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

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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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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 Tissues*\(^3\) 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.\(^5\)\(^-\)\(^7\) 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.\(^9\)\(^-\)\(^15\) 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.\(^18\)\(^-\)\(^20\) 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 al\(^10\) 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 workup 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 therapy.
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 FDCS. Soriano et al reported in a series of 14 cases with FDCS 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 FDCS remains controversial and should be considered on a case-by-case basis.

In patients with extensive disease, Saygin et al 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 FDCS, although no prospective randomized trial data exist. Regimens designed to manage advanced FDCS, although no prospective randomized trial data exist. Regimens designed to manage aggressive lymphomas, such as cyclophosphamide/vincristine/dacarbazine (ABVD), have been used. Other regimens, including carboplatin/etoposide (ICE), and doxorubicin/bleomycin/cyclophosphamide/vincristine/doxorubicin/prednisone (CHOP), ifosfamide/cisplatin/vincristine/doxorubicin/prednisone (FACOP), have been used with variable success. Currently, lymphoma-type chemotherapy remains the mainstay of treatment for disseminated FDCS. The role of allogeneic transplantation for FDCS is unclear. One study reported relapses within 1 year in 2 patients treated with allogeneic transplantation for FDCS.

### 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. IDCs originate from narrow hematopoietic precursors through the conversion of Langerhans cells as they travel to the lymph node. Unlike FDCS, 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. 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. In one series of 7 patients with chronic lymphocytic leukemia/small lymphocytic leukemia, 4 patients had features suggestive of IDCs. In these

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

<table>
<thead>
<tr>
<th>Clinical Findings (usual presentation)</th>
<th>FDCS</th>
<th>IDCS</th>
<th>INDCS</th>
<th>HS</th>
<th>FRCT</th>
<th>JXG</th>
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<tr>
<td><strong>Cytomorphology</strong></td>
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<tr>
<td>Spindle to ovoid cells with whors</td>
<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>
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<td>Spindle to ovoid cells with whors</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 whors in paracortical areas</td>
<td>Small and oval with a bland round to oval nucleus without grooves</td>
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<tr>
<th>Immunophenotypical Markers</th>
<th>CD4 (+)</th>
<th>CD21 (+)</th>
<th>CD34 (–)</th>
<th>CD45 (+/–)</th>
<th>CD68 (+)</th>
<th>Fascin (+)</th>
<th>S100 (+)</th>
<th>CD1a (–)</th>
<th>CD68 (+)</th>
<th>Lysozyme (+)</th>
<th>CD1a (–)</th>
<th>CD21 (+)</th>
<th>CD35 (–)</th>
<th>CD33 (–)</th>
<th>Vimentin (+)</th>
<th>Desmin (+)</th>
<th>Smooth muscle actin (+)</th>
<th>Factor XIIIa (+)</th>
<th>Stabilin-1 (+)</th>
<th>CD68 (+)</th>
<th>CD163 (+)</th>
<th>CD1a (–)</th>
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<tr>
<td>Treatment for Limited Disease</td>
<td>Surgical resection ± adjuvant chemotherapy or RT</td>
<td>Surgical resection or RT</td>
<td>Surgical excision</td>
<td>Surgical resection ± RT</td>
<td>Surgical resection ± RT</td>
<td>None needed for localized asymptomatic lesion</td>
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<tr>
<td>Treatment for Disseminated Disease</td>
<td>Lymphoma-type chemotherapy</td>
<td>Lymphoma-type chemotherapy</td>
<td>Multimodality</td>
<td>Lymphoma-type chemotherapy</td>
<td>Participation in a clinical trial</td>
<td>Langerhans histiocytosis–based treatment</td>
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FDCS = 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 FDCS, 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 DCS cases included 20 IDC cases.10 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 al10 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 FDCS, 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).41,45 Some cases of IDCs are positive for vimentin, HLA-DR, and fascin.25 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 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 protubercans, 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 histiocyte 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.
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-

Fig 3. — Indeterminate dendritic cell sarcoma presenting as a rapidly growing scalp nodule. (A) Low power view showing a deep tumor nodule extending to the subcutis. (B) High power view shows the dermal histiocytic infiltrate with spindly to dendritic to polygonal histiocytic cells with oval nuclei, abundant pink cytoplasm with distinct cell borders, and grooved nuclei. (C) These cells are diffusely positive for CD1a. (D) High power oil magnification view of CD68 histiocytic marker highlights the grooved or clefted nuclear folds. (E) These are typically S100 positive, similar to Langerhans cells, but are also characteristically negative for factor XIIIa, a dermal dendrocyte marker. Birbeck granules are not present on electron microscopy.
mains 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,
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).\(^1\)\(^2\) Despite this multifocal presentation, which simulates lymphoma in some cases, immunoglobulin and T-cell receptor genes are present in a germline configuration.\(^7\)

**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 patient should be encouraged to participate in a clinical trial.\(^71\)\(^73\)\(^75\)

**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**

33. Li L, Shi YH, Guo ZJ, et al. Clinicopathological features and prognosis