

# Updates in histiocytic and dendritic cell proliferations and neoplasms

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## Abstract

Tumours derived from histiocytes/macrophages and from dendritic cells are extremely rare. They mainly occur in lymphoid tissues, where they account for less than 1% of tumours, but they can be also found in extranodal sites. These neoplasms represent a heterogeneous group of diseases with a variable clinical behavior even within the same tumour entity, ranging from localized and indolent forms to systemic aggressive processes. Diagnosis is based on histological and immunophenotypic features, but overlaps occur across diseases with different biological nature and clinical course, thus correlation with clinical and radiological features is sometimes necessary for final diagnosis. The driver mutations identified during the last few years contributed to a better understanding of the pathogenesis of some of these tumours and in some of them turned out to be useful for diagnosis and treatment.

**Keywords** Dendritic cells; genetic; histiocytes; histiocytoses; immunohistochemistry; macrophages; molecular; neoplasia; pathology

## Introduction

The nomenclature of monocytes, macrophages and dendritic cells (DC) has significantly evolved during the recent years and the relationships between circulating precursors and related mature tissue cells has been clarified; these include different subsets of histiocytes (also known as tissue resident

macrophages), macrophages (inflammatory activated macrophages) and dendritic cells. Moreover, relevant information has been provided on the regulatory factors driving the differentiation pathways of these heterogeneous cell populations as well as their functions<sup>1</sup> (Figure 1).

Neoplasms derived from histiocytes/macrophages (H/M) and DCs are rare diseases compared to lymphoid tumours. The cell of origin has been identified only for some of them. Discovery of clonal somatic mutations has definitely established the neoplastic nature of diseases long retained to represent inflammatory processes, such as Langerhans cell histiocytosis and Erdheim–Chester disease. Similarly, classical Rosai–Dorfman disease may represent a neoplastic rather than a reactive process.

The first classification of H/M and DC neoplasms was provided by the Histiocyte Society in 1987. The classification has been considerably revised with the definition of five distinct groups of diseases on the basis of histological, phenotypical, molecular, clinical and radiological features. Each of the five groups further includes various sub-types of diseases<sup>2</sup> (Table 1). Correspondence of this classification with those proposed by the WHO editions, respectively of the haematopoietic and lymphoid tissues and skin tumours,<sup>3,4</sup> is only partial.

In this review, we will report the main clinical, morphological and phenotypical features of tumours derived from H/M and DC and highlight recent data on their genomic landscape. At present, diagnosis and classification of these neoplasms is supported by morphology and immunohistochemistry. Table 2 includes the most widely used markers and their specificities. During the last years, distinct driver mutations have been identified and validated. Remarkably, some of them can not only support diagnosis, but also open window of opportunity for therapeutic targeting. *BRAF*<sup>V600E</sup> mutation can be detected with acceptable analytical performances when compared with molecular techniques by using the clone VE1.<sup>5,6</sup> However, since these mutations may occur at a very low allelic frequency due to wild-type DNA contamination from normal cells, highly sensitive techniques are preferred.<sup>6,7</sup>

## Histiocytic sarcoma

Histiocytic Sarcoma (HS) consists of tumours with the morphological and phenotypic characteristics of macrophages. HS occurs at any age, most commonly in adults, with a moderate predominance in males. Co-existing lymphoma, myelodysplasia, leukaemias and mediastinal non-seminomatous germ cell tumours might occur in these patients. By definition, neoplastic proliferations with features of HS in patients with acute monocytic leukaemia are defined as myeloid sarcoma.<sup>3,8</sup>

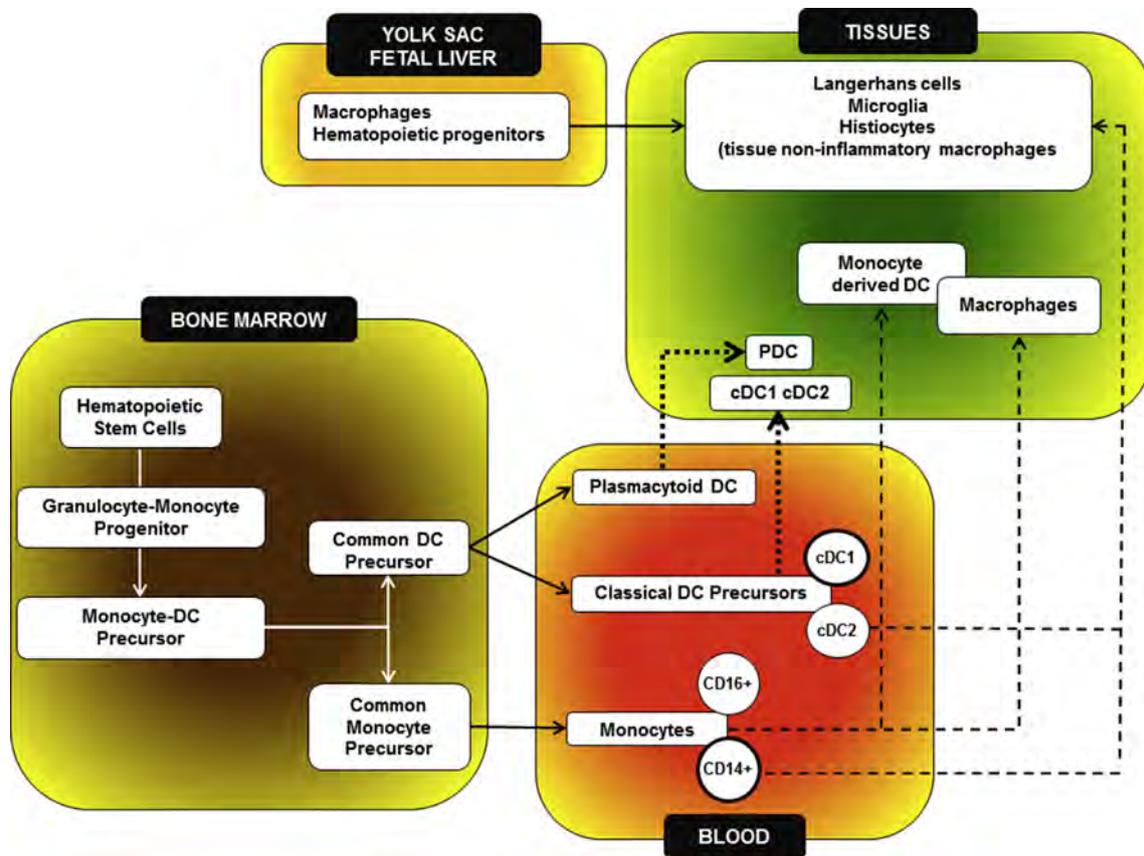
HS more often develops as a solitary mass at extranodal sites (mostly soft tissue and skin, lymph nodes, gastrointestinal tract and bones) and it is associated with systemic symptoms. Rarely it presents as disseminated disease, a condition recognized as “malignant histiocytosis”.<sup>3</sup> HS is composed of variably shaped large cells showing abundant eosinophilic or xanthomatous cytoplasm and significant nuclear atypia and mitoses; intrasinusoidal growth may occur in lymph nodes and spleen and erythrophagocytosis by tumour cells can be prominent (Figure 2a). The association with reactive inflammatory cells, including lymphocytes, neutrophils, eosinophils and plasma cells

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**Figure 1** The human mononuclear phagocytic and dendritic cells system. Histiocytes also known as tissue-resident macrophages derive from embryonal yolk-sac or fetal liver cell precursors. They include Langerhans cells and microglia, Kupffer cells and histiocytes occurring in the interstitium of various tissues. These are long living and self-renewing cells, but upon inflammation or cell damage they are replenished by bone marrow-derived precursors (dashed-line). Subsets of circulating monocytes exist, the CD14<sup>+</sup> being more numerous than the CD16<sup>+</sup>; upon inflammation they typically migrate to tissues where differentiate into macrophages and monocyte-derived dendritic cells. Classical dendritic cells and plasmacytoid dendritic cells derive from a distinct differentiation pathway. Both of them migrate from blood to different tissues in steady-state conditions and this process markedly increases during inflammation (dotted-lines). Notably, PDC in steady states are rare in non-lymphoid tissues, while classical DC are numerous.

is common. Cases with mild atypia and low proliferation index are acceptable as HS, but they should carefully be distinguished from prominent macrophage reactions occurring in lymphomas, infections, hemophagocytosis or developing after successful treatments of malignant neoplasms.<sup>3,6,8</sup>

The diagnosis of HS is based on the positivity of H/M associated markers CD163, CD11c, CD14, CD68 and lysozyme and negativity for antigens recognizing various high-grade neoplasms of haematological and non-haematological origin. Myeloid sarcoma with monocytic differentiation may be undistinguishable from HS, but it might be recognized by the expression of NMP1 mutated protein, that frequently occurs especially in myeloid sarcoma with cutaneous involvement (Figure 2b). S100 protein is positive in half of the cases of HS<sup>3,8</sup> and may indicate a co-occurring LC sarcoma component.<sup>2,6</sup>

BRAF mutations (V600E and other variants) and mutations of RAS/RAF/MEK/ERK and RAS/MAPK pathways have been reported. Activating mutations of the PI3K-AKT-MTOR pathway as well as copy loss of the CDKN2A gene are also frequently encountered. HS may show clonal relationship with an associated lymphoma component; however, clonal immunoglobulin genes rearrangements together with an aberrant somatic hypermutation

signature were recently reported also in pure HS without history of B-cell lymphoma.<sup>9</sup>

Systemic HS is aggressive and most patients die within 5 years of diagnosis. Localized and surgically removable masses have a better outcome.<sup>3,8</sup> There is no systemic standard treatment recommended, but clinical responses to BRAF and MAP2K1 inhibitors have been reported. HS is frequently positive for Programmed death ligand 1 (PD-L1) protein,<sup>6</sup> but efficacy of anti-PD1 checkpoint is unknown.

### Langerhans cell tumours (Langerhans cell histiocytosis and Langerhans cell sarcoma)

Neoplastic proliferations of Langerhans cells (LC) include LC histiocytosis (LCH) and the extremely rare LC sarcoma (LCS). LCH is a clonal disease composed of cells with phenotypical and ultrastructural features of differentiated LC.<sup>4</sup> The demonstration of clonal somatic mutations of MAPK pathway genes confirmed the neoplastic nature of LCH. Remarkably, these mutations have been identified in CD34<sup>+</sup> haematopoietic progenitors, CD14<sup>+</sup> monocytes and circulating CD1c<sup>+</sup> + classical DC2 dendritic cells, the last probably representing the immediate precursors of LCH

## Recent classifications of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

### Histiocyte society<sup>2</sup>

#### L group

LCH, ICH, ECD, mixed LCH/ECD

#### C group (non-LCH of skin and mucosa)

Xanthogranuloma family (includes JXG)

Non-xanthogranuloma family (includes MRH)

#### M group

HS, LCS, IDCS, IC sarcoma

#### R group

RDD (classical and variants)

#### H group

HLH (primary and secondary)

#### WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues<sup>3</sup>

HS

LCH and LCS

IDCT

IDCS

FDCS

DJXG

ECD

#### WHO Classification of Skin tumours<sup>4</sup>

LCH

IDCH/IDCT

RDD

JXG

ECD

MRH

DJXG, Disseminated juvenile xanthogranuloma; ECD, Erdheim Chester disease; FDCS, Follicular dendritic cell sarcoma; HLH: Hemophagocytic lymphohistiocytosis; HS, histiocytic sarcoma; IC, indeterminate cell; ICH, IC histiocytosis; IDCH/IDCT, Indeterminate dendritic cell histiocytosis/tumour; IDCS, Interdigitating dendritic cell sarcoma; JXG, juvenile xanthogranuloma; LCH, Langerhans cell histiocytosis; LCS, Langerhans cell sarcoma; MRH: multicentric reticulohistiocytosis; RDD, Rosai–Dorfman disease.

**Table 1**

cells.<sup>10</sup> Interestingly, the differentiation stage of the precursors in which somatic mutations arises may determine the clinical outcome. High-risk disseminated LCH, multifocal low-risk or single-lesion LCH may derive respectively from mutated haematopoietic stem-cells, from more committed circulating cells or from a differentiated tissue-located precursor.<sup>10</sup>

LCH mainly occurs in children and less frequently in adults and has a broad spectrum of clinical manifestations, ranging from a self-limiting single site lesion to systemic life-threatening disease.<sup>3</sup> LCH can involve almost any organ system, with a particular affinity for bones, skin, lungs and the pituitary gland. High-risk LCH occurring in children consists of multi-organ disease including liver, spleen or bone marrow. LCH can be associated with Hodgkin and non-Hodgkin lymphomas, myeloid leukaemia and non-haematological malignant neoplasms and their clonal relationship has been documented.<sup>6</sup> A mixed-histiocytosis consisting of a combination of Erdheim–Chester diseases and LCH has been reported, with both components sharing the same molecular lesion. Rarely LCH and Rosai–Dorfman disease have been reported in the same patient.<sup>11</sup>

Independently from disease spread, LCH cells display similar cytological features, represented by round-oval cells with grooved or lobulated nuclei, fine chromatin, inconspicuous nucleoli and

delicate nuclear membrane. Positivity for CD1a, CD207 and S100 protein is mandatory for the diagnosis (Figure 2c); Birbeck granules are identified on electron microscopy.<sup>4</sup> Tumour cells are regularly admixed with variable numbers of eosinophils and, especially in long-lasting lesions, macrophages, multinucleated giant cells, xanthomatous and osteoclast-like cells. Remarkably, a fraction of these cells express the LC markers (such as langerin/CD207) and even the BRAF<sup>V600E</sup> protein (unpublished personal observation), suggesting intratumoral divergent differentiation of mutated precursors (Figure 2d).

Mild-to-moderate nuclear pleomorphism and scattered mitoses can be observed in typical LCH; LC sarcoma (LCS) lacks LC traits due to pronounced atypia and pleomorphism, generally shows many mitoses and it is consequently rarely diagnosed on pure morphology. LC markers are more heterogeneous compared to LCH. Rarely LCH and LCS coexist in the same lesion, indicating tumour progression.<sup>6</sup> Combination of severe atypia and clinical aggressiveness is necessary to diagnose LCS.<sup>2</sup>

Small collections of LC indistinguishable from LCH may occur in lymph nodes involved by Hodgkin and non-Hodgkin lymphomas, as well as in tumours from different sites (e.g.: skin, thymus, thyroid, lung). In some of these cases their clonal nature has been proven by demonstration of either MAPK-pathway gene mutations or a molecular relationship with the associated lymphoid neoplasias.<sup>6</sup> In most cases, however, the reactive *versus* neoplastic nature and the biological significance of these LC foci cannot be established.<sup>12</sup> Regardless of this, these LC foci are generally limited to a single site/organ.

A similar condition might be represented by pulmonary LCH, a multifocal disease involving lungs in young adult heavy smokers; LCH nodules can be either clonal or non-clonal<sup>10</sup> and the lesions do not extend beyond the lungs and may even regress upon smoking cessation; long standing disease however progresses into severe interstitial fibrosis and respiratory failure.

Abnormal LC recruitments potentially mimicking LCH occur in the lymph node paracortex in dermatopathic lymphadenitis and in the dermis in various dermatosis and cutaneous lymphomas.<sup>4</sup> These LC reactions can be distinguished from LCH by Cyclin D1 immunostain, that results positive only in LCH. LCH tumour cells proliferation is driven by distinct and mutually exclusive mutations resulting in extracellular signal-regulated kinase (ERK) activation; about 50% of cases are variant frequency in BRAF<sup>V600E</sup> and a fraction of the BRAF wild type cases show mutations of MAP2K1, MAP3K1 or ARAF.<sup>10</sup> A recent study showed that the mutant allele fraction in LCH was not predictable by tumour cell content and had a significant impact on the efficacy of target therapy. Highly sensitive techniques are therefore recommended in the clinical management of these patients.<sup>7</sup>

Clinical course largely depends on the extent of disease at presentation; single-site LCH has ≥99% survival probability, while high mortality occurs in children with "high-risk" multi-system disease.<sup>10</sup> Focal disease can progress to multisystem involvement, mostly in infants. Moreover, treatment failure in low-risk patients is associated with an increased risk of late complications, including neurodegeneration. Recent data indicate that the presence of BRAF<sup>V600E</sup> mutation in CD34+ precursors or in plasma cell-free DNA correlates with high-risk disease, increased resistance to standard first-line treatment and neurodegenerative LCH.<sup>10</sup> Treatment with BRAF and/or MEK

### Markers most commonly used in the diagnosis of tumours derived from histiocytes/macrophages (H/M) and dendritic cells (DC)

Antigen	Main reactivity in normal cells	Diagnostic utility
<b>CD1a</b>	LC Dermal DC (subset) IDC (subset)	Required for diagnosis of LCH/LCS and IDCT Positivity excludes IDCS
<b>CD11c</b>	H/M Most DC (most epidermal LC are negative)	Sensitive marker for most H/M and DC neoplasms Exclude BPDCN diagnosis
<b>CD14</b>	H/M	H/M-derived tumours (less frequent than in monocytic leukaemias)
<b>CD68</b>	H/M PDC	Diffuse granular cytoplasmic reactivity in most H/M-derived tumours; variable in DC neoplasms variable Poor specificity (expressed by many non-haematopoietic tumours, including melanoma)
<b>CD123</b>	PDC Activated macrophages; nodal sinus lining cells high endothelial venule endothelium	High sensitivity and specificity for BPDCN Can be expressed in LCH and in H/M-derived tumours
<b>CD163</b>	H/M	Best markers for H/M-derived tumours (high sensitivity and specificity)
<b>Langerin/CD207</b>	LC IDC (subset)	Defining LCH/LCS. Exclude IDCS
<b>BDCA2/CD303</b>	PDC	High specificity for BPDCN
<b>TCL1</b>		
<b>E2-2</b>		
<b>Lysozyme</b>	H/M	Often expressed in H/M-derived tumours, but poor specificity
<b>S100 protein</b>	LC, IDC, activated H/M	Required for of LCH/LCS, IDCT, IDCS and RDD diagnosis Expressed in variable number of cells in various H/M tumours

BPDCN, blastic PDC neoplasm; DC, Dendritic cells; H/M, histiocytes/macrophages.

IDC, Interdigitating dendritic cells; IDCT, indeterminate dendritic cell tumour; IDCS, interdigitating dendritic cell sarcoma; LC, Langerhans cells; LCH, Langerhans cell histiocytosis; LCS, Langerhans cell sarcoma; PDC, plasmacytoid dendritic cells; RDD, Rosai–Dorfman disease.

**Table 2**

inhibitors has shown variable degree of clinical response, although its ability to definitely cure LCH is still not known.<sup>10</sup>

#### Indeterminate dendritic cell histiocytosis/tumour

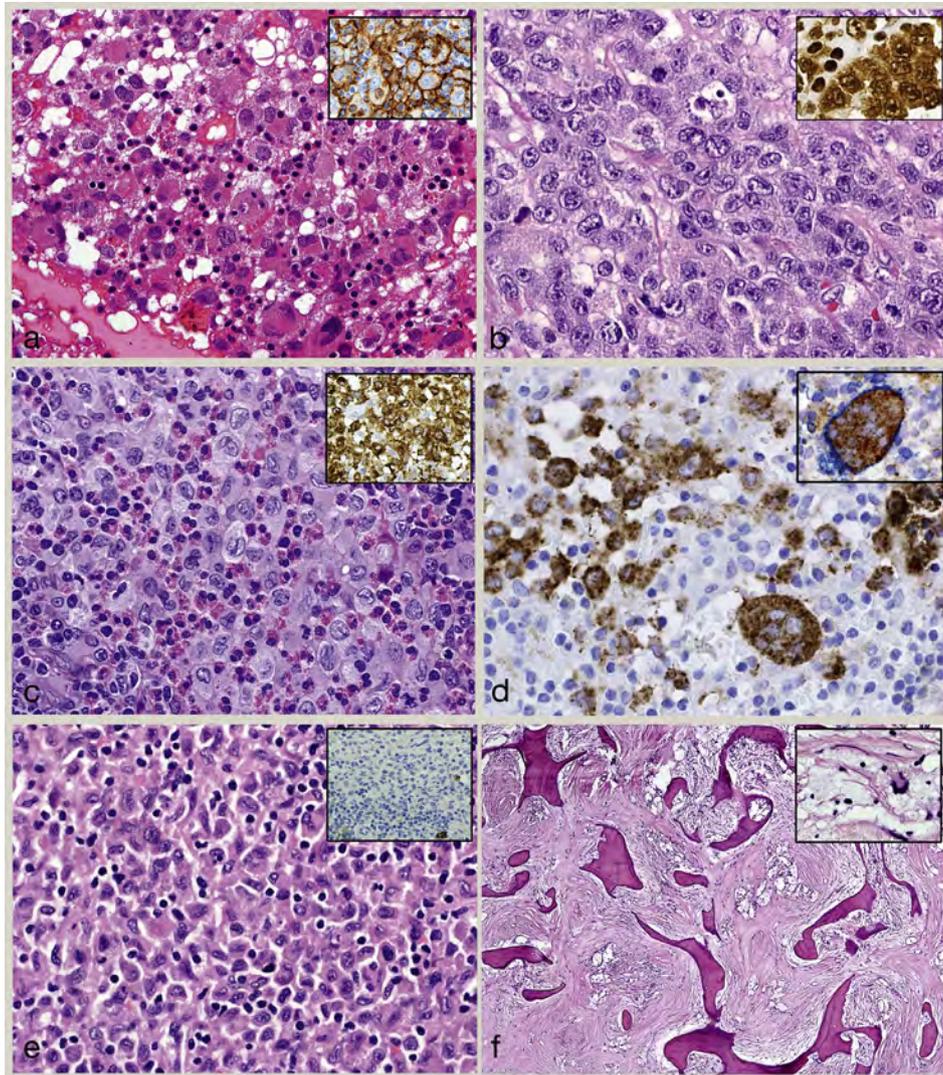
Indeterminate dendritic cell histiocytosis/Indeterminate dendritic cell tumour (IDCH/IDCT) is a rare histiocytosis whose relationship with LCH has never been elucidated, despite the expression of CD1a and S100 antigens has suggested that it may derive from precursors of LC. Unlike LCH the disease most commonly occurs in adults as single or multiple skin lesions, while only rarely it involves extra-cutaneous sites, especially lymph nodes and spleen. Similar to LCH the association with non-Hodgkin lymphomas and myeloid leukaemias also occurs in IDCH/IDCT.<sup>4,6</sup>

Skin lesions are predominantly dermal, tumour cells may resemble LCH cells or show more heterogeneous cytological features, even with a predominant spindle cell component.<sup>3,4</sup> Eosinophilic infiltrate can be extremely variable. By definition,

tumour cells do not show Birbeck granules on electron microscopy and lack langerin/CD207 expression, while macrophage markers (CD68, CD163, lysozyme) can be diffusely positive (Figure 2e). *BRAF* and other MAPK-related mutations are substantially absent in IDCT,<sup>4</sup> while *ETV3-NCOA2* gene fusion has been detected in 4 cases.<sup>13</sup> Most cases have an indolent clinical evolution, even with spontaneous regression.<sup>4</sup>

#### Erdheim–Chester disease

Erdheim–Chester disease (ECD) is a clonal systemic proliferation of macrophages commonly having a foamy (xanthomatous) component.<sup>3,4</sup> ECD is rare but its recognition has increased over the past decade.<sup>14</sup> ECD occurs mostly in adult males aged 40–60, but pediatric cases have been reported. Virtually any organ or tissue can be involved and the majority of patients have multi-organ disease at presentation.<sup>15</sup> ECD more often involves long bones (95% of cases), the cardiovascular system (aorta,



**Figure 2** (a) A case of Histiocytic sarcoma showing large cells with abundant eosinophilic cytoplasm; erythrophagocytosis is also evident in rare cells. Tumour cells show strong membrane expression of CD11c (inset). (b) A case of myeloid sarcoma showing morphological features indistinguishable from HS; in the inset, immunostain for NMP1 reveals NMP1 protein expression in both the nucleus and the cytoplasm of tumour cells, indicating that the *NPM1* mutation; this finding excludes a diagnosis of HS. Nuclear reactivity in small lymphocytes represent normal internal controls. (c) Langerhans cell histiocytosis composed of small-medium sized LC with irregularly shaped nucleus and moderate eosinophilic cytoplasm; numerous eosinophils and lymphocytes are admixed with tumour cells. The inset shows strong reactivity for CD207 in LCH cells. (d) Immunostain for VE1 (recognizing BRAF<sup>V600E</sup>) shows strong expression in LCH cells and in a multinucleated giant cell; lymphocytes are negative. The inset shows VE1 reactivity in a multinucleated cells that stains also positive for LAT (linker for activation of T cells), a marker for osteoclasts involved in RANKL-induced osteoclastogenesis. This finding indicates that LCH tumour cells or precursors may differentiate into specialized cells of the mononuclear-phagocyte system (double immunostain for anti\_VE1 (brown) and LAT (blue)). (e) Indeterminate cell histiocytosis showing morphologic and phenotypic features similar to those of LCH, except for the negativity for CD207 (inset). (f) Erdheim–Chester disease involving the bone. The medullary spaces are occupied by dense fibrosis and nests of foamy histiocytes, the latter showing also features of Touton-like cells (inset).

pericardium, right atrio-ventricular groove (50%) and in 20–30% of cases the retro-peritoneum (especially the perirenal space), the CNS and the periorbital tissues.<sup>14,15</sup>

A pathognomonic feature of ECD is osteosclerosis of long bones associated with pain affecting the distal lower limbs. However, ECD diagnosis is often delayed for years, mostly due to minimal or elusive clinical symptoms, the interpretation of which requires high diagnostic skill and careful correlation with the radiological and histological features<sup>14,15</sup>. Consensus diagnostic criteria for ECD include<sup>14</sup> (1) xanthogranulomatous lesions

containing CD68+/CD1a-histiocytes, (2) symmetric skeletal uptake of the long bones of the legs on Tc bone scintigraphy, F-FDG-PET or MR imaging and (3) involvement of at least one other organ typically affected by the diseases (e.g. xanthelasma, perinephric infiltration, “coated aorta,” pericardial infiltration).

ECD and LCH share a common mutational landscape resulting in ERK activation in almost all the cases; for both LCH and ECD the “inflammatory myeloid neoplasm” pathogenetic hypothesis has been proposed,<sup>16</sup> although precursors and cytokine differentiation drivers are partially distinct, resulting in two

significantly different diseases.<sup>17</sup> Patients with combined ECD and LCH (mixed-histiocytosis) have been reported. ECD is diagnosed after or simultaneously with LCH, but never first. BRAF(V600E) mutation was frequently found in both tumour cell components, likely indicating common precursors with divergent differentiation. In about 10% of patients with ECD and especially those with associated LCH, a myeloid neoplasm can occur, before, simultaneously or after the diagnosis of ECD.<sup>18</sup>

On histology classical ECD lesions resemble juvenile xanthogranuloma, with admixture of foamy histiocytes, multinucleated giant cells, Touton-like cells and a variable number of non-foamy histiocytes, lymphocytes, plasma cells, neutrophils and eosinophils. Fibrosis can be extensive and may largely replace the tumour cell infiltrate (Figure 2f). In addition to CD68, tumour cells express CD11c, CD163, CD14 and are negative for CD1a and langerin/CD207. S100 protein has been detected in 10%–30% of cases.<sup>5,15</sup> In exceptional cases large S100+ macrophages show emperipolesis and lesions resemble Rosai–Dorfman disease. IgG4 + plasma cells can be numerous, but never above the cut-off values for IgG4-related diseases.<sup>5</sup>

A recent study illustrated the wide morphological spectrum of ECD lesions, highlighting the risk of relying on pure histology alone for the diagnosis.<sup>5</sup> Accordingly, efforts should be made to obtain a set of tissue biopsies to warrant availability of representative lesions; appropriate and sufficient material should be considered for molecular testing.<sup>5,14</sup> For example, this is helpful in the differential diagnosis between poorly symptomatic ECD lacking typical bone involvement and disseminated variants of juvenile xanthogranuloma or RDD.<sup>2,5</sup>

Almost 95% of cases of ECD show one mutation of the MAPK pathway, with BRAF<sup>V600E</sup> found in 65% of cases, followed by MAP2K1, ARAF, MAP2K2, NRAS and KRAS. Mutations of PIK3CA have also been reported in ECD, independently from BRAF status.<sup>10</sup> ECD showing ALK translocations more likely represent cases of ALK + histiocytosis (see below).

ECD is a chronic disease the clinical course of which depends on the extent and distribution of the lesions. Cases of spontaneous regression have not been reported and disease progression is inevitable in untreated patients.<sup>15</sup> Systemic disease may follow an aggressive and rapid clinical course, but even uncontrolled slowly growing cases may result in deleterious effects on kidney and the urinary tract, the cardio-vascular system, lungs and cerebellum. CNS involvement is a major negative prognostic factor in ECD; similar to LCH, CNS lesions consist both of tumour-forming and neurodegenerative processes.<sup>14</sup> The prognosis of ECD, originally reported as very poor (mean survival of 19.2 months), improved upon the introduction of interferon-alfa treatment, with 68% 5-year overall survival rate. Targeted therapies with inhibitors of BRAF and MEK have been used with good results<sup>14,19,20</sup> in almost all patients in terms of metabolic response based on PET uptake, but recurrence is very frequent (75%) after therapy interruption.<sup>10</sup>

### Rosai–Dorfman disease (RDD)

Rosai–Dorfman disease (RDD), also known as Destombes disease or sinus histiocytosis with massive lymphadenopathy is a rare histiocytic disorder characterized by tissue infiltration by macrophages expressing S100 protein and showing emperipolesis, a

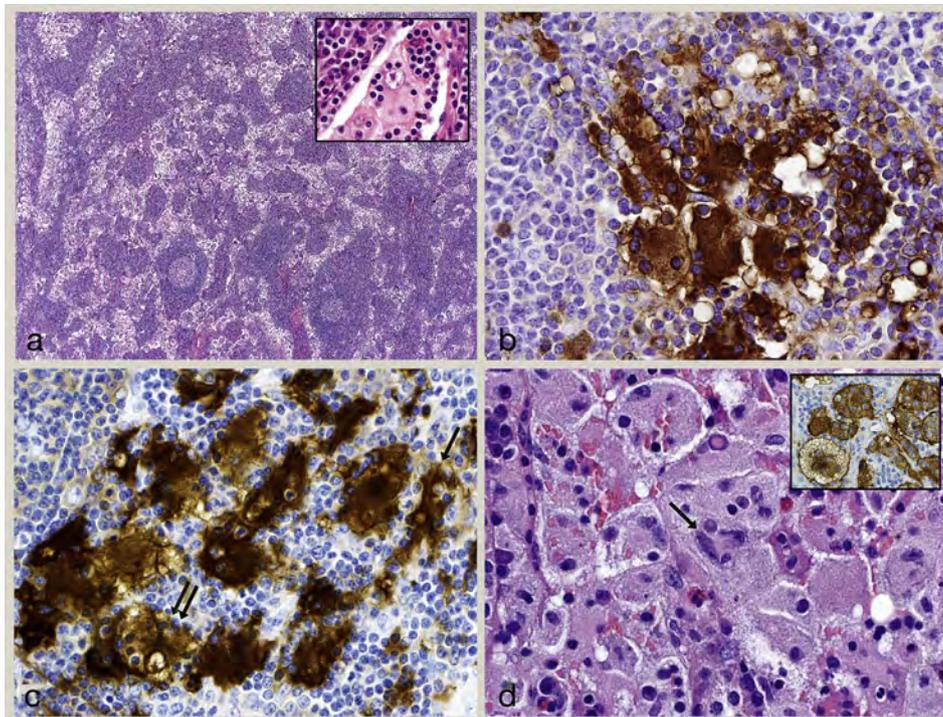
phenomenon consisting of cytoplasmic engulfment of living cells. In the updated Histiocyte Society classification of histiocytoses, RDD includes different subtypes, classical RDD, extranodal RDD, immune-disease-associated RDD, neoplasia-associated RDD and familial RDD.<sup>2</sup>

The non-neoplastic nature of classical RDD was inferred by data obtained with the HUMARA clonality assay. More recently, however, molecular analysis identified clonal activating kinase mutations involving KRAS, NRAS, MAPK1 and ARAF in a significant number of cases, suggesting that RDD represents a neoplastic process at least in some instances.<sup>11,21</sup> In contrast to LCH and ECD, BRAF mutations have been detected only very rarely in RDD.<sup>22</sup>

Classical RDD usually presents in young individuals as massive bilateral cervical lymphadenopathy, but other superficial or deep nodal sites can be involved.<sup>11,23</sup> In about 43% of cases at least one extranodal lesion also occurs, while 23% of cases are characterized by exclusive extranodal disease; 19% of patients show a systemic involvement. RDD may affect a wide range of extranodal sites, more often the nasal cavity and paranasal sinuses (11%), ophthalmic tissues (11%), skin (10%) and bones (5–10%). Central nervous system lesions occur in less than 5% of cases. Patients often present with fever, hyper-gammaglobulinemia, elevated erythrocyte sedimentation and haematological abnormalities, especially normochromic-normocytic anemia and neutrophilia; bone marrow infiltration is rare.<sup>11</sup> In 10% of the cases RDD coexists with an autoimmune disease, such as systemic lupus erythematosus, idiopathic juvenile arthritis and autoimmune hemolytic anemia. IgG4 + plasma cells can be elevated, even reaching the cut-off values of IgG4-related diseases; however, the significance of this finding remains unclear. Nevertheless, evaluation of the IgG4/IgG ratio in all patients with RDD is recommended.<sup>2</sup> RDD has been reported in patients with myelodysplasia, after bone marrow transplantation for acute leukaemia or rarely associated with LCH or ECD.<sup>24</sup>

Histopathological features of lymph nodes involved by classical RDD comprise a thick fibrotic capsule, dilated sinuses filled by large macrophages and prominent plasma cell infiltrate in the remaining parenchyma. The intra-sinusoidal macrophages show single or multiple round nuclei with fine chromatin and often prominent nucleoli. The abundant cytoplasm is pale, finely granular and eosinophilic; it contains variable numbers of undamaged lymphocytes, neutrophils and plasma cells (Figure 3a). RDD macrophages are typically positive for S100 (Figure 3b), in addition to CD11c, CD14, CD68 and CD163. CD1a and CD207 are negative, as well as HLADR.<sup>6</sup> Plasma cells are polyclonal with a variable fraction of IgG4 + cells. Extranodal RDD shows a more heterogeneous morphology and the diagnosis may not be as straightforward as in lymph nodes; typical macrophages often occur in small foci or as scattered cells, partially obscured by a dense polymorphic inflammatory infiltrate and fibrosis; moreover, they may show a partially foamy cytoplasm and emperipolesis can be negligible. In these cases, S100 immunostain is very helpful to identify residual RDD cells and emperipolesis. However, since the distinction of extranodal RDD from ECD remains potentially difficult, a clinical correlation is recommended.<sup>11</sup>

The inherited conditions predisposing to RDD include a spectrum of diseases sharing mutations of the SLC29A3 gene and include familial histiocytosis syndrome (Faisalabad



**Figure 3** (a) Classical Rosai–Dorfman disease involving a lymph node: dilated sinuses filled by macrophages with abundant pale cytoplasm. The inset shows emperipolesis. (b) Classical Rosai–Dorfman disease: strong positivity for S100 protein in the large macrophages. Note the numerous intracytoplasmic lymphocytes (emperipolesis). (c) A focus of RDD-like cells in a case of lymphocyte predominant Hodgkin’s lymphoma. The immunostain for S100 protein shows the variable morphology of the positive cells, ranging from irregularly shaped cells likely represented by interdigitating dendritic cells (single arrow) and round large macrophage-like cells with evident emperipolesis (double arrow). (d) ALK + histiocytosis resembling RDD with emperipolesis. A distinct feature of ALK + histiocytosis is the irregularity of the nuclear contour (arrow), while classical RDD cells nuclei are typically round. The inset shows positivity for ALK protein, with cell membrane and cytoplasmic expression. Note an ALK + multinucleated cells with Touton-like features.

histiocytosis), familial Rosai–Dorfman disease, H syndrome and pigmented hypertrichosis with insulin-dependent diabetes mellitus (PHID). These disorders have overlapping signs and symptoms, but all are characterized by tissue accumulation of histiocytes, with morphological and phenotypical features of RDD especially in lymph nodes or skin lesions.<sup>25</sup>

Focal RDD-like lesions may occur in lymph nodes involved by Hodgkin and non-Hodgkin lymphomas<sup>11,26</sup> and in a significant number (41%) of lymph nodes from patients with autoimmune lymphoproliferative syndrome (ALPS) type I, caused by mutations in the FAS gene *TNFRSF*.<sup>27</sup> These lesions are an incidental finding never associated with bulky RDD adenopathy or extranodal disease. According to the consensus diagnostic recommendations for RDD,<sup>11</sup> these foci should involve less than 10% of the whole node, although in a recently published series not all cases met this criterion. Notably, these RDD-like cells are often distributed at the periphery of tumour nodules<sup>26</sup> or, as in ALPS cases, at the periphery of reactive follicles and in the expanded paracortex. In contrast to classical RDD, sinuses are not involved. Moreover, the S100 macrophages lack CD163 expression.<sup>26</sup> The pathogenesis of these lesions is unknown. It has been suggested that they may result from abnormal monocyte recruitment and activation by cytokines occurring in lymphomas, or by the dysregulated immune environment taking place in ALPS. On the authors’ personal experience, these RDD-like foci may contain S100+ cells with a morphological spectrum ranging from

dendritic cells to large round S100+ macrophages with emperipolesis, suggesting a derivation from activated interdigitating dendritic cells (Figure 3c).

As discussed in the following paragraph, macrophages occurring in ALK + histiocytosis can display strong expression of S100 and emperipolesis; this advises to include stain for ALK in cases showing RDD features, especially occurring in very young individuals with multifocal disease.

RDD has usually a favorable outcome, either with spontaneous remission or chronic but stable disease. In other cases, remissions and reactivations may last for years. Death related to the diseases or to complications, mostly represented by autoimmunity, infections or amyloidosis, occurs in about 7% of patients.<sup>23</sup> Multifocal and extranodal disease, particularly with involvement of kidneys, liver or lower respiratory tract is characterized by poor clinical outcome. The identification of clonal mutations does not seem to influence the clinical behaviour,<sup>21</sup> but might offer a therapeutic opportunity in patients with aggressive RDD refractory to other standard treatments<sup>11</sup>

### ALK-positive histiocytosis

ALK + histiocytosis is a rare type of systemic histiocytic disorder, showing distinctive clinical, morphological and molecular features. Only 12 cases have been reported until now<sup>28,29</sup>; in addition, two cases occurring in adults and diagnosed as ECD probably correspond to ALK + histiocytosis, since both of them

exhibited the *KIF5B-ALK* translocation, typically found in ALK + histiocytosis.<sup>30</sup> A third case harboring the same translocation defined as “non-Langerhans cell histiocytosis”<sup>28</sup> has been reported in a 40 years-old male with systemic disease.

The typical clinical picture consists of a very young infant showing hepato-splenomegaly and transfusion-dependent severe cytopenia lasting over months. Despite the severe clinical presentation and systemic involvement by the histiocytic proliferation, often localized to the liver, spleen, bone marrow and kidney, patients gradually recover, likely due to the support of steroids and chemotherapy. Only one patient rapidly succumbed of a systemic disease involving the CNS. More rarely ALK + histiocytosis occurs in adults, mostly as localized lesions. No recurrences have been reported after surgical removal of localized tumours and one involving the cavernous sinus completely regressed after treatment with crizotinib.<sup>28</sup>

On histology the lesions are composed of large macrophages, typically showing irregularly folded, clefted or lobulated nuclei, with fine chromatin and small nucleoli; occasional cells are multinucleated. The cytoplasm is abundant and eosinophilic, sometimes with small vacuoles. Foamy cells and Touton-like cells can also be found. Occasionally the macrophages engulf in their cytoplasm cell debris and hemosiderin, or undamaged cells featuring emperipolesis (Figure 3d). Lesional macrophages are positive for CD68 and CD163; the ALK protein is expressed with a cytoplasmic or cell membrane/cytoplasmic patterns (Figure 3d). S100 protein has been detected in about 50% of cases, with variable percentage of positive cells; diffuse S100 expression and emperipolesis may coexist, thus resembling RDD.<sup>6,28</sup> CD1a, CD207 and BRAF<sup>V600E</sup> are regularly negative.

FISH using the break-apart probes to the *ALK* gene show split signals in the vast majority of cases.<sup>28,29</sup> In the study by Chang et al.<sup>28</sup> the *ALK* partner gene was investigated in 7 cases and in 5 of them (71.5%) it was represented by *KIF5B*, while *TPM3-ALK* and *COLIA2-ALK* fusions were detected in one case each. Notably, the *KIF5B/ALK* fusion is extremely rare in human tumours and its prevalence in ALK + histiocytosis indicates that it represents a distinct tumour entity.

### Interdigitating dendritic cell sarcoma

Interdigitating dendritic cell sarcoma (IDCS) is a rare disease composed of atypical cells expressing S100 protein. This phenotype characterizes the majority of normal interdigitating dendritic cells (IDC) occurring in nodal paracortex, but others also express CD1a and/or CD207 and likely represent recently immigrated Langerhans cells.

IDCS usually occurs in adults, predominantly as a solitary asymptomatic lymphadenopathy; less frequently skin, head and neck and soft tissues are involved; rarely do patients have generalized lymphadenopathy, splenomegaly or hepatomegaly. Association with lymphomas, especially low-grade B-cell lymphoma and rarely with acute myeloid leukaemia has been reported.<sup>3</sup>

The neoplastic proliferation in lymph nodes has a paracortical distribution and forms fascicles composed of spindle cells, or sheets of oval or round large cells. Nuclear shape and degree of atypia are variable, mitoses are generally not numerous; the cytoplasm is abundant and slightly eosinophilic. Small lymphocytes are intermingled with the tumour cells. By definition, the

neoplastic cells consistently express S100 protein and are negative for CD1a and CD207. Weak expression of CD68, lysozyme and CD45 can be also found.<sup>3,6</sup>

IDCS diagnosis requires a high degree of morphological suspicious and the use of a wide panel of markers. In several cases reported in the literature the initial pathological diagnosis was incorrect. At any site, melanoma has to be first and foremost considered in the differential diagnosis. Notably, SOX10 has been reported in eleven cases of IDCS from three distinct series.<sup>31</sup> Furthermore, one of these cases showed two somatic mutations (*TP534* and *ARID26*) also reported in malignant melanoma. The significance of these findings remains unknown, but caution is recommended to provide a definite diagnosis of IDCS if strong S100 and SOX10 expression is found.<sup>6</sup> IDCS morphologically can be indistinguishable from follicular dendritic cell sarcoma (FDSC), but the immunophenotype of the two diseases is completely different. Moreover, IDCS does not show desmosomes on electron microscopy, typically found in FDSC.<sup>3,32</sup>

IDCS carry no specific molecular alterations. The clinical course of IDCS is generally aggressive, with tumour-related death within 5 years diagnosis in about 50% of cases. Stage is an important prognostic factor, while histological features have not been correlated with the clinical outcome.<sup>3</sup>

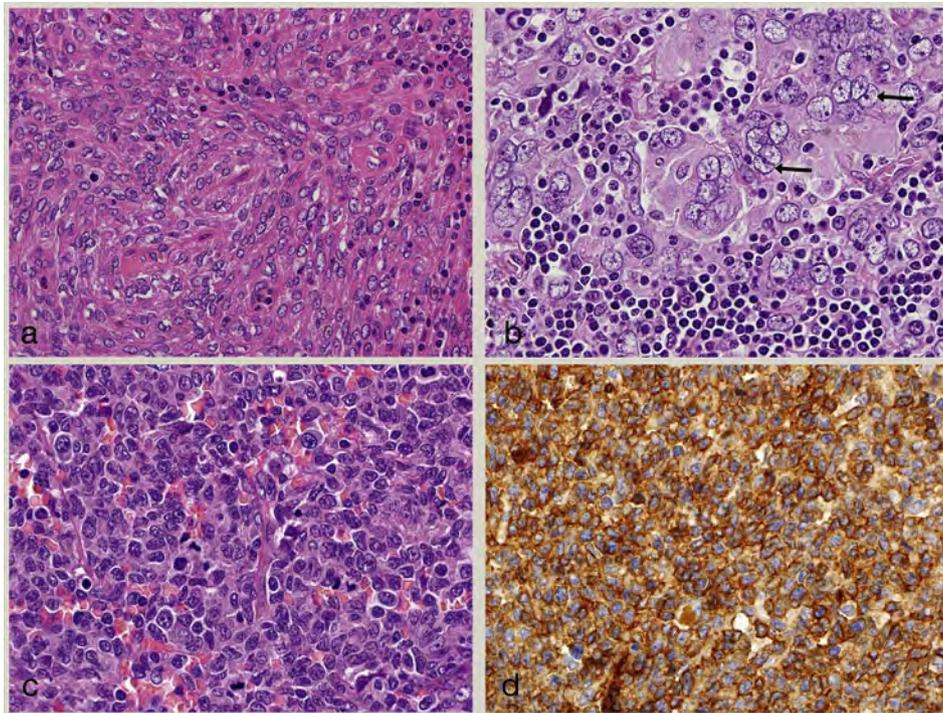
### Follicular dendritic cell sarcoma

Follicular dendritic cells (FDC) represent non-haematopoietic mesenchymal-derived dendritic cells playing a pivotal role in the immune germinal centre B-cell reaction<sup>32</sup>; the neoplasm derived from FDC is included in the list of H/M and DC tumours in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.<sup>3</sup>

Follicular dendritic cell sarcoma (FDSC) is rare, generally occurs in adulthood and sex distribution is similar; extranodal involvement is more common (60% of cases), especially in the head and neck and the abdomen. Lymph nodes are affected in about 40% of cases. The EBV-associated inflammatory pseudotumour-like (IPT) variant of FDSC typically occurs in the abdomen (spleen, liver and gastrointestinal tract) and is more common in young-middle aged women.<sup>32</sup>

In about 10% of cases FDSC develops in the context of hyaline-vascular subtype of Castleman disease, where atypical FDC occur in the follicles, but can be observed also in the interfollicular area, where they can progressively increase in number up to reach full-blown FDSC features. Occurrence of FDSC in patients with lymphoma has been reported, but much less frequently than in other DC-derived neoplasms. Unique albeit rare associations are represented by paraneoplastic pemphigus, myasthenia gravis and autoimmune multiorgan syndrome; autoimmunity may not regress after surgical intervention and contribute to higher morbidity and mortality.<sup>32</sup>

FDSC is characterized by a wide spectrum of cytological appearances and patterns of growth. Tumour cells can be spindle, ovoid or frankly epithelioid, the cytoplasm is faintly eosinophilic and poorly demarcated. Cells are arranged in fascicles, storiform arrays, or diffuse sheets. Tumour nuclei show dispersed chromatin, delicate nuclear membrane and small but distinctive eosinophilic nucleoli; nuclear moulding is frequently found in FDSC (Figure 4a, b). Atypia is generally mild, but pronounced



**Figure 4** (a) and (b) Examples of the morphological spectrum occurring in Follicular dendritic cell sarcoma; in (a) spindle-oval cells arranged in short fascicles, in (b) epithelioid cells, including multinucleated cells associated with numerous lymphocytes. Nuclear moulding is evident in some cells (arrows). (c) and (d) Blastic plasmacytoid dendritic cells: “blastic” cytologic features with mitoses (c) and a strong CD123 reactivity (d) are typically found in this aggressive neoplasm.

nuclear pleomorphism, large nucleoli, high mitotic rate and necrosis can occur and can predict worse prognosis. Variable numbers of small lymphocytes are regularly found in FDCS; in the inflammatory-pseudotumour variant they are extremely abundant and often associated with plasma cells.

Given its wide morphological spectrum, FDCS can mimic many different neoplasms of mesenchymal and epithelial origin; FDCS with pure intrafollicular growth resemble large B-cell lymphomas, while inflammatory-pseudotumour-like FDCS is barely identified as a neoplasm. Several immunohistochemical markers are available to diagnose FDCS; due to phenotypic variability and frequent antigen losses, a combination of them is recommended. The complement receptors CD21, CD23, CD35 and the CXCR5 ligand CXCL13 are the most specific, whereas clusterin and podoplanin show high sensitivity. Follicular dendritic cell secreting protein has been recently reported to represent an additional specific marker of FDCS.<sup>33</sup> FDCS may aberrantly express EMA, S100 protein, CD20, CD31, CD68 or cytokeratins. A distinctive feature of the inflammatory pseudotumour variant is the positivity of tumour cells for EBV; the infection is likely responsible for a phenotype switch occurring in some cases, resulting in the loss of FDC markers and positivity for smooth muscle actin. This tumour has been defined Fibroblastic dendritic cells sarcoma.<sup>3</sup>

The small lymphocytes interspersed between tumour cells are mainly of T-cell nature; non-clonal TdT-positive cells can be observed in some cases and correlate with higher incidence of paraneoplastic manifestations.

FDCS behaviour is variable; when it occurs as localized and surgically removable disease the prognosis is excellent;

unresectable tumours display multiple recurrences and may disseminate, with fatal evolution reported in one fifth of cases. Tumour diameter larger than 6 cm, young age (less than 40 years), high histological grade and abdominal location are associated with dismal prognosis<sup>32</sup>; however, the intraabdominal EBV + inflammatory pseudotumour-like variant is typically indolent, even when multiple local recurrences occur.<sup>3</sup>

The molecular landscape of FDCS is largely unknown. Tumour cells strongly express EGFR, but gene amplification has not been detected. Recurrent loss of functions of tumour suppressor genes involved in negative NFκB regulation (*NFKBIA*, *CYLD*) and cell cycle progression (*CDNK2A*, *RB*) have been found. In addition, FDCS shows copy number gains of chromosome 9p24 mapping *PD-L1* and *PD-L2*, as well as upregulation of *PD-L1* and *PD-L2* mRNA and PD-L1 protein.<sup>34</sup> The *BRAF*<sup>V600E</sup> mutation has not been detected in FDCS.

### Blastic plasmacytoid dendritic cell neoplasm

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) represents a rare and very aggressive haematological neoplasm derived from clonal proliferation of plasmacytoid dendritic cell (PDC) precursors; its histogenesis has been uncertain for a long time, as indicated by the great variability in terminology.<sup>35</sup> In the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues BPDCN is not included among the neoplasms derived from histiocytes and dendritic cell, but is a distinct entity of precursor myeloid neoplasms, coherent with its biological and clinical features, closely related to acute myeloid leukaemia.<sup>35,36</sup>

BPDCN is more frequent in males (male/female: 3/1) and mainly occurs in elderly individuals (median age: 67 years),

although young patients including children are also affected. The clinical presentation in most of the cases (>90%) is dominated by cutaneous lesions, which can be very heterogeneous in number, size, color and distribution; at onset skin is the only involved site in 50% of cases, or it can be associated with lymphadenopathy (40%), spleen (25%) or liver (16%) enlargement. Cytopenia and thrombocytopenia often occur at diagnosis, but peripheral blood and bone marrow involvement by BPDCN may be negligible and demonstrable only by flow cytometry or immunohistochemistry. However, they invariably increase with progression. In some cases, leukaemia and massive bone marrow infiltration occur since the beginning and in about 7% of the cases the disease is overtly leukaemic without skin lesions.<sup>35</sup> In 10–20% of the cases BPDCN occurs with or is followed by another myeloid neoplasms, more often represented by chronic myelomonocytic leukaemia.<sup>35</sup> A clonal relationship between the two diseases has been proven. BPDCN predominantly shows immature blastic cytological features, mostly resembling acute myeloid or monocytic leukaemia, or lymphoblastic leukaemia. Nuclei are irregular in shape with fine chromatin and small nucleoli. The cytoplasm is scant. Mitoses are regularly found and Ki67 is expressed in more than 30% of cells as mean percentage. Rarely tumour cells resemble immunoblasts, or large centrocytes or even marginal-zone B cells (Figure 4c).

Diagnosis requires a combination of positive and negative antigen expression, the former including at least three or more among CD4, CD56, CD123, TCL1, BDCA2/CD303 and MX1 (Figure 4d).<sup>35</sup> Remarkably, CD4, CD56 and CD123 co-expression can occur also in acute myeloid leukaemia especially with monocytic differentiation. BDCA2/CD303 and E2-2 expression virtually excludes leukaemias other than BPDCN, but their sensitivity is lower compared to other markers. Markers identifying myeloblasts (CD13, myeloperoxidase, myeloid cell nuclear differentiation antigen/MNDA), monoblasts (CD11c, CD14, lysozyme) and B and T lymphoblasts (CD19, PAX5, CD3, LAT) virtually exclude BPDCN.<sup>35</sup> Table 3 reports the immunohistochemical setting of antigen expression in BPDCN compared with normal PDC.

A clonal proliferation of mature PDC rarely occurs in patients with chronic myelomonocytic leukaemia (CMML) and has been termed mature PDC proliferation (MPDCP). It consists of large mostly nodular aggregates of mature PDC, involving especially lymph nodes, skin and bone marrow. The CMML and PDC share identical molecular anomalies, indicating a clonal relationship. This process is distinguishable from BPDCN since PDC are almost fully mature, with a very low proliferation index and express antigens as normal PDC, with some minor exceptions.<sup>35</sup>

BPDCN tumour cells frequently have an abnormal karyotype and recurrent somatic mutations, but none of them is distinctive and many also occur in other myeloid and lymphoid neoplasia.<sup>4</sup> The most common genetic anomalies involve chromosome 9 (loss of 9p21.3, affecting the *CDKN2A* gene), 12p (12p13, associated with *ETV6* mono- or bi-allelic deletions), 6q (6q23-qter) and 13q (13q13-21).<sup>37</sup> Recently, *8q24/MYC* rearrangements have been detected in different BPDCN series with variable percentages; they are associated with strong expression of *MYC* protein, immunoblastic tumour cell morphology and also the t(6;8) (p21; q24) translocation involving the *SUP3H3* gene. Patients with *MYC* anomaly are older, display more localized skin lesions, are enriched of CD56-negative cases and have shorter survival.<sup>38</sup>

Mutations occurring in BPDCN mostly affect genes involved in DNA methylation and chromatin remodeling. *TET2* are the most frequent (19%–80%), followed by *ASXL1* (29%–44%), *NRAS* (27%) and *ATM* (21%). *TET2* mutations and *ETV6* deletions represent an early oncogenic event that may play a role in tumour pathogenesis. Interestingly, an overall different mutation landscape has been found in children and adult BPDCN; moreover, *MYB* gene translocations regularly occur in childhood tumours, but only in about 50% of adult cases, suggesting biological differences of BPDCN according to patient's age, which might also explain differences in survival.<sup>39</sup>

BPDCN is an aggressive neoplasm, with rapid progression and poor survival (median survival: 10.0–19.8 months).<sup>4</sup> Age is an independent prognostic factor and children have a more favorable outcome compared to adults, regardless of clinical presentation.<sup>40</sup> For patients achieving first complete remission, allogeneic haematopoietic stem cell transplantation has been shown to improve survival even at long-term. Nevertheless, due to the overall poor results, continuous search for alternative therapies is ongoing, addressing molecules or gene pathways abnormally expressed or activated in BPDCN. Treatments with the immunotoxin combining human recombinant anti-IL-3R alpha (CD123) and diphtheria toxin obtained good clinical responses, with high percentage of patients bridged to stem cell transplantation.<sup>41</sup> Additional anti-CD123 molecules are under phase I and phase II trials (trials number: NCT02730312, NCT03386513, NCT03203369, NCT02159495). Gene expression analysis showed over-expression of the *BCL2* gene in BPDCN.<sup>42,43</sup> Accordingly, *BCL2* protein is strongly positive in almost all BPDCN cases.<sup>6</sup> This represents a remarkable finding and partial responses have been obtained in the first two patients treated with the *BCL2* selective inhibitor Venetoclax, but more significant results have been achieved in previously treated and

### Antigen expression in BPDCN and comparison with normal PDC

#### Antigens expressed in normal PDC and in BPDCN

CD4, CD123, TCL1, BDCA2, E2-2, CD2AP, BCL11a, SpiB

#### Antigens expressed in normal PDC and negative or atypically positive \* in BPDCN (dot instead of diffuse cytoplasm)

CD68\*, CLA\*, Granzyme B

#### Antigens negative in normal PDC and expressed in BPDCN

Consistent expression: CD56, BCL2

Frequent expression: CD7, CD33

Occasional expression: CD2, CD5, CD7, CD10, CD13, CD79a, CD117, MUM1/IRF4, BCL6, S100, TdT

Table 3

chemorefractory patients using Venetoclax together with other drugs.<sup>44</sup>

A rationale for novel treatments have been provided by data obtained using BPDCN tumour samples, cell lines and mouse xenografts. Sapienza et al. demonstrated that NF- $\kappa$ B pathway is activated in BPDCN and bortezomib efficiently inhibits BPDCN cells lines growth<sup>42</sup>; effectiveness of bortezomib has been confirmed by another study, showing that its activity is enhanced by the association with other molecules (e.g.: idarubicin, dexamethasone, vorinostat, statins or 5-azacytidine).<sup>45</sup> The combination of the hypomethylating agents decitabine and azacytidine efficiently reduce tumour growth in BPDCN mouse xenografts, in keeping with the observation that most BPDCN harbor mutations undermining the integrity of the methylation program.<sup>42</sup> Finally, the study by Ceribelli et al. showed that TCF4 (E2-2) represents the master regulator not only of normal PDC differentiation but also of the BPDCN oncogenic program.<sup>43</sup> TCF4 transcriptional network in BPDCN cell lines was efficiently down-regulated by BET inhibitors (BETi), which also delayed the growth of BPDCN xenografts, suggesting that BETi might represent a therapeutic strategy capable to simultaneously silence multiple BPDCN driver-genes. ◆

### Practice points

- Tumours derived from histiocytes/macrophages (H/M) and from dendritic cells (DC) are rare and diagnosis requires appropriate immunohistochemical markers and in some instances molecular tests.
- Histiocytic sarcoma should be considered in all tumours showing large atypical cells with abundant eosinophilic cytoplasm lacking markers of more common high-grade lymphoid and non-lymphoid neoplasms.
- Myeloid sarcoma and histiocytic sarcoma may show identical morphological and phenotypical features
- Diagnosis of Langerhans cell histiocytosis is substantially based on the expression of CD1a, Langerin/CD207 and S100 by tumour cells. Identification of *BRAF*<sup>V600E</sup> mutation is useful to support diagnosis in doubtful cases, but is especially recommended for treatment decision
- Indeterminate dendritic cell histiocytosis/tumour differs from Langerhans cell histiocytosis by lack of Langerin/CD207 expression
- Erdheim–Chester disease diagnosis is based on the combination of clinical, radiological and pathological features. The latter, however, can be nonspecific and mutations analysis of most commonly mutated genes (*BRAF*, *MAP2K1*, *ARAF*, *MAP2K2*, *NRAS*, *KRAS*) can be useful to support the diagnosis
- Rosai–Dorfman disease represents a heterogeneous group of disorders all characterized by tissue infiltration by S100+ large macrophages showing emperipolesis. Some cases represent a reactive process, others show clonal somatic mutations and are likely of neoplastic nature.
- Histiocytoses occurring in very young individuals and characterized by foamy histiocytes or features of Rosai–Dorfman disease should prompt to perform ALK immunohistochemistry to exclude ALK + histiocytosis.

- Follicular dendritic cell (FDC) sarcoma histopathology is extremely variable and can mimic many other tumours. Diagnosis requires expression of FDC markers (e.g.: CD21, CD23, CD35, CXCL13, clusterin) and more than one must be applied due to frequent antigen loss.
- Blastic plasmacytoid dendritic cell neoplasm is a rare haematological neoplasm composed by blasts resembling acute myeloid or lymphoid leukaemia. Diagnosis is based on the expression of at least three markers among CD4, CD56, CD123, TCL1, BDCA2/CD303 and MX1.

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