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# Systemic Histiocytosis (Langerhans Cell Histiocytosis, Erdheim–Chester Disease, Destombes–Rosai–Dorfman Disease): from Oncogenic Mutations to Inflammatory Disorders

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## Abstract

**Purpose of Review** Provide an overview of recent progress in decoding the pathogenesis and treatment of systemic histiocytoses.

**Recent Findings** Advances in molecular techniques over the last few years, enabling the identification of several MAPK mutations in lesion histiocytes, have revolutionized our understanding of histiocytosis that led to a revised classification and new treatments.

**Summary** Since the 2010 discovery of the $BRAF^{V600E}$ mutation in 57% of Langerhans cell histiocytosis (LCH) lesions, several other kinase mutations have been found, mostly in the MAPK pathway, and also in other key signaling pathways, in LCH, Erdheim–Chester Disease (ECD) and, less frequently, Destombes–Rosai–Dorfman disease (RDD). Those revolutionary breakthroughs enhanced our understanding of the pathogenesis of histiocytosis and led to trials with targeted therapies that demonstrated notable efficacy.

**Keywords** Langerhans cell histiocytosis · Erdheim–Chester disease · Destombes–Rosai–Dorfman disease · Myeloid neoplasm

## Introduction

Langerhans cell histiocytosis (LCH), Erdheim–Chester disease (ECD), and Destombes–Rosai–Dorfman disease (RDD) are rare inflammatory diseases that can be localized in a single organ or systemic with multi-organ involvement. They share histopathological features: tissue infiltration by histiocytes, with or without Langerhans cell (LC) markers, and inflammatory cells, and sometimes affect several organs.

Classifying these three disorders under the term "histiocytoses" was actually accurate, as confirmed by the pivotal breakthrough in our understanding of their pathogeneses over the past few years, i.e., the discovery of recurrent mitogen–activated protein kinase (MAPK) pathway mutations in LCH, ECD, and sometimes RDD [1, 2, 3••].

Those findings, in addition to expanding our knowledge and generating a new revised classification [4], led to targeted-therapy trials which obtained good responses [5, 6, 7•].

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This review on LCH, ECD, and RDD focuses on recent molecular discoveries, their clinical pictures at onset, and current standard of care.

## Pathogenesis: Oncogene Mutations in Hematopoietic Cells Leading to Inflammatory Histiocytic Disorders

### Discovery of the *BRAF*$^{V600E}$ Mutation: a Key to the Origin of Histiocytoses

LCH origin was largely unknown until 2010, when a mass spectrometry study targeting cancer genes highlighted the nucleotide variant *BRAF*$^{V600E}$ in 35 (57%) of 61 LCH samples [1]. The *BRAF*$^{V600E}$ mutation is involved in 7% of human cancers [8], some of which might benefit from targeted therapy [9]. This oncogene mutation renders the MAPK pathway constitutively active, because BRAF is a pivotal kinase in the RAS–RAF–MEK signaling pathway, which is involved in several cell functions, such as proliferation, apoptosis, angiogenesis, migration, and survival [8].

According to multivariate logistic regression analyses of the characteristics of a large French cohort including 315 pediatric LCH patients, *BRAF*$^{V600E}$ mutations were associated with risk organ (i.e., liver, spleen, and hematological system) involvement and multi-organ disease [10]. In 2012, a pyrosequencing study on 93 patients with different histiocytoses found 38% of those with LCH had the *BRAF*$^{V600E}$ mutation, and 54% of ECD [2], but not in other histiocytic diseases (RDD, juvenile xanthogranuloma, histiocytic sarcoma, xanthoma disseminatum, interdigitating cell sarcoma, or necrobiotic granuloma). Immunohistochemical analyses of ECD tissue samples with a *BRAF*$^{V600E}$-selective antibody confirmed the mutation's expression in the typical foamy histiocytes and Touton giant cells but not in lymphocytes, fibroblasts, or endothelial cells. In a series of 23 patients with both LCH and ECD lesions, 82% had *BRAF*$^{V600E}$ mutations, suggesting a link between the pathogeneses of these two entities [11]. ECD patients harboring the *BRAF*$^{V600E}$ mutation had more cerebellar involvement, diabetes insipidus, retro-orbital infiltration, and cardiac manifestations, especially the right atrial pseudotumors [12]. Notably, patients with LCH or ECD lesions carrying the *BRAF*$^{V600E}$ mutation tended have a more severe disease phenotype. More recently, *BRAF* mutations were reported in two RDD cases [13, 14] but data on large cohorts are lacking.

### *BRAF*$^{V600E}$ Is Not the Only Signaling Pathway Mutation in Systemic Histiocytoses

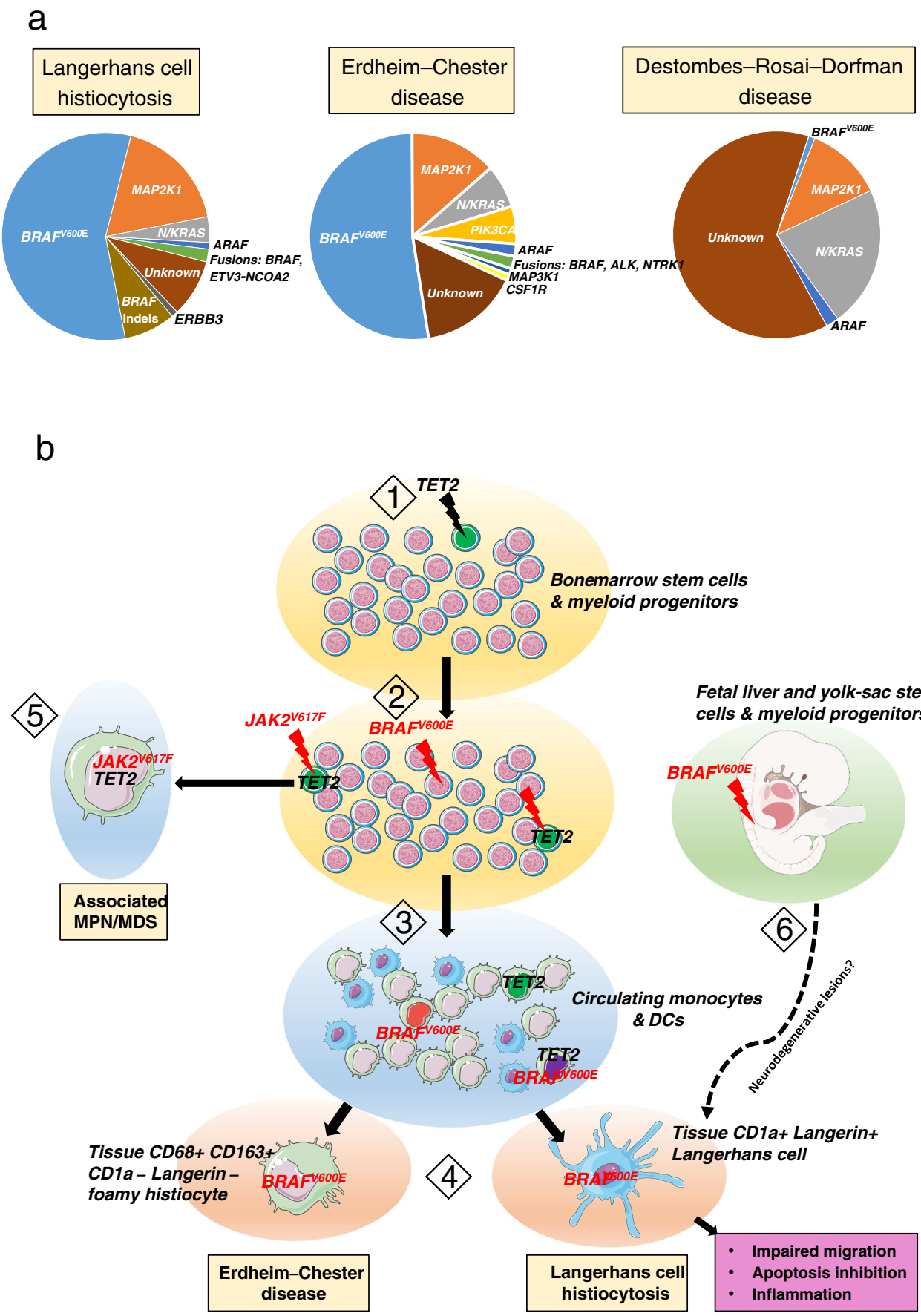
Intriguingly, 50–60% of LCH or ECD patients carry the *BRAF*$^{V600E}$ mutation but the MAPK pathway is activated in all lesions of both diseases [1]. *BRAF*-activating mutations, including in-frame deletions, fusions, and duplications, have been described in LCH lesions in the past few years [3••, 15, 16]. But *BRAF* is not the only mutated gene in histiocytosis able to activate the MAPK pathway. The results of whole exome and targeted next-generation sequencing studies demonstrated mutations of *MAP2K1* (which encodes MEK1) in 25% of LCH patients that were mutually exclusive of *BRAF* mutations [17–19]. *ARAF*, *KRAS*, and *NRAS* mutations have also been described in LCH but at lower rates than *BRAF* and *MAP2K1* [20] (Fig. 1a).

In ECD, a combined whole exome and transcriptome analysis of several tissue samples also found frequent *MAP2K1*, *ARAF*, *NRAS*, and *KRAS* mutations, and translocations involving *BRAF*, *ALK*, and *NTRK1*. Mutations in *MAP2K1* were found in about 30% of the patients, while *KRAS* or *NRAS* mutations were present in 27% [3••, 21] (Fig. 1a).

However, the MAPK pathway is not the only signaling pathway involved in histiocytosis pathogenesis, since activating *PIK3CA* mutations were also found in 11% of ECD patients [21]. Those mutations activate the PI3K–AKT pathway, which can also be induced through the MAPK pathway. Moreover, CD68+ histiocytes express cytoplasmic phosphorylated mechanistic target of rapamycin (mTOR) and p70S6K [22].

According to recent studies, 14% and 12.5% of RDD patients, respectively, had *MAP2K1* and *KRAS* mutations [23–26] (Fig. 1a). Altogether, the frequency of mutated cases in RDD is lower than in LCH or ECD; this may be due to the very low variant allele frequency. Very recently, activating *CSF1R* (also known as *M-CSFR*) mutations were identified in some patients with different histiocytoses [27].

**Fig. 1** Langerhans cell histiocytosis (LCH), Erdheim–Chester disease (ERD), and Destombes–Rosai–Dorfman disease. **a** Pie charts of their relative frequencies of activating signaling pathway mutations. **b** Ontogenies of BRAF-mutated histiocytes in LCH and ECD. ① Acquisition of epigenetic regulation gene mutations in bone marrow stem cells or myeloid progenitors (example here: *TET2*) leading to clonal hematopoiesis. ② Primary or secondary acquisition of the *BRAF*$^{V600E}$ mutation in bone marrow stem cells or myeloid progenitors. ③ Circulating monocytes and dendritic cells (DCs) harboring the *BRAF*$^{V600E}$ mutation derived from mutated myeloid progenitors. ④ Migration of *BRAF*$^{V600E}$-bearing DCs or monocytes to tissue and differentiation into either CD1a+ Langerin+ Langerhans cells (leading to LCH) or CD68+ CD163+ foamy histiocytes (leading to ECD). ⑤ Acquisition of the *JAK2*$^{V617F}$ mutation in bone marrow stem cells/progenitors, promoted by underlying clonal hematopoiesis, leading to associated myeloproliferative neoplasm (MPN)/myelodysplastic syndrome (MDS). ⑥ Acquisition of *BRAF*$^{V600E}$ in yolk sac and fetal liver hematopoietic progenitors, hypothetically leading to neurodegenerative LCH manifestations


a
Langerhans cell histiocytosis
Erdheim–Chester disease
Destombes–Rosai–Dorfman disease
BRAF V600E
MAP2K1
N/KRAS
ARAF
Fusions: BRAF, ETV3-NCOA2
Unknown
BRAF Indels
ERBB3
PIK3CA
Fusions: BRAF, ALK, NTRK1
MAP3K1
CSF1R
b
TET2
Bonemarrow stem cells & myeloid progenitors
JAK2 V617F
Fetal liver and yolk-sac stem cells & myeloid progenitors
Associated MPN/MDS
Circulating monocytes & DCs
Neurodegenerative lesions?
Tissue CD68+ CD163+ CD1a – Langerin – foamy histiocyte
Tissue CD1a+ Langerin+ Langerhans cell
Erdheim–Chester disease
Langerhans cell histiocytosis
Impaired migration
Apoptosis inhibition
Inflammation

### Cell-of-Origin: Embryogenic or Adult Hematopoiesis?

For decades, it was thought that tissue dendritic cells (DCs), LCs, and macrophages were derived from adult bone marrow myeloid precursors. We now know that embryogenic hematopoiesis, mostly from fetal liver and also yolk sac, give rise to tissue-resident macrophages and LCs [28, 29] able to self-renew. However, in any inflammatory context, myeloid precursors, such as monocytes, can differentiate into macrophages or LCs in the affected site [29]. Knowing that capacity led to questioning of the origin of mutated histiocytes in systemic histiocytoses, new information was not long in coming: the $BRAF^{V600E}$ mutation was found in the CD34+ bone marrow cells of several LCH and ECD patients, and circulating monocytes [30, 31•, 32•] (Fig. 1b-②-③). Moreover, transcription analyses showed that LCH cells more closely resembled in vitro monocyte–derived LCs than epidermal LCs [33, 34]. Notably, a mouse model with CD11c+ cells (DC progenitors) expressing $BRAF^{V600E}$ resulted in an LCH-like disease [30]. Xenotransplantation of CD34+ cells from an ECD patient into an immunocompromised mouse gave rise to ECD-like foamy histiocytes in the mouse's organs [32]. All those results strongly suggest that mutated histiocytes in LCH and ECD derive from non-fetal hematopoietic bone marrow stem cells or monocytes (Fig. 1b).

However, neurodegenerative manifestations of pediatric LCH may result from a mutation acquired during embryogenic hematopoiesis. A mouse model expressing $BRAF^{V600E}$ in yolk sac myeloid progenitors resulted in a neurodegenerative disorders similar to those seen in some pediatric LCH patients [35•] (Fig. 1b-⑥). Conversely, a subsequent study found $BRAF^{V600E}$ mutations in circulating and perivascular monocytes in central nervous system (CNS) biopsies from patients with neurological LCH [36].

Despite all the above-described discoveries, the precise cell-of-origin of systemic histiocytosis remains unknown, because CD34+ cells are heterogeneous and do not always harbor $BRAF^{V600E}$. Nevertheless, the results of numerous studies support mutated CD14+ monocytes being LCH-cell precursors [33, 34, 36].

### Association with Myeloproliferative and/or Myelodysplastic Syndromes

Because MAPK pathway mutations acquired in myeloid precursors seem to be the driving event leading to LCH and ECD, these conditions are now considered "inflammatory myeloid neoplasms." Because they could share common pathogeneses with other myeloproliferative neoplasms (MPNs) or myelodysplastic syndromes (MDSs), an international group of specialists retrospectively reviewed 189 ECD and mixed histiocytosis patients' tissue samples and medical charts, and found that 10.1% had overlapping myeloid neoplasms [37], with almost half being chronic myelomonocytic leukemia (CMML), and most of the others were MPNs or MDSs. The $JAK2^{V617F}$ mutation was the most frequent in myeloid neoplasms, followed by *NRAS*, *TET2*, *ASXL1*, and *U2AF1* mutations. It is also noteworthy that an ECD patient being treated with a BRAF inhibitor developed $JAK2^{V617F}$-mutated CMML that disappeared after stopping treatment. Moreover, sequential analyses of colonies derived from single CD34+ cells from a patient with *TET2*- and *SRSF2*-mutated CMML associated with $BRAF^{V600E}$-mutated ECD detected colonies with *BRAF* and *TET2* mutations, and the latter preceded the *BRAF* mutation [32•].

Indeed, 42% of ECD patients harbor additional mutations, with the most frequently mutated genes being *TET2*, *ASXL1*, *DNMT3A*, and *NRAS*, which are commonly seen in clonal hematopoiesis of indeterminate potential (CHIP) [38].

Those findings suggest that the pathogeneses of MPNs, MDSs, and histiocytoses could share some factors, and that underlying clonal hematopoiesis could promote a secondary driver MAPK pathway mutation leading to histiocytic disease (Fig. 1b-①-⑤).

### Impact of MAPK Pathway Activation on Histiocyte Phenotypes

Unlike cancer, LCH and ECD organ lesions do not result from a proliferative mechanism, as shown by the low Ki67 ratios (marker of proliferation) in most of their tissue histiocytes [39, 40•]. $BRAF^{V600E}$-positive cells account for < 1% of total peripheral blood mononuclear cells and bone marrow cells in those histiocytoses [30, 31•, 32•]. The lesions responsible for organ dysfunction seem to originate mostly from inflammation and fibrosis induced by the mutated histiocytes. Although several small older studies on patients' plasma samples and tissues showed production of inflammatory and profibrotic cytokines, none examined the precise impact of the $BRAF^{V600E}$ mutation on the human myeloid cell phenotype. The recent analysis of a murine model of $BRAF^{V600E}$-expressing CD11c+ cells showed that the mutation in epidermal mouse DCs induced impaired migration to lymph nodes (via CCR7 expression inhibition) and resistance to apoptosis (via increased BCL2L1 expression) that could be reversed by MEK inhibitors [40•]. Still, a need to further our understanding of the $BRAF^{V600E}$ mutation impact on the inflammatory histiocyte phenotype persists.

## Langerhans Cell Histiocytosis

### Diagnosis, Clinical Presentation, and Prognosis

LCH is diagnosed based on clinical, radiological, and histopathological findings showing lesions containing

inflammatory cells and CD1a+ and CD207+ histiocytes, which are the usual markers of epidermal LCs [41]. Histological confirmation is recommended for all cases, especially to exclude differential diagnoses.

The annual LCH incidence has been reported to be 4.6 cases/million children < 15 years old [42] and estimated at 1–2 cases/million adults [43]. No relevant risk factors have been identified for childhood LCH, but active smoking is strongly associated with adult pulmonary LCH [42]. The clinical picture at onset varies from a self-healing single-organ disease to multisystemic manifestations requiring chemotherapy or targeted treatment. Although LCH can occur in every organ, it most frequently involves the bone (80%), followed by the skin (33%), pituitary gland (25%), liver (15%), spleen (15%), bone marrow (15%), lungs (15%), lymph nodes (5–10%), and CNS (2–4%). High-risk organs are the liver, the spleen, and the hematopoietic system, while low-risk organs include the skin, bone, lung, lymph nodes, pituitary gland, and CNS.

Numerous clinical pictures have been described and accorded various names: eosinophilic granuloma for single-organ lytic bone disease; Hand–Schuller–Christian triad refers to lytic bone lesions associated with diabetes insipidus and exophthalmos; Letterer–Siwe disease is a severe rapidly progressive entity with cutaneous and multivisceral involvement that primarily affects children < 2 years old.

Although bone manifestations can occur in any bone, the hands and feet are frequently spared. Uni- or multi-focal osteal involvement is not predictive of another systemic manifestation. In children, the most frequent manifestation is a lytic skull lesion, which may be asymptomatic. Other involved sites are mostly axial and proximal bones (femur, humerus, ribs, vertebrae, pelvis) [44]. Some localizations, e.g., temporal, orbit, sphenoid, ethmoid, and zygomatic bones, are associated with a higher risk of CNS involvement.

Skin involvement is characterized by a red papular rash in the groin, or on the abdomen, chest, and/or back. Or it can manifest as a seborrheic scalp rash or ulcerative lesions behind the ears, under the breasts, or in the anogenital region [45].

The lung is more frequently involved in adults, reflecting the strong association with smoking. Pulmonary manifestations are mainly symmetrical cystic and nodular interstitial lung disease. Pulmonary cysts can evolve towards bullous formation and spontaneous pneumothorax can be the first LCH manifestation [46, 47].

Diabetes insipidus is the most frequent CNS manifestations and can occur along with panhypopituitarism [48]. Other neurological signs are divided into two major subtypes: tumors and neurodegenerative lesions. Clinical signs of tumoral infiltration or masses depend on the location and all CNS manifestations are possible (deficits, seizures, palsies, behavioral changes). The clinical symptoms of degenerative lesions are slowly progressive, seen as extrapyramidal syndrome, cerebellar syndrome, pseudobulbar palsy, or cognitive deterioration [49, 50].

The most serious liver complication is sclerosing cholangitis, which should be screened for with hepatic enzyme testing [51]. Spleen and bone marrow manifestations are not very specific, and only histological examination of bone marrow biopsies or aspirates can yield the LCH diagnosis. Hemophagocytic lymphohistiocytosis, another rare manifestation, is seen only in children [52].

Although LCH outcomes vary widely among patients, about 30–40% of them will develop permanent sequelae [53].

### Treatment

Unfortunately, despite our better understanding of LCH pathogenesis, first-line therapy at present relies on low evidence–based data. Many drugs have been used to treat LCH, but only five prospective trials have been conducted [54–58]. To summarize, for high-risk and risk-organ + LCH, treatment involves the combination of vinblastine and oral prednisone for 6 months, which can be maintained, if effective, for a total of 12 months or switched to cladribine alone or combined with cytarabine. In addition to stopping smoking, adults with pulmonary LCH may benefit from first-line cladribine [59]. Skin-limited LCH can be treated with topical steroids, or possibly oral methotrexate or thalidomide [60, 61]. Curettage or non-steroidal anti-inflammatory drugs can be prescribed for single-bone lesions near no-risk CNS sites; chemotherapy should be given when CNS involvement is present [54, 56]. CNS manifestations are difficult to treat, especially neurodegenerative lesions.

Furthermore, $BRAF^{V600E}$-mutated pediatric LCH responds more poorly to first-line chemotherapy and has higher reactivation rates [10]. The few LCH patients treated with BRAF inhibitors (vemurafenib, dabrafenib) had encouraging outcomes [6, 62–65].

## Erdheim–Chester Disease

### Diagnosis, Clinical Pictures, and Prognosis

As for LCH, ECD diagnosis relies on clinical, radiological, and histopathological findings, with fibro-inflammatory infiltrates containing foamy activated histiocytes, often accompanied by Touton giant cells [66]. Histiocytes are CD68+ CD163+ and CD1a– CD207–. However, 10–20% of the patients diagnosed with ECD also have LCH lesions, especially cutaneous or pulmonary [11, 12].

ECD is a rare disease, with about 1000 cases described worldwide. The vast majority of patients are adults (mean age 48–56 years) and predominantly males (~ 70%) [12, 67]. More frequently than for LCH, ECD is almost always

multisystemic, with all organs potentially affected. At diagnosis, almost all patients (80–95%) have symmetrical leg long-bone osteosclerosis, which can cause bone pain, and can best be visualized on [$^{18}$F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) scans.

The most frequent secondary manifestations include perinephric fat infiltration ("hairy kidney" on computed tomography (CT) scans) in 57–65% of the patients and periaortic sheathing ("coated aorta") in 62–76%. Retroperitoneal fibrosis occurs in 58%, sometimes complicated by ureterohydronephrosis, which can justify emergency JJ stenting. Cardiac involvement is also frequent, with possible infiltration of the pericardium (31%), coronary arteries (27%), and/or right atrium pseudotumor in 37–41%, with the latter being a very typical ECD lesion [66]. Xanthelasma is the most common skin manifestation, potentially found in 20% of these patients. Retro-orbital manifestations—with or without exophthalmos—are seen in 22–33%. CNS manifestations are numerous and diverse, and worsen the ECD prognosis [68]. Other frequent symptoms are diabetes insipidus (28%) and cerebellar lesions (17%).

Systemic inflammation is often present, with 80% of patients having elevated C-reactive protein concentrations. [$^{18}$F]-FDG-PET scan is a remarkable tool for initial lesion assessment and follow-up of disease activity [69]. However, cardiac and CNS manifestations are better evaluated with dedicated magnetic resonance imaging. To confirm the diagnosis, histological examination of a xanthelasma or perinephric fat biopsy is recommended [70].

Overall mortality is ~25%, with median survival at 162 months, and 82.7% 5-year survival. In a multivariate survival analysis, older age at diagnosis, CNS involvement, and lung and/or retroperitoneal manifestations were associated with poor prognosis [12].

### Treatment

As for LCH, several drugs have been prescribed. To date, no controlled prospective therapeutic trials on ECD have been conducted.

Currently, because retrospective studies showed that interferon-α (IFNα) was a major independent predictor of survival, its preferably pegylated formulation is now recommended as first-line therapy [12, 68]. However, IFNα can be responsible for numerous side effects, mostly fatigue, depression, and cytopenias.

The discovery that > 60% of ECD patients have the *BRAF*$^{V600E}$ mutation rapidly led to administration of vemurafenib, a specific BRAF inhibitor, to three patients, with highly promising responses [5]. BRAF inhibitor efficacy was confirmed by two prospective studies on 8 [71] and 22 patients [6] from different centers. Because extracellular signal–regulated kinase (ERK) phosphorylation is positively labeled in all ECD tissue samples [20] and > 25% of the patients have MAPK pathway activation mutations other than *BRAF*$^{V600E}$ (*MAP2K1*, *KRAS*, *NRAS*) [6], the use of MEK inhibitors (e.g., cobimetinib) was tried next. So far, 17 patients have been treated with MEK inhibitors (alone or in combination with a BRAF inhibitor) and their response rates seem similar to those of BRAF inhibitors [3, 7•, 72, 73]. In a retrospective study on 54 patients given BRAF and/or MEK inhibitors, 88% of the patients were responders, assessed with PET Response criteria in solid tumors (PERCIST) 6 months after starting therapy (73% partial and 15% complete metabolic responses) [7•]. The most frequent adverse events with BRAF inhibitors were skin complications (photosensitivity, keratosis pilaris, spinocellular carcinoma, drug Rash with eosinophilia and systemic symptoms (DRESS)). With MEK inhibitors, patients frequently experienced acne (53%), nausea (27%), and/or rhabdomyolysis (27%).

To assess the capacity of BRAF inhibitors to maintain long-term remissions, 20 patients in remission on BRAF inhibitors stopped their treatment. After a median of 6 months, 75% of them had confirmed relapses. Treatment was then resumed for 10 patients, all of whom again entered remission [7•]. To date, no findings support that BRAF or MEK inhibitors induce prolonged and complete ECD remission. Nonetheless, BRAF and/or MEK inhibitors are recommended as second-line therapy, after IFNα failure or intolerance, or even as first-line treatment for life-threatening manifestations.

In retrospective studies, numerous biotherapies targeting tumor necrosis factor-α (TNFα), interleukin-6–receptor (IL6-R), or IL-1β were given to ECD patients, with various efficacies [74–76]. They could be useful, especially for patients with serious inflammatory symptoms, but are not recommended as first-line therapy.

## Destombes–Rosai–Dorfman Disease

### Diagnosis, Clinical Picture, and Prognosis

RDD differs from LCH and ECD, in that it corresponds more to a histological lesion than a unique entity and can occur alone or with other diseases, especially lymphoproliferative neoplasms. Its clonal origin has not yet been clearly demonstrated, and MAPK pathway mutations seem to be far less frequent than in LCH and ECD [13, 14, 23–26]. That lower frequency explains why RDD is not listed along with LCH and ECD in the most recent revised histiocytosis classification [4].

RDD diagnosis relies on clinical and histopathological findings, demonstrating S100+ CD68+ CD1a– histiocytes with a large nucleus and abundant emperipolesis. RDD histology can be difficult to distinguish from that of ECD and an ensemble of clinical arguments is needed to differentiate the

two diseases. Furthermore, RDD can also occur in patients with LCH and/or ECD [77].

RDD prevalence is estimated at 1 case/200,000, and it is diagnosed more frequently in children and young adults [78, 79]. RDD can be associated with several neoplasias, such as Hodgkin and non-Hodgkin lymphomas (which are the main differential diagnoses) [80], MDSs [81], and cutaneous clear cell sarcoma [82]. Ten percent of RDD cases can also have immune-mediated diseases [83], such as systemic lupus erythematosus, idiopathic juvenile arthritis, autoimmune hemolytic anemia [84], and IgG4-related disease [85]. A germline *SLC29A3* mutation has been identified in patients with familial RDD; that gene is also implicated in Faisalabad histiocytosis and H syndrome [86].

Patients with classic (or nodal) RDD usually have massive, bilateral, and painless cervical lymphadenopathy, which can be accompanied by fever, weight loss, and night sweats [87]. All other lymph node areas can theoretically be affected but a retroperitoneal location is unusual [88].

Extranodal manifestations occur in 43% of RDD patients [84], involving the skin (10%), eyes (11%), head and neck (11%), bones (5–10%), CNS (< 5%), and, rarely, the thoracic (2%), retroperitoneum (4%), genitourinary system, and/or gastrointestinal system (< 1%).

Cutaneous lesions are typically painless non-pruritic red-brown plaques, nodules, or papules, with a slow, chronic evolution. They can arise anywhere on the body [87]. Neurological manifestations without lymphadenopathy are more frequent in older patients. They are often intracranial but can also affect the spinal cord, with numerous non-specific symptoms depending on the location [89, 90]. They also arise in meninges, mimicking meningioma or pachymeningitis [91, 92]. Bone lesions are usually osteolytic, and can occur in the long bones, vertebrae, and sacrum [93]. The different ophthalmic involvements include the lachrymal gland, and intra-orbital and choroid infiltrations [94].

Normochromic normocytic anemia is observed in 67% of RDD patients and leukocytosis in 60%. Thrombocytopenia, eosinophilia, hypergammaglobulinemia, and inflammatory syndrome are also frequent but bone marrow infiltration is not common [95, 96].

RDD prognosis reflects the number of nodal groups involved. Renal manifestations are associated with 40% mortality, while bone lesions often evolve favorably [84, 97].

### Treatment

Because of RDD rarity and no prospective trials, no therapeutic consensus has been reached. Surgical resection can be useful for cutaneous RDD [88]. Corticosteroids can be effective against nodal, orbital, bone, and CNS manifestations, but with the risk of developing high-level steroid dependency [98, 99]. Classical chemotherapy with sirolimus, thalidomide, and methotrexate have been tried but responses were mixed. A benefit of surgical resection or radiation therapy has been reported for patients with ear, nose and throat, and orbital involvements with a neurological mass effect.

Only one case of *KRAS*-mutated RDD has been treated with the MEK inhibitor cobimetinib with very good efficacy [24]. Prospective trials of cobimetinib for wild-type *BRAF* histiocytosis are ongoing and some RDD patients have been included.

## Conclusion

Since 2010 and the discovery of the first *BRAF*–mutated patients, our understanding of systemic histiocytosis pathogenesis continues to evolve. We now know that several patients have MAPK pathway mutations in hematopoietic stem cells and/or myeloid progenitors, leading to histiocytic disorders, such as LCH, ECD, and sometimes RDD It has also been shown that different histiocytoses may overlap. Those discoveries have led to the use of targeted-therapy (MEK and BRAF inhibitors) trials, with good responses, especially against ECD. Undoubtedly, our knowledge of the pathogeneses of these entities will continue to improve. Prospective trials are still under way to assess targeted-treatment efficacy against refractory LCH, ECD, and RDD.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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