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ORPHAN DISEASES (B MANGER, SECTION EDITOR)

Erdheim-Chester Disease: a Concise Review

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Abstract

Purpose of Review This report provides an overview of the current knowledge of molecular characterization, clinical description, and treatment of Erdheim-Chester disease (ECD), a multi-systemic adult histiocytosis of the L group.

Recent Findings The recent identification of several MAPK mutations in histiocytes of ECD lesions. Leading to targeted therapies.

Summary The discovery of the $BRAF^{V600E}$ mutation in ECD lesions followed by several other kinase mutations in the MAPK pathway has revolutionized our understanding of the disease pathogenesis and led to trials with targeted therapies that demonstrated robust efficacy.

Keywords Erdheim-Chester Disease · Histiocytosis · Histiocytic Neoplasm · Myeloid Neoplasm · Targeted Therapy

Introduction

Erdheim-Chester disease (ECD) was first described in 1930 by Jakob Erdheim and William Chester as a "lipoid granulomatosis" [1]. To date, approximately 1,500 cases have been described worldwide, demonstrating the disease rarity. Because ECD histopathological features mainly rely on histiocyte infiltration, ECD has been classified for decades along with non-Langerhans cell histiocytosis. In 2012, progress in molecular techniques led to the discovery of recurrent $BRAF^{V600E}$ mutation in histiocytes from ECD lesions [2]. Since then, several other kinase mutations have been described [3••, 4], therapies targeting BRAF and MEK have been used with robust and sustained efficacy [5, 6, 7•, 8], and a new classification of histiocytosis has emerged [9].

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

Pathogenesis

Mutations Activating the MAPK Pathway: the Origin of Erdheim-Chester Disease

The $BRAF^{V600E}$ mutation is involved in 7% of human cancers [10], some of which might benefit from targeted therapy [11].

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This oncogenic mutation constitutively activates RAS-RAF-MEK cell signaling pathway, which is involved in several cell functions, including proliferation, apoptosis, angiogenesis, migration, and survival [10]. In 2010, a mass spectrometry analysis targeting cancer genes was used in Langerhans cell histiocytosis (LCH) lesions, highlighting for the first time the nucleotide variant $BRAF^{V600E}$ in 35 (57%) of 61 samples [12]. Two years later, a pyrosequencing study of 93 patients with different histiocytosis confirmed a 38% prevalence of the $BRAF^{V600E}$ mutation in LCH lesions and discovered a 54% prevalence in ECD patients [2]. 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 [2]. The mutant allele frequency is lower than 5% in 23.6% of histiocytosis lesions [13], thus mutation detection requires methods with high sensitivity.

Because phosphorylated extracellular signal-regulated kinase (pERK) is positively labeled in ECD tissue samples [4], the presence of other activating mutations of the MAPK pathway was suspected. A combined whole exome and transcriptome analysis of several tissue samples found frequent *MAP2K1*, *ARAF*, *NRAS*, and *KRAS* mutations as well as translocations involving *BRAF*, *ALK*, and *NTRK1* [3••]. Mutations in *MAP2K1* were found in approximately 30% of the patients, while *KRAS* or *NRAS* mutations were present in 27% [3••, 9]. The MAPK pathway is not the only signaling pathway involved in ECD, since activating *PIK3CA* mutations were found in 11% of patients [4]. Those mutations activate the PI3K-AKT pathway, which can also be induced through the MAPK pathway. Moreover, CD68+ histiocytes express cytoplasmic phosphorylated mechanistic targets of rapamycin (mTOR) and p70S6K [14]. Very recently, activating *CSF1R* (also known as *M-CSFR*) mutations were identified in some patients with ECD [15] (Fig. 1).

Mutations in Erdheim-Chester Disease Occur in Adult Bone Marrow Precursors of Myeloid Cells

In a steady state, tissue-resident macrophages and dendritic cells (DCs) primarily originate from embryogenic hematopoiesis and have a self-renewal capacity [16]. However, in an inflammatory context, circulating bone marrow-derived myeloid precursors (such as monocytes) can differentiate into macrophages and DCs and accumulate in the affected sites [16]. This dual origin led to questioning the origin of mutated histiocytes in ECD. To address this question, two concomitant studies performed $BRAF^{V600E}$ sequencing in bone marrow and circulating hematopoietic cells, revealing the presence of the mutation in bone marrow CD34+ hematopoietic stem cells (HSCs), myeloid progenitors, and circulating monocytes [17•, 18•]. Moreover, xenotransplantation of CD34+ cells from an ECD patient into an immunocompromised mouse caused ECD-like foamy histiocytes in the mouse's organs [17•]. All of these results strongly suggest that mutated histiocytes in ECD derive from adult bone marrow HSCs and monocytes (Fig. 2).

Frequent Association with Myeloproliferative Neoplasms and/or Myelodysplastic Syndromes

Because they could share common pathogenesis with myeloproliferative neoplasms (MPN) or myelodysplastic syndromes (MDS), 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 [19], with almost half being chronic myelomonocytic leukemia (CMML), and most of the others were MPN or MDS. The $JAK2^{V617F}$ mutation was the most frequent in myeloid neoplasms, followed by *NRAS*, *TET2*, *ASXL1*, and *U2AF1* mutations. Moreover, sequential analyses of colonies were 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 [17•].

Prospective analysis of bone marrow cells by next-generation sequencing revealed that 42% of ECD patients harbor additional mutations, with the most frequently mutated genes being *TET2*, *ASXL1*, *DNMT3A*, and *NRAS*, which are commonly seen in myeloid neoplasms and clonal hematopoiesis of indeterminate potential (CHIP) [20].

These findings suggest that the pathogeneses of MPN, MDS, and ECD could share some factors and the underlying clonal hematopoiesis could promote a secondary driver MAPK pathway mutation leading to ECD (Fig. 2).

Inflammation and Fibrosis Drive Organ Damage in Erdheim-Chester Disease

ECD organ lesions do not usually result from a proliferative mechanism. Indeed, systemic and local inflammations seem to be the main factors driving organ damage. Systemic inflammation, testified by C-reactive protein elevation, is observed in more than 80% of patients [21]. Only a few works have studied the inflammatory profile of ECD. An immunohistochemical study of three patients showed that a complex network of cytokines and chemokines regulated histiocyte recruitment and accumulation in the lesions [22]. A study of both spontaneous and stimulated cytokine production by mononuclear cells in biopsy fragments from a single patient revealed that TNF-α was produced after stimulation and IL-6 and IL-8 were secreted spontaneously, with IL-8 acting as a chemoattractant for polymorphonuclear cells and monocytes [23]. Chemokine ligand 18 (CCL18), involved in the

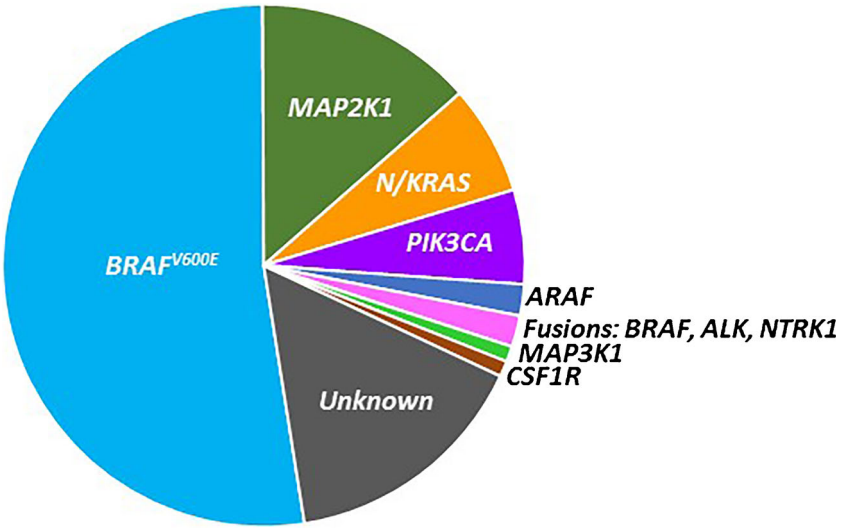

Fig. 1 Pie chart of the relative frequencies of activating signaling pathway mutations in Erdheim-Chester disease

induction and progression of fibrosis, was assessed with a 3–4-fold increase level in a series of 20 ECD patients, with high levels correlating with disease severity [24]. Serum samples from 37 ECD patients were assayed for 23 cytokines and high IFNα, IL-1/IL1-RA, IL-6, IL-12, and MCP-1 levels were found, indicating strong systemic immune activation, and suggesting Th1-oriented disturbance [25].

In solid cancers, the $BRAF^{V600E}$ mutation has been associated with oncogene-induced senescence characterized by stable proliferative arrest and an increased expression of tumor suppressor proteins such as $p16^{Ink4a}$ and p21 [26, 27]. Senescent cells have been shown to induce a complex inflammatory response that shares many similarities with ECD. Immunohistochemical analysis of ECD lesions revealed that $BRAF^{V600E}$-mutated histiocytes were also positive for the senescence marker $p16^{Ink4a}$ [28]. These results suggest that $BRAF^{V600E}$ could induce inflammation in histiocytes through a senescence program. Further studies are needed to better define the inflammatory profile of ECD and its origin.

Clinical Manifestations

Epidemiology

Due to ECD rarity, there are no strong data to assess the prevalence and incidence. The vast majority of patients are adults, predominantly male (≈ 70%), with a mean age at diagnosis of

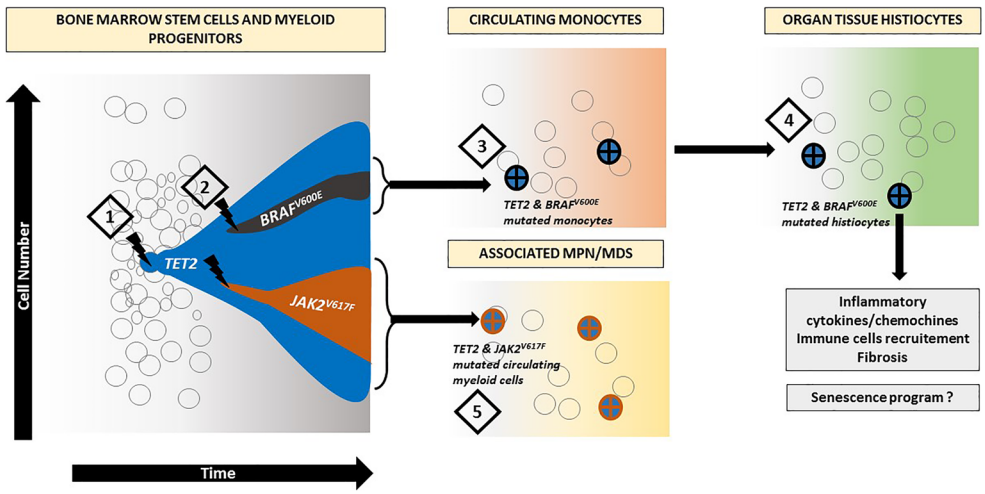

Fig. 2 Ontogenies of BRAF-mutated histiocytes in Erdheim-Chester disease. ① Acquisition of epigenetic regulation gene mutations in bone marrow stem cells or myeloid progenitors (example here: *TET2*) leading to clonal hematopoiesis. ② Secondary acquisition of the $BRAF^{V600E}$ mutation in bone marrow 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)

48–56 years [29–31]. Pediatric cases are rare and often associated with LCH [32–34].

Histopathological Features

Lesion biopsies with histological analysis and immunohistochemical (IHC) staining are mandatory for ECD diagnosis as well as to rule out differential diagnoses. Histological findings commonly include fibro-inflammatory infiltrates containing foamy-activated histiocytes, often accompanied by Touton giant cells [35]. On IHC staining, ECD histiocytes are positive for CD68, CD163, and factor XIIIa and negative for CD1a and CD207 (langerin). Positivity for S100 is rarely observed (20% cases) [31]. When possible, biopsies of xanthelasma or peri-renal fat are preferred, as these lesions are often richer in histiocytes [36] and allow molecular studies.

Clinical Manifestations

ECD is commonly multi-systemic, and all organs can virtually be affected. We will describe the most frequent manifestations (Table 1).

Bone Manifestations Long bone osteosclerosis, the most frequent ECD manifestation, is present in 80–95% of patients [29, 30]. It can manifest through mild leg bone pain in 40% [30] or be asymptomatic. It can be best visualized with ^{18}F-labeled fluorodeoxyglucose positron emission tomography (PET scan) or ^{99}Tc bone scintigraphy. At present, PET scan is preferred to bone scintigraphy because it can globally depict both the extent and activity of ECD lesions [37].

Table 1 Erdheim-Chester disease organ involvement in Pitié-Salpêtrière (n = 165) and NIH (n = 60) cohorts

Organ system and clinical findings (%)	Pitié-Salpêtrière [29]	NIH [30]
Long bone	80	95
Cardiac involvement	53	-
Right atrium pseudo-tumor	41	37
Coronary infiltration	27	-
Pericardial involvement	31	8
Vascular involvement	64	-
Coated aorta	46	62
Skin involvement	33	25
Xanthelasma	27	33
Diabetes insipidus	28	47
CNS involvement	37	38
Cerebellar involvement	17	-
Retro-orbital involvement	22	27
Lung involvement	35	52
Retroperitoneal involvement	58	65

Cerebral, Facial, and Orbital Manifestations The central nervous system (CNS) manifestations are numerous and diverse in ECD. Cerebellar and pyramidal syndromes are the most frequent neurological signs (41% and 45% of cases, respectively), and the other features described include seizures, headaches, neuropsychiatric signs or cognitive impairment, sensory disturbances, cranial nerve paralysis, and asymptomatic lesions [38]. Pseudo-degenerative involvement of the cerebellum, present in 17% of patients, is a very difficult lesion to treat. On MRI, CNS manifestations can be described either as enhancing masses or high signal density.

At imaging, meninges are involved in 23% of patients, presenting as diffuse thickening or dural masses [39]. CNS involvement can lead to severe disability and is a major prognostic factor, as a survival analysis identified this factor as an independent predictor of death (hazard ratio = 2.51; 95% confidence interval, 1.28–5.52; p = 0.006) [40].

One in four patients develops exophthalmos, which is often bilateral, due to infiltration of the retro-orbital soft tissues [29, 30, 41]. This infiltration may be massive and emergency surgical debulking may be required.

The sinuses are often infiltrated in ECD, more frequently in the maxillary and sphenoid sinuses (47%) than ethmoidal or frontal (17%). Infiltration or the cranial vault can also be observed in 27% of patients [39].

Cardiovascular Manifestations The most frequent cardiovascular sign is aorta sheathing ("coated aorta") in 46 to 62% of cases [29, 30]. This peri-aortic infiltration can occur in every aorta section. Peri-arterial infiltration may also extend to the main aortic branches. Peri-aortic infiltration is usually asymptomatic, and complications are not severe.

Right atrium pseudo-tumor, which is one of the iconic features of ECD, can be observed through dedicated magnetic resonance imaging (MRI) in 40% of patients [29, 30, 35]. The presence of the $BRAF^{V600E}$ mutation is significantly associated with right atrium pseudo-tumor (57% vs 9% in $BRAF^{WT}$ patients, $p < 0.0001$) [29], with an increased risk of cardiac and aortic infiltration (OR per 1 SD increase in $BRAF^{V600E}$ status, 4.92, 95% CI 1.46–18.56, $p = 0.0155$) [42]. Pericardial infiltration can also occur, sometimes complicated by tamponade [35]. Specific coronary artery infiltration has been described in 27% of patients [29] and can be complicated by coronary stenosis and myocardial infarction [35]. Dedicated cardiac MRI is the best imaging test to assess ECD cardiac manifestations, while computed tomography angiography (CTA) is recommended to evaluate peri-aortic sheathing.

Retroperitoneal Manifestations Abdominal CT scan reveals peri-renal fat infiltration ("hairy kidneys") in 60% of patients [29, 30]. Approximately one-third of ECD cases present with retroperitoneal fibrosis, in some cases complicated by bilateral hydronephrosis, which may require ureteral stenting. The

retroperitoneal fibrosis in ECD sheaths the walls of the aorta completely and circumferentially, while the posterior aortic wall is rarely affected in idiopathic retroperitoneal fibrosis [35].

Cutaneous Manifestations The most frequent ECD cutaneous manifestations are xanthelasma-like lesions (XLL), which occur in 25–30% of patients [29, 30, 36]. Compared with classic *xanthelasma palpebrarum*, XLL pathology more frequently involves the reticular dermis, displays more multi-nucleated or Touton cells, and shows less extensive fibrosis [36]. Other ECD cutaneous lesions are non-specific patches or papulonodular lesions, which predominantly affect the legs, back, and/or trunk [36].

Endocrine Manifestations Any endocrine organ can be affected in ECD. Diabetes insipidus is found in 33.3% of patients, frequently as the first manifestation of ECD [43]. Anterior pituitary dysfunction is found in 91.3% of patients with full anterior pituitary evaluation, including somatotropic deficiency (78.6%), hyperprolactinemia (44.1%), gonadotropic deficiency (22.2%), thyrotropic deficiency (9.5%), and corticotropic deficiency (3.1%). Infiltration of the pituitary and stalk is found with dedicated MRI in 24.4% of patients [43]. Testicular insufficiency is found in 53.1% of patients, with sonographic testicular infiltration in 29%, mostly bilateral [43]. Computed tomography adrenal infiltration is found in 39.1% of patients, but adrenal insufficiency is very rarely encountered [43].

Pulmonary Manifestations On thoracic CT scan, lung involvement can be observed in 30–50% of cases [29, 30, 44]. The pleura can be infiltrated as well as lung parenchyma, predominantly interlobular septa [44].

Other Manifestations Most organs have been reported to be involved in ECD. Autopsy has demonstrated infiltration of the thyroid and lymph nodes [45]. There are also numerous case reports describing breast infiltration presenting as masses [46].

Laboratory Findings

Systemic inflammation is frequent in ECD, demonstrated by CRP elevation in 50 to 80% of patients [21, 30]. Blood count abnormalities are frequent: anemia can be observed in 67% of patients, low platelet count in 20%, high neutrophil count in 9%, and low lymphocyte count in 25% [30]. These manifestations are usually secondary to systemic inflammation, but due to the frequent association of ECD with MPN and/or MDS [19], blood count careful monitoring is required. The presence of polycythemia, thrombocytosis, and/or persistent monocytosis must alert the physician and lead to further examinations.

Liver enzymes can be high in 5 to 10% of patients [30]. Vascular endothelial growth factor (VEGF) is elevated in approximately 30% of patients [47] and can be associated with glomeruloid hemangioma [48].

Disease Activity Assessment

Disease activity in ECD patients is assessed by regular clinical examinations and imaging (≈ every 6 months) to assess morphological changes. No disease activity score has yet reached consensus. Based on patient auto-evaluation, a recent study developed an ECD Symptom Scale (ECD-SS) that mainly relies on neurological/psychological signs, constitutional symptoms, and pain [49].

Association with Other Diseases

Association with Other Histiocytosis ECD is frequently associated with other systemic histiocytosis. Association with LCH occurs in 10 to 20% of ECD patients [50]. Most frequent LCH lesions are lytic bone lesions with cutaneous involvement. ECD and LCH tissue lesions often share common mutational status, and the $BRAF^{V600E}$ mutation is highly prevalent in patients with both diseases [50]. Due to the molecular and clinical associations, ECD and LCH are now both classified as "histiocytosis of the L-group" [9]. Destombes-Rosai-Dorfman disease (RDD) lesions are also frequently seen in ECD patients [51], but distinction between the two diseases is difficult on histopathological examination and requires specific clinical characteristics to acknowledge diagnosis.

Association with Auto-immune Diseases Prevalence of associated auto-immunity (biological and/or clinical) is higher in ECD (41%) than in LCH (20%) [52]. Auto-immunity in ECD seems independent from interferon-α (IFN-α) treatment. Auto-immune biology is mainly represented by positive anti-nuclear antibodies (ANA) in 21% of patients, with positive anti-double-strand DNA (dsDNA) antibodies in 12% and anti-SSA in 11%. Anti-phospholipid (APL) biology is also frequently seen (18%), with a predominance of anti-cardiolipid (ACL) antibodies (16%). Auto-immune diseases (AID) are present in 12% of ECD cases. The most frequent AID are auto-immune thyroiditis, primary Sjögren's syndrome, and systemic lupus erythematosus. Some patients with associated auto-immunity have been treated with targeted therapies (BRAF and/or MEK inhibitors), which enabled a decrease in the ACL titer [52].

Treatment

Due to ECD rarity, no controlled prospective therapeutic trials have been conducted. However, recent molecular discoveries

rapidly led to prescription of targeted therapies, with an efficacy never before observed (Table 2).

Interferon-α

Currently, because retrospective studies showed that IFN-α was a major independent predictor of survival, its preferable pegylated formulation is now recommended as first-line therapy for non-life-threatening manifestations [29, 40]. For CNS and cardiovascular manifestations, increasing doses of IFN-α may be needed. IFN-α's main issue is the high prevalence of side effects (especially with prolonged therapy), mostly fatigue, depression, and cytopenia, which often lead to alternative treatment.

BRAF- and MEK-Targeted Therapies

The discovery that > 60% of ECD patients have the $BRAF^{V600E}$ mutation rapidly led to administration of

Table 2 Therapeutic trials in Erdheim-Chester disease

Treatment category	Treatment	Series	Number of patients	Median treatment duration (months)	Criteria used	Overall response (%)	Complete response (%)	Partial response (%)	Stable disease (%)	Progressive disease (%)
Kinase inhibitors	Vemurafenib	Cohen-Aubart et al. [7•]	48	6	PERCIST	88	15	73	8	4
		Hyman et al. [53]	14	2	RECIST	43	7	36	57	0
		Diamond et al. [54]	22	26	RECIST	55	5	50	41	0
	Vemurafenib + cobimetinib	Cohen-Aubart et al. [7•]	8	6	PERCIST	100	25	75	0	0
	Cobimetinib	Diamond et al. [8]	12	12	RECIST	64	14	50	29	0
					PET-response	89	72	17	6	0
		Cohen-Aubart et al. [7•]	4	6	PERCIST	100	50	50	0	0
Biologics	Anakinra	Cohen-Aubart et al. [55]	9	22	PERCIST	22	11	11	23	55
		Goyal et al. [56]	7	31	Specific clinical criteria	57	14	43	0	43
					Specific radiological criteria	29	0	29	42	29
	Infliximab	Cohen-Aubart et al. [57]	12	20	PERCIST	42	0	42	25	33
		Goyal et al. [56]	5	4	Specific clinical criteria	0	0	0	80	20
					Specific radiological criteria	0	0	0	50	50
	Tocilizumab	Berti et al. [58]	3	24	Specific clinical criteria	67	67	0	33	0
					Specific radiological criteria	67	0	67	33	0
Others	Cladribine	Goyal et al. [59]	17	-	Specific clinical criteria	52	6	46	18	20
					Specific radiological criteria	54	0	54	26	20
	Sirolimus and prednisone	Gianfreda et al. [14]	10	28.5	RECIST	60	0	60	20	20

vemurafenib, a specific BRAF inhibitor, to three patients, with robust responses [5]. Because extracellular signal-regulated kinase (ERK) phosphorylation was positively labeled in all ECD tissue samples [4] and > 25% of the patients had MAPK pathway activation mutations other than $BRAF^{V600E}$ (*MAP2K1*, *KRAS*, and *NRAS*) [3••, 4], the use of MEK inhibitors (for example, cobimetinib) was tried. To date, several cases and series reported the efficacy of BRAF and MEK inhibitors, sometimes in association [7•, 8, 53, 54]. Overall response rate varies from 43 to 100%, and almost no disease progression was observed under these regimens (Table 2). To assess the capacity of BRAF inhibitors to maintain long-term remission, 20 patients in remission on BRAF inhibitors ceased treatment. After a median of 6 months, 75% had confirmed relapses. Treatment was then resumed for 10 patients, all of whom again entered remission [7•]. The most frequent adverse events with BRAF inhibitors were skin complications (photosensitivity, keratosis pilaris, spinocellular carcinoma, and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)). With MEK inhibitors, patients frequently experienced acne (53%), nausea (27%), and/or rhabdomyolysis (27%) [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.

Anti-Cytokine Biotherapies

In retrospective studies, biotherapies targeting inflammatory cytokines were administered with various efficacies (Table 2). Infliximab (targeting TNF-α) and anakinra (targeting IL-1β) are the most prescribed biotherapies [55–57]. Anakinra seems to be more efficient, with an overall response rate that varies from 22 to 57%. However, disease progression rates are high with both treatments (20 to 55%) compared with BRAF and MEK inhibitors. Tocilizumab, a biotherapy targeting the IL-6 receptor, seems promising, with an overall response rate of 67% and no disease progression, but has only been administered prospectively to three patients [58]. Interestingly, association of both BRAF inhibitor and anakinra has been tried with efficacy in a single patient [60]. To date, biotherapies targeting cytokines can be useful, especially for patients with serious inflammatory symptoms, but are not recommended as first-line therapy.

Other Treatments

For LCH, conventional chemotherapy such as cladribine, was also tried in ECD [59, 61] (Table 2), with various efficacy. Since activating *PIK3CA* mutations [4] were found in ECD and CD68+ histiocytes express cytoplasmic phosphorylated mTOR [14], sirolimus, an mTOR inhibitor, was tried associated with prednisone in 10 patients. Efficacy seemed to vary and no complete remission was achieved [14].

Conclusion

ECD pathogenesis understanding has been widely improved with the discovery of MAPK pathway mutations in hematopoietic stem cells and/or myeloid progenitors, resulting in inflammatory histiocytes in organs. These discoveries have led to the use of targeted therapy (MEK and BRAF inhibitors) trials, with major efficacy. Undoubtedly, our knowledge of the pathogeneses of ECD will continue to improve, potentially evolving into new therapeutic approaches.

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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