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Langerhans cell histiocytosis: A great imitator

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Abstract Langerhans cell histiocytosis (LCH) is an uncommon but serious inflammatory neoplasia that affects many organs, including the skin. Though uncommon, it should remain high on a clinician's differential diagnosis in treatment-resistant cases of conditions, such as seborrheic dermatitis, diaper dermatitis, arthropod bites, and many more. A thorough history and physical examination for each patient can aid in the diagnosis; however, if clinically suspicious for LCH, a punch biopsy should be performed. Histologic evaluation of LCH is often enough to differentiate it from the many clinical mimickers. Characteristic findings include a histiocytic infiltrate with "coffee bean"–cleaved nuclei, rounded shape, and eosinophilic cytoplasm. Immunohistochemical stains, including CD1a, S100, and CD207 (langerin) are often needed for a definitive diagnosis. Electron microscopy also demonstrates the ultrastructural presence of Birbeck granules, but this is no longer needed due to immunohistochemical staining. Treatment is often necessary for LCH, if systemic involvement exists.

Introduction

Langerhans cell histiocytosis (LCH) is an inflammatory neoplasia affecting multiple organ systems including the skin.[1] Though the etiology of LCH is unclear, most investigators hypothesize that LCH results from immunologic dysfunction, because higher levels of cytokines are found in the lesions compared with the normal surrounding tissue.[2] Additionally, recent evidence has demonstrated a *BRAF* gene V600E mutation in 38% to 69% of patients with LCH leading to subsequent activation of the RAS-RAF-MEK-ERK-MAP kinase pathway, suggesting insight into the etiology of LCH.[1]

Cutaneous LCH presents with diverse clinical findings, which contribute to high rates of misdiagnosis. Lesions may be either circumscribed or spread[3] and there may be either single or multiple lesions.[4] A retrospective study of 918 cases of LCH in China (newborns to patients 65 years of age) showed that cutaneous involvement typically presented as pinpoint erythematous or skin-colored papules or pustules.[5] Additionally, the wide variety of reported cutaneous morphologies of LCH also included hypopigmented or hyperpigmented macules or maculopapular lesions; papulopustular varicella–like eruptions; erythematous, lichenified, or poikilodermalike plaques; vesicles; vascular tumor–like lesions; purpuric macules; a red-blue nodule; erythematous vesiculopustules; ulcers; hemorrhagic lesions; yellow-orange papules; and violaceous papules and plaques.[1] Regardless of clinical presentation, lesions are frequently pruritic. Furthermore, one retrospective study reported that the most common sites of involvement were the trunk, head, and face, although the limbs, neck, armpits, groin, perineum, buttocks, and oral mucosa were also prevalent.[5]

Histopathologically, the lesions of LCH are composed of 12- to 15-μm cells with abundant eosinophilic cytoplasm.

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Their nuclei are irregular with prominent folds and grooves, fine chromatin, and indistinct nucleoli. Background eosinophils, lymphocytes, histiocytes, and neutrophils are often present in variable quantities. When LCH occurs within lymph nodes, it is often characterized by sinusoidal involvement. The characteristic immunophenotype of LCH includes expression of CD1a, S100, and langerin (CD207), with variable expression of CD68. On electron microscopy, elongated, zipperlike cytoplasmic structures measuring 200 to 400 nm × 33 nm, known as Birbeck granules, are observed.[1,6]

Currently, no standardized protocol exists for the treatment of isolated cutaneous LCH. Medium or high potency topical corticosteroids are considered first-line treatment, but are not always effective and recurrence is common after discontinuation.[7] In some cases, LCH can spontaneously regress without treatment. Other topical options include nitrogen mustard and tacrolimus.[8] Phototherapy with psoralen plus ultraviolet A or ultraviolet B light can be effective in patients as well.[8] Oral treatment options include methotrexate and thalidomide, both of which have been used to treat severe or recalcitrant LCH.[9,10] There are also several case reports of children and adults with cutaneous LCH being treated with imiquimod which resulted in clearance of lesions with minimal adverse effects.[7,11,12]

Due to the potential for significant organ involvement and poor prognosis, clinicians should accurately diagnose patients with this condition. This is often challenging for dermatologists, given a vast array of clinical presentations of LCH. Additionally, many commonly encountered dermatologic dermatoses clinically overlap with LCH, increasing the diagnostic difficulty (Figure 1). If clinically suspicious for LCH, a thorough physical examination and a skin biopsy for histology and immunohistochemical (IHC) staining are warranted for making the diagnosis. We discuss and differentiate LCH from the many imitators that clinicians may encounter.[1,8]

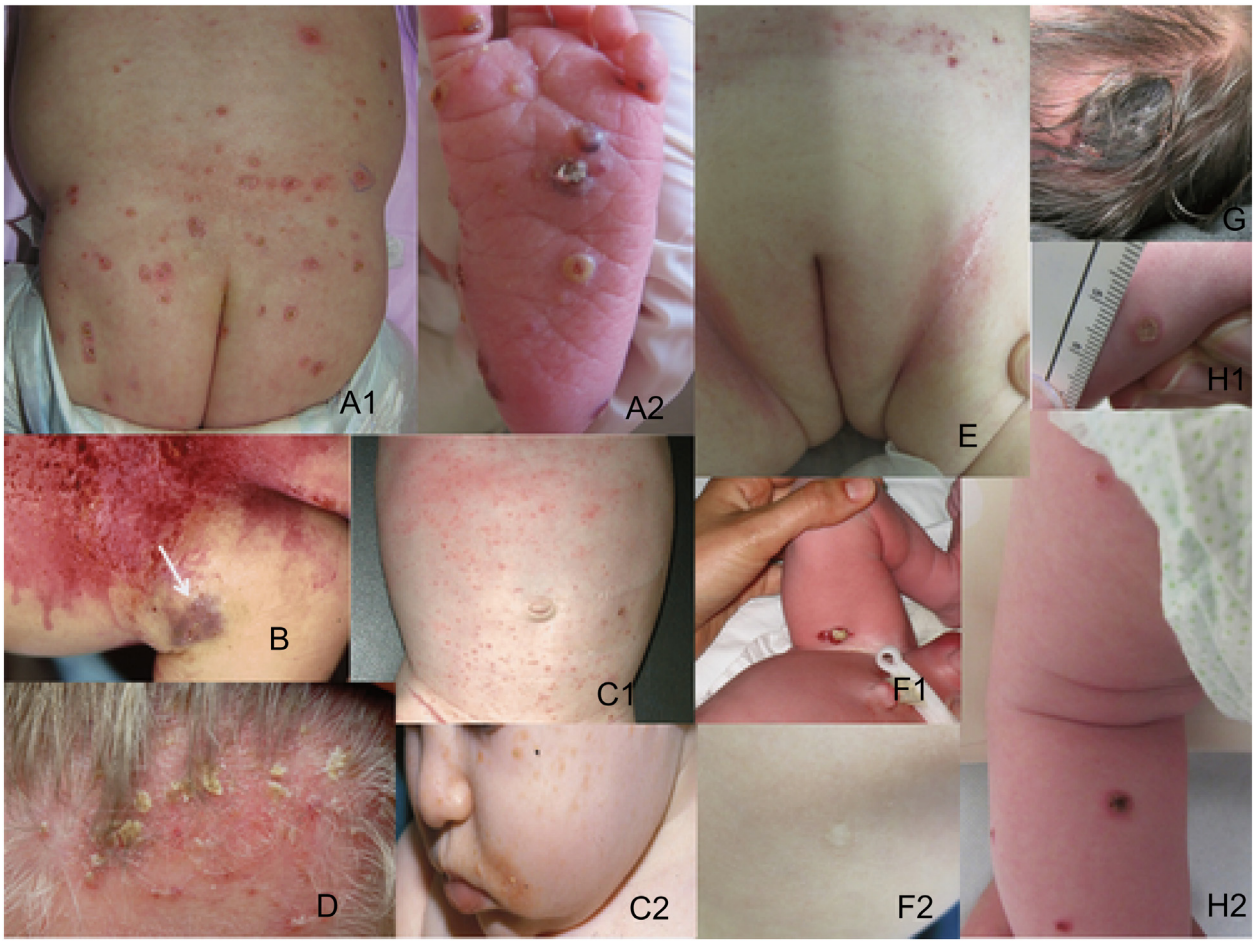

Fig. 1 The variable spectrum of skin manifestations in LCH.[13] Frames *A1* and *A2* show varicellalike eruptions from birth. Frame *B* shows red-blue nodules (arrow) at both buttocks after vaccination. Frames *C1* and *C2* show disseminated orange brown papules. Frame *D* shows purpuric seborrheic eczemalike lesions on the scalp. Frame *E* shows seborrheic eczema-like lesions and purpura. Frames *F1* and *F2* show pyogenic granuloma-like lesions, which healed leaving atrophic depigmented macules (*F2*). Frame *G* shows a solitary nodulonecrotic lesion on the scalp. Frame *H* shows widespread papulonecrotic and erosive/ulcerative lesions. LCH, Langerhans cell histiocytosis. Photo reproduced with permission from Morren et al.

Cutaneous dermatoses mimicking LCH

Seborrheic dermatitis

Seborrheic dermatitis is a common diagnosis encountered by dermatologists on a daily basis. This disease can occur in infants, also known as cradle cap, and in adults. Lesions typically consist of erythematous papules and patches with overlying greasy scale on the scalp, face, and chest. Though a benign diagnosis, recalcitrant disease or systemic manifestations should raise concern for an alternative diagnosis, such as LCH.

Like seborrheic dermatitis, LCH often presents with erythematous or brown papules on the scalp, neck, axilla, and trunk, accompanied with erosion and scale; however, on closer examination, lesions of LCH include more discrete papules, unlike the more ill-defined lesions of seborrheic dermatitis.[8] As a multisystem disease, systemic findings may also coincide with cutaneous lesions further differentiating the two entities.[14] Additionally, LCH will not respond to topical antifungal or low-potency topical corticosteroids. As a result, clinicians should have high suspicion for LCH if patients fail to respond to treatment early on.

The current literature reveals several studies reporting children with "seborrheiclike" lesions who were diagnosed with LCH. In one report of 32 patients with LCH and cutaneous lesions, 17 had seborrheic eczema–like lesions on the scalp and large folds (Figure 1, frames *D* and *E*). The misdiagnosis of patients with seborrheic dermatitis and cradle cap ultimately led to the delayed diagnosis of LCH.[13] Similarly, another report included 10 children with LCH presenting with cutaneous lesions, seven of the 10 having erythematous scaly papules on the scalp. Petechiae were also present in several of their patients; thus, they suggested that petechiae in addition to a seborrheiclike eruption might suggest a diagnosis of LCH.[15]

Additionally, a 4-month-old boy, presenting with a nonspecific eruption since birth initially treated as dermatitis, was reported. The eruption had a seborrheiclike component with scaly erythematous papules on the eyebrows and axillae (Figure 2). The eruption was much more extensive involving the patient's trunk and diaper area and had a few petechiae as well. Laboratory data indicating systemic involvement and a punch biopsy ultimately led to a diagnosis of LCH.[13]

Aside from the history and physical examination, histopathology can also aid in differentiation between seborrheic dermatitis and LCH. An eosinophilic infiltrate, as well as mononuclear epithelioid cells with kidney bean–shaped nuclei that stain positive for CD1a, S100, and langerin (CD207) via immunohistochemistry, is diagnostic of LCH.[16] Hemorrhage may also exist within the dermal papillae.[17] Alternatively, histologic examination of seborrheic dermatitis will show focal parakeratosis in the horny layer of the epidermis, plugged follicular ostia, and spongiosis.[18]

Overall, a thorough history and physical examination is often adequate to differentiate LCH from seborrheic dermatitis. If the patient only presents with cutaneous lesions, a definitive way to differentiate the two entities is by histopathology. Physicians should also consider LCH higher in their differential if disease is treatment resistant to standard treatment regimens for seborrheic dermatitis.

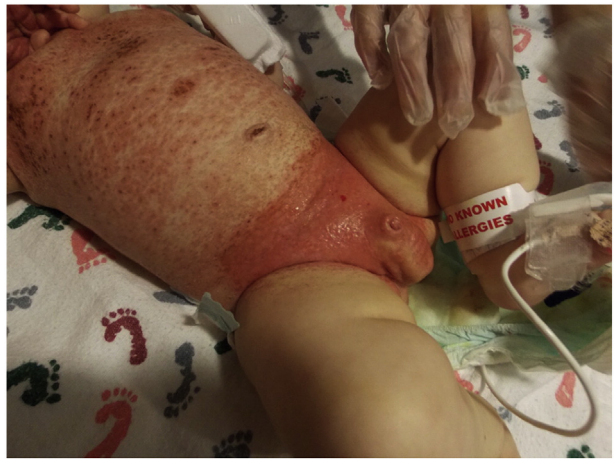

Fig. 2 Sharply demarcated erythematous, weeping eruption in the diaper area with diffusely distributed papules over the trunk.[14]. Photo reproduced with permission from Porto et al.

Diaper dermatitis

Diaper eruptions are a common skin condition among infants. Candidosis and irritant contact dermatitis account for a majority of these eruptions. Moisture, friction, urine, and feces in the diaper area will damage the stratum corneum, leaving the skin vulnerable to irritants that cause inflammation. Urine overhydrates the skin, increasing skin permeability, while also increasing the pH of the diaper area. Bile salts and other enzymes from the feces contribute to the erythema and damaged epidermis.[19] The disease begins with scattered erythematous papules and progresses to extensive erythematous punched-out lesions with maceration. Though diaper dermatitis is a benign condition, persistent cases raise the possibility of an alternative systemic disease in the infant, such as LCH.[20]

Several cases of LCH presenting as resistant diaper dermatitis exist in the literature.

There is a case of a 12-month-old girl with a nonhealing oral ulcer (Figure 3, frame *A*) and chronic diaper rash (Figure 3, frame *B*) that was resistant to topical steroids and antifungals. Physical examination revealed petechiae, and histopathologic examination demonstrated epithelioid cells with coffee bean nuclei staining positive for S100, CD1a, and CD207 (langerin). Magnetic resonance imaging revealed bone involvement consistent with multisystem LCH. Treatment for LCH was initiated, and the intraoral mass and cutaneous lesions diminished.[16]

Similarly, a 6-month-old with diaper dermatitis resistant to barrier creams and antifungals was reported. A thorough physical examination revealed hepatosplenomegaly and inguinal lymphadenopathy. A punch biopsy confirmed the diagnosis

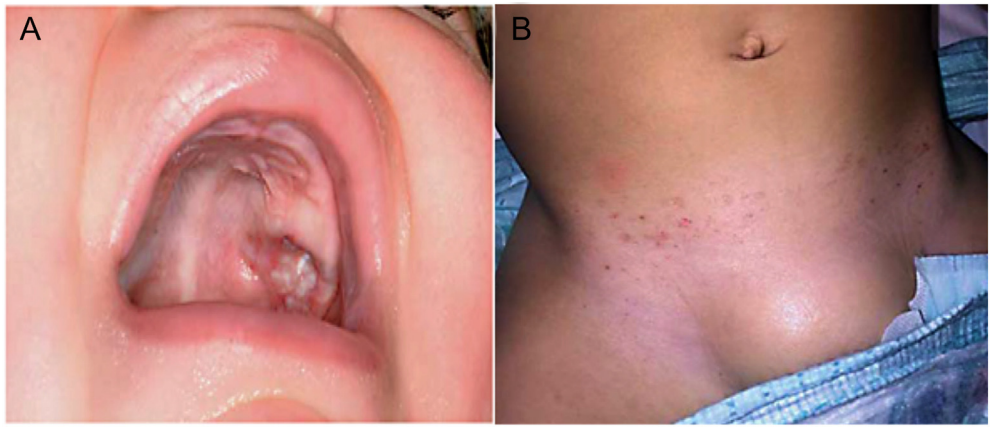

Fig. 3 LCH mimicking seborrheic dermatitis.[16] Frame *A* shows a 1.5-cm ulcerated lesion involving the left palatal mucosa. Photo reproduced with permission from Dr Leonard B. Kaban. Frame *B* shows erythematous to violaceous nonblanching papules with central hemorrhagic crust and surrounding petechiae on the right abdomen. Photo reproduced with permission from Dr Johanna S. Song. LCH, Langerhans cell histiocytosis.

of LCH.[21] A third case that has been reported revealed a patient with mucosal edema and gingival hyperplasia in addition to resistant diaper dermatitis. Ultimately, a punch biopsy confirmed LCH.[22]

Histologically, diaper dermatitides can vary, as there are different stages associated with the condition. Papillary edema and an inflammatory infiltrate are seen to a varying degree across each clinical stage. As the disease progresses, capillaries become more dilated, and endothelial swelling is more apparent. Parakeratosis, spongiosis, and a leukocytic infiltrate may be observed in advanced stages of diaper dermatitis.[23] Histiocytes should not be present, and if so, this finding would warrant further IHC staining.

Each of these cases highlights unique clinical differences, when differentiating diaper dermatitis from other dermatologic diseases. The presence of petechiae, a protuberant abdomen, or mucosal edema and gingival hyperplasia should prompt a physician to perform a punch biopsy to confirm diagnosis.[16,21,22]

Cherry angioma

Cherry angiomas are common, benign collections of dilated capillaries frequently encountered. Though common, lesions may be confused with the initial presentation of LCH. Specifically, if any secondary changes occur, they may appear as a cherry papule (Figure 1, frames *F1* and *F2*); however, if truly LCH, they will progress to erythematous, scaly papules and purpuric lesions.

The literature contains scant evidence of cherry-colored papules as the initial presentation of LCH, except for two cases. The first case was that of a 4-month-old who presented with multiple palpable, erythematous, and smooth cutaneous lesions on the trunk, resembling cherry angiomas. History and physical examination were significant for failure to thrive and respiratory distress. Histologic evaluation revealed proliferative histiocytic cells, eosinophilic cytoplasm, and hemorrhage in the dermal papillae, consistent with a diagnosis for LCH. As the patient lacked any organ involvement, he was monitored clinically with the majority of his skin lesions resolving.[17]

The second case involved a 9-month-old boy presenting with failure to thrive in addition to an intermittent erythematous scaling rash, plus purpura on the face and trunk, present since birth. Some of the lesions were erythematous and dome-shaped lesions, similar in appearance to a cherry angioma. These lesions eventually developed scaling more typical of LCH, and a skin biopsy revealed histiocytes with eosinophilic cytoplasm, hemorrhage in the dermal papillae, and Birbeck granules.[17]

As illustrated by both cases, initial lesions of LCH may be confused with cherry angiomas, but in both cases, the lesions further evolved into the typical appearance of LCH.

Additional differentiation can be made histologically because cherry angiomas are typically polypoid with the papillary dermis containing numerous dilated capillaries with thin lumina as well as endothelial cells organized in a lobular formation.[24]

Varicella

Varicella zoster is a dormant viral infection of the dorsal nerve roots typically presenting on the skin during periods of immunosuppression. Infection in childhood is often diffuse and characterized by pink umbilicated papules and vesicles on an erythematous base in different stages of evolution.[25,26] In adults, a similar rash occurs but is more often grouped and dermatomal. Given the diffuse nature of the rash (both congenital and noncongenital forms) and similarities in appearance to LCH, it can easily be misdiagnosed and treated as a viral infection (Figure 1, frames *A1* and *A2*).

Several cases in the literature describe LCH mistakenly diagnosed as varicella in children and infants. For example, a 3-week-old infant presented with a rash, where there was

concern for congenital varicella, and the infant was prescribed acyclovir therapy. The rash somewhat improved but the infant continued to develop new lesions, prompting a biopsy which diagnosed LCH.[25] A second case described a 1-day-old boy presenting with a 1-cm erosion on his left toe with surrounding vesicles and yellow papules. A direct fluorescence examination was negative for Herpes simplex virus types 1 and 2 (HSV-1, HSV-2), and histology revealed a dermal infiltrate of large histiocytic cells staining positive for S100, CD1a, and CD207 (langerin). The patient was monitored clinically, and over the next year the lesions disappeared leading to a diagnosis of self-healing LCH.[27]

A third case described a 12-month-old girl who presented with disseminated, partially crusted papules and pustules, eczematous lesions in the retroauricular region and on the scalp, and ulcerated nodules of the legs.[27] She was initially diagnosed with varicella; however, the lesions persisted, despite antiviral treatment. A computerized tomography of the chest revealed cysts and honeycombs consistent with a diagnosis of LCH. Histopathologic examination demonstrated a dermal infiltrate of large cells staining positive for S100, CD1a, and CD207 (langerin). Due to systemic involvement, she was placed on chemotherapy, and the cutaneous lesions resolved and lung involvement diminished.[27]

Lastly, a 5-month-old boy presented with multiple, pinkish-yellow, umbilicated, varicelliform vesicles starting on the scalp and spreading to the trunk and intertriginous areas. Topical antibacterial and antiviral therapies failed, but histopathologic study lead to a diagnosis of LCH.[26]

Based on these examples, a varicelliform eruption can be difficult to distinguish from LCH in infants and young children. Failure to respond to antivirals and systemic clinical manifestations should guide clinicians toward a nonviral diagnosis. Testing for HSV-1, HSV-2, and varicella zoster virus should also be performed to rule out a varicella. Histopathology, showing acantholysis, margination of nuclear chromatin, multinucleation, and nuclear inclusions, with an inflammatory infiltrate consisting of lymphocytes and neutrophils, will confirm a diagnosis of varicella over LCH.[28]

Intertrigo

Intertrigo is a common dermatosis that is the result of friction or rubbing of the skin folds, leading to erythema and maceration. Bacterial and yeast growth and seborrheic, atopic, and contact dermatitis have all been implicated as alternative etiologies. Treatment revolves around keeping the skin folds dry and protected with a barrier cream. Topical antibacterial or antifungal agents and corticosteroids may also be helpful, depending on the inciting factor. Though a common and benign disorder, intertrigo can easily be confused with LCH which also has a predilection for intertriginous regions.[29]

Several cases in the literature highlight treatment-resistant intertrigo that upon further investigation was confirmed to be LCH. A 29-year-old man with an axillary and inguinal eruption failed to respond to antifungal treatments. His lesions were circumscribed, erythematous, and nonscaly, resembling intertrigo. A punch biopsy revealed oval-shaped cells with grooved nuclei, accompanied by an inflammatory infiltrate comprised of lymphocytes and eosinophils. The ovoid cells stained positive for S100 and CD1a. Because there were no systemic findings, a diagnosis of pure cutaneous LCH was made.[29]

Additionally, there was a 59-year old woman who presented with a 3-month history of painful and ulcerated intertrigo in the inguinal and inframammary regions. The patient also had polydipsia and polyuria despite managed diabetes mellitus. The histopathology showed a histiocytic cell infiltrate in the papillary dermis with eosinophilic cytoplasm. Electron microscopy revealed Birbeck granules, and immunohistochemical stains were positive for S100 leading to the diagnosis of LCH.[30]

Lastly, a 16-month-old patient presented with 12 months of an erythematous, eroded eruption in the axillae, groin, and natal cleft. There were also overlying erythematous papules and a purulent exudate. A comprehensive workup was unremarkable including blood tests, bacterial culture, skin scraping, skeletal X ray, respiratory function testing, and bone marrow biopsy. Ultimately, a punch biopsy led to the diagnosis of LCH, and the patient's disease remitted after treatment with aqueous nitrogen mustard.[31]

As these cases highlight, the clinical presentation of intertriginous LCH can be easily confused with intertrigo. Persistence despite failed treatments is one clue, but ultimately pathologic study should make the diagnosis of LCH.[32]

Arthropod bites

Langerhans cells are typically involved in normal immune responses. Some cutaneous conditions that involve antigenic stimulation may show a Langerhans cell infiltrate and can make the differentiation of LCH from other diagnoses more difficult. Arthropod bites are one example of this, as they lead to an immune response that may result in a CD1a positive infiltrate. Additionally, arthropod bites are more likely to cause positive CD1a staining and Langerhans cell recruitment due to the insect saliva and epidermal trauma compared with other antigenic dermatoses.[33]

Scabies is one example of a typical arthropod bite that can lead to this unclear diagnosis. This is further complicated by the fact that scabies can have diverse cutaneous signs.[34] For example, scabies infestation can present as pustules, vesicles, erythematous, ulcerated papules and plaques, or petechiae and purpura.[8]

Typical histologic features of scabies include acanthosis, spongiosis, and intradermal vesicles.[35] There is also a presence of a superficial and deep dermal perivascular and interstitial infiltrate composed of T lymphocytes, macrophages, eosinophils, and histiocytes that stain positive for CD1a and S100.

This has been highlighted by the overlapping histology between these two conditions in a 6-month-old girl who presented with reddish-brown papules and nodules on her

stomach. Originally, she was diagnosed with contact dermatitis, but upon failure of treatment and the spread of her lesions to her hands and feet, along with new scaling, a skin biopsy of a lesion on her trunk was performed. Histologic findings revealed infiltrates of lymphocytes, eosinophils, and histiocytes in the upper part of the dermis. The histiocytes stained positive for CD1a and S100, and a diagnosis of LCH was made; however, an in-depth history revealed that the patient's mother had pruritus and nodules representative of scabies. A skin scraping of both the mother and patient showed mites and eggs within the lesions and a new diagnosis of scabies was made.[36]

Another case was that of a 5-month-old boy initially diagnosed with Letterer-Siwe disease, a former classification of LCH, due to the presence of an infiltrate consisting of eosinophils and atypical histiocytes. In addition, electron microscopy revealed Birbeck granules, a classic finding in LCH. Despite the histologic similarities to LCH, it was later revealed the patient had scabies.[34]

These examples demonstrated the importance of a thorough history and physical examination. In addition to a history and physical examination, the presence of pruritus may also differentiate scabies from LCH. Additionally, a skin scraping with mineral oil of a representative lesion should reveal mites and eggs, further aiding in differentiating the two entities.[36]

As both LCH and arthropod bites have similar histopathologic findings, it is necessary to distinguish the CD1a expression in an arthropod bite versus that of LCH. The histology of scabies lesion will often have scattered CD30+ lymphocytes present. Conversely, LCH will have Birbeck granules, however, there have been reported cases of Birbeck granules in patients with scabies, therefore, the presence or absence of CD30+ is a good indicator to differentiate between the two.[34] Also, the neoplastic Langerhans cells of LCH will have more irregular and grooved nuclei compared with normal Langerhans cells. Additionally, the CD1a expression in arthropod bites is dendritic, whereas in LCH they are membranous and cytoplasmic.[33]

Differentiating arthropod bites and LCH is particularly difficult due to not only similar cutaneous findings, but also remarkably similar histologic findings. A thorough history is especially important in these cases as seen in the patient, where his mother's clinical manifestations helped to determine the patient's findings. In addition, it is important to use dermatoscopy to view mites and to be well versed in the histologic differences between arthropod bites and LCH, such as noting the presence of CD30+ in arthropod bites.[33,34,36]

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic skin condition that can be caused by genetic, hormonal, and environmental factors that plug follicles, rupture the ducts, and result in inflammation, epithelized sinuses, and abscesses. The lesions are located in the axillary, inguinal, and perianal and perineal regions.[37] Similarly, LCH may manifest as brownish plaques, red or purple papules, as well as ulcers and fistulas. Thus, a thorough history and physical is necessary in a patient presenting with deep, painful acneiform nodules that are suggestive of HS to rule out LCH.

One case report described a 42-year-old man with a 22-year history of painful nodules and ulcers in the axillary and perianal regions. The lesions were reddish-purple papules, with ulcers and fistulas, and purulent discharge. The patient was initially diagnosed with HS; however, he developed a pneumothorax prompting a skin biopsy. Histology was consistent with a diagnosis of LCH (Figure 4).[38]

A second case report discussed a 32-year-old man with a previous diagnosis of HS presenting with worsening dyspnea and chest tightness. Biopsy of a skin lesion in the axilla revealed that the diagnosis was, in fact, LCH. Unfortunately, this diagnosis was made late and although his skin lesions improved with chemotherapy, his lung function continued to worsen.[39]

On histology, HS demonstrates weak support structures at the intersection of the follicular duct and sebaceous glands. Follicular occlusion and hyperkeratinization rupture pilosebaceous units. As a result, follicular contents leak out into the dermis activating the immune response and causing the resultant inflammation, tissue damage, and abscess formation. Constant keratinization of the ruptured follicle results in permanently dilated pores. These histologic findings make it easier to differentiate between HS and LCH.[40]

HS is a painful, chronic skin disease and parallels the clinical course of LCH in many ways. A comprehensive physical examination and history, coupled with histologic examination, will help differentiate HS and LCH.

Lichen aureus

Lichen aureus (LA) is a chronic condition, often affecting young adults, that presents as localized yellow- or bronze-colored macules and large, irregular plaques. The lesions are usually asymptomatic and solitary, but they may be seen as multiple macules in a linear or zosteriform arrangement with pain and pruritus.[41] LCH can occur in the same age group and presents with papules that coalesce to form plaques, as well as bronzing of the skin. The two entities can be easily confused.

The clinical similarity between the two conditions occurred in a 13-year-old boy with a slow-growing, nonpruritic lesion, in addition to golden, red-brown–colored, confluent macules and papules on the skin of his mons pubis along with overlying scale. Although the clinical manifestation mimicked LA, a biopsy revealed a superficial dermal infiltrate composed of large cells with eosinophilic cytoplasm and Birbeck granules that stained positive for S100, thus confirming LCH.[42]

Histopathologic examination of LA typically reveals vacuolization of the basal layer of the epidermis and dense inflammatory cell infiltrate in a bandlike distribution in the dermis.[43] Both lymphocytes and histiocytes are present in addition to hemosiderin-containing macrophages which can be identified with a Prussian blue stain. In half of the cases, a

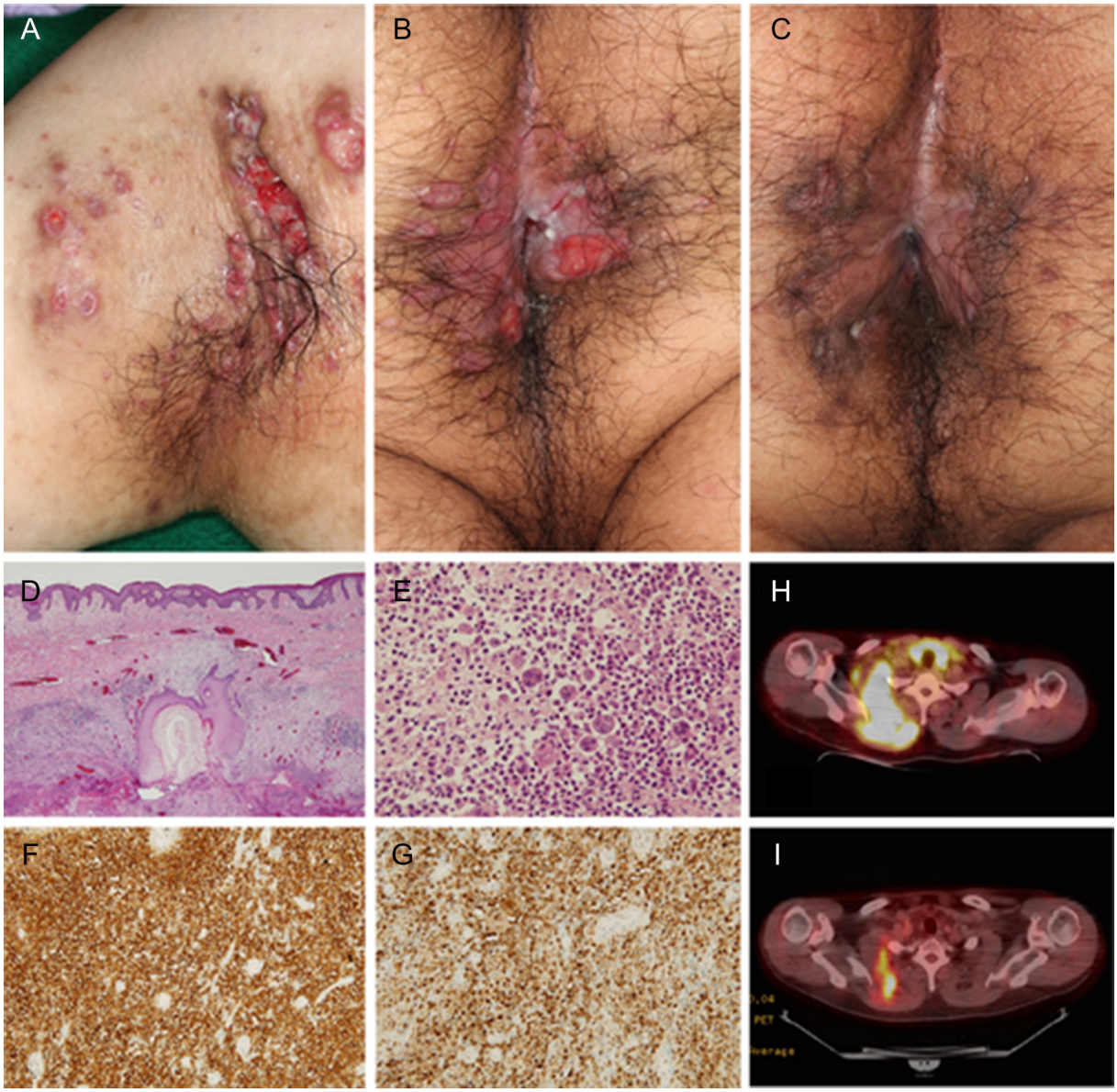

Fig. 4 Frame *A* shows brownish, indurated plaques with reddish-purplish papules, ulcers, and fistulas in the right axilla. Frame *B* shows multiple ulcers and fistulas with scars after repeated surgical drainage in the perianal region.[38] Photo reproduced with permission from Yasuda et al.

Grenz zone exists, whereas in the other half, the infiltrate extends to the dermoepidermal junction. Additionally, there are numerous blood vessels, some dilated, and most have collapsed lumina, in addition to variable extravasation of red blood cells.[41]

Cutaneous malignancies and systemic diseases mimicking LCH

Leukemia

Differentiating histiocytoses from leukemia can be challenging mainly due to the rarity of both diseases. Leukemia cutis (LC), as a sole lesion, is defined as cutaneous infiltration by myeloid or lymphoid leukemia, which includes acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), T- or B-cell lymphoblastic leukemia or lymphoma, myelodysplastic syndrome (MDS), and mixed myeloproliferative neoplasm and MDS, resulting in clinically identifiable cutaneous lesions (Figure 5, frames *A-C*).[45]

When skin is involved by leukemic cells, it often presents clinically as papules, nodules, plaques of varying sizes, purpura, ulcerated lesions, violaceous, red-brown, or hemorrhagic induration, or ecchymoses.[45] In a retrospective study that reviewed the clinical presentations of 8 patients with LC, the clinical phenotype varied.[44] Six out of eight (75%) patients presented with erythematous papules and nodules, distributed

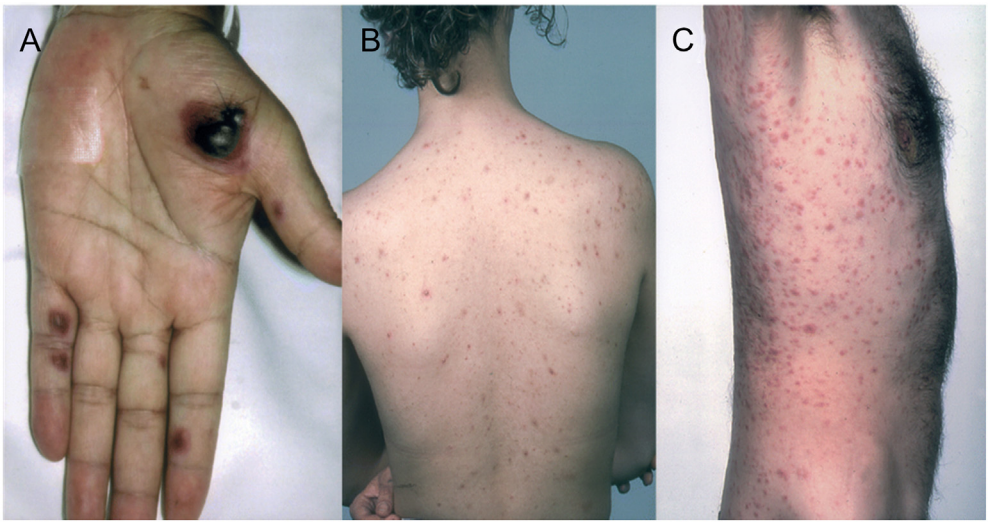

Fig. 5 LCH and leukemia. Frame *A* shows hemorrhagic infiltrated nodules and plaques of LC on the palms of a patient with AML. Frame *B* shows perifollicular acneiform LC on the trunk in a patient with AML. Frame *C* erythematous papules and nodules in a patient with LC and an underlying diagnosis of CLL.[44] AML, acute myeloid leukemia; LC, leukemia cutis; LCH, Langerhans cell histiocytosis. Photo reproduced with permission from Watson et al.

on the face, trunk, and limbs.[44] Red papules and nodules were noted in the patients with AML, CML, and CLL.[44] One of the patients with AML developed painful, hemorrhagic infiltrated plaques and nodules on the palms, whereas another patient with AML had perifollicular, acneiform papules on the trunk and upper limbs.[44]

Again, in a similar study reviewing 42 patients with LC, multiple papules and nodules occurred in 60% and infiltrated plaques in 26% of patients. Macules, ulcers, ecchymoses, and palpable purpura were also observed.[46] Because cutaneous signs are diverse and at times subtle, it can be difficult to distinguish LC from other histiocytoses, which may present similarly as discussed in previous sections.

In addition to the difficulty in differentiating leukemia from LCH, patients with LCH have a higher risk of developing secondary cancers; including leukemia.[47] The largest series available reported 22 patients with LCH in association with leukemia. A total of 16 (73%) of these cases were associated with acute nonlymphoblastic leukemia.[47] In two of the 22 patients (9%), the diagnosis of leukemia preceded that of LCH. Alternatively, in 6 (27.3%) patients both diagnoses were made concurrently, and in 14 patients (64%), an LCH diagnosis preceded leukemia by 8 months to 17 years.[47]

Several theories have developed to explain the association of leukemia with LCH. One theory is that treatment of LCH by chemotherapy (etoposide, vinblastine) induces a secondary myeloid leukemia. This secondary leukemia is typically seen months to years after treatment.[48]

Another theory is that AML is linked to LCH through the common origin for monocytic cells and Langerhans cells.[49] For example, a patient developed AML 18 months after the onset of histiocytosis X.[50] This was attributed to a defect involving the monoblast, initially with differentiation into abnormal macrophages with proliferative capacity but with a subsequent accumulation of malignant monoblasts.[50] Another patient had monoblastic leukemia, described as a neoplastic transformation in the monocytic histiocytic lineage with proliferation of an undifferentiated cell resembling the monoblast. Although one cell type would predominate, there might be a spectrum of cells at different levels of maturation.[51]

A hypothesis for LCH appearing after acute lymphoblastic leukemia (ALL), is a suggested association with notch homolog1, translocation-associated (Drosophila, also called the *NOTCH1* gene) that directly influences the programs of cell differentiation through effects on gene expression.[52]

With respect to differentiating AML from LCH, there are several clinical and histologic findings to consider. First, AML is typically associated with clinical manifestations of pancytopenia and rarely associated with lymph node enlargement compared with LCH. Lymph node enlargement should prompt a biopsy to assess for isolated or concomitant LCH. Additionally, LCH lesions have a well-defined histologic characteristic appearance on hematoxylin and eosin–stained sections. They have coffee bean–cleaved nuclei, a rounded shape, and eosinopihlic cytoplasm.[8] Mitotic features and binucleate cells may occasionally be identified.[8] Definitive differentiating stains include CD1a and CD207 (langerin), which are positive in lesions of LCH and are required for a definitive diagnosis.[53] Electron microscopy is no longer needed, because it has been shown that the expression of langerin protein correlates with the ultrastructural presence of Birbeck granules.[53]

Lymphomas

Cutaneous T-cell lymphomas are uncommon and complex malignancies that constitute a rare subset of non-Hodgkin

lymphomas of T-cell origin, including anaplastic large-cell lymphoma (ALCL), mycosis fungoides (MF) and Sezary syndrome.[54] Cutaneous lymphomas are a diagnostic challenge due to their varied clinical and pathologic presentations.

Primary cutaneous anaplastic large T-cell lymphoma frequently presents in men with solitary or localized tumors or nodules that show ulceration and do not spontaneous resolve.[55] Extracutaneous dissemination is observed in 10% of patients and mainly involves the regional lymph nodes.[55] MF typically affects photo-protected areas and classically presents with erythematous patches or plaques that may evolve to tumors or erythroderma.[55] Although MF usually has indolent behavior, Sezary syndrome is characterized by an aggressive course and presents with erythroderma and circulating malignant T lymphocytes ($\geq 1.0 \times 10^9$ cells/L) with or without peripheral lymphadenopathy.[55]

There are four reports in the literature of histiocyte-rich ALCL histopathologically mimicking LCH.[20,54,56,57] In one particular case, a patient presented to a local dermatologist with a solitary nodule on the chin, which was biopsied and diagnosed as LCH.[1] The nodule persisted and enlarged which prompted additional immunohistochemistry staining for CD1a, CD3, CD7, CD30, CD68, S-100, ALK, and MART-1. Further evaluation of the biopsy showed prominent atypical histiocytoid cells with epidermotropism and S-100, CD1a, and CD68 highlighted increased numbers of dendritic cells, again suggesting LCH.[54] However, further immunologic characterization of the atypical histiocytoid cells stained strongly positive with antibodies to the pan–T-cell marker CD3, CD7, and to CD30 with T-helper cells predominating.[54] There was also negative staining with antibodies to ALK, favoring a primary cutaneous origin. The constellation of histologic and immunologic features favored a CD30+ primary cutaneous ALCL.

Alternatively, there is the case of LCH initially diagnosed as cutaneous ALCL.[58] A patient presented to the hospital with a dome-shaped, firm, dark-red nodule measuring 25 × 25 × 4 mm on his left buttock that had been slowly growing for 3 years.[58] No superficial lymph nodes were palpable. Histologic examination of the nodule revealed a proliferation of large histiocytic cells throughout the dermis and upper part of the subcutaneous tissues.[58] The histiocytic cells had bean-shaped nuclei and acidophilic cytoplasm. Mitoses were seldom observed, and there was sparse infiltration of lymphocytes and eosinophils. The nodule was completely resected, and an initial diagnosis of cutaneous ALCL was made.

Eighteen months after surgery, the patient noticed enlarged lymph nodes in the left inguinal area in which microscopic examination of the biopsy specimen revealed a massive proliferation of large histiocytic cells that had abundant eosinophilic cytoplasm.[58] The nuclei of the histiocytic cells were irregular, pleomorphic, and bean-shaped with a vesicular chromatin pattern and one to several small distinct nucleoli. Multinucleated and mitotic figures were observed.[58] Further immunohistochemical analysis of the histiocytic cells of the original skin lesion and inguinal lymph nodes were positive for S-100 and CD1a and negative for keratin, leukocyte common antigen, and T-cell and B-cell markers. Electron microscopy of the skin and inguinal lymph node further confirmed the diagnosis of LCH by the appearance of Birbeck granules in the histiocytic cells.[58]

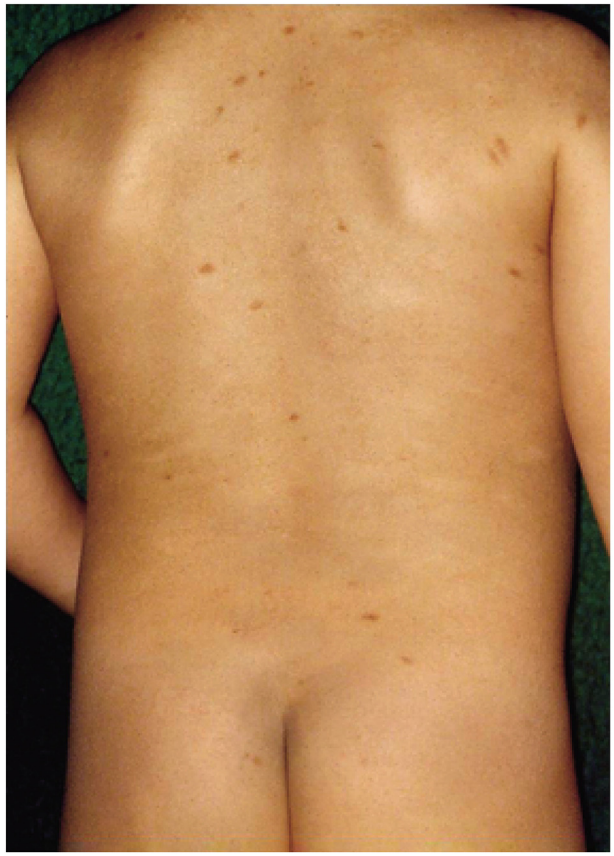

Fig. 6 LCH mimicking urticaria pigmentosa. A 2-year-old boy with slightly raised brown-red macules and papules on the back.[59] LCH, Langerhans cell histiocytosis. Photo reproduced with permission from Mitsuya et al.

These cases emphasize that, although classic LCH-like–appearing cells or clinical manifestations may be present, further immunostaining might be necessary to eliminate close mimickers, such as lymphoma. Histologic and clinical features of cutaneous LCH can be nonspecific and clinicians should consider alternative diagnoses to avoid masking an underlying lymphoproliferative disorder.

Mastocytosis

Cutaneous mast cell disorders are indolent conditions of childhood and most commonly include maculopapular cutaneous mastocytosis or urticaria pigmentosa. Both mastocytosis and LCH are proliferative processes that can have similar cutaneous manifestations such as infiltrated plaques and nodules (Figure 6). Previously, the Darier sign was thought to help clinically distinguish mastocytosis from LCH; however, a

few cases of mastocyte-rich LCH have been reported to show positive Darier sign. This entity is now called urticating histiocytosis or urticating Hashimoto-Pritzker LCH.[60]

Histologic differentiation between mastocytosis and LCH is straightforward, as, mast cells have abundant cytoplasm resembling a "fried egg," and Langerhans cells typically have reniform nuclei resembling a "kidney bean." Interestingly, atypical mast cells may show an unusual reniform and bilobed nuclei and mimic LCH, therefore, differentiation with immunohistochemistry staining is important.[61]

Mast cell cytoplasm should show metachromasia under Toluidine blue staining and be strongly reactive to antibodies against KP1 (CD68) and c-Kit.[61] Additionally, mast cells should also lack the nuclear grooves characteristic of LCH and express mast cell tryptase and CD117. Alternatively, Langerhans cells should be positive for S-100, langerin, and CD1a.[61] Occasionally, IHC staining may show mast cells intermixed with Langerhans cells. In this case, the diagnosis depends on the predominant cell infiltrate, the presence of signs of multisystem LCH or mastocytosis, and if there is an absence of monomorphic proliferation of either cell.[59]

The association of mastocytosis and histiocytosis, both bone marrow–derived cells, is not frequent.[62] Interestingly, there is a report that describes an infant who presented with congenital cutaneous LCH at 2 weeks of age that resolved without treatment by 2 months of age, whereas two subsequent mastocytomas developed at this time and at 8 months of age.[62] Although these disorders could have a common origin, their pathogeny reveals different mutations, the *BRAF* gene V600E mutation in LCH and c-Kit in mastocytosis.[62] Differentiating these entities is helpful by examining histology and performing immunochemistry.

Melanoma

The clinical morphology of LCH varies widely from macules, papules, nodules, crusty lesions, and vesicular eruptions to generalized dermatitis.[63] The most common sites of cutaneous involvement are the scalp, flexural areas, and external genitalia.[64] Histologically, cells seen in LCH can mimic those seen in a melanocytic tumor. As a result, the two entities can easily be confused.

For example, there was a patient with LCH initially diagnosed as having malignant melanoma, spitzoid variant[64] who presented to the dermatology clinic with a solitary, hyperpigmented, 5-mm macule on his right calf of unknown duration. A biopsy specimen showed epithelioid cells within the dermis, singly and in small groups, surrounded and infiltrated by collections of histiocytes and lymphocytes. It also stained positive for S-100 and negative for Melan-A. A diagnosis of malignant melanoma, spitzoid variant, was made, and the patient was sent for surgical treatment. On histologic examination of the original biopsy specimen, some of the lesional cells had reniform, vesicular nuclei with central grooves and additional immunoperoxidase staining showed strong, diffuse positivity for S-100 and CD1a and negativity for Melan-A and tyrosinase,[64] supporting the diagnosis of LCH.

Histologic features should be carefully examined to differentiate a solitary LCH from lesions of other etiologies. Lesional cells in LCH are most frequently found directly beneath the epidermis and spread upward toward the epidermis. Alternatively, malignant melanocytes usually arise at the dermal–epidermal junction and invade downward into the dermis.[64]

The inflammatory cells in LCH are composed of mixed populations of neutrophils, eosinophils, lymphocytes, mast cells, and extravasated erythrocytes, whereas lymphocytes are the predominant infiltrate in melanoma.[64] Additionally, a reniform nucleus and pleomorphism commonly depict Langerhans cells in LCH. Conversely, malignant melanocytes lack this characteristic nucleus and have less pleomorphism.[64] Lastly, although LCH and melanoma can both stain positive for S-100, LCH should stain positive for CD1a and langerin, whereas melanoma should stain positive for Melan-A.[64]

Conclusions

LCH can present as a wide array of cutaneous findings. This makes it easy to confuse with common dermatoses such as seborrheic dermatitis and arthropod bites. Fortunately, a thorough history and physical examination in conjunction with histologic study can easily differentiate LCH from these mimicking conditions. In cases where histology may overlap, immunohistochemical staining is necessary to accurately separate LCH from histologically similar entities like cutaneous leukemia and lymphoma. Although there are other conditions that could potentially mimic LCH, the conditions listed in this presentation are the most commonly misdiagnosed for LCH.

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