming, and fusion. Cytotoxic granules are released into a synaptic gap, entering the target cells to kill them. The defects in FHL and immunodeficiency syndrome (GSII, CHS, and HPSII) impair the normal process of the cytotoxic pathway. Empty granules are seen in perforin deficiency. The question mark indicates that the function of \textit{LYST}, which may be important for the correct size and function of lytic granules, is not entirely understood. (B) Activated CD8 T lymphocytes cause the activation and proliferation of NK cells with increased proinflammatory cytokines. Hypercytokinemia results in a hyperinflammatory reaction, which then leads to constitutional symptoms and systemic illness due to lymphocytic and histiocytic infiltrate. TNF-\textit{z} and IFN-\textit{y} production contribute to macrophage activation with resulting hemophagocytosis. CHS = Chédid–Higashi syndrome, CTL = CD8+ cytotoxic T lymphocyte, FHL = familial hemophagocytic lymphohistiocytosis, GSII = type 2 Griscelli syndrome, HPSII = type 2 Hermansky–Pudlak syndrome, IFN = interferon, IL = interleukin, NK = natural killer, TNF = tumor necrosis factor.

Although the precise pathogenesis of HLH is elusive, a strong link exists between the hyperinflammatory response and hemophagocytosis coupled with impaired CTL, NK activity (inherited or acquired), or both.\textsuperscript{21,24-27} The normal function of histiocytes in the innate immune reaction includes the presentation of antigen, phagocytosis, and the activation of the adaptive immune system through contact with infected or targeted cells and cytokine release.\textsuperscript{21} Antigen-presenting cells (eg, macrophages, histiocytes) are activated in HLH. The proinflammatory cytokines (ie, tumor necrosis factor [TNF] \(\alpha\), interferon [IFN] \(\gamma\), interleukin [IL] 1b, IL-6, IL-8, IL-10, IL-12, IL-18, and soluble IL-2 receptor) are produced by the uncontrolled proliferation of histiocytes and T cells. The expansion of antigen-specific CTLs that produce a high level of cytokines further activates macrophages.\textsuperscript{21,28,29} The result of HLH at the tissue and cellular level is tissue necrosis and hemophagocytosis, leading to multiorgan failure. Hemophagocytosis, which is a hallmark of activated macrophages, is mediated via the CD163 heme-scavenging receptor.\textsuperscript{21,28} A brief schematic pathway of the pathophysiology of HLH is illustrated in Fig 1B.\textsuperscript{22,23}

**Primary Hemophagocytic Lymphohistiocytosis**

**Familial Hemophagocytic Lymphohistiocytosis:**

FHLH is inherited in an autosomal recessive fashion and has 5 subtypes. Most patients with FHLH present at younger than 1 year of age.\textsuperscript{30,33} FHLH has also been reported in adolescent and adult patients without a familial history.\textsuperscript{31} In addition to type 1 FHLH, other subtypes show defects in the perforin/cytotoxic pathway (see Table).\textsuperscript{9,10,32} The 5 hypomorphic FHL mutations might correlate with late-onset HLH.\textsuperscript{33,34} According to Zur Stadt et al,\textsuperscript{35} types 2 to 4 FHLH account for 80% of the HLH cases of Turkish origin but only 30% of those of German descent.

**Type 1.** The mutation involved in type 1 FHLH is unknown.

**Type 2.** Approximately 20% to 40% of FHLH cases harbor a PRF1 mutation.\textsuperscript{35,36} The PRF1 gene was reported in 1999 and encodes a soluble pore-forming protein, perforin, synthesized and stored in cytotoxic lymphocytes, along with granzyme serine protease.\textsuperscript{35} Perforin acts as an effector for NK cells and CD8\(^+\) CTLs. Mutations in PRF2 impair the function of perforin to permeabilize the target cell membrane, allowing granzymes to enter the cells (see Fig 1A).\textsuperscript{19,21} The mutations are common in families of Middle Eastern descent.\textsuperscript{36} When carrying nonsense perforin mutations, patients with these mutations were reported to have higher serum levels of ferritin and soluble IL-2 receptor when compared with other subgroups.\textsuperscript{30}

**Type 3.** Approximately 10% to 20% of cases of FHLH have a UNC13D gene mutation.\textsuperscript{35} UNC13D encodes a protein unc-13 homolog D or Munc13-4. The protein is required for cytolytic granule fusion with cytoplasmic membrane components to process degradation or exocytosis.\textsuperscript{37} UNC13D mutation results in defective degranulation.

**Type 4.** A total of 10% to 20% of FHLH cases have mutated STX11,\textsuperscript{38} which belongs to a member of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (t-SNARE) family. STX11 binds to SNAP23 in NK cells. Similar to UNC13D, it is involved in accelerating the fusion in intracellular membrane trafficking processes.\textsuperscript{39} Mutations in STX11 result in decreased or absent STX11 protein, leading to defects in the endocytotic and exocytotic pathway.\textsuperscript{40}

**Type 5.** Mutated STXB2P2, also called Munc18-2, has been identified in type 5 FHLH.\textsuperscript{39} The encoded protein plays a critical role in intracellular trafficking, the control of the SNARE complex assembly, and the release of cytotoxic granules by NK cells.\textsuperscript{40} Study findings indicate that the STXB2P2 mutation could result in impaired granule mobilization of granules and loss of the ability to kill bacteria.\textsuperscript{41}

**Hereditary Immunodeficiencies**

Type 2 Griscelli syndrome, Chédiak–Higashi syndrome, and type 2 Hermansky–Pudlak syndrome are all inherited in an autosomal recessive fashion that predispose patients to HLH.\textsuperscript{21,28} Common clinical and laboratory features for these diseases include oculo-cutaneous albinism, increased susceptibility to infections, and defects in CTL and NK cell activity resulting in immunodeficiencies.

Type 2 Griscelli syndrome caused by the RAB27A mutation is characterized by hypomelanosis with immunological abnormalities (defective CTL and NK cell cytotoxic activity) with or without neurological impairment.\textsuperscript{39,43} The RAB27A-encoded protein interacts with Munc13-4 during the docking of cytotoxic granules to the cell membrane.\textsuperscript{44} Chédiak–Higashi syndrome is associated with granulated cells and enlarged lysosomes because of biallelic mutations in LYST, resulting in the ineffective release of cytotoxic granules.\textsuperscript{39,43,44} The AP3B1 mutation leads to type 2 Hermansky–Pudlak syndrome, which is characterized by platelet storage disease, prolonged bleeding, congenital neutropenia, pulmonary fibrosis, granulomatous colitis, and albinism.\textsuperscript{45}

**X-Linked Lymphoproliferative Syndromes**

Types 1 and 2 X-linked lymphoproliferative (XLP) syndrome are due to the hemizygous mutation of SH2D1A and the mutation of XIAP, respectively, and both are associated with a high risk of developing HLH.\textsuperscript{12,28,34,46} SH2D1A and XIAP are responsible for XLP syndrome due to signaling lymphocytic activation molecule–associated protein and deficiencies of the X-linked inhibitor of apoptosis protein, respectively.
XLP is characterized by extreme vulnerability to EBV infection, and the signaling lymphocytic activation molecule–associated protein is a key regulator of normal immune function in T cells, NK cells, and B cells. XIAP encodes a 497-amino-acid antiapoptotic molecule. Although the pathophysiology of HLH in patients deficient in the X-linked inhibitor of apoptosis protein is not fully understood, it may be due to defects in CTLs or the NK cell cytotoxic pathway (see Fig 1A). SH2D1A and XIAP are proximally located on the same chromosome and may interact with each other.

Secondary Hemophagocytic Lymphohistiocytosis

Causes of SHLH may include viral, fungal, bacterial, or parasitic infections, as well as hematological malignancies, autoimmune disorders, or immunosuppression, and particularly post–solid organ transplantation (see Table).

Infections: EBV is a ubiquitous γ-herpesvirus and is the most common pathogen associated with HLH. It causes a clonal proliferation and the hyperactivation of EBV-infected T cells in patients with SHLH. Of interest, most cases of EBV infection with concurrent HLH have been reported in children and adolescents, with the highest incidence occurring in East Asia.

According to a study of adult patients with HLH, in addition to EBV infection, histoplasmosis and cytomegalovirus (CMV) were the other 2 common infectious agents, comprising 19% (4 patients) and 14% (3 patients) of cases, respectively. In a large study of 96 patients with HLH, 30 were associated with infection. The most common types of infection were viral (41%), mycobacterial (23%), bacterial (23%), and fungal (13%). In addition to EBV, CMV, and histoplasmosis, other viral agents implicated in HLH include HIV, human herpesvirus 8, parvovirus B19, the hepatitis viruses, enterovirus, flavivirus (dengue fever), and H1N1, among others. Other infectious agents associated with SHLH appear in the Table.

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Associated Malignancies

Lymphoma is the most common hematological malignancy associated with HLH. Among lymphomas, T-cell lymphoproliferative disorders, such as anaplastic large cell lymphoma, subcutaneous panniculitis–like T-cell lymphoma, and NK cell lymphoma, were the most frequently observed. HLH has also been reported in patients with classical Hodgkin lymphoma and other B-cell lymphoproliferative disorders. Less frequently, myeloid malignancies such as acute myeloid leukemia have been reported in association with HLH.

Clinical Findings

In general, the early signs and symptoms of HLH are nonspecific. No specific laboratory tests are available for diagnosing HLH. The most common clinical symptoms and laboratory abnormalities include unexplained fevers, cytopenia, and hepatosplenomegaly. Neurological symptoms such as altered mental status, seizures, and nerve palsies can be observed. Cerebrospinal fluid cytology can reveal hemophagocytic cells, but the absence of these cells does not exclude HLH.

Typical clinical scenarios in which PHLH should be considered in the differential diagnosis include infectious mononucleosis in an infant or young child, aseptic meningitis associated with cytopenias, or a viral-like syndrome or illness with fever, cytopenias, and organomegaly. Of note, in cases of systemic juvenile arthritis, 30% to 40% of such patients had a subclinical manifestation of the disease, with 10% to 20% of them presenting with overt clinical symptomatology.

Laboratory Findings

Characteristic laboratory findings include elevated serum levels of ferritin, fasting hypertriglyceridemia (≥ 265 mg/dL), transaminitis, hyperbilirubinemia, and elevated levels of lactate dehydrogenase, along with decreased levels of fibrinogen (< 1.5 g/L). Elevated blood levels of proinflammatory cytokines, including IL-6, IL-8, IL-10, IL-12, IL-18, macrophage colony-stimulating factor, IFN-γ, and TNF-α, as well as elevated plasma levels of soluble IL-2 receptor (CD25), sCD95 ligand, and sCD163, have also been reported. The decreased or loss of NK cell activity is another laboratory abnormality that supports the diagnosis of HLH.

A laboratory search for infectious agents is necessary in patients with suspected HLH. Serological assays specific for EBV may be nondiagnostic in some
patients; however, the presence of a high EBV DNA load in plasma supports the diagnosis of EBV-associated HLH. Thus, direct molecular virological assays may allow better detection of this potentially underdiagnosed disease.

Histological Findings

Biopsies of bone marrow and other tissues (eg, lymph nodes) are useful for identifying hemophagocytosis. In general, bone marrow typically shows reactive lymphocytosis, slightly to markedly increased histiocytes, and a marked left-shift myeloid maturation regardless of etiology. In the bone marrow aspirate smear, enlarged histiocytes, engulfing red blood cells, granulocytes, lymphocytes, and occasional plasma cells can be seen; in addition, the spleen with red-pulp expansion and increased hemophagocytosis can be seen on autopsy (see Fig 2). Immunohistochemical studies using histiocyte-specific antibody, such as CD68, CD163, and CD14, are useful for highlighting phagocytic cells as well as engulfed, negative-stained hematopoietic cells.

Diagnostic Criteria

The diagnostic criteria for HLH were established in 1991 and then subsequently revised in 1997 and then updated again in 2004. These diagnostic criteria have been widely adopted clinically and represent the current guidelines for HLH. A diagnosis of HLH requires either a documented molecular confirmation or the presence of at least 5 of the following 8 clinical or laboratory parameters:

- Fever
- Splenomegaly
- Cytopenia affecting ≥ 2 lineages in the peripheral blood:
  - Hemoglobin < 90 g/L (< 100 g/L for infants < 4 weeks of age)
  - Platelets < 100 × 10^9/L
  - Neutrophils < 1.0 × 10^9/L
- Hypertriglyceridemia and/or hypofibrinogenemia, fasting triglycerides ≥ 265 mg/dL, fibrinogen ≤ 1.5 g/L
- Hemophagocytosis found in the biopsy specimen of bone marrow, spleen, or lymph nodes
- Decreased or absent NK cell activity
- Ferritin ≥ 500 mg/L
- sCD25 ≥ 2,400 U/mL

Bone marrow hemophagocytosis has a high sensitivity rate because rare hemophagocytic histiocytes can be detected prior to patients exhibiting overt clinical symptoms of HLH; however, the specificity of this test is too low to incorporate it into the panel of screening tests for diagnosing HLH. Therefore, the 2004 HLH diagnostic guidelines set forth by Henter et al suggest obtaining materials...
from the other organs if the bone marrow specimen is inconclusive. In addition, the presence of any of the following findings may also provide strong supportive evidence for the diagnosis: (a) spinal fluid pleocytosis (mononuclear cells), elevated spinal fluid protein, or both, and (b) histological results from liver biopsy resembling chronic persistent hepatitis. Other abnormal clinical and laboratory findings can include cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash, hepatic enzyme abnormalities, hypoproteinemia, hypotremia, increased very-low density lipoprotein, and decreased high density lipoprotein.

A search for novel markers for an HLH diagnosis has revealed that serum S-SMase/ceramide activity is elevated in cases of HLH; however, these patients eventually died despite appropriate treatment.

Using flow cytometry to diagnose HLH is not specific. However, qualitative abnormalities of atypical cytotoxic T cells have been reported in the majority of EBV-associated HLH cases. According to a large cohort study of 494 patients with suspected HLH, the performance of degranulation assays based on surface up regulation of CD107a on NK cells and CTLs may provide a diagnostic value in FHLH. A resting NK cell degranulation level below 5% was associated with sensitivity and specificity rates of 96% and 88%, respectively, for diagnosing genetic degranulation disorders.

Molecular studies of gene mutations have involved PRF129, UNC13D (Munc13-4), STX11, and STXBP2 (Munc18-2). RAB27A, LYST, and AP3B12 have been useful in aiding the diagnosis of inherited immunodeficiency syndromes.

**Differential Diagnosis**

HLH can be a diagnostic challenge when distinguishing between HLH and the reactive or malignant histiocytic proliferations (eg, infection-related histiocytosis). An autoimmune lymphoproliferative syndrome might mimic HLH. In neonates, HLH might be difficult to differentiate from neonatal hemochromatosis when patients present with acute liver failure or storage disease with hyperglycerinemia. A newly proposed and validated scoring system for reactive HLH called HSscore may be a practical way to exclude non-HLH cases.

**Treatment**

HLH has an aggressive clinical course with a high mortality rate in all age groups. Prognosis depends on early diagnosis and timely treatment. The HLH 2004 protocol is the most commonly used frontline treatment regimen, with the immediate goals of extinguishing the hyperinflammatory and hypercytokine status, controlling underlining disorders (eg, infection, tumor, autoimmune), and eliminating overactive macrophages in the reticuloendothelial system. In PHLH, the ultimate goal of treatment is to replace the mutated gene or defective immune system.

**General Management**

The HLH protocol is widely accepted as the standard therapeutic approach for HLH (Fig 3). The main difference distinguishing the 2004 protocol from the 1997 protocol is the administration of cyclosporine A at the onset of therapy instead of at week 9. Both protocols include dexamethasone, etoposide, and cyclosporine A for 8 weeks in patients with SHLH who do not have an identifiable genetic defect. In cases of PHLH, therapy is administered for more than 8 weeks until hematopoietic stem cell transplantation (HSCT) is initiated. Intrathecal therapy with methotrexate and corticosteroids is recommended for patients with central nervous system manifestations.

Supportive care with prophylactic antibiotics, blood and platelet transfusions, and treatment with fluids and electrolytes are all important steps in the treatment of HLH.

**Familial Hemophagocytic Lymphohistiocytosis**

Given the high mortality rate of FHLH, the initial steps of treatment are to suppress the hyperinflammatory process and eliminate abnormal T and NK cells, antigen-presenting cells, and phagocytes. A response to treatment typically takes up to 8 weeks. In a patient with low-risk HLH, corticosteroids and/or intravenous immunoglobulin or cyclosporine A may be sufficient to control the dysregulated biological processes. Moreover, etoposide is recommended to reverse lymphohistiocytic dysregulation in patients at high risk.

HSCT is recommended for patients with FHLH and genetic defects and is considered the only known curative approach. A matched related donor is preferred over an unrelated, partially, or umbilical cord blood–matched donor to achieve maximal hematopoietic stem cell engraftment and reduce the risk of severe graft–host and transplant-related mortality. Only a subset of patients (approximately 20%) have matched sibling or parental donors. The long-term experience with HSCT in patients with FHLH is limited due to the rarity of the disease. The current use of reduced intensity conditioning protocols for HSCT decreases chemotherapy-associated toxicity, including veno-occlusive disease. Patients who do not respond to treatment (based on the 2004 protocol) within 4 to 8 weeks may benefit from second-line therapy (eg, antithyroglobulin, alemtuzumab).
duction phase followed by a 6-week tapering phase. In patients with organ dysfunction or failure, immediate treatment should be started to reduce mortality. Treatment may be also beneficial for patients who have relapsed SHLH but are without genetic defects.

**Underlying Disease**

Treatment is largely dependent on clinical status. When HLH is triggered by an acute infection or another condition (eg, rheumatoid disease), treatment of the trigger is necessary to eliminate the hyperinflammatory stimulus or hyperimmunological activation. Stable patients who are less acutely ill may be able to tolerate initial treatment without HLH-specific therapy.

**Malignancies**

The treatment of HLH secondary to lymphoma frequently includes combined chemotherapy regimens according to lymphoma subtype. The use of HSCT in patients during their first remission may be of benefit for those with partial remission or refractory HLH. Selected patients with recurrent HLH in complete remission should be considered for HSCT. However, the proportion of adult patients with acquired HLH who are eligible for HSCT is low due to poor performance status, malnutrition, active infections, and complications from lymphoma therapy. Similar approaches using disease-specific therapy first should be employed for other malignancies associated with HLH.

**Infections**

Although they are rare, cases of EBV infection associated with HLH can occur in apparently EBV-immunocompetent individuals, particularly in adults living in western countries. The high mortality rate among patients with EBV-associated HLH is usually due to a delay in diagnosis or ineffective therapy. However, the 2004 protocol has improved survival rates of patients with HLH (see Fig 3). Per Kleyenberg and Schiller, studies have emphasized the importance of etoposide for the treatment of EBV infection associated with HLH, describing the drug as the most effective single agent against activating histiocytes. Although intravenous immunoglobulin has been recommended for the treatment of reactivated EBV infection, patients with EBV-associated B-lymphoproliferative disorders taking rituximab have also been found to have improved outcomes. The efficacy of a rituximab-containing regimen was investigated in 42 patients with HLH who received, on average, 3 rituximab infusions (range, 1–10) at a median dose of 375 mg/m², along with steroids, etoposide, and/or cyclosporine. The therapy was well tolerated and resulted in clinical improvements among 43% of patients. A significantly reduced EBV viral load was also observed. Because EBV can also infect T and NK cells, recurrence of EBV infection can occur in patients despite rituximab therapy; in such patients, alemtuzumab has been shown to be beneficial.

**Salvage Therapy**

The removal of cytokines with plasma or transfusion exchange in very young infants has been shown to stabilize patients until other therapies have enough time to work. Other salvage therapies include high-dose pulse corticosteroids and alemtuzumab, which suppresses CD52-expressing T or B cells and histiocytes. CMV and adenovirus viremia were common complications of this therapy. Monitoring CMV DNA viral load by weekly polymerase chain reaction is standard in patients treated with this agent. Other reported salvage therapies include an anti-TNF antibody, infliximab, and the anti-CD25 antibody.
In some patients with macrophage activation syndrome, inhibiting IL-1 and IL-6 was successful. In recent clinical trials with blinatumomab, drug-induced HLH was observed. Therapy with tocilizumab resulted in a rapid clinical improvement; Tocilizumab is a drug that could be potentially effective in other types of HLH and is currently undergoing testing in a clinical trial in children and young adults (NCT02007239). Failure of salvage regimens is an indicator for considering allogeneic HSCT. 

**Allogeneic Hematopoietic Stem Cell Transplantation**

Allogeneic bone marrow transplantation from a related, human leukocyte antigen identical donor is the treatment of choice for patients with FHLH. However, few patients have a disease-free sibling who is an identical human leukocyte antigen match. Presently, HSCT is the only available treatment to cure FHLH; thus, it represents the definitive therapy of choice for many patients. However, it is not uncommon for patients to develop recurrence of HLH before a suitable donor is identified. Thus, preparation for allogeneic HSCT should be initiated at the time of diagnosis, and it should include human leukocyte antigen typing and a search for a suitable donor for HSCT.

It is worth noting that, in 1 study, a median disease-free survival rate was achieved in 9 patients with FHLH during a follow-up period of 33 months (range, 8–69 months). In a meta-analysis, 11 studies comprising data from 342 patients with EBV-associated HLH were collected and analyzed. A total of 54 of the 342 patients underwent HSCT. The transplantation-related mortality rate was 20% (11 of 54 patients), which was lower than that seen in the control arm (32%; 93 of 288 patients); however, no statistically significant difference was seen in mortality rates found between those treated with HSCT and those treated with conventional immunotherapy. Therefore, HSCT may not be suitable for patients with EBV-associated SHLH compared with those who have FHLH.

A nationwide retrospective analysis indicated that reduced intensity conditioning followed by cord blood transplantation is an alternative and feasible treatment for PHLH or FHLH. The overall survival rate reached in that study was 65.4% ± 6.6% in 13 patients, a rate comparable with other therapeutic strategies. The treatment dilemma was with patients with engraftment failure; however, HLH could be managed in these patients through the use of secondary cord blood transplantation.

Data indicate that HSCT should be used in HLH refractory to conventional therapy. A single institutional study focusing on therapy for HLH associated with T- or B-cell lymphomas reported that the median overall survival rates of patients who had HLH and T-or B-cell lymphoma were 96 days and 330 days, respectively. Rituximab might have partially contributed to longer survival rates in patients with B-cell lymphoma–associated HLH; by contrast, allogeneic HSCT should be recommended for patients with T-cell lymphoma–associated HLH.

**Outcome and Prognosis**

Despite advances in therapy and supportive care, the cure rate for HLH, particularly in patients with multiorgan failure, is low. Clinical outcomes for children with HLH have been previously determined in 2 important clinical trials. Prior to the 1997 protocol, patients with FHLH were not likely to survive beyond 1 year. Moreover, a study conducted in 2002 suggested that overall survival rates increased once the 1997 protocol was put into practice. Patients with all types of HLH treated per the 1997 protocol had a 3-year overall survival rate of 55%, and a subgroup of patients who underwent HSCT had a 3-year overall survival rate of 62%. In a single, institutional, retrospective study of pediatric patients, the 3-year overall survival rate was 92% in patients treated with allogeneic HSCT after reduced intensity conditioning and 43% in patients who underwent myeloablative allogeneic HSCT. A review of antithymocyte globulin–based therapy in 38 patients with FHLH demonstrated a complete response rate of 73%. Sixteen of the 19 patients (84%) who underwent consolidation with HSCT were considered to be cured, and overall survival for all study participants was 55%. Japanese patients with EBV-associated HLH were shown to have a survival rate of 86%. The results of another important HLH study have not yet been published.

To date, most studies concentrate on the management of PHLH in children. Limited trials study adult patients with SHLH, and data demonstrate inferior median overall survival rates, ranging from 35 days to approximately 2 months. Among trials relating to SHLH, patients with HLH due to malignancy had the poorest clinical outcome (median overall survival, 1–12 months). Parikh et al reported that patients with HLH associated with malignant tumors had a much shorter median overall survival rate of 1.4 months compared with 22.8 months among patients who had HLH without infection, autoimmune disease, or idiopathic entity. A report of EBV-associated HLH outcomes among children revealed a 90% overall response rate to multiagent therapy, including corticosteroids, etoposide, and cyclosporin, whereas many other patients with infection-associated HLH died within days or months. Dhote et al reported an overall mortality rate of 38.5% among patients with autoimmune disease–associated HLH.
However, in a different study, a subset of patients with autoimmune disease-associated HLH treated with immunosuppressive agents, such as cyclosporine, cyclophosphamide, or tacrolimus, achieved a remission rate of 80%.130

Long-term complications of HLH encompass therapy-related morbidity — particularly following HSCT — and neurological deficits. The latter can manifest months to years following HLH; however, most patients return to their normal lives.131

Validated prognostic factors are lacking among prospective studies in order to guide treatment decisions in patients with HLH. Most of the currently available prognostic factors have been derived from literature reviews or from single institutional studies.

Earlier studies revealed that liver function abnormalities and cytopenias, along with increasing in serum levels of ferritin, soluble CD25, and soluble CD163, may be indicators of relapse.106 Kaito et al152 suggest that age older than 30 years, a fibrinogen degradation product level above 10 mg/mL, and a ferritin level above 500 mg/mL are risk factors associated with death. Another study revealed that an elevated level of soluble CD25 (> 10,000 U/mL) has a negative impact on prognosis, with a 5-year survival rate of 36% compared with 78% in the control group.135

The severity of hyperbilirubinemia, thrombocytopenia, hyperferritinemia, and cerebrospinal fluid pleocytosis may also be risk factors for early death among patients with HLH, as are lack of improvement in hemoglobin or fibrinogen levels, persisting thrombocytopenia, and persistent fever following the initiation of therapy.134 In EBV-associated HLH, a high viral DNA load is associated with poor outcomes.135 Active HLH at the time of HSCT and central nervous system involvement has been associated with worse outcomes.103,118 A single institutional, retrospective study of 62 adult patients with HLH showed that a low serum albumin level and tumor-associated HLH were 2 independent factors.17 In a univariate analysis, old age, a high lactate dehydrogenase level, a low serum albumin level, a high ferritin level, and tumor-associated HLH were all associated with a worse prognosis.17

In a study focused on infection-associated HLH, age older than 50 years, fever not subsiding within 3 days of diagnosis of HLH, and the development of disseminated intravascular coagulation were considered to be strong indicators of mortality.53

Conclusions

Comprehensive clinical, immunological, and genetic workups are required to diagnose hemophagocytic lymphohistiocytosis. Despite recent advances in the diagnostics and therapy for hemophagocytic lymphohistiocytosis, the disease is incurable for the majority of adults with secondary hemophagocytic lymphohistiocytosis. More research into the molecular biology, immunology, and genetics of hemophagocytic lymphohistiocytosis is needed to discover effective treatment options for patients with this rare disorder.

References


Kikuchi–Fujimoto disease is a rare lymphohistiocytic disorder that affects young women of Asian descent more frequently than persons of other ethnic groups.

Pathogenesis, Diagnosis, and Management of Kikuchi–Fujimeto Disease

Darcie Deaver, PhD, Pedro Horna, MD, Hernani Cualing, MD, and Lubomir Sokol, MD, PhD

**Background:** Kikuchi–Fujimoto disease (KFD) is a rare lymphohistiocytic disorder with an unknown etiopathogenesis. This disease is misdiagnosed as malignant lymphoma in up to one-third of cases and is associated with the development of systemic lupus erythematosus (SLE).

**Methods:** The medical literature between the years 1972 and 2014 was searched for KFD, and the data were collected and analyzed regarding the epidemiology, clinical presentations, diagnosis, management, and suggested diagnostic and treatment algorithms.

**Results:** Although KFD has been reported in other ethnic groups and geographical areas, it is more frequently diagnosed in young women of Asian descent. Patients with the disease typically present with rapidly evolving tender cervical lymphadenopathy, night sweats, fevers, and headache. Diagnosis is based on histopathological examination. Excisional lymph node biopsy is essential for a correct diagnosis. Apoptotic coagulation necrosis with karyorrhectic debris and the proliferation of histiocytes, plasmacytoid dendritic cells, and CD8+ T cells in the absence of neutrophils are characteristic cytomorphology features. Interface dermatitis at the onset of KFD may be a marker for the subsequent evolution of SLE. The natural course of the disease is typically benign. Short courses of steroids, nonsteroidal anti-inflammatory drugs, or hydroxychloroquine can be administered to patients with more severe symptoms.

**Conclusions:** Although KFD was described more than 40 years ago, the etiology of this disease remains unsolved. Infectious or autoimmune processes were proposed but have not been definitively confirmed. Clinical presentation with systemic B symptoms and adenopathy may lead to an erroneous diagnosis of malignant lymphoma. The introduction of modern methods into hematopathology, including immunohistochemistry, flow cytometry, and molecular clonality studies, has decreased the probability of misdiagnosis. Until reliable prognostic markers are available, patients with KFD should have continued long-term follow-up care due to their increased risk of SLE.

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Introduction
Kikuchi–Fujimoto disease (KFD), also known as Kikuchi disease, is a rare lymphohistiocytic disorder first described in 1972. KFD generally affects women of Asian descent between the ages of 20 and 35 years and has a male:female ratio of 1:2; however, new cases of KFD have also been described in non-Asian ethnic groups and children in Europe and the United States. The acute or subacute onset of adenopathy and systemic B symptoms in KFD has historically led to a misdiagnosis of malignant lymphoma, although modern hematopathological methods have made such misdiagnosis less likely. Following the resolution of KFD, concurrent autoimmune disorders have been reported; they may also be more frequently diagnosed.

Epidemiology
The precise incidence of KFD is unknown; however, a large review identified and analyzed 733 patients diagnosed worldwide since 1972. Of those cases, 140 (19%) were pediatric patients, and the male:female ratio was 1.4:1. It is worth noting that a higher propensity for male sex has only been observed in children younger than 12 years of age. The presenting symptoms in children are similar to adults, although fever and rash are more frequent in pediatric patients. Children younger than 18 years of age may also demonstrate bilateral cervical lymphadenopathy more frequently than adults.

The occurrence of KFD in family members has rarely been described. A search for a link between KFD and human leukocyte antigen class 2 alleles in the Japanese population suggested the possibility of a positive relationship between DPA1*01 and DPB1*0202 alleles and the disease. Because these alleles are much more frequent in Japan than in Europe and the United States, this finding may explain the higher prevalence of KFD in patients of Asian descent, thus supporting a possible autoimmune pathogenic mechanism.

Viral Infections
Epstein–Barr virus (EBV), human herpesvirus (HHV) types 6, 7, and 8, herpes simplex virus, HIV, human T-lymphotrophic virus, and parvovirus B19 are the most frequently studied viruses in patients with KFD.

Human Herpesviruses
Cho et al studied HHV-6 and HHV-7 in 50 archival samples of KFD and 20 controls using nested polymerase chain reaction (PCR) and found no significant difference in the viral DNA sequences between patients and controls. Labrador et al identified the DNA of HHV-7 in the affected lymph node of a young patient with KFD who presented with cervical adenopathy and maculopapular rash. However, no confirmatory studies or results from the control samples were available. Huh et al amplified sequences of HHV-8 from lymph nodes in 6 out of 26 patients with KFD (23%). They did not detect any viral sequences in the reactive lymph nodes of the study controls, suggesting that HHV-8 may play a role in the pathogenesis of KFD.

Parvovirus B19
Zhang et al searched for parvovirus B19 in 33 lymph node samples from patients with KFD and 16 controls using several different methods, including PCR, immunohistochemistry, and in situ hybridization (ISH). A significantly higher rate of B19 positivity was seen in samples from patients with KFD than in controls; B19 infected cells were mostly composed of lymphocytes and a small number of histiocytes.

Epstein–Barr Virus
Hudnall et al tested 30 lymph node samples of patients with KFD and 12 controls for the presence of EBV using real-time PCR, EBV-encoded RNA ISH, and EBV latent membrane protein with immunohistochemistry. Cells with apoptotic features positive for EBV-encoded RNA were found in the necrotic regions of many KFD cases, suggesting that the disease could be due to a hyperimmune reaction against EBV infection. Hollingsworth et al looked for EBV and HHV-6 using PCR and ISH in 20 patients with KFD, but the study results did not support a viral role in the pathogenesis of KFD. However, Yen et al reported EBV infection in a child with a cutaneous manifestation of KFD, supporting the pathogenic role of EBV infection, and Chiu et al detected EBV RNA sequences in all 10 tested samples of KFD but found only a single case of EBV-encoded proteins. No evidence of human T-lymphotrophic virus or parvovirus B19 was seen in the patient samples of this study.

Overall, the results of studies searching for a viral etiology of KFD have been inconsistent. Laboratory methods differed among laboratories, positive results were documented in a small number of samples, and confirmatory studies with control samples were often unavailable. Currently, no definitive evidence suggests that a known virus plays a key role in the pathogenesis of KFD.

Autoimmune Mechanism
Autoimmune disorders are frequently reported in patients with KFD, with systemic lupus erythematosus (SLE) being the most common disorder linked to KFD. In many reports, KFD preceded the development of SLE; however, the diagnosis of KFD has been reported to simultaneously occur or follow the diagnosis of SLE. In one study, patients with KFD were negative for antinuclear and anti-DNA an-
SLE adenopathy is usually mild, generalized, and nontender. The cytometry of enlarged lymph nodes in SLE consists of scattered plasma cells and immunoblasts, increased vascularity with Azzopardi phenomenon associated with moderate reactive follicular hyperplasia, or varying degrees of coagulative necrosis with the presence of hematoxylin bodies (Table 1).

Kim et al. reviewed patients with KFD in the context of SLE and noticed an increasing number of case reports in the medical literature. Among 9 cases of KFD and SLE, 7 patients manifested with skin disease. Histological evaluation of skin biopsies was consistent with SLE in 3 of the 7 cases. Commonly, patients with a simultaneous onset of KFD and SLE have flare-ups of lupus; therefore, some researchers have suggested that concurrent KFD and SLE diagnoses are actually lupus lymphadenitis. Other researchers suggest that KFD is a forme fruste of SLE. Lymphadenitis is not included among the 11 diagnostic criteria of SLE, so it cannot establish a diagnosis of SLE as a sole pathological finding; however, the simultaneous manifestation of histocytic necrotizing lymphadenitis with skin rash, cytopenias, arthralgias, and abnormal results on serological tests should raise suspicion of SLE and a comprehensive work-up should be completed. Paradela et al. reported on a patient with KFD and interface dermatitis who subsequently developed SLE. In 27 cases of KFD with simultaneous nodal and cutaneous involvement, 9 of whom subsequently developed SLE. Skin biopsy was consistent with interface dermatitis in all of the KFD cases that evolved into SLE. The authors suggested that interface dermatitis could be a valuable marker of evolution of KFD into SLE. However, due to differing opinions about the possibility of concurrent diagnoses of KFD and SLE, further research is necessary to reach a definitive conclusion.

**Molecular Biology**

Molecular pathways implicated in the pathobiology of KFD are not well understood. Ishimura et al. reported on a noninvasive method for diagnosing KFD using gene expression profiling on peripheral mononuclear cells. The top 5 upregulated genes included FI44L, CXCL10, GBP1, EPSTI1, and IFI27. All 5 genes belong to the family of interferon-induced genes. Ohshima et al. investigated apoptosis and cell-cycle-associated gene expression in lymph nodes from patients with KFD and nonspecific lymphadenitis (NSL). Cell-cycle–associated genes were up regulated in all patients with KFD, which is in contrast to patients with NSL. Olshima et al. studied cytokine pathways in 10 lymph node samples from patients with KFD and 4 controls with NSL using immunohistochemistry and reverse transcriptase PCR. Results of the study suggested that the cytokine and chemokine pathways of interferon γ, interleukin 18, MIG, and interferon γ–induced protein 10 play an important role in the pathogenesis of apoptosis associated with KFD.

**Table 1. — Histopathological Features of Kikuchi–Fujimoto Disease and Systemic Lupus Erythematosus**

<table>
<thead>
<tr>
<th></th>
<th>Cytomorphology</th>
<th>Immunohistochemistry</th>
</tr>
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<tbody>
<tr>
<td><strong>Kikuchi–Fujimoto Disease</strong></td>
<td>Distorted nodal architecture with cortical and paracortical nodules with proliferation of histiocytes and immunoblasts, coagulative necrosis, abundant apoptotic karyorrhexis, and crescentic histiocytic nuclei</td>
<td>CD68+&lt;br&gt;CD123+&lt;br&gt;CD4+&lt;br&gt;CD8 T-cell predominance&lt;br&gt;Myeloperoxidase positive&lt;br&gt;Lysozyme positive&lt;br&gt;T-cell immunoblasts</td>
</tr>
<tr>
<td><strong>Systemic Lupus Erythematosus</strong></td>
<td>Moderate reactive follicular hyperplasia, scattered plasma cells and immunoblasts, with increased vascularity or varying degrees of coagulative necrosis with Azzopardi phenomenon and presence of hematoxylin bodies</td>
<td>CD4+ with predominance over CD8+ T cells&lt;br&gt;Lymphoid follicles are mixture of small-and medium-sized lymphocytes&lt;br&gt;Germinal centers of the B cell are BCL2-</td>
</tr>
</tbody>
</table>
Clinical Manifestation
KFD frequently manifests as an acute or subacute illness with systemic B symptoms and painful posterior cervical lymphadenopathy (Table 2).

Erythrocyte sedimentation rate
Elevated C-reactive protein
Leukopenia
Lactate dehydrogenase
Alanine aminotransferase

Laboratory Tests
No specific laboratory test is available for diagnosing KFD. A complete blood count is usually within normal range. Two large reviews observed leukopenia in 19% to 43% and anemia in 23% of people with KFD. Other laboratory abnormalities include elevated levels of erythrocyte sedimentation (40%–79%), lactate dehydrogenase (53%), and alanine aminotransferase (23%). Circulating atypical lymphocytes have also been reported in the peripheral blood film of approximately 25% of patients with KFD.

Diagnosis

Lymph Node Biopsy
Although fine-needle aspiration biopsy (FNAB) is a valuable tool for the diagnosis of some lymphoproliferative disorders, particularly in relapse settings, excisional biopsy is the preferred diagnostic tool in patients presenting with new adenopathy. Tong et al analyzed 44 cases of patients with confirmed KFD or suggested by FNAB. The false-positive and false-negative rates were 37.5% and 50%, respectively. The overall accuracy of FNAB was about 56%. Das et al compared FNAB smears of lymph nodes between patients with KFD and reactive nodal hyperplasia and showed overlapping cytological features in both conditions, which suggests the limited diagnostic potential of this method. Up to 30% of patients with KFD are initially misdiagnosed, so lymphoma excisional biopsy should be the requested diagnostic method used for patients with suspected KFD.

Histology and Immunohistochemistry
KFD is characterized by a distortion of the normal nodal architecture with cortical and paracortical nodules with coagulative necrosis and abundant apoptotic karyorrhectic debris. Additional characteristic features include the proliferation of histiocytes and immunoblasts with an abundance of CD8+ T cells and an absence of neutrophils (Fig 1). Immunohistochemical stains reveal histiocytes expressing CD68, myeloperoxidase, and CD4 markers. A predominance of CD8+ T cells in affected lymph nodes of patients with KFD has also been described. The expression of the CD123 marker on plasmacytoid dendritic cells also supports a diagnosis of KFD.

Table 1. — Diagnostic Criteria for Kikuchi–Fujimoto Disease

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Pathological</th>
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<tbody>
<tr>
<td>Localized lymphadenopathy</td>
<td>Laboratory studies</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>Fever</td>
<td>Elevated C-reactive protein</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>Headache</td>
<td>Biopsy of the lymph node</td>
</tr>
<tr>
<td></td>
<td>Aggregates of CD68+ histiocytes with occasional crescent-shaped nuclei</td>
</tr>
<tr>
<td></td>
<td>Foci of cell death ranging from isolated apoptotic cells to large areas of geographical necrosis</td>
</tr>
<tr>
<td></td>
<td>Proliferation of plasmacytoid dendritic cells</td>
</tr>
<tr>
<td></td>
<td>No accumulation of eosinophils or neutrophils</td>
</tr>
</tbody>
</table>

Table 2. — Diagnostic Criteria for Kikuchi–Fujimoto Disease
The proliferative stage is characteristic for the expression of various histiocytes, plasmacytoid monocytes, and lymphoid cells containing karyorrhectic fragments and eosinophilic apoptotic debris. The necrotizing stage can be recognized based on the presence of a various degree of coagulative necrosis; the xanthomatous stage manifests with foamy histiocytes.

The minimum criteria for a pathological diagnosis of KFD include the presence of crescent-shaped histiocytes and plasmacytoid monocytes with scattered karyorrhexis (see Table 2). It may be histiocytic proliferation, not necrosis alone, that is more characteristic of KFD.

**Differential Diagnosis**

A differential diagnosis of KFD is wide and should include infections such as tuberculosis, toxoplasmosis, *Bartonella henselae*, HIV, and EBV, as well as connective tissue disorders (eg, SLE) and lymphoproliferative disorders (Table 3). The proliferation stage of KFD may present with features similar to lymphoma and may lead to misdiagnosis. The presence of large atypical cells and immunoblasts of T-cell lineage origin cause confusion because these cells are also characteristic of aggressive lymphoma. Necrosis may or may not be present in lymphoma. Immunohistochemical staining, flow cytometry, and molecular clonality studies can help in the differential diagnosis of these 2 disorders. Melikoglu et al reported lymphadenopathy in 23% to 34% of patients with SLE. The lymph nodes were small, nontender, and generalized in the majority of patients, which is in contrast to patients with KFD. Compared with KFD, other clinical and laboratory findings are necessary to diagnose SLE.
**Imaging Studies**

Imaging studies may be useful in the assessment of patients with peripheral adenopathy. Computed tomography helps to differentiate tuberculous lymphadenitis from KFD. Lee et al.\(^5^6\) compared computed tomographic imaging of the lymph nodes of 24 patients with KFD and 45 lymph nodes from patients with tuberculous lymphadenitis. Histologically, differences were seen between KFD and tuberculous lymphadenitis regarding the type of necrosis within the lymph nodes. By contrast to tuberculous lymphadenitis, which manifests with caseation necrosis surrounded with granulomatous tissue, KFD is characteristic for coagulation necrosis with apoptosis of various cell types. These differences may be responsible for changes seen on imaging studies. Indistinct margins of necrotic foci independently predicted the diagnosis of KFD with 80% accuracy in a multivariate analysis.\(^5^6\) Calcifications within the lymph nodes were observed in tuberculous lymphadenitis alone compared with KFD and other lymphoproliferative disorders.

Tsujikawa et al.\(^5^7\) compared the size of lymph nodes and the maximum standardized uptake value in 8 patients with KFD and 14 patients with non-Hodgkin lymphoma using 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT). The sizes of the lymph nodes were smaller in patients with KFD compared with patients with indolent or aggressive lymphomas. The maximum standardized uptake value was also higher in cases of KFD compared with indolent non-Hodgkin lymphoma. A high maximum standardized uptake value in patients with KFD has been a contributing factor to misdiagnosis with aggressive lymphoma (see Table 3).\(^5^7\)

Lo et al.\(^5^8\) examined ultrasonographic characteristics (size, shape, rims, matting, and echotexture) in 137 lymph nodes from 21 patients with KFD and 89 lymph nodes from 20 patients with malignant lymphoma. Results of this study suggested that cervical lymphadenopathies in patients with KFD are smaller in size, have a shape that is less round, a reticular echotexture that is less micronodular, and additional signs of matting and cortical widening than those with lymphoma.

**Treatment**

Treatment guidelines have not been established for KFD, and recommendations are based on case reports and expert opinion alone. Due to the self-limited, benign course of KFD, observation is the most common approach in management. Patients with symptoms or with involvement of the extranodal tissues, such as the central nervous system, skin, and eyes, can benefit from treatment with short pulses of corticosteroids, nonsteroidal anti-inflammatory drugs, and antipyretics (Fig 2). In patients with complicated KFD, glucocorticoids or hydroxychloroquine might be useful. Chen et al.\(^5^9\) reported a rapid response to hydroxychloroquine in a child with symptomatic KFD. Yoshioka et al.\(^6^0\) treated 13 patients with KFD and prolonged fever with a short course of methylprednisolone (0.5 g/day for 3 days). A dramatic resolution of fever was seen in all patients within 24 hours. Four out of 13 patients (40%) relapsed.\(^6^0\) Rezai et al.\(^6^1\) treated a patient with KFD who had systemic symptoms with a 4-day course of chloroquine and achieved a rapid response. The patient was then re-treated with oral hydroxychloroquine 200 mg twice a day for 14 days for recurrent KFD; the patient’s symptoms resolved within 12 hours.\(^6^1\) Yalcin et al.\(^6^2\) administered methylprednisolone 1 m/kg for 8 days in a symptomatic patient with KFD who achieved a complete resolution of symptoms. The researchers tapered treatment with steroids by 8 mg every 3 days, leading to the regression of lymphadenopathy.\(^6^2\) Rezayat et al.\(^6^3\) reported on a patient who initially responded to therapy with steroids; when the disease recurred, the patient was treated with single-agent hydroxychloroquine. However, following the discontinuation of each agent, the disease relapsed and the patient required dual therapy.\(^6^3\)

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**Table 3. — Differential Diagnosis of Lymphadenopathy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kikuchi–Fujimoto Disease</th>
<th>Aggressive Lymphoma</th>
<th>Systemic Lupus Erythematosus</th>
<th>Tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Slow</td>
<td>Slow</td>
</tr>
<tr>
<td>Presence of pain</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Anatomical distribution</td>
<td>Localized</td>
<td>Generalized</td>
<td>Generalized</td>
<td>Localized</td>
</tr>
<tr>
<td>Size of lymph nodes by CT, cm</td>
<td>2–4</td>
<td>&gt; 2</td>
<td>2–4</td>
<td>2–5</td>
</tr>
<tr>
<td>FDG/PET avid</td>
<td>Yes/High</td>
<td>Yes/High</td>
<td>Yes/Low, if active disease</td>
<td>Yes/Low, if active disease</td>
</tr>
</tbody>
</table>

CT = computed tomography, FDG/PET = 18F-fluorodeoxyglucose positron emission tomography.
Recurrence
In a single study, the recurrence rate of KFD was approximately 4%; however, in a more recent review, the recurrence rate was observed to be 15%. Bogusz et al identified 65 patients with recurrent KFD in the published literature until 2013. However, because approximately 800 cases of KFD have been reported thus far, the estimated frequency of recurrent KFD could be less than 10%. Recurrences can occur as long as 8 years after the initial presentation; therefore, long-term follow-up is necessary to assess the recurrence rate in KFD.

Pregnancy
Few cases have been reported of KFD manifesting during pregnancy. Two reports suggest that treatment with antibiotics, steroids, or both have no adverse impacts on the mother, fetus, or throughout the course of pregnancy. One miscarriage was described in a patient with KFD and evolving SLE.

Prognosis
In most patients with KFD, the course of disease is benign, with a spontaneous resolution of systemic symptoms and adenopathy typically occurring in 1 to 4 months. The association of KFD with SLE ranges between 3% and 28% and is higher in Asian populations.

In rare instances KFD has a fatal course. The mortality rate of KFD was reported in 2 large studies to be between 0.5% and 2.1%. The fatal course was due to an infiltration of the myocardium, cerebral hemorrhage secondary to thrombocytopenia, and an association with SLE and hemophagocytic syndrome.

Conclusions
Kikuchi–Fujimoto disease is an idiopathic, rare, benign lymphadenopathy that primarily affects younger people. Since its original description in young Japanese females, the disease has been diagnosed in other geo-
Kikuchi–Fujimoto disease is favorable; however, due to an increased risk of developing systemic lupus erythematosus, close follow-up is recommended. Few patients with severe symptoms or recurrent disease require treatment with steroids, nonsteroidal anti-inflammatory drugs, or hydroxychloroquine.

References


A high degree of clinical suspicion is needed to diagnose Rosai–Dorman disease.

Rosai–Dorfman Disease: Tumor Biology, Clinical Features, Pathology, and Treatment
Samir Dalia, MD, Elizabeth Sagatys, MD, Lubomir Sokol, MD, PhD, and Timothy Kubal, MD

**Background:** Rosai–Dorfman disease (RDD) is a rare, nonmalignant clinical entity characterized by a group of clinical symptoms and characteristic pathological features.

**Methods:** Articles that reviewed tumor biology, clinical features, pathology, and treatment for RDD were identified in a search of the literature for the years 1990 to 2014. The results from this body of literature were reviewed and summarized.

**Results:** Patients with RDD generally present with massive, painless cervical lymphadenopathy, fevers, and elevated inflammatory markers. Extranodal disease is typical, with the most common sites being the skin and the central nervous system. Rarely, the gastrointestinal tract is involved. Immunohistochemistry remains the mainstay of diagnosis with S100 and CD68 positive cells while CD1a will be negative of involved histiocytes. Histologically, the disease shows the classical characteristic finding of emperipolesis. Many patients do not require treatment; however, surgical resection remains the mainstay of treatment for symptomatic disease. The role of steroids, chemotherapy, and radiation therapy continue to be based on small case series and case reports.

**Conclusions:** RDD has a variable clinical presentation; therefore, a high degree of suspicion and a thorough pathological review are necessary to diagnose this rare clinical entity. Although some patients will experience spontaneous resolution, others may require surgical resection or steroid therapy and radiation or chemotherapy. Given the rarity of the disease and the lack of a clear therapeutic pathway, referring patients to a tertiary center is recommended for confirming the diagnosis and treatment considerations.

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**Introduction**

Rosai–Dorman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, was originally described by Destombes in 1965. Subsequently, it was characterized as a distinct clinicopathological disorder in 1969 by Rosai and Dorfman. In this nonmalignant disorder, patients typically present with fever, leukocytosis, and nonpainful cervical lymphadenopathy. Although the disease has a predilection for the lymph nodes in the head and neck, RDD can also present in any extranodal site, with common sites including the skin and soft tissue, the central nervous system (CNS), and, less commonly, the gastrointestinal tract. Histology and immunohistochemistry help
differentiate RDD from malignant disorders such as lymphoma and Langerhans cell histiocytosis. Although adenopathy can be significant and disfiguring, RDD is usually self-limiting and eventually recedes, making systemic therapy rarely required.\textsuperscript{10} The aim of this review is to provide health care professionals with the scientific framework to gain a better understanding of the tumor biology, clinical features, pathology, and treatment for RDD.

**Tumor Biology**

RDD is a disease of nonmalignant histiocytes that infiltrate lymph nodes or extranodal tissues. RDD cells exhibit emperipolesis, the nondestructive phagocytosis of lymphocytes or erythrocytes, which is the hallmark of the disease and required for diagnosis.\textsuperscript{5,8} The etiology of RDD is unknown and is considered an idiopathic histiocytosis. The search for an infectious agent linked to RDD has led to conflicting results. Some evidence suggests that immune dysfunction and viral infections, such as human herpesvirus (HHV), parvovirus B19, and Epstein–Barr virus (EBV) may play a role in the pathogenesis.\textsuperscript{9,11-13} In particular, the expression of the HHV-6 antigen has been identified in the histiocytes present in RDD, while EBV and parvovirus have been shown to be present in lymphocytes, which may eventually be phagocytosed by histiocytes.\textsuperscript{13,14} However, in situ hybridization studies for EBV-encoded RNA have shown the RDD histiocytes to be negative.\textsuperscript{11,15} In addition, 3 cases of RDD were demonstrated to be negative for HHV-6.\textsuperscript{16} Therefore, the definitive identity of an infectious agent behind RDD remains undetermined.

Although RDD has been reported in patients with immunoglobulin (Ig) G4-related disease, no clear evidence suggests that these disorders have a common etiopathogenesis. In a recent analysis of 29 patients with RDD, low numbers of IgG4-positive plasma cells and low IgG4/IgG ratios were present when compared with IgG4-related disease samples. Forkhead box P3–positive T-regulatory cells were also lower in number in patients with RDD when compared with IgG4-related disease, suggesting that RDD does not fit into the spectrum of IgG4-related disease.\textsuperscript{9,17,18} Germ-line mutations in \textit{SLC29A3}, which encodes an intracellular human equilibrative nucleoside transporter, have been reported in patients with familial RDD, suggesting that RDD may belong to a spectrum of disorders with \textit{SLC29A3} mutations, including Faisalabad histiocytosis, H syndrome, and pigmented hypertrichosis in the setting of insulin-dependent diabetes.\textsuperscript{19,21}

**Clinical Features**

Typically, RDD manifests in childhood and early adulthood, with the majority of cases reported in the second and third decades of life.\textsuperscript{11} African Americans are more often affected than Caucasians and a male predominance is present.\textsuperscript{11} Classically, most patients present in otherwise good health with symptoms of fever and massive, nonpainful cervical lymphadenopathy mimicking lymphoma.\textsuperscript{2} Patients may have night sweats and weight loss. Painless maculopapular eruptions also can be reported, and, unlike patients with Langerhans cell histiocytosis, osteolytic bone lesions are rare but sclerotic bone lesions sometimes occur.\textsuperscript{4,11,22,25}

The workup of patients with suspected RDD is similar to that of lymphoma. A detailed history and physical examination should be performed to exclude other causes of the adenopathy. It is worth noting that hepatosplenomegaly is rare in RDD, while it is commonly seen in other histiocytic disorders.\textsuperscript{11,24} Staging should include contrast computed tomography (CT) scans of the neck, chest, abdomen, and pelvis to look for distant disease. The role of bone marrow biopsy is unclear but is usually obtained because primary bone marrow disorders are included in the differential diagnosis of RDD. Laboratory workup should include screening for EBV, cytomegalovirus, HHV-6, HHV-8, and HIV. In addition, the laboratory workup should include rheumatoid factor, an antinuclear antibody test, complete blood counts, liver and kidney function tests, immunoglobulin levels, and an erythrocyte sedimentation rate (ESR). A total of 90% of patients has been reported to have an elevated ESR and polyclonal hypergammaglobulinemia with a reversal of the albumin:globulin ratio.\textsuperscript{24} Leukocytosis with neutrophilia, a normochromic normocytic anemia, and a positive rheumatoid factor or antinuclear antibody value have all been reported.\textsuperscript{11,13,24} Hemolytic anemia and eosinophilia are rare.\textsuperscript{11,24} Ideally, excisional biopsy should be performed to obtain adequate tissue for morphological and immunohistochemical analyses to make a diagnosis.

The differential diagnosis of RDD is broad and is similar to other causes of lymphadenopathy. Nonmalignant etiologies include tuberculosis, Wegener granulomatosis, sarcoidosis, IgG4-related disease, juvenile xanthogranuloma, Erdheim–Chester disease, Gaucher disease, and other histiocytic disorders such as Langerhans cell histiocytosis. Malignant etiologies in the differential diagnosis of RDD include Hodgkin lymphoma, non-Hodgkin lymphoma, melanoma, leukemia, and Langerhans cell sarcoma.

Extranodal involvement by RDD was initially thought to be uncommon, but some reports suggest that it may be present in up to 40% of cases.\textsuperscript{4,18} The most commonly involved extranodal sites include the skin, CNS, orbit and eyelid, upper respiratory tract, and the gastrointestinal tract.\textsuperscript{7,9,11,13,17,18,22,25,52} CNS involvement in the setting of RDD is uncommon and has been reported in 210 cases in the English literature.\textsuperscript{8} The mean age of patients is 39 years and a
male prevalence has been reported. Commonly, RDD presents with dura-based, extra-axial involvement of the cranium; by contrast, spinal cord and intracerebral involvement are rare. Constitutional symptoms are usually absent and neurological symptoms depend on the location of the lesion, with headaches and seizures commonly reported. Magnetic resonance imaging of the brain should be performed in suspected cases of CNS involvement followed by biopsy, if possible, to rule out other causes of the lesion, including meningioma.

The cutaneous-only form of RDD (CRDD) is a clinically distinct entity from RDD, and some researchers suggest that it may be a different clinicopathological entity from nodal RDD. In reported cases of CRDD, patients with CRDD are 45 years old compared with patients who have RDD. Women with CRDD appear to be more affected than men, and most cases have been seen among Caucasian and Asian populations. In CRDD, patients typically present with normal laboratory data and no adenopathy. Lesions in CRDD can vary, ranging from less than 1 cm to 30 cm or more at their greatest dimensions. Multiple lesions are generally present and are typically red-brown papules or nodules. Rarely, patients can develop extensive confluent infiltrates. The most common site of skin involvement is the torso followed by the head and neck region. Most patients with CRDD follow a benign clinical course, with a frequent and spontaneous resolution of lesions. The workup in patients with suspected CRDD includes a complete skin examination, punch biopsy of the suspected lesion, followed by an expert pathology review, complete blood counts, and ESR. The utility of further workup in CRDD, including CT imaging, is unclear.

Pathology

In the setting of RDD, grossly involved lymph nodes are enlarged and matted with thickened capsules. On microscopic examination, the normal lymph node architecture is altered by massive sinusoidal dilation that contains histiocytes, lymphocytes, and plasma cells. Emperipolesis within the histiocyte cytoplasm is the classical finding in RDD. The intact lymphocytes, plasma cells, and erythrocytes inside the histiocytes are contained in the intracellular vacuoles, thus allowing an escape from degradation by the cytolytic enzymes during their transit through the histiocyte cytoplasm. In addition to the histiocyctic proliferation in the dilated sinusoids, reactive lymphoid follicles may be present in the cortex of the lymph node. In the medullary region, increased plasma cells are present, as are small lymphocytes and the occasional lipid-laden macrophages. In extranodal RDD, increased amounts of fibrosis and fewer histiocytes are present in the lesions as compared with nodal RDD; lymph node structures, including sinusoids, are absent (Fig 1). With fewer histiocytes present showing emperipolesis in extranodal tissue, a careful examination of the biopsies is required and immunohistochemical stains may be helpful when RDD is included in the differential diagnosis. RDD histiocytes will be positive for immunohistochemical stains CD68 (KP-1), CD163, and S100 and are typically negative for CD1a (Fig 2). In most cases, the histiocytes in RDD are morphologically distinct from Langerhans cell histiocytosis and interdigitating dendritic cells. Immunohistochemical stains are generally sufficient to differentiate the rare, morphologically ambiguous cases. Unlike Langerhans cell histiocytosis in which BRAF V600E mutations can be found, BRAF V600E mutations in the setting of RDD are negative.

Fig 1. — Section of skin showing histiocytic infiltrate with admixed small lymphocytes in the dermis. No involvement of the overlying epidermis is present. The histiocytes have abundant eosinophilic cytoplasm and occasional forms show emperipolesis (H & E, × 200). Inset (upper left) shows 2 histiocytes with emperipolesis in the center (H & E, × 400). H & E = hematoxylin and eosin.

Fig 2. — Immunohistochemical stains show the histiocytes expressing S100 (upper left), CD68 (upper right), and CD163 (lower left) while lacking CD1a (lower right). In the S100 and CD163 images, histiocytes demonstrate emperipolesis (H & E, × 400). H & E = hematoxylin and eosin.
finding suggests that a patient’s *BRAF* V600E mutation status could help differentiate the 2 entities in extremely rare cases in which immunohistochemical stains and morphology findings are equivocal.33

### Treatment

Because RDD is a nonmalignant histiocytic disorder, treatment for the disease is advised only in patients who are symptomatic or have vital organ or system involvement (ie, CNS). In the setting of RDD, 20% of cases show spontaneous regression without therapy.34 Relapsing and remitting RDD without treatment may occur in another 70% of patients, complicating the timing of when to use therapy.34 For patients requiring treatment, surgery is an appropriate option for disease that can be excised, including single nodal areas, primary CNS involvement, or localized primary CRDD. Remissions with surgery alone have been reported in CNS-only disease.7,31 Surgery is also utilized in those with involvement of the head and neck to maintain airway patency.32 Although some morbidity exists with surgical approaches, the majority of patients will remain disease free for prolonged periods of time.7,23,31

In cases with incomplete resection of RDD involving the CNS, a “wait and watch” approach can be implemented following surgery if neurological symptoms are reversed.3,8 In the case of persistent CNS symptoms, further treatment with either external beam radiotherapy or stereotactic radiotherapy has been successful.8,35

In patients with RDD requiring systemic treatment, steroids are a first-line therapeutic option that produces responses in both classical RDD and extranodal disease; however, the reliability and durability of these responses is unpredictable. In patients with RDD, radiation can be used as a palliative option for symptomatic disease. Although no standard radiation guidelines have been established for patients with RDD, lymphoma-like approaches with total doses ranging between 30 and 50 Gy have been employed.36 Radiotherapy can also be effective for preserving vital organ and system functions such as in cases of orbital, airway, and CNS involvement.3,8,23,26,37

For patients with CRDD, therapy is not typically required; however, surgical excision remains the most effective option for treating solitary or small numbers

![Pathological Confirmation of Rosai–Dorfman Disease](image)

**Pathological Confirmation of Rosai–Dorfman Disease**

<table>
<thead>
<tr>
<th>Limited/localized disease</th>
<th>Extensive/systemic disease</th>
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</thead>
<tbody>
<tr>
<td><strong>Asymptomatic</strong></td>
<td><strong>Asymptomatic</strong></td>
</tr>
<tr>
<td>Complete surgical resection</td>
<td>Watch and wait vs surgical resection</td>
</tr>
<tr>
<td>Residual disease</td>
<td>Watch and wait</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Progression with symptoms</td>
</tr>
</tbody>
</table>

**Treatment Algorithm for Rosai–Dorfman Disease**

- **Watch and wait vs complete surgical resection**
- **Complete surgical resection**
- **Residual disease**
- **Asymptomatic**
- **Symptomatic**

**Steroids**
- Rituximab
- Interferon
- Imatinib

**Chemotherapeutics**
- Vinca alkaloids
- Anthracyclines
- Alkylating agents
- Methotrexate
- Cladribine
- Clofarabine

Fig 3. — Treatment algorithm for Rosai–Dorfman disease.

1In selected patients with a high risk of future end-organ damage (ie, airway obstruction due to progression).
2Resection of the selected mass located in an anatomical region with a high risk of end-organ damage due to disease progression.
of lesions. Radiotherapy, cryotherapy, topical chemotherapy, and topical isotretinoin have also been used but with varying success.\textsuperscript{4,5,25,28}

In cases of disseminated RDD or those refractory to surgery or other modalities (eg, radiotherapy, steroids), chemotherapy has been used with varying degrees of success.\textsuperscript{23,37,39} Due to the rarity of RDD, clinical trials have not been performed to compare different chemotherapeutic agents in patients requiring therapy. Risk–benefit analyses are based on small case series and case reports.\textsuperscript{23,37,40} Agents such as vinca alkaloids, anthracyclines, and alkylating agents have been used with varying response rates.\textsuperscript{23,39,40} In a case series of 12 patients with RDD and CNS involvement, 2 patients achieved a complete response and both were treated with methotrexate and 6-mercaptopurine.\textsuperscript{23} Thus, a review of RDD with CNS involvement concluded that there may be a benefit in using methotrexate and 6-mercaptopurine for these patients.\textsuperscript{8} Clofarabine and cladribine have also been shown to have activity in refractory RDD.\textsuperscript{11-13} Azathioprine and interferon \( \alpha \) have been shown to have a degree of efficacy in patients with RDD,\textsuperscript{38,44-46} and, in case reports, imatinib and the anti-CD20 antibody rituximab have also been shown to have clinical activity in RDD.\textsuperscript{47-50}

Data on the usage of systemic therapy in RDD are limited; therefore, health care professionals should refer patients to tertiary care centers for the treatment of refractory or widespread disease. A treatment algorithm for patients with RDD has been proposed based on the published literature as well as our experience (Fig 3).

We believe that the surveillance of patients with RDD should be similar to that of non-Hodgkin lymphoma. Patients should be closely followed for the first 2 years after complete remission or diagnosis under a “wait and watch” approach, with clinical examination and laboratory testing performed every 3 to 6 months for the first 2 years. Contrast CT scans can be obtained as clinically indicated. We recommend that follow-up after 2 years should continue at yearly intervals to assess for possible treatment-related toxicity and future relapses.

Conclusions

Rosai–Dorfman disease is a nonmalignant histiocytic disorder that classically presents with massive, painless cervical lymphadenopathy, fever, and an elevated erythrocyte sedimentation rate. Common extranodal sites include the skin and the central nervous system. A high degree of clinical suspicion is needed to make the diagnosis because the differential diagnosis includes both malignancy and other histiocytic disorders. Histology shows emperipolesis in the histiocytes, and immunohistochemistry shows histiocytes positive for S100 and CD68 and negative for CD1a. Most patients with this disorder will not require treatment, and typically the masses will spontaneously regress. For patients who require therapy, surgical resection is the mainstay of treatment. Health care professionals are urged to refer patients to tertiary care centers if radiation therapy or chemotherapy is required because a standard of care has not been established for patients with Rosai–Dorfman disease.

References


Langerhans Cell Histiocytosis
Nanette Grana, MD

Background: Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder of unknown etiopathogenesis. Its clinical presentation is variable and ranges from isolated skin or bone disease to a life-threatening multisystem condition. LCH can occur at any age but is more frequent in the pediatric population. A neoplastic origin of this disease has been suggested due to the discovery of the mutually exclusive activating somatic BRAF V600E and MAP2K1 gene mutations that occur in about 75% of patients.

Methods: A survey of recent literature focused on the diagnosis, management, and prognosis of Langerhans cell histiocytosis. Data were collected, analyzed, and discussed with an emphasis on contemporary clinical practice.

Results: LCH is common in the pediatric population; compared with adults, children usually have a more aggressive clinical course that requires systemic chemotherapy. Patients with low-risk LCH have an excellent prognosis and a long-term survival rate that may be as high as 99%; by contrast, patients with high-risk LCH have a survival rate close to 80%. Typically, adult patients present with limited skin or bone involvement that can be treated with surgical resection or focal radiation therapy, resulting in an overall survival rate of 100%. Smoking cessation can result in the improvement of respiratory symptoms and the spontaneous resolution of pulmonary LCH. Targeted therapy with BRAF inhibitors has been used in select patients with LCH, and the results have been encouraging.

Conclusions: Our understanding of LCH has improved in the last 20 years. Available treatment regimens can control the disease in the majority of patients. The discovery of novel driver mutations and the development of targeted therapy promise better outcomes with fewer long-term therapy-related adverse events, particularly for pediatric and adolescent patients.

Introduction
Histiocytic disorders are composed of a group of diverse disorders with a common primary event, ie, the accumulation and infiltration of monocytes, macrophages, and dendritic cells in the affected tissues. Langerhans cell histiocytosis (LCH), a dendritic disorder, is believed to affect fewer than 1 in 200,000 children; however, any age group can be affected.¹ LCH is the result of the clonal proliferation of immunophenotypically and functionally immature LCH cells, as well as eosinophils, macrophages, lymphocytes, and, occasionally, multinucleated giant cells.²,3 Other terms for...
LCH include histiocytosis X, eosinophilic granuloma, Letterer–Siwe disease, and Hand–Schüller–Christian disease; however, the preferred term is LCH because the pathological histiocyte common to all of these diagnoses was identified via electron microscopy to have characteristic Birbeck granules identical to those of the Langerhans cell found in the dermal–epidermal junction of the skin. Additional research has shown that the pathological histiocyte has the gene expression profile of a myeloid-derived precursor dendritic cell, not the Langerhans cell in the skin.

Controversy exists regarding whether the clonal proliferation of LCH cells results from a malignant transformation or is the result of an immunological stimulus. Regardless of the mechanism responsible for the clonal proliferation, the primary treatment, if necessary, involves chemotherapeutic agents. Select chemotherapeutic drugs also have immunomodulatory activity.

The nomenclature of histiocytic disorders has changed in the last 50 years. The current nomenclature, which represents combined efforts of the Histiocyte Society and the World Health Organization, separates LCH disorders from non-LCH histiocytic syndromes and malignancies. The nomenclature used for LCH indicates the disease extent, which may involve a single organ system (unifocal or multifocal) or multiple organs (involving a limited number or they may be disseminated; Table 1). Treatment decisions for patients are based on whether low- or high-risk organs are involved and whether LCH presents as a single- or multisystem disease.

**Diagnostic Criteria**

The diagnosis of LCH is based on a histological and immunophenotypical examination of tissue. The main feature is the morphological identification of the characteristic Langerhans cells. In addition, positive staining of the lesional cells with CD1a, langerin (CD207), or both are required for a definitive diagnosis. The expression of langerin confirms the presence of Birbeck granules, the cytoplasmic organelles typically found in Langerhans cells.

### Pathophysiology and Etiology

The diagnosis of LCH is based on hematological and histological criteria established by the Histiocyte Society in 1987. Lesions seen in cases of LCH are polymorphous that typically vary little from site to site and from patient to patient; they also feature a monoclonal population of CD1a+ monocytes.

The cause of LCH is unknown. Researchers have debated whether LCH represents a true malignancy or a reactive immune condition. Studies favoring that LCH is a malignancy have demonstrated that LCH cells from nonpulmonary lesions are monoclonal, whereas other supportive findings include the immature appearance of lesional LCH, the presence of cell-cycle dysregulation within lesions, and the presence of significant telomere shortening of the LCH cells compared with Langerhans cells from other inflammatory lesions. By contrast, research supporting LCH as a reactive process emphasizes that clonal cell populations are commonly present within the immune system and that phenotypically immature Langerhans cells often accumulate in areas of inflammation. The lesional expression of cytokines, most recently interleukin 17, which is a key cytokine in several autoimmune disorders, has been reported.

Badalian-Very et al and Davies et al have provided new insight into LCH, demonstrating that about 50% of studied cases exhibit somatic-activating mutations of the proto-oncogene BRAF. The study by Badalian-Very et al described the first molecular abnormality implicated in the pathogenesis of LCH and is important for several reasons. The identification of activating BRAF gene mutations strongly supports the hypothesis that LCH is a neoplastic process, at least in some cases. This observation has clinical implications because it suggests that alternative therapeutic approaches aimed at targeting active BRAF should be tested in the setting of LCH. Furthermore, this mutation may provide a means to assess the status of minimal residual disease in a subset of patients with LCH. Although the study did not discern whether LCH is a neoplasm or an immune dysregulation, its results provided critical information to move research in the right direction. Brown et al recently reported on the novel somatic MAP2K1 mutations in approximately 50% of patients with LCH who tested negative for BRAF V600E using a next-generation sequencing platform. Most of the mutations were in frame deletions. Mutations in BRAF and MAP2K1 were mutually exclusive, suggesting that MAP2K1 has an important role in the pathogenesis of LCH. Targeted therapy

### Table 1. — Clinical Classification of Langerhans Cell Histiocytosis

<table>
<thead>
<tr>
<th>Single System</th>
<th>Unifocal or multifocal organ system involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unifocal or multifocal bone involvement</td>
<td>Skin</td>
</tr>
<tr>
<td>Lymph node</td>
<td>Hypothalamic/pituitary/central nervous system</td>
</tr>
<tr>
<td>Other (eg, thyroid)</td>
<td>Multisystem</td>
</tr>
<tr>
<td>Involvement of ≥ 2 organs or systems</td>
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</table>

with BRAF, MEK1, or ERK inhibitors may change the treatment algorithm of LCH in the near future.

**Clinical Presentation**

**Single System**

**Skin:** Seborrheic involvement of the scalp may be mistaken for prolonged cradle cap in infants. Infants sometimes present with Hashimoto–Pritzker disease (purplish papules on their body), which is also known as congenital self-healing reticulohistiocytosis. This manifestation may be self-limited and oftentimes disappears without therapy. Patients must be closely watched for systemic disease, which may present following the initial appearance of skin lesions.

Children and adults may also develop a red papular rash on their groin, abdomen, back, or chest that resembles a rash caused by *Candida*. They may also develop seborrheic scalp involvement.

**Oral Cavity:** Lesions in the oral cavity may precede evidence of LCH elsewhere and may include hypermobile teeth, gingival hypertrophy, or ulcers of the mucosa, tongue, or lips.

**Bone:** Lytic skull lesions are the most common sites of LCH in children, and the lesion may be asymptomatic or painful and is often surrounded by a soft-tissue mass. Other frequently involved skeletal sites are the ribs, humerus, and vertebra. Spine lesions may result in the collapse of the vertebra plana. Orbital sites may be affected; proptosis from LCH of the orbit mimics neuroblastoma or rhabdomyosarcoma.

**Pituitary Gland:** The posterior part of the pituitary can be affected and may lead to central diabetes insipidus. Involvement of the anterior pituitary may result in a failure to grow and delayed or precocious puberty.

**Multisystem Disease**

In multisystem LCH, the disease presents in multiple organs or body systems, including bone, the abdomen, the gastrointestinal tract (liver and spleen), lungs, bone marrow, the endocrine and central nervous systems, skin, and the lymph nodes.

**Bone and Other Organ Systems:** Patients with LCH may present with single- or multisystem, multifocal bone lesions.

**Abdomen and Gastrointestinal Tract:** In the setting of LCH, the liver and spleen are considered high-risk organs and any disease involvement of these organs affects a patient’s prognosis. The liver and spleen may become enlarged due to the direct infiltration of LCH cells or as a secondary phenomenon of excess cytokines, which activate macrophages or infiltrate lymphocytes around the bile ducts. A serious complication of hepatic LCH is sclerosing cholangitis. A total of 75% of children with sclerosing cholangitis will not respond to chemotherapy because LCH is no longer active but fibrosis and sclerosis are still present. Liver transplantation is the only alternate treatment when hepatic function worsens.

**Spleen:** Massive splenomegaly may lead to cytopenias because of hypersplenism and may cause respiratory compromise. Typically, splenectomy provides transient relief of the cytopenias because the increasing size of the liver and reticuloendothelial activation result in peripheral blood sequestration and destruction. Splenectomy should only be performed as a life-saving measure.

**Lungs:** Lungs are less frequently involved in children than in adults due in part to smoking, which is a key etiological factor. Tachypnea with rib retractions is often the first and only clinical sign. The cystic/nodular pattern of the disease reflects the cytokine-induced destruction of lung tissue. Pulmonary involvement is present in approximately 25% of children with multisystem LCH.

**Bone Marrow:** Most patients with bone marrow involvement are young children with diffuse disease in the liver, spleen, lymph nodes, and skin; these patients usually present with significant thrombocytopenia and anemia with or without neutropenia. Patients with LCH who are considered at very high risk may present with hemophagocytosis involving the bone marrow.

**Central Nervous System:** Neurological problems involving deficits in cognition, as well as behavioral disturbances and neuromotor dysfunction due to central nervous system involvement affect at least 10% of all patients with LCH and 19% of patients with multisystem disease. Within the last 15 years, the knowledge and understanding of the findings on magnetic resonance imaging of the brain in patients with LCH have grown. Classification of central nervous system disease by the Histiocyte Society is referenced in Table 2.

In the hypothalamic pituitary region, the characteristic features seen on magnetic resonance imaging consist of an enlarged pituitary stalk with the potential progression to space-occupying tumors that extend to the pituitary and the hypothalamus. In the setting of diabetes insipidus, typically a “loss of bright spot” can be seen, correlating with the loss of antidiuretic hormone-containing granules. The LCH-associated pineal gland abnormalities comprise solid masses or cystic lesions. Other space-occupying tumors may occur, although rarely, in the meninges, choroid plexus, and in the brain parenchyma.

Another frequent presentation of LCH involving the central nervous system, excluding hypothalamic pituitary region disease, is a combination of pathological changes in the cerebellum, basal ganglia, and/or pons, with characteristic patterns seen on magnetic resonance imaging. Prosch et al termed this pattern “radiological neurodegeneration.”
Clinical symptoms depend on the site and the type of involvement within the central nervous system. Diabetes insipidus, which represents the hallmark of infiltration of the hypothalamic pituitary region, is seen in as many as 25% of patients with LCH and as many as 50% of patients with multisystem disease.26,27 Tumorous lesions of the meninges or choroid plexus can lead to headaches, seizures, and other focal symptoms as well as the obstruction of the ventricles when intracranial pressure is increased.

LCH-associated neurodegenerative lesions are associated with a highly variable clinical picture.25 Many patients will be free of neurological symptoms despite typical changes of radiological neurodegeneration that have been seen on magnetic resonance imaging for years. However, other patients may have clinical neurodegeneration, with a spectrum of clinical signs ranging from mild abnormalities of the reflexes, discrete gait disturbances, dysarthria, dysphagia, and motor spasticity to pronounced ataxia, behavioral disturbances, learning difficulties, or severe psychiatric disease.

**Therapy**

Treatment decisions are based on whether the high- or low-risk organs are involved and whether the disease is single system or multisystem (Fig). Treatment progress for LCH has benefited from the adoption of standard diagnostic criteria, the standard evaluation of the extent of disease, and stratified treatment.28 International efforts during the last 20 years have shown that combination therapy with vinblasticine/prednisone is an effective therapy for multisystem LCH. Trials conducted by the Histiocyte Society confirmed this regimen as standard therapy for multisystem LCH with and without risk organ involvement.29,30 Risk organs and their involvement were defined according to modified Lahey criteria as follows31:

- Hematopoietic: Anemia and/or leukopenia and/or thrombocytopenia
- Liver: Enlargement > 3 cm below the costal margin, dysfunction, or both
- Spleen: Enlargement > 2 cm below the costal margin
- Lung: Typical changes via high-resolution computed tomography, histopathological diagnosis, or both

Some cases of LCH have limited involvement and may not require treatment. Treatment of localized skin disease may be unnecessary because, in many cases (typically in infants), the lesions will spontaneously regress. Single bone lesions tend to spontaneously resolve during a period of months to years and may initiate healing after biopsy.

Preliminary data from a trial conducted by the Histiocyte Society suggest that, for multisystem disease, the treatment duration of 12 months reduces the risk of reactivation compared with 6 months of total treatment.32 Patients with multisystem LCH at diagnosis may have a variable clinical course. Those without risk organ involvement, as well as those with risk organ involvement but who respond to standard initial therapy, have an excellent chance of long-term survival. Combination prednisone/vinblastine has been proven to be an effective treatment with minimal toxicity; therefore, it is the standard initial therapy for all patients in whom systemic therapy is indicated.30,33 Patients with risk organ involvement who do not respond within the first 6 weeks of therapy, particularly those with evident clinical progression, have an unfavorable prognosis.28,30,34 For such patients, an early intensification of therapy is justified.

**Salvage Therapy**

The optimal treatment for relapsed or recurrent LCH has not been determined, although several regimens exist. Patients with recurrent bone disease who have recurrences months after stopping vinblastine/prednisone may benefit from treatment with vinblastine/prednisone/mercaptopurine.35 Cladribine has also been shown to be effective for recurrent, low-risk LCH.28 For patients with recurrent or refractory multisystem or multiorgan involvement, few treatment

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**Table 2. — Classification of Magnetic Resonance Imaging for Langerhans Cell Histiocytosis and Intracranial Lesions**

<table>
<thead>
<tr>
<th>Tumorous/Granulomatous Lesions</th>
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<tbody>
<tr>
<td>Granulomatous lesions of skull bones</td>
</tr>
<tr>
<td>Hypothalamic pituitary lesions</td>
</tr>
<tr>
<td>Hypothalamus</td>
</tr>
<tr>
<td>Anterior pituitary</td>
</tr>
<tr>
<td>Choroid plexus</td>
</tr>
<tr>
<td>Meninges</td>
</tr>
<tr>
<td>Nontumorous</td>
</tr>
<tr>
<td>Nongranulomatous</td>
</tr>
<tr>
<td>Cerebellar white matter</td>
</tr>
<tr>
<td>Brainstem/pons</td>
</tr>
<tr>
<td>Supratentorial white matter</td>
</tr>
<tr>
<td>Atrophy</td>
</tr>
<tr>
<td>Cerebellar</td>
</tr>
<tr>
<td>Midbrain</td>
</tr>
<tr>
<td>Supratentorial</td>
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</tbody>
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<table>
<thead>
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</table>

options exist; however, promising results have been reported with combination cladribine/cytarabine and stem cell transplantation.

**Pediatric Population**
The reported overall incidence of the long-term consequences of LCH ranges from 20% to 70%. The reason for this wide variation is due to sample size, therapy used, duration of follow-up, and method of data collection. Children at low risk for organ involvement have approximately a 20% likelihood of developing long-term sequelae. Patients with multisystem involvement have a 71% likelihood of developing long-term problems. The most commonly reported permanent consequences are diabetes insipidus, orthopedic abnormalities, hearing loss, and neurological issues.
Patients with reactivations or chronic disease may experience severe permanent consequences that reduce their quality of life, particularly when the disease affects the central nervous system, the lungs, or leads to hormone deficiencies, neurodegenerative syndrome, and lung fibrosis, among other issues.¹⁹

**Adult Population**

With the exception of pulmonary LCH, the natural history of the disease among adults is unknown. It is estimated that 1 to 2 adult cases of LCH occur per 1 million people; however, the true incidence is unknown because this disorder is often underdiagnosed. Adults with LCH may have symptoms and signs for months before receiving a definitive diagnosis. In addition, predominance of lung disease exists in adults with LCH.⁴³ The lack of clinical trials limits the ability of health care professionals to make evidence-based recommendations for adult patients with LCH.

**Prognosis**

A recent review of the Surveillance, Epidemiology, and End Results database revealed that 828 US pediatric cases with histiocytoses had been diagnosed between 1973 and 2010 and an improved survival rate was seen during the last 40 years.⁴⁴

In a large national survey study from South Korea, 603 patients with LCH were identified between 1986 and 2010. The majority of patients (69.5%) presented with single-system involvement, 14.1% with multisystem disease without risk organ involvement, and 16.4% with multisystem disease with risk organ involvement. The 5-year overall survival rates in all 3 prognostic groups were 99.8%, 98.4%, and 77.0%, respectively. Long-term adverse events of therapy were identified in 16.4% patients.⁴⁵

In a prospective clinical study from Japan, 91 patients with LCH were treated with a combined chemotherapy regimen between 1996 and 2001.⁴⁶ Five-year overall survival rates for patients with single-system multifocal and multisystem disease were 100% and 94.4%, respectively.⁴⁶

In a single institutional, retrospective study from Italy, 121 patients with LCH were treated between 1968 and 2009.⁵⁰ The overall survival rate of the group at 10 years was 93%. Patients 2 years or younger had a worse prognosis; their overall survival rate was 82% compared with 97% for patients older than 2 years. Patients with multisystemic disease with risk organ involvement also had worse outcomes compared with patients without risk organ involvement.⁵⁰

Altogether, the above data suggest that the prognosis of patients with LCH has improved within the last 40 years following the advent of modern chemotherapy regimens. Despite excellent outcomes observed in the majority of patients, LCH can be fatal in up to 20% of patients, particularly among those with multisystem risk organ involvement and age younger than 2 years.

**Conclusions**

Langerhans cell histiocytosis is a rare disease. In the United States, researchers believe that the disease goes underdiagnosed. It is most commonly seen in young children, but any age group can be affected.¹ The cause of the disease is unknown, although the possibilities of the malignant transformation of the myeloid progenitor precursor of Langerhans cell histiocytosis and immune dysregulation are being explored.²⁴ Recent discoveries of driver mutations in BRAF and MAP2K1 genes could change the therapeutic armamentarium in Langerhans cell histiocytosis from chemotherapy to targeted therapy, resulting in a better prognosis and a lower rate of long-term therapy-related adverse events.

**References**


Transplantation in Rare Lymphoproliferative and Histiocytic Disorders

Alexis Cruz-Chacon, MD, John Mathews, MD, and Ernesto Ayala, MD

Background: Some uncommon lymphoproliferative and histiocytic disorders may present with an aggressive course and require hematopoietic stem cell transplantation (HSCT) as part of the therapeutic approach.

Methods: Published research on the use of HSCT for the treatment of these disorders was reviewed and summarized.

Results: Allogeneic HSCT may be indicated in patients with blastic plasmacytoid dendritic cell neoplasia, familial or secondary recurrent hemophagocytic lymphohistiocytosis, and resistant Langerhans cell histiocytosis. Autologous HSCT may be considered in patients with Castleman disease resistant to treatment.

Conclusions: HSCT has an evolving role in the treatment of select aggressive lymphoproliferative and histiocytic disorders.

Introduction

Atypical lymphoproliferative and histiocytic disorders are composed of several entities that have in common the presence of lymphoproliferative or histiocytic cells with variable degrees of atypia, a poorly defined natural history, and an unclear prognosis. Most of these entities are infrequent and, as a consequence, treatment is not dictated by well-designed prospective trials. Some are aggressive — similar to high-grade lymphoma — and transplantation is commonly used as initial therapy or following relapse. Nearly all transplantation-related data have been derived from case reports and small, uncontrolled series.1-5

In this review, selected entities, including blastic plasmacytoid dendritic cell neoplasm (BPDCN), hemophagocytic lymphohistiocytosis (HLH), Langerhans cell histiocytosis (LCH), dendritic cell sarcoma, and Castleman disease, were included for which data on transplantation outcomes were available. Whenever possible, the role of transplantation in the treatment of each entity was approximated. A summary of the indications for transplantation in these rare lymphoproliferative and histiocytic disorders is found in Table 1.

Blastic Plasmacytoid Dendritic Cell Neoplasm

BPDCN is a rare, clinically aggressive hematological malignancy. This tumor was initially described in...
Blastic plasmacytoid dendritic cell neoplasia | Allogeneic | Consider in first remission for all patients | Myeloablative or reduced intensity
---|---|---|---
Hemophagocytic lymphohistiocytosis | Allogeneic | All patients with the familial form of disease | Myeloablative or reduced intensity
| | Patients with the recurrent or resistant secondary form of the disease | |
| | Patients with the malignancy-associated form of the disease | |
Langerhans cell histiocytosis | Allogeneic | Resistant, recurrent, or high-risk disease | Myeloablative or reduced intensity
Dendritic cell sarcoma | Allogeneic or autologous | No role | —
Castleman disease | Autologous | Multicentric following the failure of systemic therapy | High-dose melphalan

1995 as acute agranular CD4+ natural killer (NK) cell leukemia; however, the term BPDCN was introduced by the World Health Organization following the discovery that the entity arises from the precursors of plasmacytoid dendritic cells (type 2 dendritic cells).

The most common presentation in patients with BPDCN is brown to violaceous cutaneous lesions, plaques, or tumors with or without bone marrow involvement and leukemic dissemination. Some patients may have a leukemic presentation without skin involvement. Most patients present with cytopenias, lymphadenopathy, and/or splenomegaly. Liver, tonsil, paranasal cavity, lung, eye, central nervous system, and paravertebral involvement have all been reported. Identifying the specific immunophenotype of tumor cells is essential for diagnosis. BPDCN malignant cells coexpress CD4 and CD56, and the expression of other plasmacytoid dendritic cell–associated markers, including CD123, blood dendritic cell antigen 2, T-cell leukemia 1, and SPIB, is useful for the diagnosis of BPDCN. Differential diagnoses include CD56+ acute myeloid leukemias, nasal-type extranodal NK/T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and cutaneous T-cell lymphoma. About two-thirds of patients with BPDCN have genetic abnormalities, but no diagnostic cytogenetic or molecular changes have been identified.

BPDCN is characterized by an aggressive behavior with rapid systemic dissemination. Despite an initial response to systemic chemotherapy, most patients relapse and have a poor rate of overall survival (median, 12–14 months). The optimal treatment for BPDCN is unknown and small retrospective analyses alone are available to guide therapy. Studies found that the clinical course and response to therapy differ among children compared with adults. Children have a good response to similar treatment regimens used for high-risk acute lymphoblastic leukemia without the need for hematopoietic stem cell transplantation (HSCT); by contrast, BPDCN is more aggressive in adults. Prospective studies defining the most optimal frontline therapy in adults are lacking, whereas retrospective studies favor acute lymphoblastic leukemia or aggressive non-Hodgkin lymphoma therapies for the initial treatment of adults diagnosed with BPDCN. However, most patients responding to initial therapy will relapse within 2 years irrespective of the type of chemotherapy received.

For additional information on BPDCN, please see the article by Dr Riaz and colleagues on page 279.

**Hematopoietic Stem Cell Transplantation**

Due to the reported poor and transient responses to initial chemotherapy, adults with BPDCN are frequently offered allogeneic HSCT. Most of the available data regarding the outcomes following allogeneic HSCT come from small retrospective studies. The largest retrospective study included 34 patients from a European database who received myeloablative conditioning for allogeneic HSCT. The majority of patients received stem cells from a sibling or matched unrelated donor. The overall survival rate was 41% at 3 years, and no relapses were observed 27 months following HSCT. Receiving transplantation in the first complete remission was associated with a more favorable outcome than in those transplanted with more advanced disease. When the analysis was restricted to this group of patients, the 3-year disease-free survival and overall survival rates were 45% and 60%, respectively. Age, donor, source, and presence of chronic graft-vs-host disease had no impact on survival on univariate analysis.

A smaller, single institution case series demonstrated the feasibility of allogeneic HSCT in older patients with the use of reduced intensity conditioning.
Four of the 6 adults studied with BPDCN (median age, 67 years; range, 55–80 years) underwent reduced intensity conditioning for allogeneic HSCT. Two patients who received transplantsations were in complete remission and had sustained remissions at 57 and 16 months, respectively. The other 2 patients with active disease relapsed at 6 and 18 months following transplantation. Therefore, these data suggest that reduced intensity conditioning may be considered for older or comorbid patients who are not candidates for myeloablative conditioning for allogeneic HSCT. Several small case series and reports with single cases have been reported of autologous HSCT for the treatment of patients with BPDCN. Patients with chemotherapy-sensitive disease and early disease presentation alone have been found to benefit from autologous HSCT.

Few case reports exist of patients with BPDCN who have undergone cord blood stem cell transplantation. However, one such case was reported by Ramanathan et al who described successful cord blood HSCT in a patient with BPDCN using a preparative regimen of thiopeta, fludarabine, and melphalan.

Hemophagocytic Lymphohistiocytosis
HLH is a hyperinflammatory disorder characterized by the nonmalignant, reactive, uncontrolled proliferation of histiocytes. The disease results from the underlying immune dysfunction either from a primary immune deficiency (called familial HLH) or from an acquired failure of immune hemostasis associated with infection, autoimmunity, or malignancy (called reactive or secondary HLH).

HLH is a clinical syndrome biologically characterized by a highly stimulated but ineffective immune response. The activation and proliferation of T cells and macrophages are uncontrolled and inflammatory cytokines are overproduced. Although the trigger for hyperinflammation varies, the final pathway is commonly the infiltration of multiple organs by activated CD8+ T lymphocytes, macrophages, and hypercytokinemia, resulting in end-organ damage. Clinically, patients with HLH typically present with high fever, hepatosplenomegaly, cytopenias, liver and pulmonary dysfunction, and, frequently, signs of neurological involvement. Multiorgan failure typically occurs during the final stage of progressive organ injury.

HLH is commonly divided into 2 types: familial and secondary. Familial HLH is an inherited disorder characterized by various defects on granule-dependent cytotoxicity. Known genetic mutations include the PRF1 and hMunc genes, which account for approximately 20% to 40% of familial HLH cases. Other includes X-linked lymphoproliferative disorder, Chédiak–Higashi syndrome, Griscelli syndrome, and severe combined immunodeficiency. The trigger for HLH is typically infection. Secondary HLH is a broad category that includes autoimmune disorders and infections associated with HLH (commonly viral, although bacterial, fungal, and protozoan infections have been reported) as well as malignancy associated with HLH. Malignancy-associated HLH is typically associated with hematological disorders, particularly lymphoma. The most common types of lymphoma associated with HLH are NK/T-cell and diffuse large B-cell lymphoma.

No single diagnostic test will confirm HLH; rather, clinical and laboratory data must be used to confirm the diagnosis. In the first prospective study of HLH performed internationally, a diagnosis was based on the presence of 5 criteria (fever lasting > 7 days, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis). In yet another study, 3 additional criteria were introduced: low or absent NK cell activity, hyperferritinemia, and a high level of soluble interleukin 2 receptor. Currently, a diagnosis of HLH can be made either by molecular diagnosis via the detection of a genetic mutation characteristic of familial HLH or by fulfilling 5 of the 8 criteria discussed above.

Treatment
The therapeutic strategy for HLH involves treatment of severe inflammation while also addressing the underlying trigger. If the patient is acutely ill, then prompt care at an intensive care unit and the initiation of HLH-specific treatment are required. Alternatively, if the patient is stable, then a search for the trigger is initiated and treatment is provided. Typically, decisions on how to treat HLH in adult patients are extrapolated from pediatric data. Malignancy-associated HLH has a worse prognosis than other types of HLH and, generally, successful treatment of the underlying malignancy is needed prior to the resolution of HLH.

In a prospective study performed on an international level, Henter et al showed that combined chemotherapy and immunotherapy (etoposide, steroids, and cyclosporine A) improved rates of survival among patients with HLH. A total of 113 patients who were 15 years of age or younger were included. At a median follow-up of 3.1 years, the estimated 3-year overall survival rate was 55% (51% in cases of familial HLH). Patients with persistent, recurrent, or familial HLH underwent bone marrow transplantation and had a 3-year survival rate of 62%. In another study, patients receiving combination cyclophosphamide/vincristine/prednisone had a 1-year overall survival rate of 66.7%, and the treatment was especially favorable for those with infection and autoimmune disease–associated HLH. In yet another study, patients receiving treatment with combination cyclophosphamide/doxorubicin/vincristine/prednisone had a median overall survival rate of 18 weeks and a 2-year overall survival rate.
of 43.9%. However, one-half of patients will relapse with standard HLH therapy. A review of 22 pediatric and adult patients who received alemtuzumab for the treatment of refractory HLH showed that 14 patients (64%) experienced a partial response and 77% of patients survived to undergo allogeneic HSCT.

**Allogeneic Hematopoietic Stem Cell Transplantation**

In 1986, Fischer et al showed that allogeneic HSCT was curative in patients with familial HLH, a finding confirmed by other reports. In their international study, Henter et al recommended allogeneic HSCT, which was part of the treatment for all study participants with persistent, recurrent, or familial types of HLH. Of the 113 patients who entered the study, 65 underwent allogeneic HSCT (15 matched related, 25 matched unrelated, 4 mismatched unrelated, 14 haploidentical, 5 cord blood, and 2 unknown). The most common conditioning regimen included myeloablative doses of busulfan, cyclophosphamide, and etoposide. The 3-year overall survival rate was 62%, which is notable because a small number of patients had a related donor. Accumulated data have established that, for individuals with familial HLH, HSCT is the only long-term curative therapy option and should be offered to all patients. Table 2 summarizes the largest published studies in pediatric patients.

Table 2. — Selected Studies on Allogeneic Transplantation for Hemophagocytic Lymphohistiocytosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Conditioning</th>
<th>Graft Failure (%)</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henter et al</td>
<td>65</td>
<td>Busulfan/cyclophosphamide/etoposide ± antithymocyte globulin</td>
<td>Not reported</td>
<td>62% at 3 y</td>
</tr>
<tr>
<td>Baker et al</td>
<td>91</td>
<td>Busulfan/cyclophosphamide/etoposide ± antithymocyte globulin</td>
<td>9</td>
<td>53% at 5 y</td>
</tr>
<tr>
<td>Ouaché-Chardin et al</td>
<td>48</td>
<td>Busulfan/cyclophosphamide/etoposide ± antithymocyte globulin</td>
<td>22</td>
<td>58% at 5.8 y</td>
</tr>
<tr>
<td>Cooper et al</td>
<td>12</td>
<td>Fludarabine/melphalan/alemtuzumab</td>
<td>0</td>
<td>75% at 2.5 y</td>
</tr>
<tr>
<td>Cesaro et al</td>
<td>61</td>
<td>Busulfan/cyclophosphamide ± etoposide</td>
<td>5</td>
<td>58% at 8 y</td>
</tr>
</tbody>
</table>

Although the outcomes among patients with HLH have improved with the use of allogeneic HSCT, several limitations are apparent. For example, every effort should be made to achieve HLH remission prior to HSCT; if not, transplantation-related mortality rates will increase. Graft failure is also more frequent (~10%) in HLH than other nonmalignant disorders and is a cause for concern. In addition, transplantation-related mortality rates remain high (eg, recurrent HLH, graft failure, veno-occlusive disease, pneumonitis); therefore, new approaches for HSCT are needed. One such development is the introduction of reduced intensity conditioning in allogeneic HSCT for HLH. In 24 patients with HLH, Marsh et al used reduced intensity conditioning for fludarabine and melphalan with variable doses and a novel, intermediate schedule of alemtuzumab. The regimen was associated with a low incidence of graft-vs-host disease, the absence of graft failure, and a low need for subsequent stem cell products.

Compared with children, very few adults with HLH are treated with allogeneic HSCT. In 2 published case reports, allogeneic HSCT was used for the treatment of an underlying hematological malignancy or Epstein–Barr viral infection with associated HLH. At the Moffitt Cancer Center, a 22-year-old woman presented with hepatosplenomegaly, fever, and severe hypotension. Bone marrow biopsy and pathology from splenectomy showed the presence of γ/δ hepatosplenic T-cell lymphoma and HLH. Upon presentation, her ferritin level was 20,700. Initially, the patient required aggressive treatment for HLH; however, once she was clinically stable, the patient received chemotherapy and achieved a partial response and subsequently underwent allogeneic HSCT. The conditioning regimen used included fludarabine, cyclophosphamide, thiopeta, and 200 cGy of total body irradiation, followed by double umbilical cord blood transplantation. One year following HSCT, the patient remained on remission from HLH and hepatosplenic lymphoma.

Allogeneic HSCT is a curative treatment option that should be offered to all patients with familial, recurrent, or persistent types of HLH. In adults with HLH, allogeneic HSCT is frequently used to treat an underlying hematological malignancy.

**Langerhans Cell Histiocytosis**

LCH is characterized by the idiopathic proliferation of histiocytes within the reticuloendothelial system and can infiltrate virtually any organ system. It can afflict any age group, although it is predominantly seen in children. Its clinical presentation and natural history range from benign unifocal to aggressive multifocal systemic disease. Diagnosis and treatment for adults are based on pediatric data.
Data from an international registry that included 269 patients who were 18 years and older revealed slightly more affected men than women (143 vs 126) with mean ages at diagnosis of 33 years and 35 years, respectively.\textsuperscript{54} Single-system LCH was found in 86 patients (31.4\%) and isolated pulmonary LCH was found in 44 cases. A total of 188 patients (68.6\%) had multisystem disease and 81 (29.6\%) had diabetes insipidus.\textsuperscript{54}

The diagnosis is made via biopsy of the suspect lesion. The classic histopathological feature of LCH is the presence of lesional Langerhans cells with varying proportions of macrophages, multinucleated giant cells, T-lymphocytes, and eosinophils. A definitive diagnosis is based on the histopathological finding of at least 1 of the following: langerin (CD207) positivity, CD1a positivity, or the presence of Birbeck granules on electron microscopy.\textsuperscript{55} Given the minimal symptoms upon presentation, a thorough initial workup is recommended to evaluate the exact extent of involvement, including a complete history, physical examination, laboratory studies, and radiographic evaluation.\textsuperscript{53}

Treatment is based on a risk stratification system that was adopted by an expert panel of the EuroHistio-Net.\textsuperscript{53} Stratification depends on the extent and severity of disease at diagnosis. LCH can be divided into 2 major categories: Single-system LCH is subdivided further into single-site and multisite disease, and multisystem LCH is defined as the involvement of 2 or more organs at diagnosis with or without organ dysfunction.\textsuperscript{53} In the pediatric population, low-risk patients account for 20\% of all multisystem LCH and have an excellent prognosis; they also are characterized by the absence of “risk organ” involvement, including the liver, lungs, and spleen, the hematopoietic system, and tumors of the central nervous system.\textsuperscript{53} Patients at high risk make up 80\% of patients with multisystem LCH, have 1 or more risk organs involved, and have a high mortality rate.\textsuperscript{53}

In the setting of single-system LCH, unifocal involvement may be treated with careful observation and local therapy, which includes the total excision of the lesion with or without radiation therapy. Systemic therapy is required for multisystem LCH, single-system LCH with multifocal lesions, and single-system LCH with “special site” lesions, which are lesions in critical anatomical sites (eg, intraspinal, craniofacial bone). Studies focused on the treatment of adult populations with LCH are limited. However, several chemotherapy agents have shown to be effective. A retrospective study of 58 adult patients with a mean age of 32 years compared 3 commonly used regimens.\textsuperscript{56} Cytarabine was shown to have better efficacy and lower toxicity rates when compared with vinblastine/prednisone and 2-chlorodeoxyadenosine. In addition, 84\% of patients treated with vinblastine/prednisone and 59\% of patients treated with 2-chlorodeoxyadenosine either did not respond or relapsed within 1 year, whereas 21\% of patients given cytarabine failed to respond to treatment.\textsuperscript{56} In a prospective trial, 7 adult patients with multisystem LCH (n = 3) or single-system, multifocal LCH (n = 4) were given a short-course, intensive chemotherapy regimen that consisted of methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.\textsuperscript{57} The overall response rate was 100\%, with 5 complete responses and 2 partial responses seen among the participants. After a median follow-up of 6.5 years, 4 patients were in first continuous complete responses and 3 patients had relapsed after 5, 8, and 62 months.\textsuperscript{57}

Single-agent chemotherapy represents the treatment strategy used for multisystem LCH with or without involvement of “risk organs,” single-system LCH with multifocal lesions, and single-system LCH with “special site” lesions. Intensive regimens are reserved for aggressive presentations. Other treatments may include imatinib for cerebral LCH,\textsuperscript{58} zoledronic acid for bone disease,\textsuperscript{59} or lenalidomide.\textsuperscript{60}

### Hematopoietic Stem Cell Transplantation

Kudo et al\textsuperscript{6} reported their experience with 15 children who had refractory LCH and underwent HSCT in Japan. The median age at transplantation was 23 months and all of the participants had previously failed conventional chemotherapy. Myeloablative conditioning was used in 10 patients and reduced intensity conditioning was used in 5 patients.\textsuperscript{3} Umbilical cord blood was the graft source in 10 patients.\textsuperscript{3} Eleven patients became long-term survivors; a 10-year overall survival rate of 73\% was seen for the entire group and a 10-year survival rate of 55\% was seen among patients with high-risk disease.\textsuperscript{3} HSCT from parental haploidentical donors was reported in 2 girls (aged 26 months and 5 months) with refractory multisystemic LCH.\textsuperscript{61} Conditioning included myeloablative doses of busulfan, cyclophosphamide, fludarabine, and etoposide. Prophylaxis to prevent graft-vs-host disease included cyclosporine, methotrexate, mycophenolate, daclizumab, and antithymocyte globulin. Both patients survived and remained free of disease for 54 and 44 months, respectively, following HSCT.\textsuperscript{61}

Allogeneic HSCT has been reported in an adult patient with LCH, thrombocytopenia, and no radii.\textsuperscript{62} Reduced intensity conditioning for allogeneic HSCT incorporated fludarabine, busulphan, and alemtuzumab prior to transplantation. Three years following transplantation, the patient had stable donor cell engraftment, a normalized platelet count, no evidence of disease progression, and no graft-vs-host disease.\textsuperscript{62}

These limited data suggest that allogeneic HSCT may be effective therapy for patients with LCH who
have failed systemic chemotherapy or who have high-risk disease.

For additional information on LCH, please see the article by Dr Grana on page 328.

**Dendritic Cell Sarcoma**

Dendritic cell sarcoma is a rare, malignant neoplasm that arises in follicular dendritic cells that form a meshwork in the lymph node follicles and are critical for antigen presentation. Hyaline Castleman disease has been implicated as precursor of this entity. It typically occurs in young adults and most commonly begins in the lymph nodes of the neck or mediastinum; however, it can also be found in extranodal sites as the gastrointestinal tract, the liver, spleen, and bone. Diagnosis depends on a clinical examination, imaging, and pathological assessment.

The clinical behavior of the disease is similar to low-grade sarcomas with local aggressiveness. Treatment for dendritic cell sarcoma involves the complete resection of the primary lesion; however, significant risk exists for local relapse and metastatic disease. In patients with advanced or unresectable disease, chemotherapy has been used with mixed results. In case reports, selected patients with disseminated disease responded to lymphoma-oriented chemotherapy regimens.

A single case report of high-dose chemotherapy and autologous HSCT for the treatment of dendritic cell sarcoma was found in the literature. In this case, a 25-year-old man with a primary tumor of the tibia and surrounding soft tissues was treated with cyclophosphamide/doxorubicin/vincristine/prednisone and achieved minimal response. Subsequently, the patient underwent chemotherapy mobilization with etoposide/cisplatinum/methylprednisolone sodium succinate/cytarabine, followed by stem cell collection. The patient then received high-dose carmustine/etoposide/cytarabine/melphalan followed by autologous stem cell infusion. He achieved a partial response but the disease subsequently progressed to his regional lymph nodes.

At this time, data are insufficient to recommend the routine use of HSCT in patients with dendritic cell sarcoma.

For a more detailed description of dendritic cell sarcoma and histiocytic neoplasms, please see the article by Dr Dalia and colleagues on page 290.

**Castleman Disease**

Castleman disease is a rare lymphoproliferative disorder and 2 major histological variants of the disease have been identified. Abnormal follicles with regressed germinal centers characterize the hyaline vascular variant, whereas the plasma cell variant is characterized by hyperplastic germinal centers and the massive accumulation of polyclonal plasma cells in the interfollicular region. A mixed form demonstrates areas with both histological patterns.

In a major retrospective review of 113 patients, 48% of whom were men with a median age of 43 years (range, 4.2–78 years), 53% of patients studied had multicentric disease. Patients with the plasma cell variant were more likely to have multicentric disease, and these patients were more likely to be older, have B symptoms, palpable disease, peripheral neuropathy, extravascular volume overload, coexisting polynuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormality (POEMS) syndrome, bony sclerosis, anemia, leukocytosis, thrombocytosis, a high sedimentation rate, hypergammaglobulinemia, a low albumin rate, and an elevated creatinine level. The 2-, 5-, and 10-year survival rates for the entire group were 92%, 76%, and 59%, respectively. The 5-year overall survival rates among patients with unicentric and multicentric Castleman disease were 91% and 65%, respectively. A total of 80% of patients with unicentric disease was treated with surgery; of these patients, 89% achieved a partial or complete response. Patients with multicentric disease were treated with prednisone alone, alkylator-based chemotherapy, interferon, anthracycline-based chemotherapy, or rituximab.

Patients with multicentric disease may have an associated human herpesvirus 8 infection (up to 50% of the cases) and they frequently present with elevated levels of interleukin 6. Antibodies against interleukin 6 or its receptor have become available and have been tested in clinical trials.

**Hematopoietic Stem Cell Transplantation**

The use of HSCT in the setting of Castleman disease is limited to a few case reports, particularly among patients with multicentric disease who have failed other systemic therapies. The first mention of high-dose therapy concurrently with autologous HSCT was published by Repetto et al. They reported on the case of a patient with aggressive Castleman disease who received high-dose melphalan and autologous HSCT. The patient achieved a complete remission that lasted 15 months at the time of publication. Ganti et al. reported on the case of a 39-year-old man who presented with peripheral neuropathy, lymphadenopathy, pleural effusions, hepatomegaly, and splenomegaly. Monoclonal immunoglobulin A was identified in the serum and a diagnosis of POEMS syndrome was made. The initial treatment included rituximab; following a poor response to treatment, cyclophosphamide/mitoxantrone was added. The patient then underwent mobilization with cyclophosphamide and granulocyte-colony stimulating factor. Subsequently, he received high-dose chemotherapy with melphalan.
followed by an autologous stem cell infusion. Fourteen months following transplantation, the monoclonal spike had nearly disappeared, peripheral neuropathy had improved, and the patient was functional and free of symptoms.3

Tal et al reported on the case of a 52-year-old man who presented with diarrhea, weight loss, and abdominal masses. Lymph node biopsy confirmed the plasma cell variant of multicentric Castleman disease. The initial treatment was cyclophosphamide, vincristine, prednisone, and rituximab, and the patient achieved complete remission and a resolution of all his symptoms. Eighteen months later, the disease recurred and the patient was treated with vinblastine and rituximab.3 Subsequently, he received conditioning with etoposide, thiotepa, cytarabine, cyclophosphamide, and melphalan, followed by autologous peripheral blood stem cell transplantation. Fifty months following transplantation, the patient remained in remission.71

Although the evidence is limited, data suggest a role for autologous HSCT in patients with Castleman disease. Remissions have been long lasting and morbidity rates have been limited despite patients undergoing transplantation with active disease. Therefore, HSCT should be considered in patients with multicentric Castleman disease who have failed systemic therapies and, in particular, among those with associated POEMS syndrome.

For a more detailed description of Castleman disease, please see the article by Dr Soumerai and colleagues on page 266.

Conclusions

Acknowledging the paucity of the data, allogeneic hematopoietic stem cell transplantation has an accepted indication in patients with blastic plasmacytoid dendritic cell neoplasia and in those with familial, recurrent, or persistent hemophagocytic lymphohistiocytosis. It may also be considered in patients with recurrent or high-risk Langerhans cell histiocytosis.

Autologous hematopoietic stem cell transplantation may be considered in patients with Castleman disease, in particular with associated polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormality syndrome, and also in patients with blastic plasmacytoid dendritic cell neoplasia who have chemosensitive disease and are not suitable candidates for allogeneic hematopoietic stem cell transplantation. Published data do not support the routine use of hematopoietic stem cell transplantation in patients with dendritic cell sarcoma.

References


Special Report

Social Determinants of Racial and Ethnic Disparities in Cutaneous Melanoma Outcomes

Valerie M. Harvey, MD, Hitesh Patel, MS, MBA, Sophia Sandhu, MD, Sherrie Flynt Wallington, PhD, and Ginette Hinds, MD

Background: This article sought to elucidate how aspects of poverty and culture may contribute to race- and ethnicity-based disparities in cutaneous melanoma outcomes.

Methods: We identified published studies addressing the social determinants of melanoma. Selected review articles included US-based studies comprised of patients representing adults, children, and adolescents.

Results: African Americans and Hispanics diagnosed with cutaneous melanoma are more likely to present with more advanced stages of disease at diagnosis and have higher rates of mortality than their nonminority counterparts. These disparities may be a consequence of economic, social, and cultural barriers such as low income, public forms of health insurance, lower levels of education, lower levels of melanoma awareness and knowledge, and lower rates of participation in melanoma screening. No studies in the literature examined the potential impact of social injustice, English proficiency, immigrant status, and health literacy.

Conclusions: Substantial gaps exist in our knowledge of the pathways linking social determinants and race- and ethnicity-based disparities in melanoma. More studies are warranted to inform the development of effective interventions aimed at narrowing inequities and improving cutaneous melanoma outcomes among minority populations.

Introduction

Cutaneous melanoma is a significant public health concern. In 2013, 76,690 incident cases and 9,480 deaths occurred from cutaneous melanoma in the United States alone.1 The poor prognosis and limited treatment options of advanced-stage disease make early detection and diagnosis critical. Although the incidence of cutaneous melanoma is greatest in Caucasians,2 most studies have shown that racial and ethnic minorities diagnosed with cutaneous melanoma are more likely to experience worse cutaneous melanoma outcomes.2-7 Surveillance, Epidemiology, and End Results data reveal that Hispanics, African Americans, American Indians, and Asians diagnosed with cutaneous melanoma are more likely to present with advanced (regional and metastatic) cutaneous melanoma than Caucasians.3,4,8-12 Moreover, while the proportions of local stage or in situ cutaneous melanomas have increased among Caucasians, an opposing trend has been observed among Hispanic men living in California who present with thicker primary tumors at diagnosis.4 Evidence also suggests variability in the quality of care received by minority patients with cutaneous melanoma. A Surveillance, Epidemiology, and End Results–based study found that blacks were less likely than Caucasians to receive surgical treatment for melanoma,12 and those who underwent surgery experienced shorter survival time than other races.13 After accounting for demographical and clinical characteristics, minorities have an approximate two- to three-fold greater risk of melanoma-specific mortality than their nonminority counterparts.14 In African Americans, differences in mortality rates persist even after stage at diagnosis is considered.2 Although biological factors may account for some of these differences (cutaneous melanomas in minorities tend to occur at unusual anatomical sites and may be of more aggressive histological subtypes), the underlying mechanisms of these disparities remain unclear.2

Theoretical Framework

Freeman’s health disparities cancer model provides a framework for organizing racial and ethnic dis-
The model is based on the premise that social setting contributes to disease outcome and considers 3 major variables, ie, poverty, culture, and social justice, and posits an important connection between the social determinants of health and health inequities. Numerous studies have helped to further elucidate this connection to determine how individual health outcomes are shaped by individual motivation and higher-level social and structural forces (ie, social determinants of health). The model developed by Freeman and Chu suggests that many of the factors related to the successful acquisition of cancer prevention, control, and treatment are shaped and influenced by socially determined elements, including cultural and economic factors, social support networks, the physical and social environment, access to health care services, and social and health policies.

As such, based on this theoretical framework and the literature, this review summarizes how aspects of social determinants, including poverty and culture, contribute to race- and ethnicity-based disparities in the prevention, early detection, diagnosis incidence, treatment, and mortality rates of cancer. Given the paucity of literature linking race-based disparities in cutaneous melanoma to social justice, this article will focus on the domains of poverty and culture.

Methods
The medical literature was searched to identify all published studies that addressed social determinants of cutaneous melanoma within the United States using such search terms as melanoma, minorities, health disparities, social determinants, socioeconomic status, education, income, race, ethnicity, insurance, public insurance, Medicaid, Medicare, African Americans, Hispanics, Asians, Pacific Islanders, sunscreen, sun protection, skin examinations, poverty, cancer disparities, literacy, US acculturation, melanoma awareness, melanoma knowledge, and immigrants. References within selected articles were also reviewed to identify additional pertinent publications. Due to the relative paucity of studies that included minorities with cutaneous melanoma, articles addressing the aspects of social determinants in non-Hispanic whites were also reviewed to provide context.

Barriers Related to Poverty
Measures of socioeconomic status, such as level of educational attainment, occupation, income, poverty level, health insurance status, and place of residence, are key determinants for preventive skin screenings, cutaneous melanoma incidence, stage at diagnosis, and melanoma mortality rates. Regardless of the economic measure employed, the preponderance of studies demonstrates a direct correlation of the incidence of cutaneous melanoma with measures of high socioeconomic status. Conversely, lower socioeconomic status is associated with the development of thicker primary tumors, more advanced stages of disease at the time of diagnosis, and increased mortality rates.
Income
Pollitt et al\(^4\) examined the differences in incidence rates of melanoma and tumor thickness between Hispanics and non-Hispanic whites of various socioeconomic groups, which were measured by income, education, and poverty. Although most cases of cutaneous melanoma in non-Hispanic whites occurred within a high socioeconomic strata, only 35% of cutaneous melanomas in Hispanics occurred within a high socioeconomic group.\(^1\) Irrespective of race, ethnicity, or sex, patients of lower socioeconomic groups had thicker tumors (> 2 mm) at diagnosis; however, this association was most pronounced among Hispanics, a finding that suggests Hispanics may be disproportionately burdened by barriers related to poverty.\(^4\)

In their examination of cutaneous melanoma survival rates among beneficiaries of Medicare, Reyes-Ortiz et al\(^32,33\) found that patients residing in low-income regions had lower 5-year, melanoma-specific survival rates than those living in high-income areas. The researchers found that the interactions between race, ethnicity, socioeconomic status, and cutaneous melanoma survival rates were greatest among minorities, with non-Caucasians earning less than $30,000 having the highest percentages of advanced-stage melanoma and thicker tumors.\(^35\)

Treatment for melanoma also varied by socioeconomic status. Medicare enrollees living in poor areas were less likely to receive chemotherapy than their Medicare counterparts living in wealthier regions.\(^32\)

Education
The association between education and health is well established.\(^34,35\) Education and knowledge may help individuals recognize the signs and symptoms that necessitate prompt medical care and navigate through the health care system.\(^36\) Geller et al\(^31\) found that patients with cutaneous melanoma who were less educated presented with more advanced-stage disease and had greater mortality rates. Reductions in mortality rates for cutaneous melanoma between 1993 and 1997 compared with 2003 and 2007 were confined to the most highly educated individuals (≥ 13 years of education), while patients with fewer years of education experienced increases in mortality rates during that same time period.\(^31\)

Buster et al\(^37\) found that people who were less educated, elderly, or black were more likely to perceive themselves as being at low risk for developing skin cancer and were less inclined to receive skin examinations. In their survey of more than 500 patients who survived cutaneous melanoma, Pollitt et al\(^6\) found that lower levels of education were associated with decreased perception and knowledge of risk for cutaneous melanoma. They also found that physicians were less likely to counsel survivors of melanoma who had only achieved a high school education compared with their college graduate counterparts on skin cancer risks and the importance of regular self- and physician-performed skin examinations, thus demonstrating the impact of educational status on patient–physician communication.\(^5\)

Health Insurance
Health insurance status also influences cutaneous melanoma outcomes.\(^14,29,38\) Kirsner et al\(^39\) found that patients covered by Medicare health maintenance organizations (HMOs) were diagnosed in the earlier stages of cutaneous melanoma and experienced longer survival times than age-matched controls enrolled in Medicare fee-for-service programs. Similarly, Medicare HMO enrollees who were Hispanic were less likely to be diagnosed with advanced-stage melanoma than patients using fee-for-service programs.\(^40\) Although Hispanics using fee-for-service programs were more likely to have an advanced-stage cutaneous melanoma at diagnosis than non-Hispanic whites using fee-for-service programs, no significant difference was seen in stage at diagnosis or median survival rates among non-Hispanic whites and Hispanics enrolled in HMOs.\(^40\) These disparities may be explained in part by the “HMO effect.” For example, patients enrolled in HMOs are seen by their primary care physicians more often than those using a fee-for-service program; therefore, they are more likely to use preventative services such as skin cancer screenings.\(^39\)

The duration of Medicaid enrollment inversely correlates with cutaneous melanoma stage at the time of diagnosis.\(^29\) One study found that newly enrolled patients were 13 times more likely to be diagnosed with late-stage melanoma, whereas intermittently enrolled patients were twice as likely to have late-stage cutaneous melanoma as those not on Medicaid.\(^29\) Medicaid beneficiaries continuously enrolled for more than 1 year were just as likely to be diagnosed with late-stage disease as those not enrolled in Medicaid.\(^29\) A second study showed that Medicaid beneficiaries enrolled at least 3 months prior to diagnosis experienced more favorable survival outcomes than those who enrolled upon or after receiving a diagnosis of cancer.\(^41\) Together, these findings support the importance of continuous access to preventative services in improving mortality rates for melanoma and suggest that Medicaid services may be sufficient for continuously enrolled beneficiaries.

Despite the benefits of continuous enrollment, patients on Medicaid experience less favorable outcomes than their non-Medicaid counterparts.\(^41\) Possible explanations include (1) the receipt of late or inadequate treatment, (2) Medicaid beneficiaries commonly consisting of disadvantaged populations with numerous physical comorbidities, psychiatric
comorbidities, or both, which may contribute to their poor prognosis, and (3) additional barriers, including lack of transportation and psychosocial support, that may preclude the receipt of adequate treatment or continuous care.\textsuperscript{5,41} Although minority populations represent approximately one-third of the US population,\textsuperscript{42} they account for more than one-half of people covered by Medicaid.\textsuperscript{45} Health insurance status also affects the diagnostic staging evaluation of cutaneous melanoma. In one study, patients on Medicare and Medicaid were less likely than privately insured patients to undergo sentinel lymph node biopsy for cutaneous melanoma, indicating that publicly insured individuals may be understaged and possibly inadequately treated.\textsuperscript{44}

**Barriers Related to Culture**

Because culture can either amplify or reduce the expected negative effects of poverty, an understanding of the cultural contributors to cutaneous melanoma inequities is essential.\textsuperscript{45} Risk factors for melanoma, such as sun exposure behavior and the aesthetic benefits of a tanned appearance, can be rooted in cultural tendencies and preferences.

**Risk Behaviors**

Compared with Caucasians, minority populations typically engage in fewer types of behavior that increase risk for skin cancer.\textsuperscript{46} Specifically, minority populations have a lower prevalence of sunburn,\textsuperscript{47} indoor tanning use,\textsuperscript{47,48} and sunscreen consumption,\textsuperscript{49} and are more likely to seek shade than Caucasians.\textsuperscript{49} Female sex, education, income, and age are associated with sunscreen use in blacks and Hispanics.\textsuperscript{47,50,51}

**Acculturation**

Acculturation, the process by which immigrants adopt the language, attitudes, behaviors, and norms of their host country, has been associated with behavioral changes in relation to skin cancer risk among Hispanics.\textsuperscript{52-55} US cultural norms favor sunscreen use and sun tanning more than Hispanic cultural norms.\textsuperscript{52} Acculturation among Hispanics has been linked to higher perceived benefits of exposure to ultraviolet radiation,\textsuperscript{55} less worry about skin damage,\textsuperscript{55} higher rates of sunbathing,\textsuperscript{55} higher rates of indoor tanning,\textsuperscript{53} and an increased risk of sunburns.\textsuperscript{54} Of note, a subgroup analysis of Mexicans and Puerto Ricans revealed that differences in sun protection behaviors varied by country of origin,\textsuperscript{54} exemplifying the limitations of aggregating heterogeneous populations.

**Perception of Skin Cancer Risk**

In general, the medical literature as it pertains to cancer has shown that a patient's lack of perceived risk of cancer is a barrier to risk reduction and that perceived risk of cancer is a positive predictor of preventative behaviors.\textsuperscript{37,56-58} Blacks\textsuperscript{57,59} and Hispanics\textsuperscript{59-62} perceive themselves to be at very low risk for developing skin cancer. A study by Pichon et al\textsuperscript{50} observed no difference in sunscreen use among blacks who reported they perceived a high risk of skin cancer versus those who perceived no risk of skin cancer. These findings are in contrast to the medical literature on cancer, which shows a positive correlation between perceived cancer risks and preventative behaviors.

A study by Buster et al\textsuperscript{57} found that blacks placed less emphasis on the importance of regular skin examinations as a method for early detection of skin cancer than whites. Both blacks and Hispanics believed that they could do little to reduce their risk of skin cancer, primarily because too many recommendations exist about preventing skin cancer to know which ones to follow.\textsuperscript{37}

**Awareness and Knowledge**

Temoshok et al\textsuperscript{64} found that both a low level of knowledge about cutaneous melanoma prior to diagnosis and a poor understanding of melanoma treatment were associated with greater tumor thickness. Compared with non-Hispanic whites, both Hispanics\textsuperscript{60,61,64-66} and blacks\textsuperscript{64,66,67} appear to be less knowledgeable about melanoma. Blacks and Hispanics may also be less likely to seek medical care if they have a suspicious skin lesion.\textsuperscript{2,67} Even when comparing Hispanics and non-Hispanic whites with similar access to health care, Hispanics continued to demonstrate lower levels of melanoma awareness.\textsuperscript{61} Among middle school students, knowledge emerged as the strongest sun safety predictor for Hispanics.\textsuperscript{68} Knowledge-based interventions have been shown to increase monthly self-skin examinations in minority populations.\textsuperscript{59} However, the evidence is not sufficient to determine how and if knowledge gaps contribute to race- and ethnic-based disparities in melanoma outcomes.

Individuals are more likely to perform skin self-examinations if they have a high level of knowledge and awareness about melanoma.\textsuperscript{66} and patients practicing skin self-examinations can potentially decrease cutaneous melanoma mortality rates by 63%.\textsuperscript{69} Several studies have reported that the rates of skin self-examinations\textsuperscript{53,61,67,71} among minority populations and physician-assisted skin examinations\textsuperscript{49,71,72} are significantly lower than those of non-Hispanic whites. Among Hispanics, factors associated with higher rates of skin self-examinations and physician-assisted skin examinations include greater US acculturation, older age, an increased number of melanoma risk factors, physician recommendations,\textsuperscript{62,73,74} fewer skin self-examination barriers,\textsuperscript{74} country of origin,\textsuperscript{73} tanning indoors, a higher level of knowledge about skin cancer, a high level of perceived skin cancer severity, a low worry of skin
cancer, and added physician-assisted skin examination benefits. The primary reasons Hispanics cited for not performing skin self-examinations were lack of awareness regarding the necessity of skin self-examinations and lack of knowledge about how to conduct such an examination. The primary reasons Hispanics provided for not receiving physician-assisted skin examinations were inadequate amount of time with the physician and not knowing to ask or how to ask for a physician-assisted skin examination.

**Language Fluency**

Low English proficiency has been linked to having less access to care, receiving lower quality care, and having poor health outcomes. Although numerous studies have found detrimental associations between

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<th>Table. — Select US Studies Addressing Social Determinants Across the Cancer Care Continuum for Racial and Ethnic Minorities</th>
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<tr>
<td><strong>Domain</strong></td>
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limited English proficiency and health outcomes, we were unable to find any studies that investigated the role of English proficiency on outcomes among patients with cutaneous melanoma.

Gaps in Knowledge
No studies have explored the potential impact of social justice, English proficiency, health beliefs, health literacy, disability, immigrant status, or housing status despite the fact that these variables have been shown to contribute to ethnic and racial disparities in many other malignancies. We were also unable to identify studies addressing the post-treatment quality of life among minority patients with cutaneous melanoma. Much remains unknown about cutaneous melanoma in other US minority groups, including Asians, Pacific Islanders, American Indians, and Native Alaskans. The Table illustrates our current knowledge on this topic organized along the cancer continuum.

Conclusions
Hispanics and African Americans diagnosed with cutaneous melanoma typically present at diagnosis during the advanced stages of disease and experience high mortality rates. The literature on the social determinants of cutaneous melanoma outcomes in minorities is limited. In addition, decreased access to dermatological care is associated with poor melanoma outcomes; however, how this impacts outcomes among minority populations is unclear. Poverty and insurance status are key contributors of socioeconomic status–based disparities in patients with cutaneous melanoma. Barriers related to poverty also disproportionately burden minorities who are more likely to be impoverished and publicly insured. Hispanics and blacks possess lower self-perceived risk for melanoma than their counterparts, and they have less awareness and knowledge about melanoma. They are also less likely to participate in melanoma prevention and screening. Furthermore, the increasing US acculturation among Hispanics is associated with increased skin cancer risk behaviors.

This review also exposes the paucity of literature addressing the social determinants of inequities in outcomes among patients with cutaneous melanoma. Although the low incidence and prevalence rates of cutaneous melanoma among Hispanics and blacks contribute to the sparseness of studies on this topic, many of the barriers discussed are potentially modifiable; therefore, they are important to understand. Additional studies are needed to unravel the cultural, economical, and biological complexities that contribute to the observed inequities in outcomes among patients with cutaneous melanoma. This information may be valuable for the development of effective interventions in the future as well as developing cancer prevention measures and cancer control strategies targeting these specific populations.

References
28. Clegg LX, Reichman ME, Miller BA, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the


Fruit and Vegetable Intake Among Jordanians: Results From a Case-Control Study of Colorectal Cancer

Reema F. Tayyem, PhD, Ihab Shehadah, MD, Suhad S. Abu-Mweis, PhD, Hiba A. Bawadi, PhD, Kamal E. Bani-Hani, MD, PhD, Tareq Al-Jaberri, MD, PhD, Majed Al-Nusairr, MD, and Dennis D. Heath, MS

Background: Diets that include fruits and vegetables have been suggested as one way to reduce the risk of developing colorectal cancer (CRC); however, the association between consuming fruits and vegetables and CRC risk is not clear. The objective of the present study is to compare fruit and vegetable intake between 2 groups of Jordanians and further investigate this possible relationship.

Methods: A history of fruit and vegetable consumption was obtained from 220 people with CRC and 281 healthy controls, all of whom were from Jordan. Both groups were matched for age, sex, occupation, and marital status. Fruit and vegetable consumption was quantified for the previous 12 months in both groups.

Results: Total vegetable intake was associated with the risk of developing CRC. Consuming 5 servings of vegetables a day decreased the risk of developing CRC when compared with no more than 1 serving a day (odds ratio [OR] = 0.23; 95% confidence interval [CI]: 0.55–0.97). A significant direct relationship between CRC risk and consuming cauliflower and cabbage was found; however, no association was found for raw or cooked leafy vegetable and other vegetable types. Consuming several types of fruits also revealed no association with risk of CRC, although an increased intake of dates and figs was associated with a reduced risk of developing CRC. The ORs for the highest intake of servings compared with the lowest intake were 0.48 (95% CI: 0.27–0.87; P = .004) for dates and 0.604 (95% CI: 0.35–1.06; P = .003) for figs.

Conclusions: Consuming fruits and vegetables did not significantly correlate with a lowered incidence of CRC. However, a trend of protection was detected for several types of fruits and vegetables.

Introduction
In Jordan, cancer is a major cause of morbidity and mortality. Colorectal cancer (CRC) ranks second for newly diagnosed cancer cases among Jordanians; according to the World Cancer Research Fund, CRC ranks first among men and second among women. Generally, many external and internal factors may be involved in the development of cancer, and some of these factors may act in tandem or separately to initiate or promote cancer development.

Some research studies have suggested that a low intake of fruits and vegetables may prevent the development of cancer. Typically, a diet rich in fruits and vegetables will provide a good source of carotenoids, folate, vitamin C, flavonoids, organosulfides, isothiocyanates, and protease inhibitors. These compounds act as antioxidants and may play a role in preventing and reducing the risk of developing cancer, and some data suggest that dietary fiber contributes to a reduction in the risk of developing CRC. Furthermore, according to Steinmetz and Potter, increasing a person's intake of fruits and vegetables to more than 3.4 servings per day might reduce the risk of developing cancer. By contrast, other studies have found no association between fruit and vegetable consumption and CRC. However, Vogtmann et al showed that fruit intake was inversely associated with the risk of CRC development, whereas consuming vegetables was unrelated to risk among middle-aged and older Chinese men. Koushik et al reported that vegetable and fruit intake was inversely related to CRC risk among men but not among women, and the researchers argued that this association was stronger for colon than for rectal cancer.

Many studies that have evaluated the effect of fruit and vegetable consumption on developing CRC are controversial, and knowledge is lacking with regard...
to the association of the CRC process and commonly consumed fruits and vegetables among those in the Middle East. The change in the Jordanian diet from being high in fruits, vegetables, whole grains, and olive oil to a diet low in fruits and vegetables and high in red meat and saturated fat may increase the risk of developing CRC. Therefore, the present study aimed to investigate the possible association between the number of servings and frequency of fruits and vegetables commonly consumed by Jordanians and the risk of developing CRC.

Materials and Methods

Study Population

A total of 504 volunteers participated in the study (men = 220; women = 281). Of those, 220 had CRC and 281 were healthy controls. Participants were enrolled in the study from January 2010 to December 2012. Those diagnosed with CRC were recruited from 5 large Jordanian hospitals with oncology services (King Hussein Cancer Center, King Abdullah University Hospital, Prince Hamzeh Hospital, Jordan University Hospital, and Al-Basheer Hospital).

Inclusion and Exclusion Criteria

To be included in the study, volunteers had to be of Jordanian nationality, aged 18 years or older, and able to verbally communicate. They also had to be free of cancer other than CRC, diabetes mellitus, liver disease, and/or rheumatoid arthritis. Those with CRC must have received a confirmatory diagnosis no later than 1 year from the time of the first interview. Participants were excluded if they had a critical illness or were currently hospitalized. To control for confounding variables, the control group was recruited from hospital personnel, outpatients, visitors, and accompanying persons, and were then matched by age, sex, occupation, and marital status. Control participants were subjected to the same inclusion and exclusion criteria. When control participants were enrolled in the study and were listed as visitors or accompanying persons, we ensured that they were unrelated to any study volunteers diagnosed with CRC. The ratio of volunteers diagnosed with CRC to controls was approximately 1:1. The ethical committees of all 5 hospitals approved the study protocol, and written informed consent was obtained from all participants prior to starting the study.

Data Collection

Trained research assistants collected the data via private interviews in which the participants were informed about the purpose of the research. During the interview, different valid questionnaires were used to collect personal and family histories, diet (current and past), and physical activity level.

Food Frequency Questionnaire

A validated Food Frequency Questionnaire (FFQ) in Arabic was used for to assess the diets of the volunteers. The FFQ was modified from the Diet History Questionnaire I of the US National Cancer Institute and was validated for use in the Jordanian setting.

Participants were asked about their food intake (specifically fruits and vegetables) before being diagnosed for the CRC group. A 1-year period was chosen for the data collected by the FFQ so that seasonal variations of fruits and vegetables would be available, although most participants indicated a constant dietary pattern during the last 5 years.

Food lists in the modified FFQ questions were classified based on 21 types of vegetables and 21 types of fruits and juices. For each type of food, participants were asked whether they separately consumed each food item (eg, apple, banana, oranges, broccoli, sweet pepper). An answer in the affirmative resulted in additional questions related to frequency and amount of food consumed in its season (if the fruit is seasonal). Additional details were obtained for types of food available in different forms (eg, whole, juice, cooked, raw). If the participant’s diet did not include a food type, then related questions were skipped and the research assistant moved to another question. Participants were asked how frequently on average during the last year they consumed 1 standard serving of a specific food item from 9 different categories (< 1 per month, 2–3 per month, 1–2 per week, 3–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day, or 6 per day). Food models and standard measuring tools were used to help participants estimate the portion size they consumed. Responses on consumption frequency of a specified serving size for each food item were converted into average daily intake rates. Dietary intake rates were then analyzed using dietary analysis software (ESHA Food Processor SQL version 10.1.1; ESHA, Salem, Oregon) with additional data on foods commonly consumed in Jordan.

Physical Activity Level

The 7-day Physical Activity Recall (PAR) was originally developed by Sallis et al and was used in this study to measure physical activity level. The 7-day PAR is an organized questionnaire that charts a participant’s recall of time spent practicing physical activity during a 7-day period. It involves various levels of physical activity intensity, such as aerobic exercise, work-related activities, walking, gardening, recreation, and leisure activities. The frequency, intensity, duration, and type of the physical activity are typically taken into consideration when measuring the level of physical activity.

Participants were asked to respond to a PAR question based on the way they used to behave prior
to being diagnosed with CRC. The number of hours spent in different activity levels were obtained and converted into metabolic equivalents (METs). The average METs for walking are 3.3, 4.0 for moderate activity, and 8.0 for vigorous activity. The score expressed as MET minute per week was calculated as MET level × minutes of activity ÷ day × days per week. The total physical activity MET minutes per week was obtained by summing the METs and then performing categorical analysis (inactive, minimally active, or health enhancing physical activity active).

**Anthropometric Measurements**

Weight (measured to the nearest 0.1 kg), height (measured to the nearest 1.0 cm), and body mass index (BMI) were calculated per the previously published protocol. A family history of CRC was obtained by asking participants if any of their first- or second-degree relatives had CRC or any other type of cancer.

**Statistical Analyses**

All statistical analyses were conducted using IBM SPSS Statistics for Windows version 19.0 (IBM; Armonk, New York). Descriptive analyses were conducted to examine the frequency of different variables. The consumption of fruit and of vegetables was computed in 2 ways, either grouped into 5 categories based on number of servings consumed daily (< 1.0 servings per day [referent category], 2 servings per day, 3 servings per day, 4 servings per day, > 5 servings/day) or grouped based on frequency (daily, weekly, monthly, monthly, rarely). The referent group was the category with the lowest intake for both types of computation.

Multinomial logistic regression was used to calculate odds ratios (ORs) and confidence intervals (CIs), and linear regression was used to calculate $P$ values for trend. Age (continuous), sex, BMI (continuous), physical activity level (continuous), total energy intake (continuous), occupation, education level, marital status, and family history of CRC were evaluated as potential confounders. Chi-square was used to detect the differences among categorical variables. The significance level was set at $P < .05$.

**Results**

Table 1 shows the distribution of standard risk factors for the study participants by the number of servings of fruits and vegetables consumed each day. Cases and controls were matched for several parameters, including age, sex, occupation, and marital status. Therefore, no significant differences were detected in those parameters when the participants were categorized according to sex and number of fruit or vegetable servings. In addition, no significant differences were seen in BMI, tobacco use, family history of CRC, total energy intake, or physical activity level between the different levels of fruit and vegetable consumption among men and women.

Statistical analysis (not shown here) revealed that a significant difference was detected in BMI between the female cases and controls. A trend in family history of CRC was seen to decrease as the number of fruits and vegetable servings in both men and women increased. For men, regular physical activity was significantly different between the categories of vegetable consumption ($P < .022$).

Table 2 shows the adjusted ORs of CRC by number of fruit and vegetable servings in the cases and controls. In general, as the number of total vegetable servings increased to 5 servings per day, the incidence of CRC significantly decreased (OR 0.23, 95% CI: 0.55–0.97). Moreover, increasing cauliflower consumption to more than 2 servings per week increased CRC risk (OR 1.352, 95% CI: 0.21–8.69, $P = .001$). By contrast, consuming figs and dates revealed an inverse association with CRC development. As the number of servings increased up to 1 serving per day, the risk for developing CRC decreased (from OR 0.60, 95% CI: 0.34–1.06, $P = .003$, to OR 0.48, 95% CI: 0.27–0.89, $P = .006$). No relationship was found for all fruits, raw or cooked leafy vegetables, tomato, salad, green beans, peas, carrots, sweet peppers, apples, pears, banana, peach, grapes, melon, watermelon, strawberry, oranges, grapefruit, apricots, bummali, aloe vera, and dried fruits.

The adjusted ORs and CIs for the frequency of consuming individual fruits, vegetables, and starchy vegetable items are shown in Table 3. After adjusting potential confounders, the results show that daily consumption of citrus fruit, apple, peach, melon, watermelon, strawberry, and apricot had no effect on CRC risk. Both fig fruits (OR 0.51, 95% CI: 0.28–0.92), and dates (OR 0.52, 95% CI: 0.27–0.98) had a significant daily protective effect against CRC risk, while kiwi (OR 0.69, 95% CI: 0.34–1.41) had a weekly protective effect (for all: $P$ value for trend $< 0.05$).

Consuming different types of vegetables was seen to either increase or decrease the risk of developing CRC (Table 4). However, no significant association was detected between any type of vegetable and the risk of developing CRC. Leafy vegetables (raw and cooked), tomato, and salad showed a protective but insignificant association with CRC risk. In addition, the risk of CRC tended to increase when participants increased their daily consumption of cabbage (OR 2.30, 95% CI: 0.28–19.14, $P$ trend = .001) and cauliflower (OR 4.46, 95% CI: 0.72–27.68, $P$ trend = .001). For mixed vegetables, the risk of CRC was reduced even more (OR 0.53, 95% CI: 0.08–3.56, $P$ trend = .017) when consuming mixed vegetables on a daily basis.
Table 1. — Characteristics of Study Participants by Frequency of Fruit and Vegetable Intake

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<tr>
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<td>33.3</td>
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<tr>
<td>Working, %</td>
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<td>No. of men</td>
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<td>7</td>
<td>8</td>
<td>92</td>
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<td>62</td>
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<td>27.9</td>
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<td>Family history of colorectal cancer, %</td>
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<td>2.2</td>
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<td>5692.5</td>
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<td>5145.0</td>
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<tr>
<td>Total caloric intake&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>4828.2</td>
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<td>5320.2</td>
<td>.458</td>
<td>3772.7</td>
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<tr>
<td>Education (above high school), %</td>
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<td>2.5</td>
<td>2.9</td>
<td>.105</td>
<td>37.2</td>
<td>24.7</td>
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<tr>
<td><strong>Marital status, %</strong></td>
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<td>Married</td>
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<td>13.1</td>
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<td>3.4</td>
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<td>33.3</td>
<td>33.3</td>
<td>33.3</td>
</tr>
<tr>
<td>Divorced</td>
<td>100</td>
<td>16.7</td>
<td>20.8</td>
<td>8.3</td>
<td>—</td>
<td>33.3</td>
<td>33.3</td>
<td>33.3</td>
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<tr>
<td>Widower</td>
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<td>75</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>25</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Working, %</td>
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<td>4.8</td>
<td>4.8</td>
<td>.348</td>
<td>43.2</td>
<td>20.8</td>
</tr>
<tr>
<td>Tobacco use, %</td>
<td>51.4</td>
<td>28.6</td>
<td>11.4</td>
<td>5.7</td>
<td>2.9</td>
<td>.317</td>
<td>37.1</td>
<td>21.4</td>
</tr>
</tbody>
</table>

<sup>a</sup>By number of servings per day.

<sup>b</sup>Mean value.

Fruits and vegetables were compiled according to cultural influences. For example, tomatoes and sweet peppers were categorized as vegetables, not fruits; aloe vera is known culturally as a fruit because it is eaten as a dessert rather than as a vegetable closely related to the onion/garlic family. MET = metabolic equivalent.
Table 2. — Adjusted ORs* and CIs of Colorectal Cancer by Fruit and Vegetable Servings Among Jordanians

<table>
<thead>
<tr>
<th>Food Item</th>
<th>≤ 1 Serving per Day</th>
<th>2 Servings per Day</th>
<th>3 Servings per Day</th>
<th>4 Servings per Day</th>
<th>5 Servings per Day</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Fruits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>1.08 (0.62–1.89)</td>
<td>1.00 (0.48–2.07)</td>
<td>0.88 (0.23–3.37)</td>
<td>0.97 (0.22–4.47)</td>
<td>.230</td>
</tr>
<tr>
<td><strong>All Vegetables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>1.04 (0.59–1.83)</td>
<td>0.61 (0.33–1.13)</td>
<td>0.90 (0.37–2.23)</td>
<td>0.23 (0.55–0.97)</td>
<td>.153</td>
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<tr>
<td><strong>Cooked Leafy Vegetable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>0.67 (0.31–1.45)</td>
<td>0.639 (0.24–1.72)</td>
<td>2.82 (0.21–37.65)</td>
<td>0.77 (0.05–12.95)</td>
<td>.453</td>
</tr>
<tr>
<td><strong>Raw Leafy Vegetable</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>0.93 (0.49–1.75)</td>
<td>0.64 (0.31–1.28)</td>
<td>0.84 (0.17–4.05)</td>
<td>0.76 (0.41–1.41)</td>
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<td><strong>Tomato</strong></td>
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<td></td>
</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>0.74 (0.30–1.79)</td>
<td>0.78 (0.36–1.67)</td>
<td>0.54 (0.18–1.60)</td>
<td>0.53 (0.29–1.02)</td>
<td>.269</td>
</tr>
<tr>
<td><strong>Salad</strong></td>
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</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>1.16 (0.32–3.32)</td>
<td>1.04 (0.44–1.53)</td>
<td>0.82 (0.58–2.28)</td>
<td>1.15 (0.61–2.23)</td>
<td>.962</td>
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<tr>
<td><strong>Cabbage</strong></td>
<td></td>
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</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>2.11 (0.37–11.95)</td>
<td>—</td>
<td>0.80 (0.06–10.22)</td>
<td>—</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Carrot</strong></td>
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<td></td>
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</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>1.67 (0.73–3.77)</td>
<td>1.18 (0.56–2.50)</td>
<td>1.83 (0.28–11.96)</td>
<td>0.56 (0.23–1.36)</td>
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<tr>
<td><strong>Green Bean</strong></td>
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</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>1.04 (0.31–3.51)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>.154</td>
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<tr>
<td><strong>Pea</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>1.78 (0.56–5.64)</td>
<td>1.02 (0.06–17.66)</td>
<td>—</td>
<td>—</td>
<td>.171</td>
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<tr>
<td><strong>Corn</strong></td>
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<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>0.44 (0.13–1.51)</td>
<td>0.68 (0.15–3.03)</td>
<td>—</td>
<td>0.24 (0.06–0.96)</td>
<td>.129</td>
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<tr>
<td><strong>Cauliflower</strong></td>
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</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>1.01 (0.46–2.22)</td>
<td>1.36 (0.42–4.33)</td>
<td>—</td>
<td>1.35 (0.21–8.69)</td>
<td>.001</td>
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<tr>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>0.81 (0.41–1.60)</td>
<td>1.72 (0.85–3.49)</td>
<td>0.37 (0.08–1.70)</td>
<td>1.21 (0.64–2.27)</td>
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<tr>
<td><strong>Apple</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>0.81 (0.37–1.77)</td>
<td>1.00 (0.53–1.89)</td>
<td>1.05 (0.26–4.17)</td>
<td>0.87 (0.49–1.53)</td>
<td>.549</td>
</tr>
<tr>
<td><strong>Pear</strong></td>
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<td></td>
</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>0.69 (0.31–1.53)</td>
<td>0.80 (0.36–1.78)</td>
<td>2.69 (0.43–16.72)</td>
<td>1.25 (0.66–2.37)</td>
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<tr>
<td><strong>Banana</strong></td>
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<td></td>
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</tr>
<tr>
<td>AOR (95% CI) Total</td>
<td>1 (ref)</td>
<td>0.57 (0.27–1.19)</td>
<td>1.02 (0.55–1.89)</td>
<td>1.04 (0.28–3.75)</td>
<td>1.05 (0.57–1.95)</td>
<td>.139</td>
</tr>
</tbody>
</table>

*continues on page 355
Table 2. — Adjusted ORs\(^a\) and CIs of Colorectal Cancer by Fruit and Vegetable Servings Among Jordanians (continued)

<table>
<thead>
<tr>
<th>Fruits</th>
<th>AOR (95% CI)</th>
<th>≤ 1 Serving per Week</th>
<th>2 Servings per Week</th>
<th>3–4 Servings per Week</th>
<th>5–6 Servings per Week</th>
<th>1 Serving per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pear</strong></td>
<td> </td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>AOR (95% CI)</td>
<td>1 (ref)</td>
<td>46</td>
<td>0.69 (0.31–1.53)</td>
<td>2.69 (0.434–16.72)</td>
<td>1.25 (0.66–2.37)</td>
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<tr>
<td><strong>Banana</strong></td>
<td>1 (ref)</td>
<td>70</td>
<td>0.57 (0.27–1.19)</td>
<td>1.04 (0.286–3.75)</td>
<td>1.05 (0.57–1.95)</td>
<td>79</td>
</tr>
<tr>
<td><strong>Peach</strong></td>
<td>1 (ref)</td>
<td>66</td>
<td>0.36 (0.17–0.76)</td>
<td>1.52 (0.38–6.13)</td>
<td>0.64 (0.34–1.19)</td>
<td>103</td>
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<tr>
<td><strong>Grape</strong></td>
<td>1 (ref)</td>
<td>96</td>
<td>0.67 (0.30–1.51)</td>
<td>2.34 (0.51–10.69)</td>
<td>1.11 (0.62–1.98)</td>
<td>62</td>
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<tr>
<td><strong>Melon</strong></td>
<td>1 (ref)</td>
<td>45</td>
<td>0.51 (0.26–1.00)</td>
<td>1.51 (0.19–11.61)</td>
<td>0.90 (0.43–1.87)</td>
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</tr>
<tr>
<td><strong>Watermelon</strong></td>
<td>1 (ref)</td>
<td>62</td>
<td>0.51 (0.23–1.14)</td>
<td>1.24 (0.27–5.54)</td>
<td>0.72 (0.39–1.32)</td>
<td>93</td>
</tr>
<tr>
<td><strong>Strawberry</strong></td>
<td>1 (ref)</td>
<td>16</td>
<td>0.85 (0.31–2.30)</td>
<td>1.066 (0.43–2.63)</td>
<td>—</td>
<td>1.015 (0.37–2.78)</td>
</tr>
<tr>
<td><strong>Orange</strong></td>
<td>1 (ref)</td>
<td>76</td>
<td>1.07 (0.530–2.18)</td>
<td>2.78 (0.65–11.92)</td>
<td>0.85 (0.47–1.54)</td>
<td>81</td>
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<tr>
<td><strong>Grapefruit</strong></td>
<td>1 (ref)</td>
<td>12</td>
<td>0.84 (0.22–3.17)</td>
<td>0.95 (0.248–3.68)</td>
<td>—</td>
<td>1.00 (0.36–2.82)</td>
</tr>
<tr>
<td><strong>Apricot</strong></td>
<td>1 (ref)</td>
<td>25</td>
<td>0.52 (0.24–1.12)</td>
<td>1.151 (0.47–2.79)</td>
<td>0.83 (0.39–1.75)</td>
<td>166</td>
</tr>
<tr>
<td><strong>Fig</strong></td>
<td>1 (ref)</td>
<td>43</td>
<td>0.69 (0.31–1.57)</td>
<td>0.82 (0.12–5.54)</td>
<td>0.60 (0.34–1.06)</td>
<td>143</td>
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<tr>
<td><strong>Aloe Vera</strong></td>
<td>1 (ref)</td>
<td>17</td>
<td>0.64 (0.16–2.64)</td>
<td>1.13 (0.36–3.51)</td>
<td>1.52 (0.60–3.89)</td>
<td>193</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td>1 (ref)</td>
<td>34</td>
<td>0.60 (0.235–1.55)</td>
<td>0.27 (0.03–2.69)</td>
<td>0.482 (0.27–0.86)</td>
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<tr>
<td><strong>Kiwi</strong></td>
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<td>5</td>
<td>0.29 (0.05–1.48)</td>
<td>—</td>
<td>1.20 (0.28–5.21)</td>
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<tr>
<td><strong>Bommali</strong></td>
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<td>4</td>
<td>2.05 (0.43–9.74)</td>
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<td>1.14 (0.23–5.64)</td>
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</tr>
<tr>
<td><strong>Dried Fruit</strong></td>
<td>1 (ref)</td>
<td>3</td>
<td>4.13 (0.40–42.91)</td>
<td>—</td>
<td>0.00</td>
<td>209</td>
</tr>
</tbody>
</table>

\(^a\)Estimated from multinomial logistic regression models and adjusted for age, sex, total energy, MET minutes/week, tobacco use, education level, marital status, work, income, and family history of colorectal cancer.

Fruits and vegetables were compiled according to cultural influences. For example, tomatoes and sweet peppers were categorized as fruits, not vegetables; aloe vera is known culturally as a fruit because it is eaten as a dessert rather than as a vegetable closely related to the onion/garlic family. AOR = adjusted odds ratio, CI = confidence interval, MET = metabolic equivalent, OR = odds ratio.
### Table 3. — AORs* and CIs for Common Fruits Consumed Among Jordanians

<table>
<thead>
<tr>
<th>Item</th>
<th>Category of Consumption</th>
<th>Rarely*</th>
<th>Monthly</th>
<th>Weekly</th>
<th>Daily</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td></td>
<td></td>
<td></td>
<td></td>
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*continues on page 357
Table 3. — AORs and CIs for Common Fruits Consumed Among Jordanians (continued)

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<th>Weekly</th>
<th>Daily</th>
<th>P Value for Trend</th>
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<td>0.93 (0.49–1.73)</td>
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<td>1.56 (0.44–5.43)</td>
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<td>1.14 (0.25–5.06)</td>
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<td>Daily</td>
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<td>4</td>
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<td>1.56 (0.44–5.43)</td>
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<td>0.00 (0.00–0.00)</td>
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<sup>a</sup>Adjusted for age, sex, total energy, physical activity, occupation, education level, marital status, and family history of colorectal cancer.

<sup>b</sup>Reference group.

Fruits and vegetables were compiled according to cultural influences. For example, tomatoes and sweet peppers were categorized as fruits, not vegetables; aloe vera is known culturally as a fruit because it is eaten as a dessert rather than as a vegetable closely related to the onion/garlic family.

AOR = adjusted odds ratio, CI = confidence interval.

**Discussion**

The association between fruit and vegetable consumption and CRC risk is inconclusive. Although the association between total number of fruit and vegetable servings consumed on a daily basis and CRC risk is insignificant, the present study shows that a significant protective effect was detected when the serving number of vegetables increased to 5 servings per day. No association was found between the CRC development and consuming leafy vegetables (raw and cooked), tomato, and salad. Similar results were seen with the daily consumption of citrus fruit, apple, peach, melon, watermelon, strawberry, and apricot.

The results from the current study are in agreement with observations reported elsewhere. One large prospective trial that studied dietary fiber and CRC risk found an inverse association between fruit and vegetable consumption and CRC risk. However, the results of other large prospective studies have been less clear. A prospective trial conducted by Koushik et al. enrolled 5,838 volunteers and found that the relative risk for a high level of fruit consumption was 0.93 (95% CI: 0.85–1.02), 0.94 for a high level of vegetable consumption (95% CI: 0.86–1.02), and 0.91 for a high consumption level of both fruits and vegetables (95% CI: 0.82–1.01). These results suggest that high intakes of fruits and vegetables have — at most — a modest inverse association with CRC risk, a fact that is similar to the results of the current study.

The potentially protective effects of fruit and vegetable consumption have been attributed to numerous compounds, including polyphenol, capsaicin, flavonoids, lycopene, isothiocyanate, selenium, vitamins A, C, and E, folic acid, and beta carotene. Fiber can act as antitumorogenic substance within the colon through several mechanisms, one of which is the formation of short-chain fatty acids via fermentation by colonic bacteria. Fiber also helps reduce intestinal transit time and increase fecal bulk, decreasing the possibility of absorbing toxic and carcinogenic substances. In addition, fiber may reduce the production of secondary bile acid and enhance insulin sensitivity.

The unexpected outcome of the current study was the increase seen in CRC risk as the daily consumption of cruciferous vegetables (cabbage, cauliflower) increased; in the case of cauliflower, consuming 2 servings or more each week increased this risk. A possible explanation for this result is the storage and
Table 4. — AORs\(^a\) and CIs for Common Vegetables Consumed Among Jordanians

<table>
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<th>Item</th>
<th>Category of Consumption</th>
<th>Rarely(^b)</th>
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<th>Weekly</th>
<th>Daily</th>
<th>(P) Value for Trend</th>
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<td>0.53 (0.08–3.56)</td>
<td>.017</td>
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\(^a\)Adjusted for age, sex, total energy, physical activity, occupation, education level, marital status, and family history of colorectal cancer.

\(^b\)Reference group.

Fruits and vegetables were compiled according to cultural influences. For example, tomatoes and sweet peppers were categorized as fruits, not vegetables; aloe vera is known culturally as a fruit because it is eaten as a dessert rather than as a vegetable closely related to the onion/garlic family.

AOR = adjusted odds ratio, CI = confidence interval.
culinary processing conditions of cruciferous vegetables, which could affect their glucosinolate contents. When vegetables are frozen and thawed, chopped, or shredded during cooking preparation, the enzyme myrosinase converts glucosinolates (a chemically stable compound) to isothiocyanates. If these vegetables are not cut prior to cooking, then cooking them at high temperatures will denature their myrosinase content, which results in a lower conversion rate of glucosinolates to isothiocyanates. Song and Thornalley demonstrated that vegetables boiled for more than 30 minutes have no detectable isothiocyanate or amine degradation product. Jordanian cuisine largely depends on cooking cabbage and cauliflower as whole pieces and for long periods of time using high temperatures. In addition, cauliflower may be deep-fried and cabbage is usually stuffed, as a whole leaf, with fatty minced meat. Therefore, these vegetables might be considered to be fatty dishes; thus, consuming them would significantly contribute to a person’s daily fat intake. This suggests that the cooking practices within the culture are working against the protective effects of cabbage and cauliflower. Broccoli intake is low in Jordan because it is not considered to be a traditional vegetable. Mixed vegetables were found to be protective, particularly in men. We propose that a complementary effect of all the combined vegetables gives this potential protective effect against CRC.

Consuming 2 to 4 servings of grapes per week and 2 servings of kiwi per week was found to be protective against CRC; however, as the number of servings increased, the risk of CRC increased (P for trend < 0.05). Jordanians eat the whole grape, including the seeds, so the protective effect of grapes could be due to compounds found in grape seed, which has been documented in other studies of grape seed, grape seed extract, or both. Other research has also revealed that grape seeds increase cancer cell apoptosis and inhibit multiple processes, including the signaling related to epigenetics, growth, proliferation, oncogenes, metastasis, and inflammation. Ko et al demonstrated that consuming grape and kiwi or the juices of these fruits may reduce cell damage from oxidative stress, suggesting that this effect may be a consequence of the antioxidant activity of fruits in scavenging the reactive oxygen species generated during the metabolic processes. A study by Platt et al revealed that kiwi exerts a protective effect against the genotoxic effects of carcinogenic heterocyclic aromatic amines in immortal mammalian cells. Alternatively, an in vitro study showed that açai, cashew apple, kiwi, and strawberry had mutagenic effects when assayed at high concentrations (5%, 10%, and 15%). This could partially explain the results of the current study that demonstrated exceeding 2 servings of kiwi per week may be associated with CRC risk.

Jordanians eat dates throughout the year and on a daily basis; for religious reasons, they may also eat the whole fig fruit when the fruit is in season. With regard to consuming figs and dates, the present study shows an inverse association with the development of CRC. As the number of servings of figs or dates increased by no more than 1 serving a day, the risk for developing CRC significantly decreased. We are not aware of any research on the association between figs or dates and any type of cancer. However, in vitro studies have demonstrated an antitumor effect in some substances found in figs (benzaldehyde) and dates (β-D-glucan). In a study conducted by Fu et al, 7 fruits were found to possess high antioxidant capacities and phenolic contents, and these fruits could be an important dietary source of natural antioxidants for disease prevention, particularly diseases caused by oxidative stress (eg, cancer). Solomon et al investigated the correlation of the skin color of figs with their antioxidant capacity and found that the extracts of darker-colored varieties had higher contents of phytochemicals compared with the lighter-colored varieties.

Study Limitations

Limitations of the current study emerged from the dependence on self-reported data, which were not validated with records; therefore, recall bias is expected. However, the FFQ has previously been validated to be adequate for measuring macronutrient and micronutrient intake. In addition, participants were conveniently selected, and the impact of cooking on the bioavailability of different nutrients was not taken into consideration.

Conclusions

Total vegetable consumption was significantly associated with a reduced risk of developing colorectal cancer. Although the consumption of cruciferous vegetables was positively associated with colorectal cancer, the consumption of figs and dates were inversely associated with colorectal cancer risk. Therefore, patients should be encouraged to consume a variety of fruits and vegetables on a daily basis. Further studies are recommended to investigate the findings of the current study, particularly in relation to the consumption of cruciferous vegetables.

The authors would like to thank the Higher Council of Science and Technology for sponsoring this research project. They would also like to thank Hana A. Marie for tabulating the results and her help with the manuscript.

References


Lymphoproliferative and Histiocytic Diseases

Ten Best Readings Relating to Rare Lymphoproliferative and Histiocytic Diseases


Single-agent chemotherapy is typically effective in HIV-associated multicentric Castleman disease; however, chemotherapy cannot be discontinued in most patients. Rituximab has been shown to be effective and safe in patients with HIV infection and chemotherapy-dependent, multicentric Castleman disease.


Siltuximab in combination with best supportive care was superior to best supportive care alone for patients with symptomatic multicentric Castleman disease and was well tolerated with prolonged exposure.


Researchers discovered that treatment with SL-401 consisting of the catalytic and translocation domains of diphtheria toxin fused to interleukin 3 resulted in a high response rate among patients with blastic plasmacytoid dendritic cell neoplasm.


These data demonstrate that most patients with localized disease are treated similar to soft-tissue sarcoma with primary surgical resection with or without radiation. No chemotherapy data were available in the Surveillance, Epidemiology, and End Results database. The roles of chemotherapy and radiation therapy remain unclear.


In this large series of adults with secondary hemophagocytic lymphohistiocytosis (HLH) treated at a single tertiary care center, patients with low levels of serum albumin and tumor-associated HLH had poor survival rates. HLH remains elusive and challenging to health care professionals who must maintain a high index of suspicion. The recent discovery of several novel diagnostic and therapeutic modalities may improve outcomes of adult patients with HLH.


Molecular studies using paraffin-embedded archival samples showed no evidence of a positive association between Kikuchi–Fujimoto disease and viral infections, including Epstein–Barr virus and human herpesviruses 6 and 8.


High prevalence, recurrent BRAF mutations in Langerhans cell histiocytosis indicate that it is a neoplastic disease that may respond to RAF pathway inhibitors.


Reactivations of multisystem Langerhans cell histiocytosis (MS-LCH) are reduced by prolonging initial chemotherapy. In addition, the previously high mortality rates of children at high risk for MS-LCH have been reduced.


The aim of this study was to assess the results of hematopoietic stem cell transplantation (HSCT) in refractory Langerhans cell histiocytosis. The researchers concluded that HSCT for refractory Langerhans cell histiocytosis can be highly toxic but can also achieve sustained disease control.


In this review, the authors discuss recent progress in the use of hematopoietic stem cell transplantation in patients with hemophagocytic lymphohistiocytosis and potential future strategies, including the use of reduced intensity conditioning regimens.

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Peer review is the indispensable and critical element in the evaluation of all manuscripts being considered for publication in our journal. The oncology professionals who took part in our peer review process last year are listed below, and we thank them for their invaluable efforts on behalf of Cancer Control.

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FACULTY POSITION: CUTANEOUS MEDICAL ONCOLOGIST

Moffitt Cancer Center, an NCI-designated Comprehensive Cancer Center, is seeking a Medical Oncologist for its Cutaneous Oncology Program. A competitive salary package with excellent benefits, a high level of clinical resources, and outstanding infrastructural research support are available, including protected time for research endeavors. The prospective candidate will be appointed at the Assistant Member level or higher if warranted.

Extensive Cancer Center Core facilities for translational research are available, and their use by the candidate for innovative clinical trials will be encouraged. The patient population at Moffitt Cancer Center is a diverse and outstanding resource for the conduct of clinical trials. At Moffitt, significant growth in clinical and translational research, laboratory space resources, and faculty recruitment will be a high priority in the next decade.

In 2007, Moffitt established the Comprehensive Melanoma Research Center made possible by a generous philanthropic gift of $20.4 million from Donald A. Adam. This Center conducts research in melanoma and translates it into cutting-edge patient treatment. Moffitt was also recently awarded an NIH Specialized Program in Research Excellence (SPORE) grant for melanoma, and the prospective candidate will be expected to have a substantive role in the clinical and translational research activities of the SPORE and will have access to the career development and other developmental resources provided by the SPORE.

Applicants must have a Florida medical license or be eligible for one, an MD, or MD/PhD and be board certified or eligible in internal medicine and board eligible/certified or equivalent in medical oncology. The applicant should be familiar with a multidisciplinary academic clinical practice setting. The successful candidate must have clinical expertise in melanoma and a desire to participate in and design clinical trials, including those involving drug development. Familiarity with other cutaneous malignancies besides melanoma is a plus. Background in clinical and/or translational research is essential, as is an interest in education and teaching. Knowledge of scientific research methods, knowledge of federal guidelines related to conducting clinical trials, knowledge of quality assurance, and excellent spoken and written communication skills are required. An opportunity exists to participate in the clinical activities of other Moffitt clinical programs as well.

For inquiries about the position, contact Vernon K. Sondak, MD, Chair, Cutaneous Oncology Department, at Vernon.Sondak@Moffitt.org or 813-745-8788.

To apply, visit our Web page at MOFFITT.org/careers.

The H. Lee Moffitt Cancer Center & Research Institute, a rapidly growing NCI-designated Comprehensive Cancer Center, is committed to education through a wide range of residency and fellowship programs. The Cancer Center is composed of a large ambulatory care facility, a 206-bed hospital, with a 36-bed blood and marrow transplant program, 15 state-of-the-art operating suites, a 30-bed intensive care unit, a high-volume screening program, and a basic science research facility. The Moffitt Research Institute is composed of approximately 150 principal investigators, 58 laboratories, and 306,000 square feet of research space. The Moffitt Cancer Center is affiliated with the University of South Florida. Primary and secondary university appointments are available as applicable. Academic rank is commensurate with qualifications and experience.
FACULTY POSITION: NEUROLOGIST

Moffitt Cancer Center’s Neuro-Oncology Department is seeking a neurologist. The Neuro-Oncology Program employs an interdisciplinary approach, offering comprehensive therapy for patients with primary and metastatic tumors of the brain and spinal cord, as well as neurological complications of cancer and its treatments. In addition to focusing on the neurological complications of cancer and its treatment, the neurologist would provide in-house consultation for general neurological problems to the Cancer Center. The successful candidate will develop a strong, clinical, or translational program in general neurology in cancer.

The ideal candidate will have significant expertise in general neurology in a cancer setting with an emphasis on neurology. Clinical research and the ability to work closely with an interdisciplinary team of experts, including neurosurgical oncology, neuropathology, neuroradiology, neuropsychology, and laboratory scientists, are required. Moffitt Cancer Center has strong preclinical programs in immunotherapy, drug discovery, genomics, cell-based therapies, and bioinformatics. There is also an extraordinary effort in personalized medicine partnering with the biotechnology/pharmaceutical industry.

The Neuro-Oncology Program at Moffitt is a high-volume program, with approximately 500 new patients with brain tumors every year, and is active in the initiation and completion of numerous clinical trials with a well-developed clinical and translational research infrastructure. The Neuro-Oncology Program is an active participant in the National Comprehensive Cancer Network.

Successful candidates must have a Florida medical license or be eligible for one, an MD, be board certified/eligible in neurology, and fellowship trained in neurology. Experience in a clinical, multidisciplinary academic setting is preferred. A commitment to develop clinical research studies is required. The candidate should be experienced in performing and interpreting electroencephalography and electromyography. With a very active Cancer Spine Program and Neurosurgical Division, experience in physical medicine and rehabilitation medicine would be desirable.

For inquiries about the position, contact Peter Forsyth, MD, Chair, Department of Neuro-Oncology, at Peter.Forsyth@Moffitt.org or 813-745-3063.

To apply, visit our Web page at MOFFITT.org/careers.

FACULTY POSITIONS: PALLIATIVE CARE SPECIALISTS

Moffitt Cancer Center is seeking to fill faculty positions in palliative care in its growing Supportive Care Medicine Department. Moffitt recently attained certification in advanced palliative care by The Joint Commission and offers comprehensive interdisciplinary palliative care throughout the course of cancer care. Fellowship training in palliative medicine is preferred, but experience or training may replace this requirement. Clinical and research background in an oncology setting is beneficial but not necessary. The candidate should be board certified or eligible in palliative medicine.

Responsibilities include attending on the inpatient pain and palliative care consultation service, sharing in the ambulatory care practice, supervising and instructing palliative care fellows and other trainees, and participating in the clinical, educational, and research activities of the Service. Applicants must be Florida licensed or eligible.

For inquiries about the position, contact Diane Portman, MD, Chair, Department of Supportive Care Medicine, at Diane.Portman@Moffitt.org or 813-745-1246.

To apply, visit our Web page at MOFFITT.org/careers.
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COURSE DIRECTORS Peter Forsyth, MD • Frank Vrionis, MD, MPH, PhD
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