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ORPHAN DISEASES (B MANGER, SECTION EDITOR)

Erdheim–Chester Disease

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Abstract Erdheim–Chester disease (ECD) is a rare (approximately 500 known cases worldwide), non-inherited, non-Langerhans form of histiocytosis of unknown origin, first described in 1930. It is characterized by xanthomatous or xanthogranulomatous infiltration of tissues by foamy histiocytes, "lipid-laden" macrophages, or histiocytes, surrounded by fibrosis. Diagnosis of ECD involves the analysis of histiocytes in tissue biopsies: these are typically foamy and CD68+ CD1a− in ECD, whereas in Langerhans cell histiocytosis (LCH) they are CD68+ CD1a+. ^{99}Technetium bone scintigraphy revealing nearly constant tracer uptake by the long bones is highly suggestive of ECD, and a "hairy kidney" appearance on abdominal CT scan is observed in approximately half of ECD cases. Central nervous system involvement is a strong prognostic factor and an independent predictor of death in cases of ECD. Optimum initial therapy for ECD seems to be administration of interferon α (or pegylated interferon α), and prolonged treatment significantly improves survival; however, tolerance may be poor. Cases of ECD present with strong systemic immune activation, involving IFNα, IL-1/IL1-RA, IL-6, IL-12, and MCP-1, consistent with the systemic immune Th-1-oriented disturbance associated with the disease. More than half of ECD patients carry the $BRAF^{V600E}$ mutation, an activating mutation of the proto-oncogene BRAF. A small number of patients harboring this mutation and with severe multisystemic and refractory ECD have been treated with vemurafenib, a BRAF inhibitor, which was proved very beneficial.

Keywords Erdheim–Chester disease · Histiocytosis · Langerhans-cell histiocytosis · Interferon alpha · Vemurafenib · BRAF · NRAS · Pathophysiology · Epidemiology · Treatment

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Introduction

Erdheim–Chester disease (ECD) was first described as the "lipoid granulomatose" by Jakob Erdheim and his pupil William Chester in 1930 [1]. It is a non-Langerhans form of histiocytosis, of unknown origin, and is rare: up to January 2013, only 500 cases had been reported [2, 3, 4••]. ECD involves xanthomatous or xanthogranulomatous infiltration of tissues by foamy histiocytes, "lipid-laden" macrophages, or histiocytes, surrounded by fibrosis [5, 6]. ECD can be distinguished from Langerhans cell histiocytosis (LCH) by the immunohistological characteristics of histiocytes, which in ECD are: positive for CD68 and negative for CD1a, and negative for the S-100 protein in 80 % of cases.

ECD is a multisystemic disease: patients may present with skeletal involvement with bone pain, exophthalmos, diabetes insipidus, xanthelasma, interstitial lung disease, bilateral adrenal enlargement, retroperitoneal fibrosis with perirenal and/

or ureteral obstruction, renal impairment, testis infiltration, and involvement of the central nervous system (CNS) and/or cardiovascular system [4••, 5].

The extent and distribution of the disease determine the clinical course. Some cases present with only asymptomatic bone lesions, and others with multisystemic, life-threatening forms. Here, we review 53 cases reported in 2011 (Table 1) [4••]. Our experience has kept increasing since then; we have now seen 101 patients who have attended our center since 1991, most of whom have been followed with regular assessments. Many of the patients live in France, although 21 live elsewhere, mainly Europe but also Israel and South Africa. Twenty-two of these patients have died (22 %).

Histiocytoses are heterogeneous diseases and in some cases, different types of histiocytoses are associated (overlap forms). The associated histiocytoses are most often ECD and LCH, but Rosai–Dorfman disease (RDD), a non-Langerhans form of histiocytosis which usually has a better outcome, may also be present [7–9]. Indeed, 15 % of the 101 patients attending our center up to August 2013 presented with such associations: ECD and LCH in 11 cases, ECD and RDD in two, and LCH, ECD, and RDD in one. The frequency of these overlap forms is too high to be likely to be coincidental, and implies a common cause of the different histiocytic disorders. Thus, patients with LCH should be tested for ECD if specific symptoms are present.

Table 1 Frequency of the main clinical and radiological characteristics of Erdheim–Chester disease

	From the literature (%)	Personal experience (%)[a]
Bone pain	50	40[b]
Peri-aortic infiltration	60	66
"Coated aorta" (sheathing of the whole thoraco-abdominal aorta)	30	23[b]
Pericardial involvement	45	42
Exophthalmos	27	25
Diabetes insipidus	27	25[b]
Xanthelasma	19	28
"Hairy kidney" aspect	ND	68
CNS involvement	15–25	51
Pulmonary involvement	22	43
Death	60	26

ND: no data available

[a] In all cases, unless mention of comparison with another series, based on the 53-patient series published in 2011 [4••]

[b] Compared with the 48 patients followed at Pitié-Salpêtrière Hospital (taken from the 53 patients from the series published in 2011 [4••])

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Diagnostic Criteria

ECD is mostly diagnosed by histological analysis (Fig. 1): the typical pattern is polymorphic granuloma infiltrated with CD68-positive and CD1a-negative foamy histiocytes, and fibrosis or xanthogranulomatosis [5, 6]. These characteristic histiocytes may be found in almost any tissue in cases of ECD.

Uptake of tracer by the long bones during ^{99}Technetium (Tc) bone scintigraphy (Fig. 2) is observed in almost all patients (96 % of our 53 patients) [10, 11]. Abdominal CT scanning reveals "hairy kidneys" (Fig. 3) in approximately half of patients with ECD [12, 13]. Because histology biopsy is required for the diagnosis of ECD, ultrasound-guided biopsy of the perirenal infiltration (observed in approximately two thirds of patients) is an approach to be recommended [14].

The diagnostic criteria for ECD used in our center are:

1. Characteristic histological findings (Fig. 1): foamy histiocyte infiltration of polymorphic granuloma and fibrosis or xanthogranulomatosis, with CD68-positive and CD1a-negative immunostaining;
2. Characteristic skeletal abnormalities: a) bilateral and symmetric cortical osteosclerosis of the diaphyseal and metaphyseal parts of the long bones on X-rays, and/or b) symmetric and abnormally intense labeling of the distal ends of the long bones of the legs, and in some cases arms, as revealed by ^{99}Tc bone scintigraphy.

We used these ECD criteria for our literature reviews in 1996, 2004, and 2011. All cases followed at our center fulfilled the first criterion. However, four ECD patients did not fulfill the second criterion, and did not present with long-bone involvement, which is otherwise characteristic of the disease. Bone scintigraphy, X-ray, MRI, and PET–CT investigations did not reveal pathological signs in these four cases.

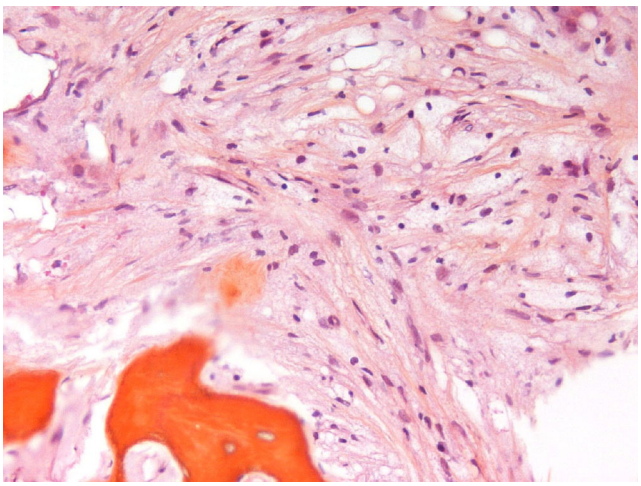

Fig. 1 Erdheim–Chester disease, surgical biopsy of the femur: spongy bone tissue in which the medullary spaces are infiltrated by foamy histiocytes within a fibrous stroma (hematein-eosin-saffron, X200)

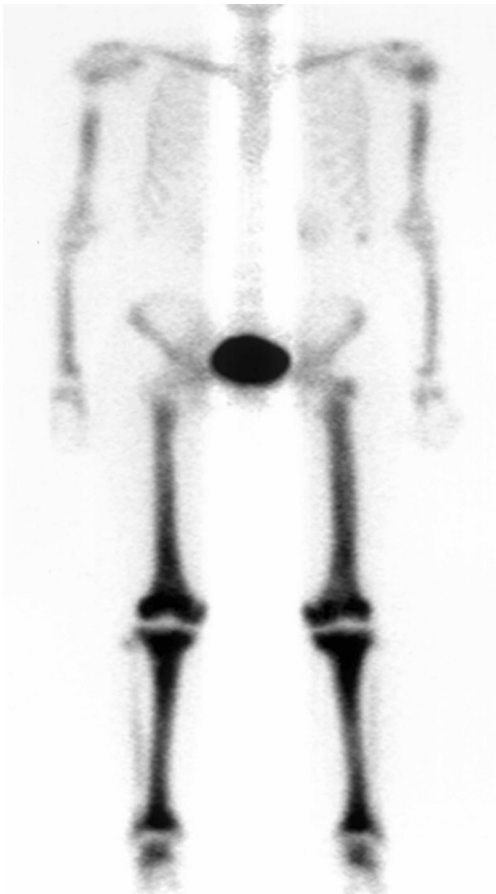

Fig. 2 Symmetric and abnormally increased metaphyso-diaphyseal labeling of the long bones, predominantly in the lower limbs, on ^{99}Technetium bone scintigraphy. (*Reprinted from* Haroche et al. [60]. Copyright 2013; with permission from Elsevier)

Epidemiology

Most of the 101 patients followed at our center are men (75 % men and 25 % women), as has been the case throughout our experience of this disease [4••]. The mean age at diagnosis has not changed substantially as the number of patients seen by our center has grown, and was 55 yr±14 yr (range, 16–80 yr) in the 2011 series [4••, 5]. Only eight pediatric cases have ever been reported, and none had cardiac involvement [15, 16].

In our preliminary study in 2006, the delay before diagnosis was between a few months and several years (up to 25); in recent years, this delay has been reduced, probably because awareness of the disease has improved [11].

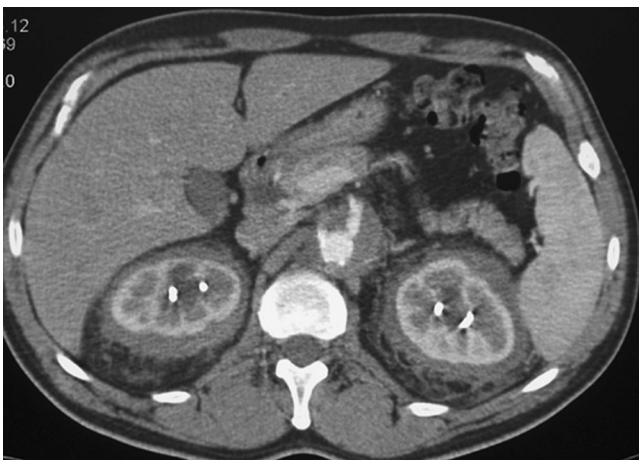

Fig. 3 Contrast-enhanced axial CT scan showing the origin of the superior mesenteric artery, which is stenosed. Note the "coated aorta" aspect, and the symmetrical infiltration of the perirenal fat and of the perirenal fascia taking the appearance of "hairy kidneys"

Clinical Manifestations (Table 1)

Osseous Involvement

Although skeletal involvement is extremely frequent (96 % of the 53 patients included in the 2011 series), only 50 % of patients suffer bone pain. Nevertheless, bone pain is the most common clinical feature of ECD [11]. This pain is often mild; it can start at any time during the course of the disease, and mostly affects the legs. X-ray evidence of bilateral and symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions of the long bones is typical in cases of ECD; also, symmetric and abnormally strong labeling of the distal ends of the long bones of the legs, and sometimes the arms, is often revealed by ^{99}Tc bone scintigraphy [5, 6]. The axial skeleton and the mandible are often involved in LCH, but not in cases of ECD. Recently, positron-emission tomography (PET) with 18F-labeled fluorodeoxyglucose (PET–CT) has been used in place of bone CT scans [17, 18]. In some cases, MRI of the long bones can be informative, because it may reveal epiphyseal involvement of the long bones and periostitis, which is not detected by X-rays [19]. MRI may also be valuable in the rare cases of ECD for which anomalies are not detected by bone CT scans.

Cardiovascular Involvement

Progress in radiological imaging has made it more likely that cardiovascular involvement will be detected. The most frequent cardiovascular sign is the circumferential sheathing of the thoracic and/or abdominal aorta (66 % of cases in our series in 2011) [4••, 5]. Serratrice et al. described cases in which the whole aorta is sheathed as having a "coated aorta" (38 % of cases in our series reported in 2006 had this feature) [11, 20]. Periarterial infiltration may extend to the main aortic branches. The clinical consequences are not classically severe, apart from reno-vascular hypertension which is the most frequent (20 % of our 101 patients); this problem can be treated by renal artery stenting [5].

The most frequent heart lesion is pericardial (42 % of the 53 patients), with few cases of tamponade [5, 21]. The myocardium and endocardium may be involved. Among 37

patients who underwent systematic retrospective cardiovascular screening (MRI and/or heart CT scan) in 2009, 70 % had abnormal heart imaging results: abnormal infiltration of the right heart in 49 %, including 30 % with "pseudo-tumoral" infiltration of the right atrium, and infiltration of the auriculo-ventricular sulcus in 19 % [22].

Fifteen patients with myocardial infarctions secondary to pericoronary infiltration have been reported, leading to death in some cases [5, 23, 24]. In a series of 53 patients, 17 % had symptomatic heart valve disease (aortic and mitral regurgitations) [4••]. Valve replacement was required for three patients, including one case in our center [5, 25]. This operation is technically difficult because of the extensive infiltration of heart tissue, and therefore should only be performed at a specialist center, and only in appropriately selected cases.

Retro-Orbital Infiltration

One in four of our patients developed exophthalmos, often bilateral, caused by infiltration of the retro-orbital soft tissues [26, 27]. In a small number of cases, the infiltration is massive, and in such cases it may be refractory to conventional therapy such that surgical debulking is required.

Endocrine Involvement

Diabetes insipidus, caused by infiltration of the pituitary gland, is the most frequent endocrine manifestation of ECD (25 % of our patients). Rare cases of pituitary or hypothalamic infiltration have been reported, with other endocrine consequences, including hyperprolactinemia, gonadotropin insufficiency, and abnormally low levels of IGF-1 [28, 29].

We reported that seven of a series of 22 ECD patients had adrenal gland enlargement, with adrenal insufficiency in one case [30]. The diagnosis was radiological in all seven cases, and was confirmed by autopsy for one patient. Thus, adrenal infiltration is not rare in ECD patients and may possibly be associated with adrenal insufficiency.

Cutaneomucosal Involvement

Xanthelasma affected 28 % of our 53 patients, and usually involved the eyelids or the peri-orbital spaces. Papulonodular lesions [31] and infiltrations of the vulva and of the clitoris may be observed, but are less frequent [1].

Urological and Nephrological Infiltrations

Approximately one third of ECD cases present with pseudo "retroperitoneal fibrosis", in some cases complicated by bilateral hydronephrosis that may require ureteral stenting [32]. Involvement of the pelvic ureters has never been described, and the inferior vena cava is rarely affected in ECD. In ECD, the "fibrosis" sheaths the aortic walls completely and circumferentially, whereas the posterior aortic wall is rarely affected in idiopathic retroperitoneal fibrosis [5].

Lung Involvement

In 2008, we performed a retrospective analysis of the lungs of 34 consecutive patients with ECD [33]. Involvement of the lung parenchyma in 53 % of the cases, and of the pleura in 41 %, was revealed by high-resolution thoracic CT scans [34•]. The lesions mainly affect the interlobular septa. Lung involvement in this series was not a significant prognostic factor for ECD, contrasting with previous findings for small numbers of patients. A MEDLINE search identified reports of lung involvement in 70 (22 %) of 319 ECD cases published before November 2008, but the descriptions were mostly incomplete.

CNS Involvement

CNS involvement is common in ECD (15–25 %) [11], and was extensively described in the largest neurological series reported [35]: this multi-center literature review in 2006 analyzed 66 ECD patients (including six personal cases) with neurological involvement. Cerebellar and pyramidal syndromes were the most frequent neurological manifestations (41 % and 45 % of cases, respectively), and the other features described included seizures, headaches, neuropsychiatric manifestations or cognitive impairment, sensory disturbances, cranial nerve paralysis, and asymptomatic lesions. Neurological involvement led to severe functional disability in almost all patients, and CNS involvement is a major prognostic factor for ECD: survival analysis suggests that it is an independent predictor of death (hazard ratio=2.51; 95 % confidence interval, 1.28–5.52; P=0.006) [4••].

We reviewed brain MRI findings for 33 ECD patients followed at the Pitié-Salpêtrière Hospital up to 2009. Only three patients had normal imaging results [36], and two or more different anatomic sites were affected in most patients. Lesions are frequent in the brain, meninges, facial bones, and orbits in ECD patients. Consequently, MRI and CT should be used systematically to investigate the brain for all, even asymptomatic, ECD patients.

Other Infiltrations

The range of organs reported to be involved in ECD is broad. Autopsy has revealed the involvement of testes, thyroid, and lymph node [37]. There as also numerous case reports describing breast infiltration [38, 39].

Assessing Disease Activity

The clinical course of ECD seems to be typical of a chronic disease, but has not been described in detail. Lesions accumulate in the organs and systems affected, and rarely regress spontaneously. Serum C-reactive protein (CRP) levels are elevated in more than 80 % of cases [11], but the therapeutic consequences of this are small once the diagnosis is established. Regular clinical examination, radiological investigations (approximately every six months), and imaging to assess morphological changes are used to follow disease activity in ECD; note that no disease activity score has been established.

We have found that PET scanning is particularly informative about ECD activity [17]. Follow-up PET scans enable CNS involvement to be detected, and can reveal early responses of CNS lesions to therapy; any changes in such lesions are apparent on MRI. PET scanning can also be used to investigate the cardiovascular system, and the heart and the entire vascular tree can be studied during a single session. We therefore recommend PET investigations of ECD patients, because no other single technique provides as much information about as many of the lesions frequently associated with ECD. Our recent pilot study of use of BRAF inhibitors for ECD patients illustrates the value of PET investigations [40••].

Interferon Alpha (IFNα) Is the Best-Choice Initial Treatment for ECD

Before 2005, the standard treatments for ECD included steroids, cytotoxic agents [41], and double autologous hematopoietic stem-cell transplantation [42, 43]. The efficacy of these treatments has been difficult to establish, because some have been administered to only small numbers of patients, or in combination with other drugs; also, the follow-up periods were short. Braiteh et al. reported rapid, marked, and persistent regression of retroorbital infiltration, and progressive improvement in bone lesions, pain, and diabetes insipidus, in three ECD patients given IFNα [44]. However, for eight patients with ECD treated with low-dose IFNα (3 MU× 3 week^{-1}), we found that the efficacy differed according to the site involved in the disease [14]. In some cases, the symptoms failed to respond to such low-dose IFNα; this is true in particular of patients with severe multisystem forms of ECD (CNS and cardiovascular involvement) [4••]. We therefore recommend higher doses, 9 MU×3 week^{-1} if possible, because such doses may be more effective against meningeal infiltrations, sub and retro-sellar masses, and pericardial and pseudo-atrial infiltrations. IFNα treatment needs to be long-term, but this may lead to side effects including depression and fatigue. In cases of pseudo-degenerative forms of cerebellar involvement (similar to that observed in LCH), IFNα treatment has had disappointing results.

Nevertheless, IFNα seems to be the best choice for the initial prolonged treatment of ECD. Survival analysis of our series of 53 patients indicated that treatment with IFNα and/or PEGylated IFNα was a major independent predictor of survival (HR=0.32; 95 % CI, 0.14–0.70; P=0.006) [4••]. Usually, we currently start treatment with PEGylated forms of IFNα, because it is in most cases better tolerated than IFNα in the long-term.

There were reports in 2010 that imatinib mesylate was effective in cases of histiocytosis [45]; however, our preliminary experience with this treatment for six ECD patients was disappointing [46]. The treatment of two ECD patients (neither with cardiovascular or CNS involvement) with recombinant human interleukin-1 receptor (anakinra) was described at this time, and seemed to be promising [47]. We therefore treated ten ECD patients at our institution with anakinra: overall, the efficacy was poor. Cladribin may be beneficial for treating CNS localizations of the disease that are not responsive to IFNα [41], although a small number of patients at our center were administered this treatment and the outcome was not favorable. Infliximab treatment obtained benefits, after 12 to 18 months, for two ECD patients with cardiac involvement [48•]. The recent efficacy of a BRAF inhibitor (vemurafenib) for three patients is even more promising [40••].

BRAF Inhibition as an Alternative to IFNα for ECD Patients Carrying the *BRAF^{V600E}* Mutation

The RAS-RAF-MEK-ERK pathway is a cellular signaling pathway, and is involved in diverse tumors [49]. Many human tumors carry the BRAFV600E mutation [50], an activating mutation of the proto-oncogene BRAF causing activation of the RAS-ERK pathway, independently of RAS activation. Inhibition of BRAF activation by vemurafenib improves the survival of patients with metastatic melanomas carrying the BRAFV600E mutation [51]. BRAFV600E mutations were reported in patients with LCH in 2010 [52], and we therefore screened patients with other types of histiocytosis for this mutation. We used pyrosequencing to test DNA, from paraffin-embedded samples from 127 patients with histiocytoses, for BRAFV600 mutations, and reassessed histology findings [53••]. The samples were from cases diagnosed as ECD (n=46), LCH (n=39), RDD (n=23), juvenile xanthogranuloma n=12), histiocytic sarcoma (n=3), xanthoma disseminatum (n=2), interdigitating dendritic cell sarcoma (n=1), and necrobiotic xanthogranuloma (n=1). The BRAF status was successfully identified in 93 cases: BRAFV600E mutations were detected in 13 of the 24 (54 %) ECD samples, 11 of the 29 (38 %) LCH samples,

and none of the other histiocytosis samples. We have also detected BRAF mutations in nineteen of a series of 37 ECD patients [54].

Vemurafenib is an inhibitor of mutant BRAF, and has some efficacy against both BRAFV600E-associated melanoma and hairy-cell leukemia [55]. We conducted a pilot study of vemurafenib treatment for three patients who had multisystemic and refractory ECD and carried the BRAFV600E mutation. Two of the patients also had skin or lymph node LCH involvement [40••]. Vemurafenib treatment led to substantial and rapid clinical and biological improvement in all three cases, as assessed by clinical, biological (CRP values), histological (skin biopsy), and morphological (PET, CT, and MRI) follow-up. The tumor response was confirmed by PET, CT, and/or MRI after one month of treatment. For one patient, response as assessed by PET involved continued improvement between months one and four of treatment. The treatment remained effective after nine months of follow-up, although one patient continued to suffer disease activity. We therefore recommend that vemurafenib treatment should be considered for all patients with severe and refractory $BRAF^{V600E}$ histiocytoses, particularly if life-threatening.

Recently, Diamond et al. reported one patient with ECD *NRAS* mutations [56•]. Our team has also found these mutations—which have been shown to be a gain-of-function mutation in melanoma—in two *BRAF* wild-type ECD patients and in one patient with histiocytic sarcomas (manuscript submitted for publication). We suspect that ECD patients with *NRAS* mutation may benefit from targeted anti-MEK therapy, as did some patients with metastatic melanomas.

Follow-Up

We reported two series from before the "IFNα era", and these studies provide evidence of the poor prognosis of ECD [5, 6]. In 2004, 35 (60 %) of the 58 patients for whom data were available died, and the mean survival after diagnosis was 19.2 months (range, 0 to 120 months). However, a survival analysis of our patients in 2011 indicated that overall mortality after treatment with IFNα was only 26 %, and the five-year survival was 68 % [4••].

Pathophysiology

Until recently, the pathogenesis of ECD had not been well described, largely because previous studies included only small numbers of patients. Stoppacciaro et al. reported an immunohistochemical study of three patients, revealing that a complex network of cytokines and chemokines regulates histiocyte recruitment and accumulation in the lesions [57]. Dagna et al. studied both spontaneous and stimulated cytokine production by mononuclear cells in biopsy fragments from a single patient [58]: tumor necrosis factor 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. Aouba et al. reported evidence from two patients indicating that targeting the IL-1 pathway might be beneficial [47]. We recently assayed serum samples from 37 ECD patients for 23 cytokines [59••], and found high IFNα, IL-1/IL1-RA, IL-6, IL-12, and MCP-1 titers, indicating strong and systemic immune activation. Thus, there is evidence that ECD is associated with systemic immune Th-1-oriented perturbation; further work on this subject may enable the development of better-targeted therapeutic agents.

The recent finding that more than half of ECD patients carry $BRAF^{V600E}$ mutations indicates that the pathophysiology of this disorder is even more complex than previously suspected. This finding is also evidence of clonal proliferation (associated with the $BRAF^{V600E}$ mutation) in addition to the non-clonal accumulation of histiocytes in affected tissues (associated with circulating chemokines and pro-inflammatory cytokines).

Conclusions

ECD is a rare and orphan disease. Having long been poorly recognized, numerous cases have recently been diagnosed, and more than 300 new cases have been published in the past 10 years. This is mainly the result of greater awareness among pathologists, radiologists, and clinicians of different aspects of this previously obscure disease. There has been substantial progress in recent years. In particular, the efficacy of IFNα has been revealed, systemic pro-inflammatory cytokine signatures have been described, and BRAF inhibition in severe cases of $BRAF^{V600E}$-mutation-associated ECD has been found to be highly effective. More than half of ECD patients tested have been found to carry *BRAF* mutations. Further analysis of the disease, and especially an improved understanding of its pathogenesis, should lead to the development of better-targeted and more effective therapy.

Compliance with Ethics Guidelines

Conflict of Interest Julien Haroche has received honoraria from GlaxoSmithKline. Jean-François Emile has received honoraria from GlaxoSmithKline and Roche. Laurent Arnaud, Fleur Cohen-Aubart, Baptiste Hervier, Frédéric Charlotte, and Zahir Amoura declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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- • Of importance
- •• Of major importance

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