Clinical Characteristics and Treatment of Histiocytic Disorders in Children

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KEYWORDS

• Histiocytosis • Langerhans cell histiocytosis • Juvenile xanthogranuloma
• Rosai-Dorfman-Destombes • ALK+ histiocytosis

KEY POINTS

- Langerhans cell histiocytosis (LCH) and juvenile xanthogranulomas are the most common histiocytic neoplasms in children.
- Standard chemotherapy is often effective in children with histiocytic neoplasms who require systemic therapy. Targeted agents, especially MAPK pathway inhibitors, offer potential alternatives, especially in refractory cases.
- Rosai-Dorfman-Destombes disease is a non-LCH that typically presents as bilateral, "massive," cervical lymph node enlargement.
- ALK-positive histiocytosis is a recently described and rare non-LCH that requires further study to better understand and manage.

INTRODUCTION

Histiocytes are tissue-resident hematopoietic cells that are derived from myeloid progenitors in bone marrow. Normally, their function is to phagocytose pathogens and cellular debris and to present antigen to other immune cells. Histiocytic neoplasms are characterized by accumulation of neoplastic histiocytes, often accompanied by an inflammatory infiltrate, in various tissues. These diseases occur in people of all ages; in children, the most frequently encountered is Langerhans cell histiocytosis (LCH). Non-LCHs are a heterogeneous group of rare disorders that includes juvenile

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Abbreviations	
ALK	anaplastic lymphoma kinase
AVPD	arginine vasopressin deficiency
ECD	Erdheim-Chester disease
GI	gastrointestinal
ICC	International Consensus Classification
ICH	indeterminate dendritic cell histiocytosis
JXG	juvenile xanthogranuloma
LCH	Langerhans cell histiocytosis
LCH-ND	Langerhans cell histiocytosis-neurodegeneration
NF1	neurofibromatosis type 1
RDD	Rosai-Dorfman-Destombes
RO	risk organs
WHO	World Health Organization

xanthogranuloma (JXG), Rosai-Dorfman-Destombes Disease (RDD), ALK + histiocytosis, and others. Clinical behavior and optimal treatment of histiocytoses are remarkably variable.

CLASSIFICATION OF HISTIOCYTIC/DENDRITIC CELL NEOPLASMS

The World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues 5th edition and the International Consensus Classification (ICC) classifications are essentially similar with inclusion of LCH and Langerhans cell sarcoma under 'Langerhans cell neoplasms', indeterminate dendritic cell histiocytosis/tumor (ICH), and interdigitating dendritic cell sarcoma under 'other dendritic cell neoplasms', and JXG, Erdheim-Chester disease (ECD), RDD, ALK-positive histiocytosis, and histiocytic sarcoma under 'histiocytic/macrophage neoplasms'.[1,2] In the WHO 5th edition, follicular dendritic cell sarcoma and fibroblastic reticular cell tumor have been moved into a separate category of 'stromal-derived neoplasms of lymphoid tissues,' whereas these entities are retained in the histiocytic/dendritic cell neoplasm category in the ICC classification. Plasmacytoid dendritic cell neoplasms have been included in the WHO histiocytic/dendritic cell neoplasm classification, but not the ICC.

The Histiocyte Society classification separates histiocytic/dendritic cell disorders into several groups based on common clinicopathologic or genetic features.[3] The "L" or Langerhans group includes LCH, ICH, ECD, mixed ECD/LCH, and extracutaneous or disseminated JXG. The "C" group includes cutaneous and mucocutaneous histiocytosis, namely a broad group of rare non-LCH histiocytosis that involve the skin and mucosa, along with xanthoma disseminatum and multicentric reticulohistiocytosis, which are considered cutaneous non-LCH histiocytosis with a major systemic component. The "R" group includes familial, classic (nodal), and extranodal RDD, excluding limited cutaneous RDD, which is classified within the C group. The "H" group includes primary and secondary hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Finally, the "M" group includes malignant histiocytosis including histiocytic sarcoma (HS), langerhans cell sarcoma (LCS), interdigitating cell (IDC) sarcoma, and indeterminate cell sarcomas but excludes follicular dendritic cell sarcoma.

DIFFERENTIAL DIAGNOSIS

Histiocytes and dendritic cells may accumulate in the setting of various benign inflammatory, infectious, or metabolic disorders. The histopathologic features of some of these conditions are illustrated in **Fig. 1**. In lymph nodes, nodular paracortical

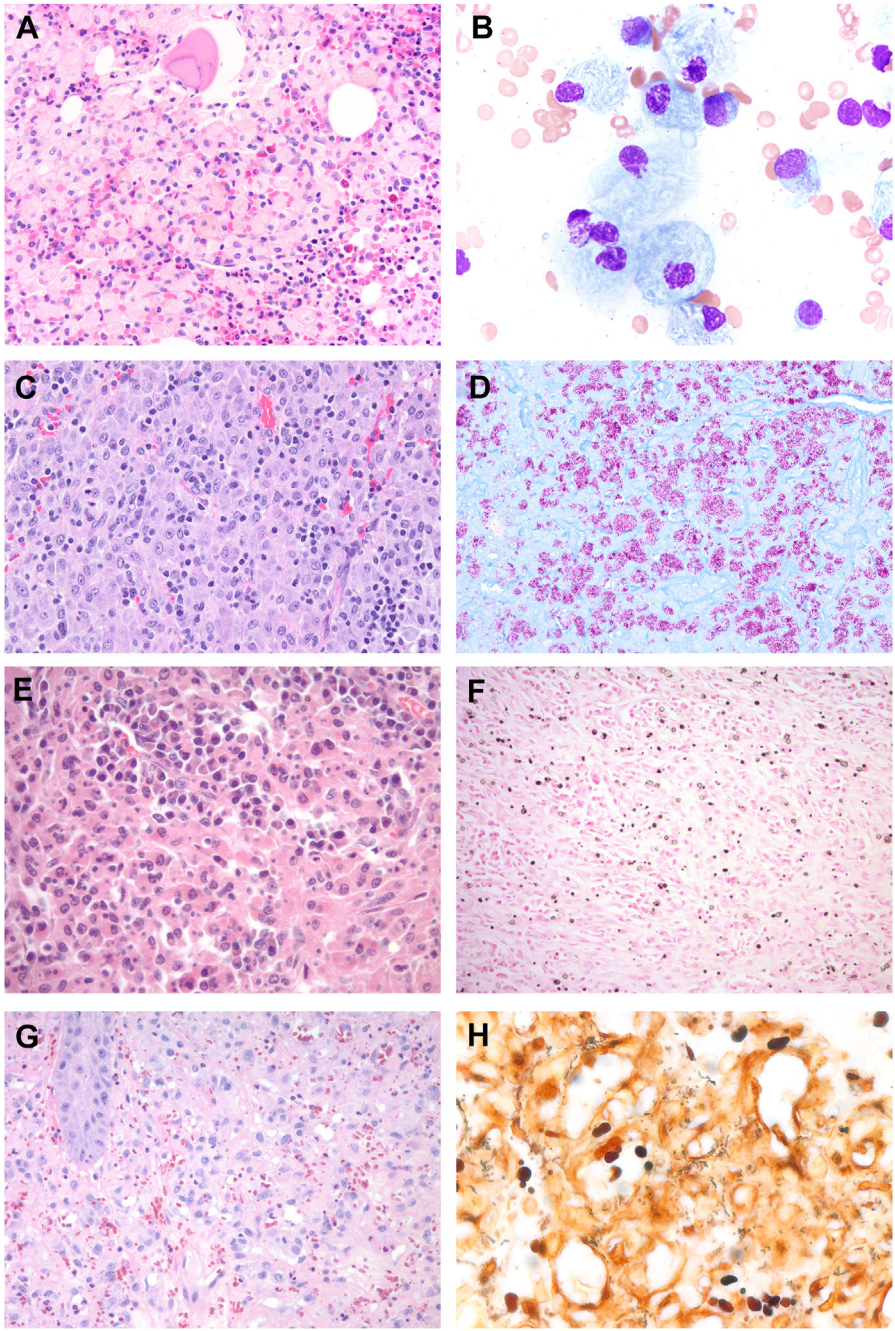

Fig. 1. The histopathologic differential diagnosis of histiocytic disorders includes accumulation of histiocytes due to various reactive disorders including infections and inflammatory conditions, and storage disorders. (*A*, *B*) Gaucher's disease leads to accumulation of histiocytes with round nuclei and abundant cytoplasm with a crystalloid or laminated quality that imparts a "tissue paper-like" appearance on H&E-stained sections (*A*) and

accumulation of histiocytes, including some pigmented histiocytes containing melanin, and dendritic cells including frequent Langerhans cells occurs in the setting of dermatopathic lymphadenopathy; in contrast, nodal LCH typically demonstrates a sinusoidal, or in some cases, a more diffuse pattern of lymph node involvement.

LANGERHANS CELL HISTIOCYTOSIS

Although LCH is the most common histiocytic neoplasm in children, it is still rare. The estimated incidence is in the range of 5 per million children less than 15 years; there is a slight male predominance.[4,5] The incidence rate is highest in babies in the first year of life, at roughly 15 cases per million. LCH does not typically run in families. However, a higher incidence in individuals of American/Indian and Hispanic ancestry and lower incidence among African Americans,[6] as well as linkage to a germline *SMAD6* variant,[7] suggest that inherited factors may play a role.

The fundamental nature of LCH was long a matter of controversy. The finding that LCH is a clonal disease[8,9] and, more recently, the observation that approximately half of cases harbor the *BRAF V600 E* mutation,[10] definitively placed LCH in the category of neoplastic disorders. Dysregulation of the MAPK cellular signaling pathway is now understood to be the key driver of LCH. Dedicated review of the molecular basis of LCH and other histiocytic neoplasms is presented elsewhere in this issue.

Pathology/Diagnostic Evaluation

The diagnosis of LCH rests on biopsy of lesional tissue. Despite clinical heterogeneity, the histopathology of LCH is remarkably consistent regardless of the site of biopsy. Unlike benign Langerhans cells, which demonstrate a spindled or dendritic cytomorphology and occur as single or loose clusters of cells, LCH lesions demonstrate aggregates or sheets of intermediate-sized to large atypical Langerhans cells with rounded/epithelioid cytomorphology, folded or grooved nuclei imparting a “coffee bean” appearance, and moderate to abundant eosinophilic cytoplasm (**Fig. 2**A–D). Nuclear atypia and mitotic activity are variably present and in some cases can be conspicuous, and necrosis may be present. Background inflammatory cells include small lymphocytes and often, but not invariably, frequent eosinophils. Electron microscopy is rarely used in clinical diagnosis but demonstrates tennis racket-shaped Birbeck granules, a hallmark of the disease. By immunohistochemistry, LCH cells express S100 (nuclear and cytoplasmic), CD1a, langerin, CD68, cyclin D1, and BRAFV600 E in cases harboring that variant.[11,12] MAPK pathway alterations are frequent, including *BRAF*

Wright-Giemsa-stained smears (*B*). (*C, D*) Mycobacterial pseudotumor is characterized by accumulation of histiocytes with an epithelioid (*C*) and/or spindled morphology and granular cytoplasm containing Mycobacterial organisms that can be visualized on AFB (*D*) or FITE (not shown) stains. (*E, F*) Malakoplakia is exceedingly uncommon in children and is characterized by accumulation of epithelioid histiocytes with bright pink cytoplasm on H&E stain (*E*); Von Hansemann cells in the setting of chronic bacterial infection. The histiocyte cytoplasm contains laminated concretions (Michaelis-Gutmann bodies) that are subtle on H&E stain and are best demonstrated by Von Kossa stain (*F*). (*G, H*) Bacillary angiomatosis due to chronic infection by *Bartonella spp.* is very infrequent in children and most commonly affects the skin with accumulation of epithelioid histiocytes and mixed inflammatory cells (*G*), with reactive vascular proliferation. Warthin-Starry silver stain (*H*) highlights the bacterial organisms. (*A, C, E, G*: H&E stain. *A, D, F, G*: 200x original magnification. *C, E*: 400x original magnification. *B, H*: 1000x original magnification.)

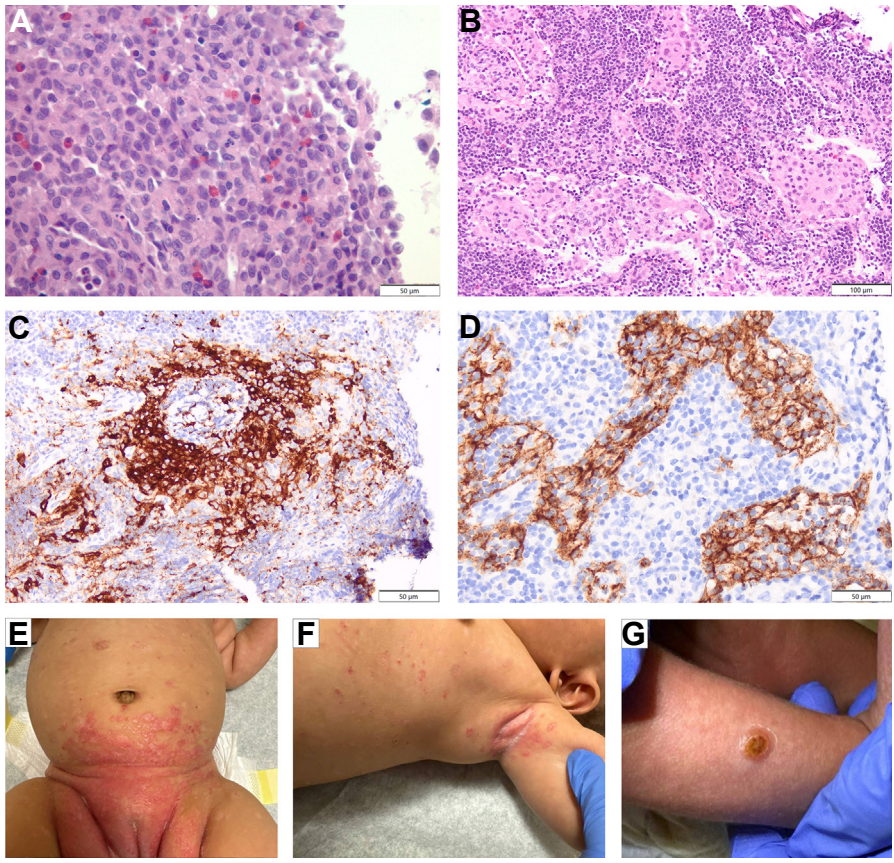

Fig. 2. Langerhans cell histiocytosis. (*A*) H&E stain demonstrates clusters and sheets of atypical epithelioid Langerhans cells with irregular nuclei with a characteristically grooved or "coffee-bean"-like appearance, dispersed chromatin, and a moderate amount of eosinophilic cytoplasm. Often there are frequent background eosinophils, a clue to the diagnosis. (*B*) Lymph node involvement by LCH is frequently in a sinusoidal pattern. Immunohistochemistry is positive for CD1a (*C*), langerin (*D*), and S100 (not shown). (*E*, *F*) Multisystem Langerhans cell histiocytosis (skin, eyes, lymph nodes) with characteristic involvement of the "*seborrheic regions*". (*G*) Self healing solitary reticulohistiocytosis (LCH) often presents at birth on extremities as a nodule with central ulceration. (*A, C, D*: 400x original magnification. *B*: 200x original magnification.)

and *MAP2K1* mutations.[10,13] Langerhans cell sarcoma is an exceedingly rare proliferation of Langerhans cells with overtly malignant pleomorphic tumor cells that may not be recognizable as Langerhans cells on routine morphology, necessitating immunophenotyping for diagnosis.

Routine laboratory testing at initial diagnosis of LCH should include, at minimum, complete blood count and liver tests, that is, transaminases, bilirubin, albumin. Additional testing typically includes measurement of inflammatory markers (sedimentation rate, C-reactive protein, ferritin), serum electrolytes and coagulation studies. If arginine vasopressin deficiency (AVP-D, formerly known as diabetes insipidus) is suspected, urine and serum osmolality should be checked. In the subset of patients with disseminated, *BRAF V600 E+* LCH, peripheral blood testing for the mutation using highly

sensitive cell free DNA or digital droplet polymerase chain reaction (PCR) assays may be obtained as a baseline for monitoring response to therapy.[14]

Radiographic staging evaluation is needed to determine the extent of disease, which is the primary determinant of treatment. In the past, bone involvement was assessed using the combination of technetium bone scan and skeletal survey. However, fludeoxyglucose F18 (FDG) - positron emission tomography (PET) imaging has replaced bone scan due to its ability to detect both osseous and nonosseous lesions. Whole body PET is combined with anatomic imaging, either computed tomography (CT) or MRI, of areas of concern. PET scans at baseline and at follow-up timepoint(s) are used to monitor response to treatment. In children less than 1 year, PET imaging may be omitted due to risk of anesthesia, lower incidence of bone lesions in this age group, and lower likelihood that results will influence treatment. Addition of skeletal survey to PET scan is advised because it increases detection of bone lesions in extremities.[15] In infants and in any older child with organomegaly, liver dysfunction or cytopenia(s), abdominal ultrasound is recommended. In patients with skull lesions, AVP-D or neurologic symptoms, MRI of brain is advised. Patients with respiratory symptoms or abnormal findings on chest radiograph, should undergo high-resolution chest CT.

Bone marrow infiltration by histiocytes is sometimes observed in patients with disseminated LCH; this finding is closely associated with concomitant peripheral blood cytopenia(s), that is, hematologic involvement. Hemophagocytosis may be present in the bone marrow. Analysis of bone marrow aspirate/biopsy is not routinely advised in LCH staging evaluation, except if needed to rule out alternative causes of low blood counts.[16]

Clinical Features

LCH presents along a clinical spectrum with signs and symptoms related to the location and extent of disease involvement. LCH can be limited to 1 site (unifocal), 1 system (single system, multifocal), or more than 1 system (multisystem). Multisystem LCH is further subclassified based on the absence or presence of involvement of the hematopoietic system, spleen or liver, so-called risk organs (RO). Multisystem LCH without RO involvement is associated with an excellent prognosis. In contrast, patients with low blood counts, splenomegaly, and/or liver dysfunction, are at much higher risk of treatment failure, severe illness, and death. RO positive LCH is strongly associated with age less than 2 years.

Bone: Bone is the most commonly involved tissue, occurring in about 80% of children with LCH.[4] In many cases, especially in older children, the disease is limited to a single bone. Typical symptoms are pain, tenderness, and swelling. The most frequent bones involved are skull, femur, rib, vertebra, and humerus. On imaging, lesions appear as a “hole” in the affected bone; an accompanying soft tissue mass may be present. Vertebral body lesions may present with compression of the vertebral body (vertebra plana). PET scan and skeletal survey can reveal clinically unsuspected lesions in multiple bones. Bone involvement is relatively less common in infants compared with older children.

Skin: Skin is the second most frequently involved system and is particularly common among infants with LCH. Cutaneous LCH typically presents as pink papules with hemorrhagic crusting in the scalp and intertriginous locations, and may resemble “cradle cap,” seborrheic dermatitis, cutaneous candidiasis, or viral infection (**Fig. 2**E–G). In some infants, the disease is initially limited to skin, but subsequently becomes apparent in other organ systems, that is, a site of multisystem disease.[17,18]

Central nervous system (CNS): LCH affects the brain in distinct patterns.[19] Infiltration of the pituitary infundibulum may cause posterior pituitary dysfunction, leading

to AVP-D. On MRI, thickening of the pituitary stalk and absence of the posterior pituitary bright spot are observed. AVP-D is usually irreversible once it develops, conferring a lifelong need for desmopressin. Deficiency of hormone(s) produced by the anterior pituitary also occurs, but less commonly. Isolated AVP-D, without lesions outside of the CNS, is caused by neoplastic disease in about half of cases and in about half of these, LCH is the underlying cause. CNS germ cell tumor must be excluded.[20] Pituitary biopsy is sometimes necessary.

LCH-neurodegeneration (LCH-ND) is a poorly understood entity that develops in a small subset of patients years after LCH diagnosis. It is associated with multisystem disease, AVP-D, skull base/orbital bone lesions and presence of *BRAF V600E*.[21] Brain MRI shows symmetric parenchymal lesions of cerebellum and basal ganglia and clinical features, which are highly variable, include dysmetria, ataxia, and cognitive changes. Recently it was shown that brain biopsies of LCH-ND patients demonstrated that *BRAF V600E* monocytes/macrophages were enriched at sites of LCH-ND suggesting that the disease arises from mutated hematopoietic precursors.[22]

Lung: The lung is an uncommon site of disease in children with LCH. In contrast to pulmonary LCH in adults, it is not linked to cigarette smoking. In children, lung involvement occurs always in the context of multisystem disease. Bilateral interstitial infiltrates in a reticulonodular pattern are seen on chest imaging; cystic changes and pneumothorax can be seen. In the absence of involvement of hematopoietic, liver or spleen involvement, it is not an independent adverse prognostic indicator.[23]

Other: Virtually any organ system may be involved in children with LCH. Lymph nodes, thymus and gastrointestinal (GI) involvement are uncommon but well-described sites. GI involvement occurs only in the context of multisystem disease; when RO are also involved it is an added adverse prognostic factor.[24] GI LCH presents with diarrhea, hypoalbuminemia, and failure to thrive. Diagnosis is confirmed on endoscopic biopsy.

TREATMENT

Unifocal LCH: Once the diagnosis of LCH is established and staging is completed, unifocal LCH of the axial and appendicular skeleton is typically managed conservatively; that is, without systemic therapy. Lesions and associated symptoms usually resolve even if complete excision of the lesion has not been accomplished. Instillation of steroid directly into the lesion can alleviate pain and promote healing. LCH involvement of the skull base/orbital bones, referred to in Histiocyte Society trials as “CNS-risk” sites, is associated with higher risk of AVP-D and LCH-ND.[25] For this reason, systemic chemotherapy is usually advised for these patients even though it has not been proven to lower the risk of adverse outcomes.[26] The standard combination of vinblastine and prednisone for 6 to 12 months as in the Histiocyte Society LCH-III protocol may be applied.[27] Isolated cutaneous LCH often resolves without systemic treatment, especially in infants. However, patients should be monitored for at least 2 years for progression to multisystem disease, which develops in about 40%.[18]

Multifocal/multisystem LCH: Systemic therapy is indicated for children with multifocal and multisystem LCH. The standard approach, as defined by the series of multicenter clinical trials conducted by the Histiocyte Society, consists of the combination of prednisone and vinblastine typically for 1 year.[27–29] Several other conventional chemotherapeutic agents, either instead of or in addition to the standard, such as vincristine, cytarabine, etoposide, mercaptopurine, and methotrexate, are active in LCH, but none have proven to be superior in the upfront setting. The standard treatment approach is generally effective and well-tolerated and it is associated with no

significant long-term effects. The vast majority of patients respond to this approach. However, a lower response rate, in the range of about 70%, is observed in patients with RO+ LCH.

Refractory/recurrent LCH: Standard chemotherapy with vinblastine plus prednisone has certain limitations. Some patients, typically those with RO+ multisystem involvement, experience early treatment failure, which is a major risk factor for severe illness and even death. Intensified chemotherapy with clofarabine[30] or cladribine plus cytarabine[31] is effective in some cases. Importantly, the use of MAPK pathway inhibitors has emerged as a promising alternative approach for these patients. *BRAF V600E*+ inhibitors demonstrate remarkable activity in children with *BRAF V600E*+ LCH refractory to chemotherapy.[32,33] For patients lacking the *BRAF V600E* mutation, MEK inhibitor therapy is an option.[34] An important consideration with the use of targeted agents is the relatively high incidence of disease reactivation after drug discontinuation. So far, published data on the use of MAPK inhibitors in pediatric histiocytic neoplasms is very promising but experiential. Results of prospective studies are not available at this time.

After standard first-line chemotherapy, recurrence occurs in approximately 30% to 50% of children with multisystem LCH and long-term consequences (including AVP-D) develop in 20% to 50%.[35,36] Importantly, RO- LCH recurrence is not a life-threatening disease and survival approaches 100%. Optimal treatment of these patients has not been established; options include clofarabine, cladribine, vincristine plus cytarabine,[37] or targeted therapy. Recurrence usually arises within 2 years of initial diagnosis. Some patients experience multiple disease recurrences.[35]

JUVENILE XANTHOGRAULOMA

JXG is the most common of several non-LCH that occur in children. Typically, JXG presents in the first few years of life as single or multiple skin lesions.[38] The true incidence of JXG is not known; it is likely that many cases are not recognized or reported. While most cases are idiopathic, JXG occurs in up to 10% of patients with neurofibromatosis type 1 (NF1).[39]

Pathology/Diagnostic Evaluation

Histologically, JXG appears as a circumscribed nodule of xanthomatous histiocytes with finely vacuolated or foamy cytoplasm and ovoid nuclei without nuclear grooves. Touton giant cells with circumferentially oriented nuclei imparting a wreath-like appearance are a useful diagnostic feature (**Fig. 3**A, B). Mixed inflammatory cells are frequent in the background. By immunohistochemistry, JXG cells are positive for histiocyte markers CD68 and CD163, in rare cases may express partial or weak S100, and do not express CD1a, langerin, or ALK1.[40] Pathologically, JXG resembles ECD, a non-LCH of adults that is extremely rarely seen in children.[41] However, JXG and ECD do not share typical clinical and mutational characteristics.[42] Somatic genomic alterations are not observed in cutaneous JXG in children but they are often detected in extracutaneous/systemic cases.[43,44]

In an otherwise healthy infant presenting with a characteristic, single skin lesion, that is highly suspicious for JXG, biopsy may be deferred. A thorough family history and physical exam should include assessment for stigmata of NF1. In the absence of symptoms or clinical concerns for multifocal or systemic/visceral involvement, radiographic staging evaluation is not advised. However, in patients with symptoms or clinical concerns for extracutaneous JXG, CT or MRI of brain and imaging of chest and abdomen is prudent. The eye is an uncommon but well-described site of

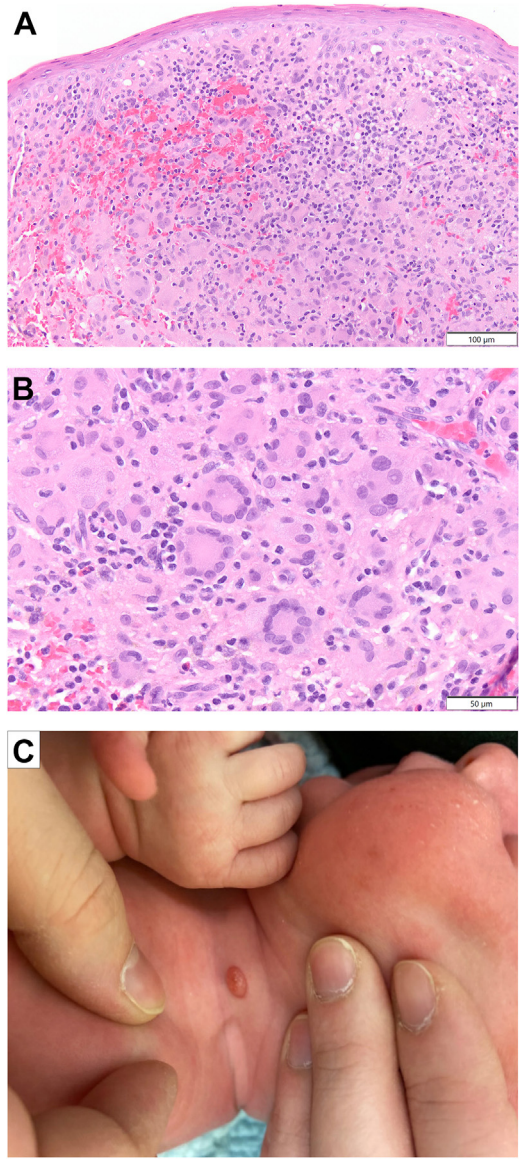

Fig. 3. JXG. (*A*) H&E stain shows a subepithelial nodule of mixed inflammatory cells including frequent histiocytes with ovoid nuclei and abundant pink cytoplasm, admixed with small lymphocytes and giant cells. (*B*) Touton giant cells with concentric peripherally placed nuclei imparting a *wreath-like* appearance, are characteristic of JXG. Histocytes and Touton giant cells typically demonstrate xanthomatous features characterized by fine cytoplasmic vacuolization creating a bubbly cytoplasmic appearance. (*C*) JXG with characteristic yellow-orange dome shaped appearance. (*A*: 40x original magnification. *B*: 400x original magnification.)

extracutaneous JXG, presenting more often than not, as a solitary site. Routine eye examination is not necessary in patients with solitary cutaneous JXG[45] but should certainly be done for patients with multiple skin lesions, ocular symptoms and for patients with CNS or visceral involvement.

Clinical Features

JXG most often presents within the first 2 to 3 years of life as a solitary yellowish-brown firm papule (**Fig. 3**C). Typically, lesions grow, then stabilize in size, then shrink or involute. Residual skin atrophy or discoloration may persist.

Less than 5% of cases of JXG have systemic involvement and about half of patients with systemic involvement have skin lesions. The CNS is most common, but involvement of liver, lung, eye and other organs is reported.[46] CNS involvement is itself variable and may consist of intra-axial tumor or extra-axial, dural-based mass.

Treatment

Most patients with cutaneous JXG do not require treatment. Lesions typically involute and resolve spontaneously. If a lesion is large or in a cosmetically sensitive area, it is reasonable to excise it to minimize permanent disfigurement.

For JXG patients who require treatment, there is no clear standard. In some settings, surgical resection can be curative. When surgery is not an option, clinicians have tended to rely on chemotherapy approaches used for LCH, that is, vinblastine and prednisone as first-line and nucleoside analogs for refractory patients.[47] In the rare instance of aggressive or mutilating, or multisystemic disease, genomic testing performed on lesional tissue may reveal rational targeted treatment options.[48,49]

ROSAI-DORFMAN-DESTOMBES

RDD is an enigmatic and highly variable non-LCH. Only approximately 100 new cases are diagnosed per year in the United States and the mean age at diagnosis is about 20 years. Classically, RDD presents with bilateral cervical lymphadenopathy; 43% of patients present with extranodal disease.[50] MAPK pathway mutations have been detected in a minority of cases.[51] Occasionally, RDD arises in association with an underlying condition such as the Histiocytosis-lymphadenopathy plus syndrome (also known as SLC29A3 spectrum disorder),[52] cancer, or immunologic disorders.

Pathology/Diagnostic Evaluation

Nodal RDD (also known as Sinus Histiocytosis with Massive Lymphadenopathy) demonstrates marked sinusoidal expansion by mixed inflammatory cells including large histiocytes with ovoid atypically enlarged nuclei and prominent nucleoli, and abundant pale cytoplasm. Emperipolesis is a key diagnostic feature of RDD characterized by the presence of intact inflammatory cells (lymphocytes, plasma cells, granulocytes) within the cytoplasm of RDD histiocytes (**Fig. 4**). Extranodal RDD demonstrates histiocytes with identical features present in the background of abundant mixed inflammation which in some cases may mask the presence of the RDD histiocytes, complicating diagnosis. Frequent plasma cells are invariably present and are a diagnostic clue to look for RDD histiocytes. By immunohistochemistry RDD histiocytes express nuclear and cytoplasmic S100 in addition to CD68 and CD168, and do not express CD1a or langerin. In most cases, RDD histiocytes also express strong and diffuse cyclin D1 and OCT2, stains which may be diagnostically helpful.[53,54] As noted above, MAPK pathway alterations including *KRAS* or *MAP2K1* mutations may be detected.[51]

After biopsy, further diagnostic evaluation of a patient with RDD should include thorough history and physical examination in search of an associated disorder. Complete blood count, metabolic panel, measurement of inflammatory markers and chest radiograph should be performed. Additional testing for immune disorders or

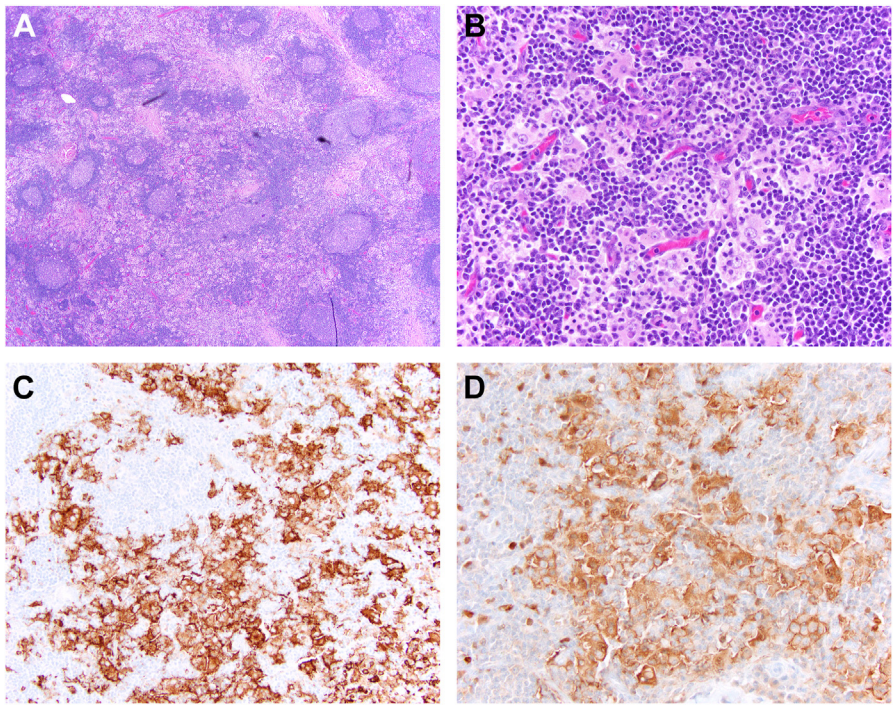

Fig. 4. Rosai-Dorfman disease involving a lymph node. (*A*) The lymph node is enlarged with reactive lymphoid follicles and interfollicular expansion by a mixed inflammatory cell infiltrate including frequent histiocytes and plasma cells. (*B*) The histiocytes are enlarged with atypical large nuclei with vesicular chromatin, prominent nucleoli, and abundant eosinophilic cytoplasm with conspicuous emperipolesis of inflammatory cells including lymphocytes, plasma cells, and granulocytes. By immunohistochemistry the large atypical histiocytes express CD163 (*C*) and S100 (*D*), both of which highlight emperipolesis of inflammatory cells within the histiocyte cytoplasm. (*A*: 40x original magnification. *B, D*: 400x original magnification. *C*: 200x original magnification.)

autoinflammatory conditions should be based on clinical concern. Full body PET scan is advised for staging, accompanied by dedicated anatomic imaging (CT or MRI) of involved areas.

Clinical Features

The classic presentation of RDD is bilateral, "massive," cervical lymph node enlargement. Involved nodes are painless, mobile, and rubbery in texture. Systemic symptoms, that is, fevers, night sweats, and/or weight loss, are sometimes, but not always, present. A wide range of extranodal sites can be seen, including skin/subcutaneous, central nervous system, and bone.

Treatment

Once the diagnosis of RDD is established, no specific treatment is required in up to half of cases, especially those with nodal or skin involvement. Complete surgical resection may be curative but usually is not feasible. For symptomatic patients who do require systemic therapy, there is no established standard. Corticosteroid is typically the first approach and is sometimes effective, at least transiently. Several

chemotherapeutic agents have been used with variable success; options include low-dose methotrexate, mercaptopurine, vinca alkaloids, cladribine, clofarabine. If a targetable MAPK pathway mutation is detected, a targeted agent, that is, MEK inhibitor, should be considered.

ALK-POSITIVE HISTIOCYTOSIS

ALK-positive histiocytosis is a recently described and apparently very rare non-LCH. The disease may involve 1 system, most often the CNS, or multiple systems. Multisystem cases can be subdivided to a group of very young infants with liver and hematopoietic involvement and a group of older children and adults with combination of CNS, bone, lung, liver, skin, and/or lymph node involvement.[55]

Pathology/Diagnostic Evaluation

The lesional histiocytes demonstrate variably epithelioid, spindled, and/or xanthomatous morphology with ovoid to irregular nuclei, and there may be frequent admixed benign mixed inflammatory cells, resulting in histopathology that mimics many other inflammatory and neoplastic processes (Fig. 5). Therefore, when histiocytic lesions are encountered in a child or adolescent a low threshold for ALK immunohistochemical staining is necessary to identify this disorder. The lesional cells express CD68, CD163, and ALK, and do not express CD1a or langerin. ALK immunostaining typically demonstrates a cytoplasmic or less frequently a membranous or Golgi dot pattern, depending on the fusion partner. fluorescence in situ hybridization (FISH) or fusion

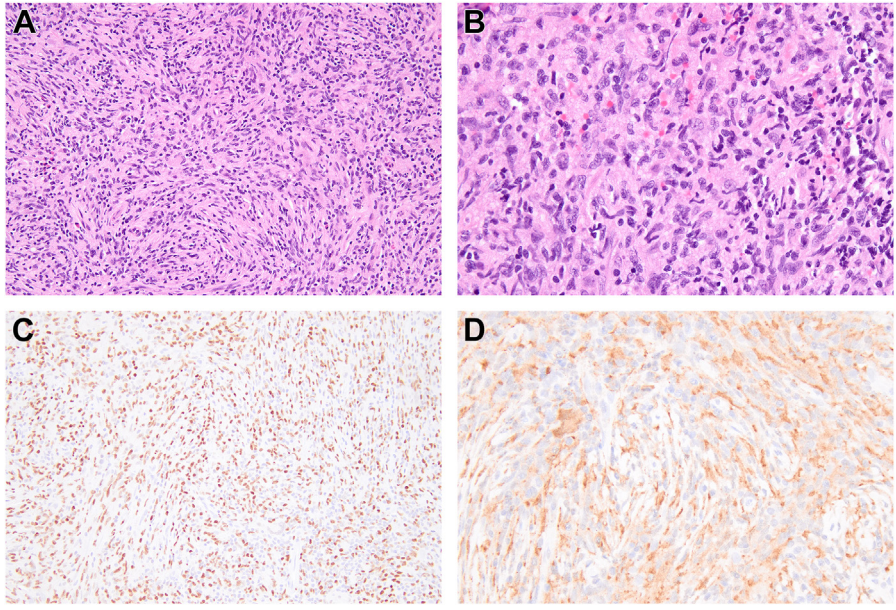

Fig. 5. ALK-positive histiocytosis. (*A, B*) H&E stain demonstrates sheets of spindled to epithelioid cells with ovoid to elongated nuclei, vesicular chromatin, and moderate to abundant pink cytoplasm. The lesional cells express histiocytic markers PU.1 (*C*), CD68 (not shown), and ALK1 (*D*) with a cytoplasmic staining pattern. (*A, C*: 200x original magnification. *B, D*: 400x original magnification.)

analysis is useful to demonstrate the *ALK* rearrangement. The fusion partner is variable with *KIF5B* being the most common, present in the majority of cases.[55,56]

Since ALK-positive histiocytosis is defined by the presence of ALK rearrangement in the appropriate histologic context, biopsy of lesional tissue is key to making this diagnosis. Staging evaluation should include blood counts, liver tests, coagulation studies as well as abdominal ultrasound and imaging of brain. PET/CT scan should be considered in patients over 1 year.

Clinical Features/Treatment

As suggested above, clinical characteristics of ALK-positive histiocytosis are variable and treatment is individualized. Spontaneous resolution is observed in some cases, particularly and paradoxically among young infants with multisystem disease. Conventional chemotherapeutic agents as have been used for other histiocytic neoplasms, have shown variable efficacy. Importantly, recognition of this specific entity has led to the application of ALK inhibitor medications in affected patients and produced dramatically favorable responses.[55]

SUMMARY

Several distinct neoplastic disorders of bone marrow-derived cells of histiocyte lineage occur in children. They range in incidence from rare to extremely rare. The diseases share some characteristics in common: they show predilection for bone, skin, lymph nodes, and CNS and may also involve the bone marrow and liver, leading to hematopoietic and liver dysfunction. Even within the same diagnostic category, disease behavior ranges from self-resolving to life threatening. Clinical research to define best management has been hampered by the rarity and heterogeneity of the diseases. In the case of LCH, standard upfront chemotherapy is reasonably effective. The advent of molecular testing has led to important new advances in understanding the pathobiology of the diseases, especially the relevance of the mitogen-activated protein kinase (MAPK) signaling pathway. This in turn is opening new avenues to develop rational treatments for future exploration.

CLINICS CARE POINTS

- Histiocytic neoplasms are rare and heterogeneous. The relative incidence of specific entities within this group of diseases and the current approach to treatment differs between adults and children.
- LCH is the most common histiocytic neoplasm in children. Histopathology of LCH is consistent and pathologic diagnosis is usually straightforward. LCH is driven by activating mutations in MAPK pathway genes arising in hematopoietic progenitors; BRAFV600E mutation is present in about half of pediatric cases.
- LCH is clinically heterogeneous. Blood tests and imaging studies are used to determine the need for and the duration of systemic treatment.
- Standard-of-care systemic chemotherapy for LCH in children is based on results from clinical trials conducted by the Histiocyte Society. MAPK pathway inhibitors have been shown to be effective in the setting of relapsed/refractory LCH.
- Long-term cure of high-risk LCH and management of LCH-related neurodegeneration are unresolved challenges.
- JXG is the most common non-LC histiocytosis in children. The histopathology and the mutational profile of JXG differ from LCH. MAPK pathway mutations are observed in systemic cases but BRAFV00E is uncommon.

- Most often, JXG affects young children and is limited to skin. Only a small proportion have systemic disease. Treatment of systemic JXG relies on regimens used for LCH. In some cases, molecular testing may reveal rational targeted treatment options.
- Histologically, RDD is characterized by expansion of the lymph node sinus by large histiocytes containing intact inflammatory cells (emperipolesis). Extranodal RDD occurs very rarely. Chemotherapy is not always indicated and there is no established standard.
- ALK+ histiocytosis is a newly-identified, molecularly-defined entity. Clinical presentation and treatment are variable and CNS involvement is often featured. ALK inhibitors have demonstrated efficacy in cases requiring systemic therapy.

DISCLOSURE

None of us have relevant disclosures.

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