Immunohistology of Leukemia Cutis and Histiocytic Tumors

11

Maria Teresa Fernández Figueras, Gustavo Tapia, José Luis Mate, and Aurelio Ariza

Introduction

The diseases studied in this chapter constitute a heterogeneous group of lesions that range from reactive conditions to highly aggressive neoplasms. These entities have been grouped into two main sections. The first one deals with myeloproliferative neoplasms and includes mastocytosis as well, since even in cases of mastocytosis with clinical symptoms seemingly limited to the skin a potential systemic involvement should be investigated. Also in the first section, leukemia cutis and myeloid sarcoma have been put together due to the considerable overlap of these two entities. The second group includes conditions caused by proliferation of dendritic cells such as Langerhans cell histiocytosis, Langerhans cell sarcoma, and indeterminate dendritic cell tumor. Then, the chapter deals with macrophage-related diseases, including juvenile xanthogranuloma and related diseases, hemophagocytic lymphohistiocytosis, multicentric reticulohistiocytosis, reticulohistiocytoma, Rosai-Dorfman disease, cutaneous Kikuchi-Fujimoto disease, and cutaneous intralymphatic histiocytosis. Multicentric reticulohistiocytosis and solitary reticulohistiocytoma, also known as solitary epithelioid histiocytoma, have been considered separately since despite their sharing many microscopical and immunohistochemical features they are distinct entities with striking clinical differences. Multicentric reticulohistiocytosis can involve extracutaneous locations and is frequently associated with a rheumatological disease, whereas solitary reticulohistiocytoma seems to be tumoral in nature. Finally, the malignant histiocytic and dendritic cell sarcomas include histiocytic sarcoma, follicular dendritic cell sarcoma, and interdigitating dendritic cell sarcoma. During the elaboration of this book, a revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages has been proposed (Blood 2016;127:2672–81). The authors divide the histiocytosis into five groups: (1) Langerhans-related histiocytosis, (2) cutaneous and muco-cutaneous histiocytosis, (3) malignant histiocytoses, (4) Rosai-Dorfman disease, and (5) haemophagocytic lymphohistiocytosis and macrophage activation syndrome. In addition, they include Erdheim–Chester disease among the group of Langerhans cell histiocytosis. This recent proposal of a new paradigm shows how dynamic this field continues to be.

M.T.F. Figueras, M.D. (✉) • G. Tapia, M.D.
J.L. Mate, M.D. • A. Ariza, M.D.
Department of Pathology, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Barcelona 08916, Spain
e-mail: maiteffig@gmail.com

J.A. Plaza, V.G. Prieto (eds.), *Applied Immunohistochemistry in the Evaluation of Skin Neoplasms*, DOI 10.1007/978-3-319-30590-5_11

Myeloproliferative Neoplasms and Leukemic Infiltrates

Leukemia Cutis/Myeloid Sarcoma

Leukemia cutis (LC) is defined as skin infiltration by lymphoid or myeloid malignant cells [1]. According to the World Health Organization (WHO), the term myeloid sarcoma (MS) is used when the infiltrate consists of myeloid blasts, with or without maturation, and the lesion presents as a tumor mass effacing normal tissue architecture [2]. MS has also been designated as granulocytic sarcoma and chloroma. In this chapter, we will focus on myeloid LC (MLC) and MS.

Regarding lymphocytic leukemias, the percentage of LC largely depends on the leukemia subtype. Skin involvement is frequent in T-cell prolymphocytic leukemia and adult T-cell leukemia/lymphoma, often as the first manifestation of the disease [3, 4]. In contrast, B-cell chronic lymphocytic leukemia, the most common form of leukemia in adults, seldom involves the skin, although LC may be the first manifestation in rare instances [5–7].

With regard to myeloid leukemias, skin infiltration occurs in 2–20 % overall. Most cases correspond to acute myeloid leukemias (AMLs), especially those with monocytic differentiation (M4 and M5 subtypes of the FAB classification), followed by chronic myelomonocytic leukemia (CMML) [8–10]. Myelodysplastic neoplasms (MDNs) and myeloproliferative neoplasms (MPNs) rarely infiltrate the skin and, when they do, it is often a reflection of disease progression [11, 12]. MLC is more frequent in pediatric than adult leukemias and may also develop in association with congenital leukemia [13].

In regard to the underlying hematologic disease, three main onset forms of skin infiltration have been described. MLC develops in patients with a known hematologic malignancy in about 65 % of cases, in some of which it represents disease progression or relapse. In up to 28 % of cases MLC appears at the time the myeloid disorder is diagnosed and the cutaneous lesions may be the initial sign leading to the leukemia diagnosis. Finally, in about 7 % of patients MLC is found in the absence of any underlying hematologic malignancy, the terms "aleukemic LC" and "aleukemic MS" having been used in these cases [1, 8, 14].

Clinically, MLC usually presents as multiple, infiltrated plaques and/or nodules of red-brown or violaceous appearance. Solitary lesions account for less than one-third of cases. Distribution of lesions varies among different reports, the regions more often involved being the scalp, trunk, and extremities (Fig. 11.1).

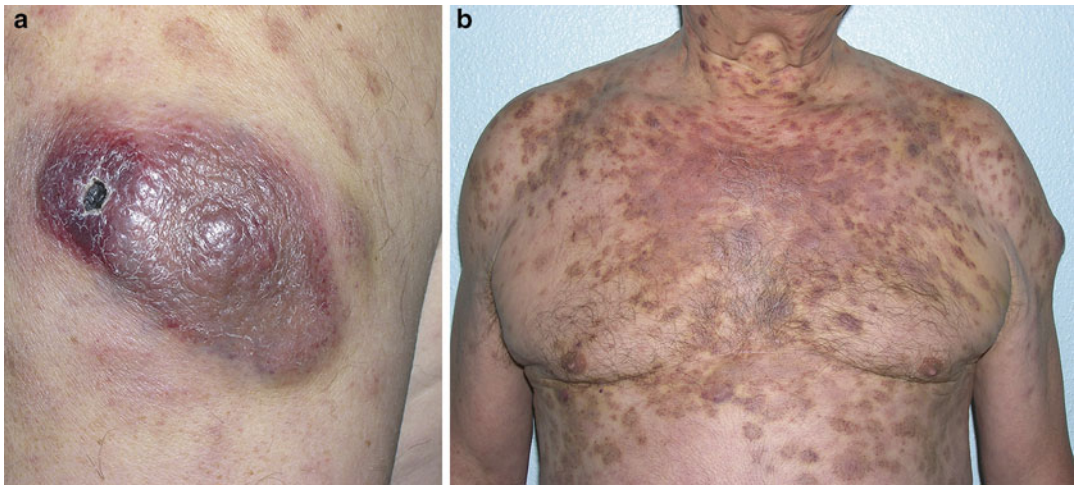


Fig. 11.1 (**a**) Violaceous, tumoral nodule surrounded by erythematous macules in the arm of a patient with acute myeloid leukemia. (**b**) Multiple brown, infiltrated macules in the trunk of a patient with leukemia cutis (Courtesy of Dr. JM Carrascosa, Dpt. of Dermatology, Hospital Germans Trias i Pujol, Badalona, Spain)

Leukemic gingival hyperplasia and oral lesions are particularly frequent in AML with monocytic differentiation [1, 8]. Unusual presentations include hyperpigmentation [15], fingertip hypertrophy [16], facial erythema [17], vasculitis [18], and drug-like eruption [19]. Nonleukemic cutaneous manifestations, referred to as "leukemids," are frequent and may be due to drug reaction, opportunistic infection, or cytopenias [8].

Morphologic evaluation of skin biopsies shows a dermal, nodular or diffuse, interstitial infiltration of immature myeloid cells, often with perivascular and periadnexal accentuation. The infiltrate density is very variable (Figs. 11.2 and 11.3). In some cases, an "Indian-file"-like pattern between collagen bundles may be seen (Fig. 11.4). The subcutaneous fat is frequently infiltrated. A Grenz zone is appreciated between the lesion and the typically uninvolved epidermis, although epidermal ulceration may be seen in some cases. Mitotic figures and apoptotic bodies are frequent [1, 8–10]. The myeloid cell infiltrate composition depends largely on the leukemia subtype, there being a morphologic correlation between bone marrow and peripheral blood findings. Thus, in FAB AML M1 and M2 subtypes, myeloblasts and immature myeloid cells are the predominant cell components; in FAB M4 and M5 subtypes, the infiltrate shows a monocytic morphology, with oval- or kidney-shaped blast cells; and in CMML, MDS, and MPN the infiltrate is heterogeneous, with blast cells intermingled with mature granulocytes, eosinophils, and mast cells [1, 8]. Aleukemic forms of LC are associated with an aggressive histology including high mitotic indeces, apoptotic bodies, and highly dense, diffuse patterns of infiltration (Fig. 11.5) [8].

Vasculitis [18], abundant giant cells [20], granuloma annulare-like [8], and Sweet-like patterns [21] are among the rare morphologic manifestations described in LC.

Immunohistochemistry

Even though several studies have found some bone marrow and skin discrepancies concerning myeloid neoplastic cells immunophenotypes, immunohistochemistry plays a pivotal role in the diagnosis of myeloid LC. The most sensitive markers are CD68, lysozyme, CD43, and CD33, which are expressed in nearly all LC instances. Myeloperoxidase, found in just half the cases, is less useful. CD34 and CD117, both immature myeloid cell markers, are immunoreactive in less than one-third of cases, in contrast to their common positivity in the bone marrow. Importantly, CD4, CD56, and C123 may be positive in some cases, raising the possibility of a blastic plasmacytoid dendritic cell neoplasm (BPDCN). Other immunohistochemical stains found in a variable proportion of cases include CD163, CD14, CD11c, CD45, and CD15. B-cell (CD20, PAX5, CD79) and T-cell (CD2, CD3, CD5) markers are negative [8, 10, 22–25].

Molecular Biology

Molecular biology techniques play an important role in the diagnosis, differential diagnosis, and prognostic evaluation of MLC. Molecular or chromosomal alterations may be demonstrated in about 50 % of cases, and closely mirror those found in their leukemic counterpart [26–28]. An increased incidence of aneuploidy of chromosome 8 has been repeatedly reported [29, 30].

Differential Diagnosis

Differential diagnosis of MLC includes B-cell lymphomas (especially diffuse large B-cell lymphoma), T-cell lymphomas (especially anaplastic large cell lymphoma and lymphomatoid papulosis), Merkel cell carcinoma, metastatic carcinoma, melanoma, and BPDCN. B-cell and T-cell malignancies express B-cell (CD20, CD79 and PAX5) or T-cell (CD2, CD3, and CD5) lineage-specific markers, frequently show clonal immunoglobulin or T-cell receptor genes, and are negative for myeloid markers. Merkel cell carcinoma and metastatic carcinoma may be excluded with the aid of cytokeratin and S100-protein immunostains, respectively.

Distinction between BPDCN and MLC may be very difficult, as both diseases share morphological and immunohistochemical properties. Moreover, the presence of blastic plasmacytic cells has been described in MLC lesions. Differential diagnosis between these entities is

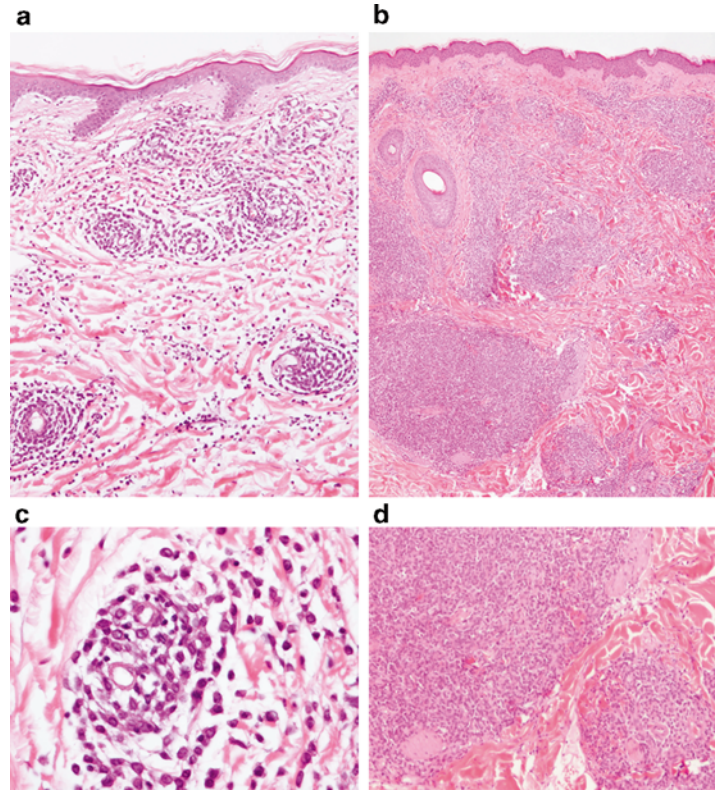


Fig. 11.2 Two examples of leukemia cutis. (**a**–**c**) A case showing mild perivascular infiltration (**a**, Hematoxilin-Eosin; 40×) of blastic leukemic cells (**c**, Hematoxilin-eosin; 400×). (**b**–**d**) In this case the infiltration is more dense, with perivascular nodules of neoplastic cells (**b**, Hematoxilin-eosin; 40× and 100×)

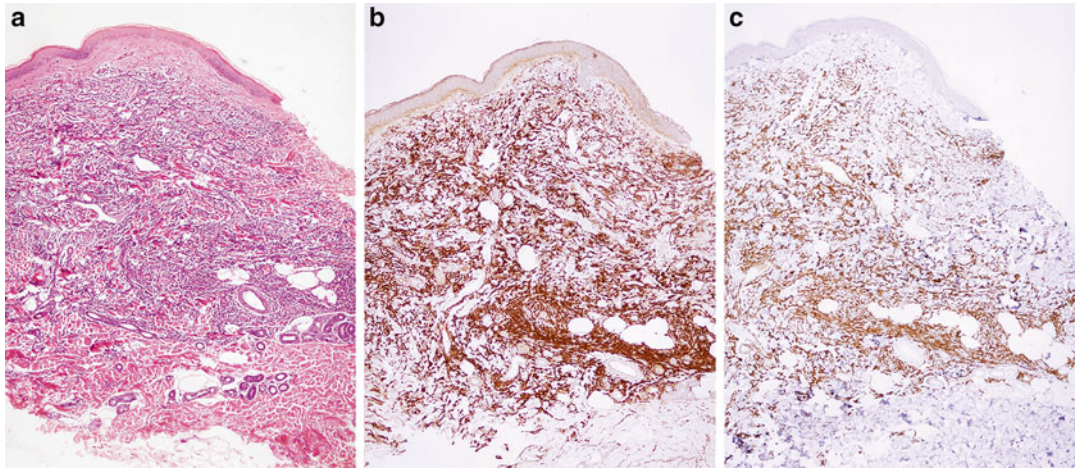


Fig. 11.3 Myeloid leukemia cutis showing interstitial and perivascular infiltration (**a**, Hematoxilin-eosin; 40×). Neoplastic cells are positive for lysozyme (**b**; 40×) and CD68 (**c**, 40×)

further *discussed* in the description of BPDCN [24, 25].

Immunohistochemistry-based diagnostic algorithms have been proposed [1, 23].

Clues and Pitfalls

- Consider the diagnosis of MLC in any infiltrate of blast-appearing cells, even in patients with unknown hematologic malignancy. The

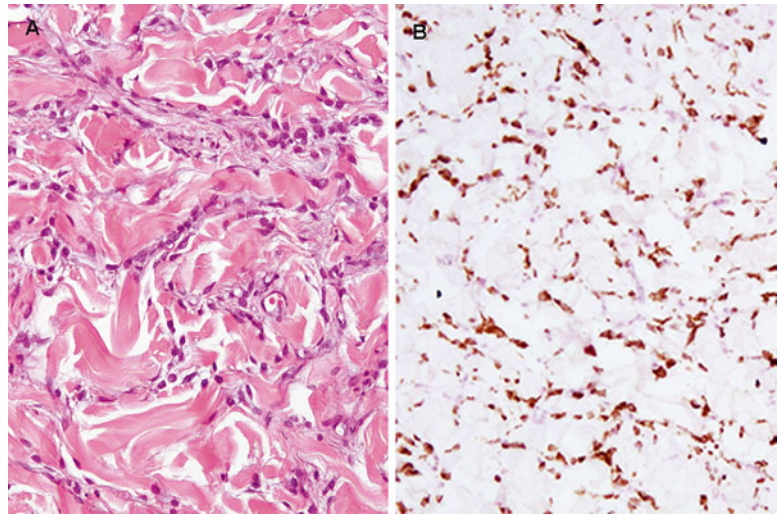


Fig. 11.4 Infiltration by leukemic cells among collagen bundles with an "Indian-file"-like pattern [Hematoxilin-eosin (**a**) and CD68 immunostain (**b**); 200×]

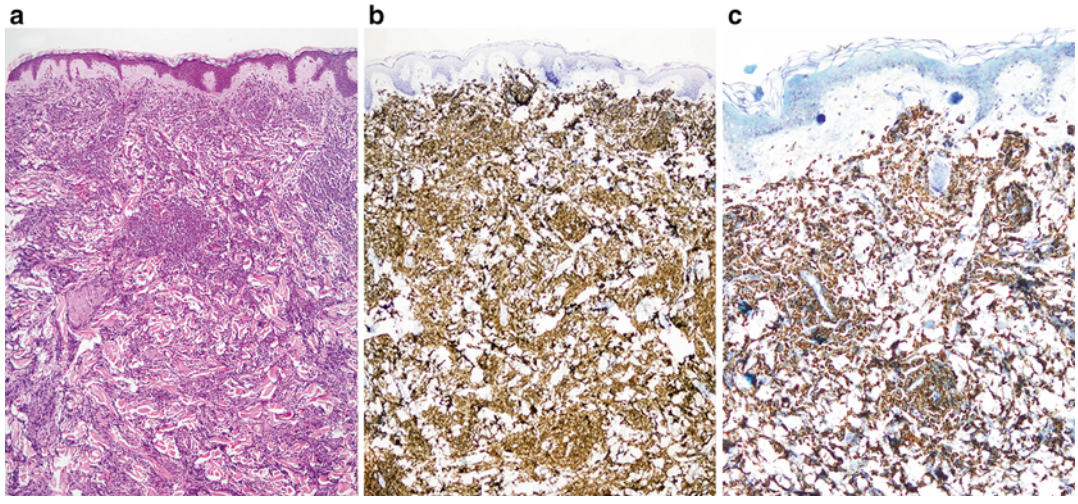


Fig. 11.5 Myeloid sarcoma showing a dense, diffuse infiltrate of leukemic cells in the dermis without epidermal involvement (**a**) (Hematoxilin-eosin; 40×). The cells are positive for CD33 (**b**; 40×) and myeloperoxidase (**c**; 100×)

initial immunohistochemical panel should include CD68, lysozyme, or CD43.

- Expression of CD4, CD56, CD123, or other blastic plasmacytoid dendritic cell-associated markers may be seen in a variable proportion of MLC cases. Consider the differential diagnosis with BPDCN.
- MLC has been seen in patients with suspected diagnosis of Sweet syndrome, especially the histiocytoid variant described by Requena et al. Thus, when a diagnosis of histiocytoid Sweet syndrome is being considered, additional immunohistochemical and /or molecular studies should be performed in order to exclude MLC [21, 31].

Blastic Plasmacytoid Dendritic Cell Neoplasm

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive hematological tumor produced by the clonal proliferation of immature plasmacytoid dendritic cells (PDCs) (professional

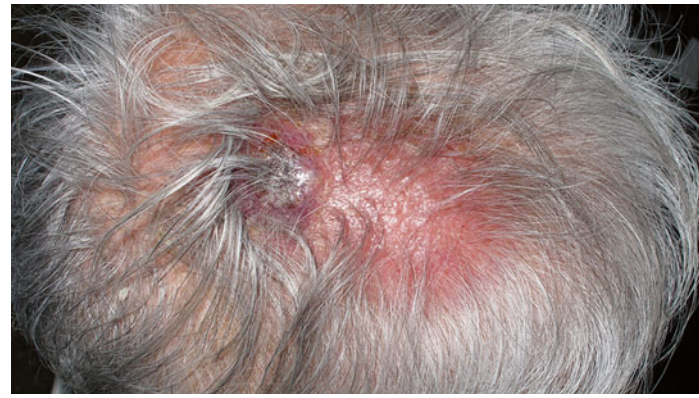


Fig. 11.6 Erythematous macule on the scalp with a nodular, hyperkeratotic area

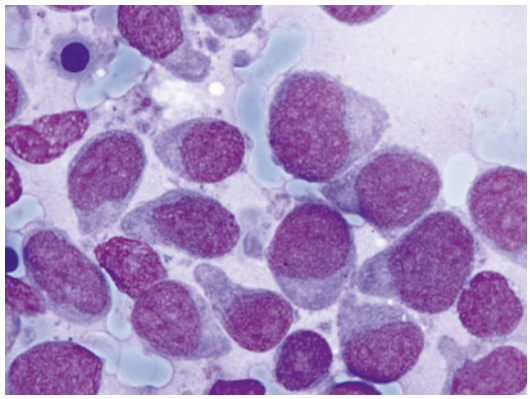


Fig. 11.7 Bone marrow aspirate shows infiltration by blast cells with fine chromatin and abundant, peripheral cytoplasm (May-Grünwald-Giemsa, 1000×)

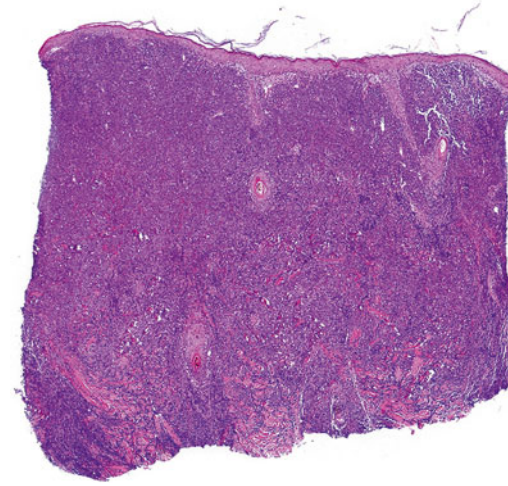


Fig. 11.8 Panoramic view of a nodular skin lesion. Blast cells diffusely infiltrate the dermis, without epidermal involvement (Hematoxilin-eosin, 20×)

type-1 interferon-producing cells) [32]. The uncertainties about BPDCN histogenesis had for the last 20 years are reflected in the variety of terms used to define this entity, including "agranular CD4+ natural killer (NK) cell leukemia" [33], "blastic NK cell leukemia/lymphoma" [34] and "CD4+ CD56+ hematodermic neoplasm/tumor" [35]. BPDCN is classified as an acute myeloid leukemia in the current 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues [32].

BPDCN shows a male/female ratio of 2–3:1. Most patients are older adults, with a mean age between 60 and 70 years, although BPDCN may occur at any age [36]. Patients usually show localized or disseminated cutaneous manifestations, such as nodules, bruise-like lesions, or erythematous plaques (Fig. 11.6). Lymphadenopathies, bone marrow, and peripheral blood involvement is common at diagnosis, and it invariably develops during disease's progression (Fig. 11.7) [36, 37]. A relationship with myeloid and myelomonocytic leukemia has been reported in 10–20 % of cases [38, 39].

Skin lesions typically show a monomorphic infiltration of medium-sized blast cells with irregular nuclei, fine chromatin, one to three small nucleoli, and scanty cytoplasm devoid of granulation. The infiltration is diffuse and dense in nodular lesions and perivascular with scattered nodules in bruise-like and plaque lesions. The epidermis is uninvolved, with a Grenz zone, and the subcutaneous fat may be infiltrated as the neoplasm progresses (Figs. 11.8 and 11.9). Angioinvasion/

angiodestruction and coagulative necrosis are absent. Mitotic activity is variable, but usually not prominent [36–38].

Immunohistochemistry

Neoplastic cells coexpress CD4, CD56, CD45RA, CD43, and PDC-related antigens such as CD123, T-cell leukemia-1 (TCL1) [40], cutaneous lymphocyte-associated antigen (CLA) [41], interferon α-dependent molecule MxA, blood dendritic cell antigen 2 (BDCA2/CD303) [42], Spi-B transcription factor [43], CD2-associated protein (CD2AP) and BCL11A, among others [44]. However, up to 50 % of cases show an incomplete dendritic cell phenotype (Fig. 11.10) [36].

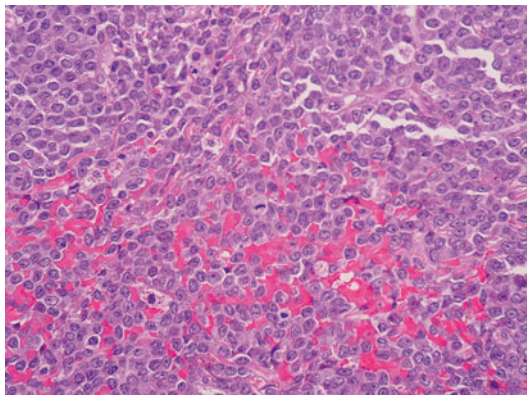


Fig. 11.9 The blasts are medium-sized, with fine chromatin, small nucleoli, and moderate cytoplasm without granulation (Hematoxilin-eosin, 200×)

BPDCN is negative for lineage-specific markers of B cells (CD20, CD79, and CD19), T cells (CD3 and CD5), myeloid and monocytic cells (myeloperoxidase, CD15, CD13, CD14, and lysozyme), with the exception of CD33 and CD7. Interestingly, terminal deoxynucleotidyl transferase (TdT) is positive in up to one third of cases while the hematopoietic precursor cell markers CD34 and CD117 are consistently negative. Epstein–Barr virus-encoded small RNAs (EBERs) are negative [36, 39, 42, 44].

Although this neoplasm definition was based on CD4 and CD56 positivity, negativity for CD4 or CD56 has been reported in rare instances [36]. This negative result does not exclude the diagnosis of BPDCN, if the remaining characteristics and phenotype are present. According to the WHO 2008 criteria, cases that share some, but not all, immunophenotypic markers with PDCs should be better classified as "acute leukemia of ambiguous lineage" [32].

Molecular Biology

T-cell and B-cell receptor genes are usually germline in most cases [6]. Karyotypic analysis and array-based comparative genomic hybridization have shown multiple genetic alterations in two-thirds of cases, mostly deletions on chromosomes 5q, 12p, 13q, 6q, 15q, 7p 9p, and 9q [45, 46]. Gene-expression profiling studies have found canonical activation of NFkB pathway [47] and

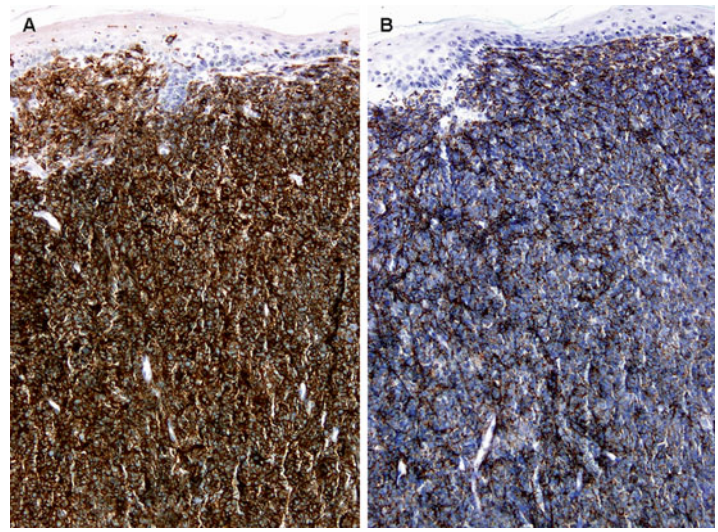


Fig. 11.10 The infiltrate is positive for CD4 (**a**) and CD56 (**b**) (100×)

next-generation sequencing approaches have evidenced mutations in several genes including TET2, IKZF3, and ZEB2 [48, 49]. However, none of these genetic abnormalities are specific for BPDCN and may be detected in other hematological malignancies.

Differential Diagnosis

The differential diagnosis of BPDCN is broad and includes T acute lymphoblastic leukemia/lymphoma (T-ALL), acute myeloid leukemia/myeloid sarcoma (AML/MS), cutaneous T/NK cell nasal-type lymphoma and Langerhans cell histiocytosis. Careful clinical evaluation and extensive immunophenotypic analysis is required, as immunophenotypic overlap with these neoplasms is frequent.

Expression of cytoplasmic CD3 and CD34 and T-cell receptor clonal rearrangement are helpful features to differentiate T-ALL from BPDCN, while TdT is not useful in this setting. T/NK cell nasal-type lymphomas are CD56+ and may occasionally express CD4, but neoplastic cells are rather pleomorphic, angioinvasion and necrosis are frequent, cells express cytoplasmic CD3 and TIA-1 and, importantly, are EBER positive, which excludes BPDCN [50]. Langerhans cell histiocytosis may exhibit a blastic morphology, expresses CD4 and CD56 and may be CD123-positive, but the correct diagnosis must be made with the aid of appropriate markers (S100, CD1a, and langerin) [51]. Differential diagnosis with AML/MS may be challenging, since cases with monocytic differentiation may show positivity for CD4, CD56, and CD123. Moreover, some PDC-related antigens may be expressed in AML/MS. Consequently, a broad panel of immunohistochemical markers is mandatory to make an accurate diagnosis. Findings indicative of AML/MS are the presence of granulated myeloid cells on close inspection, positivity for myeloperoxidase or lysozyme, CD13, CD14, CD34, or CD117, and negativity for MxA, TCL1, and TdT. Immunohistochemistry for BDCA2 and CLA is not useful in this context [24, 25, 52].

Clues and Pitfalls

- Consider BPDCN in any monomorphic and diffuse blast cell infiltration of the dermis, especially in elderly patients.
- CD4 and CD56 positivity strongly suggests BPDCN, but may be found in several other entities. In the presence of CD4+CD56+ infiltrates, a complete immunohistochemical panel must be performed, including antibodies for B-cell, T-cell, myelo-monocytic, and PDC-related antigens.
- Negativity for CD4, CD56, or PDC-related antigens does not rule out the diagnosis of BPDCN if other features of this condition are present.
- Non-neoplastic aggregates of PDC may be seen in association with myeloid disorders [22].

Precursor Lymphoblastic Leukemia/Lymphoma

Lymphoblastic lymphoma (LBL) is the tumor form of lymphoblastic leukemia. Both LBL and lymphoblastic leukemia consist of precursor cells (lymphoblasts) that may show a B-cell or T-cell phenotype. The leukemic presentation form predominates among B-cell neoplasms, in which it accounts for 90 % of cases. In contrast, T-cell neoplasms present as lymphomas in 85–90 % of cases [53, 54].

Bone marrow infiltration by over 25 % lymphoblasts is the criterion to be met for the diagnosis of leukemia. B lymphoblastic lymphoma (B-LBL) usually involves the skin, soft tissue, bone, and lymph nodes and may coexist with a certain degree of leukemic expression [55–57]. T lymphoblastic lymphoma (T-LBL) usually presents as a large mediastinal mass, enlarged lymph nodes, or involvement of organs such as the skin, tonsils, spleen, liver, testes, or central nervous system [58].

Skin involvement takes place more often in LBL than in lymphoblastic leukemia, its frequency being higher in B-LBL (15–20 %) than in T-LBL (<5 %). Lesions appear as reddish or purple subcutaneous nodules which usually are solitary and involve the head and neck of children in B-LBL, whereas in T-LBL they are often multiple and involve the chest wall, legs, and back of adolescent or young adults [59, 60]. A dermal lesion may be the first manifestation of disease of the cellular infiltrate in both B-LBL

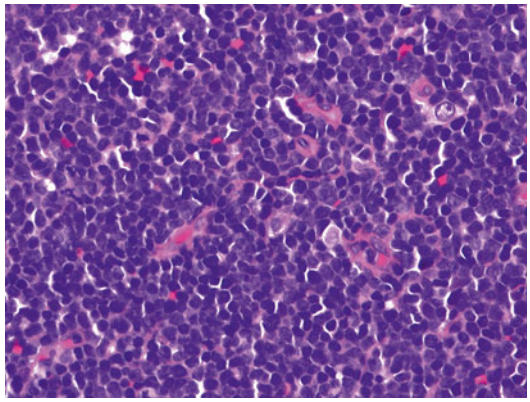


Fig. 11.11 Lymphoblastic leukemia. Dermal infiltrate in a patient diagnosed with T-cell lymphoblastic lymphoma. Note the marked monotony of the cellular infiltrate

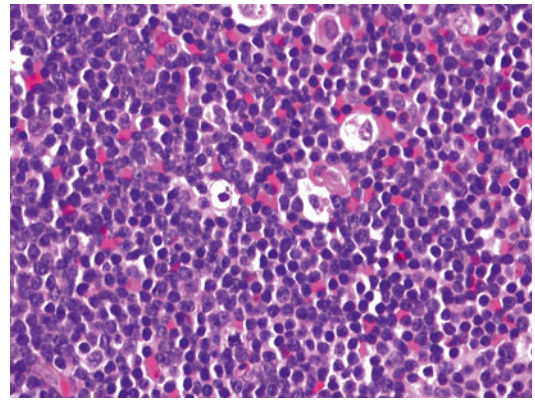


Fig. 11.12 Lymphoblastic leukemia. Focal starry-sky pattern

and T-LBL, so that at times a biopsy is performed when pertinent clinical information and peripheral blood and bone marrow study results are still unavailable.

Histologically, there is a diffuse monotonous infiltration of the dermis by intermediate-sized atypical lymphoid elements with scanty cytoplasms and round or convoluted nuclei showing finely particulated chromatin and visible nucleoli. Mitotic figures are common and areas with a "starry-sky" pattern are often seen. The epidermis is spared and it is uncommon for the neoplasm to destroy annexial structures (Figs. 11.11 and 11.12).

Immunohistochemistry

B-LBL is characterized by the expression of precursor cell markers (such as terminal deoxynucleotidyl transferase, TdT), CD99 or, less often, CD34 [61] (Fig. 11.13). B-cell marker expression is variable. Among the latter, the more useful are CD20, CD79a, and, particularly, PAX5. There may be positivity for CD10. In some cases, myeloid lineage cell markers such as CD13 or CD33 may be positive. Therefore, a too restricted immunohistochemical study may cause problems of diagnostic interpretation.

T-LBL usually expresses TdT, CD99, and, less commonly, CD34. T-cell markers (CD1a, CD2, CD3, CD4, CD5, and CD8) are variably expressed [62] (Fig. 11.14). Coexpression of

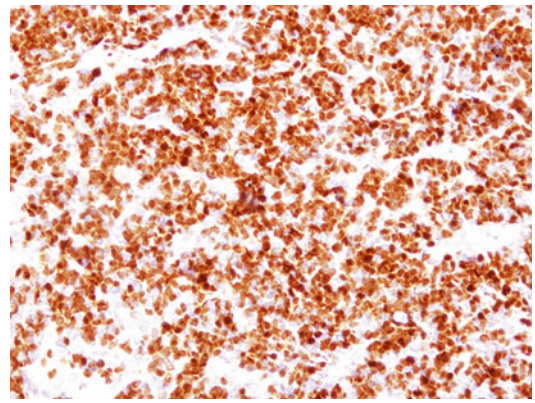


Fig. 11.13 Lymphoblastic leukemia. TdT nuclear immunostain of tumor cells

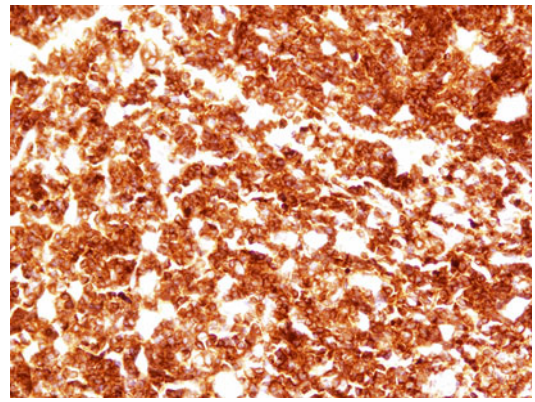


Fig. 11.14 Lymphoblastic lymphoma. Cells strongly positive for CD3 in lymphoblastic T-cell lymphoma

CD4 and CD8 is frequent and CD10 is positive in a high number of cases. Similarly to B-LBL, there may be expression of CD13 or CD33.

Molecular Biology

IGH DJ rearrangement is present in most B-ALL cases. TCR rearrangement may coexist with IGH DJ rearrangement in up to 70 % of B-ALL cases. TCR may be clonal in T-LBL, but up to 20 % of cases may show IgH clonality. Therefore, the utility of IGH DJ and TCR rearrangement studies to confirm B-cell or T-cell lineage is limited.

Some B-LBL cases are associated with characteristic cytogenetic alterations (*BCR-ABL1* translocation, *MLL* rearrangement, etc) that identify specific clinicopathological entities [53].

Differential Diagnosis

LBL diagnosis should pose no problems if appropriate clinical information is available and a complete immunohistochemical study is performed. Major difficulties may arise when clinical information is incomplete or the disease starts as a skin lesion. In these settings monotony and immaturity of the cell infiltrate and patient age are of great help in suggesting the correct diagnosis. When in doubt, immunohistochemistry may confirm the diagnosis by showing combined positivity for precursor cell markers (TdT and CD99), CD10, and B-cell markers (in B-LBL) or T-cell markers (in T-LBL). Obviously, the hematologist should be contacted so that a comprehensive study of the patient is carried out [63].

The cell infiltrate monotony could induce confusion with skin involvement by blastoid mantle cell lymphoma. However, the problem is solved by knowledge of relevant clinical features in conjunction with a complete immunohistochemical study including cyclin D1 or SOX11 [64–66]. Combined positivity for T-cell markers and CD10 may suggest angioimmunoblastic lymphoma with cutaneous involvement. Again, clinical information and immunohistochemical study of TdT and other markers greatly help.

Expression of CD34 and myeloid lineage markers may be reminiscent of myeloid sarcoma in some cases, but a more extensive immunophenotypic study may solve the problem.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), although mostly seen in old patients, may present at any age and usually causes dermal lesions, which are histopathologically similar to T-LBL. The CD3–, CD4+, CD123+, and CD56+ immunophenotype is very characteristic of this entity. Nonetheless, it should be kept in mind that up to a third of BPDCN cases may express TdT. Usually, T-LBL will be positive for other T-cell antigens such as CD2, CD3, CD5, and CD7. A complete hematologic study is necessary to establish the diagnosis in some cases [67].

Nonhematologic small round-cell tumors such as Ewing's sarcoma, neuroblastoma, malignant rhabdoid tumors, and Merkel cell carcinoma may present with skin lesions. These tumors should be ruled out with the aid of appropriate immunohistochemical panels when there is negativity for lymphoblastic lymphoma markers [68]. It should be noted that positivity for TdT and PAX5 has been observed in nearly 80 % of cases of Merkel cell carcinoma [69, 70].

Clues and Pitfalls

- The immunohistochemical study should include TdT and CD99 when confronted with a difficult-to-classify dermal lymphoproliferative lesion, particularly in children, adolescents, or young adults.
- Expression of myeloid lineage markers such as CD13 or CD33 does not exclude LBL.
- Angioimmunoblastic lymphoma may coexpress T-cell markers and CD10, but is negative for precursor cell markers (TdT).
- BPDCN should be ruled out when a dermal lesion is positive for CD4 and CD56, even in the presence of TdT immunoreactivity.

Mastocytosis

Mastocytosis comprises a heterogeneous group of diseases characterized by proliferation and accumulation of clonal mast cells in one or more organs. The World Health Organization (WHO) variants of mastocytosis are shown in Table 11.1. Skin is the organ most commonly involved in mastocytosis, and three main clinical-

pathological subtypes are recognized: (1) urticaria pigmentosa (UP)/maculopapular cutaneous mastocytosis (MPCM), (2) diffuse cutaneous mastocytosis (DCM), and (3) mastocytoma of skin (nodular mastocytosis) [71]. Cutaneous infiltration in mast cell leukemia and mast cell sarcoma is extremely rare.

Table 11.1 World Health Organization classification of mastocytosis[a]

	Skin lesions
Cutaneous mastocytosis (CM)	+
Urticaria pigmentosa (UP)/ maculopapular CM (MPCM)	–
Diffuse CM	–
Mastocytoma of skin	
Indolent systemic mastocytosis (SM)	+
Smoldering SM	+
Isolated bone marrow mastocytosis	–/+
Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease (SM-AHNMD)	–
Aggressive systemic mastocytosis (ASM)	–/+
Lymphadenopathic mastocytosis with eosinophilia	
Mast cell leukemia (MCL)	–
Aleukemic MCL	
Mast cell sarcoma (MCS)	–
Extracutaneous mastocytoma	–

[a]Horny HP, Metcalfe DD, Bennett JM, Bain BJ. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H et al. eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon France: IARC Press; 2008:54–63

UP is the most common variant of cutaneous mastocytosis (CM), accounting for 70–90 % of patients, and up to 75 % onset in the first years of life. Adult-onset UP is in most cases indicative of systemic mastocytosis (SM), and appropriate investigation of bone marrow and serum tryptase should be performed (Fig. 11.15) [72–74]. Telangiectasia macularis eruptiva perstans (TMEP) is considered a rare form of MPCM. DCM (1–3 % of patients) and mastocytoma of skin (10–30 % of patients) are almost exclusive of childhood [75].

Lesions of CM vary in the different clinical-pathological subtypes. The Darier's sign is useful in clinical diagnosis. UP/MPCM generally presents with an eruption of multiple hyperpigmented macules or, less frequently, papules. The trunk is the most common localization of lesions, followed by the extremities. The rare TMEP variant is characterized by slightly pigmented macules with telangiectasia. In DCM, skin is diffusely thickened and erythematous and blistering is common. Mastocytoma presents as solitary nodular lesions of the trunk, head, or wrists (Fig. 11.16).

The histopathological findings of CM are characterized by cutaneous infiltration of mast cells, predominantly in the upper third of the dermis; the number of mast cells varies in the clinical subtypes (Fig. 11.17). In the usual UP/MPCM lesions, fusiform mast cells are found mostly around blood vessels, with some eosinophils and superficial edema. Nodular aggregates of mast cells are rarely found. Basal hyperpigmentation

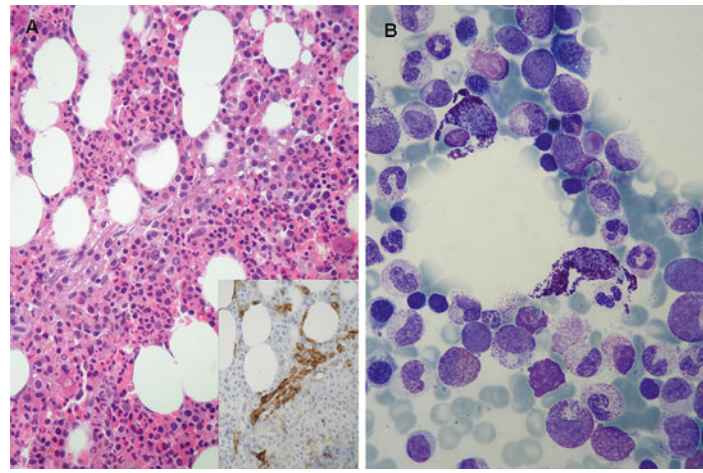


Fig. 11.15 Bone marrow infiltration by mast cells in a case of systemic mastocytosis (**a**, Hematoxilin-eosin, 200×). CD117 inmunostain highlight the mast cells (inset). Bone marrow aspirate shows elongated mast cells (**b**, May-Grünwald-Giemsa, 1000×)

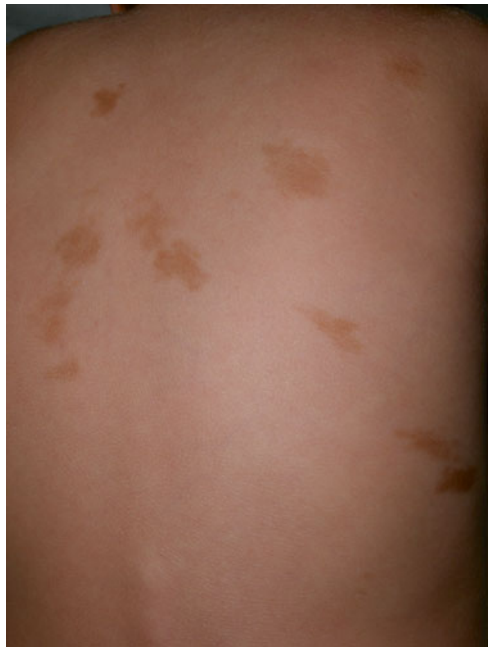


Fig. 11.16 Presence of multiple hyperpigmented macules on the back of a child with cutaneous mastocytosis (Courtesy of Dr. JM Carrascosa, Dpt. Of Dermatology, Hospital Germans Trias I Pujol, Badalona, Spain)

of the epidermis is a diagnostic clue. The rare TMEP is characterized by dilated vessels and a slight increase in perivascular mast cells that can be undetectable without appropriate immunohistochemical stains. In DCM, a band-like or dermal diffuse, sheet-like infiltrate of round mast cells is found (Fig. 11.18a, b). Subepidermal edema with vesiculobullous changes is frequent in infants. Mastocytoma of the skin is characterized by dense aggregates of round mast cells that infiltrate diffusely the papillary and reticular dermis, sometimes extending to subcutaneous tissues (Fig. 11.18c, d). The overlying epidermis is often elevated but uninfiltrated [76, 77].

Immunohistochemistry

Mast cells are positive for CD45, CD68, CD33, CD43, HLA-DR, CD117 (CKIT), and Tryptase. Of these, Tryptase is the most lineage-specific marker. Both CD117 and tryptase are commonly used to highlight mast cells in tissue samples. Aberrant expression of CD2 and/or CD25 in cutaneous mast cells may be indicative of SM

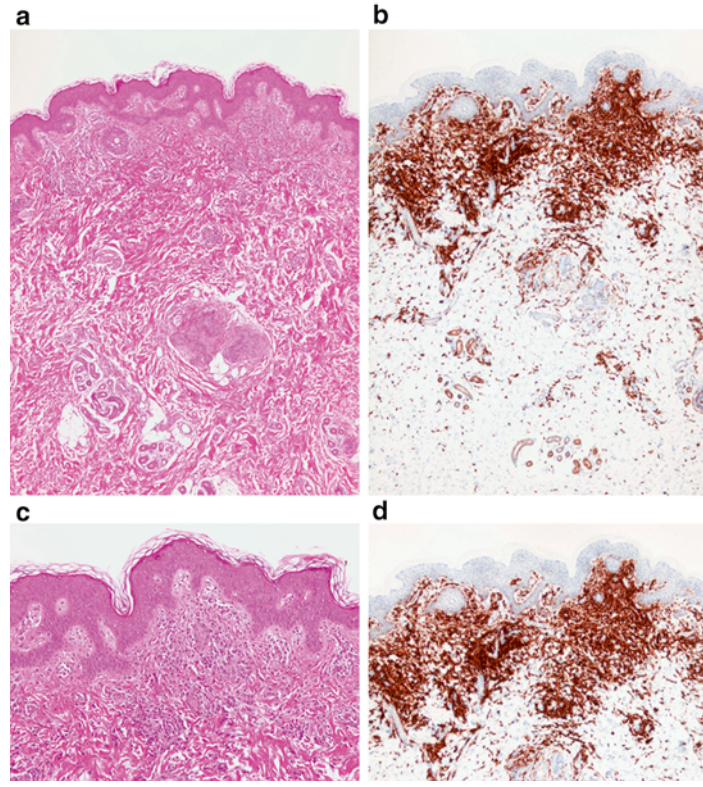


Fig. 11.17 A case of cutaneous mastocytosis with weak infiltration. Panoramic view shows a dermal superficial infiltration of mast cells (**a**, Hematoxilin-eosin; 40×). High power examination shows the interstitial and perivascular distribution of the infiltrate (**c**, Hematoxilin-eosin; 200×). Tryptase stain highlights the mast cell infiltrate (**b**; 40×, **d**; 200×)

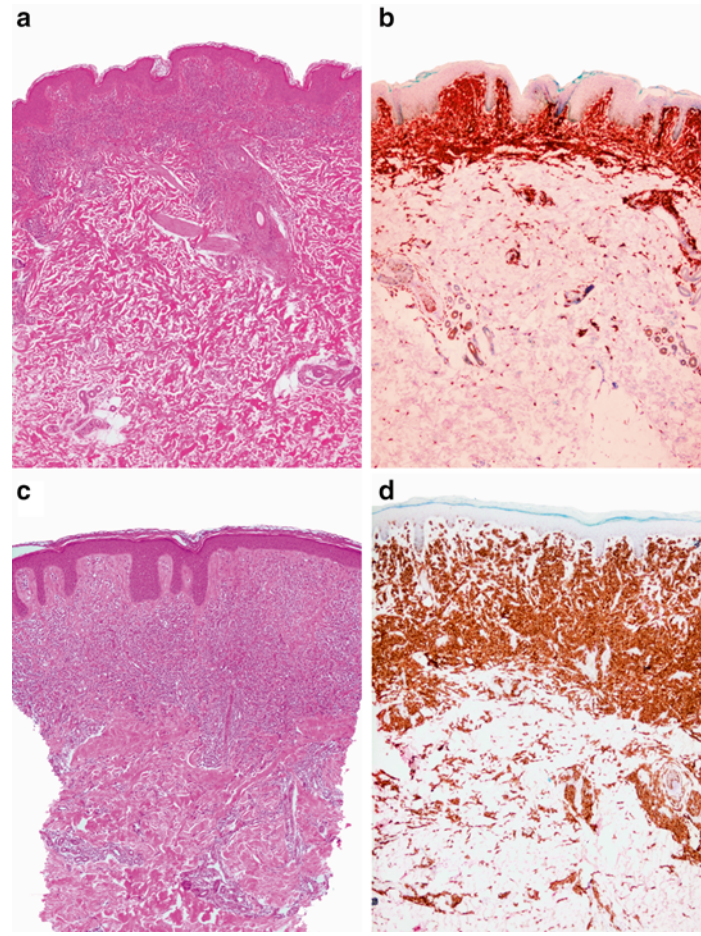


Fig. 11.18 Two representative cases of cutaneous mastocytosis. (**a**, **b**) Superficial, band-like infiltrate of mast cells in the dermis, without epidermal involvement (**a**, Hematoxilin-eosin, 40×; **b**, CD117, 40×). (**c**, **d**) Dense infiltration of papillary and reticular dermis by mast cells (**c**, Hematoxilin-eosin, 40×), positive for CD117 (**d**, Hematoxilin-eosin, 40×)

with secondary cutaneous involvement [78–80]. Recently, CD30 expression has been demonstrated in SM, including indolent and aggressive forms, and could be a potential target-based therapy [81, 82]. One case of CD30 positive CM has been reported, although it probably represented a secondary skin infiltration by SM [83].

Molecular Biology

Activating point mutations in KIT gene (especially D816V) are present in almost all patients with SM (Fig. 11.19). Early reports suggested that KIT mutations were not present in CM cases, but recent data show activating point mutations in 67–83 % of CM both in infants and adults. Interestingly, alternative mutations (other than D816V) are frequently found in CM [84–86].

Differential Diagnosis

The histopathological and clinical features of CM, including Darier's sign, are characteristic enough as to provide the correct diagnosis in almost all patients. Lesions with subtle infiltration by mast cells could be missed without suitable clinical information and special stains that highlight mast cells.

Clues and Pitfalls

- CD117 and/or tryptase positivity must be necessary to highlight mast cells in CM with scarce infiltration. CD117 is also positive in hematopoietic progenitor cells and tryptase in basophils, which eventually can lead to a misdiagnosis.
- Diagnosis of CM requires appropriate investi-

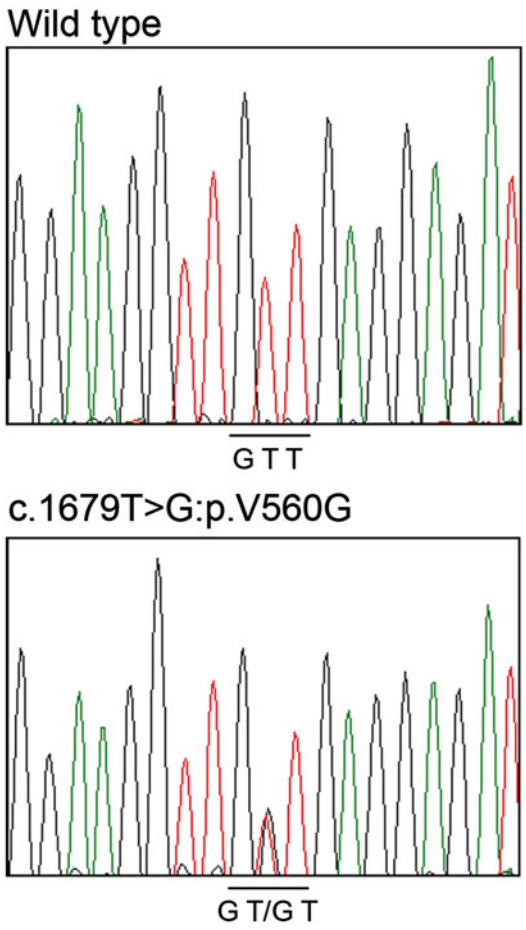


Fig. 11.19 Identification of V560G mutation in the c-Kit gene by PCR

gation in order to exclude SM, especially in adult-onset instances or in cases with CD25 expression.

Histiocytic and Dendritic Cell Disorders

Langerhans Cell Histiocytosis/ Langerhans Cell Sarcoma

Langerhans cell histiocytosis (LCH) is a rare disease more commonly seen in children, although it may present at any age. For more than 50 years it has been much debated whether LCH is an inflammatory, infectious, immunologic, or neoplastic condition. Recently, demonstration of clonality and *BRAF* mutations in LCH has lent support to the neoplastic character of this peculiar disorder [87].

LCH localized form with involvement of only one site (classic eosinophilic granuloma) shows very few symptoms and a strong trend towards spontaneous resolution [88, 89]. An osteolytic lesion with spread to the adjacent soft tissue is more commonly observed, but lymph nodes, lung, or skin may be alternatively involved. Multifocal forms combine simultaneous lesions in several of these locations. Skull and mandible involvement is quite common. Skull lesions may be associated with diabetes insipidus (Hand-Schülller-Christian). The more severe disseminated form (Abt-Letterer-Siwe) is seen in children, who add liver and spleen involvement to skin and bone lesions [88, 89].

Independently of clinical presentation and aggressiveness, LCH diagnosis is based on the identification of characteristic Langerhans cells (LCs). LCs show a peculiar elongated folded nucleus with little atypia, finely particulated chromatin, a discrete nucleolus, and variable proliferative activity. Cytoplasms are eosinophilic and moderately abundant. LCH lesions show an inflammatory/granulomatous appearance and consist of numerous LCs intermingled with eosinophils, histiocytes, multinucleated cells, neutrophils, and lymphocytes (Fig. 11.20). LCs relative density diminishes as the lesions mature and LCs are replaced by foamy histiocytes and fibrous tissue. The first structural evidence leading to the grouping of the various LCH forms was the observation of Birbeck granules. Subsequently, immunohistochemical techniques have greatly facilitated the study of these conditions [87, 88].

Langerhans cell sarcoma (LCS) is the obviously malignant counterpart of LCH. LCS usually presents in adults in a multiorganic fashion, with common infiltration of the skin and neighboring tissues. Histologically, LCS shows marked atypia, pleomorphism, and a high mitotic index, with no features suggestive of LC differentiation. Consequently, LCS diagnosis is mostly based on immunohistochemical findings and/or ultrastructural demonstration of Birbeck granules [89, 90].

Immunohistochemistry

LCH diagnosis requires evidence of CD1a and langerin (CD207) expression in LCs (Figs. 11.21 and 11.22) [88, 91]. Although S-100 protein is usually positive, its diagnostic usefulness is not as robust as that of CD1a and langerin owing to its low specificity [92]. In contrast, CD1a and langerin are highly specific for LCH and very useful for the differential diagnosis with other histiocytosis [93]. Additionally, CD68, CD4, and vimentin are often immunoreactive in LCH, although as happens with S-100 protein their low specificity makes their use unpractical.

There is a good correlation between the presence of *BRAF* mutations and immunoreactivity with specific antibodies against mutant BRAF-V600E protein. Although not all cases with the mutant protein are immunohistochemically positive, discrepancies are few [94, 95]. Even so, we believe that the diagnostic usefulness of anti-BRAF antibodies is limited, since a positive immunoreaction is obtained in just 60 % of LCH cases. That notwithstanding, the screening use of this antibody for detection of potentially mutated cases susceptible of treatment with specific inhibitors is very promising.

LCS usually expresses LC markers. Nevertheless, expression is focal and irregular in some cases, in which ultrastructural evidence of Birbeck granules may be extremely helpful (Fig. 11.23) [96].

Molecular Biology

In the last few years proof has accrued on the existence of a constitutive activation of the RAS-

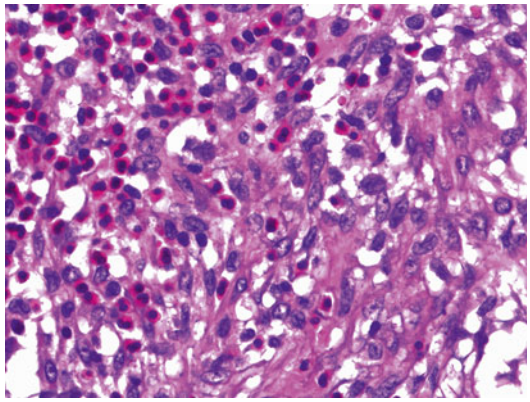


Fig. 11.20 Langerhans cell histiocytosis. Dermal infiltrate of granulomatous appearance containing numerous Langerhans cells and eosinophils

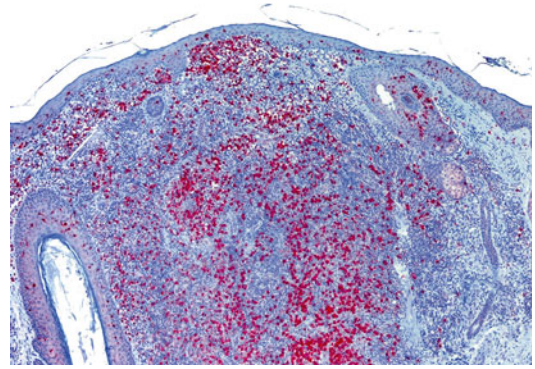
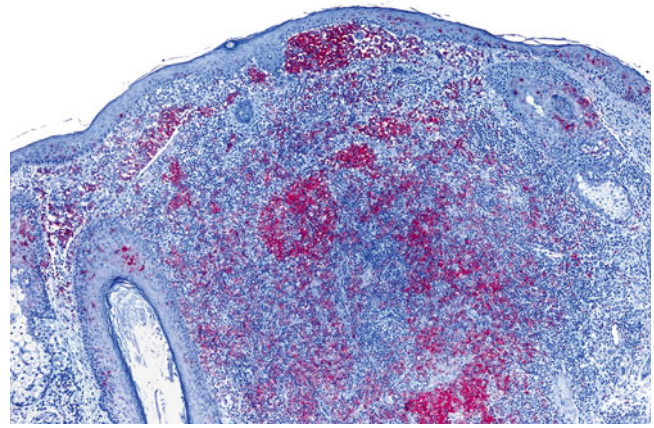


Fig. 11.22 Langerhans cell histiocytosis. Langerin (CD207) is the most specific immunohistochemical marker of Langerhans cell histiocytosis (courtesy of Dr. L. Requena, Dept of Dermatology, Fundación Jiménez Díaz, Madrid, Spain)

Fig. 11.21 Langerhans cell histiocytosis. CD1a cytoplasmic immunostaining of Langerhans cells (courtesy of Dr. L. Requena, Dept of Dermatology, Fundación Jiménez Díaz, Madrid, Spain)



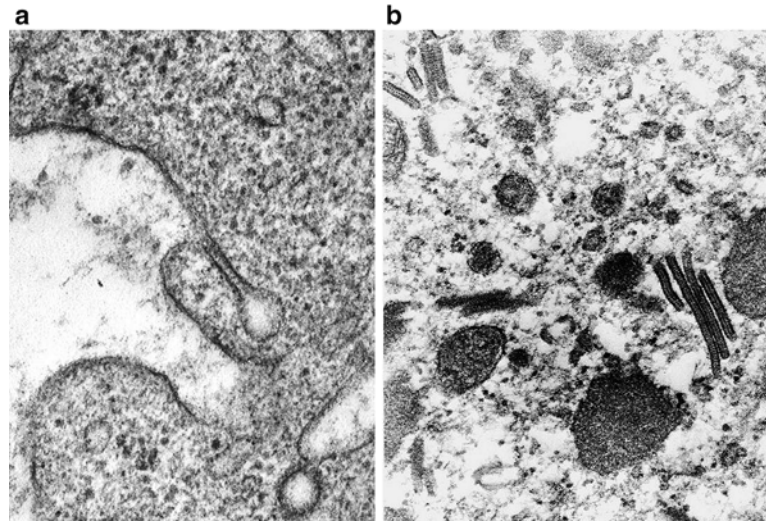


Fig. 11.23 Langerhans cell histiocytosis. Birbeck granules are the ultrastructural hallmark of Langerhans cells. They can appear in the typical tennis-racquet shape (**a**) or as trilaminate structures (**b**)

RAF-MAPK-ERK pathway in LCH. In about 60 % of LCH cases, activation of extracellular signal-regulated kinase (ERK) is caused by BRAF exon 15 V600D mutation. A similar biologic effect is achieved by somatic MAP2K1 mutations in approximately 27 % of LCH cases. Interestingly, both mechanisms are mutually exclusive. In rare LCH cases other mutations, such as those of ARAF, may induce ERK activation in the absence of BRAF mutations. These alterations, which ultimately result in ERK activation, take place in both unifocal and multifocal LCH cases, and even in congenital instances of the disease [97–101].

Probably, molecular determination of the aforesaid alterations will play a more important role in the selection of specific therapeutic targets than as diagnostic tools. In this context, the results recently obtained with specific inhibitors are highly promising. Most likely, the design of powerful specific inhibitors will soon provide efficient therapeutic weapons for the management of LCH [102, 103].

Differential Diagnosis

Generally speaking, LCH differential diagnosis includes inflammatory conditions totally or partially constituted by histiocytes (non-Langerhans cell histiocytosis).

The latter include juvenile xantogranuloma, a morphologically different lesion with foamy histiocytes and Touton giant cells. Lack of positivity for CD1a and langerin provides the diagnosis in doubtful cases [104].

Rosai-Dorfman disease occasionally involves the skin and may mimic LCH. The presence of foamy histiocytes with emperipolesis and, again, CD1a and langerin negative immunostaing are key features in support of this condition.

Erdheim-Chester disease is a systemic disease that at times involves the skin. Collections of enlarged histiocytes with clear cytoplasm are characteristic. Immunohistochemical studies including langerin and CD1a are diagnostically very helpful.

Usually, the differential diagnosis with dendritic cell tumors is not problematic, since their high tumor cell density and negativity for LC markers lead to their identification. Indeterminate dendritic cell tumor, a rare tumor of dendritic cells, may express CD1a and S-100 protein. Nevertheless, their negative langerin immunostaining and lack of Birbeck granules point to the correct diagnosis [105].

Mast cell proliferations, histiocytic sarcoma, myelomonocytic leukemia, and anaplastic large cell lymphoma may give rise to cutaneous lesions that occasionally cause diagnostic problems.

Clinical data and a complete immunophenotypic study are essential for the diagnosis.

Clues and Pitfalls

- When confronted with an inflammatory/histiocytic lesion, CD1a and langerin expression should be investigated to rule out LCH. Other less-specific markers, such as S-100 protein and CD4, must be cautiously evaluated, since other histiocytic conditions may create diagnostic confusion.
- Indeterminate dendritic cell tumor may give rise to differential diagnosis problems, since it may be positive for S-100 protein and CD1a. Absence of langerin and Birbeck granules are helpful diagnostic clues.
- Immunoreactivity for BRAF may be useful for selecting treatments with specific inhibitors.
- LCS may show partial expression of LCH markers. In these cases, electron microscopic study may solve the issue.

Indeterminate Dendritic Cell Tumor

Indeterminate dendritic cell tumor, also known as indeterminate cell histiocytosis (ICT), is an uncommon entity of unclear histogenesis. Its ill-defined morphologic features are intermediate between those of Langerhans cell hitiocytosis and other histiocytic conditions [106]. Clinically, ICT is characterized by solitary or multiple dermal papulonodular lesions involving the trunk, neck, face, and limbs. These lesions are usually asymptomatic and show a benign behavior. Spontaneous regression, at least partial, is a common outcome [107, 108].

There are ICT cases with extracutaneous osseous or corneal involvement and systemic symptoms, but they are exceptional [109, 110]. It is quite intriguing that this rare disease is occasionally associated with malignant hematologic conditions such as follicular lymphoma, acute myeloid leukemia, and lymphoblastic lymphoma [105, 106, 111, 112].

Histologically, ICT shows a dense dermal infiltrate that may reach the subcutis and rarely exhibits epidermotropism. The infiltrate consists of a mixture of lymphocytes, eosinophils, and large-sized cells with wide cytoplasms and oval folded or indented nuclei showing fine chromatin, inconspicuous nuclei, and delicate membranes (Fig. 11.24). Multinucleated giant cells may be seen as well. Cell atypia is generally absent and mitoses are either very scanty or not present.

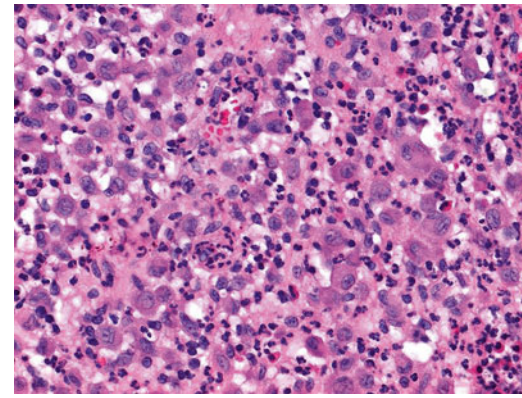


Fig. 11.24 Indeterminate dendritic cell tumor. Inflammatory appearance, with histiocyte-like cells, polymorphonuclear leukocytes and eosinophils (Courtesy of Dr. C. Barranco, Hospital del Mar, Barcelona, Spain)

Immunohistochemistry

ICT has a distinctive immunohistochemical profile. Similarly to what happens in LCH, dendritic cells are positive for S-100 protein and CD1a in ICT, but the latter lacks Birbeck granules and, consequently, shows negativity for langerin (CD207) (Figs. 11.25 and 11.26). It should be kept in mind, however, that positive immunostainings for S-100 protein and CD1a are irregularly distributed in some ICT cases [105, 110].

CD45 and histiocytic markers (CD68 and CD4) may be positive. CD30 and other B or T lymphoid markers are negative, as are follicular dendritic cell markers such as CD21, CD23, and CD35.

Molecular Biology

No much knowledge is available of the molecular changes related to this condition. Occasional cases associated with neoplastic hematologic disease have shown a clonal relationship

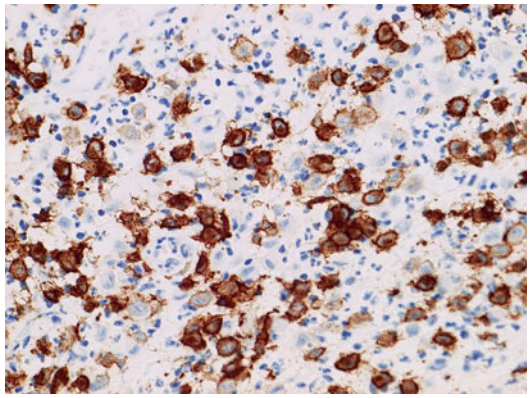


Fig. 11.25 Indeterminate dendritic cell tumor. Positive CD1a immunostaining of dendritic cells (Courtesy of Dr. C. Barranco, Hospital del Mar, Barcelona, Spain)

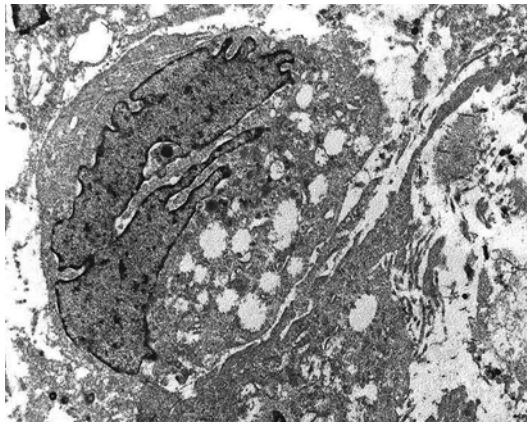


Fig. 11.26 Indeterminate dendritic cell tumor. There is no ultrastructural evidence of Birbeck granules (Courtesy of Dr. J Lloreta, Hospital del Mar, Barcelona, Spain)

between ICT and the accompanying lymphoid neoplasm. Specifically, t(14:18) has been identified in both ICT lesions and associated follicular lymphoma cells. Possibly, divergent differentiation from a common cell precursor is the underlying mechanism in some of these instances. Clonality has not been detected in ICT cases unrelated to hematologic neoplasms [105, 112]. Understanding of ICT molecular mechanisms is in need of much study and there is no proof that it shares the molecular alterations recently described in LCH.

Differential Diagnosis

ICT differential diagnosis includes genuinely histiocytic conditions and LCH. The combination of positive immunoreactivity for CD1a and S-100 protein and negative immunostaining for langerin is characteristic of this entity [106].

Juvenile xanthogranuloma and reticulohistiocytoma may partially mimic ICT, but their negativity for both S-100 protein and CD1a is very helpful. Other genuinely histiocytic conditions, such as Rosai-Dorfman disease, show distinctive morphologic features that allow their distinction, although recourse to immunohistochemistry greatly helps to clarify doubtful cases.

Dendritic cell tumors may express S-100 protein, but their densely cellular appearance and lack of CD1a expression are very useful diagnostic clues.

LCH may be morphologically very similar to ICT and then poses significant differential diagnostic problems. In this setting immunohistochemistry for CD1 and langerin is essential, langerin negativity being very suspicious for ICT. Electron microscopic demonstration of lack of Birbeck granules is also recommended to confirm de diagnosis of ICT.

Clues and Pitfalls

- When confronted with a lesion suspicious for LCH, langerin expression should be investigated. Langerin negativity is very suggestive of ICT.
- When ICT is associated with a malignant hematologic condition, there may be a clonal relationship between both. Investigation of clonality is advised in these circumstances.

Xanthogranuloma and Related Disorders

Juvenile xanthogranuloma (JXG) is a non-Langerhans dendritic cell histiocytic disorder that usually appears in the first two decades of life [113]. Most JXGs are solitary dermal nodules measuring from a few millimeters to 1–2 cm, although giant forms (often 4–5 cm in diameter) have also been described [114]. A high proportion of cases occur on the face or trunk and are

skin colored, yellowish, or erythematous. Less frequently, patients present with multiple lesions, exhibit a lichenoid appearance [115] or show involvement of deep-seated cutaneous locations [116]. Visceral or systemic involvement is rare but, when present, it may be the cause of death, especially in neonates [113]. Nevertheless, the clinical course of most JXGs is self-limited.

Microscopically, JXG consists of an intradermal proliferation of spindle cells, mononuclear histiocytes, and multinucleated giant cells, some of them Touton type. Touton cells are characterized by multiple nuclei in a ring disposition around an area of dense pink cytoplasm, which is surrounded by a rim of foamy cytoplasm (Fig. 11.27). Touton cells are less frequent in JXG in extracutaneous locations [113]. The epidermis is usually separated from the proliferation by a thin band, but periadnexal involvement is quite common (Fig. 11.28a, b). Lymphocytes and eosinophils can also be present within the histiocytic infiltrate. Nonlipidized [117] and mitotically active cases can simulate malignant mesenchymal neoplasms [118].

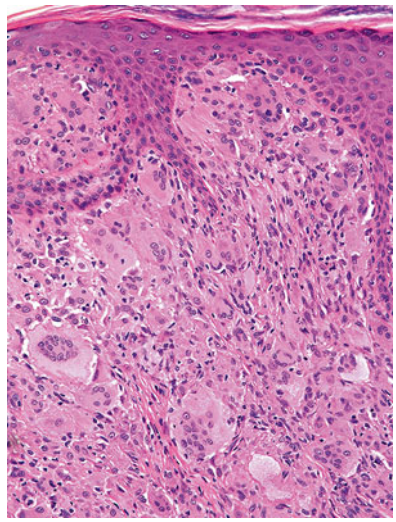


Fig. 11.27 Juvenile xanthogranuloma consisting of an intradermal proliferation of histiocytes, most of them multinucleated. Foamy cytoplasms, a result of xanthomization, tend to occupy the periphery, whereas nuclei are centrally located forming a ring

The association of JXG and neurofibromatosis types 1 and 2 (NF1 and NF2) [119, 120] is well recognized and may form a triad with juvenile chronic myelogenous leukemia (JCML) [121, 122]. The combination of JXG and Langerhans cell histiocytosis (LCH) in the same patient has been interpreted as an argument in favor of their common histogenesis [123].

JXG is one of the conditions in a group of related disorders including cephalic histiocytosis, spindle cell xanthogranuloma, disseminated juvenile xanthogranuloma, progressive nodular histiocytosis (PNH), generalized eruptive histiocytosis, xanthoma disseminatum, and Erdheim-Chester disease (ECD) (Fig. 11.29). Among these disorders, some are more frequent in adults [124–126], some are multifocal and/or show extracutaneous

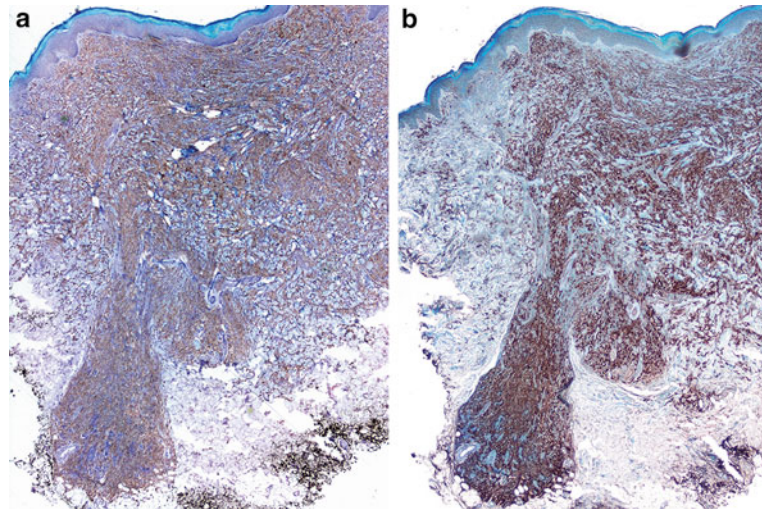


Fig. 11.28 Juvenile xanthogranuloma separated from the epidermis by a thin layer of dermal collagen but extending downward surrounding a follicle. The histiocytes are positive for both CD68 (**a**) and factor XIIIa (**b**)

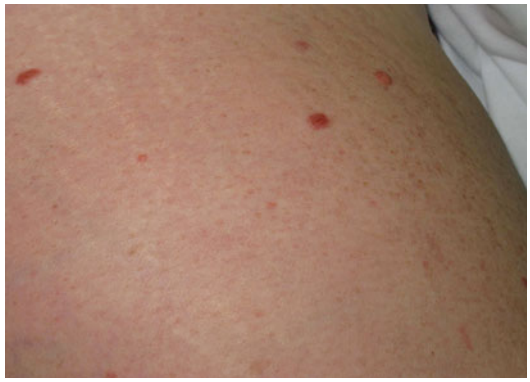


Fig. 11.29 Patient with Erdheim-Chester disease under study for neurological symptoms. Until the dermatological examination, these inconspicuous cutaneous papules had been clinically missed (Courtesy of Dr. I. Bielsa, Dept. of Dermatology, Hospital Germans Trias i Pujol, Badalona, Spain)

involvement and some have important impact on the quality of life, causing serious illness or even death.

The diagnosis of JXG-related disorders can be challenging. First, because cutaneous lesions are often microscopically and immunophenotypically indistinguishable from solitary JXG. Second, because of the rarity of most of these entities, which makes difficult to achieve a general agreement on their classification and the establishment of clear-cut diagnostic criteria.

Patients with PNH are adults that develop multiple xanthomatous papules and pedunculated or deep-seated nodules. The lesions, which measure 1-3 cm in diameter, may be disfiguring. Some patients also present systemic symptoms and visceral involvement [124, 125].

Worse still is ECD, characterized by the involvement of internal organs, especially bone and lung. Symmetrical osteosclerosis of long bones is a frequent manifestation. Heart, retroperitoneum, and periaortic spaces are other common sites in this condition, as is the central nervous system, whose involvement may cause diabetes insipidus [126]. ECD patients often complain of systemic symptoms such as fever, weakness, and weight loss. ECD cutaneous lesions tend to be periocular [124]. The clinical course varies considerably and depends to a great extent on the extension of the disease, some cases being paucisymptomatic, whereas others are rapidly fatal [126].

Immunohistochemistry

All JXGs are positive for usual histiocytic markers [113, 128] such as CD68 (KP1 and PG-M1) (Fig. 11.28a), CD31 [129], CD163 [130] and fascin [128], often with a coarse granular pattern. JXG also immunostains for factor XIIIa (a marker of dermal dendrocytes) (Fig. 11.28b), LCA, CD4, CD14, HLA-DR, and vimentin [113, 128]. Although most cases are negative for S100 protein, there are some reports of positivity [131] mainly in the first months of life [132], with loss of expression in parallel with maturation [133]. All JXG cases are negative for langerin, CD1a, CD3, CD21, CD34, and CD35 [128].

Molecular Biology

The cellular origin and causes of proliferation in JXG and related entities are not well known. Nevertheless, molecular biology studies are providing the basis to better understand the complex mechanisms underlying JXG pathogenesis. The roles of proinflammatory cytokines and several oncogenic pathways have been invoked in this regard. A clonal T-cell receptor gamma (TCR-γ) rearrangement was demonstrated in the cells of a JXG associated with acute lymphoblastic leukemia, with both conditions presenting an identical bi-allelic rearrangement [134]. Clonal mutations have also been demonstrated in Erdheim-Chester disease [135], which similarly to Langerhans cell histiocytosis (LCH) also shows a high prevalence of *BRAF(V600E)* mutations (>50 % of patients) [136–139]. The latter phenomenon has never been reported in JXG [143].

The demonstration of *BRAF (V600E)* mutation has provided new insights on the pathogenesis of these diseases. It has been hypothesized that mutated *BRAF* might trigger a process of oncogene-induced senescence, with cell-cycle arrest and induction of pro-inflammatory molecules that would be responsible for the inflammatory local and systemic infiltrates [139].

Differential Diagnosis

With the exception of *BRAF*-mutated ECD cases, there are no reliable microscopic or immunohistochemical clues to differentiate a JXG cutaneous lesion from one associated with some other JXG-related disorder (Fig. 11.30) [136–139]. Consequently, the differential diagnosis among the various entities in this group should be based on their clinical features. CD4 and LCA expression in JXG may be used to distinguish it from dermatofibroma when the latter is heavily lipidized or the former is not [128]. JXG distinction from reticulohistiocytoma is usually based on histopathological criteria, but frequent factor XIIIa expression in the former and usual lack thereof in the latter help to its distinction. Some nonspecific tissue inflammatory reactions may also simulate JXG [140].

Solitary JXG may also mimic Spitz nevus [141] and occasional positivity of JXG cells for S100 protein may further complicate their telling apart. Immunohistochemical expression of histiocytic markers and the absence of melanocytic markers such as Melan A or Sox 10 may be very helpful.

Clues and Pitfalls

- Expression of CD31 (usually considered a vascular marker) in histiocytic disorders [129] may be the cause of JXG misdiagnosis, especially in multiple, disseminated, or giant lesions [142].
- Xanthogranulomas developed at irradiation sites may be clinically misinterpreted as tumor relapse, or even as angiosarcoma, due to their CD31 positivity [143, 144].

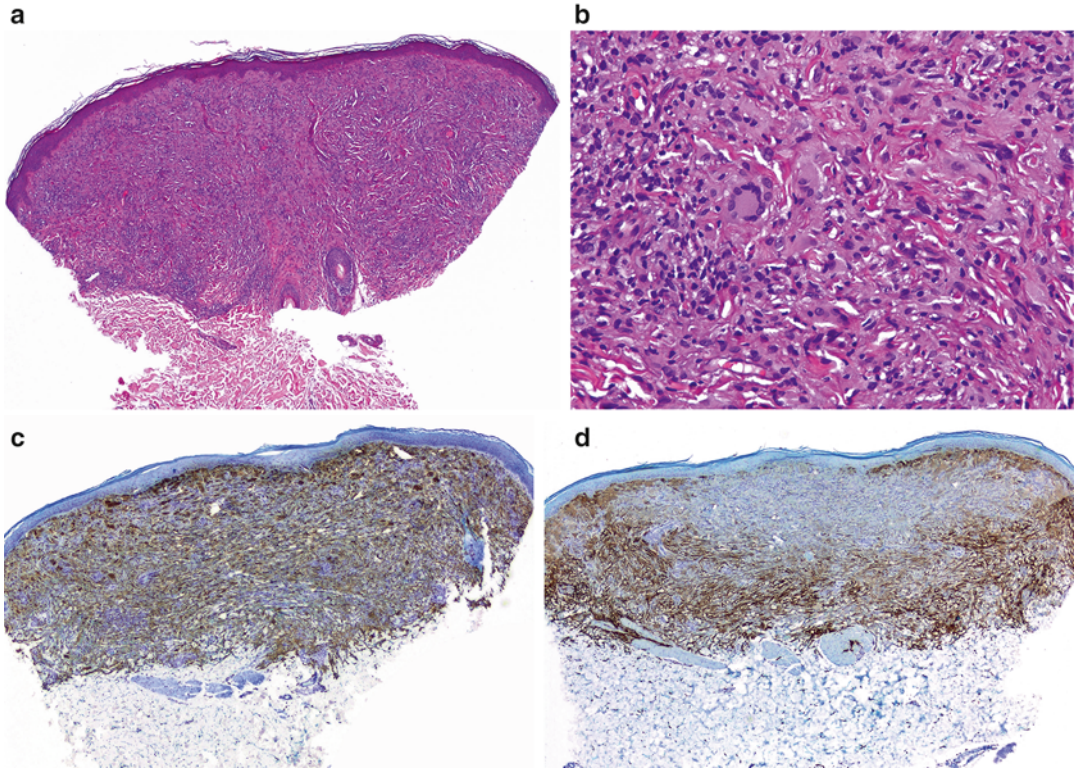


Fig. 11.30 Microscopical appearance of a cutaneous lesion from an Erdheim-Chester disease patient. The discrete histiocytic proliferation (**a**), with mild xanthomization (**b**), and the inmmunohistochemical profile, with expression of CD68 (**c**) and factor XIIIa (**d**), do not differ significantly from a typical juvenile xanthogranuloma

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening disorder of the immune regulatory system that may arise in any age group in relation to many different conditions. HLH is considered to be a hyperinflammatory syndrome more than a single disease [145–148].

HLH may occur in two forms: primary or familiar and secondary or sporadic. Primary HLH usually develops in infancy, although reports in adults and adolescents are becoming increasingly frequent [149]. Primary HLH is associated with gene defects in the familial hemophagocytic lymphohistiocytosis (FHL) locus, which codifies molecules involved in perforin-dependent cytotoxicity. Some congenital immunodeficiency syndromes with multisystemic disorders (frequently associated with albinism) present an increased incidence of HLH, which can be the first manifestation of the disease [148, 150]. In secondary HLH the usual triggering factor is an infection that is usually viral [146], herpes viruses and particularly EBV being the most frequent causes [145]. Rheumatologic diseases, immunodeficiency syndromes, and neoplasms, mainly T-cell lymphomas, are other conditions commonly related to secondary HLH. The term macrophage-activation syndrome (MAS) is used for a hemophagocytic syndrome associated with an inflammatory or autoimmune disease [145, 151]. Some patients with secondary HLH present mild genetic defects resulting in limited expression of the same proteins involved in primary cases [145].

In HLH pathogenesis a disproportionate cytokine production is responsible for excessive activation of macrophages [152, 153]. An infection is often the initiating factor and activation of toll-like receptors may contribute to the development of the condition [146, 148]. A defect of perforin-dependent cytotoxic function reduces the activity of natural killer and cytotoxic lymphocytes, which normally eliminate the infected antigen-presenting cells. As a result, uncontrolled expansion of cytotoxic T- cells and activated macrophages replaces physiological homeostatic mechanisms [146, 148].

The most frequent presenting symptoms are prolonged fever, lymphadenopathies, hepatosplenomegaly, and seizures or confusion. At the time of presentation, 80 % of patients present cytopenias that later on may evolve to pancytopenia. Hypertriglyceridemia, high serum ferritin levels, and coagulopathy are also common. Many patients develop hepatitis, renal failure, respiratory failure, encephalitis, and hypotension. Skin rashes occur in 25 % of patients and range from erythroderma with edema to purpuric or petequial rash [145–148]. Cases presenting multisystem failure, neurological deterioration, and superinfection secondary to cytopenia are usually fatal [145].

The diagnosis of HLH relies more on clinical and laboratory findings than on the histopathological study. Hemophagocytosis, the hallmark of the disease, is not a requisite symptom to make the diagnosis, and may well be absent in the early stages of the disease [145]. Microscopically, hemophagocytosis consists of the presence of macrophages containing phagosized erythrocytes, leukocytes, megakaryocytes and platelets or their cellular debris (Fig. 11.31a). Bone marrow, spleen, lymph node, and liver are the best sites to look for images of hemophagocytosis [145–148].

Cutaneous hemophagocytosis in the context of HLH is extremely rare, but erythrophagocytosis, a form of hemophagocytosis, has been reported in the skin of one MAS patient (Fig. 11.32) and in two patients with rheumatological diseases that could be considered incomplete forms of MAS [154].

Immunohistochemistry

Macrophages in hemophagocytosis express CD68 (KP1 and PG-M1) (Fig. 11.33) and CD163. The soluble form of the latter is also a useful marker for the diagnosis of MAS [155]. A significantly high population of CD8-positive T lymphocytes in the infiltrate, accompanied by a decrease in the number of CD5-expressing cells, is both a frequent finding and a useful diagnostic clue in Epstein-Barr virus-associated HLH [156].

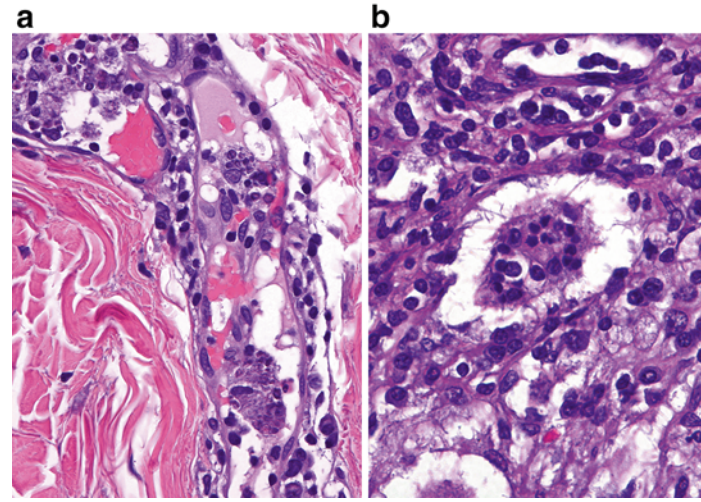


Fig. 11.31 (**a**) Hemophagocytosis with engulfed inflammatory cells in the cytoplasm of a macrophage showing different grades of degeneration should be distinguished from (**b**) emperipolesis, which is characterized by the presence of intact inflammatory cells in the cytoplasm of a macrophage, sometimes surrounded by a retraction halo

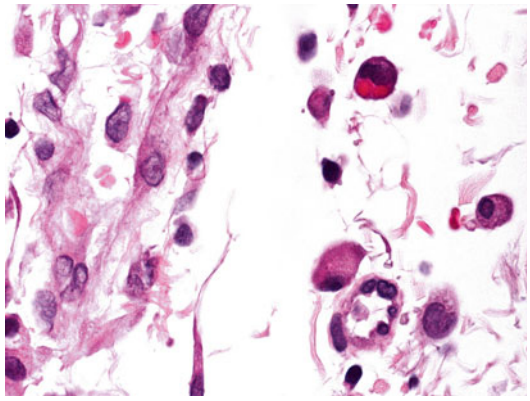


Fig. 11.32 Cutaneous erythrophagocytosis in a case of macrophage activation syndrome (courtesy of Prof. Dr. H. Kerl, Medical University of Graz, Graz, Austria)

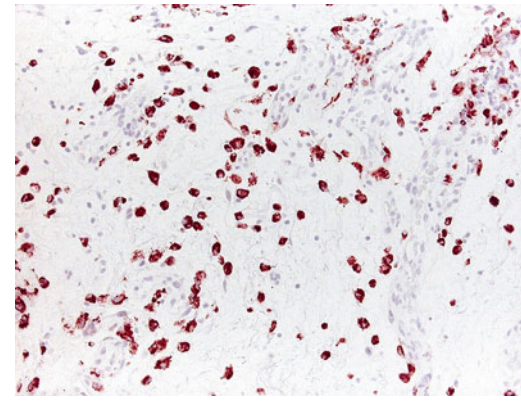


Fig. 11.33 Diffuse CD68 expression in macrophages from a case of cutaneous erythrophagocytosis in a case of macrophage activation syndrome (courtesy of Prof. Dr. H. Kerl, Medical University of Graz, Graz, Austria)

In addition, macrophages and activated T cells express high levels of cytokines (Fig. 11.34). When a virus is the triggering factor, immunohistochemical staining may contribute to its identification [157]. In the case of EBV, a type II latency-gene expression pattern has been demonstrated [158].

Molecular Biology

Many HLH cases contain clonal B-cell or T-cell populations, especially in cases related to EBV [159], but the demonstration of clonality does not carry a worse prognosis. Conversely, an abnormal karyotype would point towards a systemic EBV-driven T-cell lymphoproliferative disorder with clinical and histopathological overlap with EBV-related HLH and a high mortality rate [160].

Differential Diagnosis

Residual lesions of leucocytoclastic vasculitis may present perivascular hemophagocytosis [161, 162]. This finding, in the adequate clinical context, may raise the possibility of HLH. Although its presence makes further investigations advisable, the diagnosis of HLH should be based on the established criteria [163]. Hemophagocytosis should be distinguished from emperipolesis, in which intracytoplasmic cells are intact (Fig. 11.31b).

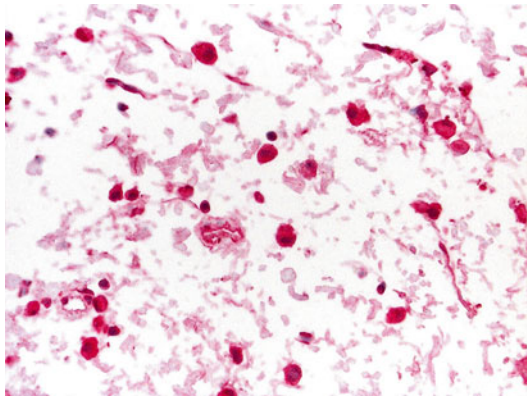


Fig. 11.34 Strong interferon γ expression in macrophages from a case of macrophage activation syndrome (courtesy of Prof. Dr. H. Kerl, Medical University of Graz, Graz, Austria)

Clues and Pitfalls

- If HLH is suspected, performance of immunohistochemical or in situ hybridization tests for detection of viruses (mainly members of the herpes virus family such as EBV and CMV) may help to unveil the triggering factor.
- The common phenomenon of phagocytosis of cellular debris in macrophages at areas of inflammation may be misinterpreted as hemophagocytosis. A background of long-standing inflammation with residual acute inflammatory infiltrates, necrosis, or fibrosis is an uncommon feature in HLH and favors inflammatory resolution with macrophagic infiltration.

Multicentric Reticulohistiocytosis

Multicentric reticulohistiocytosis (MRH) is a rare form of idiopathic non-Langerhans cell histiocytosis that manifests itself in the skin as papulonodular mucocutaneous lesions [164]. Destructive polyarthritis is present in almost half the cases, in which it causes a severe form of joint destruction known as arthritis mutilans. These cutaneous and rheumatological manifestations may coexist, appear in isolation, or follow one after the other [164, 165]. The dermatological features may range from tiny papules to nodules that may coalesce forming clusters or furrowing and coarsening the skin [164–167]. Skin lesions grow slowly, are often asymptomatic, show a skin-colored, translucent, reddish or yellowish surface and rarely ulcerate [164, 165]. Any skin site and occasionally the external mucosa may be affected, the hands and face being the most common locations [164, 165]. Clustering of papulonodules overlying the periungual areas may result in the characteristic "coral-bead" appearance [166]. Diffuse facial infiltration is less common, but it was the cause of a leonine facies in one case [167]. Patients may complain of malaise and systemic symptoms and rare instances of pulmonary, myocardic, and liver histiocytic infiltration have been reported [168, 169]. In other patients lung involvement consists of nonspecific fibrosis only [170]. Some lesions may be induced by ultraviolet light [171] and photodistribution is sometimes present [172]. The pathogenesis of MRH is not known but there are many evidences in favor of an immunological basis. Elevated cytokine serum levels seem to play a role in bone destruction [173]. In addition, TNF-alpha increase in both serum and lesional epidermis [174, 175] might trigger monocyte chemoattractant protein-1 (MCP-1) overexpression [176] leading to histiocyte attraction. Furthermore, MRH histiocytes show osteoclast-like characteristics that contribute to bone destruction [177]. Near a quarter of MFH cases are associated with neoplasia, but the two diseases do not necessarily follow a parallel course [178]. Autoimmune diseases have also been reported in association with MRH [179]. Spontaneous resolution occurs after an average of 8 years, but the diagnosis must be quickly established and aggressive therapy promptly initiated to prevent irreversible articular damage [180].

Microscopically, skin lesions are nodular and dermal-based but may spread to the subcutaneous tissue. The infiltrate is made up of large histiocytes, many of them multinucleated, with abundant pale or eosinophilic ground-glass cytoplasm and occasional fibrosis and xanthomization (Fig. 11.35) [181, 182]. T lymphocytes and neutrophils may also be present. An abundant accompanying population of dermal dendrocytes is identified in some cases. Additionally, an identical histological appearance is present in polyarthritis-related synovial membranes and in rarely involved internal organs [168, 169].

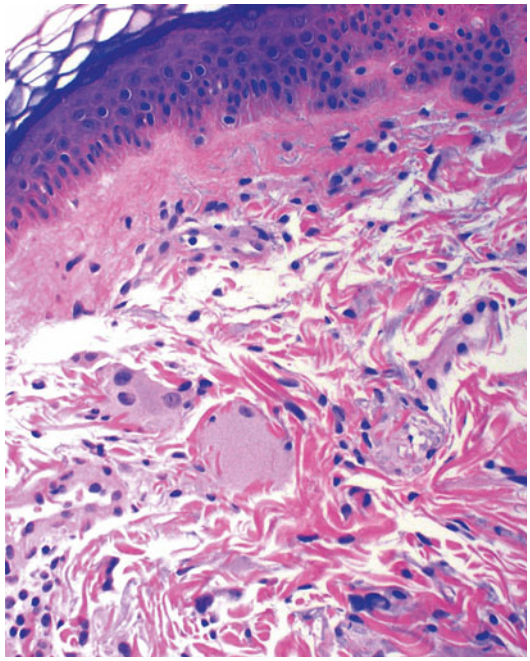


Fig. 11.35 Large multinucleated histiocytes with eosinophilic cytoplasm are scattered in the dermis in a case of multicentric reticulohistiocytosis

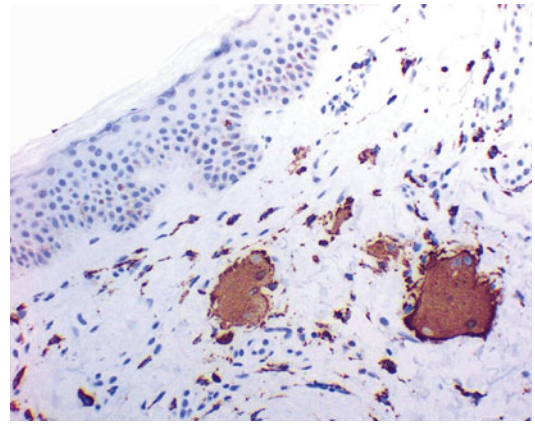


Fig. 11.36 Multicentric reticulohistiocytosis with CD68 KP1 positive cells

Immunohistochemistry

Immunohistohemically, cells express CD68 (KP1 and PGM1) (Fig. 11.36), CD163 and other histiocytic markers, as well as vimentin. Rare cases are S100-protein positive [183] or show light Factor XIIIa expression [184]. More often, positivity for these markers is due to a population of Langerhans cells and dermal dendrocytes, respectively. CD10 has been found to be positive in one case [185] and p53 in two cases associated with urological neoplasms [186]. MRH is consistently negative for both CD1a and CD34.

Molecular Biology

MRH is a non-neoplastic histiocytic proliferation caused by immunological dysregulation that may heal spontaneously. Cytogenetic alterations or clonality have never been described in the infiltrate [173–179].

Differential Diagnosis

At the initial stages, MRH shows clinical resemblance to rheumatic diseases such as rheumatoid arthritis [187], fibroblastic rheumatism [188] or dermatomyositis [189, 190]. MRH intense and rapid articular damage, much more aggressive than in other rheumatological diseases, is a clue to the diagnosis. Nevertheless, an etiopathogenic pathway common to other rheumatological diseases cannot be excluded [179]. Cytological study of the synovial fluid is a quick and easy method [191] for obtaining the correct diagnosis, thus avoiding treatment delays. Nevertheless, in some cases a biopsy of the cutaneous or synovial lesions will be necessary.

Clues and Pitfalls

- MRH is a multisystemic disorder in which the presence of extracutaneous symptoms is the best clue to recognize the disease, since cutaneous lesions may be rather inconspicuous.
- A biopsy of an extracutaneous location demonstrating a histiocytic infiltrate that shares the immunophenotype and microscopical appearance of the cutaneous infiltrate is a highly specific method to confirm the diagnosis.
- S100-protein positive MRH cases could be unawarely misdiagnosed as LCH but their CD1a negativity allows to rule out LCH.

Solitary Reticulohistiocytoma (Solitary Epithelioid Histiocytoma)

Solitary lesions with a microscopic and immunohistochemical appearance similar to MRH lesions

have been denominated solitary reticulohistiocytoma (SRH) [181, 182, 192] or solitary epithelioid histiocytoma [182]. In spite of these immunophenotypical similarities, there are many differences that have led to the conclusion that they are distinct entities. Whereas SRH occurs more frequent in young adults with a slight predominance in males, MRH is more common in middle-aged females. In addition, SRH does not usually involve the face or digits, which are the most typical locations of MRH [181, 182].

Ganglion-like histiocytes with finely granular and eosinophilic cytoplasm are the hallmark of SRH and MRH, but whereas in SRH they are the main component of the infiltrate, in MRH there is more fibrosis and xanthomization (Fig. 11.37). Besides, some cases of SRH with granular cell change have been described [192, 193].

Immunohistochemistry

The immunohistochemical profile of SRH does not differ from that of MRH. The large epithelioid histiocytes are positive for vimentin and histiocytic markers such as CD68 KP1 and PGM1 (Fig. 11.38) and CD163. Factor XIIIa and S-100 protein (Fig. 11.39) may be focally expressed, but widespread expression of these markers militates against the diagnosis of SRH. Expression of CD45 is also variable, whereas CD1a, CD3, CD20, CD30, and CD34 are consistently negative. T lymphocytes and neutrophils may be abundant [181, 182, 193, 194].

Molecular Biology

Clonal rearrangement of the anaplastic lymphoma kinase (*ALK*) gene resulting in VCL-ALK and SQSTM1-ALK gene fusions has been reported in a case of SRH [195]. This finding has been interpreted as an additional argument in favor of considering this lesion as a neoplastic process.

Differential Diagnosis

Juvenile xanthogranuloma (JXG) and Rosai-Dorfman disease (RDD) may cause problems in

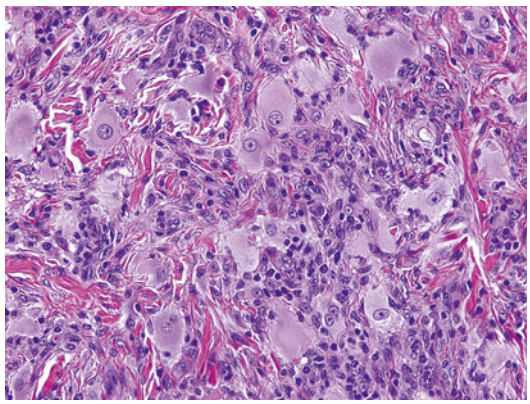


Fig. 11.37 Solitary reticulohistiocytoma with large multinucleated cells exhibiting ganglion-like features, in a background of lymphocytes, mononucleated histiocytes and dense collagen

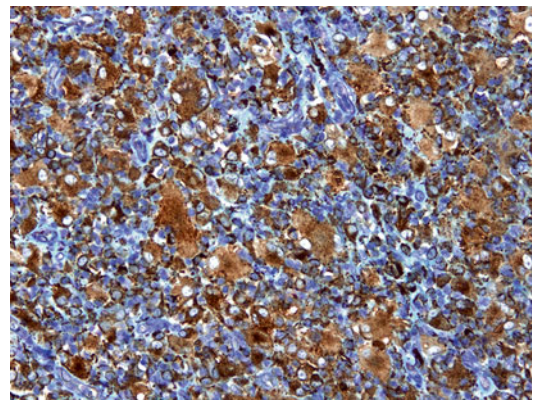


Fig. 11.38 CD68 PGM1 immunoreactivity decorates both the large histiocytes typical of solitary reticulohistiocytoma and the mononucleated cells

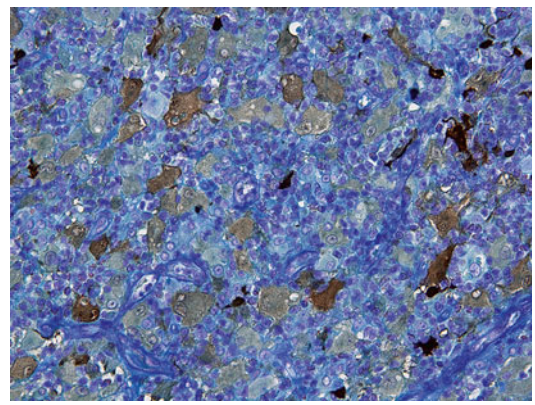


Fig. 11.39 Large histiocytes in solitary reticulohistiocytoma may show some positivity for S100 protein

SRH differential diagnosis. Nevertheless, the associated inflammatory infiltrate, microscopical characteristics of histiocytes and their immunophenotype provide definite clues for their distinction. Unlike what happens in SRH, JXG frequently contains eosinophils but neutrophils are rare. JXG may show histiocytes with large cytoplasms, but they tend to show xanthomization and factor XIIIa positivity. As for RDD, the infiltrate usually contains many plasma cells and large histiocytes, but they show emperipolesis and strong positivity for S100 protein. The latter, if present in SRH, is only focal.

SRH may also resemble melanoma and Spitz tumor. The presence of focal positivity for S100 protein and microphthalmia transcription factor (MITF) in some SRH instances [196] makes these two markers inadequate for this differential diagnosis, that should rely on a panel of antibodies including histiocytic markers such as CD68 and melanocytic markers such as Melan A.

SRH cases, especially those with a polypoid silhouette and granular cytoplasm, may simulate granular cell tumors. Their distinction from primitive polypoid granular-cell tumor is particularly difficult [193, 194].

Clues and Pitfalls

- When considering the diagnosis of SRH, pay attention to the associated inflammatory infiltrate. Consider the possibility of JXG if eosinophils are predominant or RDD whenever the plasma cell infiltrate in abundant. Look at the cytoplasm of large histiocytes, whose xanthomization points to JXG, whereas the presence of intact inflammatory cells (emperipolesis) makes RDD the first option.
- SRH may present focal and/or weak S100 protein positivity, a finding potentially leading to the wrong diagnosis of RDD or melanocytic lesion.
- Since SRH may focally express S100 protein and MITF, Use of a panel of histiocytic and melanocytic markers (other than those mentioned) is advisable when confronted with any supposed melanocytic lesion showing predominance of large cells with eosinophilic cytoplasm.

Rosai-Dorfman Disease

Rosai-Dorfman disease (RDD) is a non-neoplastic proliferative histiocytic disorder of unknown etiology. RDD was originally described in lymph nodes with the name of sinus histiocytosis with massive lymphadenopathy [197] due to the large-sized adenopathies shown by these patients, particularly in the cervical and submandibular regions. For many years extranodal involvement has been considered a rare event [198], but quite probably its real incidence has been underestimated due to unawareness. The number of extranodal cases, most of them cutaneous, has increased notably as diagnostic accuracy has improved, to the point that extranodal cases outnumbered nodal forms in a recent series [199].

Cutaneous RDD may occur in any age group, but whereas nodal cases are more common in young males of African origin, cutaneous RDD tends to appear in middle-aged white women [198, 200]. There are reports of RDD cases associated with lymphoproliferative disorders and histiocytosis [201, 203], viral infections (Epstein-Barr virus, human herpes virus 6, parvovirus B19, and polyomavirus) [204, 205] and Crohn's disease [206].

The relationship between RDD with IgG4-related disease (IgG4-RD) is not well established. Both entities share microscopical features and many cases of RDD show increased numbers of IgG4-positive cells (>40 % IgG4/IgG-positive cells after averaging three high-power fields) [207–209]. Nevertheless, it is not clear whether IgG4 antibodies have a truly significant role in the pathogenesis of these diseases. Conversely, the T helper cells present in the infiltrate seem to be better candidates as key agents of tissue damage [207, 209].

Clinically, RDD cutaneous lesions often are papules or nodules with orange or erythematous discoloration that may involve any location but seem to be more common on the upper part of the body [200, 210].

The microscopic appearance of nodal and extranodal RDD is quite similar [200] and consists of a nonclonal proliferation of large histiocytes with abundant pale cytoplasm. Typically,

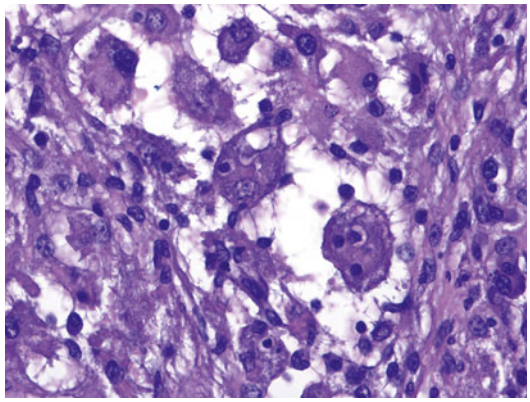


Fig. 11.40 The presence of large histiocytes with intact lymphocytes and neutrophils, a phenomenon known as emperipolesis, is a typical feature of Rosai Dorfman disease

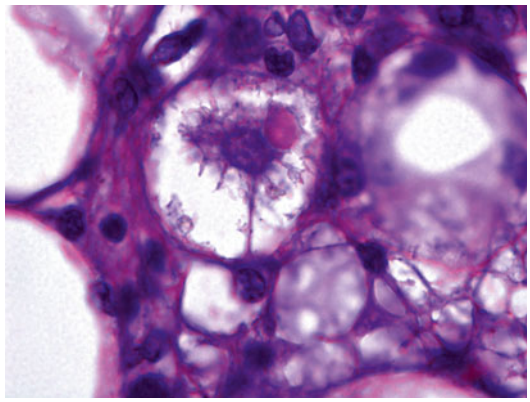


Fig. 11.41 Small eosinophilic inclusions in the cytoplasm of histiocytes from Rosai-Dorfman disease, simulating a viral infection

the cytoplasms of many histiocytes contain intact lymphocytes or neutrophils, a phenomenon known as emperipolesis (Fig. 11.40) [211]. Small granular pink cytoplasmic inclusions and nuclear viral-like changes can also be observed (Fig. 11.41) [206]. An inflammatory background of mature lymphocytes, plasma cells, and occasional eosinophils accompanies the histiocytic proliferation, often forming aggregates that provide RDD extranodal lesions an appearance reminiscent of a lymph node with sinus histiocytosis (Fig. 11.42a). A variable degree of stromal fibrosis with a storiform or lobulated pattern is often present [210].

The clinical course of RDD is unpredictable. Although the evolution in most cases is indolent and self-limited, fatal cases do exist [212]. Patients with severe and widespread forms, refractory to the usual therapeutic approaches, may require potent treatments [213].

Immunohistochemistry

Immunohistochemically, the proliferating histiocytes typically show intense S100-protein expression (Figs. 11.42b and 11.43). CD68 (KP1 and PGM1), (Figs. 11.42c and 11.44), CD163 and vimentin are also positive, although their intensity is more variable [200]. Some mesenchymal markers associated with the epithelial mesenchymal transition, such as β-catenin, N-cadherin, fibronectin, and Slig, have also been found to be positive [214]. Coexpression of histiocytic and mesenchymal markers in proliferating cells has led to speculate whether RDD might be considered a histiocytic mesenchymal transition disorder [214]. In one case, expression of p53, p16, and PTEN was also found [214], whereas CD1is consistently negative [200, 214].

The histiocytic proliferation is usually accompanied by a prominent lymphoplasmacytic infiltrate containing a mixed population of CD20-positive B lymphocytes and CD3-positive T lymphocytes.

Molecular Pathology

Genomic analysis have failed to demonstrate any significant mutation in the serum or the tissues involved [137, 214].

Differential Diagnosis

Lymphoproliferative disorders, histiocytosis, and autoimmune diseases (including IgG4-RD) constitute the main differential diagnosis. Actually, RDD may coexist, follow or precede various lymphoma types [201, 202]. A complete immunohistochemical profiling of the infiltrates allows to tell them apart.

S100 protein expression in RDD giant cells permits ruling out JXG, whereas RDD negativity

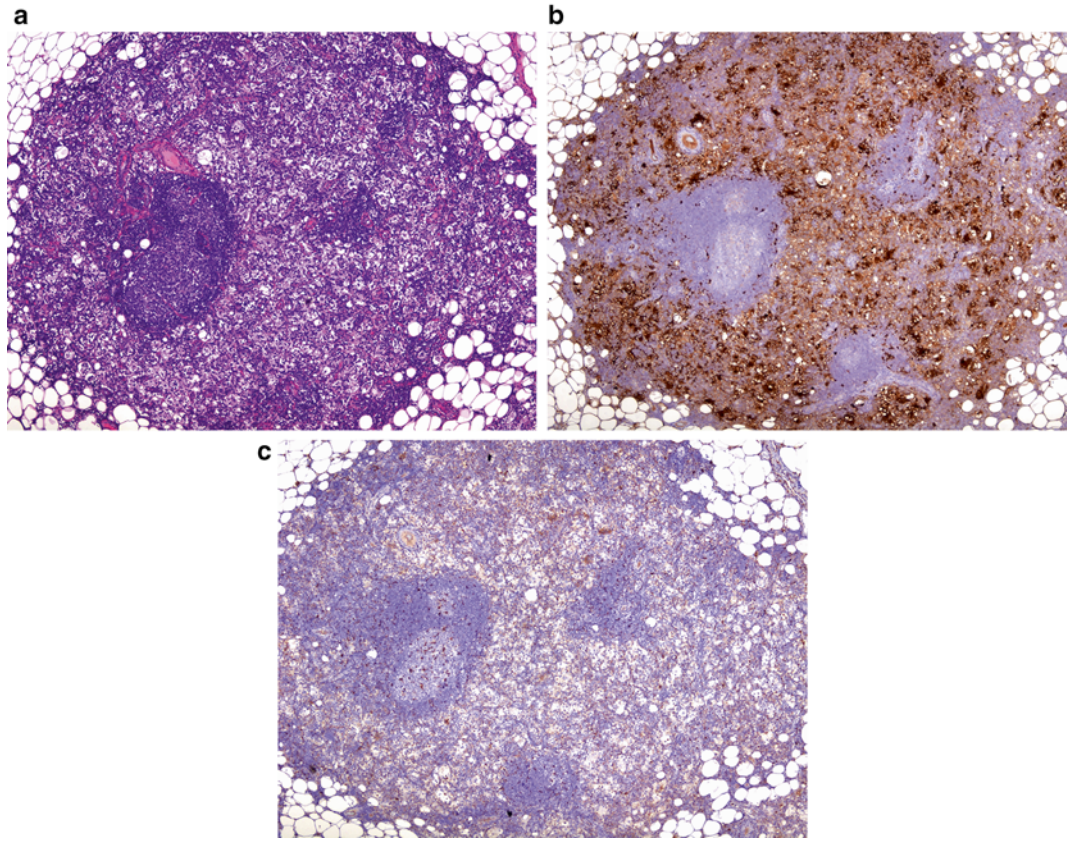


Fig. 11.42 (**a**) Nodular aggregate of histiocytes surrounding aggregates of lymphocytes containing germinal centers. The whole image of the infiltrate in this case of Rosai-Dorfman disease is reminiscent of a lymph node with massive sinus histiocytosis. Nevertheless, the infiltrate is located in the subcutaneous tissue, far from any lymph node. (**b**) Intense positivity for S100 in the histiocytic proliferation (**c**) Moderate CD68 PGM1 expression in the histiocytic proliferation

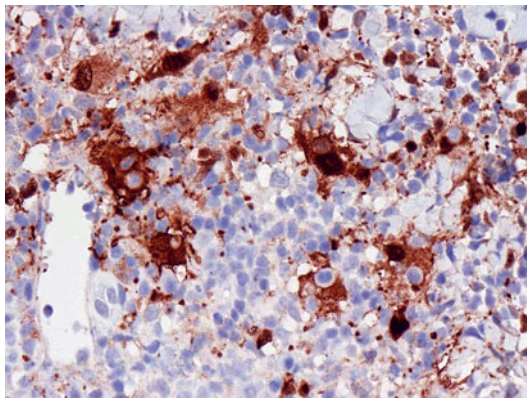


Fig. 11.43 Immunostaining for S100 highlights the phenomenon of emperipolesis, typical of Rosai-Dorfman disease, which appears in the form of nonstained cytoplasmic dots

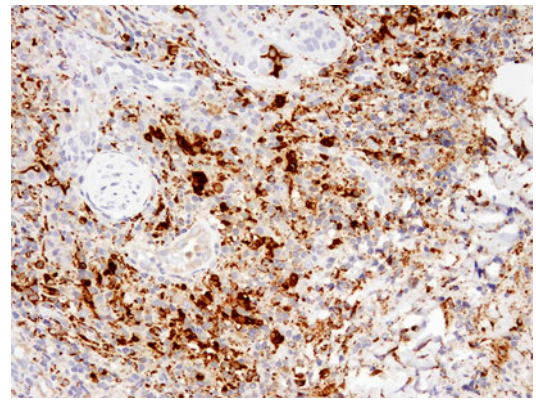


Fig. 11.44 Rosai-Dorfman disease with CD68 (PGM1)-positive histiocytic infiltrate among sweat glands

for CD1a and langerin contributes to the distinction from Langerhans cell histiocytosis (LCH). Nevertheless, there are exceptional reports of the coexistence of both histiocytosis [202].

Autoimmune disorders such as lupus erythematosus may produce dense inflammatory infiltrates, usually with lymphocytic predominance, but they rarely contain a prominent histiocytic infiltrate. IgG4-RD may exhibit an inflammatory infiltrate similar to RDD, but lacks the characteristic S100 protein-positive histiocytes with emperipolesis. Only the nodal and dermal infiltrates of H syndrome may display a microscopic and immunophenotypic appearance identical to RDD [20–22]. H syndrome is an autosomal recessive disorder with marked clinical variability. Patients with H syndrome often show low height, phalangeal flexion contractures, hearing loss, and hyperpigmented hypertrichotic cutaneous plaques [215–217]. Other systemic manifestations are hepatosplenomegaly, heart anomalies, hypogonadism, and hyperglycemia.

H syndrome is caused by the *SLC29A3* gene mutation, which results in alterations of hENT3, a member of the human equilibrative nucleoside transporter family [216]. The same mutation has been described in Faisalabad histiocytosis, also known as familial RDD, but has never been identified in sporadic cases of RDD [214].

Clues and Pitfalls

- The presence of emperipolesis with well-preserved granulocytes and some lymphocytes in the cytoplasm of proliferating histiocytes may be difficult to recognize using hematoxylin-eosin stainings, but it can be highlighted using S100 protein immunostaining, that shows nonstained dots corresponding to the internalized cells (Fig. 11.43).
- Conversely, the inflammatory cells internalized in the cytoplasm of histiocytes may be underlined with the aid of CD20, CD3, or myeloperoxidase antibodies.
- The deeply eosinophilic inclusions present in the cytoplasm of some histiocytes (Fig. 11.41) may be misinterpreted as viral infections. Immunostaining with antibodies specific for CMV and other herpes viruses may help to rule out this possibility.

Cutaneous Kikuchi-Fujimoto Disease

Kikuchi-Fujimoto Disease (KFD), first described in 1972 and also known as histiocytic necrotizing lymphadenitis, is a rare lymphohistiocytic disorder of unknown pathogenesis [218]. It affects predominantly young adults, especially females of Asian descent. Patients often present with cervical lymphadenopathy, fever, and leukopenia, usually with spontaneous resolution in 1–4 months [219]. Several viruses, including HHV6, HHV8, Epstein-Barr virus, HTLV-1, and cytomegalovirus, have been incriminated in the pathogenesis of KFD, but the results of different studies have been contradictory [220].

Cutaneous involvement occurs in 4–14% of KFD patients [219, 221, 222]. Cutaneous lesions are nonspecific, most frequently in the form of rash or erythematous macules or papules, although atypical presentations have also been described [223].

Histologically, there are superficial and deep perivascular infiltrates of lymphocytes and histiocytes with lichenoid reaction, basal vacuolar change, and necrotic keratinocytes. Extension to the subcutis is common. Non-neutrophilic karyorrhectic debris, often phagocytosed by histiocytic cells, are frequent. Scattered plasma cells and eosinophils must be seen, but neutrophils are not present [223, 224]. KFD diagnostic criteria have been proposed on the basis of these microscopic findings [224].

Lymph nodes may show three histopathological images, probably representing different stages of disease progression [225]. In the most frequent necrotizing type, there is karyorrhectic necrosis in the paracortex with hystiocytes, plasmacytoid dendritic cells, and T lymphocytes, while neutrophils are absent (Figs. 11.45, 11.46, 11.47, and 11.48).

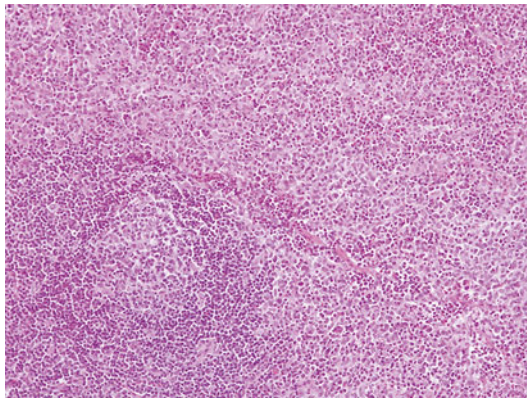


Fig. 11.45 Lymph node with Kikuchi-Fujimoto, disease showing parafollicular expansion with karyorrhectic necrosis (*upper-right* corner) and a reactive germinal center (Hematoxilin-eosin; 100×)

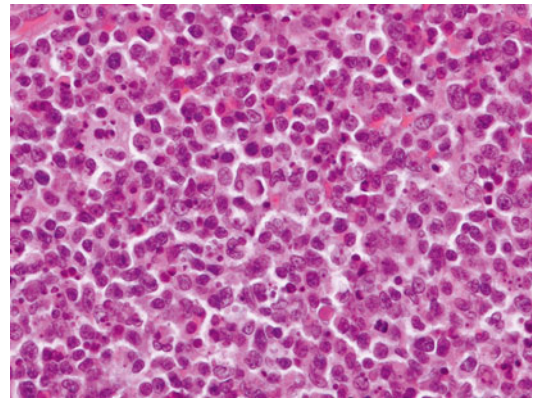


Fig. 11.47 Kikuchi-Fujimoto disease. High-power view showing karyorrhectic debris admixed with histiocytes, plasmacytoid dendritic cells and T lymphocytes, without neutrophils (Hematoxilin-eosin; 400×)

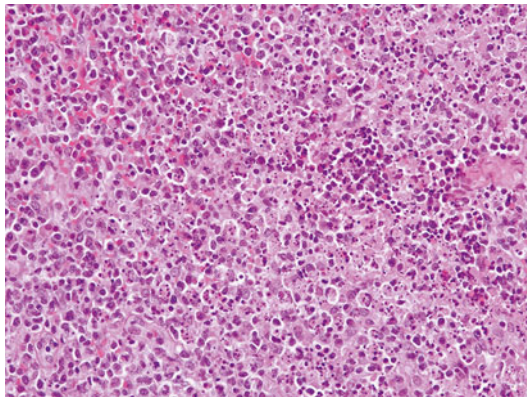


Fig. 11.46 Kikuchi-Fujimoto disease. Panoramic view of a Karyorrhectic necrotic focus (Hematoxilin-eosin; 200×)

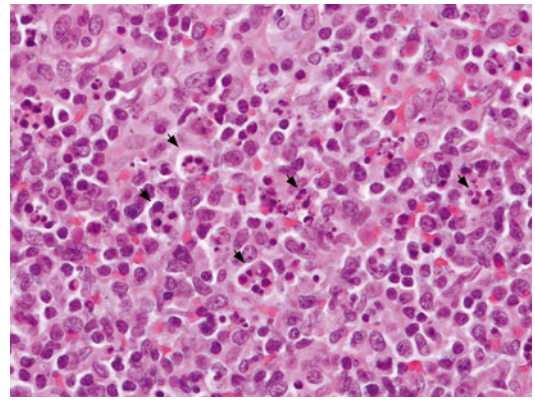


Fig. 11.48 Kikuchi-Fujimoto disease. Macrophages with phagosized karyorrhectic debris can be seen (Hematoxilin-eosin; 400×)

Immunohistochemistry

The infiltrate is composed of a mixture of hystiocityc cells (CD68+, CD4+,CD163+, myeloperoxidase+), plasmacytoid dendritic cells (CD68+, CD4+, CD123+, BDCA2+), and T lymphocytes (CD3+, with CD8+ cells outnumbering CD4+ cells) [224, 226, 227].

Molecular Biology

The molecular mechanisms that underlie KFD are largely unknown. A study based on gene-expression profiling (GEP) found upregulation of apoptosis-associated genes and downregulation of apoptosis-inhibitory genes compared to non-specific lymphadenitis [228]. Another GEP-based study found upregulation of interferon-induced genes both in lymph node and peripheral blood mononuclear cells of KFD [229]. A t(2:16) has been reported in a single case [230].

Differential Diagnosis

KFD must be differentiated from systemic lupus erythematosus (SLE), since both conditions may present with fever, lymphadenopathy, and cutaneous lesions. From a pathological point of view, in both KFD and SLE there is interface dermatitis with basal vacuolar change and apoptotic keratinocytes. The presence of abundant plasma cells

and granular deposition of IgG, IgM, and IgA at the dermoepidermal junction favors SLE, whereas the observation of non-neutrophilic karyorrhectic debris favors KFD. Clinicopathological correlation, ANA screening, and long-term follow-up is encouraged to exclude SLE [222–224].

In some cases, differential diagnosis may also include panniculitis-like T-cell lymphoma (PTL), pityriasis lichenoides et varioliformis acuta (PLEVA) or erythema multiforme [224].

Clues and Pitfalls

- Always consider KFD in a cutaneous lymphohistiocytic infiltrate with interface damage, basal vacuolar change, and non-neutrophilic karyorrhectic debris.
- Clinical evaluation, ANA screening, and follow-up are mandatory in order to exclude SLE.

Cutaneous Intralymphatic Histiocytosis

Cutaneous intralymphatic histiocytosis (ILH) is a rare benign disorder characterized by dilated lymphatic vessels containing aggregates of mononuclear histiocytes (Fig. 11.49) [231, 232]. In most cases only the reticular dermis is involved. The inflammatory response in the adjacent dermis is usually scarce. Occasionally, granulomatous [233] or dense lymphocytic infiltrates forming follicles, abundant plasma cells or intense edema may be present [232]. ILH was initially described in relation to rheumatoid arthritis [234] and this seems to be the most common association, but ILH may also overly surgical scars [231] or orthopedic metal implants [235] or may be associated with neoplasia (breast cancer [231], Merkel cell carcinoma [231] and colon carcinoma) [236]. Cases of primary ILH, without any recognizable association, may also occur [232]. A single ILH case of the oral mucosa in a patient with multiple dental gold crowns simulating a lymphangioma circumscriptum has also been described [237].

Clinically, non-tender, poorly demarcated, erythematous lesions form patches, plaques, or nodules, sometimes with pseudovesicles or livedo reticularis-like features. These lesions are usually located in the extremities and tend to overlie the inflamed joints in patients with rheumatoid arthritis. Lesions associated with joint prosthesis are also close to the articulation [231].

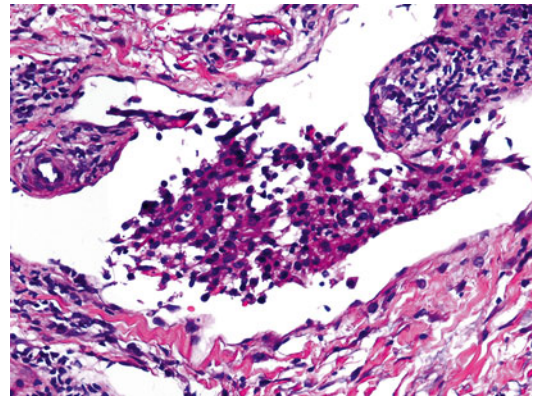


Fig. 11.49 Lymphatic vessel containing compact aggregate of histiocytes (courtesy of Dr. L. Requena, Dept. of Dermatology, Fundación Jiménez Díaz, Madrid, Spain)

IJH is a benign reactive condition, but its exact pathogenesis is unknown. For some authors this could be considered the early stage of intravascular reactive angioendotheliomatosis [231, 238] or the consequence of local lymphatic damage or obstruction [231]. A recent hypothesis links ILH to the concept of the immunocompromised district [239], according to which a lesion develops at a cutaneous site that has been immune-marked by a previous clinical event. The local immune response would make this area especially susceptible to subsequent episodes of opportunistic infections, tumors, and immune disorders [240].

Immunohistochemistry

The immunohistochemical profile of ILH reflects, on the one hand, the histiocytic nature of the intravascular cells, which are positive for CD68 KP1 and PGM1 (Fig. 11.50), CD163 and CD31 and show variable positivity for myeloperoxidase, CD31, and podoplanin [231, 232]. On the other hand, vascular structures express markers characteristic of lymphatic endothelial cells such as podoplanin (Fig. 11.51), CD31, CD34, D2-40, Lyve-1, and Prox-1 [231, 232].

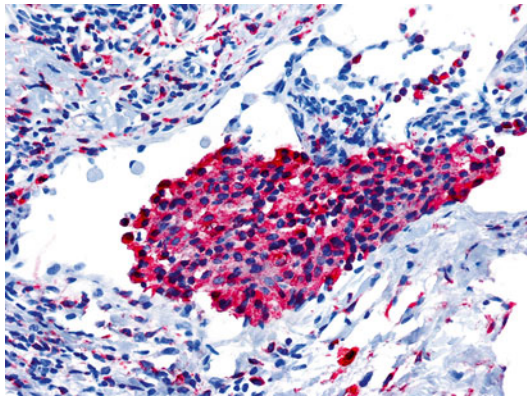


Fig. 11.50 Histiocytes present in the lumen of lymphatic vessels showing intense expression of CD68 PGM1 (courtesy of Dr. L. Requena, Dept. of Dermatology, Fundación Jiménez Díaz, Madrid, Spain)

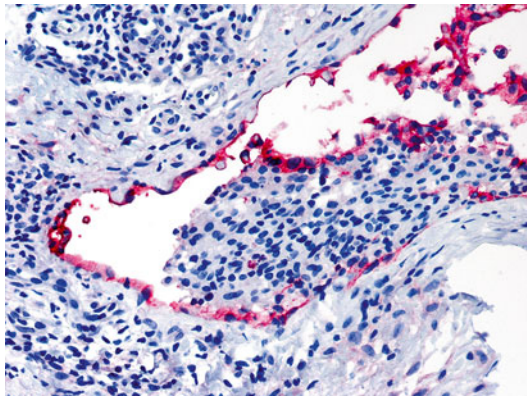


Fig. 11.51 Vessels walls in intralymphatic histiocytosis are typically positive for podoplanin. This antibody is also expressed in the cytoplasm of some histiocytic cells (courtesy of Dr. L. Requena, Dept. of Dermatology, Fundación Jiménez Díaz, Madrid, Spain)

Differential Diagnosis

The sole presence of dilated lymphatic vessels containing histiocytes in a focal area cannot be considered bona fide ILH, since it may be observed in many common dermatoses [241]. For instance, this finding may be present in contact dermatitis (Fig. 11.52), cheilitis granulomatosa, or RDD [241].

Two cases of necrotic genital lesions with intravascular histiocytosis (IVH) have been reported, but the changes involved blood vessels in which lymphatic markers were shown to be negative. One of these cases involved the scrotum of a young man with associated tonsillitis [242] and the other the vulva of an elderly woman [243] with lupus anticoagulant and elevated anticardiolipin antibodies. In both instances, the phenomenon was probably secondary to thrombogenic diathesis associated with a hypercoagulability state.

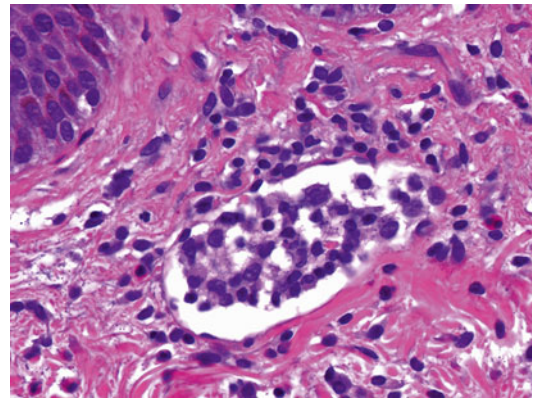


Fig. 11.52 Accumulation of histiocytes inside a lymphatic vessel at the base of an area of contact dermatitis (courtesy of Dr. L. Requena, Dept. of Dermatology, Fundación Jiménez Díaz, Madrid, Spain)

Reactive endotheliomatosis [244] and intravascular lymphomas [245] may also simulate IVH but in the first case the intravascular proliferation consist of endothelial cells and in the second case of lymphocytes, usually B-cells. Benign atypical intravascular CD30+ T-cell proliferation, a mimicker of intravascular lymphoma [246], may also be included in this differential diagnosis. An immunohistochemical study may easily demonstrate the absence of histiocytic markers in the intravascular cells of these lesions and the expression of the endothelial or lymphoid markers characteristic of each of them.

Clues and Pitfalls

- Not all intravascular accumulations of histiocytoid cells correspond to cutaneous ILH. Clinicopathological correlation may provide some clues to the nature of the lesion. A location overlying an orthopedic metal implant favors ILH.
- Conversely, the presence of large cells within hemangioma vessels is more probably a

benign intravascular CD30-positive proliferation or an intravascular lymphoma [247].

- The coexistence of intravascular histiocytosis and intravascular reactive angioendotheliomatosis has been reported. To confirm this rare association it is necessary to characterize endothelial cells with immunohistochemical markers other than CD31. The latter's positivity in histiocytic cells does not allow discrimination between the two differentiation lineages [248].
- In contrast to intralymphatic histiocytosis, the incidental accumulation of histiocytes inside a lymphatic vessel in the setting of inflammatory dermatosis is limited to one or very few vessels and shows the presence of an inflammatory infiltrate in the adjacent dermis.

Histiocytic Sarcoma

Histiocytic sarcoma (HS) is an aggressive and extremely rare neoplasm that may present at any age, although cases tend to cluster in two groups (0–29 and 50–69 years) [249, 250]. Lymph node involvement is frequent but extranodal involvement (gastrointestinal tract, spleen, soft tissue, or skin) is even more common. Tumor cells show morphologic and immunophenotypic features characteristic of histiocytes. In the skin, HS presents as either solitary or multiple tumors of the trunk and limbs. In cases suspicious for HS, it is mandatory to rule out other aggressive neoplasms with the aid of a broad immunohistochemical panel [249, 251, 252]. In fact, the diagnosis of HS requires exclusion of other conditions that are much more common [249].

Histologically, HS shows a diffuse, noncohesive growth of large round or oval cells that focally may adopt a sarcomatoid appearance. Cytoplasms usually are wide and eosinophilic and tend to be vacuolated. Images of hemophagocytosis may be present. Tumor cell nuclei are round or oval, often large, atypical and eccentric, with vesicular chromatin and variably sized nucleoli. Binucleation or multinucleation is common and high mitotic activity is frequently seen (Fig. 11.53) [51, 249, 253].

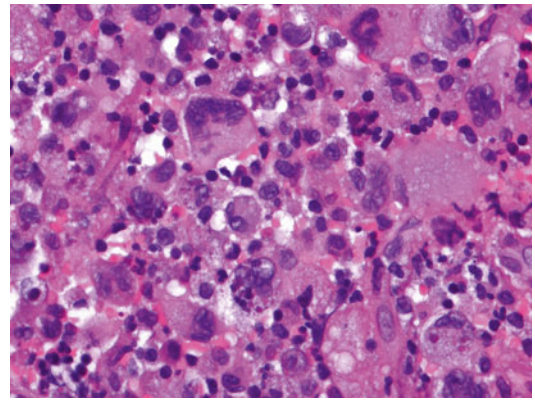


Fig. 11.53 Histiocytic sarcoma. Multinucleated neoplastic cells with abundant cytoplasm and nuclear atypia

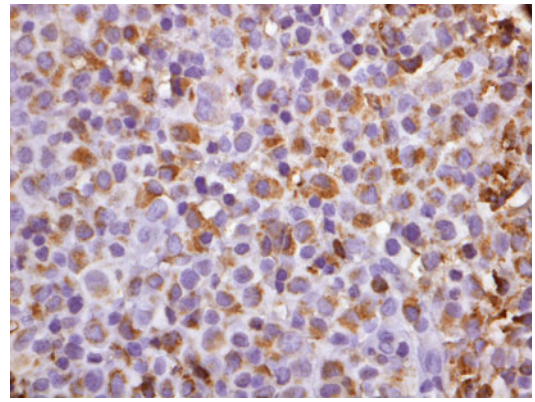


Fig. 11.54 Histiocytic sarcoma. Granular cytoplasmic immunoreactivity for CD68 in neoplastic cells

Immunohistochemistry

It is mandatory that neoplastic cells express some histiocytic markers in conjunction with their negativity for other tumor markers. The histiocytic markers more commonly used are CD163, CD68 (KP1 and PG-M1), and lysozyme. CD163 (Fig. 11.54), which shows plasma membrane and cytoplasmic positivity, is considered more specific than CD68 [254–256]. Granular cytoplasmic expression of CD68 is very reproducible, but may be found in melanoma, carcinoma, lymphoma, and dendritic cell tumor as well.

The immunohistochemical study should demonstrate negativity for Langerhans cells (CD1a and langerin), follicular dendritic cells (CD21 and CD35), myeloid cells (CD33, CD13, and myeloperoxidase), melanoma (HMB-45 and

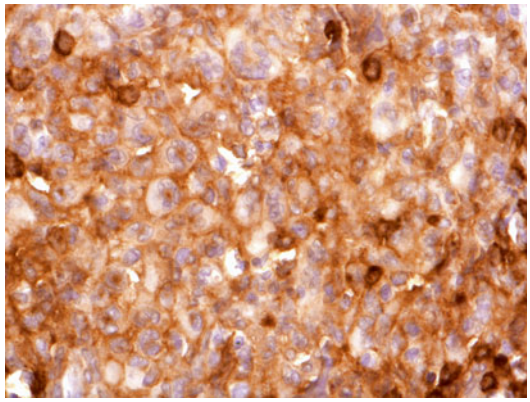


Fig. 11.55 Histiocytic sarcoma. Tumor cells are weakly positive for CD4. Follicular dendritic cell sarcoma and interdigitating dendritic cell sarcoma

Melan A) and epithelial cell (cytokeratins and EMA). Specific markers for B-cell and T-cell lymphomas should be negative. CD30 immunoreactivity has to be equally negative. In contrast, S-100 protein, CD15, and CD1a may show some positivity, while CD4, CD45, CD45RO, and HLA-DR are commonly positive (Fig. 11.55) [51, 249, 250].

Molecular Biology

IgH or *TCR* rearrangements have been detected in some HS cases. These findings have been interpreted as transdifferentiation phenomena taking place in a previous or simultaneous B-cell or T-cell lymphoma. Indeed, several HS instances associated with previous or synchronic B-cell or T-cell lymphoblastic lymphoma or low grade B-cell lymphoma have been reported. Interestingly, in these cases HS and lymphoma share a clonality feature such as a *IgH, IGK* or *TCR* rearrangement, or a t(14:18) or t(11:14) translocation. This genetic connection with a well-characterized lymphoproliferative disease does not preclude the diagnosis of HS [257–263].

Recently, BRAF(V600E) mutations have been reported in over 60 % of HS cases [5]. Nevertheless, it should be kept in mind that these mutations have also been described in Langerhans cell tumors and dendritic cell sarcomas. Additional studies are necessary to evaluate the diagnostic role of these alterations and their potential to serve as predictors of therapeutic response to specific inhibitors [264].

Differential Diagnosis

HS differential diagnosis should be carried out with aggressive hematologic conditions such as diffuse large B-cell lymphoma, peripheral T-cell lymphoma, and anaplastic large cell lymphoma. Therefore, the immunohistochemical assessment should include B-cell and T-cell markers, CD30, and ALK-1 [249, 250, 265].

Equally important is to rule out poorly differentiated carcinoma and melanoma. In this regard, it should be remembered that CD68 expression may be present in both melanoma and carcinoma and, on the other hand, keratin expression may be absent in poorly differentiated carcinoma. In some cases, a generous sampling of the lesion is sufficient to identify with certainty focal histologic features characteristic of carcinoma [51, 249, 250, 253].

Langerhans cell histiocytosis has to be ruled out by demonstrating negativity for CD1a and, particularly, for langerin. Follicular dendritic cell sarcoma is easier to rule out, since follicular dendritic cell markers are negative in HS. In contrast, interdigitating dendritic cell sarcoma poses more differential diagnostic difficulties due to the fact that, as HS, it may be positive for both S-100 protein and CD68 [51, 249, 250, 253].

Clues and Pitfalls

- Positivity for histiocytic markers such as CD68 is not sufficient to establish the diagnosis of HS. It is mandatory to rule out the diagnosis of other aggressive neoplasms such as lymphoma, carcinoma, and melanoma.
- Although they are not diagnostically useful, CD15 and S100 protein may be focally positive in HS.
- Detection of *IgH* or *TCR* rearrangements does not preclude the diagnosis of HS. Nonetheless, the presence of an aggressive lymphoma should always be ruled out by using the appropriate immunohistochemical panel.
- In HS cases associated with lymphoma, the demonstration of shared clonality with the aid of molecular techniques is of interest.
- HS may show BRAF(V600E) mutations.

Follicular Dendritic Cell Sarcoma and Interdigitating Dendritic Cell Sarcoma

Introduction

Follicular dendritic cells (FDCs), whose origin is mesenchymal, are found in normal lymph node germinal centers, where they play an important role in the development of the immune response. Normal interdigitating dendritic cells (IDCs) are antigen-processing cells located in the paracortical T-cell zone of lymph nodes. Unlike FDCs, and similarly to Langerhans cells and histiocytes, IDCs arise from bone marrow precursor cells. Therefore, FDCs and IDCs are characterized by different immunophenotypes [266–268].

Follicular dendritic cell sarcoma (FDCS)is a rare tumor resulting from the transformation of FDCs. FDCS usually presents in adults as slowly growing tumor lesions involving cervical or abdominal lymph nodes, although extranodal sites such as the oral cavity, gastrointestinal tract, skin, mediastinum, liver, and spleen have also been described. Castleman disease may precede o coincide with FDCS. Paraneoplastic associations of FDCS with myasthenia gravis and pemphigus have been observed [269–273].

Histologically, FDCS shows moderately atypical cells that form fascicles, diffuse sheets, storiform arrays, or ill-defined nodules. Tumor cells reveal oval or elongated nuclei, vesicular or finely dispersed chromatin, and thin nuclear membranes (Fig. 11.56). Binucleated or multinucleated cells may be seen. Significant cytologic atypia, a high mitotic index, and necrosis are occasionally identified as well. Some cases show lymphoid infiltrates arranged in perivascular nests [269, 272, 274].

Interdigitating dendritic cell sarcoma (IDCS) is even rarer than FDCS. IDCS is usually seen in adults but may also arise in children. Commonly, it is a solitary lesion confined to lymph nodes, although disseminated cases have been described. Extranodal locations of IDCS include the skin, kidney, breast, lung, urinary bladder, and genitalia. Some IDCS instances associated with lymphoma have been reported [106, 274].

Histologically, IDCS may be very similar in appearance to FDCS. IDCS form fascicles and may exhibit a storiform pattern. Tumor cells

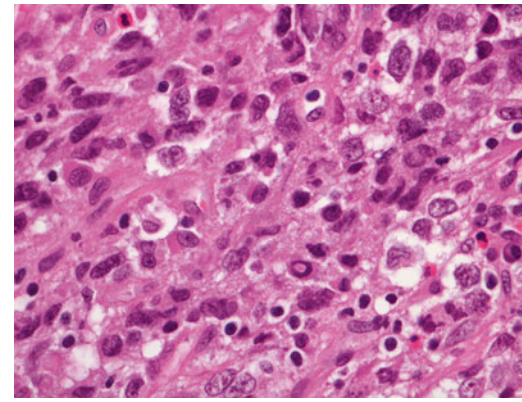


Fig. 11.56 Follicular dendritic cell sarcoma. Atypical spindle cell proliferation with some nuclear pseudoinclusions

show fusiform or ovoid indented nuclei, slightly eosinophilic abundant cytoplasm, and ill-defined cell borders. Multinucleated cells may be present and associated lymphoid infiltrates are commonly observed. Images of emperipolesis may also be present [106, 274].

Immunohistochemistry

FDCS usually shows immunopositivity for .several FDC markers (CD21, CD23, CD35, KIM4p, and CNA.42) (Figs. 11.57 and 11.58). Clusterin. is positive, often strongly so, whereas plasma membrane positivity for D2-40 is also very helpful. Additionally, positive immunoreactivity for CD4, CD20, CD45, CD68, EMA, S-100 protein, epithelial membrane antigen, fascin, and vimentin has been described in FDCS. In contrast, CD1a, langerin, CD3, CD34, CD79a, and HMB45 are negative [269, 272, 275–277].

As for IDCS, it is negative for FDC markers (CD21, CD23, and CD35), while S-100 protein, vimentin, and fascin are positive. With few exceptions CD1a and langerin are negative in IDCS. On the other hand, there is positivity for markers such as CD4, CD45, CD68, CD11c, CD14, and epithelial membrane antigen. The associated lymphoid infiltrate is mostly composed of T cells [106, 275, 277].

Molecular Biology

There is no IGH or TCR rearrangement in FDCS. Some IDCS cases associated with lymphoma have shown cytogenetic alterations characteristic

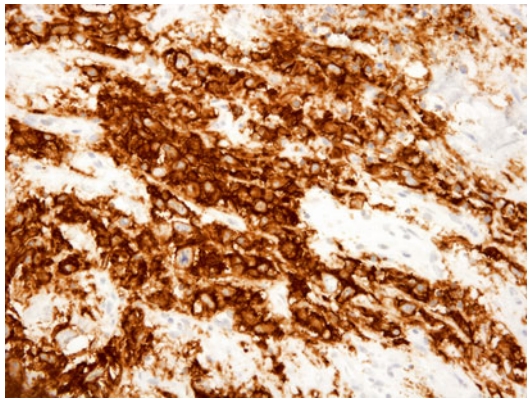


Fig. 11.57 Follicular dendritic cell sarcoma. CD23 cytoplasmic immunostaining of tumor cells

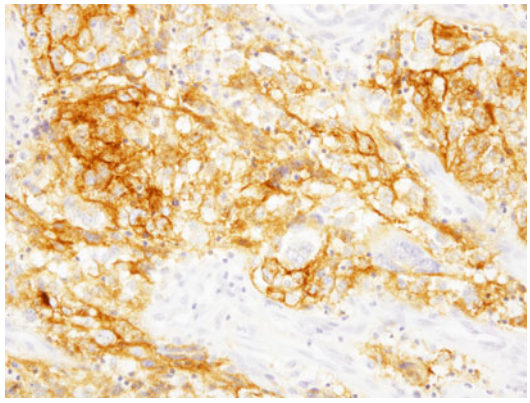


Fig. 11.58 Follicular dendritic cell sarcoma. .CD21 immunostaining showing predominantly membrane positivity in tumor cells

of the latter [106, 269, 278–280]. Recently, *BRAF* V600E mutations have been detected by direct Sanger sequencing in five of 27 FDCS instances. In contrast, this mutation was absent in an IDCS case included in the study [281]. Assessment of the diagnostic and therapeutic usefulness of these findings needs further study.

Differential Diagnosis

Morphologically, FDCS and IDCS may be very similar. Therefore, their distinction requires accurate immunophenotyping. Specifically, it is important to evaluate the expression of FDC markers (CD21, CD23, and CD35), as well as that of clusterin and D2-40 [282]. As already mentioned, clusterin usually is very strongly positive in FDCS [264, 269, 276, 277]. Although clusterin may be weakly positive in IDCS, its negativity for D2-40 and the FDC marker profile allows its distinction from FDCS [264, 269, 276, 277].

Langerhans cell histiocytosis (LCH) usually shows a more heterogeneous histologic appearance, with accompanying inflammatory infiltrates and a distinctive immunohistochemical profile. Although IDCS may express CD1a and S-100 protein, it is negative for langerin.

Immunohistochemical findings in histiocytic sarcoma (HS) may be similar to those of IDCS (positivity for S-100 protein and CD68 and negativity for FDC markers and langerin) [106, 269, 276].

Clues and Pitfalls

- FDCS shows characteristically strong positivity for clusterin and plasma membrane immunoreactivity for D2-40.
- Langerin immunostaining allows the distinction between LCH and IDCS.
- The T-cell immunophenotype is predominant in IDCS the lymphocytes of.
- Positivity for FDC markers distinguishes FDCS from IDCS, LCH, and histiocytic conditions.

References

1. Cho-Vega JH, Medeiros LJ, Prieto VG, Vega F. Leukemia cutis. Am J Clin Pathol. 2008;129(1):130–42.
2. Pileri SA, Orazi A, Falini B. Myeloid sarcoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press; 2008. p. 140–1.
3. Hsi AC, Robirds DH, Luo J, Kreisel FH, Frater JL, Nguyen TT. T-cell prolymphocytic leukemia frequently shows cutaneous involvement and is associated with gains of MYC, loss of ATM, and TCL1A rearrangement. Am J Surg Pathol. 2014;38(11):1468–83.
4. Tokura Y, Sawada Y, Shimauchi T. Skin manifestations of adult T-cell leukemia/lymphoma: clinical, cytological and immunological features. J Dermatol. 2014;41(1):19–25.
5. Robak E, Robak T. Skin lesions in chronic lymphocytic leukemia. Leuk Lymphoma. 2007;48(5):855–65.

6. Cerroni L, Zenahlik P, Höfler G, Kaddu S, Smolle J, Kerl H. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia: a clinicopathologic and prognostic study of 42 patients. Am J Surg Pathol. 1996;20(8):1000–10.
7. Tapia G, Mate JL, Fuente MJ, Navarro JT, Fernández-Figueras MT, Juncà J, et al. Cutaneous presentation of chronic lymphocytic leukemia as unique extramedullar involvement in a patient with normal peripheral blood lymphocyte count (monoclonal B-cell lymphocytosis). J Cutan Pathol. 2013;40(8):740–4.
8. Bénet C, Gomez A, Aguilar C, Delattre C, Vergier B, Beylot-Barry M, et al. Histologic and immunohistologic characterization of skin localization of myeloid disorders: a study of 173 cases. Am J Clin Pathol. 2011;135(2):278–90.
9. Hurley MY, Ghahramani GK, Frisch S, Armbrecht ES, Lind AC, Nguyen TT, et al. Cutaneous myeloid sarcoma: natural history and biology of an uncommon manifestation of acute myeloid leukemia. Acta Derm Venereol. 2013;93(3):319–24.
10. Amador-Ortiz C, Hurley MY, Ghahramani GK, Frisch S, Klco JM, Lind AC, et al. Use of classic and novel immunohistochemical markers in the diagnosis of cutaneous myeloid sarcoma. J Cutan Pathol. 2011;38(12):945–53.
11. Mathew RA, Bennett JM, Liu JJ, Komrokji RS, Lancet JE, Naghashpour M, et al. Cutaneous manifestations in CMML: indication of disease acceleration or transformation to AML and review of the literature. Leuk Res. 2012;36(1):72–80.
12. Patel LM, Maghari A, Schwartz RA, Kapila R, Morgan AJ, Lambert WC. Myeloid leukemia cutis in the setting of myelodysplastic syndrome: a crucial dermatological diagnosis. Int J Dermatol. 2012; 51(4):383–8.
13. Klco JM, Welch JS, Nguyen TT, Hurley MY, Kreisel FH, Hassan A, et al. State of the art in myeloid sarcoma. Int J Lab Hematol. 2011;33(6):555–65.
14. Aboutalebi A, Korman JB, Sohani AR, Hasserjian RP, Louissaint Jr A, Le L, et al. Aleukemic cutaneous myeloid sarcoma. J Cutan Pathol. 2013;40(12): 996–1005.
15. Angulo J, Haro R, González-Guerra E, Fariña MC, Martín L, Requena L. Leukemia cutis presenting as localized cutaneous hyperpigmentation. J Cutan Pathol. 2008;35(7):662–5.
16. Freiman A, Muhn CY, Trudel M, Billick RC. Leukemia cutis presenting with fingertip hypertrophy. J Cutan Med Surg. 2003;7(1):57–60.
17. Hattori T, Amano H, Nagai Y, Ishikawa O. Leukemia cutis in a patient with acute monocytic leukemia presenting as unique facial erythema. J Dermatol. 2008;35(10):671–4.
18. Cañueto J, Meseguer-Yebra C, Román-Curto C, Santos-Briz A, Fernández-López E, Fraile C, et al. Leukemic vasculitis: a rare pattern of leukemia cutis. J Cutan Pathol. 2011;38(4):360–4.
19. Martínez-Escanamé M, Zuriel D, Tee SI, Fried I, Massone C, Cerroni L. Cutaneous infiltrates of acute myelogenous leukemia simulating inflammatory dermatoses. Am J Dermatopathol. 2013;35(4): 419–24.
20. Baksh FK, Nathan D, Richardson W, Kestenbaum T, Woodroof J. Leukemia cutis with prominent giant cell reaction. Am J Dermatopathol. 1998;20(1): 48–52.
21. Chavan RN, Cappel MA, Ketterling RP, Wada DA, Rochet NM, Knudson R, et al. Histiocytoid Sweet syndrome may indicate leukemia cutis: a novel application of fluorescence in situ hybridization. J Am Acad Dermatol. 2014;70(6):1021–7.
22. Cibull TL, Thomas AB, O'Malley DP, Billings SD. Myeloid leukemia cutis: a histologic and immunohistochemical review. J Cutan Pathol. 2008;35(2): 180–5.
23. Cronin DM, George TI, Sundram UN. An updated approach to the diagnosis of myeloid leukemia cutis. Am J Clin Pathol. 2009;132(1):101–10.
24. Sangle NA, Schmidt RL, Patel JL, Medeiros LJ, Agarwal AM, Perkins SL. Optimized immunohistochemical panel to differentiate myeloid sarcoma from blastic plasmacytoid dendritic cell neoplasm. Mod Pathol. 2014;27(8):1137–43.
25. Cronin DM, George TI, Reichard KK, Sundram UN. Immunophenotypic analysis of myeloperoxidase-negative leukemia cutis and blastic plasmacytoid dendritic cell neoplasm. Am J Clin Pathol. 2012; 137(3):367–76.
26. Murphy MJ. Molecular testing of leukemia cutis. J Cutan Pathol. 2013;40(2):286–8.
27. Pileri SA, Ascani S, Cox MC, Campidelli C, Bacci F, Piccioli M, et al. Myeloid sarcoma: clinicopathologic, phenotypic and cytogenetic analysis of 92 adult patients. Leukemia. 2007;21(2):340–50.
28. Falini B, Lenze D, Hasserjian R, Coupland S, Jaehne D, Soupir C, et al. Cytoplasmic mutated nucleophosmin (NPM) defines the molecular status of a significant fraction of myeloid sarcomas. Leukemia. 2007;21(7):1566–70.
29. Sen F, Zhang XX, Prieto VG, Shea CR, Qumsiyeh MB. Increased incidence of trisomy 8 in acute myeloid leukemia with skin infiltration (leukemia cutis). Diagn Mol Pathol. 2000;9(4):190–4.
30. Agis H, Weltermann A, Fonatsch C, Haas O, Mitterbauer G, Müllauer L, et al. A comparative study on demographic, hematological, and cytogenetic findings and prognosis in acute myeloid leukemia with and without leukemia cutis. Ann Hematol. 2002;81(2):90–5.
31. Requena L, Kutzner H, Palmedo G, Pascual M, Fernández-Herrera J, Fraga J, et al. Histiocytoid Sweet syndrome: a dermal infiltration of immature neutrophilic granulocytes. Arch Dermatol. 2005; 141(7):834–42.
32. Facchetti F, Jones DM, Petrella T. Blastic plasmacytoid dendritic cells neoplasm. In: Swerdlow SH,

Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press; 2008. p. 146–7.
33. Brody JP, Allen S, Schulman P, Sun T, Chan WC, Friedman HD, et al. Acute agranular CD4-positive natural killer cell leukemia. Comprehensive clinicopathologic studies including virologic and in vitro culture with inducing agents. Cancer. 1995;75(10): 2474–83.
34. DiGiuseppe JA, Louie DC, Williams JE, Miller DT, Griffin CA, Mann RB, et al. Blastic natural killer cell leukemia/lymphoma: a clinicopathologic study. Am J Surg Pathol. 1997;21(10):1223–30.
35. Petrella T, Comeau MR, Maynadié M, Couillault G, De Muret A, Maliszewski CR, et al. "Agranular CD4+ CD56+ hematodermic neoplasm" (blastic NK-cell lymphoma) originates from a population of CD56+ precursor cells related to plasmacytoid monocytes. Am J Surg Pathol. 2002;26(7):852–62.
36. Julia F, Dalle S, Duru G, Balme B, Vergier B, Ortonne N, et al. Blastic plasmacytoid dendritic cell neoplasms: clinico-immunohistochemical correlations in a series of 91 patients. Am J Surg Pathol. 2014;38(5):673–80.
37. Petrella T, Bagot M, Willemze R, Beylot-Barry M, Vergier B, Delaunay M, et al. Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. Am J Clin Pathol. 2005;123(5): 662–75.
38. Khoury JD, Medeiros LJ, Manning JT, Sulak LE, Bueso-Ramos C, Jones D. CD56(+) TdT(+) blastic natural killer cell tumor of the skin: a primitive systemic malignancy related to myelomonocytic leukemia. Cancer. 2002;94(9):2401–8.
39. Herling M, Jones D. CD4+/CD56+ hematodermic tumor: the features of an evolving entity and its relationship to dendritic cells. Am J Clin Pathol. 2007;127(5):687–700.
40. Herling M, Teitell MA, Shen RR, Medeiros LJ, Jones D. TCL1 expression in plasmacytoid dendritic cells (DC2s) and the related CD4+ CD56+ blastic tumors of skin. Blood. 2003;101(12):5007–9.
41. Petrella T, Meijer CJ, Dalac S, Willemze R, Maynadié M, Machet L, et al. TCL1 and CLA expression in agranular CD4/CD56 hematodermic neoplasms (blastic NK-cell lymphomas) and leukemia cutis. Am J Clin Pathol. 2004;122(2):307–13.
42. Pilichowska ME, Fleming MD, Pinkus JL, Pinkus GS. CD4+/CD56+ hematodermic neoplasm ("blastic natural killer cell lymphoma"): neoplastic cells express the immature dendritic cell marker BDCA-2 and produce interferon. Am J Clin Pathol. 2007; 128(3):445–53.
43. Montes-Moreno S, Ramos-Medina R, Martínez-López A, Barrionuevo Cornejo C, Parra Cubillos A, Quintana-Truyenque S, et al. SPIB, a novel immunohistochemical marker for human blastic plasmacytoid dendritic cell neoplasms: characterization of its expression in major hematolymphoid neoplasms. Blood. 2013;121(4):643–7.
44. Marafioti T, Paterson JC, Ballabio E, Reichard KK, Tedoldi S, Hollowood K, et al. Novel markers of normal and neoplastic human plasmacytoid dendritic cells. Blood. 2008;111(7):3778–92.
45. Leroux D, Mugneret F, Callanan M, Radford-Weiss I, Dastugue N, Feuillard J, et al. CD4(+), CD56(+) DC2 acute leukemia is characterized by recurrent clonal chromosomal changes affecting 6 major targets: a study of 21 cases by the Groupe Français de Cytogénétique Hématologique. Blood. 2002;99(11): 4154–9.
46. Lucioni M, Novara F, Fiandrino G, Riboni R, Fanoni D, Arra M, et al. Twenty-one cases of blastic plasmacytoid dendritic cell neoplasm: focus on biallelic locus 9p21.3 deletion. Blood. 2011;118(17): 4591–4.
47. Sapienza MR, Fuligni F, Agostinelli C, Tripodo C, Righi S, Laginestra MA, et al. Molecular profiling of blastic plasmacytoid dendritic cell neoplasm reveals a unique pattern and suggests selective sensitivity to NF-kB pathway inhibition. Leukemia. 2014;28(8): 1606–16.
48. Alayed K, Patel KP, Konoplev S, Singh RR, Routbort MJ, Reddy N, et al. TET2 mutations, myelodysplastic features, and a distinct immunoprofile characterize blastic plasmacytoid dendritic cell neoplasm in the bone marrow. Am J Hematol. 2013; 88(12):1055–61.
49. Menezes J, Acquadro F, Wiseman M, Gómez-López G, Salgado RN, Talavera-Casañas JG, et al. Exome sequencing reveals novel and recurrent mutations with clinical impact in blastic plasmacytoid dendritic cell neoplasm. Leukemia. 2014;28(4):823–9.
50. Assaf C, Gellrich S, Whittaker S, Robson A, Cerroni L, Massone C, et al. CD56-positive haematological neoplasms of the skin: a multicentre study of the Cutaneous Lymphoma Project Group of the European Organisation for Research and Treatment of Cancer. J Clin Pathol. 2007;60(9):981–9.
51. Pileri SA, Grogan TM, Harris NL, Banks P, Campo E, Chan JK, et al. Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. Histopathology. 2002;41(1):1–29.
52. Vermi W, Facchetti F, Rosati S, Vergoni F, Rossi E, Festa S, et al. Nodal and extranodal tumor-forming accumulation of plasmacytoid monocytes/ interferon-producing cells associated with myeloid disorders. Am J Surg Pathol. 2004;28(5):585–95.
53. Borowitz MJ, Chan JKC. T lymphoblastic leukemia/ lymphoma. In: Swerdlow SHCE, Harris NL, Jaffe ES, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC; 2008. p. 176–8.
54. Borowitz MJ, Croker BP, Metzgar RS. Lymphoblastic lymphoma with the phenotype of common acute

lymphoblastic leukemia. Am J Clin Pathol. 1983; 79(3):387–91.
55. Nabhan C, Tolentino A, Meyer A, Tallman MS. Cutaneous involvement with B-lineage acute lymphoblastic leukemia. Leuk Lymphoma. 2012;53(5): 987–9.
56. Boccara O, Laloum-Grynberg E, Jeudy G, Aubriot-Lorton MH, Vabres P, de Prost Y, et al. Cutaneous B-cell lymphoblastic lymphoma in children: a rare diagnosis. J Am Acad Dermatol. 2012;66(1):51–7.
57. Lin P, Jones D, Dorfman DM, Medeiros LJ. Precursor B-cell lymphoblastic lymphoma: a predominantly extranodal tumor with low propensity for leukemic involvement. Am J Surg Pathol. 2000; 24:1480–90.
58. Gallagher G, Chhanabhai M, Song KW, Barnett MJ. Unusual presentation of precursor T-cell lymphoblastic lymphoma: involvement limited to breasts and skin. Leuk Lymphoma. 2007;48: 428–30.
59. Shafer D, Wu H, Al-Saleem T, Reddy K, Borghaei H, Lessin S, et al. Cutaneous precursor B-cell lymphoblastic lymphoma in 2 adult patients: clinicopathologic and molecular cytogenetic studies with a review of the literature. Arch Dermatol. 2008;144(9):1155–62.
60. Lee WJ, Moon HR, Won CH, Chang SE, Choi JH, Moon KC, et al. Precursor B- or T-lymphoblastic lymphoma presenting with cutaneous involvement: a series of 13 cases including 7 cases of cutaneous T-lymphoblastic lymphoma. J Am Acad Dermatol. 2014;70(2):318–25.
61. Suzumiya J, Ohshima K, Kikuchi M, Takeshita M, Akamatsu M, Tashiro K. Terminal deoxynucleotidyl transferase staining of malignant lymphomas in paraffin sections: a useful method for the diagnosis of lymphoblastic lymphoma. J Pathol. 1997;182:86–91.
62. Savage NM, Johnson RC, Natkunam Y. The spectrum of lymphoblastic, nodal and extranodal T-cell lymphomas: characteristic features and diagnostic dilemmas. Hum Pathol. 2013;44(4):451–71.
63. Chimenti S, Fink-Puches R, Peris K, Pescarmona E, Pütz B, Kerl H, et al. Cutaneous involvement in lymphoblastic lymphoma. J Cutan Pathol. 1999;26(8): 379–85.
64. Ishibashi M, Yamamoto K, Kudo S, Chen KR. Mantle cell lymphoma with skin invasion characterized by the common variant in the subcutis and blastoid transformation in the overlying dermis. Am J Dermatopathol. 2010;32(2):180–2.
65. Cao Q, Li Y, Lin H, Ke Z, Liu Y, Ye Z. Mantle cell lymphoma of blastoid variant with skin lesion and rapid progression: a case report and literature review. Am J Dermatopathol. 2013;35(8):851–5.
66. Motegi S, Okada E, Nagai Y, Tamura A, Ishikawa O. Skin manifestation of mantle cell lymphoma. Eur J Dermatol. 2006;16(4):435–8.
67. Shi Y, Wang E. Blastic plasmacytoid dendritic cell neoplasm: a clinicopathologic review. Arch Pathol Lab Med. 2014;138(4):564–9.
68. Machado I, Traves V, Cruz J, Llombart B, Navarro S, Llombart-Bosch A. Superficial small round-cell tumors with special reference to the Ewing's sarcoma family of tumors and the spectrum of differential diagnosis. Semin Diagn Pathol. 2013;30(1): 85–94.
69. Kolhe R, Reid MD, Lee JR, Cohen C, Ramalingam P. Immunohistochemical expression of PAX5 and TdT by Merkel cell carcinoma and pulmonary small cell carcinoma: a potential diagnostic pitfall but useful discriminatory marker. Int J Clin Exp Pathol. 2013;6(2):142–7.
70. Buresh CJ, Oliai BR, Miller RT. Reactivity with TdT in Merkel cell carcinoma: a potential diagnostic pitfall. Am J Clin Pathol. 2008;129(6):894–8.
71. Horny HP, Metcalfe DD, Bennett JM, Bain BJ. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon France: IARC Press; 2008. p. 54–63.
72. Berezowska S, Flaig MJ, Ruëff F, Walz C, Haferlach T, Krokowski M, et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. Mod Pathol. 2014;27(1):19–29.
73. Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattan C, Brockow K, et al. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. Allergy. 2014;69(10):1267–74.
74. Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest. 2007;37(6): 435–53.
75. Kiszewski AE, Durán-Mckinster C, Orozco-Covarrubias L, Gutiérrez-Castrellón P, Ruiz-Maldonado R. Cutaneous mastocytosis in children: a clinical analysis of 71 cases. J Eur Acad Dermatol Venereol. 2004;18(3):285–90.
76. Wolff K, Komar M, Petzelbauer P. Clinical and histopathological aspects of cutaneous mastocytosis. Leuk Res. 2001;25(7):519–28.
77. Chiu A, Orazi A. Mastocytosis and related disorders. Semin Diagn Pathol. 2012;29(1):19–30.
78. Hollmann TJ, Brenn T, Hornick JL. CD25 expression on cutaneous mast cells from adult patients presenting with urticaria pigmentosa is predictive of systemic mastocytosis. Am J Surg Pathol. 2008; 32(1):139–45.
79. Morgado JM, Sánchez-Muñoz L, Teodósio CG, Jara-Acevedo M, Alvarez-Twose I, Matito A, et al. Immunophenotyping in systemic mastocytosis diagnosis: "CD25 positive" alone is more informative than the "CD25 and/or CD2" WHO criterion. Mod Pathol. 2012;25(4):516–21.
80. Valent P, Cerny-Reiterer S, Herrmann H, Mirkina I, George TI, Sotlar K, et al. Phenotypic heterogeneity, novel diagnostic markers, and target expression

profiles in normal and neoplastic human mast cells. Best Pract Res Clin Haematol. 2010;23(3):369–78.
81. Morgado JM, Perbellini O, Johnson RC, Teodósio C, Matito A, Álvarez-Twose I, et al. CD30 expression by bone marrow mast cells from different diagnostic variants of systemic mastocytosis. Histopathology. 2013;63(6):780–7.
82. Sotlar K, Cerny-Reiterer S, Petat-Dutter K, Hessel H, Berezowska S, Müllauer L, et al. Aberrant expression of CD30 in neoplastic mast cells in high-grade mastocytosis. Mod Pathol. 2011;24(4):585–95.
83. Baek JO, Kang HK, Na SY, Lee JR, Roh JY, Lee JH, et al. N822K c-kit mutation in CD30-positive cutaneous pleomorphic mastocytosis after germ cell tumour of the ovary. Br J Dermatol. 2012;166(6): 1370–3.
84. Yanagihori H, Oyama N, Nakamura K, Kaneko F. c-kit Mutations in patients with childhood-onset mastocytosis and genotype-phenotype correlation. J Mol Diagn. 2005;7(2):252–7.
85. Bodemer C, Hermine O, Palmérini F, Yang Y, Grandpeix-Guyodo C, Leventhal PS, et al. Pediatric mastocytosis is a clonal disease associated with D816V and other activating c-KIT mutations. J Invest Dermatol. 2010;130(3):804–15.
86. Ma D, Stence AA, Bossler AB, Hackman JR, Bellizzi AM. Identification of KIT activating mutations in paediatric solitary mastocytoma. Histopathology. 2014;64(2):218–25.
87. Badalian-Very G, Vergilio JA, Fleming M, Rollins BJ. Pathogenesis of Langerhans cell histiocytosis. Annu Rev Pathol. 2013;8:1–20.
88. Jaffe R, Weis LM, Facchetti F. Tumours derived from Langerhans cells. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2008. p. 358–630.
89. Favara BE, Feller AC, Pauli M, Jaffe ES, Weiss LM, Arico M, et al. Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol. 1997;29(3):157–66.
90. Valentín-Nogueras SM, Seijo-Montes R, Montalván-Miró E, Sánchez JL. Langerhans cell sarcoma: a case report. J Cutan Pathol. 2013;40(7):670–5.
91. Valladeau J, Duvert-Frances V, Pin JJ, Dezutter-Dambuyant C, Vincent C, Massacrier C, et al. The monoclonal antibody DCGM4 recognizes Langerin, a protein specific of Langerhans cells, and is rapidly internalized from the cell surface. Eur J Immunol. 1999;29(9):2695–704.
92. Kim HK, Park CJ, Jang S, Cho YU, Park SH, Koh KN, et al. Bone marrow involvement of Langerhans cell histiocytosis: immunohistochemical evaluation of bone marrow for CD1a, Langerin, and S100 expression. Histopathology. 2014;65(6):742–8.
93. Lau SK, Chu PG, Weiss LM. Immunohistochemical expression of Langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorders. Am J Surg Pathol. 2008;32(4):615–9.
94. Roden AC, Hu X, Kip S, Parrilla Castellar ER, Rumilla KM, Vrana JA, et al. BRAF V600E expression in Langerhans cell histiocytosis: clinical and mmunohistochemical study on 25 pulmonary and 54 extrapulmonary cases. Am J Surg Pathol. 2014; 38(4):548–51.
95. Méhes G, Irsai G, Bedekovics J, Beke L, Fazakas F, Rózsa T, et al. Activating BRAF V600E mutation in aggressive pediatric Langerhans cell histiocytosis: demonstration by allele-specific PCR/direct sequencing and immunohistochemistry. Am J Surg Pathol. 2014;38(12):1644–8.
96. Sagransky MJ, Deng AC, Magro CM. Primary cutaneous langerhans cell sarcoma: a report of four cases and review of the literature. Am J Dermatopathol. 2013;35(2):196–204.
97. Badalian-Very G, Virgilio J, Degar BA, MacConaill LE, Brandner B, Calicchio ML, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010;116(11):1919–23.
98. Brown NA, Furtado LV, Betz BL, Kiel MJ, Weigelin HC, Lim MS, et al. High prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. Blood. 2014;124(10): 1655–8.
99. Hicks MJ, Bonilla DL, Dwyer KC, Berres ML, Poulikakos PI, Merad M, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. Blood. 2014;124(19):3007–15.
100. Nelson DS, Quispel W, Badalian-Very G, van Halteren AG, van den Bos C, Bovée JV, et al. Somatic activating ARAF mutations in Langerhans cell histiocytosis. Blood. 2014;123(20):3152–5.
101. Kansal R, Quintanilla-Martinez L, Datta V, Lopategui J, Garshfield G, Nathwani BN. Identification of the V600D mutation in Exon 15 of the BRAF oncogene in congenital, benign langerhans cell histiocytosis. Genes Chromosomes Cancer. 2013;52(1):99–106.
102. Haroche J, Cohen-Aubart F, Emile JF, Arnaud L, Maksud P, Charlotte F, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood. 2013;121(9):1495–500.
103. Baiocchi RA. Driving toward targeted therapy for LCH. Blood. 2014;124(10):1546–8.
104. Weitzman S, Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. Pediatr Blood Cancer. 2005;45(3):256–64.
105. Rezk SA, Spagnolo DV, Brynes RK, Weiss LM. Indeterminate cell tumor: a rare dendritic neoplasm. Am J Surg Pathol. 2008;32(12):1868–76.

106. Weis LM, Chan JKC, Fletcher CDM. Other rare dendritic cell tumors. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2008. p. 365.
107. Ferran M, Toll A, Gilaberte M, Barranco C, Lloreta J, Pujol RM. Acquired mucosal indeterminate cell histiocytoma. Pediatr Dermatol. 2007;24(3):253–6.
108. Tardío JC, Aguado M, Borbujo J. Self-regressing S100-negative CD1a-positive cutaneous histiocytosis. Am J Dermatopathol. 2013;35(4):57–9.
109. Calatayud M, Güell JL, Gris O, Puig J, Arrondo E, Huguet P. Ocular involvement in a case of systemic indeterminate cell histiocytosis: a case report. Cornea. 2001;20(7):769–71.
110. Ratzinger G, Burgdorf WH, Metze D, Zelger BG, Zelger B. Indeterminate cell histiocytosis: fact or fiction? J Cutan Pathol. 2005;32(8):552–60.
111. Ventura F, Pereira T, da Luz DM, Marques H, Pardal F, Brito C. Indeterminate cell histiocytosis in association with acute myeloid leukemia. Dermatol Res Pract. 2010;2010:569345.
112. Buser L, Bihl M, Rufle A, Mickys U, Tavoriene I, Griskevicius L, et al. Unique composite hematolymphoid tumor consisting of a pro-T lymphoblastic lymphoma and an indeterminate dendritic cell tumor: evidence for divergent common progenitor cell differentiation. Pathobiology. 2014;81(4):199–205.
113. Dehner LP. Juvenile xanthogranulomas in the first two decades of life: a clinicopathologic study of 174 cases with cutaneous and extracutaneous manifestations. Am J Surg Pathol. 2003;27(5):579–93.
114. Zelger BG, Zelger B, Steiner H, Mikuz G. Solitary giant xanthogranuloma and benign cephalic histiocytosis—variants of juvenile xanthogranuloma. Br J Dermatol. 1995;133(4):598–604. 40.
115. Torrelo A, Juarez A, Hernández A, Colmenero I. Multiple lichenoid juvenile xanthogranuloma. Pediatr Dermatol. 2009;26(2):238.
116. Koren J, Matecek L, Zamecnik M. Mitotically active deep juvenile xanthogranuloma. Ann Diagn Pathol. 2010;14(1):36–40.
117. Newman CC, Raimer SS, Sánchez RL. Nonlipidized juvenile xanthogranuloma: a histologic and immunohistochemical study. Pediatr Dermatol. 1997;14(2):98–102.
118. Ngendahayo P, de Saint Aubain N. Mitotically active xanthogranuloma: a case report with review of the literature. Am J Dermatopathol. 2012;34(3):e27–30.
119. Fenot M, Stalder JF, Barbarot S. Juvenile xanthogranulomas are highly prevalent but transient in young children with neurofibromatosis type 1. J Am Acad Dermatol. 2014;71(2):389–90.
120. Iyengar V, Golomb CA, Schachner L. Neurilemmomatosis, NF2, and juvenile xanthogranuloma. J Am Acad Dermatol. 1998;39(5 Pt 2):831–4.
121. Zvulunov A, Barak Y, Metzker A. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous leukemia. World statistical analysis. Arch Dermatol. 1995;131(8):904–8.
122. Shin HT, Harris MB, Orlow SJ. Juvenile myelomonocytic leukemia presenting with features of hemophagocytic lymphohistiocytosis in association with neurofibromatosis and juvenile xanthogranulomas. J Pediatr Hematol Oncol. 2004;26(9):591–5.
123. Tran DT, Wolgamot GM, Olerud J, Hurst S, Argenyi Z. An "eruptive" variant of juvenile xanthogranuloma associated with langerhans cell histiocytosis. J Cutan Pathol. 2008;35 Suppl 1:50–4.
124. Gonzalez Ruíz A, Bernal Ruíz AI, Aragoneses Fraile H, Peral Martinez I, García MM. Progressive nodular histiocytosis accompanied by systemic disorders. Br J Dermatol. 2000;143(3):628–31.
125. Lüftl M, Seybold H, Simon Jr M, Burgdorf W. Progressive nodular histiocytosis—rare variant of cutaneous non-Langerhans cell histiocytosis. J Dtsch Dermatol Ges. 2006;4(3):236–8.
126. Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, Wechsler J, Brun B, Remy M, et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. Medicine. 1996;75(3):157–69.
127. Mazor RD, Manervich-Mazor M, Shoenfeld Y. Erdheim Chester Disease: A comprehensive review of the literature. Orphanet J Rare Dis. 2013;8:137.
128. Kraus MD, Haley JC, Ruiz R, Essary L, Moran CA, Fletcher CD. "Juvenile" xanthogranuloma: an immunophenotypic study with a reappraisal of histogenesis. Am J Dermatopathol. 2001;23(2):104–11.
129. Tidwell WJ, Googe PB. Tissue histiocyte reactivity with CD31 is comparable to CD68 and CD163 in common skin lesions. J Cutan Pathol. 2014; 41(6):489–93.
130. Pouryazdanparast P, Yu L, Cutlan JE, Olsen SH, Fullen DR, Ma L. Diagnostic value of CD163 in cutaneous spindle cell lesions. J Cutan Pathol. 2009;36(8):859–64.
131. Tomaszewski MM, Lupton GP. Unusual expression of S-100 protein in histiocytic neoplasms. J Cutan Pathol. 1998;25(3):129–35.
132. Amouri M, Gouiaa N, Chaaben H, Masmoudi A, Zahaf A, Boudawara T, et al. Disseminated juvenile xanthogranuloma expressing protein S100. Ann Dermatol Venereol. 2012;139(2):128–31.
133. Yamamoto Y, Kadota M, Nishimura Y. A case of S-100-positive juvenile xanthogranuloma: a longitudinal observation. Pediatr Dermatol. 2009;26(4): 475–6.
134. Perez-Becker R, Szczepanowski M, Leuschner I, Janka G, Gokel M, Imschweiler T, et al. An aggressive systemic juvenile xanthogranuloma clonally related to a preceding T-cell acute lymphoblastic leukemia. Pediatr Blood Cancer. 2011;56(5): 859–62.
135. Emile JF, Diamond EL, Hélias-Rodzewicz Z, Charlotte F, Hyman DM, Kim E, et al. Recurent RAS and PIK3CA mutations in Erdheim-Chester disease. Blood. 2014;124(19):3016–09.

136. Haroche J, Charlotte F, Arnaud L, von Deimling A, Hélias-Rodzewicz Z, et al. High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood. 2012;120(13):2700–3.
137. Bubolz AM, Weissinger SE, Stenzinger A, Arndt A, Steinestel K, Brüderlein S, et al. Potential clinical implications of BRAF mutations in histiocytic proliferations. Oncotarget. 2014;5(12):4060–70.
138. Janku F, Vibat CR, Kosco K, Holley VR, Cabrilo G, Meric-Bernstam F, et al. BRAF V600E mutations in urine and plasma cell-free DNA from patients with Erdheim-Chester disease. Oncotarget. 2014;5(11): 3607–10.
139. Cavalli G, Biavasco R, Borgiani B, Dagna L. Oncogene-induced senescence as a new mechanism of disease: the paradigm of Erdheim-Chester disease. Front Immunol. 2014;5:281. doi:10.3389/fimmu.2014.00281.eCollection2014.
140. Aldabagh B, Ly MN, Hessel AB, Usmani AS. Molluscum contagiosum involving an epidermoid cyst with xanthogranuloma-like reaction in an HIV-infected patient. J Cutan Pathol. 2010;37(2): 282–6.
141. Nakamura Y, Nakamura A, Muto M. Solitary spindle cell xanthogranuloma mimicking a spitz nevus. Am J Dermatopathol. 2013;35(8):865–7.
142. Berti S, Coronella G, Galeone M, Balestri R, Patrizi A, Neri I. Giant congenital juvenile xanthogranuloma. Arch Dis Child. 2013;98(4):317.
143. Cohen PR, Prieto VG. Radiation port xanthogranuloma: solitary xanthogranuloma occurring within the irradiated skin of a breast cancer patient-report and review of cutaneous neoplasms developing at the site of radiotherapy. J Cutan Pathol. 2010;37(8): 891–4.
144. Shimada R, Fujimura T, Kambayashi Y, Ohtani T, Nasu M, Numata Y, et al. CD163+ adult xanthogranuloma arising from Merkel cell carcinoma treated with local radiotherapy. Acta Derm Venereol. 2012;92(6):631–2.
145. Janka GE, Lehmberg K. Hemophagocytic syndromes—an update. Blood Rev. 2014;28(4): 135–42.
146. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014;383(9927):1503.
147. Li J, Wang Q, Zheng W, Ma J, Zhang W, Wang W, et al. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. Medicine. 2014; 93(2):100–5.
148. Janka GE, Lehmberg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematology Am Soc Hematol Educ Program. 2013; 2013:605–11.
149. Zhang K, Jordan MB, Marsh RA, Johnson JA, Kissell D, Meller J, et al. Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult onset familial HLH. Blood. 2011;118(22):5794–8.
150. Jessen B, Bode SF, Ammann S, Chakravorty S, Davies G, Diestelhorst J, et al. The risk of hemophagocytic lymphohistiocytosis in Hermansky-Pudlak syndrome type 2. Blood. 2013;121(15): 2943–51.
151. Lin CI, Yu HH, Lee JH, Wang LC, Lin YT, Yang YH, et al. Clinical analysis of macrophage activation syndrome in pediatric patients with autoimmune diseases. Clin Rheumatol. 2012;31(8):1223–30.
152. Risma K, Jordan MB. Hemophagocytic lymphohistiocytosis: updates and evolving concepts. Curr Opin Pediatr. 2012;24(1):9–15.
153. Brisse E, Wouters CH, Matthys P. Hemophagocytic lymphohistiocytosis (HLH): a heterogeneous spectrum of cytokine-driven immune disorders. Cytokine Growth Factor Rev. 2014. doi:10.1016/j.cytogfr.2014.10.001.
154. Kerl K, Wolf IH, Cerroni L, Wolf P, French LE, Kerl H. Hemophagocytosis in cutaneous autoimmune disease. Am J Dermatopathol. 2015;37(7): 539–43.
155. Schaer DJ, Schleiffenbaum B, Kurrer M, Imhof A, Bächli E, Fehr J, et al. Soluble hemoglobinhaptoglobin scavenger receptor CD163 as a lineage-specific marker in the reactive hemophagocytic syndrome. Eur J Haematol. 2005;74:6–10.
156. Wada T, Sakakibara Y, Nishimura R, Toma T, Ueno Y, Horita S, et al. Down-regulation of CD5 expression on activated CD8+ T cells in familial hemophagocytic lymphohistiocytosis with perforin gene mutations. Hum Immunol. 2013;74(12):1579–85.
157. Ohkuma K, Saraya T, Sada M, Kawai S. Evidence for cytomegalovirus-induced haemophagocytic syndrome in a young patient with AIDS. BMJ Case Rep. 2013; 2013.
158. Ito Y, Kawamura Y, Iwata S, Kawada J, Yoshikawa T, Kimura H. Demonstration of type II latency in T lymphocytes of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2013;60(2):326–8.
159. Ahn JS, Rew SY, Shin MG, Kim HR, Kim HR, Yang DH, et al. Clinical significance of clonality and Epstein-Barr virus infection in adult patients with hemophagocytic lymphohistiocytosis. Am J Hematol. 2010;85:719–22.
160. Smith MC, Cohen DN, Greig B, Yenamandra A, Vnencak-Jones C, Thompson MA, et al. The ambiguous boundary between EBV-related hemophagocytic lymphohistiocytosis and systemic EBV-driven T cell lymphoproliferative disorder. Int J Clin Exp Pathol. 2014;7(9):5738–49.
161. Draper NL, Morgan MB. Dermatologic perivascular hemophagocytosis: a report of two cases. Am J Dermatopathol. 2007;29(5):467–9.
162. Valentín SM, Montalván E, Sánchez JL. Perivascular hemophagocytosis: report of 2 cases and review of the literature. Am J Dermatopathol. 2010;32(7): 716–9.
163. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and

therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124–31.
164. Sroa N, Zirwas MJ, Bechtel M. Multicentric reticulohistiocytosis: a case report and review of the literature. Cutis. 2010;85(3):153–5.
165. Baek IW, Yoo SH, Yang H, Park J, Kim KJ, Cho CS. A case of multicentric reticulohistiocytosis. Mod Rheumatol. 2014:1–4. [Epub ahead of print] PMID: 25211404.
166. Kandiah DA. Multicentric reticulohistiocytosis. Mayo Clin Proc. 2014;89(8):e73. doi:10.1016/j.mayocp.2013.10.036.
167. Lu YY, Lu CC, Wu CH. Leonine facies in the cutaneous form of multicentric reticulohistiocytosis. Intern Med. 2012;51(15):2069–70.
168. West KL, Sporn T, Puri PK. Multicentric reticulohistiocytosis: a unique case with pulmonary fibrosis. Arch Dermatol. 2012;148(2):228–32.
169. Yang HJ, Ding YQ, Deng YJ. Multicentric reticulohistiocytosis with lungs and liver involved. Clin Exp Dermatol. 2009;34(2):183–5.
170. Webb-Detiege T, Sasken H, Kaur P. Infiltration of histiocytes and multinucleated giant cells in the myocardium of a patient with multicentric reticulohistiocytosis. J Clin Rheumatol. 2009;15(1):25–6.
171. Taniguchi T, Asano Y, Okada A, Sugaya M, Sato S. Ultraviolet light-induced Köbner phenomenon contributes to the development of skin eruptions in multicentric reticulohistiocytosis. Acta Derm Venereol. 2011;91(2):160–3.
172. Arai S, Katsuoka K, Ishikawa A. Multicentric reticulohistiocytosis presenting with the cutaneous features of photosensitivity dermatitis. J Dermatol. 2012;39(2):180–1.
173. Bennàssar A, Mas A, Guilabert A, Julià M, Mascaró-Galy JM, Herrero C. Multicentric reticulohistiocytosis with elevated cytokine serum levels. J Dermatol. 2011;38(9):905–10.
174. Kovach BT, Calamia KT, Walsh JS, Ginsburg WW. Treatment of multicentric reticulohistiocytosis with etanercept. Arch Dermatol. 2004;140(8):919–21.
175. Lovelace K, Loyd A, Adelson D, Crowson N, Taylor JR, Cornelison R. Etanercept and the treatment of multicentric reticulohistiocytosis. Arch Dermatol. 2005;141(9):1167–8.
176. Iwata H, Okumura Y, Seishima M, Aoyama Y. Overexpression of monocyte chemoattractant protein-1 in the overlying epidermis of multicentric reticulohistiocytosis lesions: a case report. Int J Dermatol. 2012;51(4):492–4.
177. Codriansky KA, Rünger TM, Bhawan J, Kantarci A, Kissin EY. Multicentric reticulohistiocytosis: a systemic osteoclastic disease? Arthritis Rheum. 2008;59(3):444–8. doi:10.1002/art.23320.
178. Nicol C, Quereux G, Renaut JJ, Renac F, Dreno B. Paraneoplastic multicentric reticulohistiocytosis. Ann Dermatol Venereol. 2011;138(5):405–8.
179. Ben Abdelghani K, Mahmoud I, Chatelus E, Sordet C, Gottenberg JE, Sibilia J. Multicentric reticulohistiocytosis: an autoimmune systemic disease? Case report of an association with erosive rheumatoid arthritis and systemic Sjogren syndrome. Joint Bone Spine. 2010;77(3):274–6.
180. Macía-Villa CC, Zea-Mendoza A. Multicentric reticulohistiocytosis: case report with response to infliximab and review of treatment options. Clin Rheumatol. 2016;35(2):527–34.
181. Zelger B, Cerio R, Soyer HP, Misch K, Orchard G, Wilson-Jones E. Reticulohistiocytoma and multicentric reticulohistiocytosis. Histopathologic and immunophenotypic distinct entities. Am J Dermatopathol. 1994;16(6):577–84.
182. Miettinen M, Fetsch JF. Reticulohistiocytoma (solitary epithelioid histiocytoma): a clinicopathologic and immunohistochemical study of 44 cases. Am J Surg Pathol. 2006;30(4):521–8.
183. Bialynicki-Birula R, Sebastian-Rusin A, Maj J, Wozniak Z, Baran E, Dziegiel P. Multicentric reticulohistiocytosis with S100 protein positive staining: a case report. Acta Dermatovenerol Croat. 2010;18(1):35–7.
184. Perrin C, Lacour JP, Michiels JF, Flory P, Ziegler G, Ortonne JP. Multicentric reticulohistiocytosis. Immunohistological and ultrastructural study: a pathology of dendritic cell lineage. Am J Dermatopathol. 1992;14(5):418–25.
185. Tashiro A, Takeuchi S, Nakahara T, Oba J, Tsujita J, Fukushi J, et al. Aberrant expression of CD10 in ground-glass-like multinucleated giant cells of multicentric reticulohistiocytosis. J Dermatol. 2010;37(11):995–7.
186. Tan BH, Barry CI, Wick MR, White KP, Brown JG, Lee A, et al. Multicentric reticulohistiocytosis and urologic carcinomas: a possible paraneoplastic association. J Cutan Pathol. 2011;38(1):43–8.
187. Krause ML, Lehman JS, Warrington KJ. Multicentric reticulohistiocytosis can mimic rheumatoid arthritis. J Rheumatol. 2014;41(4):780–1.
188. Trotta F, Colina M. Multicentric reticulohistiocytosis and fibroblastic rheumatism. Best Pract Res Clin Rheumatol. 2012;26(4):543–57.
189. Mun JH, Ko HC, Kim MB. Multicentric reticulohistiocytosis masquerading as dermatomyositis: similar and different features. J Dermatol. 2012;39(1):104–7.
190. Fett N, Liu RH. Multicentric reticulohistiocytosis with dermatomyositis-like features: a more common disease presentation than previously thought. Dermatology. 2011;222(2):102–8.
191. Spadaro A, Riccieri V, Sili-Scavalli A, Innocenzi D, Pranteda G, Taccari E. Value of cytological analysis of the synovial fluid in multicentric reticulohistiocytosis. A case. Rev Rhum Ed Fr. 1994;61(7–8):554–7.
192. Zak FG. Reticulohistiocytoma ("ganglioneuroma") of the skin. Br J Dermatol Syph. 1950;62(9):351–5.
193. Rabkin MS, Vukmer T. Granular cell variant of epithelioid cell histiocytoma. Am J Dermatopathol. 2012;34(7):766–9.

194. Caltabiano R, Magro G, Vecchio GM, Lanzafame S. Solitary cutaneous histiocytosis with granular cell changes: a morphological variant of reticulohistiocytoma? J Cutan Pathol. 2010;37(2):287–91.
195. Jedrych J, Nikiforova M, Kennedy TF, Ho J. Epithelioid cell histiocytoma of the skin with clonal ALK gene rearrangement resulting in VCL-ALK and SQSTM1-ALK gene fusions. Br J Dermatol. 2015;37(7):539–43.
196. Miettinen M, Fernandez M, Franssila K, Gatalica Z, Lasota J, Sarlomo-Rikala M. Microphthalmia transcription factor in the immunohistochemical diagnosis of metastatic melanoma: comparison with four other melanoma markers. Am J Surg Pathol. 2001; 25(2):205–11.
197. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. Arch Pathol. 1969;87: 63–70.
198. Brenn T, Calonje E, Granter SR, Leonard N, Grayson W, Fletcher CD, et al. Cutaneous rosai-dorfman disease is a distinct clinical entity. Am J Dermatopathol. 2002;24(5):385–91.
199. Zhu F, Zhang JT, Xing XW, Wang DJ, Zhu RY, Zhang Q, et al. Rosai-Dorfman disease: a retrospective analysis of 13 cases. Am J Med Sci. 2013; 345:200–10.
200. Frater JL, Maddox JS, Obadiah JM, Hurley MY. Cutaneous Rosai-Dorfman disease: comprehensive review of cases reported in the medical literature since 1990 and presentation of an illustrative case. J Cutan Med Surg. 2006;10(6):281–90.
201. Fernandez-Vega I, Santos-Juanes J, Ramsay A. Rosai-Dorfman disease following a classical Hodgkin lymphoma, nodular sclerosis subtype. Am J Dermatopathol. 2014;36(3):280–1.
202. Llamas-Velasco M, Cannata J, Dominguez I, García-Noblejas A, Aragües M, Fraga J, et al. Coexistence of Langerhans cell histiocytosis, Rosai-Dorfman disease and splenic lymphoma with fatal outcome after rapid development of histiocytic sarcoma of the liver. J Cutan Pathol. 2012;39(12):1125–30.
203. Venkataraman G, McClain KL, Pittaluga S, Rao VK, Jaffe ES. Development of disseminated histiocytic sarcoma in a patient with autoimmune lymphoproliferative syndrome and associated Rosai-Dorfman disease. Am J Surg Pathol. 2010;34(4):589–94.
204. Arakaki N, Gallo G, Majluf R, Diez B, Arias E, Riudavets MA, et al. Extranodal Rosai-Dorfman disease presenting as a solitary mass with human herpesvirus 6 detection in a pediatric patient. Pediatr Dev Pathol. 2012;15(4):324–8.
205. Al-Daraji W, Anandan A, Klassen-Fischer M, Auerbach A, Marwaha JS, Fanburg-Smith JC. Soft tissue Rosai-Dorfman disease: 29 new lesions in 18 patients, with detection of polyomavirus antigen in 3 abdominal cases. Ann Diagn Pathol. 2010;14(5): 309–16.
206. Salva KA, Stenstrom M, Breadon JY, Odland PB, Bennett D, Longley J, et al. Possible association of cutaneous Rosai-Dorfman disease and chronic Crohn disease: a case series report. JAMA Dermatol. 2014;150(2):177–81.
207. Zhang X, Hyjek E, Vardiman J. A subset of Rosai-Dorfman disease exhibits features of IgG4-related disease. Am J Clin Pathol. 2013;139(5):622–32.
208. Menon MP, Evbuomwan MO, Rosai J, Jaffe ES, Pittaluga S. A subset of Rosai-Dorfman disease cases show increased IgG4-positive plasma cells: another red herring or a true association with IgG4-related disease? Histopathology. 2014;64(3):455–9.
209. Liu L, Perry AM, Cao W, Smith LM, Hsi ED, Liu X, et al. Relationship between Rosai-Dorfman disease and IgG4-related disease: study of 32 cases. Am J Clin Pathol. 2013;140(3):395–402.
210. Vuong V, Moulonguet I, Cordoliani F, Crickx B, Bezier M, Vignon-Pennamen MD, et al. Cutaneous revelation of Rosai-Dorfman disease: 7 cases. Ann Dermatol Venereol. 2013;140(2):83–90.
211. Cangelosi JJ, Prieto VG, Ivan D. Cutaneous Rosai-Dorfman disease with increased number of eosinophils: coincidence or histologic variant? Arch Pathol Lab Med. 2011;135(12):1597–600.
212. Foucar E, Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. An analysis of 14 deaths occurring in a patient registry. Cancer. 1984;54:1834–40.
213. Sasaki K, Pemmaraju N, Westin JR, Wang WL, Khoury JD, Podoloff DA, et al. A single case of Rosai-Dorfman disease marked by pathologic fractures, kidney failure, and liver cirrhosis treated with single-agent cladribine. Front Oncol. 2014;4:297.
214. Zheng M, Bi R, Li W, Landeck L, Chen JQ, Lao LM, et al. Generalized pure cutaneous Rosai-Dorfman disease: a link between inflammation and cancer not associated with mitochondrial DNA and SLC29A3 gene mutation? Discov Med. 2013;16(89): 193–200.
215. Avitan-Hersh E, Mandel H, Indelman M, Bar-Joseph G, Zlotogorski A, Bergman R. A case of H syndrome showing immunophenotye similarities to Rosai-Dorfman disease. Am J Dermatopathol. 2011;33(1):47–51.
216. Colmenero I, Molho-Pessach V, Torrelo A, Zlotogorski A, Requena L. Emperipolesis: an additional common histopathologic finding in H syndrome and Rosai-Dorfman disease. Am J Dermatopathol. 2012;34(3):315–20.
217. Molho-Pessach V, Ramot Y, Camille F, Doviner V, Babay S, Luis SJ, et al. H syndrome: the first 79 patients. J Am Acad Dermatol. 2014;70(1):80–8.
218. Kikuchi M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes. Acta Hematol Jpn. 1972;35:379–80.
219. Kim TY, Ha KS, Kim Y, Lee J, Lee K, Lee J. Characteristics of Kikuchi-Fujimoto disease in children compared with adults. Eur J Pediatr. 2014; 173(1):111–6.
220. Bosch X, Guilabert A, Miquel R, Campo E. Enigmatic Kikuchi-Fujimoto disease: a comprehensive

review. Am J Clin Pathol. 2004;122(1): 141–52.
221. Kucukardali Y, Solmazgul E, Kunter E, Oncul O, Yildirim S, Kaplan M. Kikuchi-Fujimoto disease: analysis of 244 cases. Clin Rheumatol. 2007; 26(1):50–4.
222. Cheng CY, Sheng WH, Lo YC, Chung CS, Chen YC, Chang SC. Clinical presentations, laboratory results and outcomes of patients with Kikuchi's disease: emphasis on the association between recurrent Kikuchi's disease and autoimmune diseases. J Microbiol Immunol Infect. 2010;43(5):366–71.
223. Atwater AR, Longley BJ, Aughenbaugh WD. Kikuchi's disease: case report and systematic review of cutaneous and histopathologic presentations. J Am Acad Dermatol. 2008;59(1):130–6.
224. Kim JH, Kim YB, In SI, Kim YC, Han JH. The cutaneous lesions of Kikuchi's disease: a comprehensive analysis of 16 cases based on the clinicopathologic, immunohistochemical, and immunofluorescence studies with an emphasis on the differential diagnosis. Hum Pathol. 2010;41(9):1245–54.
225. Kuo TT. Kikuchi's disease (histiocytic necrotizing lymphadenitis). A clinicopathologic study of 79 cases with an analysis of histologic subtypes, immunohistology, and DNA ploidy. Am J Surg Pathol. 1995;19(7):798–809.
226. Nomura Y, Takeuchi M, Yoshida S, Sugita Y, Niino D, Kimura Y, et al. Phenotype for activated tissue macrophages in histiocytic necrotizing lymphadenitis. Pathol Int. 2009;59(9):631–5.
227. Pilichowska ME, Pinkus JL, Pinkus GS. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease): lesional cells exhibit an immature dendritic cell phenotype. Am J Clin Pathol. 2009;131(2):174–82.
228. Ohshima K, Karube K, Hamasaki M, Makimoto Y, Fujii A, Kawano R, et al. Apoptosis- and cell cycle-associated gene expression profiling of histiocytic necrotising lymphadenitis. Eur J Haematol. 2004;72(5):322–9.
229. Ishimura M, Yamamoto H, Mizuno Y, Takada H, Goto M, Doi T, et al. A non-invasive diagnosis of histiocytic necrotizing lymphadenitis by means of gene expression profile analysis of peripheral blood mononuclear cells. J Clin Immunol. 2013;33(5): 1018–26.
230. Robertson KE, Forsyth PD, Batstone PJ, Levison DA, Goodlad JR. Kikuchi's disease displaying a t(2:16) chromosomal translocation. J Clin Pathol. 2007;60(4):433–5.
231. Requena L, El-Shabrawi-Caelen L, Walsh SN, Segura S, Ziemer M, Hurt MA, et al. Intralymphatic histiocytosis: a clinicopathologic study of 16 cases. Am J Dermatopathol. 2009;31:140–51.
232. Bakr F, Webber N, Fassihi H, Swale V, Lewis F, Rytina E, et al. Primary and secondary intralymphatic histiocytosis. J Am Acad Dermatol. 2014;70(5):927–33.
233. Watanabe T, Yamada N, Yoshida Y, Yamamoto O. Intralymphatic histiocytosis with granuloma formation associated with orthopedic metal implants. Br J Dermatol. 2008;158:402–4.
234. O'Grady JT, Shahidullah H, Doherty VR, Al-Nafussi A. Intravascular histiocytosis. Histopathology. 1994;24:265–8.
235. Rossari S, Scatena C, Gori A, Grazzini M, Corciova S, Scarfì F, et al. Intralymphatic histiocytosis: cutaneous nodules and metal implants. J Cutan Pathol. 2011;38(6):534–5.
236. Echeverrıa-Garcıa B, Botella-Estrada R, Requena C, Guillen C. Intralymphatic histiocytosis and cancer of the colon. Actas Dermosifiliogr. 2010;101:257–62.
237. Park YJ, Kwon JE, Han JH, Kim CH, Kang HY. Intralymphatic histiocytosis mimicking oral lymphangioma circumscriptum. Am J Dermatopathol. 2014;36(9):759–61.
238. Rieger E, Soyer HP, Leboit PE, Metze D, Slovak R, Kerl H. Reactive angioendotheliomatosis or intravascular histiocytosis? An immunohistochemical and ultrastructural study in two cases of intravascular histiocytic cell proliferation. Br J Dermatol. 1999;140(3):497–504.
239. Piccolo V, Ruocco E, Russo T, Baroni A. A possible relationship between metal implant-induced intralymphatic histiocytosis and the concept of the immunocompromised district. Int J Dermatol. 2014;53(7), e365.
240. Ruocco V, Brunetti G, Puca RV, Ruocco E. The immunocompromised district: a unifying concept for lymphoedematous, herpes-infected and otherwise damaged sites. J Eur Acad Dermatol Venereol. 2009;23(12):1364–73.
241. Franz R, Andres C. Cheilitis granulomatosa and Melkersson-Rosenthal syndrome. Intralymphatic histiocytosis as valuable diagnostic indication. Pathologe. 2014;35(2):177–81.
242. Asagoe K, Torigoe R, Ofuji R, Iwatsuki K. Reactive intravascular histiocytosis associated with tonsillitis. Br J Dermatol. 2006;154:560–2.
243. Pouryazdanparast P, Yu L, Dalton VK, Haefner HK, Brincat C, Mandell SH, et al. Intravascular histiocytosis presenting with extensive vulvar necrosis. J Cutan Pathol. 2009;36 Suppl 1:1–7.
244. Rongioletti F, Rebora A. Cutaneous reactive angiomatoses: patterns and classification of reactive vascular proliferation. J Am Acad Dermatol. 2003; 49(5):887–96.
245. Cathébras P, Laurent H, Guichard I. Generalized telangiectasia revealing intravascular large B-cell lymphoma. Br J Haematol. 2013;161(2):155.
246. Riveiro-Falkenbach E, Fernández-Figueras MT, Rodríguez-Peralto JL. Benign atypical intravascular CD30(+) T-cell proliferation: a reactive condition mimicking intravascular lymphoma. Am J Dermatopathol. 2013;35(2):143–50.
247. Adachi Y, Kosami K, Mizuta N, Ito M, Matsuoka Y, Kanata M, et al. Benefits of skin biopsy of senile hemangioma in intravascular large B-cell lymphoma: a case report and review of the literature. Oncol Lett. 2014;7(6):2003–6.

248. Aung PP, Ballester LY, Goldberg LJ, Bhawan J. Incidental simultaneous finding of intravascular histiocytosis and reactive angioendotheliomatosis: a case report. Am J Dermatopathol. 2015;37(5): 401–4.
249. Grogan TM, Pileri SA, Chan JKC, Weiss LM, Fletcher CDM. Histiocytic sarcoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, et al., editors. World Health Organization Classification of Tumours, WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2008. p. 356–7.
250. Takahashi E, Nakamura S. Histiocytic sarcoma :an updated literature review based on the 2008 WHO classification. J Clin Exp Hematop. 2013;53(1):1–8.
251. Ralfkiaer E, Delsol G, O'Connor NT, Brandtzaeg P, Brousset P, Vejlsgaard GL, et al. Malignant lymphomas of true histiocytic origin. A clinical, histological, immunophenotypic and genotypic study. J Pathol. 1990;160(1):9–17.
252. Kamel OW, Gocke CD, Kell DL, Cleary ML, Warnke RA. True histiocytic lymphoma: a study of 12 cases based on current definition. Leuk Lymphoma. 1995;18(1–2):81–6.
253. Hornick JL, Jaffe ES, Fletcher CD. Extranodal histiocytic sarcoma: clinicopathologic analysis of 14 cases of a rare epithelioid malignancy. Am J Surg Pathol. 2004;28(9):1133–44.
254. Nguyen TT, Schwartz EJ, West RB, Warnke RA, Arber DA, Natkunam Y. Expression of CD163 (hemoglobin scavenger receptor) in normal tissues, lymphomas, carcinomas, and sarcomas is largely restricted to the monocyte/macrophage lineage. Am J Surg Pathol. 2005;29(5):617–24.
255. Lau SK, Chu PG, Weiss LM. CD163: a specific marker of macrophages in paraffin-embedded tissue samples. Am J Clin Pathol. 2004;122(5):794–801.
256. Vos JA, Abbondanzo SL, Barekman CL, Andriko JW, Miettinen M, Aguilera NS. Histiocytic sarcoma: a study of five cases including the histiocyte marker CD163. Mod Pathol. 2005;18(5):693–704.
257. Soslow RA, Davis RE, Warnke RA, Cleary ML, Kamel OW. True histiocytic lymphoma following therapy for lymphoblastic neoplasms. Blood. 1996;87(12):5207–12.
258. Feldman AL, Minniti C, Santi M, Downing JR, Raffeld M, Jaffe ES. Histiocytic sarcoma after acute lymphoblastic leukaemia: a common clonal origin. Lancet Oncol. 2004;5(4):248–50.
259. Chen W, Lau SK, Fong D, Wang J, Wang E, Arber DA, et al. High frequency of clonal immunoglobulin receptor gene rearrangements in sporadic histiocytic/dendritic cell sarcomas. Am J Surg Pathol. 2009;33(6):863–73.
260. McClure R, Khoury J, Feldman A, Ketterling R. Clonal relationship between precursor B-cell acute lymphoblastic leukemia and histiocytic sarcoma: a case report and discussion in the context of similar cases. Leuk Res. 2010;34(2):71–3.
261. Bouabdallah R, Abéna P, Chetaille B, Aurran-Schleinitz T, Sainty D, Dubus P, et al. True histiocytic lymphoma following B-acute lymphoblastic leukaemia: case report with evidence for a common clonal origin in both neoplasms. Br J Haematol. 2001;113(4):1047–50.
262. Kumar R, Khan SP, Joshi DD, Shaw GR, Ketterling RP, Feldman AL. Pediatric histiocytic sarcoma clonally related to precursor B-cell acute lymphoblastic leukemia with homozygous deletion of CDKN2A encoding p16INK4A. Pediatr Blood Cancer. 2011;56(2):307–10.
263. Hure MC, Elco CP, Ward D, Hutchinson L, Meng X, Dorfman DM, et al. Histiocytic sarcoma arising from clonally related mantle cell lymphoma. J Clin Oncol. 2012;30(5):49–53.
264. Go H, Jeon YK, Huh J, Choi SJ, Choi YD, Cha HJ, et al. Frequent detection of BRAF(V600E) mutations in histiocytic and dendritic cell neoplasms. Histopathology. 2014;65(2):261–72.
265. Pletneva MA, Smith LB. Anaplastic large cell lymphoma: features presenting diagnostic challenges. Arch Pathol Lab Med. 2014;138(10):1290–4.
266. Wu J, Qin D, Burton GF, Szakal AK, Tew JG. Follicular dendritic cell-derived antigen and accessory activity in initiation of memory IgG responses in vitro. J Immunol. 1996;157(8): 3404–11.
267. Yamada K, Yamakawa M, Imai Y, Tsukamoto M. Expression of cytokine receptors on follicular dendritic cells. Blood. 1997;90(12):4832–41.
268. Steinman RM, Pack M, Inaba K. Dendritic cells in the T-cell areas of lymphoid organs. Immunol Rev. 1997;156:25–37.
269. Chan JKC, Pileri SA, Delsol G, Fletcher CDM, Weis LM, Grogg KL. Follicular dendritic cell sarcoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2008. p. 363–4.
270. Meijs M, Mekkes J, van Noesel C, Nijhuis E, Leeksma O, Jonkman M, et al. Paraneoplastic pemphigus associated with follicular dendritic cell sarcoma without Castleman's disease; treatment with rituximab. Int J Dermatol. 2008;47(6):632–4.
271. Lee IJ, Kim SC, Kim HS, Bang D, Yang WI, Jung WH, et al. Paraneoplastic pemphigus associated with follicular dendritic cell sarcoma arising from Castleman's tumor. J Am Acad Dermatol. 1999; 40:294–7.
272. Chan JK, Fletcher CD, Nayler SJ, Cooper K. Follicular dendritic cell sarcoma. Clinicopathologic analysis of 17 cases suggesting a malignant potential higher than currently recognized. Cancer. 1997; 79(2):294–313.

273. Cokelaere K, Debiec-Rychter M, De Wolf-Peeters C, Hagemeijer A, Sciot R. Hyaline vascular Castleman's disease with HMGIC rearrangement in follicular dendritic cells: molecular evidence of mesenchymal tumorigenesis. Am J Surg Pathol. 2002; 26(5):662–9.
274. Saygin C, Uzunaslan D, Ozguroglu M, Senocak M, Tuzuner N. Dendritic cell sarcoma: a pooled analysis including 462 cases with presentation of our case series. Crit Rev Oncol Hematol. 2013;88(2): 253–71.
275. Weiss LM, Grogan TM, Chan JKC. Interdigitating dendritic cell sarcoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2008. p. 361–2.
276. Fonseca R, Yamakawa M, Nakamura S, van Heerde P, Miettinen M, Shek TW, et al. Follicular dendritic cell sarcoma and interdigitating reticulum cell sarcoma: a review. Am J Hematol. 1998;59(2):161–7.
277. Grogg KL, Macon WR, Kurtin PJ, Nascimento AG. A survey of clusterin and fascin expression in sarcomas and spindle cell neoplasms: strong clusterin immunostaining is highly specific for follicular dendritic cell tumor. Mod Pathol. 2005;18(2):260–6.
278. Grogg KL, Lae ME, Kurtin PJ, Macon WR. Clusterin expression distinguishes follicular dendritic cell tumors from other dendritic cell neoplasms: report of a novel follicular dendritic cell marker and clinicopathologic data on 12 additional follicular dendritic cell tumors and 6 additional interdigitating dendritic cell tumors. Am J Surg Pathol. 2004; 28(8):988–98.
279. Shao H, Xi L, Raffeld M, Feldman AL, Feldman AL, Ketterling RP, et al. Clonally related histiocytic/dendritic cell sarcoma and chronic lymphocytic leukemia/small lymphocytic lymphoma: a study of seven cases. Mod Pathol. 2011;24(11):1421–32.
280. Feldman AL, Arber DA, Pittaluga S, Martinez A, Burke JS, Raffeld M, et al. Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone. Blood. 2008;111(12): 5433–9.
281. Fraser CR, Wang W, Gomez M, Zhang T, Mathew S, Furman RR, et al. Transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma to interdigitating dendritic cell sarcoma: evidence for transdifferentiation of the lymphoma clone. Am J Clin Pathol. 2009;132(6):928–39.
282. Xie Q, Chen L, Fu K, Harter J, Young KH, Sunkara J, et al. Podoplanin (d2-40): a new immunohistochemical marker for reactive follicular dendritic cells and follicular dendritic cell sarcomas. Int J Clin Exp Pathol. 2008;1(3):276–84.