CASE REPORT

Cutaneous langerhans cell histiocytosis: A diagnostic challenge, two case reports and review of literature

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ABSTRACT

Langerhans Cell Histiocytosis (LCH) is a rare disease resulting from proliferation and accumulation of Langerhans cells in the affected tissues. The clinical presentation is extremely variable, ranging from mild self healing to life threatening. There pathophysiology remains unclear, and treatment is nonspecific. Isolated cutaneous disease is rare, and has unpredictable but usually benign course. This article describes two different clinical presentation of LCH along with a review of literature.

INTRODUCTION

Langerhans cell histiocytosis is a rare disease, with an estimated incidence of 2-10 per million in children and 1-2 per million in adults.[1] Males are affected more than females with ratio of 2:1 but disease tends to be more aggressive in females.[2]

LCH is defined as a clonal proliferation and accumulation of Langerhans cells, bone marrow-derived immature myeloid dendritic cells, in various tissues.[3] It may affect any organ or system of the body, but those more frequently affected are bone, skin and the pituitary gland in descending order.[4] It is not clear whether LCH is caused by a neoplastic process or immune dysregulation. The benign morphology of the proliferating Langerhans cells and the abundant expression of inflammatory cytokines suggest inflammatory disorder.[5] Nevertheless, familial cases of LCH exist, highlighting the genetic role.[6] Moreover, recent studies found that 57% of LCH cases harbored BRAF V600E mutation in diseased tissue, reinforcing the neoplastic etiology in most cases.[7,8]

LCH has a broad spectrum clinical behavior that ranges from a self-healing isolated lesion to a disseminated disease with life-threatening consequences.[4,5]

Classically, LCH is subdivided into eosinophilic granuloma, Hand-Sculler-Christian syndrome, Letterer-Siwe syndrome, Hashimoto-Pritzker syndrome. These variants have overlapping clinical features, thus this classification is no longer used. With the advent of ultrastructural studies and immunohistochemical staining techniques, they have helped to unify the above mentioned diseases under the rubric of LCH, regardless of different clinical presentation. Instead, the Histiocyte Society recommended stratification of patients based on the disease extent, broadly into single system LCH, unifocal or multifocal and multi-system LCH with or without risk organs involvement (hematopoietic system, spleen or liver).[4]

Skin is one of the most frequently involved organs with LCH in 33% of case.[4] Cutaneous lesions are the initial presentation in approximately 50%

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of patients.[9] LCH limited to the skin in adults is rare,[10, 11, 12] yet it was reported in 83-year-old female.[13]

All cutaneous lesions can be a manifestation of LCH, It can present as macules, papules, plaques, or nodules with or without ulceration and crustation.[2, 12, 13 ,14] The condition classically presents with multiple lesions, but It can be solitary.[15, 16] The age seems to influence the LCH clinical presentation; where vesicles and bullae are most commonly seen in early infancy, dermatitis in seborrheic distribution may occur up to late infancy.[4]

LCH can mimic various dermatological diseases. It may appear as prurigo nodularis, seborrheic dermatitis, psoriasis, eczema, or dermatophytosis.[2,12,13] It can manifest as acne, hidradenitis suppurativa, cellulitis and erythroderma.[2, 17, 18, 19] It might be even difficult to differentiate LCH from neoplastic lesions clinically when presenting as noduloulcerative lesion. Val Bernal et al reported a case of eosinophilic granuloma presenting as noduloulcerative lesion on the lower lip in 81-year-old man, where the initial diagnosis was lymphoepithelioma-like carcinoma.[10]

Unusual variants may present as hemorrhagic vesiculopustular eruption, urticarial plaques with a positive Darier sign, "blueberry muffin" - like lesions, or even molluscum-like papules.[16, 20, 21]

Sites most frequently involved with LCH are the scalp, trunk, flexural intertriginous areas and external genitalia.[13] Lesions involving the perianal and vulvar areas are rare. Only 52 cases of LCH restricted to the vulvar region were reported in literature.[2] Vulvar LCH is often recalcitrant and occasionally heralds subsequent disseminated and aggressive clinical course.[22]

Oral presentation may be the first or only sign of LCH.[23] It may show single or multiple ulcerated lesions, gingivitis, bleeding and necrosis accompanied by adenopathies. Nail changes in LCH are extremely uncommon, especially as the presenting manifestation of the disease. Both finger and toe nails are effected.[24] It presents as onycholysis, subungual hyperkeratosis, purpuric striae, grooving, subungual pustules, paronychia and hemorrhages.

LCH and non-LCH can co-exist in the same patient, although its rare, less than ten cases of xanthogranulomas developing in patients with a history of LCH have been reported.[25,26,27] In addition, LCH has been found in association with other skin lesions and systemic conditions. But no definitive conclusion exists for this phenomenon. LCH co-occurring with Spitz nevi has been reported by Berk and Lane.[28] Perianal LCH in association with anal fistula,[29] vulvar LCH in setting of vulvar lichen sclerosis,[24] and even the transformation of a BCC into LCH[30] have been published. Furthermore, Pan et al were first to report a case of LCH intermixed with vascular lesion at site of previous radiation.[31]

The diagnosis of LCH is made by morphologic identification of Langerhans cells that stain CD1a and Langerin (CD207). The expression of Langerin fully correlates with the presence on electron microscopy of Birbeck granules, Thus, the electron microscopy is no longer recommended.[4] Authors in Assir centre (KSA) and Assuit University (Egypt) have demonstrated that not only the clinical behavior of LCH is pleomorphic, but also histological picture. They found three histological patterns: granulomatous, histiocytic and xanthomatous in descending order.[32] Since about 50 percent of

cases manifest cutaneous involvement, a skin biopsy provides a rapid and accessible mean to secure the diagnosis.

The Histiocyte Society has established a set of guidelines to assist in the diagnosis and study of LCH. Once a diagnosis of LCH is made, Patients should undergo a full work-up including hematological, biochemical, radiological tests to determine the extent of disease. Although, some authorities advocate bone marrow examination in every baseline evaluation, it is not required unless symptoms or blood tests suggest such an involvement. Lastly, the patient must have a complete skeletal radiographic survey and chest radiography. The patients with identified abnormalities require more specific studies, such as pulmonary function tests and lung biopsy, small bowel series, liver biopsy, panoramic dental films, CT or MRI of the brain with particular attention paid to the hypothalamic-pituitary axis, endocrine evaluation and otolaryngology consultation with audiogram.[4]

Primary cutaneous LCH runs a benign course and often carries a better prognosis than those with systemic disease. It can regress spontaneously. However, fatality has been reported in an elderly woman with disseminated cutaneous lesions.[11] Furthermore, LCH initially presenting with cutaneous lesions in adults carries an increased risk of a second hematological malignancy.[33] So, caregivers should be cognizant that patients with LCH are at risk for second malignancies, including solid tumors and hematopoietic conditions. Systemic involvement may follow cutaneous disease by several years, therefore, close monitoring is imperative.[2,13] Follow up studies are required every month to 6-months, depending upon organ involvement and the degree of organ dysfunction. Patients with involvement of the spleen, lung, liver or hematopoietic system often have a worse prognosis.[4]

The treatment for LCH is variable and depends on the extent of the disease and the degree of the organ involvement. In the last 20 years, several drugs have been used in treatment of LCH, yet a limited number of therapeutic trials have been conducted. The Histiocyte Society recommends no therapy for patients with limited cutaneous disease; their conduct is clinical follow up and await for spontaneous regression. If therapy is required, topical steroids may be tried as a first line treatment.[4] Patients, who are non-responsive to steroids, can utilize topical nitrogen mustard, narrow-UVB or PUVA therapy as viable second-line options.[4,34,35,36,37] Treatment of multi-organ disease is controversial. Currently, the LCH III treatment protocol, a total of 12 months treatment with vinblastine 6 mg/m^2 i.v. bolus every 3 weeks, along with prednisone at 40 mg/m^2/ day given orally in three divided doses for 5 days, is probably the most common therapeutic strategy used in children with multi-organ involvement. As a result of recent therapeutic trials, it has been shown that the single best prognostic indicator is a patient's response to chemotherapy during the 6-week induction phase.[4]

More recent studies showed a good response to thalidomide in patients with recalcitrant cutaneous lesions, specially anogenital lesions. But it is less effective in extra-cutaneous manifestations with high recurrence rate after suspension of the drug.[2,12,13] As science advances, newer treatment options are being made available for LCH. Recently, some cases were reported to express platelet-derived growth factor receptors α and β or c-KIT, suggesting that they may be treated

with tyrosine kinase inhibitors.[38] Furthermore, Vemurafenib, an inhibitor of mutated BRAF, was reported to induce a dramatic response in 3 patients with histiocytosis harboring BRAF V600E mutations.[39]

Molecular analysis revealed that isolated and tissue-bound LCH cells only selectively express the Notch ligand Jagged 2. This suggests that JAG2-mediated Notch activation confers phenotypic and functional aspects of LCH to DCs. Thus, interference with Notch signaling may be an attractive strategy to combat this disease in near future.[40]

Due to the highly variable clinical presentation and the morphological similarity to other conditions, cutaneous LCH remains a diagnostic challenge. We report two cases of LCH with isolated cutaneous involvement detected in two infants that responded differently to the same treatment.

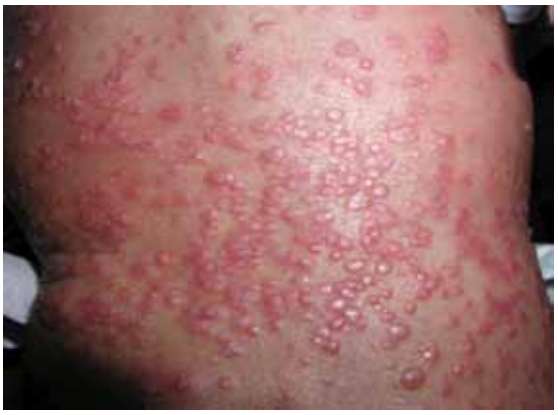

Fig. 1 Multiple flat-topped lichenoid papules and plaques, few scaly lesions on trunk.

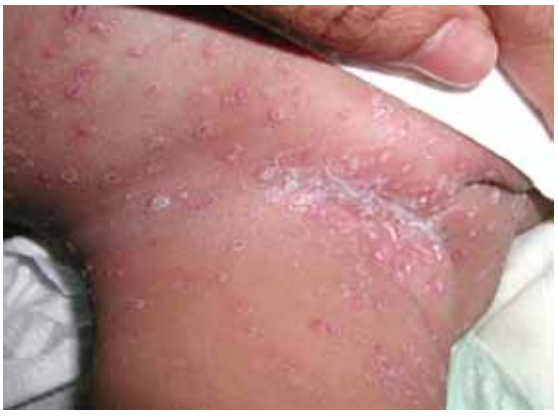

Fig. 2 Ptyriasiform scaly erythematous papules

CASE-1

A 4 month old male child presented with widespread skin lesions involving trunk and inguinal area of one month duration. Cutaneous findings were polymorphic, consisting of multiple scaly erythematous shiny papulonodules and plaques on back, and flat-topped lichenoid lesions on abdomen. Also, discrete and confluent scaly psoriasiform and ptyriasiform papules were seen in groins (Fig. 1, 2). The patient was a product of full-term induced vaginal delivery to nonconsanguineous parents. He had 2 older, healthy female siblings. Family history was negative for skin and other systemic diseases. Beside 7 days Neonatal ICU admission for neonatal jaundice and hypoglycemia, he developed gustatory sweating while feeding since birth. The gustatory sweating raised concern for cardiac defect, so echocardiogram was done and it showed a small atrial septal defect causing a 3 mm left-to-right shunt with no treatment needed. The clinical differential diagnosis was lichen planus, psoriasis, congenital syphilis and histiocytosis. A lesional skin biopsy was taken. During the follow up visit, the patient was noticed to have developed a respiratory tract infection, and was referred to a pediatrician for further assessment. His condition got complicated with single episode of generalized tonic-clonic seizure. He was in respiratory distress with oxygen saturation of 70% on 5L of oxygen. Mild hepatomegaly was felt, but no lymphadenopathy. With regard to his chest condition, primitive diagnosis of pneumonia was formulated. Empirical therapy, which including

systemic antibiotics and mucolytes, was started. All laboratory investigations were normal. Full septic workout showed no growth. Chest X-ray showed right lung collapse with compensating left lung expansion. Abdominal ultrasound didn't reveal any hepatic enlargement, clinical palpable liver was insignificant. Unfortunately his condition deteriorated necessitating artificial ventilation. Fortunately, he improved eventually and was slowly weaned off the ventilator. Cutaneous histopatholgic findings showed superficial infiltration of atypical histiocytes which were positive for CD1a and focally positive for S-100 (Fig. 3). Further investigations were carried on to assess other organs involvement. CT chest, head, and neck were normal; collapsed lung got re-inflated. Bone marrow biopsy revealed a normocellular marrow with no evidence of LCH. Patient initially was managed with potent topical steroid, mometasone furoate 0.1% ointment for 2 weeks with no satisfactory response and his skin condition progressed. Systemic chemotherapy was considered. Pediatric oncologist was consulted, and treatment began according to the International LCH III Protocol for low risk patient. He was started on Prednisone 40 mg/m^2/day for 5 days and Vinblastine 6 mg/m^2/day IV push, every 3 weeks for the next 6 months. After completed therapy, reassessment was made. All cutaneous lesions healed completely with residual hypopigmented macules (Fig. 4). After a follow up of 4 years, the patient remained clinically free and his growth parameters were not effected by atrial septal defect.

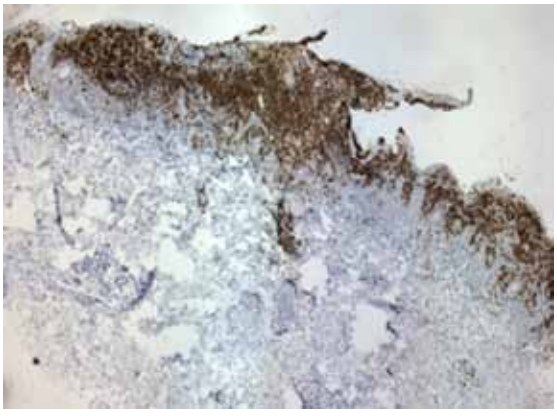

Fig. 3 Infiltrating cells demonstrated immunopositivity for CD1a.

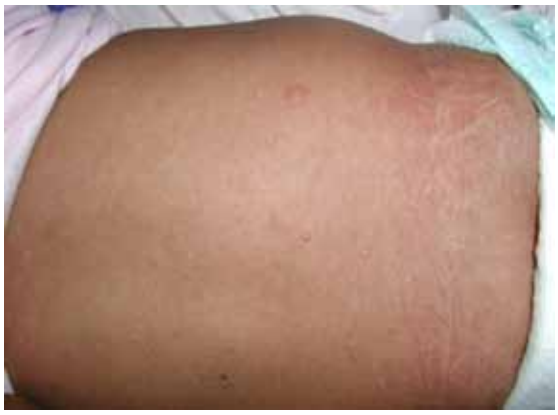

Fig. 4 Back of the patient after treatment, showing almost complete clearance of the skin lesions.

CASE-2

The second patient was a 6 month-old girl presented with three months history of skin lesions. The skin eruption consisted of dome shaped papulonodules of variable colors, ranging from bright red, yellowish to light brown (Fig. 5). Some lesions had depressed surface, whereas others showed necrosis and crustation resembling PLEVA. Papules were firm in consistency, scattered over trunk, head and neck. Suprapubic area showed a patch of faint erytherma and thin branny scales. The patient was a product of a full term normal vaginal delivery to non-consanguineous parents. Family history was negative for skin disease and other systemic disease. The suggested clinical differential diagnosis included: disseminated juvenile xanthogranuloma, LCH, and PLEVA. Skin biopsy was taken from trunk and it showed atypical

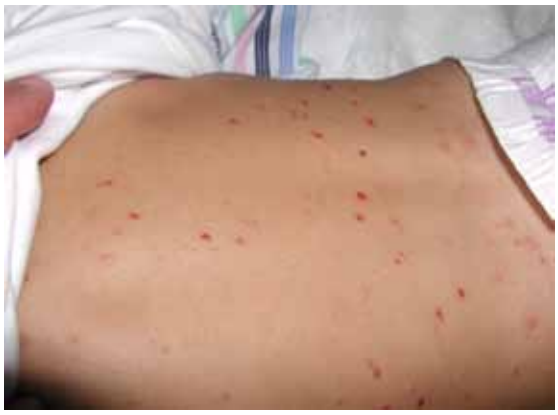

Fig. 5 Dome shaped reddish papules with central depression on the back.

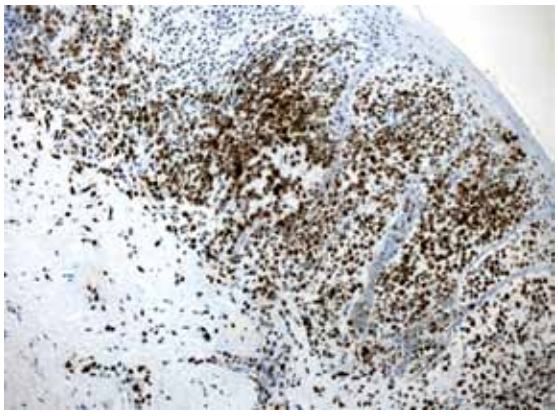

Fig. 6 Infiltrating cells demonstrated immunopositivity for CD1a

cellular proliferation in superficial dermis, that wer CD1a positive (Fig. 6). The diagnosis of LCH was confirmed. Symptoms of other organs involvement was tackled in history; parents were asked about symptoms suggestive of pulmonary involvement such as dyspnea and hemoptysis, osteolytic involvement like aural discharge and hearing loss. The patient had a normal developmental milestones with no evidence of any cognitive defects. Parents denied history of convulsion events. No symptoms suggestive of systemic involvement was reported in history; base line evaluation was carried. Full blood count, biochemical profile, coagulation studies and urine microscopy were normal. Imaging studies including abdominal ultrasound, chest radiography and skeletal radiograph survey did not detect any pathology. The diagnosis was an isolated cutaneous LCH. She was managed with topical steroid of moderate potency, mometasone furoate 0.1% cream, once daily. Clinical response was desirable, over period of 6 week all skin lesions cleared completely. The child showed no relapse of the disease 3 years after the diagnosis.

DISCUSSION

Langerhans cell histiocytosis is a disease spectrum of unknown etiology characterized by the proliferation of bone marrow-derived Langerhans cells in one or multiple organ systems. LCH most commonly develops in children, though it can develop at any age with a male:female ratio 2:1. Cutaneous involvement in children is seen in 15% with single system, and in 60% with multisystem LCH and in a number of series was the earliest manifestation of disease. However, the variable cutaneous presentation can lead to misdiagnosis. In the first case, LCH presented with generalized cutaneous lesions which were polymorphic. It consisted of multiple erythematous flat topped lichenoid papules with glistening surface. Few papules had depressed center, whereas others were psoriasiform. Lesions involving the groins were assuming a pytriasiform appearance. Therefore, our clinical differential diagnoses were lichen plans, psoriasis, congenital syphilis and histiocytosis. Detailed medical history failed to reveal any familial disease or congenital infections. Apart from nonspecific pulmonary findings evident on chest X-ray and clinically insignificant atrial septal defect, full clinical workout were normal. So, skin biopsy might provide a readily accessible means of prompt diagnostic confirmation. The skin biopsy specimen demonstrated a dermal

infiltrate of large cells with pale cytoplasm and "kidney shaped" nuclei with prominent epidermal exocytosis. Immunopositivity of infiltrating cells for CD1a confirmed the diagnosis of LCH. Pulmonary involvement, while rare as isolated disease in childhood, is reported in 20% to 50% of children with multisystem LCH, and disease may be asymptomatic. Although not diagnostic, a finding of greater than 5% CD1a-positive cells in the bronchioalveolar lavage aspirate is highly suggestive of active pulmonary LCH in children.[42] In this case, respiratory distress was suggestive of pulmonary LCH. However, the unremarkable findings in chest radiology and CT scan as well as the recovery on supportive treatment before starting chemotherapy, rule out pulmonary LCH. So, the patient was labeled as isolated cutaneous LCH. Although the first line of treatment according to Histiocyte Society recommendation in pure skin involvement is to wait and see; this patient was treated with topical steroid because of the extensive cutaneous involvement.[4] However, he didn't respond, and his condition continued to progress. With reported high relapse rate on discontinuation of nitrogen mustard, it was not considered.[34] For LCH patients with extensive multifocal skin-limited disease such as our patient, phototherapy might be considered . NB-UVB therapy is reported to be effective in treating superficial lesions, but not tumoral deep lesions of LCH as seen in our case.[35,36] In addition, considering the hazards of phototherapy, and the young age of patient this option was crossed out. As a final resort, systemic therapy was considered. According to LCH-III protocol systemic therapy is based on vinblastine along with prednisone given in three divided doses for 4 weeks and then tapered over the following 2 weeks. At end of treatment, disease status is evaluated and treatment continued accordingly. Fortunately, he responded well to systemic chemotherapy with complete clearance of all skin lesions (Fig. 4).

The second case presented with generalized eruptions as well. It was less intense than the first one, but still pleomorphic. The yellow discoloration of papules pointed more towards juvenile xanthogranulomas. Whereas, the brown color was more towards disseminated spitz nevi. LCH cooccurring with Spitz nevi and xanthogranuloma has been reported. Necrotic crusted lesions raised suspicion for PLEVA. Our clinical differential diagnoses included the three disorders mentioned up, in addition to LCH. Skin biopsy specimen showed the characteristic features of langerhans cells. As it was evident in laboratory and radiological investigations, no other organ was involved. Here again, it was a single system cutaneous LCH. The conduct recommended by the Histiocyte Society in such cases is clinical follow up and wait for spontaneous regression.[4] Ramyar et al reported a case of neonate presenting with disseminated papulonodular eruption that completely cleared leaving hypopigmented macules corresponding to initial eruption.[40] So, in our case it is unclear whether her condition self healed or responded to topical steroid treatment.

Progression from cutaneous SS to MS disease in children is reported in 40% of cases, with no reliable predictors for dissemination. Even patients diagnosed with congenital self-healing LCH have been shown to have late relapses and/or progression to systemic disease.[15] Therefore, all infants require long-term follow-up, including those successfully treated. Because, all have the propensity to relapse or disseminate. In our patients, neither relapse nor progression has been

detected four years after diagnosis.

The cases we reported are interesting because both were difficult to differentiate from other dermatological diseases on clinical grounds. Furthermore, the two cases are infants presenting with a generalized skin-limited LCH, but each one of them progressed in different way.

CONCLUSION

Cutaneous LCH whether its SS skin manifestation or part of MS involvement present broad spectrum of clinical presentations. Thus, the diagnosis is often missed or delayed. High index of suspicion is required to detect LCH. The pathognomonic features of langerhans cells on skin specimens are of a valuable aid in reaching the correct diagnosis. Which will always be based on clinical-pathological correlation. Management is not uniform in all the patients, and therapeutic approach should be individualized to every patient needs and response.

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