Histiocytic Disorders of Childhood

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PRACTICE/EDUCATION GAPS

Pediatric histiocytic disorders present with a wide range of signs and symptoms. Primary care providers play an essential role in early diagnosis and referral, which are essential for optimal outcomes. Most patients with histiocytic disorders also experience long-term sequelae that require collaboration between specialty services and primary care providers.

OBJECTIVES *After completing this article, readers should be able to:*

1. Recognize the clinical signs and symptoms of children presenting with histiocytic disorders (eg, Langerhans cell histiocytosis, juvenile xanthogranuloma, Rosai-Dorfman disease, and hemophagocytic lymphohistiocytosis).
2. Understand concepts of pathogenesis and updated disease classification of pediatric histiocytic disorders.
3. Discuss models of pathogenesis, clinical presentation, diagnosis, and management for pediatric histiocytic disorders.

ABSTRACT

Histiocytic disorders of childhood represent a wide spectrum of conditions that share the common histologic feature of activated or transformed "histiocytes." Langerhans cell histiocytosis (LCH) is the most common, with an incidence of approximately 5 per million children. LCH may be difficult to distinguish from more ubiquitous causes of skin rashes, bone pain, or fever. Current chemotherapy fails to cure more than 50% of children with multifocal disease, and treatment failure is associated with increased risks of long-term sequelae. Somatic activating mitogen-activated protein kinase (MAPK) pathway–activating mutations (most often *BRAF*V600E) have been identified in hematopoietic precursors in patients with LCH. Opportunities to improve outcomes with targeted therapies are under investigation. Juvenile xanthogranuloma (JXG) and Rosai-Dorfman disease (RDD) are less common than LCH and are distinguished by specific histologic and clinical

AUTHOR DISCLOSURE: Drs Eckstein and Picarsic have disclosed no financial relationships relevant to this article. Dr Allen has served as a consultant for SOBI and Atara. Except for emapalumab and hemophagocytic lymphohistiocytosis, no drugs have Food and Drug Administration (FDA) approval for the treatment of pediatric histiocytic disorders. Therefore, unapproved and investigative treatments are discussed.

ABBREVIATIONS

CNS	central nervous system
CT	computed tomography
DI	diabetes insipidus
HLH	hemophagocytic lymphohistiocytosis
IFN-γ	interferon-γ
JXG	juvenile xanthogranuloma
LN	lymph node
LCH	Langerhans cell histiocytosis
LCH-ND	Langerhans cell histiocytosis–associated neurodegeneration
MAPK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
NACHO	North American Consortium for Histiocytosis
PET-CT	fluorodeoxyglucose positron emission tomography–computed tomography
RDD	Rosai-Dorfman disease

features. Recurrent MAPK pathway gene mutations are also identified in JXG and RDD. In many cases, these conditions spontaneously resolve, but disseminated disease can be fatal. Although there has been historic debate regarding the nature of these conditions as inflammatory versus neoplastic, LCH, JXG, and RDD are now considered myeloid neoplastic disorders. In contrast, hemophagocytic lymphohistiocytosis (HLH) is clearly a disorder of immune dysregulation. HLH is characterized by extreme immune activation driven by hyperactivated T cells. HLH arises in approximately 1 child per million and is nearly universally fatal without prompt recognition and immune suppression. Outcomes of treated children are poor, with approximately 60% survival. Emapalumab, which targets interferon-γ signaling, was recently approved for patients with recurrent or refractory HLH, and additional cytokine-directed therapies are under investigation.

INTRODUCTION

Histiocytic disorders of childhood encompass a variety of diseases, including Langerhans cell histiocytosis (LCH), non–Langerhans cell histiocytoses (juvenile xanthogranuloma [JXG] and Rosai-Dorfman disease [RDD]), and hemophagocytic lymphohistiocytosis (HLH). The term *histiocyte* historically referred to tissue macrophages, although we now know that histiocytic disorders include abnormal differentiation and/or function of macrophages, dendritic cells, and their hematopoietic precursors. (1) The classification of histiocytic disorders was originally based on histologic features of lesions and comparison with presumed physiologic counterparts. (2) Advances in the understanding of pathogenic mechanisms have prompted efforts to update classification taking into account cell of origin, somatic mutations, and organ involvement, as well as histology of terminally differentiated histiocytes within lesions (Fig 1). (3)

LANGERHANS CELL HISTIOCYTOSIS

Epidemiology

Historically, the nomenclature of LCH has been complicated with multiple alternative terms, such as *eosinophilic granuloma* (bone lesion), *Hand-Schüller-Christian disease* (pituitary, orbital, and bone lesions), and *Letterer-Siwe disease* (disseminated multifocal disease), that referred to distinct patterns of presentation. (1) Histiocytosis X was proposed as a unifying diagnosis based on common histology and was subsequently updated to LCH based on shared histologic features with epidermal Langerhans cells (Fig 1). (4)(5) LCH is relatively rare, with an estimated 5 cases per 1 million children, a comparable incidence to pediatric Hodgkin lymphoma or acute myeloid leukemia. LCH can occur at any age, including during adulthood, with peak incidence at 1 to 3 years of age and a slight male predominance. LCH does not have a high recurrence rate within families, and it does not seem to be a heritable disease. (6)(7)(8) However, LCH arises more often in children of Hispanic ethnicity and rarely occurs in children of African descent, suggesting that there are some genetic factors that may predispose to disease risk. (9)(10)

Pathogenesis

For decades, the pathogenesis of LCH was uncertain, with frequent debates over whether it was an inflammatory or a neoplastic process. (11) LCH lesions are characterized by $CD1a^+/CD207^+$ histiocytes with characteristic reniform or coffee bean–shaped nuclei surrounded by inflammatory infiltrate, including T cells, myeloid-derived suppressor cells, and variable numbers of eosinophils (Fig 1). (12)(13) Previously, these pathologic cells were thought to derive

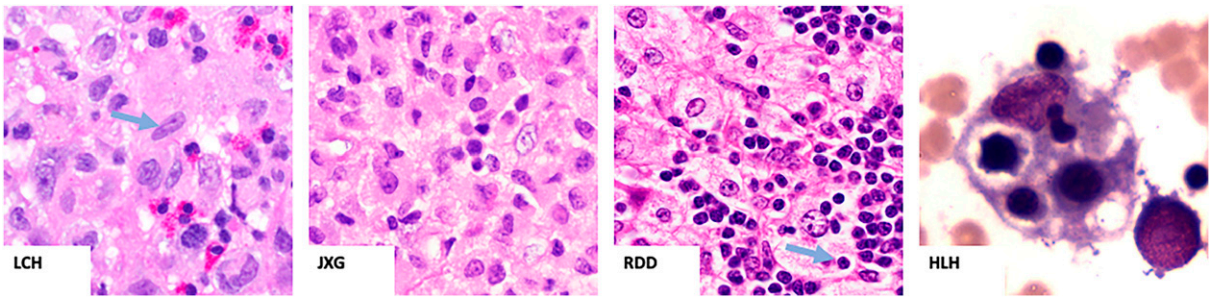

Figure 1. Histology of pediatric histiocytic disorders. Hematoxylin-eosin staining of characteristic histiocytosis lesions (Langerhans cell histiocytosis [LCH], juvenile xanthogranuloma [JXG], and Rosai-Dorfman disease [RDD]) and hemophagocytic lymphohistiocytosis [HLH] bone marrow aspirate are presented. LCH lesion biopsy demonstrates typical reniform (or kidney/coffee bean–shaped) nuclei (arrow). Emperipolesis (viable lymphocytes trafficking through histiocytes) is highlighted in RDD (arrow).

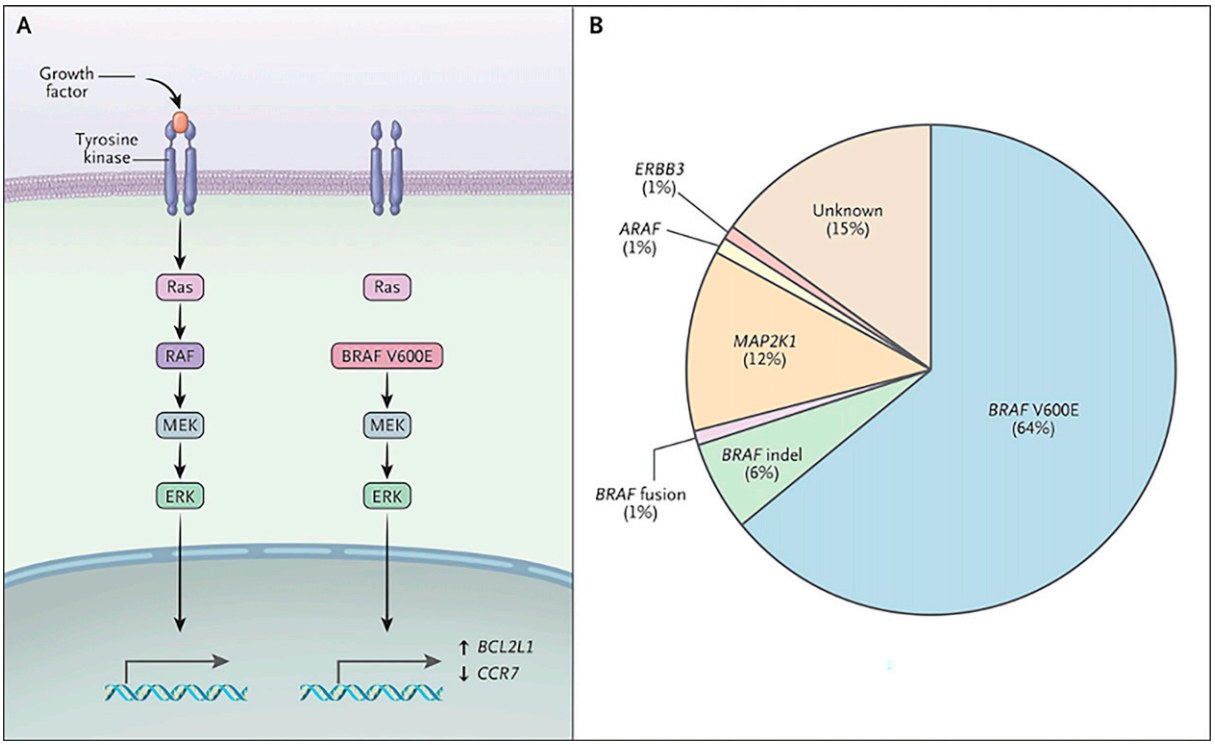

Figure 2. Activating mitogen-activated protein kinase (MAPK) pathway mutations in Langerhans cell histiocytosis. A, Canonical MAPK signaling transduces extracellular signal through receptor tyrosine kinase, which activates Ras, then RAF, then MEK, and then extracellular signal-regulated kinase (ERK) proteins, which, in turn, regulate cell-specific nuclear targets and gene transcription programs. Activating mutations such as *BRAF*V600E drive constitutive ERK activation and downstream transcriptional targets, including *BCL2L1* (upregulated) and *CCR7* (downregulated). B, The proportions of cases with specific activating MAPK mutations in a primarily pediatric series from 1 center. (Reprinted with permission from Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. *N Engl J Med.* 2018;379[9]:856–868.)

from transformed epidermal Langerhans cells due to the common feature of Birbeck granules. (5) Discussions for decades focused on models of pathologic activation versus transformation of epidermal Langerhans cells. In 2010, somatic, clonal *BRAF*V600E mutations were identified in approximately 50% of LCH lesions. (14) Subsequently, mutually exclusive activating mitogen-activated protein kinase (MAPK) pathway gene mutations have been identified in almost all patients with LCH. (1)(15)(16) The most commonly identified somatic mutations are *BRAF*V600E (60%-70% of lesions) and *MAP2K1* (encodes MEK1, 10%-15% of lesions) (Fig 2). In addition, circulating tumor cells with *BRAF*V600E have been found in peripheral blood and bone marrow of patients with disseminated disease. (17) MAPK activation drives differentiation of precursor cells, traps pathogenic cells in lesions with downregulation of the chemokine CCR7 that is required for trafficking of physiologic dendritic cells to lymph nodes (LNs), and activation of a senescence program, rendering cells resistant to cell death and promoting local and systemic inflammation. (13)(18)(19) Identification of clonal hematopoietic precursors with activating MAPK pathway somatic gene mutations has created a paradigm shift in the understanding of this disease, now recognized as a myeloid neoplasm by the National Cancer Institute. Pathologic MAPK activation is clinically relevant, offering potential therapeutic strategies (eg, BRAF-V600E inhibitors or MEK inhibitors).

Clinical Presentation

LCH can mimic much more common diseases in childhood, making it a popular contribution to morning report differential diagnosis lists (Fig 3). It is, therefore, challenging for general pediatricians in practice to maintain a high index of suspicion given the relative rarity of this disease and its broad range of clinical presentations. Signs and symptoms of LCH can easily be mistaken for alternative neoplasms, skin conditions, infections, autoimmune diseases, or endocrine disorders. Clinically, LCH is categorized as single lesion, multifocal low risk, or multifocal high risk. Low or high risk refers to risk of death associated with LCH lesions in the liver, spleen, and/or bone marrow (Fig 3 A–C). (20) Central nervous system (CNS) risk lesions are associated with increased risks of developing diabetes insipidus (DI) and LCH-associated neurodegeneration (LCH-

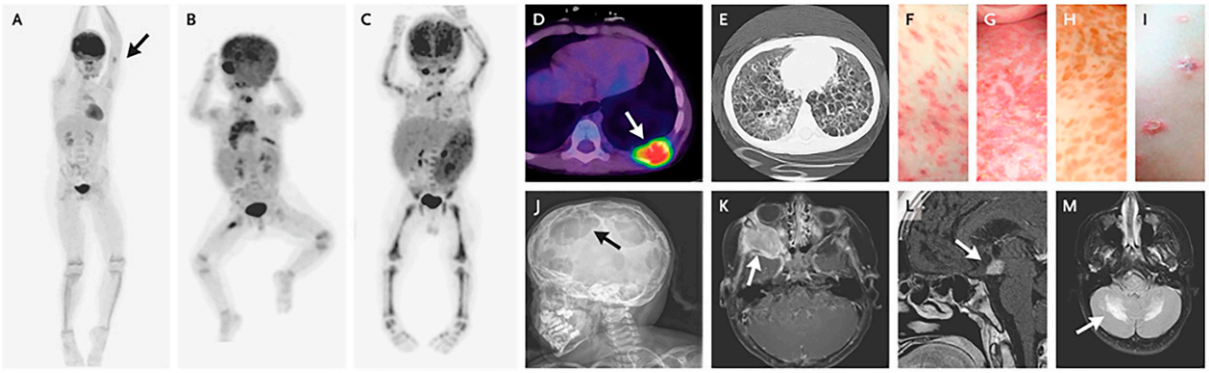

Figure 3. Clinical spectrum of Langerhans cell histiocytosis (LCH). Positron emission tomographic images show a single bone lesion involving the humerus (A); low-risk lesions involving the orbit, lymph nodes, bone (multifocal lesion), and thymus (B); and high-risk lesions involving the liver, spleen, and bone marrow (C). Other classic presentations include a lytic bone lesion (D), cystic lung lesions (E), and various skin lesions (F–I). Examples of LCH lesions involving the skull and brain include multifocal skull lesions (J), an orbital lesion (K), a pituitary lesion (L), and LCH-associated neurodegeneration (M). (Reprinted with permission from Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. *N Engl J Med*. 2018;379[9]:856–868.)

ND). (21)(22) Specific sites of disease and associated clinical signs and symptoms are discussed later herein.

Bone Disease. Bone lesions are the most common type of LCH, presenting in approximately 75% of patients. LCH can involve any bone, but the most common sites are the skull, long bones, ribs, pelvis, and vertebrae. Bone lesions can present with pain or decreased use of an extremity, or may be asymptomatic. Radiography and computed tomography (CT) will show osteolytic, expansile bone defects (Fig 3 A and J). Skull lesions often present with headaches, swelling, or palpable indentations sometimes noticed by parents when washing their child's hair. Vertebral bone involvement may result in vertebra plana (flattening of the vertebral body), which may reflect active disease or bone damage from previous lesions. Mastoid bone disease is often bilateral and usually presents with chronic or recurrent otorrhea/otitis externa, a mass in the ear canal, or decreased hearing that may be confused with chronic otitis media or otitis externa. Maxillary bone disease may present with gingival bleeding or hypertrophy, pain with mastication, loose or "floating" teeth on radiography, and/or premature eruption of teeth in infants. Orbital bone disease is typically unilateral and can present with pain, periorbital swelling, or proptosis and may be confused with rhabdomyosarcoma or infections (Fig 3K).

Skin. Approximately 40% of patients with LCH have skin involvement. LCH can be challenging to diagnose due to variable appearance and distribution that is easily confused with chronic or recurrent rashes in infants and children, especially in infants with seborrheic dermatitis ("cradle cap") or persistent diaper rash. Whereas the most common early-onset or congenital form of skin LCH often appears scaly and bears a resemblance to eczema or candida, LCH lesions can also have a waxy, papulonodular, vesicular, or purpuric/petechial appearance (Fig 3 F–I). Skin biopsy is required to make the diagnosis. Congenital self-healing reticulohistiocytosis (also known as Hashimoto-Pritzker disease) with LCH limited to the skin may self-resolve over time, but approximately 50% of infants with LCH skin lesions have systemic LCH. Therefore, we recommend that all infants with skin disease undergo complete staging evaluation by a pediatric oncologist to ensure that they do not have other sites of disease, which could be life-threatening and may require treatment with systemic chemotherapy.

Lymph Nodes. Approximately 20% of patients with LCH will present with lymphadenopathy, most frequently affecting the cervical LNs, although mediastinal lymphadenopathy and thymic disease can also occur and cause superior vena cava syndrome or orthopnea related to compression of large thoracic vessels or airways, respectively. Notably, physiologic LCs and $CD207^+$ dermal dendritic cells traffic from skin to LNs as part of immune responses. Therefore, isolated LN involvement should be confirmed by pathologists with experience evaluating histiocytic disorders.

Risk Organs: Bone Marrow, Liver, and Spleen. LCH may infiltrate bone marrow, inducing cytopenias, or in some cases may induce macrophage-activating syndrome, leading to extreme inflammation meeting the criteria for HLH. (23) Notably, clonal hematopoietic precursors and LCH cells in bone marrow may not express CD207 but may maintain a less differentiated mononuclear phenotype or skew toward macrophage differentiation ($CD163^+$). (12)(24) Liver disease usually presents with abnormal hepatic function, resulting in a combination of elevated alkaline phosphatase,

aspartate aminotransferase, alanine aminotransferase, γ-glutamyl aminotransferase, and bilirubin levels, but it can also cause hypoalbuminemia with ascites/effusions and abnormal synthetic function. Patients with liver disease can have hepatomegaly with or without circumscribed tumors, and imaging typically shows diffuse or localized hypermetabolic activity on fluorodeoxyglucose positron emission tomography–CT (PET-CT) (Fig 3C). Liver disease is often more resistant to treatment than LCH involving other organ systems and in extreme cases may progress to sclerosing cholangitis requiring liver transplant. As with bone marrow, LCH cells may not express characteristic $CD207^+$ in liver, but in some cases, mutated cells can be identified with antibody against *BRAF*V600E or with polymerase chain reaction. Involvement of the spleen is sometimes difficult to assess, but lesions may be identified by splenomegaly on physical examination and/or by imaging with ultrasonography, CT, or PET-CT. If splenomegaly is severe, patients can develop secondary respiratory insufficiency and/or consumptive cytopenias; splenectomy is generally avoided except for very rare cases.

Lungs. Although pulmonary LCH can cause life-threatening complications, the lungs are no longer considered a risk organ because recent clinical trials have not associated pediatric lung LCH with increased risk of death. (25) Approximately 5% to 10% of children with LCH have lung disease, which usually presents with a chronic dry cough, chest pain, or dyspnea on exertion. Pulmonary LCH is a fairly common cause of spontaneous pneumothorax, and patients are at high risk for recurrent pneumothoraces until the disease is under control with systemic therapy. Imaging with high-resolution CT, ideally combined with PET, usually shows characteristic features with multiple nodular and cystic areas in the upper and mid-thoracic regions (Fig 3E). It is usually not necessary to obtain bronchoalveolar lavage and diagnostic biopsy to confirm lung involvement if LCH has been proved at another site of disease. (26)

CNS and Pituitary. The CNS and pituitary can be affected by LCH at the time of diagnosis or as later events, sometimes years after systemic presentation. Patients who have CNS risk lesions (orbit, mastoid, temporal, maxilla, ethmoid, sphenoid, clivus) seem to have a higher risk of eventually developing LCH-ND, even years after apparent remission. Neurodegenerative LCH can have significant effects on cognition, behavior, balance/coordination, and speech/swallowing abilities and may cause severe disabilities in previously developmentally normal children. Diagnosis of LCH-ND is based on careful history and physical examination, prompting magnetic resonance imaging (MRI) of the brain with contrast. T2-weighted MRI typically shows distinct bilateral enhancing symmetrical lesions most often in the cerebellum, basal ganglia, dentate nucleus, and pons, which usually correspond with clinical signs and symptoms, but in some cases may be observed in patients without (or before) development of clinical symptoms (Fig 3M). (22) Screening MRI may, therefore, be helpful in patients at risk for LCH-ND after completion of chemotherapy. Rare brain biopsies of patients with LCH-ND demonstrate clonal (*BRAF*V600E^+) microglia-like cells with perivascular concentration, suggesting hematopoietic origins. (27)

The pituitary may be infiltrated by LCH (10%-20% of cases) and can result in central DI by damaging the posterior pituitary's ability to produce antidiuretic hormone, as well as cause anterior pituitary hormone deficiencies (Fig 3L). In most cases, endocrinopathies persist after treatment, although some patients may recover partial or full antidiuretic hormone levels. Patients presenting with DI without a surgically accessible mass should have full staging evaluation for LCH because more easily accessible tissue for biopsy may be discovered. Differential diagnosis of isolated DI also includes germinoma and pituitary hypophysitis.

Gastrointestinal System/Mucosa. Although uncommon and affecting only approximately 2% to 3% of patients, LCH lesions are occasionally observed in the gastrointestinal system, anywhere from the mouth through the anus. Patients may present with ulcers in the mouth, diarrhea, failure to thrive due to malabsorption, or hematochezia with anemia. Colonoscopy and/or endoscopy may be informative for patients with unexplained nutritional deficiencies or hypoalbuminemia.

Diagnostic Evaluations

Diagnostic Biopsy. As with other neoplasms, biopsy of a suspected LCH lesion is an essential step in determining the diagnosis. Referral to a pediatric oncologist may be helpful when LCH is suspected to expedite imaging and diagnostic biopsy. In an institutional series, median time to diagnostic biopsy in children with LCH skin lesions exceeded 3 months. (28) Clonal histiocytes with surface expression of CD1a and CD207 with characteristic histology and patterns of presentation are typically considered diagnostic for LCH (Fig 1). (28) Mixed histiocytic lesions may include cells with a phenotype characteristic of LCH ($CD1a^+$/$CD207^+$) admixed with cells with other histiocytic diagnoses, such as JXG ($CD163^+$/$CD14^+$/factor $XIIIa^+$). (3)

Extent of Disease. Staging of patients includes an extensive history and review of systems and a thorough physical examination. History of otorrhea or recurrent/chronic otitis, hearing/speech problems, abnormal gum bleeding/

unusual teeth issues/oral ulcers, headaches, bone pain, limp, chest pain, orthopnea, diarrhea, abnormal bleeding/bruising, abdominal distention, polyuria/polydipsia, growth delay/failure to thrive, ataxia, recurrent diaper rash or cradle cap, chronic cough, or respiratory symptoms can inform sites and duration of disease. Laboratory testing can indicate bone marrow infiltration (complete blood cell count with differential count), liver involvement (aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, γ-glutamyl aminotransferase), and systemic inflammation (erythrocyte sedimentation rate, C-reactive protein). When LCH is suspected, a skeletal survey may identify bone lesions. Once diagnosed, we typically obtain baseline imaging to define extent of disease, including PET-CT and brain MRI in cases with clinical concern for CNS involvement. We perform bone marrow biopsy for all patients younger than 2 years or with other risk organ (eg, spleen or liver) involvement due to a higher likelihood of bone marrow disease in these patients.

Treatment

Treatment for LCH depends on the extent of disease. For single bone lesions, curettage and/or corticosteroid injection may be sufficient. Skin-limited disease in infants is thought to arise from an embryonic precursor. Without a renewable precursor, these lesions typically resolve spontaneously over several months. For clinically severe skin-limited lesions, topical corticosteroids or low-dose chemotherapy (eg, oral methotrexate or hydroxyurea) may improve symptoms. (29) Patients with multifocal disease typically require systemic chemotherapy. Histiocyte Society trials over the past decades have tested various empirical therapies, and the LCH-III trial has established vinblastine and prednisone for 1 year (plus mercaptopurine for high-risk patients) as the current standard of care. Overall survival was nearly 100% for patients with low-risk disease. However, improvements are needed because approximately 10% of high-risk patients still die of their disease. The LCH-III approach failed to cure more than 50% of patients, (25) and treatment failure in both high- and low-risk patients is associated with increased risks of long-term sequelae, including LCH-ND. (30) Data to guide therapy after first relapse are largely limited to case studies. Nucleoside analogues (cytarabine, cladribine, clofarabine) have activity in LCH, with higher cure rates (and higher toxicity) with increasing doses. (31) Hematopoietic cell transplant can be curative in highly refractory cases. (32) The central role of somatic activating mutations in MAPK pathway signaling in LCH pathogenesis has generated interest in evaluating potential therapeutic benefit of MAPK inhibition. Early-phase studies with adults demonstrate very high response rates to BRAF-V600E inhibition (in patients with *BRAF*V600E mutations) and MEK inhibition (applied broadly). (33)(34)(35)(36)(37) However, disease typically recurs with cessation of therapy. (37) Pediatric series report similar high response rates and relapse with therapy cessation. (38)(39) Clinical trials are ongoing to optimize frontline chemotherapy (LCH-IV: 1 vs 2 years of vinblastine/prednisone [NCT02205762]; LCH REASON: 1 year of vinblastine/prednisone vs 1 year of cytarabine monotherapy [NCT02670707]; and, to optimize salvage therapy, North American Consortium for Histiocytosis [NACHO]-COBI: 1 year of cobimetinib [MEK inhibitor] monotherapy [NCT04079179]). In the United States, the NACHO and the Children's Oncology Group have dedicated efforts underway to continue to improve outcomes for children with LCH through clinical risk stratification and development of novel therapeutic strategies.

NON–LANGERHANS CELL HISTIOCYTOSES

Juvenile Xanthogranuloma

The true incidence of JXG is not well-defined, but it most commonly develops in young children. In a large national registry, JXG was approximately 15% as frequent as LCH. (40) As with LCH, activating mutations in the MAPK pathway have been identified in JXG. (16) Interestingly, children with neurofibromatosis-1 have an increased risk of developing JXG, likely influenced by *NF1*-driven MAPK pathway activation. BRAF-V600E has been noted in the context of CNS-JXG–based lesions. (41) Cases with *ALK* fusions may be separately categorized as *ALK*-related histiocytosis. (28) Most JXG (>80%) arises as skin-limited lesions in children younger than 2 years. Characteristic histologic features of JXG include histiocytes with foamy cytoplasm and Touton giant cells (large cells with nuclei organized in a peripheral wreath-like pattern); however, many different histologic patterns may be observed (Fig 1). Immunohistochemical analysis identifies expression of CD163, CD14, fascin, and factor XIIIa. The cutaneous form of JXG typically presents as a nodular yellow to red-purple papule and is most often confused with molluscum contagiosum. Although JXG lesions are usually limited to the skin and mucosa, lesions can arise in virtually any organ, and systemic signs and symptoms reflect extent of lesion involvement. We recommend referral of patients with a diagnosis or suspicion of JXG to an oncology subspecialist for comprehensive evaluation, which may include laboratory evaluations, PET-CT, and brain MRI if there is concern for systemic or CNS lesions (Fig 4 A–C). Patients who have disease limited to the skin are typically observed long-term with the guidance of an oncologist to monitor for development of systemic disease. However, patients

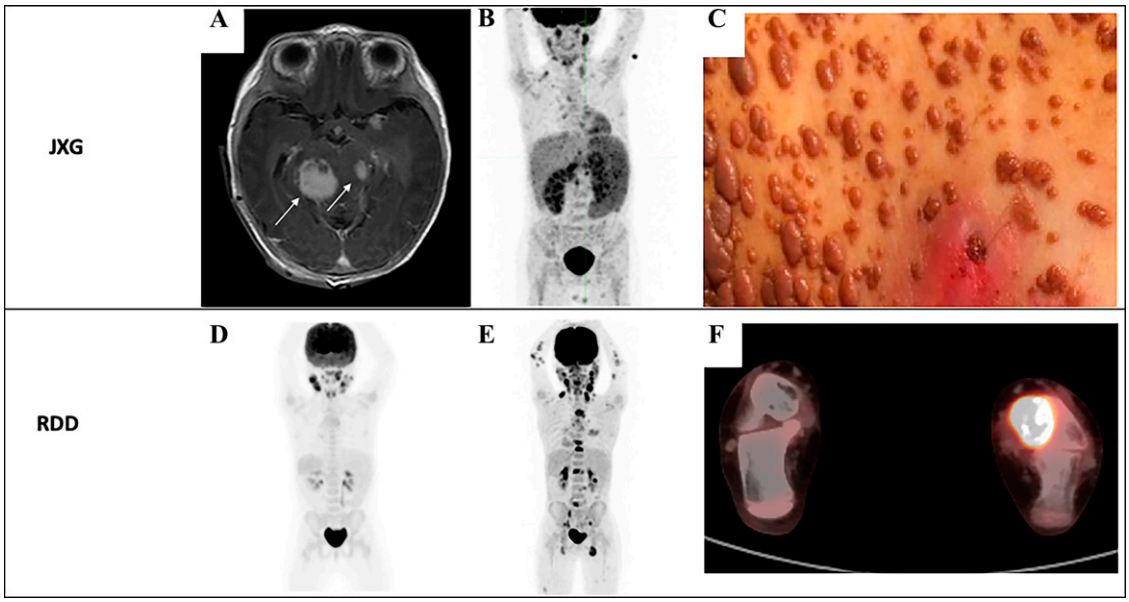

Figure 4. Clinical features of pediatric juvenile xanthogranuloma (JXG) (top) and Rosai-Dorfman disease (RDD) (bottom). A, Brain magnetic resonance image shows JXG brain lesions (arrows). B, Fluorodeoxyglucose positron emission tomography–computed tomography (PET-CT) scan shows a patient with disseminated JXG: cervical and supraclavicular hypermetabolic lymph node and diffuse splenic involvement. C, Photograph of a young woman with severe JXG skin lesions. PET-CT scans show classic RDD with significant but limited cervical lymphadenopathy (D), more disseminated RDD with lymphadenopathy in several lymph node regions (E), and osseous RDD lesion in the left medial malleolus and talus (F).

with severe cutaneous disease, systemic organ disease, or brain involvement require treatment with chemotherapy. Evidence supporting specific therapeutic strategies is limited to case series, with some successful experiences with LCH-based therapy, including clofarabine. (42)(43) Safety and efficacy of MAPK pathway inhibition with cobimetinib for JXG is currently being tested in NACHO-COBI.

RDD (Sinus Histiocytosis with Massive Lymphadenopathy)

RDD, also known as Rosai-Dorfman-Destombes disease, also known as sinus histiocytosis with massive lymphadenopathy, is a relatively rare histiocytic disorder that typically affects LNs. Approximately 100 new cases arise in the United States annually, at a median patient age of 21 years. RDD is most common in males and individuals of African descent. Activating mutations in MAPK pathway genes have been described in many cases of RDD, but MAPK hyperactivation may not be a universal feature. (16)(44) RDD has also been associated with inherited mutations in *TNFRSF5* (encodes FAS) associated with autoimmune lymphoproliferative syndrome. (45) Germline mutations in *SLC29A3* have been reported in patients with familial RDD. (46) RDD may present in the setting of other hematologic malignancies or autoimmune diseases. A specific association has been reported with IgG4-related disease and RDD. (45)(47) Compared with other histiocytic disorders, RDD may represent a common histologic end point from a range of pathogenic mechanisms.

Classic clinical presentation is bilateral, massive, and painless lymphadenopathy. (48)(49) Extranodal lesions arise in slightly less than half of RDD cases with signs and symptoms related to organs involved (Fig 4 D–F). Patients with more extensive disease often present with overlapping features with lymphoma, with elevated inflammatory markers (erythrocyte sedimentation rate), hypergammaglobulinemia, and "B" symptoms (fever, night sweats, weight loss). RDD is defined histologically by LNs with sinusoids and interfollicular regions massively enlarged by large pale-staining histiocytic cells by hematoxylin-eosin with characteristic immunostaining patterns ($CD1a^-$, $CD207^-$, $CD68^+$, $CD163^+$, $fascin^+$, $OCT2^+$, $CD68^+$, $CD163^+$), large and rounded hypochromatic nuclei, and often with the feature of emperipolesis, a phenomenon of intact viable lymphocytes and plasma cells trafficking through histiocytes (Fig 1). (28) RDD may be self-limited and can be followed by observation. Even in some dramatic clinical presentations, lymphadenopathy may resolve spontaneously over time (sometimes years). In one series, 7% of patients died of RDD, with multifocal extranodal disease as a risk factor. (49)(50) Lesions and lymphadenopathy typically respond transiently to corticosteroid therapy, which may be required in rare cases of airway compression or other emergencies. LCH-directed therapy (eg, vinblastine/prednisone or clofarabine) may be effective in some cases. (43)(49) MAPK pathway inhibitors have also been effective in some adult patients with RDD with MAPK-activating mutations.

Table. HLH-2004 Criteria

A molecular diagnosis consistent with HLH (eg, pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*)
OR
5 of the following 8 criteria are fulfilled:
1. Fever (≥100.9°F [≥38.3°C])
2. Splenomegaly
3. Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood): Hemoglobin, <9 g/dL (<90 g/L) (in infants aged <4 wk: hemoglobin, <10 g/dL [<100 g/L]) Platelets, $<100\times10^3$/mL Neutrophils, $<1\times10^3$/mL
4. Hypertriglyceridemia (fasting triglycerides, ≥265 mg/dL [≥2.99 μmol/L]) and/or hypofibrinogenemia (fibrinogen, ≤150 mg/dL [≤1.5 g/L])
5. Hemophagocytosis in bone marrow or tissue
6. Low or absent natural killer cell activity
7. Ferritin, >500 ng/mL (>500 μg/L)[a]
8. Elevated soluble CD25 (soluble interleukin-2 receptor alpha)[b]

HLH=hemophagocytic lymphohistiocytosis.
[a]Although the HLH-2004 protocol uses a ferritin level greater than 500 ng/mL (>500 μg/L), we generally view a ferritin level greater than 3,000 ng/mL (>3,000 μg/L) as concerning for HLH and a ferritin level greater than 10,000 ng/mL (>10,000 μg/L) as highly suspicious.
[b]Elevations above age-adjusted, laboratory-specific normal levels (defined as >2 SD from the mean).

(36) Treatment for RDD in the setting of malignancy or autoimmune disease is typically directed at the associated condition.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

HLH is a syndrome of excessive inflammation that is associated with inherited defects in cytotoxic lymphocyte function. Histologically, HLH is characterized by hemophagocytosis, or macrophages ingesting red blood cells (as well as lymphocytes and neutrophils) (Fig 1). However, this phenomenon is neither sensitive nor specific for HLH. Notably, HLH is typically driven by T-cell activation, with the hemophagocytic histiocyte as a downstream indicator of extreme immune activation. HLH, unlike the other conditions discussed in this section, is a syndrome of immune dysregulation and not a myeloid neoplastic disorder. (3)(51)

HLH is a major clinical challenge. A typical presentation is a previously healthy infant or toddler who develops persistent fever and multisystem organ failure over hours to weeks. Approximately 60% of patients meeting diagnostic criteria for HLH die, and timely diagnosis and treatment are essential for a chance at cure. Initial signs and symptoms overlap with other conditions in critically ill children. Furthermore, confounding diagnoses, such as infections, autoimmune disease, and malignancy, do not necessarily exclude concurrent diagnosis of HLH. Patients may also develop CNS inflammation (as an isolated finding or along with systemic inflammation) characterized by focal neurologic deficits, seizures, MRI findings, and/or pleocytosis in CSF.

The incidence of familial HLH is estimated to be approximately 1 per 1.2 million children. (52) At our institution, we estimated 1 of 3,000 inpatient admissions to be diagnosed as having HLH. (53) The first case of what is now recognized as familial HLH was reported in 1952, with 2 siblings who developed rapid onset of fatal fever and hepatosplenomegaly. (54) In 1999, defects in *PRF1* (encoding perforin) were discovered as the first inherited gene defect underlying HLH. Before this discovery, consensus criteria for the HLH-94 clinical trial were established, which continue to serve as de facto diagnostic criteria (with some modifications for the HLH-2004 trial) (Table). Although these criteria have not been validated, they are frequently used as de facto diagnostic criteria for HLH, with at least 5 of 8 criteria supporting the diagnosis. Although no single diagnostic criterion is sufficient to make a diagnosis of HLH, a highly elevated serum ferritin level (>10,000 mg/L) is a sensitive biomarker for HLH in children, and simultaneously elevated soluble interleukin-2 receptor alpha and/or chemokine ligand 9 levels increase the specificity for this diagnosis. (53)(55)

In addition to the clinical and laboratory features described previously herein, proven pathogenic variants in familial HLH–associated genes that regulate cytotoxic function in natural killer and T cells (eg, *PRF1, UNC13D, STXBP2, STX11, STXBP, RAB27A, LYST, AP3B1, SH2D1A,* and *XIAP/BIRC*) can identify a genetic predisposition to developing HLH. We envision HLH as a syndrome of extreme immune activation that can arise in several settings, including inherited predisposition and/or persistent or intense immune challenges that drive pathologic inflammation characterized by exuberant interferon-γ (IFN-γ) pathway activation. (56)(57) Whole exome sequencing of an institutional series of children that met the diagnostic criteria for HLH revealed a high frequency (>50) of pathogenic germline variants associated with a broad range of immune disorders. (58) In addition, infection, malignancy,

and autoimmune disease can drive symptoms of HLH in patients with historically normal immune function. Such cases are frequently referred to as secondary HLH, although the lines between familial and secondary may be blurred. We favor the nomenclature of HLH due to X. "X" can include inherited and/or acquired factors.

Before conceptualization of HLH syndrome and treatment with immune-modulating therapy, almost no children with HLH survived. (59) The Histiocyte Society HLH-94 protocol tested immune suppression strategy with a combination of corticosteroids and etoposide, followed by hematopoietic cell transplant. The overall estimated 3-year survival on this protocol was 55%, and a follow-up study (HLH-2004) adding early use of cyclosporine was not statistically superior. We, therefore, consider HLH-94 to be a current standard of care for frontline therapy for HLH. (51)(60)(61) The addition of rituximab may be helpful for patients with HLH associated with Epstein-Barr virus infection that localizes to B lymphocytes. Emapalumab, a human antibody against IFN-γ, was recently approved by the Food and Drug Administration (FDA) for the treatment of recurrent and refractory HLH. In a pivotal prospective trial, responses were observed in 63% of patients receiving emapalumab as salvage therapy. (62) Ruxolitinib, which blocks JAK/STAT signaling that also affects IFN-γ signal transduction, is currently being tested in pediatric HLH (NACHO-RUXO [NCT04551131]). The journey of children and young adults with HLH from diagnosis to disease control to cure with hematopoietic cell transplant (where indicated) is complicated and potentially treacherous. Clinical suspicion and screening by frontline providers are important for these patients to have a chance at survival, with referral to specialty centers with experience treating HLH and comprehensive critical care services.

Summary

- Based on consensus as well as observations during the conduct of research studies, histiocytic disorders present with a wide range of clinical signs and symptoms that can mimic more common disorders. To improve outcomes for patients, a high index of suspicion is required to promptly identify an accurate diagnosis and initiate appropriate therapy. (1)(49)(51)
- Based on strong translational research data, the recent discovery of hematopoietic precursors with activating mitogen-activated protein kinase pathway gene mutations defines Langerhans cell histiocytosis (LCH), juvenile xanthogranuloma, and Rosai-Dorfman disease as myeloid neoplastic disorders. (1)(3)15)(16)(17)
- Based on results of randomized clinical trials, the current standard for frontline therapy for LCH based on randomized phase 3 clinical trials is 1 year of therapy with vinblastine/prednisone (mercaptopurine for high-risk LCH). However, outcomes with this approach remain suboptimal, and continued research is needed. (1)(25)(31)
- Based on early-phase clinical data and retrospective studies, early-phase trials in adults and pediatric case series demonstrate high response rates of LCH and related disorders to mitogen-activated protein kinase pathway inhibitors, although patients have been observed to relapse with cessation of therapy. (34)(35)(36)(37)(38)(39)
- Based on observational reports (case series and case reports) and expert consensus, juvenile xanthogranuloma and Rosai-Dorfman disease may spontaneously regress. However, disseminated disease may be life-threatening and require chemotherapy or targeted therapy. (40)(43)(49)
- Based on observational studies (case series) and expert consensus, hemophagocytic lymphohistiocytosis (HLH) is almost universally fatal without prompt recognition and therapy. (51)(59)
- Based on nonrandomized prospective trials and expert consensus, the current standard for frontline therapy for HLH is based on the HLH-94 trial (dexamethasone/etoposide). (51)(60)(61)
- Based on nonrandomized prospective trials, HLH may be driven by interferon-γ pathway activation. Emapalumab, a monoclonal antibody that blocks interferon-γ signaling, has recently been approved by the Food and Drug Administration (FDA) for relapsed and refractory HLH. (56)(62)

Acknowledgments

The authors thank the Texas Children's Cancer and Hematology Centers Histiocytosis Program from the HistioCure Foundation and the St. Baldrick Foundation Innovation Grant (Dr Allen) for their support. In addition, the North American Consortium for Histiocytosis is supported by the St. Baldrick Foundation and the Leukemia & Lymphoma Society. Dr Eckstein has also received support from the Pediatric Oncology Clinical Research Training Program (grant K512CA090433).

References and teaching slides for this article can be found at https://doi.org/10.1542/pir.2021-005367.

PIR QUIZ

1. An 18-month-old boy is brought to the physician with a 4-week history of drainage from the left ear. He has been treated with high-dose amoxicillin without improvement. He has swelling behind the left ear and around his right orbit. On physical examination, a nontender swelling is noted in the left mastoid. A skull radiograph shows multiple osteolytic lesions, including the bones around the orbits. A biopsy is obtained and reveals Langerhans cell histiocytosis (LCH). A mutation is most likely to be found in which of the following genes?

   A. *BRAF*V600E.
   B. FXN.
   C. PAX3.
   D. P53.
   E. RB1.

2. A 3-year-old boy with LCH involving the orbit, maxilla, temporal bone, and pituitary is being treated with chemotherapy including vinblastine and prednisone. He is at increased risk for which of the following complications?

   A. Cardiac failure.
   B. Hepatic involvement.
   C. Neurodegenerative disease.
   D. Pulmonary toxicity.
   E. Skin involvement.

3. A 2-year-old girl is seen in your office with a history of recurrent otitis media, a persistent diaper rash, and recent onset of increased urination and thirst. You suspect LCH and obtain a biopsy of the skin lesions. Which of the following findings is most likely to confirm your suspicion?

   A. Lack of INI staining.
   B. Surface expression of CD1A.
   C. Surface expression of CD10.
   D. Surface expression of CD15.
   E. Surface expression of CD163.

4. A 1-year-old boy is found to have 2 yellowish-to-red rubbery papules on the skin of the trunk. He has been well and has no other symptoms. He is referred to a dermatologist, who performs a biopsy that reveals juvenile xanthogranuloma. An evaluation by a pediatric oncologist does not show any other skin lesions or metastatic disease. Which of the following is the most appropriate initial treatment for this patient?

   A. Focal radiotherapy.
   B. Observation.
   C. Surgical removal.
   D. Topical chemotherapy.
   E. Topical corticosteroids.

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5. An 8-month-old boy is admitted to the hospital with recurrent fever to a temperature of 102.2°F (39°C) for the past 2 to 3 weeks. He has had fatigue and poor appetite. On physical examination he has a temperature of 102.6°F (39.2°C), heart rate of 120 beats/min, blood pressure of 90/54 mm Hg, and respirations of 25 breaths/min. He appears ill. His examination is positive for clear lungs, with normal cardiac examination findings. He is noted to have a palpable liver, and his spleen is palpated 2 to 3 cm below the left costal margin. There is scattered bruising. Initial laboratory studies show a white blood cell count of 3,000/μL (3.0×10^9/L) with 15% neutrophils, hemoglobin level of 8.5 g/dL (85 g/L), and platelet count of 50,000/μL. A bone marrow biopsy is performed and does not show evidence of leukemia but reveals decreased cellularity and macrophages with hemophagocytosis. Additional laboratory studies show an alanine aminotransferase level of 150 U/L (2.5 μkat/L), C-reactive protein level of 20 mg/dL (20 mg/L), and ferritin level of 8,000 ng/mL (8,000 μg/L). The child is begun on intravenous cefepime after blood cultures are obtained. The mother then informs you that they had had a previous child who died suddenly of a similar disorder several years before the birth of this child. No specific diagnosis was made on that child. This patient is most likely to have a mutation in which of the following genes?

   A. ELANE.
   B. FANCA.
   C. PRF1.
   D. P53.
   E. SBSD.