Histiocytoses

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Abbreviations

CNS	Central nervous system
CTLs	Cytotoxic T cells
ECD	Erdheim-Chester disease
HHV6	Human herpesvirus 6
HIV	Human immunodeficiency virus
HLH	Haemophagocytic lymphohistiocytosis
IFN-y	Interferon-y
IFNα	Interferon-α
IL-12	Interleukin-12
LCH	Langerhans cell histiocytosis
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NK	Natural killer
PET	Positron emission tomography
RDD	Rosai-Dorfman disease
Th1	T-helper 1

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Introduction

Histiocytoses are rare, often systemic diseases hallmarked by tissue infiltration by abnormal histiocytes bearing peculiar morphological and immunohistochemical characteristics. Despite the significant advances made in the past decades in defining the clinical and molecular profile of this spectrum of diseases, the cells of origin of the different forms of histiocytosis are still incompletely understood. The abnormal histiocytes that infiltrate target organs or tissues share the phenotype of dendritic cells and monocytes/macrophages. Macrophages are usually large ovoid cells with pleiotropic functions (e.g. clearance of apoptotic cells and pathogens), whereas dendritic cells are stellate cells specialised in antigen presentation and T-cell activation. Langerhans cells are a subset of dendritic cells physiologically residing in the skin; they express characteristic antigens such as CD1a and possess Birbeck granules that can be seen on electron microscopy [1].

Until recently, the histiocytoses were classified as Langerhans cell, non-Langerhans cell and malignant. Studies performed during the past few

G. Ragab et al. (eds.), *The Microbiome in Rheumatic Diseases and Infection*,
https://doi.org/10.1007/978-3-319-79026-8_29

years have revolutionised the field: in particular, the discovery of recurrent somatic mutations of some proto-oncogenes shed light on the aetiopathogenesis of several histiocytic disorders and provided the rationale for targeted treatments that have now largely replaced previous empirical approaches. In parallel, large cohort studies have been performed; these have allowed a better understanding of the natural history of the disease, contributed to a better phenotyping of these disorders and their subsets and led to the identification of previously unrecognised overlap forms of Langerhans and non-Langerhans cell histiocytoses [2], which suggest a common ontogeny of the pathologic histiocytes. These significant advances have culminated into a new classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages (Table 29.1) that comprises five distinct groups: the "L" group, including classical Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD) and overlap forms; the "C" group, mainly including cutaneous and mucocutaneous forms; the "M" group, encompassing primary malignant and secondary malignant forms, the latter occurring after or sometimes simultaneously with another haematologic neoplasm; the "R" group, covering Rosai-Dorfman disease (RDD) and other non-cutaneous, non-Langerhans cell histiocytoses; and the "H" group, comprising haemophagocytic lymphohistiocytosis (HLH), either primary or secondary to infectious or immune-mediated diseases [3].

Table 29.1 Revised classification of histiocytoses according to Emile et al. (adapted from Ref. [3])

L group
Langerhans cell histiocytosis
Erdheim-Chester disease
Indeterminate cell histiocytosis
Mixed Langerhans cell and Erdheim-Chester (overlap histiocytosis)
C group
Cutaneous non-Langerhans cell histiocytosis
Xanthogranuloma family (e.g. juvenile xanthogranulomatosis, adult xanthogranuloma)
Non-xanthogranuloma family (e.g. cutaneous Rosai-Dorfman disease)
Cutaneous non-Langerhans cell histiocytosis with a major systemic component
R group
Familial Rosai-Dorfman disease
Sporadic Rosai-Dorfman disease (e.g. classical and extra-nodal, associated with neoplasia or autoimmune disease)
M Group
Primary malignant histiocytoses
Secondary malignant histiocytoses (e.g. following or associated with another haematologic malignancy)
H group
Primary haemophagocytic lymphohistiocytosis (e.g. monogenic inherited conditions)
Secondary haemophagocytic lymphohistiocytosis (non-Mendelian)
Haemophagocytic lymphohistiocytosis of unknown/uncertain origin

Since this *textbook* focuses on systemic rheumatic disorders and their relationships with infections, this *chapter* will mainly deal with systemic forms of histiocytosis of the L, R and H groups, as they may share clinical features with rheumatic diseases or recognise, in some cases, infectious triggers.

Langerhans Cell Histiocytosis

LCH is an often systemic histiocytic disorder characterised by tissue infiltration by $CD1a^+$/$CD207^+$ histiocytes (Fig. 29.1). The pathologic histiocytes in LCH are mononucleated cells with coffee bean- or kidney-shaped nuclei that diffusely infiltrate target tissues, often accompanied by abundant eosinophils and multinucleated giant cells [3]. Electron microscopy may reveal the presence of Birbeck granules, although the search for this hallmark ultrastructural feature has been replaced in clinical practice by immunohistochemical analysis on paraffin-embedded samples for typical Langerhans cell markers such as CD1a and CD207 (Figs. 29.1 and 29.2) [3]. Elegant studies have explored the origin of pathologic histiocytes in LCH: transcriptional profiling showed that LCH cells are more similar to their bone marrow-derived monocyte and dendritic cell precursors than to epidermal Langerhans cells [4]. In line with this view, studies tracking the $BRAF^{V600E}$ mutation (which is found in LCH lesions in approximately 55% of the cases) in

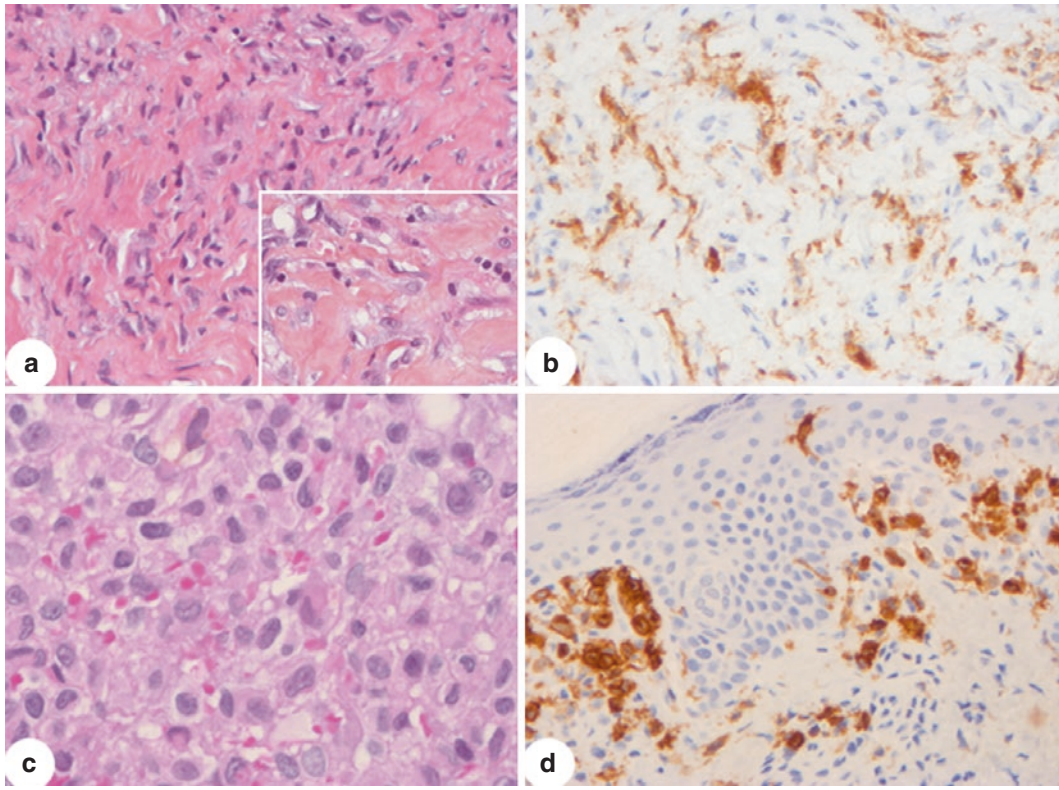

Fig. 29.1 Main histopathologic characteristics of Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis (LCH). (**a**) Perirenal tissue biopsy from a patient with ECD showing fibrosis with histiocytes (some of which have a foamy cytoplasm) and small lymphocytes (inset). Haematoxylin and eosin (H&E), original magnification 200× (400× in the inset). (**b**) CD68+ immunostaining decorates the histiocytes in an ECD case. (**c**) Skin biopsy from an LCH patient shows infiltration by histiocytes with small, round or oval nuclei (H&E, 400×). In (**d**) the histiocytes shown in C are CD207+ (200×)

haematopoietic precursors were able to detect this mutation in $CD34^+$ bone marrow cells in some (although not all) cases [5]. These data suggest that LCH derives from aberrant progenitor cells that acquire somatic mutations such as $BRAF^{V600E}$ and that eventually infiltrate target tissues. Mutations other than $BRAF^{V600E}$ have been detected in LCH, such as those involving *MAP2K1*, which encodes MEK1; *BRAF* and *MAP2K1* mutations seem to be mutually exclusive [6]. Overall, the genetic abnormalities encountered in LCH lead to activation of the RAF-MEK-ERK pathway.

LCH is more frequent in children; its annual incidence is 5–9 cases/million in subjects younger than 15 years of age and declines to 1 case/million in patients older than 15 years of age [7]. In adults, LCH with lung involvement is strongly associated with smoking. LCH may vary from organ-limited, clinically silent forms to disseminated and life-threatening forms. Although nearly all organs or systems can be involved, the most frequently affected sites are the bone (80% of patients), the skin (30–40%), the pituitary gland (25%), the bone marrow, the liver, the spleen and the lungs (all around 10–15%) [8]. Lung involvement is more frequent in adults [1]. The main "risk organ" is the haematopoietic system, whose involvement is commonly associated with liver and spleen infiltration.

Bone lesions are very common in LCH and frequently involve the skull, the jaw, the spine (especially the cervical tract), the ribs, the pelvis and the long bones. Bone lesions in LCH are usu-

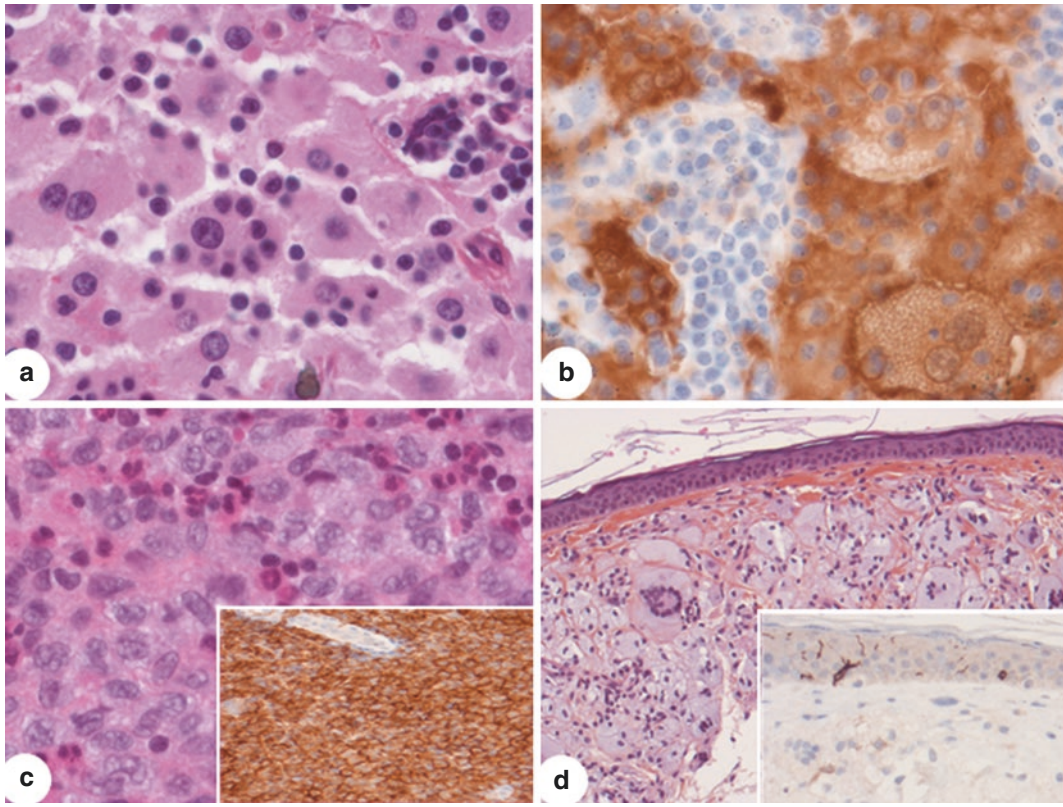

Fig. 29.2 Main histopathologic features of Rosai-Dorfman disease and of a case with overlap Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD). (**a**) Lymph node biopsy in a patient with RDD showing small lymphocytes, plasma cells and histiocytes with images of emperipolesis (see text for details) (H&E, 400×). (**b**) In an RDD biopsy, the histiocytes are S-100+ and show emperipolesis (400×). (**c**, **d**) Showing images of a patient with overlap LCH-ECD. (**c**) Tissue biopsy showing LCH histiocytes which stain positive for CD1a (H&E, 400×, CD1a staining in the inset, 200×). (**d**) Skin biopsy from an ECD lesion showing diffuse infiltration by foamy histiocytes with large cytoplasm and small nuclei; multinucleated Touton giant cells are also observed (H&E, 100×); the histiocytes are CD1a negative (inset, 200×)

ally lytic (Fig. 29.3) but may be accompanied by soft tissue masses. They may cause fractures or vertebral collapse, or when localised to the maxillofacial bones or the skull base, they can cause scalp or facial swelling, otitis media, hearing loss, mastoiditis, loss of teeth and other cranial or central nervous system (CNS) manifestations [1].

CNS involvement may be severe and usually consists of either tumour-like or degenerative lesions, which may coexist. Patients with tumour-like lesions have a wide spectrum of neurological manifestations, ranging from focal neurological deficits to cranial nerve palsies, seizures and symptoms secondary to intracranial hypertension. Conversely, neurodegenerative complications of LCH lead to progressive cerebellar syndrome, cognitive impairment, tetrapyramidal syndrome and other slowly progressive manifestations. Focal CNS lesions may mimic primary or metastatic CNS neoplasms, granulomatous or infectious diseases, and can involve almost every portion of the CNS, with particular tropism for the hypothalamic-pituitary axis and the brainstem [1].

Skin lesions include brown to purplish papules, eczematous rashes resembling *Candida* infections and pustular, purpuric, vesicular or papulo-nodular lesions; oral lesions such as intra-

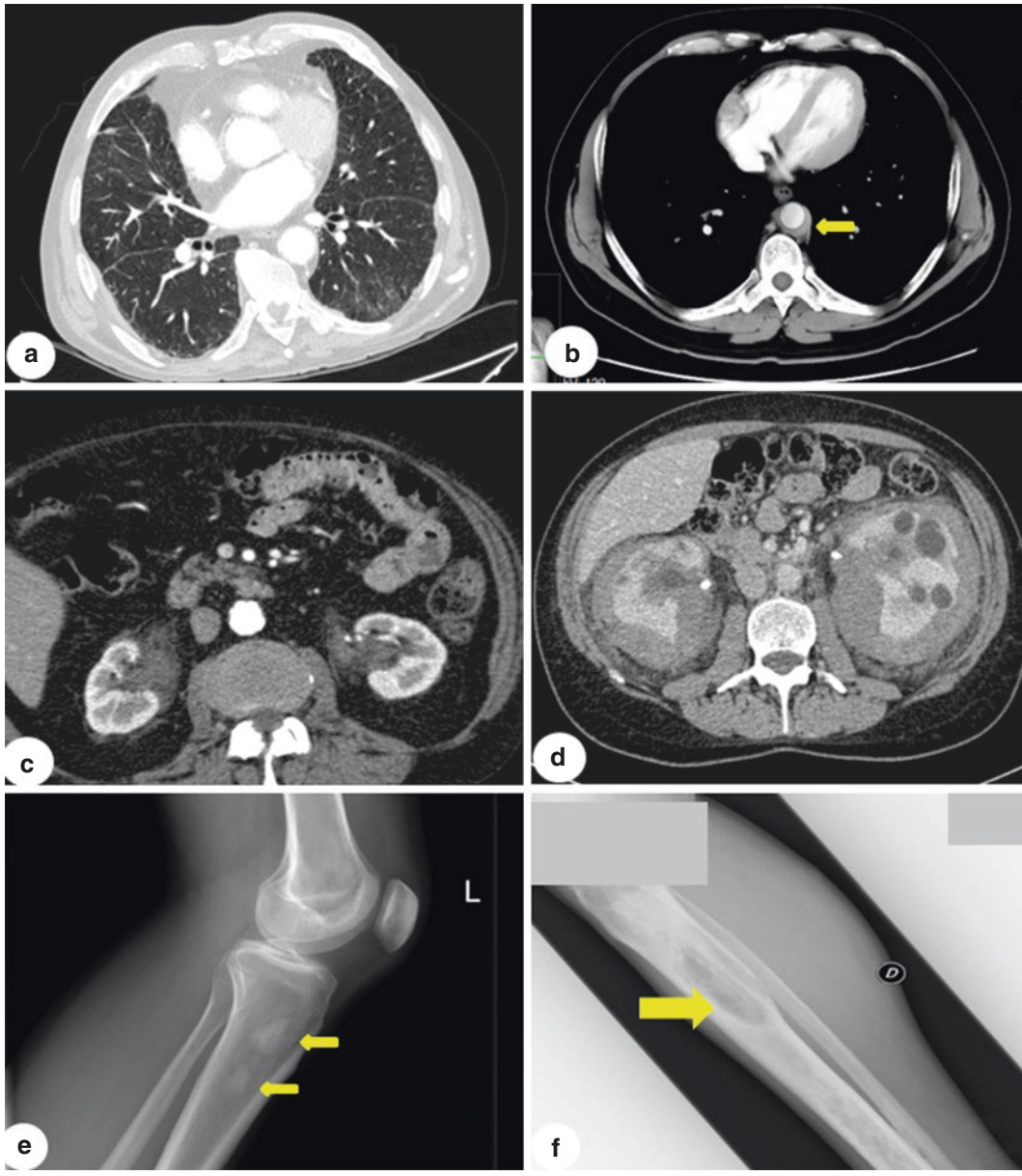

Fig. 29.3 Imaging findings in patients with Erdheim-Chester disease (ECD) and overlap Langerhans cell histiocytosis and ECD (LCH-ECD). (**a**, **b**) Showing thoracic involvement in LCH-ECD cases: (**a**) CT scan showing interstitial lung fibrosis, well represented in interlobular septa; (**b**) CT scan of thoracic aorta involvement (periaortitis) (arrow). (**c**, **d**) Showing abdominal involvement in patients with ECD: (**c**) abdominal CT scan shows infiltration of both kidneys around the renal pelvis; (**d**) CT scan showing perirenal infiltration with typical "hairy kidney" appearance. (**e**, **f**) Showing bone involvement in ECD and overlap LCH-ECD: (**e**) plain radiograph of osteosclerotic bone lesions localised in the diaphysis of the tibia in ECD (arrows); (**f**) plain radiograph of osteolytic bone lesion localised in the tibia in a LCH-ECD overlap case (arrow)

oral masses, gingivitis, ulcers and loose teeth may also occur. The involvement of the haematopoietic system represents an adverse prognostic factor in LCH. Patients with bone marrow involvement often show peripheral blood count abnormalities such as anaemia and thrombocytopenia, but some patients may have no abnormalities at all. Importantly, bone marrow involvement is usually associated with liver and spleen infiltration leading to organomegaly, tumour-like or cystic lesions and eventually organ failure.

Among the other LCH-associated manifestations, it is worth mentioning that diabetes insipidus is the most frequent endocrinopathy; it can precede or be the sole clinical manifestation of LCH in many cases. About 15% of patients with an apparently isolated diabetes insipidus were found to have LCH [9]. Lung involvement is rare and is best diagnosed using high-resolution computed tomography, which usually reveals interstitial thickening (Fig. 29.3) as well as small cysts and nodules especially in the upper and mid lung.

The diagnosis of LCH relies on histological examination of the affected tissue and immunohistochemical confirmation of the nature of the infiltrating histiocytes. Biopsy of the bone or skin lesions is usually preferred, but its interpretation must be in the context of the systemic disease manifestations and the possible differential diagnoses, which include ECD (that can also overlap with LCH), juvenile xanthogranuloma, other forms of histiocytosis and multiple myeloma.

Treatment of LCH is based on the use of several chemotherapeutic drugs along with glucocorticoids and, in some cases, surgery. Among the most used chemotherapeutic agents are vinblastine (particularly in the induction phase, in combination with glucocorticoids) and cladribine [1]. Response to treatment is better for symptomatic tumour-like lesions than for degenerative lesions, for which treatment options are mainly empirical and include all-trans retinoic acid and intravenous immunoglobulins. LCH patients bearing the *BRAF*^{V600E} mutation have an increased frequency of risk organ involvement and show poorer response to standard therapy with glucocorticoids and vinblastine; additionally, they are more prone to relapse and more frequently experience permanent sequelae of disease and treatment [8]. To date, selective inhibition of *BRAF*^{V600E} with vemurafenib or other agents is not yet of proven efficacy. Further studies are needed to evaluate the efficacy of targeted therapies and to tailor treatment on the basis of the underlying mutations.

Erdheim-Chester Disease

ECD is a rare histiocytosis of the L group mainly occurring in adulthood, hallmarked by the accumulation of "foamy" histiocytes staining positive for CD68, negative for CD1a and CD207 (Langerin) (Figs. 29.1 and 29.2) and usually negative for S100. In addition to tissue accumulation of foamy, lipid-laden macrophages, the pathology of ECD also shows abundant fibrosis, chronic lymphoplasmacytic infiltrates and often Touton giant cells. ECD is usually a multisystemic disease, with its hallmark feature being the symmetric involvement of the long bones that typically produces osteosclerotic lesions (Fig. 29.3) [10].

ECD was initially thought to be a primary inflammatory disease: in the affected tissues, the pathologic histiocytes express several chemokines and their receptors and also produce proinflammatory cytokines. In addition, serum cytokine profiling of ECD patients showed a prominent T-helper 1 (Th1) polarisation, with upregulation of interleukin (IL)-12, interferon (IFN)-g-inducible protein-10 and monocyte chemotactic protein-1 [11]. However, the recent identification of mutations or translocations in several proto-oncogenes or genes controlling cell proliferation such as *BRAF*, *MAP2K1*, *NRAS* and *KRAS* supports the hypothesis that ECD is a clonal disease [12]. The infiltrating histiocytes in ECD also show activation of the mammalian target of rapamycin (mTOR) pathway, which is involved in the control of cell metabolism and proliferation [13]. The clinical relevance of these findings is strongly supported by the evidence that targeting the mutated kinases and mTOR often leads to objective responses in ECD patients [14]. Overall, a new concept of inflammatory myeloid neoplasia is emerging for ECD as well

as for LCH [1]. However, the cell of origin of the ECD histiocytes is still unclear.

ECD is an extremely rare disease, with no more than 800 cases reported up to 2016; however, its prevalence has dramatically increased in the last decade, mainly due to increased recognition of the disease. ECD usually occurs in adults with only few paediatric cases reported in the literature; it affects men more frequently than women (M:F ratio of approximately 3:1), and its incidence peaks in the fifth decade [1].

Among the clinical complications of ECD, involvement of the long bones is definitely the most common as it occurs in nearly 90% of the cases. The diaphyses and metaphyses of long bones (particularly of the lower limbs) are usually involved symmetrically (Fig. 29.3). They show increased ^{99}Tc uptake on bone scans; X-rays or other imaging studies such as computed tomography or magnetic resonance imaging (MRI) demonstrate that these lesions are generally osteosclerotic. Bone pain is common in ECD patients, as it occurs in 50% of the cases.

Another typical finding in ECD is retroperitoneal infiltration, which usually involves the adipose surrounding the kidneys, the renal pelvis and the proximal ureter, giving rise to the so-called hairy kidneys; peri-ureteral infiltration is a common cause of ureteral obstruction (Fig. 29.3) with consequent hydronephrosis and sometimes renal failure. The abdominal aortic wall and the surrounding retroperitoneum are also commonly infiltrated, and so is the adventitia of thoracic aorta (Fig. 29.3) and of the origin of the epiaortic arteries; the involvement of the whole (thoracoabdominal) aorta is usually referred to as "coated aorta" and is found in 30% of the cases [10]. Heart involvement is also a prominent feature of ECD (40% of patients) and is also considered an adverse prognostic factor. ECD affects the pericardium (often with pericardial effusion which can lead to tamponade) and the myocardium, where the infiltration almost invariably involves the right atrium and the right atrioventricular sulcus (Fig. 29.4). Entrapment of the right coronary artery is not uncommon. Interestingly, heart involvement is usually associated with a disseminated disease [15].

The CNS is involved in 25–50% of the cases. ECD lesions are often located in the brainstem and in the dentate nuclei of the cerebellum but may develop almost anywhere in the CNS and also involve the meninges; these lesions are usually tumour-like and gadolinium enhancing on MRI (Fig. 29.4) and may mimic meningiomas, granulomatous diseases or even CNS infiltration by LCH or Rosai-Dorfman disease. Spinal cord infiltration is also reported. As in LCH, CNS infiltration in ECD can also cause degenerative lesions especially in the cerebellum. Overall, CNS lesions clinically cause a variety of neurological syndromes, the most frequent of which include cerebellar (ataxia and dysarthria) and brainstem symptoms. Interestingly, ECD patients also have diffuse grey matter reduction and may progressively develop cognitive dysfunction [16].

Other manifestations of ECD include skin lesions, particularly xanthelasmas, neuroendocrine abnormalities such as diabetes insipidus, other endocrine dysfunctions (e.g. hypogonadism, adrenal insufficiency), infiltration of serosa and effusion, interstitial lung disease and orbital infiltration with consequent exophthalmos (Fig. 29.4) [10].

The diagnosis of ECD relies on the demonstration of typical long bone lesions and compatible histology, according to the criteria proposed by Veyssier-Belot et al. [17]. Biopsies of the affected lesions are currently required not only for the diagnosis but also for molecular testing of the aforementioned mutations involving *BRAF* and other genes. Skin and perirenal tissue lesions are the easiest to biopsy and usually yield representative material. A thorough evaluation of disease extent and severity is based on a combination of imaging techniques dedicated to the study of specific organs or systems (e.g. cardiac or CNS MRI, bone scintigraphy) and laboratory tests; however, metabolic imaging studies such as positron emission tomography (PET) have become crucial in the evaluation of disease activity and response to therapy [13, 14].

The treatment of ECD has been empirical for several years, based on the use of various chemotherapeutic or immunosuppressive agents and

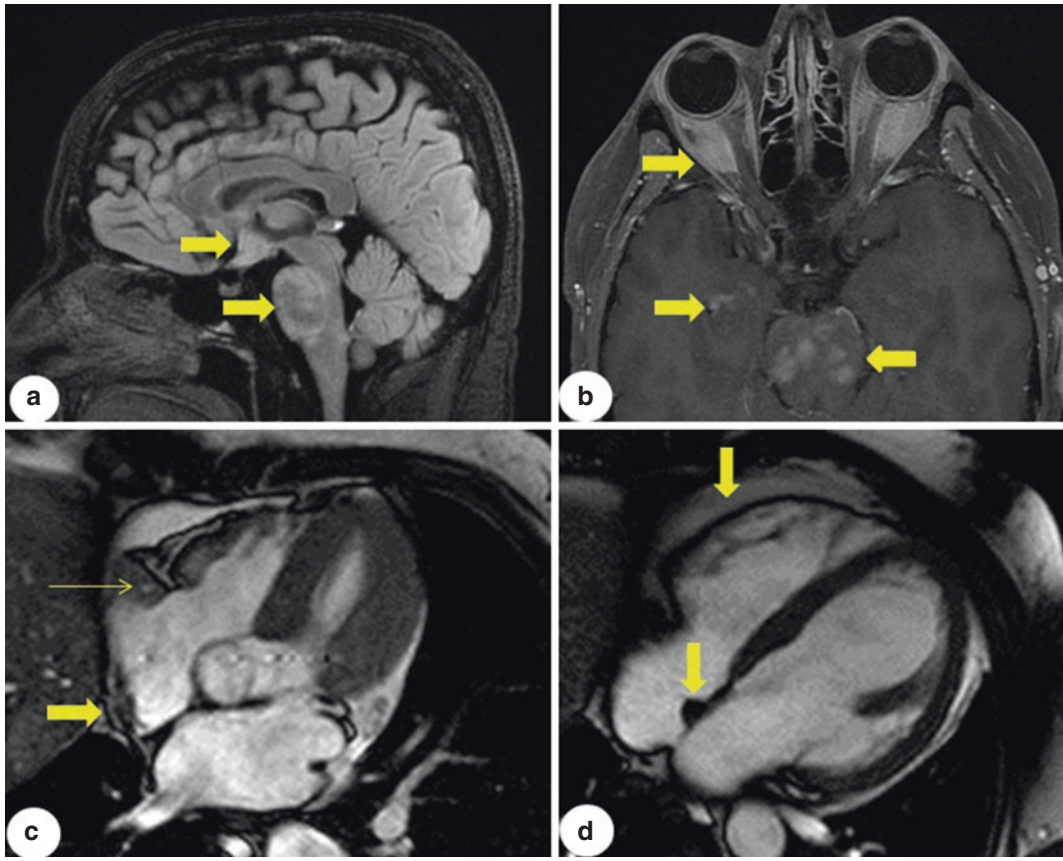

Fig. 29.4 Brain and cardiac imaging findings in patients with Erdheim-Chester disease (ECD) and overlap Langerhans cell histiocytosis and ECD (LCH-ECD). (**a**, **b**) Central nervous system involvement in an ECD patient: (**a**) brain MRI (sagittal) showing pathologic and increased gadolinium uptake in the hypothalamus (upper arrow) and pons (lower arrow). (**b**) Brain MRI (axial): irregularly increased intensity in the pons (right-hand arrow), parahippocampal region (lower left-hand arrow) and retroorbital space (upper left-hand arrow), where the pathologic solid tissue surrounds the optical nerve. (**c**, **d**) Heart involvement in ECD and in an overlap LCH-ECD: (**c**) cardiac MRI (four-chamber view) in a case of LCH-ECD overlap form: solid tissue in the posterior wall of the right atrium (thick arrow) and in the right atrium-ventricle sulcus, surrounding the right coronary artery (thin arrow); (**d**) cardiac MRI in a ECD case: pericardial thickening with effusion (upper arrow) and a round mass within the right side of the atrial septum wall (lower arrow)

glucocorticoids. A major breakthrough was the discovery of the efficacy of interferon-α (IFNα), which is thought to induce terminal differentiation or immune-mediated killing of immature, pathologic histiocytes. IFNα (or its pegylated form, peg-IFNα) has largely been used for ECD; it is able to induce objective responses and still represents the first-line therapy for ECD in *BRAF* wild-type patients, although its use is limited by significant toxicity [18].

The discovery of the high prevalence of $BRAF^{V600E}$ mutations in ECD (approximately 55–60% of the cases) led to the use of its specific inhibitor vemurafenib, which proved dramatically effective in inducing rapid and sustained objective responses [14]. Vemurafenib is therefore considered the first-line therapeutic option in $BRAF^{V600E}$ patients with multisystemic or organ-threatening disease [1]. A panoply of other drugs have been proposed for ECD, including biologic agents targeting the IL-1 receptor [19], the MEK inhibitor cobimetinib [20] and the mTOR inhibitor sirolimus [15]. Overall, the advances made in the diagnosis and management of ECD have dra-

matically changed its prognosis: while in the late 1990s the 3-year mortality associated with the disease was reported to be up to 60% [17], it has dropped to approximately 20% in most recent years [1]. However, long-term follow-up studies are needed to ascertain the efficacy and safety of newer agents for the treatment of ECD.

Rosai-Dorfman Disease

RDD, also known as "sinus histiocytosis with massive lymphadenopathy" since Rosai's and Dorfman's seminal description, is another rare form of non-Langerhans cell histiocytosis characterised by tissue (often lymph node) infiltration by $CD68^+/CD1a^-/S100^+$ histiocytes; the infiltrating histiocytes show emperipolesis, a non-destructive form of phagocytosis of lymphocytes and erythrocytes (Fig. 29.2) [21]. In the affected lymph nodes, there is marked sinusoidal dilation containing histiocytes, plasma cells and lymphocytes. In the affected extra-nodal sites, pathologic examination discloses increased amounts of fibrosis and fewer histiocytes; as $IgG4^+$ plasma cells are not uncommon in RDD lesions, RDD- and IgG4-related disease may be in differential diagnosis.

RDD is hallmarked by heterogeneity both in its phenotype and clinical course. Patients with RDD may have concurrent haematologic (e.g. Hodgkin and non-Hodgkin's lymphoma) or autoimmune disorders (e.g. systemic lupus erythematosus, juvenile idiopathic arthritis) and overlapping histiocytic diseases such as LCH and ECD [1]. Interestingly, systemic lesions whose pathology is compatible with RDD can be found in patients with autoimmune lymphoproliferative syndromes and hereditary histiocytic conditions [22]. This broad spectrum of RDD-associated disorders suggests that RDD has an uncertain pathogenesis and that multiple mechanisms can be involved. Unlike LCH and ECD, RDD does not seem to be driven by $BRAF^{V600E}$ mutations; evidence supporting the role of other somatic mutations is lacking. Only in extremely rare cases of familial RDD have germline mutations in the *SLC29A3* gene been described [23]. Therefore, it has been hypothesised that immune-mediated mechanisms leading to the accumulation of pathologic histiocytes in the tissue are involved. Infectious triggers have also been postulated; this topic will be discussed below in the paragraph on infections and histiocytoses.

RDD arises more commonly in children or young adults, although it can really occur at any age; it seems to be more frequent in African-Americans than in Caucasians and has male predominance. Most RDD patients present with symptoms of fever, sometimes night sweats, weight loss and massive, usually non-painful, cervical lymphadenopathy, which raises the suspicion of lymphoma. Actually, the diagnostic work-up of RDD is similar to that of lymphoma; in addition, autoimmune diseases and viral infections must be searched for [24].

According to the revised classification of histiocytoses by the Histiocyte Society [3] (Table 29.1), classic RDD (with isolated involvement of single or regional lymph nodes) must be distinguished from RDD involving the skin or other organs. Extra-nodal RDD accounts for up to 40% of all RDD cases, the most frequently involved sites being the skin, the head and neck region, the bone (with mostly osteosclerotic lesions) and the CNS. Intracranial RDD has an intriguing presentation as it often develops without extracranial lymphadenopathy and may present as masses involving the meninges (commonly with pleocytosis in the cerebrospinal fluid); unlike in LCH and ECD, intracranial lesions in RDD do not cause neurodegenerative complications [1].

The clinical course of RDD is extremely variable: sustained phases of remission and disease flares may alternate, and the disease is often considered to be self-limiting. However, extra-nodal RDD, involving particularly the brain or the head and neck and therefore potentially causing life-threatening manifestations, requires prompt treatment that can be surgical (debulking or complete resection) and/or medical, using a variety of chemotherapeutic or immunosuppressive drugs. Given the rarity of the disease and its extremely protean clinical manifestations, no trials have been performed. Among the drugs most fre-

quently reported in the literature are vinca alkaloids, anthracyclines, alkylating agents and cladribine but also IFN-α, methotrexate and the anti-CD20 rituximab [24].

Haemophagocytic Lymphohistiocytosis

HLH includes a spectrum of diseases characterised by excessive immune activation and tissue infiltration by macrophages and histiocytes that clinically presents with fever, cytopenias, hepatosplenomegaly and hyperferritinemia. Other common abnormalities include hypertriglyceridemia, coagulopathy, low fibrinogen levels, high transaminase levels and neurological symptoms. Although not routinely available, testing soluble CD25 (soluble IL2-receptor) serum levels may be of diagnostic help and denotes lymphocyte activation [25].

HLH has traditionally been divided into primary and secondary forms, where the former are due to disorders with Mendelian inheritance linked to gene mutations affecting immune function, while the latter occur as a consequence of infections, solid or haematologic malignancies or autoimmune disorders (e.g. rheumatoid arthritis, systemic lupus erythematosus). HLH associated with systemic rheumatic disorders is usually referred to as macrophage-activation syndrome (MAS) (also see Chap. 14); for this HLH subset, the term MAS-HLH has been suggested [3]. Actually, infections may trigger both primary and secondary HLH, and genetic defects have also been found in patients with suspected secondary HLH. In clinical practice, the distinction between primary and secondary HLH is not essential for the diagnosis and initial management of the disease, while it becomes crucial for the subsequent follow-up.

The pathology of HLH shows a diffuse accumulation of lymphocytes and macrophages with frequent evidence of haemophagocytosis in the affected tissues, particularly the spleen, the liver (where the disease mimics chronic persistent hepatitis) and the bone marrow [26].

Although a review of the pathogenic mechanisms of the different forms of HLH is beyond the scope of this chapter, it is worthwhile mentioning that the main cell types involved in the development of the disease are natural killer (NK) cells, cytotoxic T cells (CTLs) and macrophages. In HLH, NK cells and CTLs are deficient, and activated macrophages accumulate. As a result, there is excessive macrophage activation and production of cytokines (particularly IFN-γ), which are thought to be main mediators of damage in HLH. NK- and CTL-mediated destruction of macrophages is usually a perforin-dependent mechanism; this enables NK cells and CTLs to release cytotoxic granules (containing proteases, granzyme B) into the macrophage. Genetic defects involving this cell death pathway may be involved in primary forms of HLH [26]. Infectious triggers are also usually necessary to initiate the disease and will be discussed below in the following paragraph.

The diagnostic work-up of HLH requires the exclusion of cancer using appropriate laboratory and imaging studies; MRI of the brain as well as cerebrospinal fluid evaluation is also required in almost all cases. Bone marrow aspiration or biopsy is warranted to investigate the cause(s) of cytopenia and demonstrates haemophagocytosis and macrophage infiltration and can also be sent for culture. Molecular analysis of mutations in genes involved in primary HLH forms should be performed in specialised centres, particularly in cases occurring in childhood and with no evidence of an associated rheumatological disorder.

If left untreated, HLH is a life-threatening disorder with a survival of weeks to months, but HLH-specific therapy is able to dramatically improve prognosis and overall survival [27]. Clinically stable patients should be carefully screened and receive treatment for potential underlying conditions (e.g. infection, autoimmune disorder). Conversely, acutely ill and rapidly deteriorating patients should receive cytolytic therapy with etoposide and dexamethasone, with intrathecal steroids and methotrexate for those with severe CNS involvement. The use of cyclosporine is debated. Other options include alemtuzumab (anti-CD52 antibody). Patients with HLH gene mutations or with refractory disease, haematologic malignancies that cannot be

cured, or severe CNS involvement usually require allogeneic haematopoietic cell transplantation.

Infections and Histiocytoses

There is no clear evidence supporting a role for infections in the pathogenesis of LCH and ECD. The hypothesis that these two forms of histiocytosis are clonal disorders is now well accepted, especially after the discovery of recurrent somatic mutations (particularly *BRAF*^{V600E}) impacting on the activation of the RAS-RAF-MEK-ERK pathway. It must also be acknowledged that both LCH and ECD show intense inflammation and fibrosis in addition to histiocyte proliferation, which has led to the concept of inflammatory myeloid neoplasia. Whether an accompanying infectious trigger drives inflammation is still unknown.

On the other hand, the clinical presentation and the disease associations of RDD and HLH suggest, at least in some cases, a "reactive" nature of these conditions. In RDD, some evidence suggests a role of viruses in disease pathogenesis. In particular, the human herpesvirus 6 (HHV6) antigen has been demonstrated in RDD histiocytes [28], although HHV6 is so common in lymphoid tissues that its pathogenic significance in RDD remains questionable. In addition, immunohistochemistry for parvovirus B19 antigens VP1/VP2 was found to be positive in some cases of RDD [29], although this finding has not been consistently replicated. Other viral infections, caused by Epstein-Barr and polyoma viruses, have been implicated, but there is no solid evidence supporting these data. Finally, RDD-like changes in draining lymph nodes were also found during the course of bacterial infections (e.g. *Salmonella*) [30].

With regard to HLH, clear evidence supports a causal role for infections. In fact, although infections can act as triggers also in primary forms of HLH, secondary forms may recognise a purely infectious aetiology and are therefore divided into secondary to viral, bacterial, parasitic and fungal infections. Epstein-Barr virus, Cytomegalovirus, influenza virus and human immunodeficiency virus (HIV) are the most common causes of HLH associated with viral infection. It is interesting to note that HLH may develop soon after the initiation of antiretroviral therapy for HIV infection. Among the bacterial causes, mycobacteria certainly play a central role, as do *Leishmania* and different plasmodia species among parasitic infections. Finally, histoplasmosis is probably the main cause of secondary HLH associated with fungal infections [3]. Notably, infections with *Mycobacterium tuberculosis*, cytomegalovirus or *Histoplasma* can occur in patients with rheumatological conditions (which may predispose to HLH per se) after specific immunosuppressive therapies such as those with antitumour necrosis factor-α antibodies [31].

It is also important to underline that the conditions predisposing to HLH include various types of immunodeficiency, which can in turn expose patients to an increased risk of infections. These can therefore activate a vicious circle that promotes infections, and infections can act as triggers of HLH.

Conclusions

Histiocytoses encompass a broad spectrum of conditions characterised by accumulation of pathologic histiocytes in the affected tissues. These syndromes can be due to primary histiocytic neoplasia such as LCH or ECD, which can be multisystemic and recognise recurrent mutations activating the RAS-RAF-MEK-ERK pathway as main drivers; however, as is the case of HLH or RDD, these can be of inherited monogenic origin, or associated with infections or other immune-mediated disorders, and probably have a "reactive" origin. Further studies investigating the potential role of infectious triggers are warranted.

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