



Review Article



Pediatric Histiocytic Disorders: Morphology, Immunophenotype, and Genetics

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Abstract

Histiocytic disorders are rare in childhood and often present with a wide spectrum of histological and clinical symptoms, making their diagnosis challenging. The pathological classification of histiocytic disorders has been evolving during the last few decades, and new diagnostic criteria and classifications have been recently updated. Herein, we review pediatric histiocytic disorders, focusing on the pathological features of morphology, immunophenotype, and newly discovered molecular data. These insights shed light on the pathogenesis of these disorders and may become therapeutic biomarkers.

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Introduction

Histiocytic disorders are rare in childhood, characterized by aberrant accumulation of dendritic cells or macrophages; they often present with a wide spectrum of clinical symptoms.¹⁻⁵ Dendritic cells, monocytes, and macrophages are members of the mononuclear phagocyte system, mostly derived from common myeloid progenitors, and express overlapping but different terminal immunophenotypes.^{2,3}

The early Working Group of Histiocytoses classified histiocytic disorders into Langerhans cell histiocytosis (LCH), non-Langerhans histiocytosis, and malignant histiocytosis, based on Langerhans cell antigen expression and clinical

presentation.⁶ With the adoption of new molecular methods and integration of clinical, radiographic, pathological, phenotypic, genetic, and/or molecular features, Emile *et al.*⁷ divided histiocytic disorders into five groups, namely L (LCH and Erdheim-Chester disease [ECD]), C (cutaneous non-LCH), R (familial and sporadic Rosai-Dorfman-Destombes disease [RDD]), M (primary and secondary malignant histiocytoses), and H (hemophagocytic lymphohistiocytosis [HLH]). Moreover, multiple studies have revealed that LCH, ECD, juvenile xanthogranuloma (JXG), and RDD are characterized by pathological extracellular signal-regulated kinase (ERK) activation driven by activating somatic mutations in MAPK pathway genes.⁸⁻¹⁶ Nevertheless, novel molecular pathogenesises, such as *ALK* gene rearrangements, have been reported in histiocytic disorders, some of which have been included as new entities in the 5th World Health Organization (WHO) classification and the International Consensus Classification of histiocytic/dendritic cell neoplasms.¹⁷⁻²¹

HLH, often associated with macrophage activation and extreme inflammation, consists of familial and acquired subtypes.^{22,23} Familial HLH represents a syndrome of immune dysregulation instead of a myeloid neoplasm. The spectrum of pathogenic variants in familial HLH-associated genes has been expanding.²² However, the diagnosis and treatment of familial HLH remain challenging.²⁴

Herein, we review the pediatric histiocytic disorders encountered in our hematopathology practice, focusing on the pathological features of morphology, immunophenotype, genetics, and clinical presentations (Tables 1 and 2).

LCH

LCH was first reported around the year 1900, with reports of children with skin lesions, lytic bone lesions, and diabetes insipidus, which were classified as Hand-Schüller-Christian disease.²⁵ LCH can occur at any age, although it most commonly affects children. Multiple studies have shown that LCH is an inflammatory myeloid neoplasm in which genetic aberrancies are acquired in early hematopoietic progenitors and present along their differentiation into mononuclear dendritic/histiocytic cells.²⁶⁻²⁸ *BRAF* V600E mutations have been identified in approximately 50% of all LCH cases, and *MAP2K1* mutations are the main genetic driver alterations in *BRAF*-wild type LCH,^{29,30} both of which cause continuous activation of the RAS-RAF-MAPK-ERK pathway and result in proliferation,

Keywords: Juvenile xanthogranuloma; Histiocytic sarcoma; *ALK* histiocytosis; Rosai-Dorfman-Destombes disease; Hemophagocytic lymphohistiocytosis.

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EBV*, Epstein-Barr virus; *ERK*, extracellular signal-regulated kinase; *FISH*, fluorescence *in situ* hybridization; *HLH*, hemophagocytic lymphohistiocytosis; *HS*, histiocytic sarcoma; *JXG*, juvenile xanthogranuloma; *LCH*, Langerhans cell histiocytosis; *LCS*, Langerhans cell sarcoma; *LCS*, langerhans cell sarcoma; *MAPK*, mitogen-activated protein kinase; *N/A*, not applicable; *NF*, neurofibromatosis; *PI3K*, phosphoinositide 3-kinase; *RDD*, Rosai-Dorfman-Destombes disease; *sHS*, histiocytic sarcoma secondary to hematopoietic malignancies; *WHO*, World Health Organization.

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Table 1. Clinical, pathological, and genetic features of pediatric histiocytic neoplasms

Disease	Clinical presentation	Pathology	Genetics
LCH	Most common in childhood; solitary or multiple lesions involving bone, skin, lymph node, or other organs	Atypical cells with coffee bean-like nuclei and cytoplasmic Birbeck granules CD1a+, Langerin+, S100+, CD68+, CD163+, factor XIIIa-, CD4+	<i>BRAF</i> V600E (approximately 50% of LCH); <i>MAP2K1</i> or <i>ARAF</i> mutations in <i>BRAF</i> -wild type LCH
JXG	Most common in infants and children; solitary skin common; occasional multiple lesions involving the central nervous system, bone marrow, or other organs	Foamy histiocytes with occasional Touton-type giant cells CD1a-, Langerin-, ALK1-, CD14+, CD68+, CD163+, factor XIIIa+, S100+ in subset cases	Association with NF type 1; mutations in RAS/MAPK or PI3K signaling pathways
RDD	Cervical lymphadenopathy; can also involve other nodes or extranodal sites; can be primary or associated with neoplasm or immune diseases	Emperipolesis; abundant lymphoplasmacytic cells in the background S100+, CD1a-, Langerin-, ALK1-, CD68+, CD14+, CD163+	RAS/MAPK mutations described in 40% of primary cases Sporadic cases secondary to other immune neoplastic processes
ALK-positive histiocytosis	Very rare; multifocal hematopoietic and/or central nervous system involvement; or solitary lesion in children	Nonspecific morphology overlapping with other non-LCH CD1a-, Langerin-, S100+/-, CD68+, CD163+, factor XIIIa+/-, ALK1+	<i>ALK</i> gene rearrangement with or without additional mutations
HS	Primary HS is extremely rare in childhood; secondary HS occurs; aggressive clinical presentation	Cytological atypia, increased mitoses CD1a-, Langerin-, S100+/-, CD163+, CD68+, CD4+	Mutations in the RAS/MAPK signaling pathway are common in both primary HS and sHS

ALK, anaplastic lymphoma kinase; EBV, Epstein-Barr virus; HS, histiocytic sarcoma; JXG, juvenile xanthogranuloma; LCH, Langerhans cell histiocytosis; LCS, Langerhans cell sarcoma; RDD, Rosai-Dorfman-Destombes disease.

Table 2. Comparison of current classifications of histiocytic disorders

WHO 4 th Edition	International Consensus Classification	WHO 5 th Edition
Tumors derived from Langerhans cells	Tumors derived from Langerhans cells	Langerhans cell and other dendritic cell neoplasms
LCH	LCH	LCH
LCS	LCS	LCS
Indeterminate dendritic cell tumor	Indeterminate dendritic cell histiocytosis	Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma	Interdigitating dendritic cell sarcoma	Interdigitating dendritic cell sarcoma
WHO 4 th Edition	International Consensus Classification	WHO 5 th Edition
Histiocytic neoplasms	Histiocytic neoplasms	Histiocytic neoplasms
Disseminated JXG	Disseminated JXG	JXG
Erdheim-Chester disease	Erdheim-Chester disease	Erdheim-Chester disease
N/A	RDD	RDD
N/A	ALK-positive histiocytosis	ALK-positive histiocytosis
HS	HS	HS
N/A	N/A	Mesenchymal dendritic cell neoplasms
Follicular dendritic cell sarcoma	Follicular dendritic cell sarcoma	Follicular dendritic cell sarcoma
Inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma	EBV+ inflammatory follicular dendritic cell/fibroblastic reticular cell tumor	EBV+ inflammatory follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor	Fibroblastic reticular cell sarcoma	Fibroblastic reticular cell tumor
N/A	N/A	Myofibroblastic tumors

ALK, anaplastic lymphoma kinase; EBV, Epstein-Barr virus; HS, histiocytic sarcoma; JXG, juvenile xanthogranuloma; LCH, Langerhans cell histiocytosis; LCS, Langerhans cell sarcoma; RDD, Rosai-Dorfman-Destombes disease. N/A, not applicable.

apoptosis defects, and inflammation dysregulation.²⁷ Interestingly, Xerri *et al*.³¹ performed array-comparative genomic hybridization and targeted next-generation sequencing studies on several patients with morphological features of Langerhans cell sarcoma (LCS) and reported a somatic homozygous loss affecting the *CDKN2A/B* locus and somatic *NOTCH1* mutations in LCS cases but not in the control LCH cases. Previous studies revealed that the Notch ligand, its receptor, and Notch activation contribute to the pathogenesis of Langerhans cell neoplasms.^{32,33} The significance of *CDKN2A/B* deletion in LCH and LCS is uncertain and warrants further investigation.

The cells of origin for LCH are CD1a+, S100+, and CD207+ proliferating cells, consistent with bone marrow-derived Langerhans cells that represent antigen-presenting dendritic cells commonly located in the skin and mucosa. Consequently, the diagnosis of LCH relies on the morphology and immunophenotype of positive immunostaining for CD1a, Langerin, and S100.^{34,35} CD1a, S100, and Langerin might be partially expressed or completely absent in LCS. LCH neoplastic cells characteristically contain Birbeck granules, cytoplasmic structures associated with langerin.³⁶ LCH cells also morphologically show irregular and elongated nuclei with prominent nuclear grooves and folds, fine chromatin and indistinct nucleoli, and abundant eosinophilic cytoplasm. Abundant eosinophils are usually present in the background. Rarely, LCH shows features overlap with intermediate cell histiocytosis, a predominantly adult disorder characterized by the proliferation of indeterminate cells that are immunophenotypically marked by positive staining for CD1a, CD68, and faint/focal S100, but a lack of CD207 (langerin) expression.

The clinical presentation of LCH varies greatly, ranging from unifocal to single-system multifocal, or multisystem disease. Pulmonary LCH (PLCH), as an example of single-system LCH, is an extremely rare disease in children. Recent studies on PLCH detected *BRAF* V600E mutations in some cases, indicating potential non-smoking etiologies, which are different from the pathogenesis of adult PLCH. For patients newly diagnosed with LCH, extensive imaging and laboratory workups might be required to assess the disease extent.²⁵ Bone marrow biopsy and aspirate investigations are often recommended in patients with cytopenia. Current risk stratification is mainly based on the affected sites of LCH and response to initial therapy, while the genetic aberrancies have not been associated with overall survival.²⁵ Recent studies suggest that bone marrow involvement (detection of *BRAF* V600E mutation by allele-specific droplet digital polymerase chain reaction or the presence of atypical LCH cells identified by flow cytometry) may indicate a higher risk for disease progression.^{27,37}

Treatment options for LCH include the following: topical steroids, nitrogen mustard, and imiquimod; surgical resection of isolated lesions; phototherapy; and systemic methotrexate, 6-mercaptopurine, vinblastine/vincristine, thalidomide, cladribine, and/or cytarabine.²⁵ The detailed treatment protocols have been well summarized in the literature.^{25,38–40}

JXG

JXG is a rare non-LCH disorder, with more than half of reported cases occurring in the first year of life.⁴¹ The majority of pediatric patients with JXG present with solitary cutaneous nodules in the head and neck or other body areas.⁴¹ Extracutaneous JXG has been reported in the testis, central nervous system, liver, lungs, and other visceral organs.^{41–47} Systemic dissemination has been reported in less than 5% of JXG cases.^{41,47} In a recent study, patients with extracutaneous JXG generally had good outcomes, whereas those with intracranial lesions showed comorbidities and/or permanent damage.⁴⁷

The diagnosis of JXG is straightforward in most cases, based on its morphology and immunophenotype. The classic morphology of JXG exhibits dermal infiltration of foamy histiocytes with occasional Touton giant cells, which often extend into subcutaneous tissue. However, JXGs occasionally show unusual morphology, such as mononuclear and non-foamy or rarely spindle cell morphology, which overlaps with other histiocytic disorders. These histiocytes are positive for CD68, CD163, CD4, CD11c, and factor XIIIa, but are generally negative for CD1a and S100, although S100 expression was reportedly observed in up to 32% of JXGs.⁴⁸ In cases of typical JXG, diagnosis of ALK-positive histiocytosis is recommended if ALK1 immunostaining or gene rearrangement is detected.¹⁸ The morphology, immunophenotype, genetics, and clinical presentations of JXG may also overlap with ECD.^{13,49,50} However, the mean age at diagnosis of ECD is approximately 46 years.^{49,51} Although there are rare instances of ECD in children,^{52–54} establishing a definite diagnosis of pediatric ECD is extremely difficult.

Molecular studies have revealed copy number aberrations and proved clonality in JXG, in support of a neoplastic process, although the comprehensive genetic profile of JXG is largely unknown.¹⁰ It appears that systemic or more advanced JXGs tend to have more genomic complexity.¹⁰ Moreover, few studies of JXG have reported mutations in the MAPK signaling pathway.^{9,10,55–57}

Most cutaneous JXGs are self-limiting or are treated by local resection, and systemic therapies are not needed. In patients with extracutaneous JXGs, complete resection appears to yield more favorable outcomes. For instance, JXG of the testis might recur after partial resection without an orchiectomy, whereas no relapse has been reported in testicular JXG after orchiectomy.⁴⁶ Similarly, some JXGs of the central nervous system require additional chemotherapy and/or radiotherapy.⁵⁸ Currently, there is no standard treatment for disseminated JXGs, although targeted therapy using trametinib has been attempted.⁵⁹

RDD

RDD, newly recognized in the latest WHO classification, is a rare non-LCH disorder affecting both children and adults.^{7,60–62} Many patients present with lymphadenopathy of unilateral or bilateral cervical lymph nodes, though axillary, inguinal, and other nodes can also be affected. Up to 40% of cases of RDD involve extranodal sites such as the skin, nasal cavity, bone, and any other body sites.^{63–67} Since the first report, the etiology of RDD has remained a mystery and infectious, genetic, and inflammatory processes have been postulated.⁶⁸ Recent studies have identified *KRAS* and *MAP2K1* mutations in a subset of RDD, which result in activation of the MAPK/ERK signaling pathway, as seen in many other histiocytic disorders.^{61,69,70} RDD or RDD-like lesions are also observed in immune dysregulation diseases such as RAS-associated autoimmune leukoproliferative disease,⁷¹ and autoimmune lymphoproliferative syndrome,^{61,72} or secondary to certain lymphoid neoplasms.^{73,74} Rare cases of familial RDD have been reported and might be associated with certain germline mutations.⁷⁵

The diagnosis of RDD relies on the characteristic morphology of emperipolesis, which is described as an active, non-destructive engulfment of leukocytes including lymphocytes, plasma cells, and granulocytes by histiocytes. Inflammatory cells and fibrosis are often seen in the background of RDD, making it challenging to differentiate it from other inflammatory processes (Fig. 1). The typical immunophenotype of RDD shows positivity for histiocytic markers such as S100, CD11c,

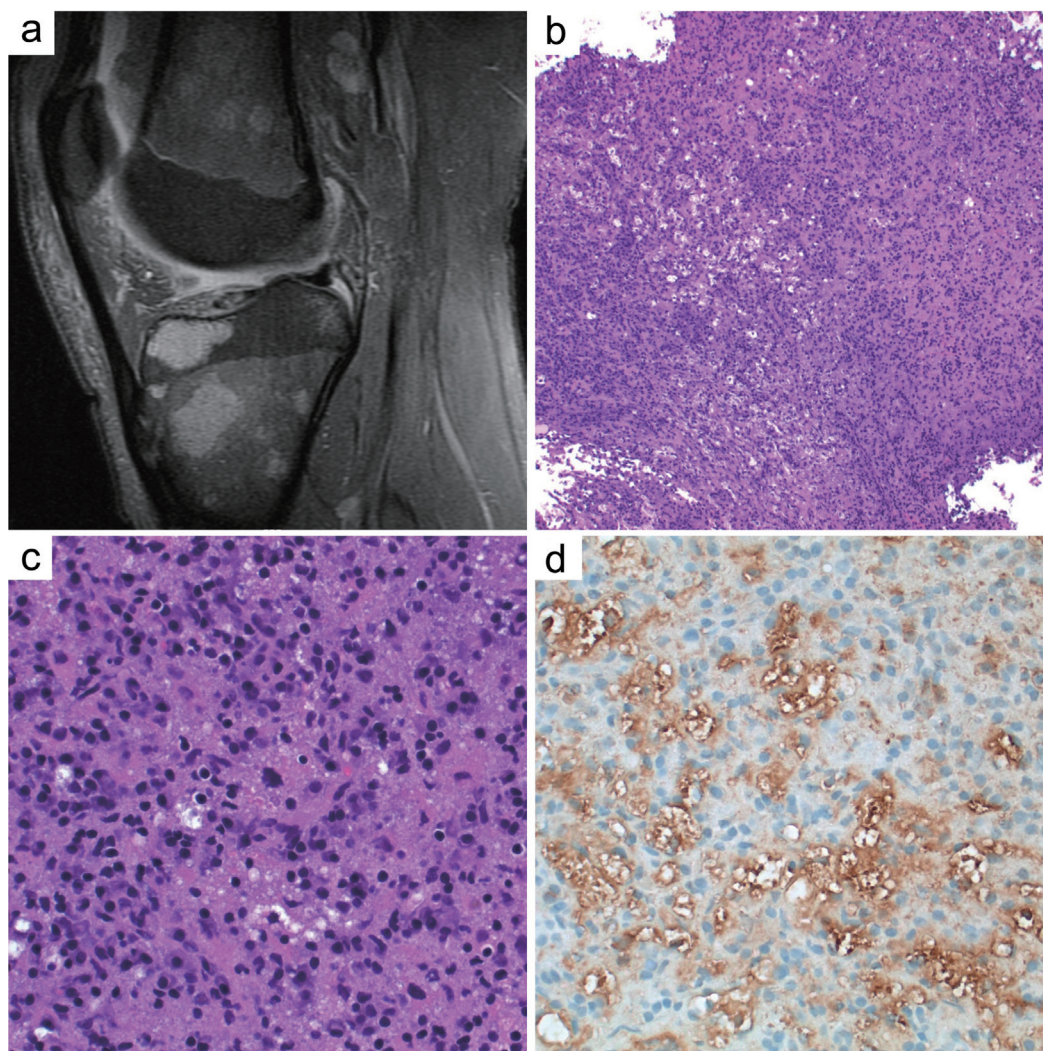


Fig. 1. Example of Rosai-Dorfman-Destombes disease (RDD). A 15-year-old boy presented with lymphadenopathy and multiple lytic bone lesions. (a) Magnetic resonance imaging (sagittal T2) shows multifocal bone lesions. (b) Biopsy and hematoxylin and eosin analysis, 100 $\times$. (c-d) An inflammatory lesion with lymphoplasmacytic cells and occasional atypical histiocytes with emperipolesis (c), positive for S100 immunostaining (d), is shown at 400 $\times$. Subsequent lymph node excision biopsy also confirmed the diagnosis of RDD by an expert hematopathologist (data not shown). RDD, Rosai-Dorfman-Destombes disease.

CD68, CD163, cyclin D1, and OCT2.^{76,77} In contrast, markers such as CD1a and CD207/Langerin are usually negative.

Treatment of RDD depends on its clinical presentation. Sporadic RDD is often self-resolved.^{59–61} However, most RDDs might need local resection, and few patients have been reported to respond to targeted therapies.^{59,78} Moreover, some patients show resistance to conventional treatments and consequently have poor outcomes. Identifying these high-risk patients and establishing a risk stratification of RDD will be critical in the future.

ALK-positive histiocytosis

ALK-positive histiocytosis, recently recognized in the latest WHO classification, was first reported by Chan *et al.*⁷⁹ in three infants with multiorgan involvement including the bone marrow, spleen, and liver. Additional cases in older children and adults were identified by Chang *et al.*²⁰ A recent study of a large cohort of 39 cases by Emile *et al.*¹⁸ described the heterogeneous pathological and clinical features of this entity.

In their study, a group of patients with multisystemic ALK-positive histiocytosis were divided into two groups: Group 1A, comprised of cases similar to infantile cases reported by Chan *et al.*,⁷⁹ and Group 1B, comprised of cases featuring central nervous system involvement in both children and adults. Among the remaining patients with solitary disease manifestations, more than 80% were children.¹⁸ Both the morphology and immunophenotype of the ALK-positive histiocytosis are heterogeneous, substantially overlapping with other non-LCH such as JXG.^{18,19,80,81} The diagnostic criteria include confirming ALK1 immunoreactivity and/or identifying an *ALK* gene rearrangement. The specific D5F3 clone of the ALK antibody can identify false negative cases.¹⁸ Although the partners of *ALK* fusion genes are varied, most patients respond to ALK inhibitor therapy according to a recent study.¹⁸

Moreover, depending on the cell origin of ALK1 immunoreactivity on histiocytes or myofibroblasts, occasional atypical cases of ALK-positive histiocytosis show ambiguous morphology and immunophenotype and overlap with inflammatory myofibroblastic tumors and other soft tissue tumors.^{82–85}

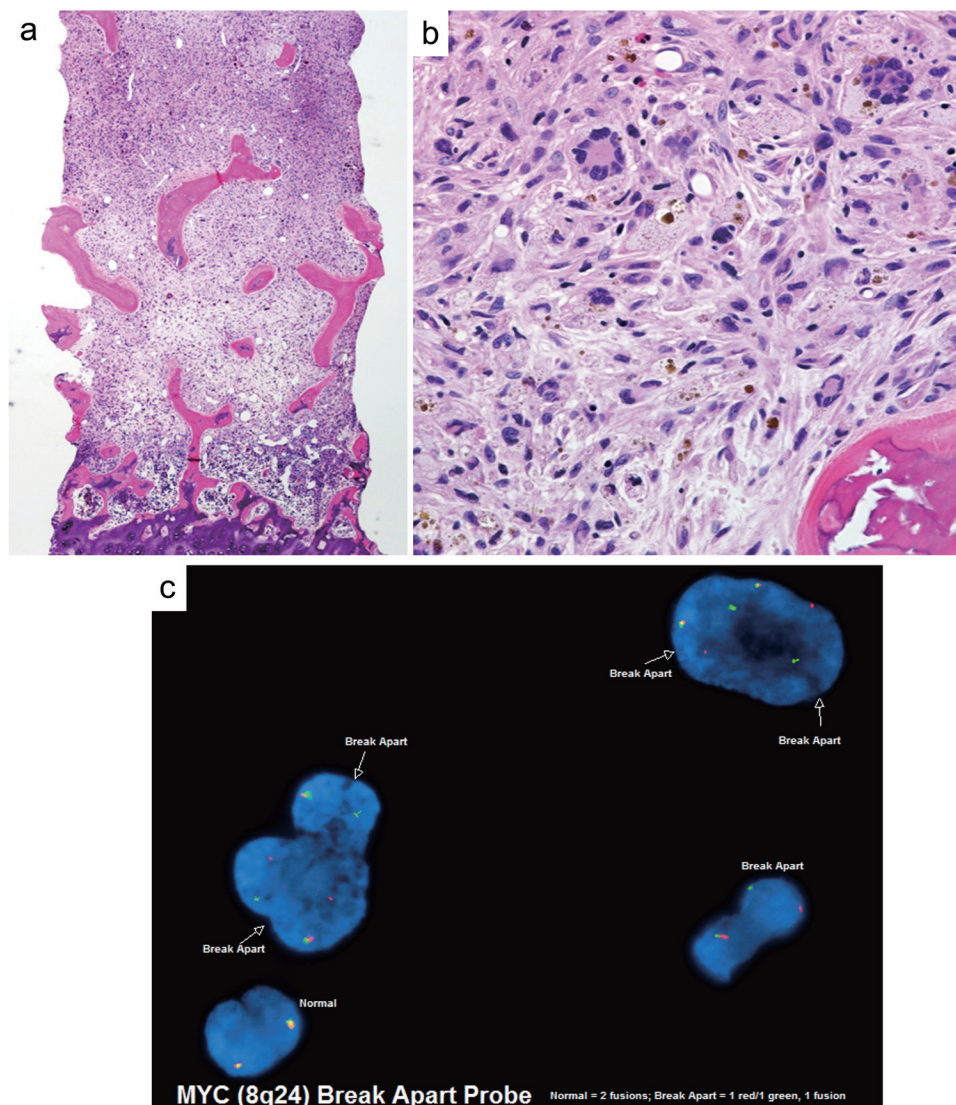


Fig. 2. Example of histiocytic sarcoma secondary to T-lymphoblastic leukemia with MYC proto-oncogene (MYC) gene rearrangement. A 2 year-old boy with mediastinal mass, hepatosplenomegaly, and circulating blasts was diagnosed with T-lymphoblastic leukemia with *MYC*-gene rearrangement by fluorescence *in situ* hybridization (FISH) and aberrant cytogenetics displaying 46,XY,t(8;14)(q24;q11.2) and der(12)t(12;20)(q11;q13.3), der(20)t(12;20)(q21;q13.3)[9]/46,XY[5]. The patient was partially responsive to chemotherapy before receiving a matched unrelated donor cord blood transplant. (a-b) On day 110 after transplant, bone marrow biopsy revealed diffuse infiltration of atypical histiocytes and occasional Touton giant cells, as shown here under hematoxylin and eosin staining at (a) 40× magnification and (b) 400× magnification. (c) FISH confirmed the persistence of *MYC* gene rearrangement. Positron emission tomography-computed tomography scan revealed disseminated disease. The patient died despite chemotherapy following the Langerhans cell histiocytosis III protocol. FISH, fluorescence *in situ* hybridization.

Histiocytic sarcoma

Malignant histiocytosis was initially reported by Rappaport⁸⁶ as a systemic, progressive, invasive proliferation of morphologically atypical histiocytes and their precursors. Recently, this condition became more commonly referred to as histiocytic sarcoma (HS). HS predominantly affects adults, although it can occur at any age.^{7,15,16,87} It can arise as a primary neoplasm or in the context of transdifferentiation from other antecedent or concurrent hematologic malignancies.^{15,16,88,89}

Primary HS is extremely rare in children, whereas HS secondary to hematopoietic malignancies (sHS) commonly occurs in pediatric patients.^{15,90} A recent study by Egan *et al.*¹⁵ reported mutations in RAS/MAPK pathway genes in 14 out of 16 cases of sHS associated with mature or precursor B-cell and T-cell neoplasms. Interestingly, sHS shares a similar

mutation profile and somatic hypermutation of *IGH* genes to its associated mature B-cell neoplasms, indicating a possible transdifferentiation process in sHS. For sHS associated with precursor hematopoietic malignancies, the sHS and their associated precursor neoplasms share common genetic aberrations and clonal divergence.^{15,90}

The current diagnostic criteria for HS rely on the integration of cytological atypia, histiocytic immunophenotype, genetic abnormalities, and aggressive clinical presentation.^{15,16,74,86,91} However, occasionally, JXG and LCH can show aggressive clinical presentation without malignant histopathological features such as cytological atypia or increased mitoses.^{44,92,93} This makes it difficult to determine whether a case should be diagnosed as sHS or disseminated JXG secondary to hematopoietic malignancy (Fig. 2). Nev-

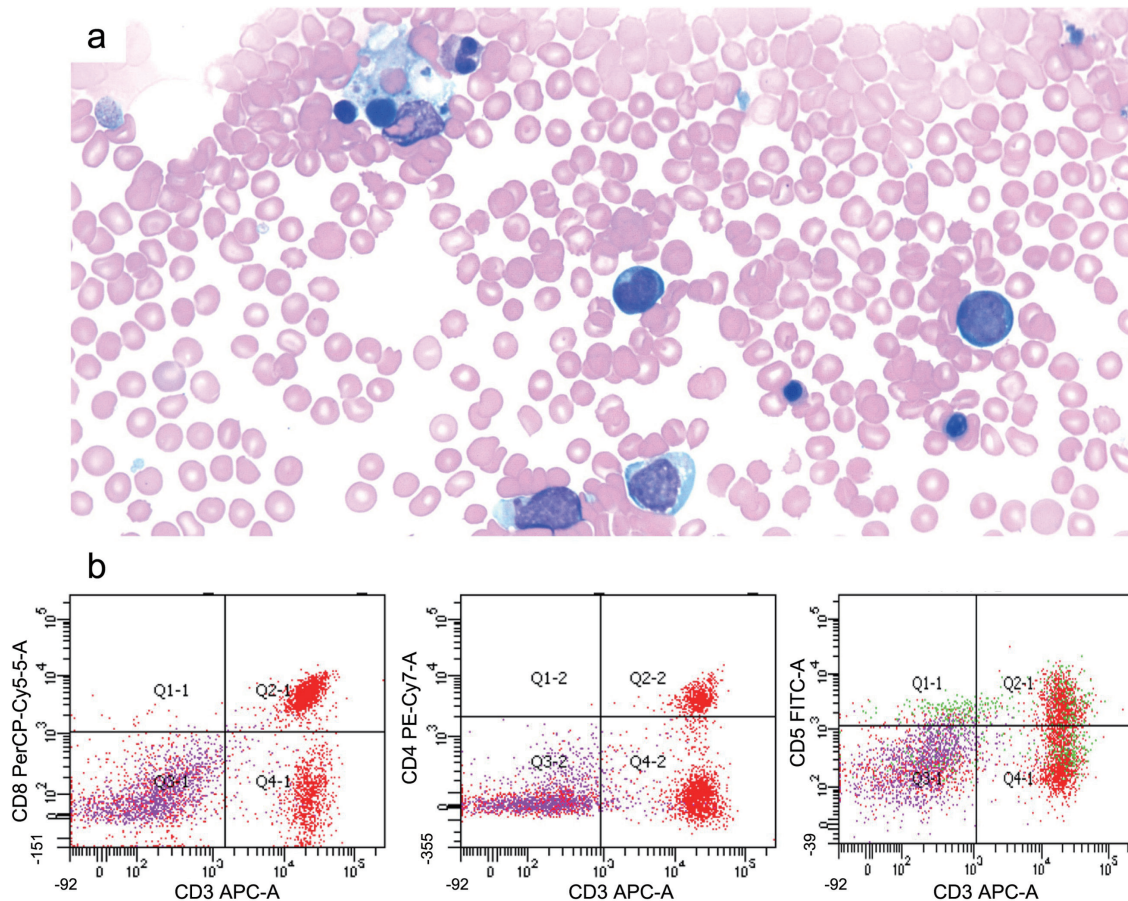


Fig. 3. Example of aberrant T-cell population in familial hemophagocytic lymphohistiocytosis. A 1-month-old female infant presented with multiorgan failure and cytopenia and underwent a bone marrow biopsy. (a) Aspirate showed hemophagocytosis (Giemsa stain, 100 $\times$). (b) Flow cytometry identified an abnormal CD8⁺ CD5⁻ T-cell population. Genetic testing confirmed a mutation in the *PRF1* gene. Despite aggressive treatment, the patient died shortly thereafter.

ertheless, in the era of precision medicine, identification of underlying mutations in the RAS/MAPK signaling pathway is important to guide future therapeutic strategies.^{94,95}

HLH

HLH is a syndrome characterized by severe systemic hyperinflammation. Patients present with unremitting fever, cytopenias, hepatosplenomegaly, elevation of HLH biomarkers, multiorgan failure, and a high mortality rate.^{22,23} HLH can be driven by genetic abnormalities (familial) or acquired (secondary) etiologies associated with infection, autoimmune, or malignant processes.^{96,97}

Familial HLH is associated with genetic mutations in *PRF1*, *UNC13D*, *STXBP2*, and *STX1*. Other less frequent genetic defects affect genes involved in granule/pigment abnormalities (*RAB27A*, *LYST*, and *AP3B1*), X-linked lymphoproliferative disease genes (*SH2D1A* and *XIAP*), and others such as *NLR4* and *CDC42*. HLH is also associated with diseases that involve susceptibility to the Epstein-Barr virus (EBV), such as primary immune deficiencies and inborn errors of metabolism.²² The acquired etiology of HLH is broad, including underlying rheumatologic diseases, autoinflammatory disorders, infections, and malignancies.

The diagnosis of HLH is challenging. The criteria proposed by the Histiocyte Society, which are widely accepted, include fever, splenomegaly, cytopenias, hypertriglyceridemia and/

or hypofibrinogenemia, hemophagocytosis, decreased natural killer-cell function, elevated ferritin level, and elevated soluble IL-2 receptor level. A diagnosis of HLH should be considered if a patient meets five out of these eight criteria. Genetic screening for HLH-associated mutations or evaluation of the triggered etiologies can help establish the diagnosis. Macrophage activation syndrome, a form of secondary HLH, often occurs in febrile patients with systemic juvenile inflammatory arthritis or other rheumatologic conditions. This syndrome is characterized by fever, high ferritin levels, thrombocytopenia, elevated aspartate aminotransferase levels, elevated triglycerides, and low fibrinogen levels.⁹⁸

HLH is thought to result from impaired function of cytotoxic T-cells and natural killer cells, which can be identified by flow cytometry analysis. For instance, McCall *et al.*⁹⁹ and Lin *et al.*¹⁰⁰ observed an expansion of CD8 T-cell populations with variable decrease or loss of expression of CD5, CD7, and/or CD3 in both EBV-associated and non-EBV-associated HLH. Further studies showed that this aberrant T-cell immunophenotype may help discriminate EBV-negative secondary HLH from EBV-positive and familial HLH.^{101,102} Occasionally, clonal CD8⁺ T-cell expansion may be detected in HLH (Fig. 3), which poses a diagnostic challenge as it can resemble T-cell neoplasm.¹⁰³

Treatment of HLH should start as soon as this disease is suspected. Besides promptly addressing the underlying etiology, the current treatment for HLH often consists of im-

munosuppressive and chemotherapeutic drugs and targeted therapy to eliminate T-cell and macrophage activation and mitigate the cytokine storm.^{22,104}

Conclusions

Pediatric histiocytic disorders present with a wide range of clinical signs and symptoms, pathologies, and genetic aberrations. Accurate diagnosis by specialized pathologists is essential for effective management of these conditions. Close follow-up is critical to monitor any long-term sequelae in these patients.

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Conflict of interest

The authors declare that they have no conflicts of interest related to the publication of this manuscript.

Author contributions

Study concept and design (JC), acquisition of data (JC, GZ, MP, JM, SG, ZP), analysis and interpretation of data (JC, GZ, MP, JM, SG, ZP), drafting of the manuscript (JC), critical revision of the manuscript for important intellectual content (JC, GZ, MP, JM, SG, ZP). All authors have made a significant contribution to this study and have approved the final manuscript..

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