Eight-Spotted Skimmer. Photograph courtesy of Sherri Damlo. www.damloedits.com.

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

Rosai–Dorfman Disease: Tumor Biology, Clinical Features, Pathology, and Treatment

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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.*

Introduction

Rosai–Dorman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, was originally described by Destombes in 1965.[1] Subsequently, it was characterized as a distinct clinicopathological disorder in 1969 by Rosai and Dorfman.[2] 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.[3-9] Histology and immunohistochemistry help

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Submitted July 5, 2014; accepted August 12, 2014.

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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.[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.[2,8] 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.[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.[13,14] However, in situ hybridization studies for EBV-encoded RNA have shown the RDD histiocytes to be negative.[11,15] In addition, 3 cases of RDD were demonstrated to be negative for HHV-6.[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.[9,17,18] Germline mutations in *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 *SLC29A3* mutations, including Faisalabad histiocytosis, H syndrome, and pigmented hypertrichosis in the setting of insulin-dependent diabetes.[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.[11] African Americans are more often affected than Caucasians and a male predominance is present.[11] Classically, most patients present in otherwise good health with symptoms of fever and massive, nonpainful cervical lymphadenopathy mimicking lymphoma.[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.[4,11,22,23]

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.[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.[24] Leukocytosis with neutrophilia, a normochromic normocytic anemia, and a positive rheumatoid factor or antinuclear antibody value have all been reported.[11,13,24] Hemolytic anemia and eosinophilia are rare.[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.[4,18] The most commonly involved extranodal sites include the skin, CNS, orbit and eyelid, upper respiratory tract, and the gastrointestinal tract.[7-9,11-13,17,18,22,25-32]

CNS involvement in the setting of RDD is uncommon and has been reported in 210 cases in the English literature.[8] The mean age of patients is 39 years and a

male prevalence has been reported.[8] Commonly, RDD presents with dura-based, extra-axial involvement of the cranium; by contrast, spinal cord and intracerebral involvement are rare.[3,8] Constitutional symptoms are usually absent and neurological symptoms depend on the location of the lesion, with headaches and seizures commonly reported.[3,8] 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.[28] In reported cases of CRDD, patients with CRDD are 45 years older compared with patients who have RDD.[4] Women with CRDD appear to be more affected than men, and most cases have been seen among Caucasian and Asian populations.[4,28] 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.[4] 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.[10] Emperipolesis within the histiocyte cytoplasm is the classical finding in RDD.[2,9,11] 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 histiocytic 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.[10] 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).[2,11] 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.[10] 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.[33] This

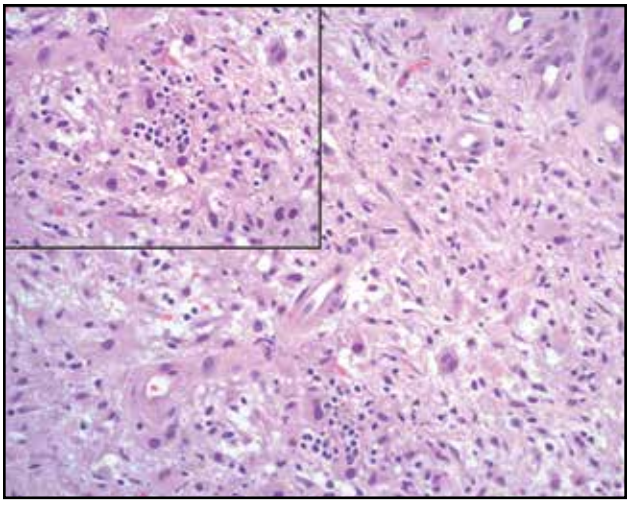

Fig 1. — Section of skin showing histiocytic infiltrate with admixed small lymphocytes in the dermis. No involvement of the overlying epidermis is present. The histiocytes have abundant eosinophilic cytoplasm and occasional forms show emperipolesis (H & E, × 200). Inset (upper left) shows 2 histiocytes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

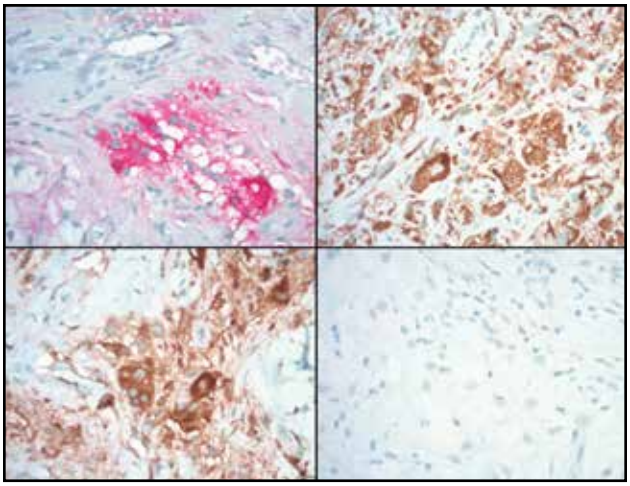

Fig 2. — Immunohistochemical stains show the histiocytes expressing S100 (upper left), CD68 (upper right), and CD163 (lower left) while lacking CD1a (lower right). In the S100 and CD163 images, histiocytes demonstrate emperipolesis (H & E, × 400). H & E = hematoxylin and eosin.

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

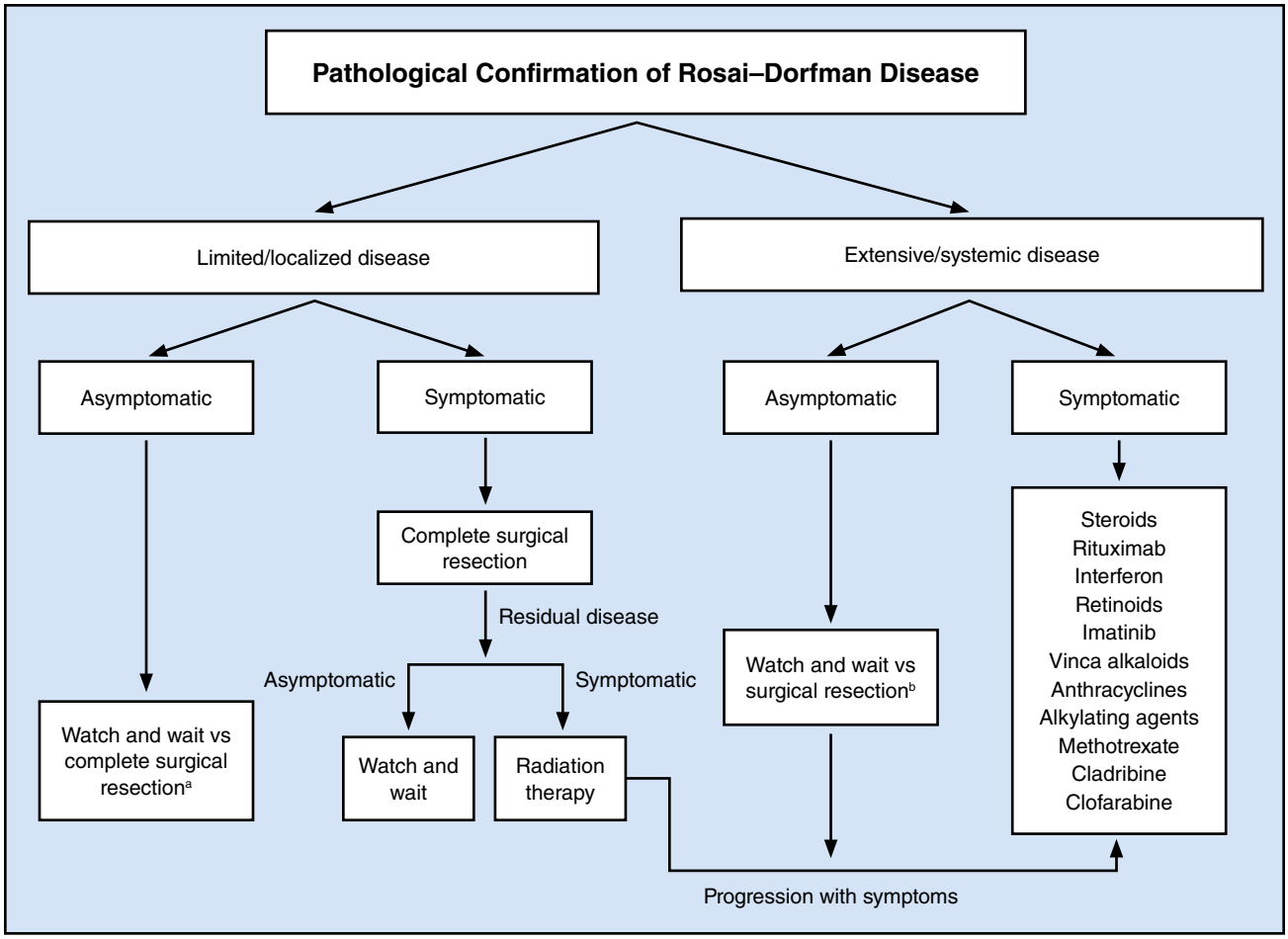

Fig 3. — Treatment algorithm for Rosai–Dorfman disease.

[a]In selected patients with a high risk of future end-organ damage (ie, airway obstruction due to progression).

[b]Resection 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.[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.[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.[23,37-40] Agents such as vinca alkaloids, anthracyclines, and alkylating agents have been used with varying response rates.[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.[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.[8] Clofarabine and cladribine have also been shown to have activity in refractory RDD.[41-43] Azathioprine and interferon α have been shown to have a degree of efficacy in patients with RDD,[38,44-46] and, in case reports, imatinib and the anti-CD20 antibody rituximab have also been shown to have clinical activity in RDD.[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.

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