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Skin Biopsy Diagnosis of Langerhans Cell Neoplasms

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1. Introduction

This chapter reviews the clinical presentation, histopathology, immunoprofile and molecular features of Langerhans cell neoplasms of the skin including Langerhans cell histiocytosis (LCH) and its malignant counterpart, Langerhans cell sarcoma (LCS). Biopsy of the skin is a useful method to confirm LCH/LCS diagnosis, as cutaneous involvement is seen in more than 50% cases. Skin can be the only presenting site of LCH, but it is usually seen as an integral part of multisystemic disease involvement.

Langerhans cells (LC) are bone marrow-derived antigen presenting cells [1]. Although LC, dendritic cells and monocytic/histiocytic cells share a common multipotential progenitor cells that reside in the bone marrow, to the date, myeloid derived macrophages and dendritic cells constitute divergent lines of differentiation from bone marrow precursors [2]. However, recent evidence demonstrates that LC can be generated from lymphoid-committed CD4^{low} precursors, suggesting the role of lineage plasticity/ trans-differentiation and clonal infidelity [3-4].

LC can be found in the epidermis and mucosal lining of multiple organs including cervix, vagina, stomach and esophagus. The specific immunophenotypic profile is helpful distinguishing LCs, as they can express CD1a and langerin (CD207); in addition the detection of Birbeck granules, seen in both pathological and resting LC is a prominent feature [5].

LCH encompasses a spectrum of disease characterized by an uncontrolled proliferation of LC [5]. The etiology of LCH/LCS is unknown in most cases, and there is not clear understanding of the pathogenesis. Although LCH is believed to be a clonal proliferation of LC [2, 6], the exact nature is controversial, as pulmonary LCH is thought to be a reactive/inflammatory disorder rather than a neoplastic process, and spontaneous remissions have been documented [7-8]. In a recent study of well characterized LCH cases, 30% had clonal immunoglobulin heavy chain (IGH@), immunoglobulin kappa light chain (IGK@) or T-cell receptor gamma (TCRG@) gene

rearrangements, suggesting a close relationship between LCH and lymphoid lineage [3]. Additional data that suggests LCH is in fact a clonal disease is the presence of specific mutations such as BRAF V600E, which have been found in up to 76% of tumors in children <10 years of age [7, 9].

2. Langerhans cell histiocytosis

2.1. Clinical presentation

LCH can affect a wide range of patients, including neonates, young children and adults. In children younger than 2 years of age, cutaneous involvement is the most common presentation [10]. In neonates and young infants, skin is frequently involved, as solitary or multiple papules or nodules with ulceration or necrosis. Patients usually present with dermatitis-like lesions that involves scalp, trunk, intertriginous skin folds and perineum with brownish/whitish papules covered with scales and crust [11]. In neonates, eruptions may affect most of the body surface. In contrast, in adults, LCH with initial presentation occurring in the skin is unusual [12].

LCH can be localized, multifocal or multisystemic. Systemic disease can involve organs such as bone marrow, liver, central nervous system, gastrointestinal tract, lungs and spleen. Systemic forms include Letterer-Siwe disease (with skin, lymph node and visceral involvement) and Hand-Schuller-Christian syndrome (in young children).

Congenital disease is rare and often clinically benign, presented in the form of reticulohistiocytosis (Hashimoto-Pritzker disease) as a self-healing or regressive form of the disease. Congenital disease usually presents at birth or in the first few weeks of life as a widespread cutaneous eruption of red-brown nodules that resolves spontaneously [10, 13], although it can rarely be associated with multiorgan involvement [10, 14].

2.2. Histopathology

Recognition of morphologic and immunohistochemical features is essential to establish both the diagnosis and the LC origin. The skin shows a predominant diffuse papillary dermal infiltrate composed of large cells with lobulated, eccentric grooved nuclei with “coffee-bean shape” appearance and inconspicuous nucleoli. The epidermis may be ulcerated and epidermotropism is commonly seen (FIGURE 1).

A variable polymorphic infiltrate of eosinophils, lymphocytes, plasma cells and neutrophils is usually admixed with neoplastic cells. Eosinophils are often but not invariably present, and sometimes can be quite numerous, masking LC (FIGURE 2). Mitotic activity may be brisk. In some cases, LC may resemble histiocytes or Touton cells. Sometimes, a granulomatous reaction with histiocytic infiltrate can be identified.

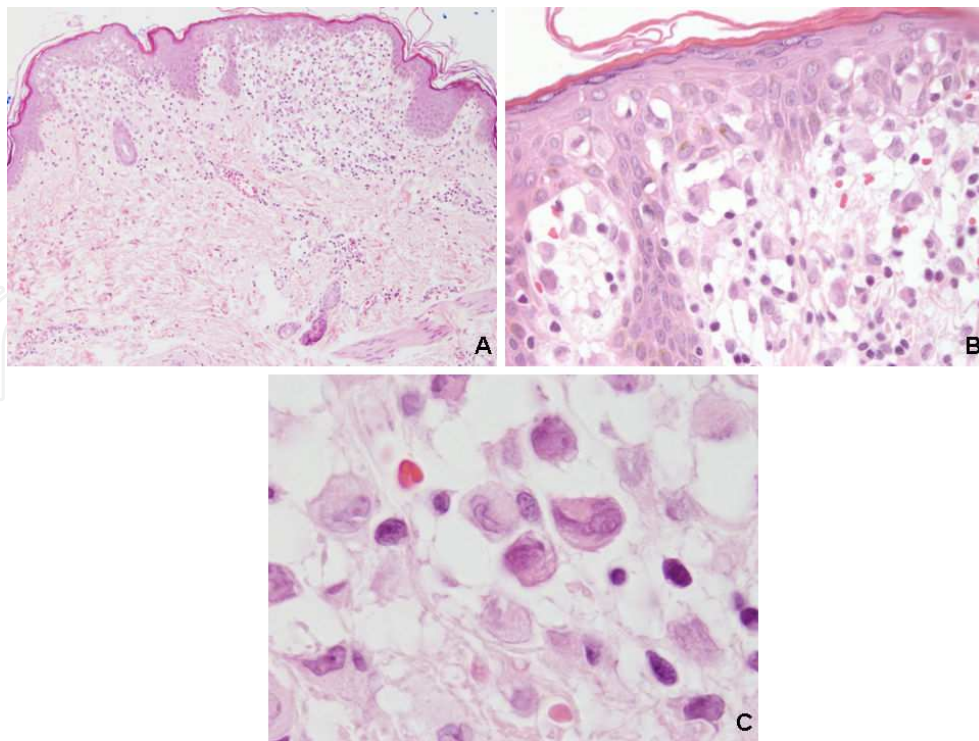


Figure 1. Histological features of Langerhans cell histiocytosis (LCH). A and B. Skin shows dermal infiltrate with epidermotropism. C. Cells with grooved nuclei.

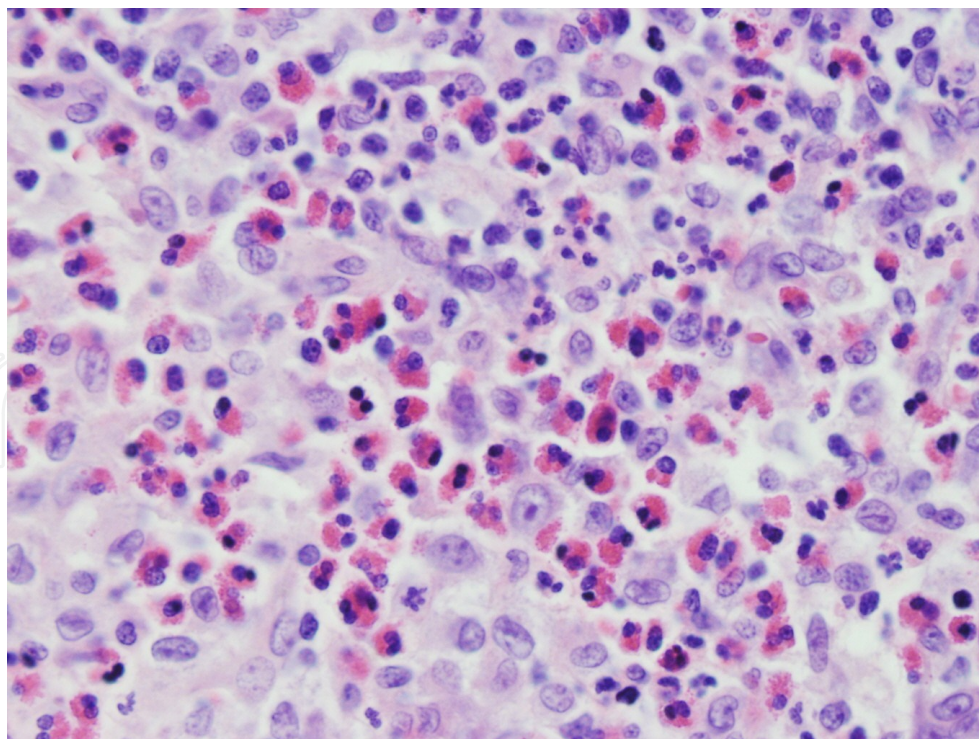


Figure 2. Histological features of Langerhans Cell Histiocytosis (LCH). Skin with inflammatory infiltrate composed of Langerhans cells admixed with abundant eosinophils and neutrophils.

2.3. Immunoprofile and electron microscopy

Identification of LC may be done by routine hematoxylin-eosin alone. However, confirmation requires positive staining for CD1a, S100 and langerin (CD207) (FIGURE 3), with variable expression of CD68 and usually absence of CD163 stain.

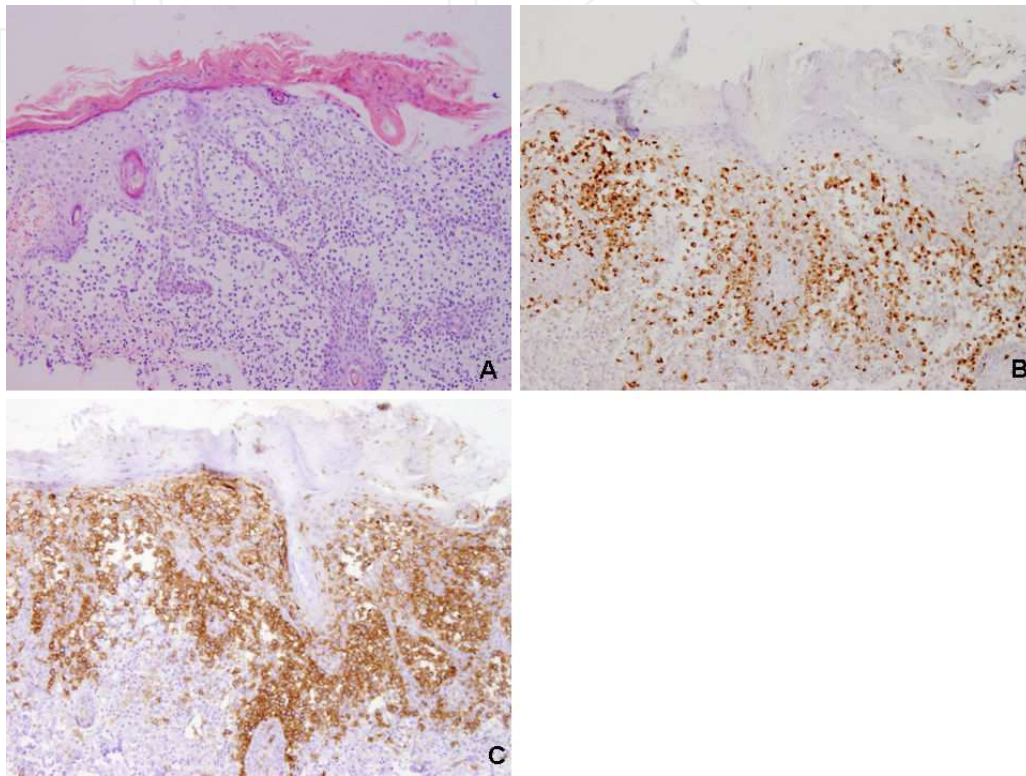


Figure 3. Histological features and immunophenotypic profile of Langerhans Cell Histiocytosis (LCH). A. Skin with dermal infiltrate and epidermotropism. B. Langerin immunostain (CD207) highlights neoplastic Langerhans Cells (LC). C. LC are positive for CD1a.

A novel antibody, JL1, has been described as a specific marker in LCH. Interestingly, LC in the epidermis of normal skin express langerin but not JL1; however both antibodies are expressed in inflamed skin [5]. In addition, a recent specific antibody to detect BRAFV600E mutation in LCH by immunohistochemistry is identified that can be used for routine screening [15]. E-cadherin expression has been reported as well (FIGURE 4). Electron microscopy can be used to demonstrate intracytoplasmic Birbeck granules of approximately 300 nm with a tennis-racket shape.

2.4. Differential diagnosis

Related and unrelated histiocytic disorders and benign LC proliferations lead to diagnostic pitfalls in LCH. Localized LC proliferations are seen in a vast number of skin conditions that may be reactive, but are often neoplastic. Similarly, histiocytic infiltrates in the dermis are very common, and appear in response to inflammatory conditions, infections and neoplasms.

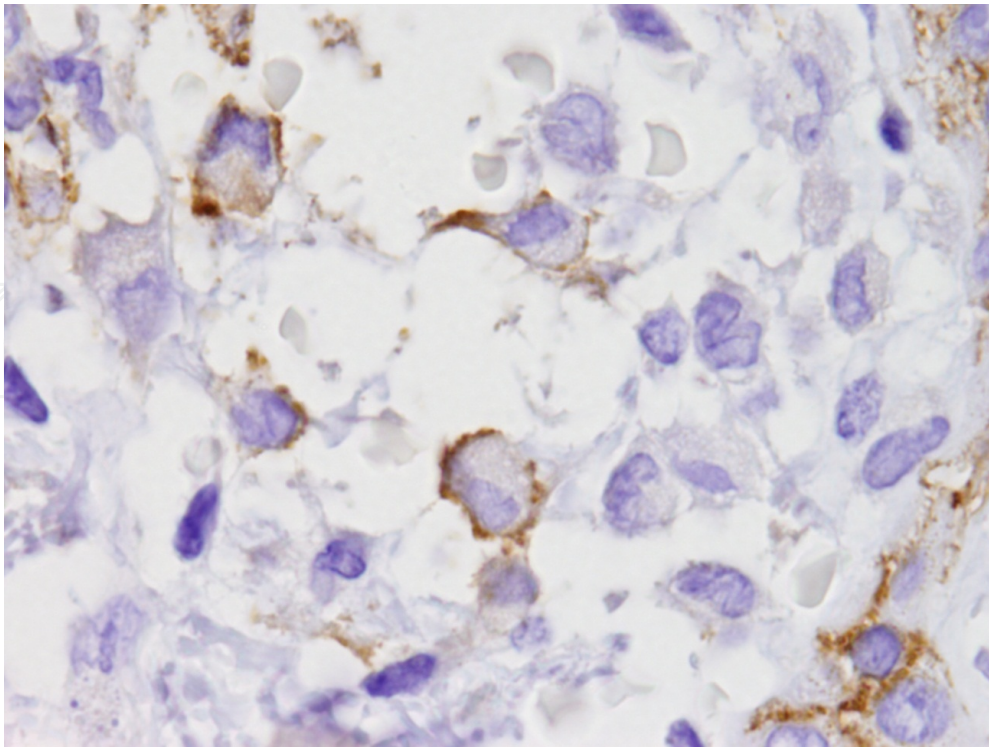


Figure 4. Immunoprofile of Langerhans Cell Histiocytosis. E-cadherin is positive in scattered LC.

LC microabscesses can sometimes be seen in the epidermis of spongiotic dermatitides and lichenoid dermatitis. LC are usually seen as small to large collection of pale staining/mononuclear cells, positive for CD1a and S100. These aggregates can mimic Pautrier's microabscesses in mycosis fungoides [16].

In children with eczematous eruptions and histiocytic infiltrates, langerhans cell hyperplasia (LCHP) has to be ruled out. LCHP can mimic LCH and has been reported in cases of human scabies, arthropod bite reaction, contact dermatitis and pityriasis lichenoides and usually cells express CD1a and S100 [17-20]. The increased in LC in the dermis can be explained by the antigenic stimulation and cutaneous trauma that produce LC migration into the skin, especially when occurs in perivascular areas. Therefore, the clinical context in which the lesion or proliferation arises is important in the differential diagnosis.

Likewise, reactive histiocytosis in the skin can be seen secondary to foreign body reactions to implants and polarizable material is often identified [21]. LC can also mimic dermal histiocytes found in inflammatory and infectious conditions (mycobacteria, fungal and parasitic processes), thus clinicopathologic correlation, immunostains and appropriate special stain can be helpful in the differential. Eosinophils, a common finding in LCH can also be seen in a variable number of conditions such as drug eruptions, urticaria and Wells syndrome.

Furthermore, a group of conditions named as non-Langerhans cells histiocytosis (N-LCH) can mimic LCH. These entities are characterized by accumulation of histiocytes and immunohistochemistry is a useful adjuvant for the distinction; some of them will be describe in the following pages [22].

Rosai-Dorfman disease (RDD) is a self-limiting histio-proliferative disorder that can compromise almost any organ, and occasionally involves the skin [23]. Cutaneous RDD is characterized by the presence of a dense infiltrate of foamy histiocytes with emperipolesis surrounded by a background of lymphocytes, plasma cells and neutrophils. Occasionally, eosinophils can be increased [24]. Histiocytic cells in RDD usually express CD68 and S100 and lack of CD1a staining.

The Juvenile Xantogranuloma (JXG) family is a spectrum of conditions characterized by expression of factor XIIIa, CD68, CD163, fascin and CD14 but lack immunoexpression for CD1a and S100 [22, 24]. The clinical setting is useful to differentiate the entities. JXG is a common member of this family. JXG presents as a solitary skin lesion, most commonly seen throughout the first two decades of life, although some cases have been described in extracutaneous sites. JXG is characterized by circumscribed dermal nodules composed of true foamy histiocytes and Touton giant cells. Touton giant cells are seen in the majority of cases, and show a wreath of nuclei around a homogenous eosinophilic cytoplasm and xanthomatous periphery (FIGURE 5) [22, 25]. JXG has been reported associated with neurofibromatosis type 1, hemophagocytic lymphohistiocytosis and juvenile myelomonocytic chronic leukemia [26-27].

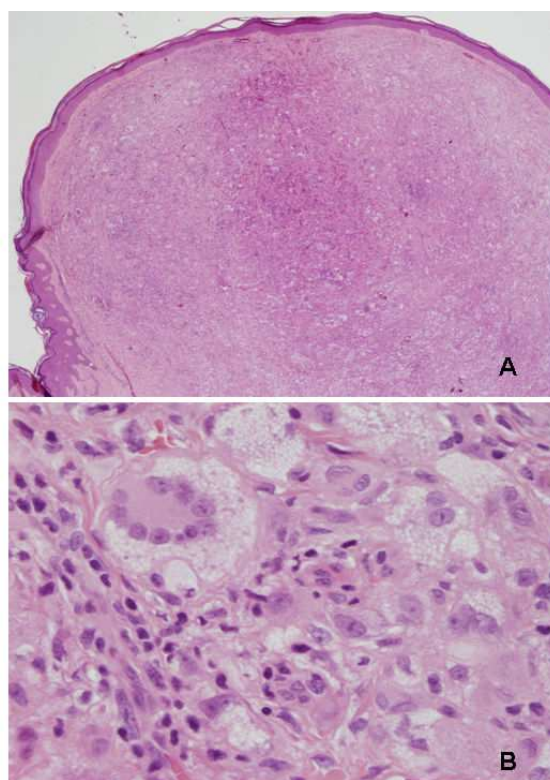


Figure 5. Juvenile Xantogranuloma (JXG). A. Dome shape lesion with dermal infiltrate. B. Touton giant cells in JXG.

Erdheim-Chester disease (ECD) may also be confused by LCH. ECD is a systemic disease which usually presents with lung and symmetrical long bony lesions. It can also involve the skin and clinically appears with pruritic rash, xanthelasma and eyelid xanthomas, in a background of normal lipid profile [28]. ECD displays collections of enlarged histiocytes with

clear cytoplasm. ECD can be differentiated from LCH by immunohistochemical studies; ECD cells usually express CD68, CD163, fascin, while negative for S100, langerin and CD1a. Birbeck granules are absent [22].

Finally, a hybrid entity, indeterminate cell histiocytosis (immature dendritic cells) is an uncommon disease with features between LCH and N-LCH. Although it shows immunophenotypic similarities with LCH such as CD1a positivity and variable expression of S100 and CD68, lacks of Birbeck granules by electron microscopy.

Malignant neoplasms such as histiocytic sarcoma (HS), myelomonocytic leukemia, anaplastic large cell lymphoma and mast cell proliferations should also be considered into the differential diagnosis [24, 29]. HS is a malignant proliferation of mature histiocytes. Skin presentation is often seen, although multisystemic involvement is a frequent feature. Histologically, HS show cytologic atypia, pleomorphism and mitotic activity; the immunophenotypic profile demonstrates that the malignant cells are usually positive for CD68, CD163, CD14, CD4, CD11c and lysozyme. Birbeck granules are not seen [30].

Interestingly, cases of LCH have been found in association with malignancy including solid tumors and hematologic neoplasms [31-32]. In a recent study, adult patients with LCH presenting in the skin have shown an increased risk of a second hematological malignancy [12]. They can present with a solitary papule/nodule or multiple reddish-brown papules. The literature includes reports of LCH and non-Hodgkin lymphoma, Hodgkin lymphoma, acute lymphoblastic leukemia [33] and acute myeloid leukemia (AML) [31, 34-38]. One of the current theories that could explain the association between LCH and AML relates to trans-differentiation of hematopoietic lineages as LC, dendritic cells, and monocytic/histiocytic cells share common multipotential progenitor cells that reside in the bone marrow [39-42]. These cases suggest a clonal relation between the two neoplastic diseases and support the theories of lineage plasticity in mature and immature lymphoid tumors.

2.5. Prognosis

LCH is a heterogeneous disease with different outcomes including self healing-limited and life-threatening or fatal disease [14]. Clinical staging is a prognostic marker in neonates and infants [14, 43]. Unifocal/localized disease has a good prognosis and long term survival. In contrast, the clinical course and the prognosis of multifocal and multisystemic disease are difficult to predict. When disseminated disease is present at the time of diagnosis, the disease is usually associated with poor outcome [14, 43]. Therefore, identification of specific biomarkers is needed in order to determine who will have limited disease and who will benefit from systemic therapy.

Using OncoMap, the activating mutation BRAF V600E mutation has been recently identified as a recurrent molecular genetic aberration in LCH, however, its clinical significance is still unknown [7, 9, 14]. BRAF V600E mutations have been identified in LCH and ECD, however, they have not seen in RDD and JXG [44]. Interestingly, inhibition of BRAF V600E may be used in the near future as a therapeutic target for LCH similar to what is being done for melanoma, gliomas and hairy cell leukemia. Patients with positive mutation status and protein expression

by screening may be allowed for protocol or clinical trial entry with use of Zelboraf (vemurafenib), an FDA approved therapy. Recently, a variant BRAF V600D mutation has been reported in congenital, benign, self-regressive LCH [14]. E-cadherin expression was found as a marker of good prognosis and limited disease, however, the results have not been validated in separated studies [10, 45]. The role of Ki67 as a prognostic marker is limited. One of the most common abnormalities seen in LCH is TP53 over-expression (FIGURE 6); however, TP53 mutations have not been identified [7, 9, 46].

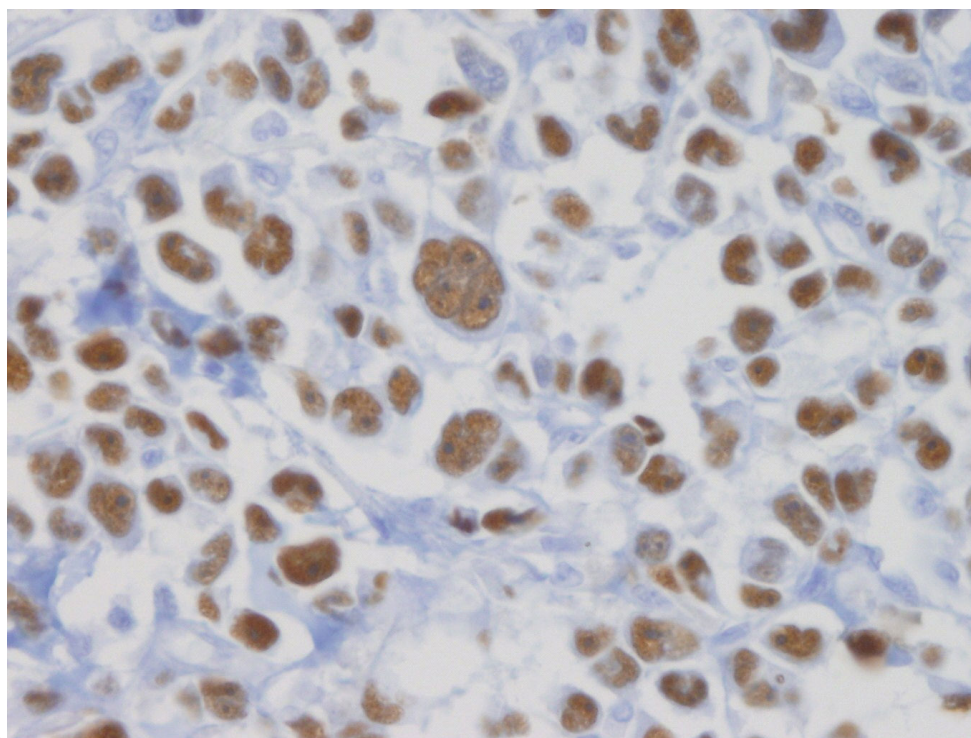


Figure 6. TP53 over-expression in Langerhans Cell Histiocytosis (LCH)

2.6. Treatment

Patients require complete clinical history, physical examination, and a comprehensive laboratory and radiographic evaluation [47]. The Histiocyte Society recommends that in order to determine the adequate research protocol, patients should be stratified based upon extension of the disease (unifocal, multifocal/multysystemic), involvement of risk organs (hematolymphoid including spleen and liver) and central nervous system risk lesions [48-49]. Patients with unifocal disease limited to the skin require follow up-and usually no additional treatment

is necessary as spontaneous regression may occur. Topical therapy with steroids or PUVA may be used [48]. In cases of multiorgan/multisystemic involvement, the treatment is controversial as those patients have a variable clinical course; it includes systemic chemotherapy with assessment of clinical response after the first 6 weeks of treatment. Monoclonal antibodies are under research. In one large study, Vinblastine with or without prednisolone was the most common chemotherapy regimen, and the overall survival and event free survival rates were 84% and 51.5%, respectively with a medium follow-up time of 8 years [50]. The LCHIII treatment protocol is a common strategy used in patients with multiorgan involvement [51]. Targeted therapy with vemurafenib, an inhibitor of mutated BRAF, has been used in few patients with LCH harboring BRAF V600E mutation [52].

3. Langerhans cell sarcoma

3.1. Clinical presentation

Thirty one cases of LCS have been reported to date [53]. Skin can be a single site involved by LCS or can be seen as part of widespread disease. Cutaneous involvement is present in more than half of cases. Multiorgan involvement includes lymph node, lungs, liver, spleen and bone. Skin biopsy is an accessible and a useful way to demonstrate malignant LC. LCS occurs in all age groups with a male:female ratio 1:1. LCS can appear as an increasingly progressive malignant disease followed by multiple LCH recurrences, *de novo* and with underlying myeloproliferative disease [53-55]. *De novo* or primary LCS has been reported exclusively in adults, without previous evidence of LCH. In a recent publication, a case of trans-differentiation of acute B-lymphoblastic leukemia into a LCS has been documented, as both show identical IGH@ gene rearrangements [54].

3.2. Histopathology

Skin biopsy usually shows an infiltrative and poorly defined high grade malignant neoplasm composed of large cells with grooved nuclei, granular chromatin, prominent nucleoli and high mitotic rate. Although inflammatory infiltrate can be present and abundant, especially if there is associated necrosis, eosinophils are usually scattered. Epidermis can be ulcerated and epidermotropism is seen [2, 55]. (FIGURE 7)

3.3. Immunoprofile and electron microscopy

Malignant LC are usually positive for CD1a, S100 and Langerin (CD207) (FIGURE 8). There is lack of reactivity for T and B cell antigens. Neoplastic cells have a high proliferative Ki67 index and overexpress p53. CD56 /neural cell adhesion molecule (NCAM) positivity has been found expressed in LCS [56]. A broad panel of immunohistochemical stains is used to confirm LC due to the atypical features of the neoplasm, and electron microscopy is usually performed for identification of intracytoplasmic Birbeck granules.

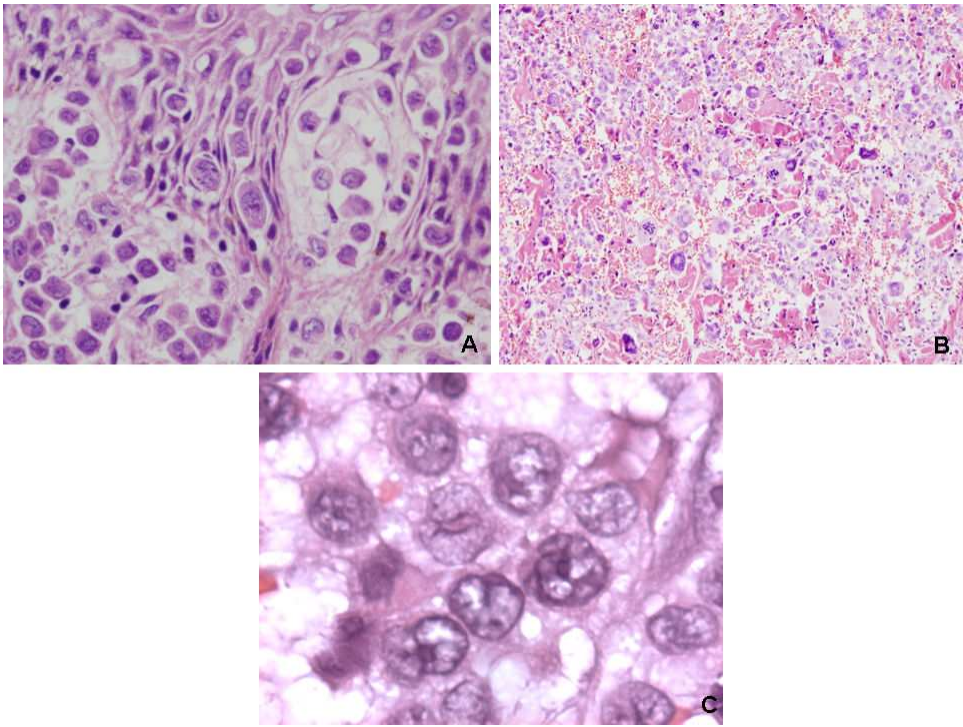


Figure 7. Histological appearance of Langerhans Cell Sarcoma (LCS). A. Dermal infiltrate of large atypical cells with epidermotrophism. B. Bizarre and pleomorphic cells with abundant mitotic figures and lack of cohesiveness. C. Detailed figure of LCS cells with prominent intranuclear inclusions.

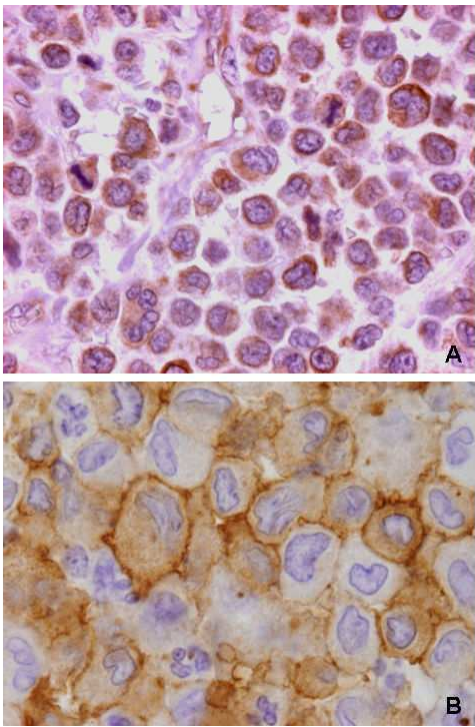


Figure 8. Immunoprofile of Langerhans Cell Sarcoma (LCS). A. Langerin (CD207) expression in cells with malignant features. Numerous mitotic figures are identified. B. Malignant cells retain CD1a expression.

3.4. Differential diagnosis

Because of the marked pleomorphism and cytologic atypia, hematologic and nonhematologic entities must be considered in the differential diagnosis including malignant melanoma, carcinoma, mesenchymal malignant neoplasms and lymphomas with anaplastic features. Pleomorphic large cells may be mistaken for malignant melanoma, which shares S100 positivity but also expresses other melanocytic markers. LCS comprises cells with bizarre pleomorphic nuclei and abundant cytoplasm mimicking hematolymphoid neoplasms including anaplastic large cell lymphoma, anaplastic diffuse large B-cell lymphoma, plasma cell neoplasm with anaplastic features, lymphomatoid papulosis, peripheral T cell lymphoma and myeloid sarcoma (FIGURE 9) (TABLE 1) [55]. In those cases, immunohistochemical and molecular features are useful to distinguish the cell of origin.

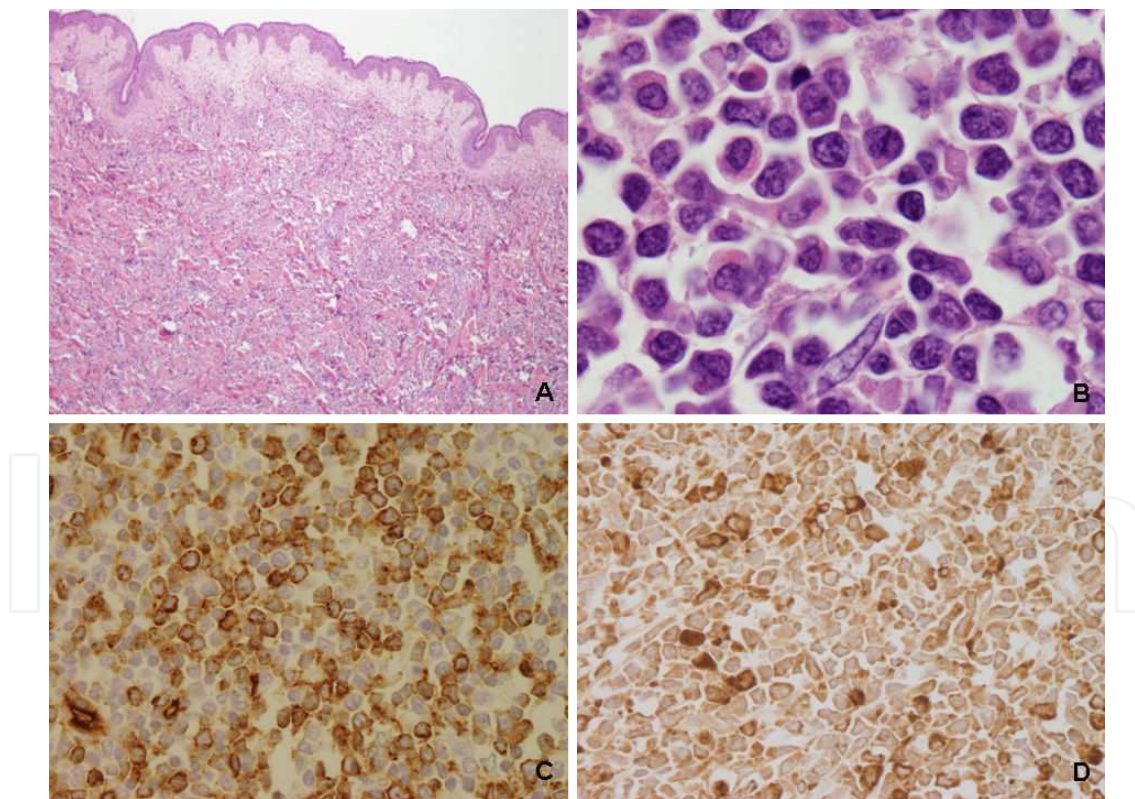


Figure 9. Myeloid Sarcoma. A. Skin shows a diffuse dermal infiltrate composed of malignant cells. B. Features of neoplastic cells with promyelocytic differentiation. C. CD34 stain is positive in the majority of cells. D. Myeloperoxidase (MPO) positivity in tumor cells.

DIFFERENTIAL DIAGNOSIS	Immunohistochemical marker
Melanoma	S100+, Melan A+, HMB45+
Anaplastic large cell lymphoma	CD30+, ALK+/-, EMA+, CD3-/+, CD43+
Histiocytic Sarcoma	CD68+, CD163+, CD14+, CD4+, lysozyme, S100+/-
Follicular Dendritic Cell Sarcoma	CD21+, CD23+, CD35+, CD68+/-, S100+/-, Clusterin+, CD45+/-
Interdigitating Dendritic Cell Sarcoma	S100+, CD21-, CD35-, CD1a-, fascin +, CD68-/+
Myeloid Sarcoma	CD34+, CD117+, MPO+, CD68+, lysozyme+

Table 1. Langerhans Cell Sarcoma (LCS) - Differential Diagnosis

3.5. Prognosis and treatment

Currently, no specific marker has demonstrated to predict prognosis in LCS. In a study, CD56 expression was associated to poor prognosis and the results have not been validated in a different set of patients [56]. Despite combination chemotherapy/radiotherapy and surgery, LCS is an aggressive high grade malignancy with poor prognosis, frequent recurrences and short survival, usually resulting in death within 1 year [2, 53, 55].

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