Molecular Pathogenesis of the Histiocytic and Dendritic Cell Neoplasms

Benjamin H. Durham, MD[a,b,c,*]

KEYWORDS

• Histiocytosis • Langerhans cell histiocytosis • Erdheim-chester disease
• MAP kinase signaling • *BRAF* • *MAP2K1* • Vemurafenib • MEK1/2 inhibitors

KEY POINTS

- Histiocytic and dendritic cell neoplasms (HDCNs) have a molecular pathogenesis largely driven by aberrant MAP kinase, PI3K-AKT-mTOR, and/or receptor tyrosine kinase (RTK) signaling.
- *BRAF*^{V600E} is the most common alteration in Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD) but not in other HDCNs subtypes.
- ALK-positive histiocytosis is the first molecularly characterized diagnostic subtype of the histiocytic and dendritic cell neoplasms (HDCNs).
- Next-generation sequencing (NGS) molecular studies are extremely useful for guiding therapy decisions in HDCNs and diagnosing some subtypes of HDCNs.
- Molecularly inspired therapeutics targeting the MAP kinase, PI3K-AKT-mTOR, and RTK signaling pathways have been clinically effective in HDCNs.

INTRODUCTION

The mitogen-activated-protein-kinase (MAPK) pathway has a long association with human neoplasia. A key player is *BRAF*, which encodes a BRAF serine/threonine kinase belonging to the RAF family of serine/threonine kinases, which also includes ARAF and RAF1. These kinases transduce mitogenic signals from the cell membrane to the nucleus and regulate MEK-Extracellular-signal-regulated kinases (ERK) signaling. Of the RAF kinases, BRAF is most frequently mutated in human cancers with *BRAF*^{V600E} accounting for 90% of activating mutations.[1] Similarly, the neoplastic

[a] Department of Pediatrics, Division of Hematology-Oncology, Rutgers Cancer Institute, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ 08903, USA; [b] Department of Pathology and Laboratory Medicine, Division of Hematopathology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ 08903, USA; [c] Department of Oncological Pathology, Rutgers Cancer Institute, New Brunswick, NJ 08903, USA
* Rutgers Cancer Institute, 195 Little Albany Street, Room 4557, New Brunswick, NJ 08903.
E-mail address: bd559@cinj.rutgers.edu

Hematol Oncol Clin N Am 39 (2025) 471–490
https://doi.org/10.1016/j.hoc.2025.03.001 **hemonc.theclinics.com**

Abbreviations	
AXG	adult xanthogranuloma
ECD	Erdheim-Chester disease
FDA	Food and Drug Administration
HDCNs	histiocytic and dendritic cell neoplasms
ICH	indeterminate cell histiocytosis
JXG	juvenile xanthogranuloma
KIF5B	kinesin family member 5B
LCH	Langerhans cell histiocytosis
MAPK	mitogen-activated-protein-kinase
RDD	Rosai-Dorfman-Destombes disease
SH2	Src homology 2
WHO	World Health Organization

cells of the histiocytic and dendritic cell neoplasms (HDCNs) have nearly universal ERK overexpression suggesting constitutive activation of MAPK signaling in these distinct hematologic neoplasms (**Fig. 1**).[2–4]

Although quite rare in hematological disorders, *BRAF* mutations are strikingly enriched in Langerhans cell histiocytosis (LCH)[2] and Erdheim-Chester disease (ECD).[3] Furthermore, additional sequencing efforts identified recurrent mutations in *MAP2K1* in LCH,[5,6] ECD, and other non-LCH neoplasms.[7,8] Interestingly, $BRAF^{V600E}$ is frequently present in LCH and ECD (50%–60%)[2,3]; meanwhile, *MAP2K1* mutations are the second most frequent molecular alterations across the HDCNs (~25%) (see **Figs. 1** and **2**).[5–8] However, despite their common molecular alterations, the HDCNs are a heterogeneous group of hematologic neoplasms with different clinical presentations and biology. Nonetheless, the discovery of recurrent $BRAF^{V600E}$ and *MAP2K1* mutations in the HDCNs has guided new therapeutic approaches, as well as an opportunity to explore how common genetic events give rise to these enigmatic diseases (see **Figs. 1** and **2**).[7,9–14] This review discusses the amalgamation of diverse kinase alterations uncovered in the HDCNs during the past 15 y of molecular progress and underscore how new insights have refined our understanding of these disorders as clonal neoplasms with constitutive MAPK and PI3K-AKT-mTOR activation. We will also highlight how our concepts of the cellular origins of the MAPK-driven hematologic neoplasms and molecular therapeutics have evolved.

OVERVIEW OF THE HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

Histiocytic neoplasms are a heterogeneous group of disorders broadly classified as LCH and non-LCH that share the common pathologic features of infiltration and accumulation of neoplastic histiocytes in tissues with nearly universal ERK activation and an accompanying inflammatory milieu.[2,3,15,16] However, a revised 2016 classification re-categorized LCH and non-LCH into the following: “L” Langerhans group (LCH, ECD, disseminated juvenile/adult xanthogranuloma [JXG/AXG], and indeterminate cell histiocytosis [ICH]); “C” group (cutaneous JXG/AXG and Rosai-Dorfman-Destombes disease [RDD]); “R” group (non-cutaneous RDD); and “M” group (malignant histiocytoses-most commonly histiocytic sarcoma [HS]) (**Table 1**).[17]

CLINICAL AND PATHOLOGIC FEATURES OF LANGERHANS CELL HISTIOCYTOSIS

LCH has diverse manifestations from self-resolving, single-organ lesions to multi-organ disease, which is associated with 10% to 20% mortality.[18,19] Bone (75%) and skin (34%) are the most commonly involved organs with lytic bone lesions, frequently

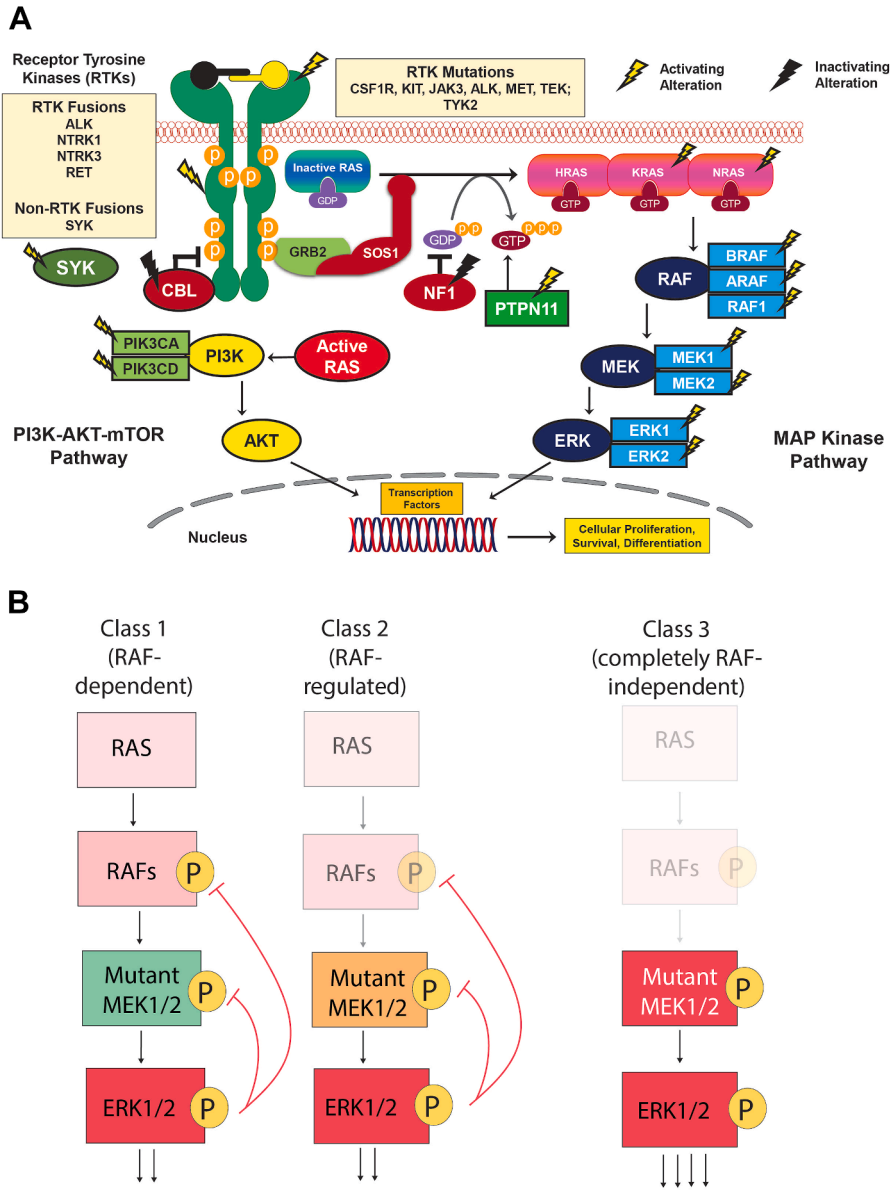

Fig. 1. Overview diagrams of the aberrant MAP kinase, PI3K-AKT-mTOR, and tyrosine kinase signaling underlying the molecular pathophysiology of the histiocytic and dendritic cell neoplasms. (*A*) Diagram of the MAPK and PI3K-AKT signaling pathways with description of the activation of the RAS proteins (HRAS, KRAS, and NRAS) with annotation of the signaling proteins affected by genetic alterations in the histiocytic and dendritic cell neoplasms. (*B*) Diagram of biochemical classes of MEK1 mutations. Class 1 mutants are dependent on and hyperactivated by phosphorylation of MEK1/2 from RAF kinases. Therefore, they are sensitive to ERK-dependent feedback inhibition (*red lines*). Class 2 mutants have some degree of basal RAF-independent activity but are further activated by RAF. Class 3 mutants however, completely RAF independent, drive high levels of ERK1/2 activation, are insensitive to ERK-dependent feedback inhibition, and are predicted to be the most likely of any class of MEK1 mutations to transform cells.

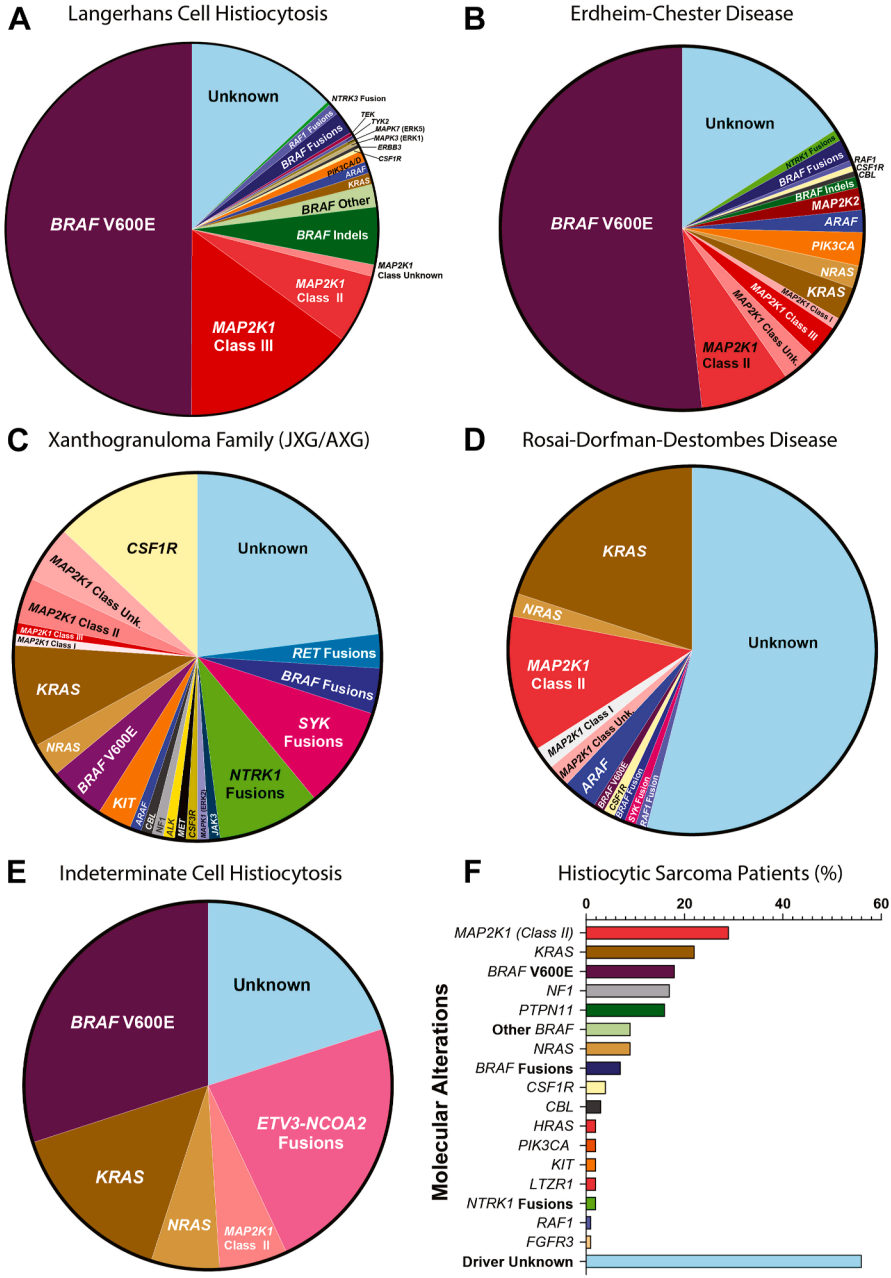

Fig. 2. Summary of diverse kinase alterations discovered in the histiocytic neoplasms. (*A*) Pie chart illustrating a composite of the known driver kinase alterations in Langerhans cell histiocytosis. (*B*) Pie chart showing a composite of the known driver kinase alterations in Erdheim-Chester disease. (*C*) Pie charts demonstrating the published kinase alterations in the xanthogranuloma (XG) family of histiocytic neoplasms (juvenile/adult xanthogranulomatosis [JXG/AXG]). (*D*) Pie charts illustrating the composite of published driver kinase alterations in Rosai-Dorfman-Destombes disease. (*E*) Pie charts showing the composition of published driver alterations in indeterminate cell histiocytosis. (*F*) Histogram illustrating the molecular driver alterations published in the most common malignant histiocytosis known as histiocytic sarcoma, which often has multiple, co-occurring driver alterations.

Table 1
Summary of the classification and pathologic features of the histiocytic neoplasms

Disease	LCH	ECD	XG Family (JXG/ AXG)	RDD	HS	ICH	ALK+
Broad Classification	LCH	Non-LCH	Non-LCH	Non-LCH	Non-LCH	Non- LCH	Non-LCH
2016 Revised Classification Groupings	L	L	L (Extracutaneous) & C (Cutaneous)	C (Cutaneous) & R (Other RDD)	M	L	Not Applicable
Immunophenotypic Features							
CD68	+	+	+	+	+	+	+
CD163	−/+	+	+	+/−	+	−/+	+
CD14	-	+	+	+	+	-	+
CD1a	+	-	-	-	-	+	-
CD207 (Langerin)	+	-	-	-	-	-	-
S100	+	−/+	−/+	+	+/−	+	+/−
Factor XIIIa	-	+	+	−/+	+/−	-	+
CD45	+	+	+	+	+	+	+
Cyclin D1	+	+/−	+/−	+	+	+	+
OCT-2	−/+	-	-	+	+/−	−/+	+/−
ALK	-	-	-	-	-	-	+
Characteristic Features							
Birbeck Granules	Yes	No	No	No	No	No	No
Xanthomatous Histiocytes	No	Yes	Yes	No	No	No	Yes
Touton Giant Cells	No	Yes	Yes	No	No	No	Yes
Emperipolesis (Intractyoplasmic Lymphocytes)	No	Occasional	Occasional	Abundant	Occasional	No	No

Abbreviations: −/+: negative in a majority of cases; positive in a minority (<50% cases); +/−: positive in a majority of cases (>50% cases); negative in a minority; AXG, adult xanthogranuloma; C Group, cutaneous and mucocutaneous; ECD, Erdheim-Chester disease; HS, histiocytic sarcoma; ICH, indeterminate cell histiocytosis; JXG, juvenile xanthogranuloma; L Group, Langerhans-related; LCH, langerhans cell histiocytosis; M Group, malignant histiocytoses; non-LCH, non-Langerhans cell histiocytosis; R Group, Rosai-Dorfman disease; RDD, Rosai-Dorfman-Destombes disease; XG, xanthogranuloma.

involving the skull.[20,21] Besides skin, LCH may arise in any mucosal tissue (gingiva, gastrointestinal tract).[20,22,23] "High-risk" LCH includes diffuse infiltration or focal lesions of spleen, liver, or bone marrow with a 5-y survival rate of 84% compared to 99% in "low-risk" LCH.[24] LCH may also involve the central nervous system, presenting with mass lesions, diabetes insipidus, or progressive neurodegenerative symptoms arising decades after initial presentation.[25–27]

Pathologically, LCH is characterized by lesions composed of clonal, pathologic "histiocytes" with reniform (coffee-bean-shaped) nuclei and abundant, pink cytoplasm with immunoreactivity for CD1a and langerin (CD207) and pathognomonic Birbeck granules (see **Table 1**).[15,28–30] Histology also shows a milieu of pathologic dendritic cells (DCs) and recruited inflammatory cells (lymphocytes, eosinophils, and macrophages).[31–34]

CLINICAL AND PATHOLOGIC FEATURES OF XANTHOGRANULOMA FAMILY OF HISTIOCYTIC NEOPLASMS (JUVENILE/ADULT XANTHOGRANULOMATOSIS)

JXG/AXG was originally described in the early 1900s and was believed to be endothelium derived and was named "nevoxanthoendothelioma".[35] JXG/AXG is usually self-limiting with dermal lesions in the majority of patients; but 4% present with disseminated disease.[36,37] Histologically, JXG/AXG shows xanthomatous histiocytes with admixed multinucleated and Touton giant cells that are immunoreactive for CD68, CD163, CD14, fascin, and Factor XIIIa with variable positivity for S100 and no immunoreactivity for CD1a or CD207 (see **Table 1**).[15,37–39]

CLINICAL AND PATHOLOGIC FEATURES OF ERDHEIM-CHESTER DISEASE

ECD is a rare, systemic, non-LCH with around 1000 reported cases in the literature that was first described as a "lipoid granulomatosis" in 1930 by Erdheim and Chester. ECD has diverse clinical manifestations ranging from localized presentations (bone-only disease) to multisystem disease that are extensively discussed elsewhere.[37–43] The diagnosis of ECD requires combining the histologic criteria and the appropriate clinical and radiologic setting.[15,37–39] Radiographically, bilateral and symmetric diaphyseal and metaphyseal osteosclerosis of the legs are observed in most patients. Histologically, ECD shows xanthomatous histiocytes with surrounding fibrosis, as well as admixed multinucleated giant cells with immunoreactivity for CD68, CD163, CD14, fascin, and Factor XIIIa and negativity for CD1a and CD207 (see **Table 1**).[15,37–39]

CLINICAL AND PATHOLOGIC FEATURES OF ROSAI-DORFMAN-DESTOMBES DISEASE

RDD is a rare, non-LCH hematologic disorder known has "sinus histiocytosis with massive lymphadenopathy" that was first described by Destombes, Rosai, and Dorfman.[39,44–46] RDD has heterogeneous clinical manifestations and can occur as an isolated disorder or in association with hereditary, autoimmune, or neoplastic conditions. The majority of RDD patients present with classical (nodal) RDD that primarily manifests as bilateral, massive, and painless cervical lymphadenopathy with or without fever, night sweats, and weight loss. However, 43% of patients develop extra-nodal RDD with 19% showing multisystem RDD, and prognosis has been correlated with the number of extra-nodal systems affected with a detailed clinical discussion reviewed elsewhere.[39,47] Histologically, the abnormal, xanthomatous histiocytes of RDD demonstrate abundant emperipolesis of erythrocytes, lymphocytes, and plasma cells. The abnormal histiocytes are immunoreactive for CD14, CD68, CD163, and S100 with negativity for CD1a and CD207 (see **Table 1**).[15,37,39,48]

CLINICAL AND PATHOLOGIC FEATURES OF INDETERMINATE CELL HISTIOCYTOSIS

ICH is a rare, non-LCH neoplasm first described in 1985 that predominantly involves the skin and is characterized by the presence of dendritic cells that are morphologically and immunophenotypically similar to LCH. However, ICH shows a dense dermal infiltration of neoplastic histiocytes admixed with lymphocytes without significant eosinophilic infiltration and is immunoreactive for CD68, S100, and CD1a but not for CD163 and CD207. Therefore, unlike LCH, ICH lacks CD207 and Birbeck granules (see **Table 1**).[49,50]

CLINICAL AND PATHOLOGIC FEATURES OF HISTIOCYTIC SARCOMA

HS is defined by the World Health Organization (WHO) as "a malignant proliferation of cells showing morphologic and immunophenotypic features of mature tissue histiocytes".[51,52] These are rare non-LCH neoplasms most of which present in extranodal sites that can appear as solitary lesions or with innumerable tumor loci. Histologically, HS is a diffuse, non-cohesive proliferation of monomorphic-to-pleomorphic large histiocytes with large, round-to-oval, irregularly folded, and eccentrically-placed nuclei. Prominent mitotic activity and atypical mitoses are noted. The immunophenotype shows immunoreactivity for CD14, CD68, and CD163 and are negative for CD1a and CD207 (see **Table 1**).[51–55] Recent studies have demonstrated constitutive activation of the MAPK pathway in HS.[53–56]

CLINICAL AND PATHOLOGIC FEATURES OF ALK-POSITIVE HISTIOCYTOSIS

ALK-positive histiocytosis is a non-Langerhans cell histiocytic neoplasm with overexpression of the ALK- receptor tyrosine kinase based on the fusion involving *ALK* and a 5′ partner gene that is most commonly *KIF5B* (Kinesin Family Member 5B). This neoplasm was officially recognized by the WHO and International Consensus Classification classifications of hematopoietic tumors as a distinct HDCN in 2022 and the first diagnostic molecular subtype of the HDCNs.[51,52] It was initially reported in infants but can also occur in adults.[57,58] Most cases in the pediatric age group present with multisystem disease with hepatosplenomegaly and involvement of bone marrow.[58] Clinical manifestations include anemia, thrombocytopenia, and systemic symptoms.[59] Skin involvement has been reported but is not common. Neurologic involvement is common, approximately 50%.[58,60] Patients with involvement of the central nervous system present with diverse symptomatology including seizures, ataxia, headache, and paresis. Infrequent presentations include localized disease involving bone, soft tissue, and skin. Adults are more likely to present with isolated lesions involving breast, gastrointestinal tract, and soft tissue.[61,62] Involvement of lung and lymph nodes has been reported.

The histologic features resemble xanthogranuloma. The histiocytes have plump foamy cytoplasm.[58] However, the morphology is variable with some cases having cells with a more spindle-shaped appearance, or epithelioid morphology.[62,63] The nuclear features are generally bland with oval-to-indented nuclei, finely stippled chromatin, and small nucleoli. Touton-type giant cells may be present, and emperipolesis is occasionally seen.[64] However, other inflammatory cells including eosinophils are largely absent from the tissue microenvironment. A mildly fibrotic background is noted. The bone marrow is usually not diffusely involved. In the liver, the cells tend to infiltrate the hepatic sinusoids.[57] The cells display immunophenotypical markers consistent with a histiocytic lineage with expression of CD68, CD163, and Factor XIIIa (see **Table 1**).[64] The expression of ALK is confirmed by immunohistochemistry, with cytoplasmic staining

in the lesional cells and should be performed in all cases of histiocytosis. S100 is positive in about 50% of cases, but CD1a and langerin are negative. Expression of OCT-2, p-ERK, and Cyclin D1 is often seen (see **Table 1**).[58]

MOLECULAR PATHOGENESIS OF THE HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

Prior to the molecular era, the determination of whether or not histiocytoses were reactive or neoplastic was unclear and constituted a historic debate.[65,66] Furthermore, the cellular heterogeneity of histiocytoses and the limitations of molecular technology precluded classification of histiocytoses as neoplasms.[32,67,68] However, the dawning of the molecular era revealed a series of activating kinase alterations involved in MAP kinase, PI3K-AKT-mTOR, and RTK signaling were discovered in the HDCNs (see **Figs. 1** and **2**).

RAF Isoforms

The discovery of *BRAF* mutations in the histiocytoses occurred after $BRAF^{V600E}$ was reported in 57% of LCH[2] and 54% of ECD.[3] Later studies uncovered $BRAF^{V600E}$ in JXG/AXG, RDD, and ICH but were not prevalent in HDCNs other than LCH and ECD.[13,69–71] Besides $BRAF^{V600E}$, HDCN case reports have revealed other activation segment *BRAF* mutations ($BRAF^{V600D}$; $BRAF^{V600insDLAT}$).[72,73] Additionally, a *BRAF* splicing mutation (*BRAF* c.1511_1517 + 2 duplication) was reported.[74] Furthermore, activating, in-frame deletions in *BRAF* exon 12 (encodes the β3-αC loop critical for kinase activation) and numerous *BRAF* fusions have been described in HDCNs (see **Figs. 2** and **4**).[13,75–77] Other whole exome sequencing (WES) studies have revealed activating *ARAF* mutations in LCH[78] and non-LCH (ECD; JXG/AXG; RDD) along with *RAF1* mutations in ECD and HS (see **Fig. 2**).[7,12,13]

MAP2K1/MAP2K2

In $BRAF^{V600E}$-negative histiocytoses, Next-generation sequencing (NGS) studies found *MAP2K1* to be a second recurrently mutated gene locus in LCH[5,6] and non-LCH (ECD, JXG/AXG, RDD. ICH, and HS).[7,79] Functionally, the *MAP2K1* mutations occurred within mutational hot-spots and clustered in the N-terminal regulatory domain (exon 2) and N-terminal kinase domain (exon 3) resulting in MAPK activation.[6,7,79,80] However, there are different biochemical classes of *MAP2K1* (encodes MEK1) mutations. Class I mutants are dependent on and hyperactivated by phosphorylation of MEK1/2 from RAF kinases. Therefore, they are sensitive to ERK-dependent feedback inhibition. Class II mutants have some degree of basal RAF-independent activity but are further activated by RAF. Class III mutants, however, are completely RAF-independent, drive high levels of ERK1/2 activation, are insensitive to ERK-dependent feedback inhibition, and are predicted to be the most likely of any class of MEK1 mutations to transform cells. Furthermore, in vitro studies within solid tumor cell lines have shown that biochemical Class III MEK1 mutations do not respond well to allosteric MEK1/2 inhibitors (trametinib, cobimetinib, etc.).[81] Additionally, ECD sequencing found recurrent $MAP2K2^{Y134H}$ in the MEK2 kinase domain that activated MAPK signaling (see **Figs. 1** and **2**).[12,13]

RAS Isoforms and Regulators of Rat Ssarcoma Virus (RAS) Activation

The RAS isoforms encode small GTPases that regulate the MAPK and PI3K-AKT-mTOR signaling pathways. First, *NRAS* mutations were found in single cases of LCH and ECD.[82,83] Afterward, studies confirmed that *NRAS*/*KRAS* mutations are recurrent in HDCNs and affected the GTP-binding domains leading to constitutive

MAPK activation (see Figs. 1 and 2).[7,13,77,79,84,85] Interestingly, regulators of RAS activation are frequently affected in HS but very rarely in the other HDCNs. Activating mutations in *PTPN11* (positive regulator of RAS activation) and inactivating mutations in *NF1* (negative regulator of RAS activation) are frequently uncovered in HS or co-occur with other kinase driver alterations (see Figs. 1 and 2).[53–55]

Extracellular-Signal-Regulated Kinases Isoforms

As the molecular age continued to interrogate *BRAF*^{V600}-negative histiocytoses, rare mutations started to emerge in the ERK isoforms. An activating *MAPK1*^{D321N} affecting the ERK2 C-terminal-docking domain surfaced in JXG and showed *in vitro* sensitivity to ERK inhibition but not RAF or MEK inhibition.[86] Another WES study of LCH found *MAPK3*^{V121M} in the ERK1 kinase domain and *MAPK7*^{R400L} affecting the ERK5 C-terminal-domain with both mutations influencing MAPK signaling (see Figs. 1 and 2).[13]

PI3K Isoforms

The PI3K isoforms include phosphatidylinositol-4,5-bisphosphate-3-kinase catalytic subunit alpha (*PIK3CA*) and catalytic subunit delta (*PIK3CD*), members of the PI3K-AKT signaling pathway. Recurrent *PIK3CA* mutations were first revealed in ECD,[84] and then in LCH.[87] Later studies primarily identified *PIK3CA* mutations as recurrent events in ECD with rare *PIK3CD* mutations in JXG and LCH. *PIK3CA* mutations clustered in the α-helical and kinase domains leading to PI3K-AKT-mTOR activation (see Figs. 1 and 2).[6,7,13]

ALK Receptor Tyrosine Kinase Fusions

ALK-rearrangements can be confirmed by fluorescence in situ hybridization (FISH) or RNA sequencing. *KIF5B* serves as a microtubule-dependent motor involved in the normal distribution of mitochondria and lysosomes and is the most common 5′ fusion partner for ALK with several variable fusion breakpoints within *KIF5B*, but *CLTC::ALK*, *TPM3::ALK*, *TFG::ALK*, *EML4::ALK*, *SQSTM1::ALK*, and *DCTN1::ALK* fusions have been described as well (Fig. 3). All the described ALK fusions have an intact kinase domain fused with different 5′ partner genes where the N-terminal protein has a coiled-coil or other heterodimerization domains that can lead to ligand-independent constitutive activation of the intact, intracellular ALK kinase domain leading to inappropriate overexpression of ALK and constitutive activation of the MAPK and PI3K-AKT-mTOR signaling pathways within the neoplastic histiocytes (see Fig. 1).[57,58]

Other Tyrosine Kinase Alterations

Continued sequencing of histiocytoses implicated the RTKs. A WES study found a case of *ERBB3*-mutated LCH.[6] Later studies uncovered recurrent *NTRK1* fusions in ECD and the xanthogranuloma family (JXG/AXG).[7,77] Then, a large WES/NGS study evaluated 270 histiocytoses patients and discovered recurrent, activating mutations in *CSF1R*, the RTK critical for monocyte and macrophage development, which was enriched in JXG/AXG but found across histiocytoses; and this study was really the first time that activating *CSF1R* mutations have been implicated in cancer. Additionally, other RTK alterations were uncovered in the xanthogranuloma family (JXG/AXG) (*KIT*, *JAK3*, *ALK*, *MET*, and *CSF3R*) and in LCH (TEK), as well as the first *RET* and *NTRK3* fusions in the histiocytoses (see Figs. 2 and 4).[13,58,88,89]

Quite recently, recurrent and functional *SYK* fusions were implicated in the pathogenesis of xanthogranuloma family (JXG/AXG) neoplasms with *CLTC*::*SYK* being the most common. SYK is a nonreceptor tyrosine kinase that is primarily expressed in hematopoietic cells (B cells, monocytes, and macrophages). The kinase domain

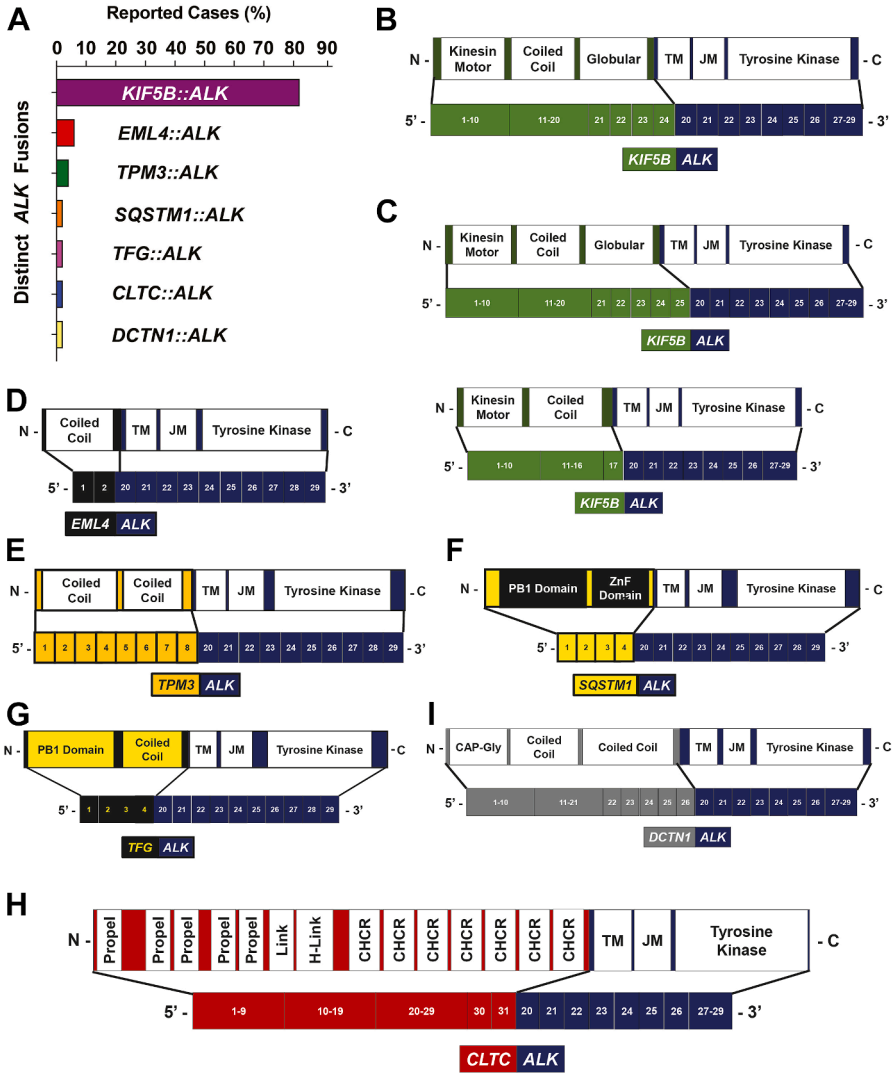

Fig. 3. Summary of the *ALK* fusions uncovered in ALK-positive histiocytosis. (*A*) Histogram showing the current frequencies of distinct *ALK* fusions in ALK-positive histiocytosis. (*B*) Illustrations of the recurrent *KIF5B::ALK* fusions with the most common *KIF5B* (exons 1–24) and *ALK* (exons 20–27) fusion, as well as (*C*) fusions with variant breakpoints involving *KIF5B* across the ALK-positive histiocytosis. Diagrams of the less common fusions: (*D*) *EML4::ALK* fusions, (*E*) *TPM3::ALK* fusions, (*F*) *SQSTM1::ALK* fusion, (*G*) *TFG::ALK* fusion, (*H*) *CLTC::ALK* fusion, and (*I*) *DCTN1::ALK* fusion.

of SYK is held in an inactive confirmation by the Src homology 2 (SH2) domains; however, the *CLTC*::*SYK* fusion results in the deletion of these SH2 domains (see **Figs. 2** and **4**) and thereby in a continuously active kinase.[89]

ETV3-NCOA2 Fusions

ETV3-NCOA2 fusions were described to be enriched in ICH and then reported in one LCH case.[77,90,91] These fusions involve exons 1 to 4 of *ETV3* and exons 14

to 23 of *NCOA2*. This leads to the preservation and fusion of the C-terminal transcriptional activation domains of NCOA2 to the N-terminal ETS domain of ETV3 (**Fig. 4**),[90,92,93] and prior studies of *NCOA2* gene fusions have demonstrated that the AD1 and CID domains in the C-terminus are required for the transformation of NCOA2 fusion proteins (see **Figs. 2** and **4**).[48,90–92,94–97] However, extensive functional characterization of the role of the *ETV3-NCOA2* fusion in histiocytoses pathogenesis is warranted.

Overall, the molecular age demonstrates most HDCNs patients harbor diverse alterations in MAPK, PI3K-AKT-mTOR, and RTK pathway genes supporting that histiocytoses are clonal, hematopoietic neoplasms with many potential molecular therapeutic targets.

MOLECULARLY INSPIRED HISTIOCYTIC AND DENDRITIC CELL NEOPLASM THERAPEUTIC TARGETS

Over the past 5 to 10 y, therapy for histiocytoses has dramatically changed with the emergence of targeted therapy and the first US-Food and Drug Administration (FDA)-approved HDCNs treatment resulting in an improved prognosis for ECD (5-y survival of 43% in 1996 but 83% currently).[43,98]

Since 50% to 60% of HDCNs patients harbor *BRAF*^{V600E},[2,3] a vemurafenib phase II clinical trial studied *BRAF*^{V600}-mutated ECD and LCH and demonstrated a nearly 100% metabolic response rate, as did several case series. As a result, the US-FDA approved vemurafenib for use in *BRAF*^{V600}-mutated ECD in November 2017.[9,11,14,99–102] Although BRAF inhibition generally achieves robust and durable responses in *BRAF*^{V600}-mutated histiocytoses, the LOVE study showed 75% of patients who discontinued vemurafenib relapsed in 6 mo but were able to recapture their prior responses when restarted on BRAF inhibitors (vemurafenib; dabrafenib).[103,104] Additionally, BRAF inhibitor resistance in the SH is rare and has only been reported in one instance where a dabrafenib-treated *BRAF*^{V600E}-mutated ECD patient acquired a *KRAS* mutation, which responded to trametinib.[105]

Accumulating molecular knowledge in *BRAF*^{V600}-negative SH led to investigations into MEK inhibitors (cobimetinib; trametinib)[7,12,103,106] with the cobimetinib phase II clinical trial showing an 89% overall response rate by fluorodeoxyglucose (FDG)-PET-computed tomography (CT) irrespective of disease site. As a result, the US-FDA granted approval in November 2022 to cobimetinib in the treatment of *BRAF*^{V600}-negative histiocytoses.[12] However, *in vitro* studies have shown that there are different biochemical classes of *MAP2K1* (encodes MEK1) mutations (second most frequent alterations across HDCNs) where biochemical class III MEK1 mutations show response heterogeneity to the FDA-approved, allosteric MEK1/2 inhibitors (trametinib, cobimetinib, etc.).[12,81] Therefore, alternative targeted therapies to biochemical class III MEK1 mutations beyond allosteric MEK1/2 inhibitors will likely need to be explored.

Moreover, molecular discovery of recurrent *ALK*, *NTRK1*, *RET,* and *SYK* fusions*,* as well as *CSF1R* mutations in diverse histioctyoses have stimulated investigations into other targeted therapies. These studies have provided *in vitro* functional data or clinical reports supporting the use of ALK inhibitors (crizotinib; alectinib); the RET-specific inhibitor selpercatinib; NTRK inhibitors; and *CSF1R*-inhibitors (pexidartinib) in HDCNs.[7,13,64,77,107] Therefore, the molecular age has provided many exciting therapeutic options for HDCNs patients, but molecularly-targeted therapies beyond BRAF and MEK inhibitors need to be scrutinized in future clinical trials. Also, questions about the optimal dosing, treatment duration, and therapy response assessments require further study, especially in pediatric HDCNs patients.

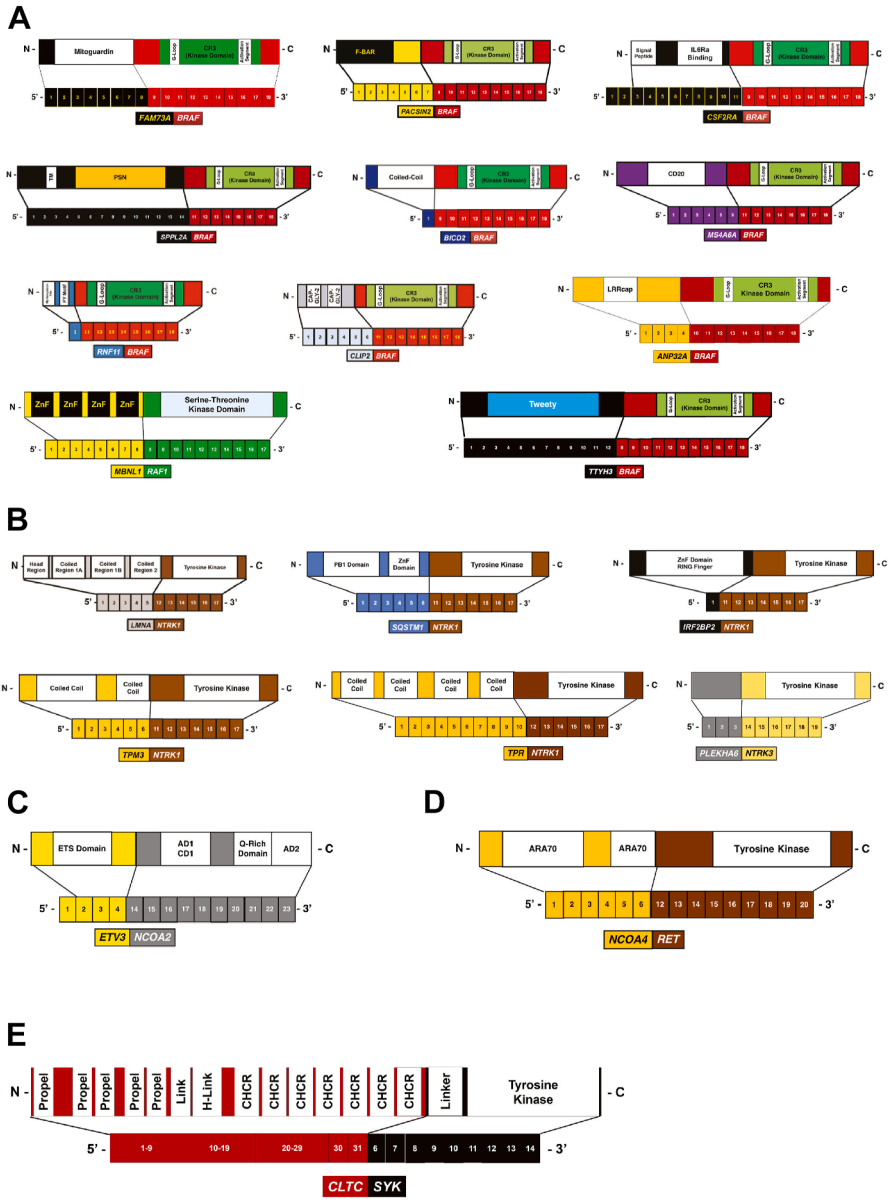

Fig. 4. Summary of the diverse kinase fusions in histiocytic neoplasms. (*A*) Illustrations of recurrent *BRAF* fusions discovered in the histiocytic neoplasms. (*B*) Illustrations of the recurrent *NTRK1* fusions uncovered in non-Langerhans cell histiocytoses and an *NTRK3* fusion in Langerhans cell histiocytosis (LCH). (*C*) Illustration of the recurrent *ETV3::NCOA2* fusion discovered in indeterminate cell histiocytosis. (*D*) Illustration of the recurrent *NCOA4::RET* fusion recently discovered in non-LCH. (*E*) Illustration of the recurrent *CLTC::SYK* fusions in the xanthogranuloma (XG) family of histiocytic neoplasms (juvenile/adult xanthogranulomatosis[JXG/AXG]).

SUMMARY AND FUTURE DIRECTIONS

Molecular advancements over the past 15 y have helped unravel the molecular pathophysiology and therapeutic targets in the MAPK-driven hematologic neoplasms. Since the description of *BRAF*^{V600E} in LCH and ECD,[2–4] there has been an onslaught of molecular progress linking diverse kinase alterations activating MAPK, PI3K-AKT-mTOR, and RTK signaling to the diverse histiocytic and dendritic cell neoplasms (see **Figs. 1–4**). These recent discoveries have refined the current pathologic understanding of the histiocytoses as clonal, myeloid neoplasms with constitutive activation of MAPK and PI3K-AKT-mTOR signaling. Furthermore, molecular progress has reimagined therapeutic options for patients with these disorders. Additionally, many biomarkers are now available that have enhanced our biologic understanding of the cellular pathogenesis and ontogeny of the HDCNs. However, our functional genomic conceptualization of the molecular pathogenesis and histogenesis of the HDCNs are just emerging with many aspects still enshrouded in mystery requiring systematic dissection with studies employing single-cell and spatial molecular and epigenetic analyses, detailed proteomics analyses, and intricate metabolomic studies, as well as pre-clinical models. Finally, as the molecular era continues to unfold, future comprehensive studies to elucidate why the HDCNs share common MAP kinase, PI3K-AKT-mTOR, and RTK alterations but are phenotypically diverse neoplasms with differing clinical presentations, pathophysiology, suspected cellular origins, and responses to targeted therapeutics are a desperately needed dimension of investigation.

CLINICS CARE POINTS

- Next-generation sequencing (NGS) molecular studies are recommended when evaluating histiocytic and dendritic cell neoplasms (HDCNs) for molecular therapeutic guidance across the histiocytic neoplasms.
- Pathological diagnostic evaluation of HDCNs now warrants the use of ALK immunohistochemistry and molecular studies for ALK rearrangements/fusions.
- RAF inhibitors (vemurafenib; dabrafenib) have significant clinical efficacy in BRAFV600-mutated HDCNs while allosteric MEK1/2 inhibitors (trametinib; cobimetinib) have been clinically efficacious in BRAFV600-negative HDCNs.

ACKNOWLEDGMENTS

B.H. Durham has been supported by the Fellow Scholar Award in Basic/Translational Research from the American Society of Hematology, a grant from the Erdheim-Chester Disease Global Alliance Foundation, a K08 CA218901 from the National Cancer Institute, United States of the the National Institutes of Health, and in-kind instutional start-up funding from Rutgers Cancer Institute.

DISCLOSURES

The authors have nothing to disclose.

REFERENCES

1. Wellbrock C, Karasarides M, Marais R. The RAF proteins take centre stage. Nat Rev Mol Cell Biol 2004;5(11):875–85.

2. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 2010;116(11):1919–23.
3. Haroche J, Charlotte F, Arnaud L, et al. High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood 2012;120(13):2700–3 [published Online First: 2012/08/11].
4. Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. N Engl J Med 2011;364(24):2305–15 [published Online First: 2011/06/11].
5. Brown NA, Furtado LV, Betz BL, et al. High prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. Blood 2014;124-(10):1655–8.
6. Chakraborty R, Hampton OA, Shen X, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. Blood 2014;124(19):3007–15.
7. Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. Cancer Discov 2016;6(2):154–65.
8. Durham BH, Diamond EL, Abdel-Wahab O. Histiocytic neoplasms in the era of personalized genomic medicine. Curr Opin Hematol 2016;23(4):416–25.
9. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 2015;373(8):726–36 [published Online First: 2015/08/20].
10. Tiacci E, Park JH, De Carolis L, et al. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. N Engl J Med 2015;373(18):1733–47. [published Online First: 2015/09/09].
11. Diamond EL, Subbiah V, Lockhart AC, et al. Vemurafenib for BRAF V600-mutant erdheim-chester disease and langerhans cell histiocytosis: analysis of data from the histology-independent, phase 2, open-label VE-BASKET study. JAMA Oncol 2018;4(3):384–8.
12. Diamond EL, Durham BH, Ulaner GA, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature 2019;567(7749):521–4 [published Online First: 2019/03/15].
13. Durham BH, Lopez Rodrigo E, Picarsic J, et al. Activating mutations in CSF1R and additional receptor tyrosine kinases in histiocytic neoplasms. Nat Med 2019;25(12):1839–42 [published Online First: 2019/11/27].
14. Haroche J, Cohen-Aubart F, Emile JF, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood 2013;121(9): 1495–500 [published Online First: 2012/12/22].
15. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Revised 4th edition. Lyon: International Agency for Research on Cancer; 2017.
16. Ozkaya N, Rosenblum MK, Durham BH, et al. The histopathology of Erdheim-Chester disease: a comprehensive review of a molecularly characterized cohort. Mod Pathol 2018;31(4):581–97 [published Online First: 2017/12/01].
17. Emile J, Abla O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 2016;127:2672–81.
18. Arceci RJ. The histiocytoses: the fall of the Tower of Babel. Eur J Cancer 1999; 35(5):747–67; discussion 67-9 doi: S0959804999000398 [pii].
19. McClain KL, Natkunam Y, Swerdlow SH. Atypical cellular disorders. Hematology Am Soc Hematol Educ Program 2004;283–96.

20. Guyot-Goubin A, Donadieu J, Barkaoui M, et al. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000-2004. Pediatr Blood Cancer 2008;51(1):71–5.
21. Stalemark H, Laurencikas E, Karis J, et al. Incidence of Langerhans cell histiocytosis in children: a population-based study. Pediatr Blood Cancer 2008;51(1):76–81.
22. Broadbent V, Egeler RM, Nesbit ME Jr. Langerhans cell histiocytosis–clinical and epidemiological aspects. Br J Cancer Suppl 1994;23:S11–6.
23. A multicentre retrospective survey of Langerhans' cell histiocytosis. 348 cases observed between 1983 and 1993. The French Langerhans' Cell Histiocytosis Study Group. Arch Dis Child 1996;75(1):17–24.
24. Gadner H, Minkov M, Grois N, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood 2013;121(25):5006–14.
25. Grois NG, Favara BE, Mostbeck GH, et al. Central nervous system disease in Langerhans cell histiocytosis. Hematol Oncol Clin N Am 1998;12(2):287–305.
26. Grois N, Fahrner B, Arceci RJ, et al. Central nervous system disease in Langerhans cell histiocytosis. J Pediatr 2010;156(6):873–81.e1.
27. Heritier S, Barkaoui MA, Miron J, et al. Incidence and risk factors for clinical neurodegenerative Langerhans cell histiocytosis: a longitudinal cohort study. Br J Haematol 2018;183(4):608–17.
28. Favara BE, Feller AC, Pauli M, et al. Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol 1997;29(3):157–66.
29. Chikwava K, Jaffe R. Langerin (CD207) staining in normal pediatric tissues, reactive lymph nodes, and childhood histiocytic disorders. Pediatr Dev Pathol 2004;7(6):607–14.
30. Nezelof C, Basset F, Rousseau M. Histiocytosis X histogenetic arguments for a Langerhans cell origin. Biomedicine/[publiée pour l'AAICIG] 1973;18(5):365.
31. Laman JD, Leenen PJ, Annels NE, et al. Langerhans-cell histiocytosis 'insight into DC biology'. Trends Immunol 2003;24(4):190–6.
32. Senechal B, Elain G, Jeziorski E, et al. Expansion of regulatory T cells in patients with Langerhans cell histiocytosis. PLoS Med 2007;4(8):e253. https://doi.org/10.1371/journal.pmed.0040253.
33. Allen CE, Li L, Peters TL, et al. Cell-specific gene expression in Langerhans cell histiocytosis lesions reveals a distinct profile compared with epidermal Langerhans cells. J Immunol 2010;184(8):4557–67.
34. Berres ML, Lim KP, Peters T, et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med 2014;211(4):669–83.
35. McDonagh J, McDonagh J. A contribution to our knowledge of the naevo-xantho-endotheliomata. Br J Dermatol 1912;24:85–99.
36. Allen CE, Parsons DW. Biological and clinical significance of somatic mutations in Langerhans cell histiocytosis and related histiocytic neoplastic disorders. Hematology Am Soc Hematol Educ Program 2015;2015:559–64.
37. Weitzman S, Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. Pediatr Blood Cancer 2005;45(3):256–64.
38. Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Blood 2014;124(4):483–92 [published Online First: 2014/05/23].

39. Haroche J, Abla O. Uncommon histiocytic disorders: Rosai-Dorfman, juvenile xanthogranuloma, and Erdheim-Chester disease. Hematology Am Soc Hematol Educ Program 2015;2015:571–8.
40. Haroche J, Cohen-Aubart F, Rollins BJ, et al. Histiocytoses: emerging neoplasia behind inflammation. Lancet Oncol 2017;18(2):e113–25.
41. Chester W. Über lipoidgranulomatose. Virchows Arch Pathol Anat Physiol Klin Med 1930;279(2):561–602.
42. Estrada-Veras JI, O'Brien KJ, Boyd LC, et al. The clinical spectrum of Erdheim-Chester disease: an observational cohort study. Blood Adv 2017;1(6):357–66.
43. Cohen-Aubart F, Emile JF, Carrat F, et al. Phenotypes and survival in Erdheim-Chester disease: results from a 165-patient cohort. Am J Hematol 2018;93(5):E114–7 [published Online First: 2018/02/10].
44. Destombes P. [Adenitis with lipid excess, in children or young adults, seen in the Antilles and in Mali. (4 cases)]. Bull Soc Pathol Exot Filiales 1965;58(6):1169–75.
45. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. Arch Pathol 1969;87(1):63–70.
46. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: a pseudolymphomatous benign disorder. Analysis of 34 cases. Cancer 1972;30(5):1174–88.
47. Abla O, Jacobsen E, Picarsic J, et al. Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood 2018;131(26):2877–90 [published Online First: 2018/05/04].
48. Durham BH. Molecular characterization of the histiocytoses: neoplasia of dendritic cells and macrophages. Semin Cell Dev Biol 2019;86:62–76 [published Online First: 2018/03/13].
49. Rezk SA, Spagnolo DV, Brynes RK, et al. Indeterminate cell tumor: a rare dendritic neoplasm. Am J Surg Pathol 2008;32(12):1868–76.
50. Wood GS, Hu CH, Beckstead JH, et al. The indeterminate cell proliferative disorder: report of a case manifesting as an unusual cutaneous histiocytosis. J Dermatol Surg Oncol 1985;11(11):1111–9.
51. Campo E, Jaffe ES, Cook JR, et al. The international Consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee. Blood 2022;140(11):1229–53.
52. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36(7):1703–19 [published Online First: 2022/06/22].
53. Shanmugam V, Griffin GK, Jacobsen ED, et al. Identification of diverse activating mutations of the RAS-MAPK pathway in histiocytic sarcoma. Mod Pathol 2019;32(6):830–43 [published Online First: 2019/01/09].
54. Egan C, Nicolae A, Lack J, et al. Genomic profiling of primary histiocytic sarcoma reveals two molecular subgroups. Haematologica 2020;105(4):951–60 [published Online First: 2019/08/22].
55. Ruan GJ, Zanwar S, Ravindran A, et al. Clinical characteristics, molecular aberrations, treatments, and outcomes of malignant histiocytosis. Am J Hematol 2024;99(5):871–9 [published Online First: 2024/02/26].
56. Kordes M, Roring M, Heining C, et al. Cooperation of BRAF(F595L) and mutant HRAS in histiocytic sarcoma provides new insights into oncogenic BRAF signaling. Leukemia 2016;30(4):937–46 [published Online First: 2015/11/19].

57. Chan JK, Lamant L, Algar E, et al. ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy. Blood 2008;112(7):2965–8 [published Online First: 2008/07/25].
58. Kemps PG, Picarsic J, Durham BH, et al. ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition. Blood 2022;139(2):256–80.
59. Kemps PG, Hebeda KM, Pals ST, et al. Spectrum of histiocytic neoplasms associated with diverse haematological malignancies bearing the same oncogenic mutation. J Pathol Clin Res 2021;7(1):10–26 [published Online First: 2020/08/27].
60. Bhatia A, Hatzoglou V, Ulaner G, et al. Neurologic and oncologic features of Erdheim-Chester disease: a 30-patient series. Neuro Oncol 2020;22(7):979–92.
61. Gupta GK, Xi L, Pack SD, et al. ALK-positive histiocytosis with KIF5B-ALK fusion in an adult female. Haematologica 2019;104(11):e534–6 [published Online First: 2019/08/01].
62. Kashima J, Yoshida M, Jimbo K, et al. ALK-positive histiocytosis of the breast: a clinicopathologic study highlighting spindle cell histology. Am J Surg Pathol 2021;45(3):347–55.
63. Osako T, Kurisaki-Arakawa A, Dobashi A, et al. Distinct clinicopathologic features and possible pathogenesis of localized ALK-positive histiocytosis of the breast. Am J Surg Pathol 2022;46(3):344–52.
64. Chang KTE, Tay AZE, Kuick CH, et al. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. Mod Pathol 2019;32(5):598–608 [published Online First: 2018/12/20].
65. Arceci RJ, Brenner MK, Pritchard J. Controversies and new approaches to treatment of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12(2):339–57.
66. Degar BA, Rollins BJ. Langerhans cell histiocytosis: malignancy or inflammatory disorder doing a great job of imitating one? Dis Model Mech 2009;2(9–10):436–9.
67. da Costa CE, Szuhai K, van Eijk R, et al. No genomic aberrations in Langerhans cell histiocytosis as assessed by diverse molecular technologies. Genes Chromosomes Cancer 2009;48(3):239–49.
68. Merad M, Manz MG, Karsunky H, et al. Langerhans cells renew in the skin throughout life under steady-state conditions. Nat Immunol 2002;3(12):1135–41 [published Online First: 2002/11/04].
69. Techavichit P, Sosothikul D, Chaichana T, et al. BRAF V600E mutation in pediatric intracranial and cranial juvenile xanthogranuloma. Hum Pathol 2017;69:118–22 [published Online First: 2017/05/10].
70. Fatobene G, Haroche J, Helias-Rodzwicz Z, et al. BRAF V600E mutation detected in a case of Rosai-Dorfman disease. Haematologica 2018;103(8):e377–9 [published Online First: 2018/05/10].
71. O'Malley DP, Agrawal R, Grimm KE, et al. Evidence of BRAF V600E in indeterminate cell tumor and interdigitating dendritic cell sarcoma. Ann Diagn Pathol 2015;19(3):113–6 [published Online First: 2015/03/05].
72. Satoh T, Smith A, Sarde A, et al. B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease. PLoS One 2012;7(4):e33891. https://doi.org/10.1371/journal.pone.0033891 [published Online First: 2012/04/10].
73. Kansal R, Quintanilla-Martinez L, Datta V, et al. Identification of the V600D mutation in Exon 15 of the BRAF oncogene in congenital, benign langerhans cell

histiocytosis. Genes Chromosomes Cancer 2013;52(1):99–106 [published Online First: 2012/09/21].
74. Heritier S, Helias-Rodzewicz Z, Chakraborty R, et al. New somatic BRAF splicing mutation in Langerhans cell histiocytosis. Mol Cancer 2017;16(1):115.
75. Chakraborty R, Burke TM, Hampton OA, et al. Alternative genetic mechanisms of BRAF activation in Langerhans cell histiocytosis. Blood 2016;128(21):2533–7 [published Online First: 2016/10/11].
76. Zarnegar S, Durham BH, Khattar P, et al. Novel activating BRAF fusion identifies a recurrent alternative mechanism for ERK activation in pediatric Langerhans cell histiocytosis. Pediatr Blood Cancer 2018;65(1). https://doi.org/10.1002/pbc.26699 [published Online First: 2017/07/27].
77. Lee LH, Gasilina A, Roychoudhury J, et al. Real-time genomic profiling of histiocytoses identifies early-kinase domain BRAF alterations while improving treatment outcomes. JCI Insight 2017;2(3):e89473. https://doi.org/10.1172/jci.insight.89473 [published Online First: 2017/02/09].
78. Nelson DS, Quispel W, Badalian-Very G, et al. Somatic activating ARAF mutations in Langerhans cell histiocytosis. Blood 2014;123(20):3152–5.
79. Garces S, Medeiros LJ, Patel KP, et al. Mutually exclusive recurrent KRAS and MAP2K1 mutations in Rosai-Dorfman disease. Mod Pathol 2017;30(10):1367–77 [published Online First: 2017/06/30].
80. Nelson DS, van Halteren A, Quispel WT, et al. MAP2K1 and MAP3K1 mutations in Langerhans cell histiocytosis. Genes Chromosomes Cancer 2015;54(6):361–8 [published Online First: 2015/03/31].
81. Gao Y, Chang MT, McKay D, et al. Allele-specific mechanisms of activation of MEK1 mutants determine their properties. Cancer Discov 2018;8(5):648–61 [published Online First: 2018/02/26].
82. Ozono S, Inada H, Nakagawa SI, et al. Juvenile myelomonocytic leukemia characterized by cutaneous lesion containing Langerhans cell histiocytosis-like cells. Int J Hematol 2011;93(3):389–93 [published Online First: 2011/02/25].
83. Diamond EL, Abdel-Wahab O, Pentsova E, et al. Detection of an NRAS mutation in Erdheim-Chester disease. Blood 2013;122(6):1089–91.
84. Emile JF, Diamond EL, Helias-Rodzewicz Z, et al. Recurrent RAS and PIK3CA mutations in Erdheim-Chester disease. Blood 2014;124(19):3016–9 [published Online First: 2014/08/26].
85. Shanmugam V, Margolskee E, Kluk M, et al. Rosai-dorfman disease harboring an activating KRAS K117N missense mutation. Head Neck Pathol 2016;10(3):394–9 [published Online First: 2016/02/27].
86. Chakraborty R, Hampton OA, Abhyankar H, et al. Activating MAPK1 (ERK2) mutation in an aggressive case of disseminated juvenile xanthogranuloma. Oncotarget 2017;8(28):46065–70.
87. Heritier S, Saffroy R, Radosevic-Robin N, et al. Common cancer-associated PIK3CA activating mutations rarely occur in Langerhans cell histiocytosis. Blood 2015;125(15):2448–9.
88. Cai J, Huang X, Yin M, et al. A novel fusion gene PLEKHA6-NTRK3 in langerhans cell histiocytosis. Int J Cancer 2019;144(1):117–24 [published Online First: 2018/10/26].
89. Kemps PG, Baelde HJ, Vorderman RHP, et al. Recurrent CLTC::SYK fusions and CSF1R mutations in juvenile xanthogranuloma of soft tissue. Blood 2024;144-(23):2439–55.

90. Brown RA, Kwong BY, McCalmont TH, et al. ETV3-NCOA2 in indeterminate cell histiocytosis: clonal translocation supports sui generis. Blood 2015;126(20): 2344–5 [published Online First: 2015/10/05].
91. Kemps PG, Woei AJF, Quint KD, et al. Recurrent ETV3::NCOA2 fusions and MAPK pathway mutations in indeterminate dendritic cell histiocytosis. Blood Adv 2025;9(3):439–44.
92. Wang L, Motoi T, Khanin R, et al. Identification of a novel, recurrent HEY1-NCOA2 fusion in mesenchymal chondrosarcoma based on a genome-wide screen of exon-level expression data. Genes Chromosomes Cancer 2012; 51(2):127–39 [published Online First: 2011/10/27].
93. Mesquita B, Lopes P, Rodrigues A, et al. Frequent copy number gains at 1q21 and 1q32 are associated with overexpression of the ETS transcription factors ETV3 and ELF3 in breast cancer irrespective of molecular subtypes. Breast Cancer Res Treat 2013;138(1):37–45 [published Online First: 2013/01/18].
94. Carapeti M, Aguiar RC, Goldman JM, et al. A novel fusion between MOZ and the nuclear receptor coactivator TIF2 in acute myeloid leukemia. Blood 1998;91(9): 3127–33.
95. Deguchi K, Ayton PM, Carapeti M, et al. MOZ-TIF2-induced acute myeloid leukemia requires the MOZ nucleosome binding motif and TIF2-mediated recruitment of CBP. Cancer Cell 2003;3(3):259–71.
96. Strehl S, Nebral K, Konig M, et al. ETV6-NCOA2: a novel fusion gene in acute leukemia associated with coexpression of T-lymphoid and myeloid markers and frequent NOTCH1 mutations. Clin Cancer Res 2008;14(4):977–83.
97. Sumegi J, Streblow R, Frayer RW, et al. Recurrent t(2;2) and t(2;8) translocations in rhabdomyosarcoma without the canonical PAX-FOXO1 fuse PAX3 to members of the nuclear receptor transcriptional coactivator family. Genes Chromosomes Cancer 2010;49(3):224–36.
98. Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. Medicine (Baltim) 1996;75(3):157–69.
99. Cohen-Aubart F, Emile JF, Maksud P, et al. Marked efficacy of vemurafenib in suprasellar Erdheim-Chester disease. Neurology 2014;83(14):1294–6 [published Online First: 2014/08/29].
100. Haroche J, Cohen-Aubart F, Emile JF, et al. Reproducible and sustained efficacy of targeted therapy with vemurafenib in patients with BRAF(V600E)-mutated Erdheim-Chester disease. J Clin Oncol 2015;33(5):411–8 [published Online First: 2014/11/26].
101. Borys D, Nystrom L, Song A, et al. Erdheim Chester disease with appendicular skeletal, renal and pleural involvement responding to Zelboraf (BRAF inhibitor) treatment: case report. Skelet Radiol 2016;45(10):1397–402 [published Online First: 2016/07/16].
102. Bhatia A, Ulaner G, Rampal R, et al. Single-agent dabrafenib for BRAF(V600E)-mutated histiocytosis. Haematologica 2018;103(4):e177–80 [published Online First: 2018/02/22].
103. Cohen Aubart F, Emile JF, Carrat F, et al. Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). Blood 2017;130(11):1377–80 [published Online First: 2017/06/30].
104. Vaglio A, Diamond EL. Erdheim-Chester disease: the “targeted” revolution. Blood 2017;130(11):1282–4.

105. Nordmann TM, Juengling FD, Recher M, et al. Trametinib after disease reactivation under dabrafenib in Erdheim-Chester disease with both BRAF and KRAS mutations. Blood 2017;129(7):879–82 [published Online First: 20161209].
106. Cohen Aubart F, Emile JF, Maksud P, et al. Efficacy of the MEK inhibitor cobimetinib for wild-type BRAF Erdheim-Chester disease. Br J Haematol 2018;180(1):150–3 [published Online First: 2016/10/06].
107. Taylor J, Pavlick D, Yoshimi A, et al. Oncogenic TRK fusions are amenable to inhibition in hematologic malignancies. J Clin Investig 2018;128(9):3819–25 [published Online First: 2018/08/06].