

**Case report**

**Congenital cutaneous Langerhans cell histiocytosis and cutaneous mastocytoma in a child**

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**Abstract**

Langerhans cell histiocytosis and mastocytoma are clonal disorders of bone-marrow-derived cells, most commonly seen in the pediatric age. Infiltration of mast cells and Langerhans cells in the same lesion has been published before, but, to our knowledge, this is the first time that the occurrence of two mastocytomas and Langerhans cell histiocytosis is reported. It could be hypothesized that both clonal disorders of bone-marrow-derived cells could have a common origin.

**Keywords: Langerhans cell histiocytosis, mastocytoma, mastocytosis, neonate.**

**Introduction**

Langerhans cell histiocytosis is a proliferation of immature myeloid dendritic cells, with a broad clinical spectrum from isolated skin lesions to multisystem life-threatening disease. Mastocytomas are a common type of cutaneous mastocytosis, which generally appear in the first year of life and resolve during childhood. Both are clonal disorders of bone-marrow-derived cells, most commonly seen in the pediatric age. The occurrence of two mastocytomas and Langerhans cell histiocytosis has never been described.

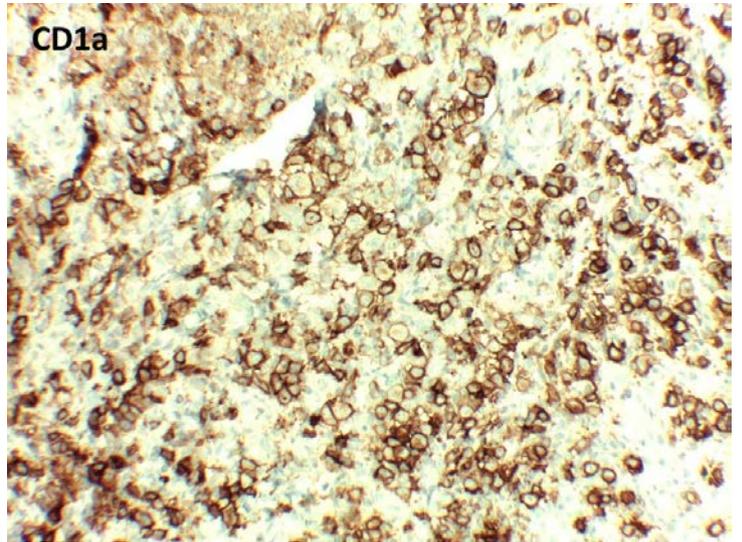
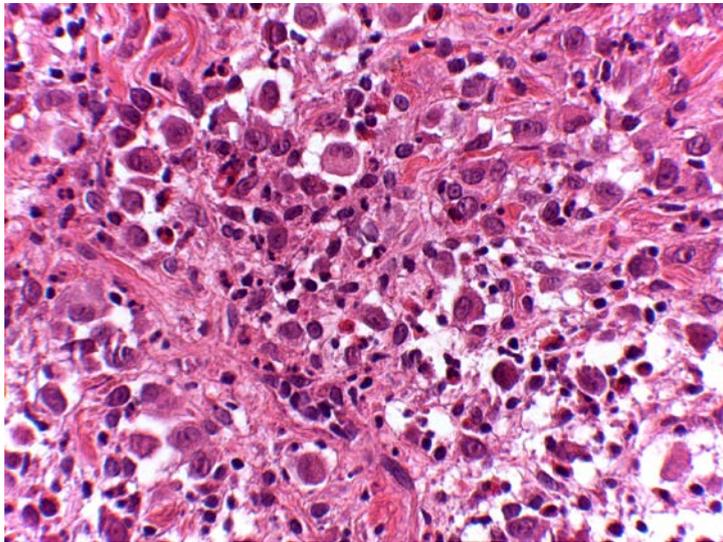
**Case synopsis**

A 2-week-old boy, born at term after an uncomplicated pregnancy, presented with multiple congenital skin lesions. They consisted of brown to red papules and nodules (3-8 mm in size, 10 lesions), most of them ulcerated, on his scalp, lower left eyelid, trunk, and upper and lower limbs (Figure 1, 2). Physical examination was otherwise normal.

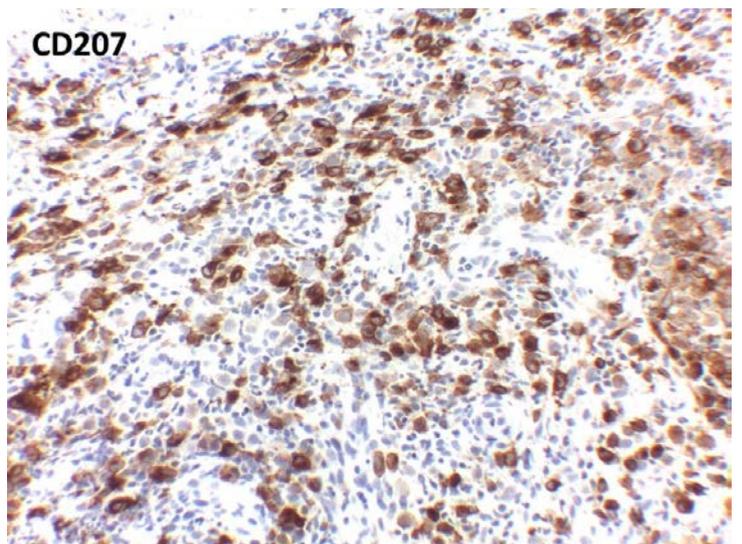
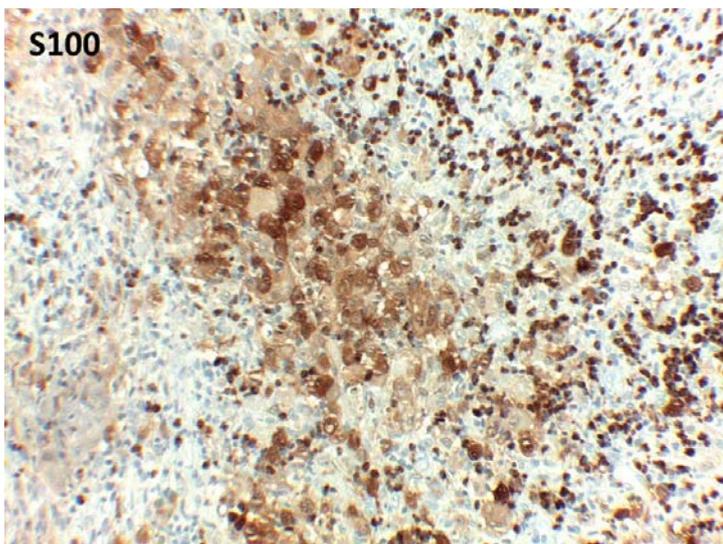
The skin biopsy showed an ulcerated epidermis and a dermal infiltrate of large oval cells, with reniform (coffee bean) nuclei and abundant eosinophilic cytoplasm, admixed with eosinophils, multinucleated histiocytes, and lymphocytes. The large oval cells exhibited strong immunoreactivity for CD1a, CD207 (langerin) and S-100 protein (Figures 3-6). Mastocytes were not increased in number.



**Figure 1.** Crusted nodule on the lower left eyelid, 1 month. **Figure 2.** Crusted nodule on the leg, 1 month.



**Figure 3.** Hematoxylin and eosin. Dermal infiltrate of Langerhans cells, with reniform nuclei and abundant eosinophilic cytoplasm, admixed with eosinophils and lymphocytes, (20x). **Figure 4.** Strong immunoreactivity for CD1a, (20x).



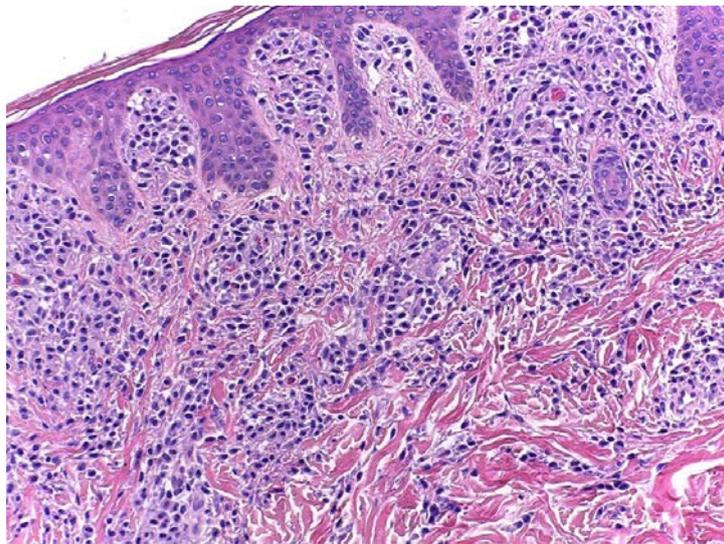
**Figure 5.** Strong immunoreactivity for S100, (20x). **Figure 6.** Strong immunoreactivity for CD207, (20x).

Blood count, coagulation studies, liver and kidney function tests, urine analysis, chest radiography, skeletal survey, and abdominal ultrasound were normal. Therefore, a diagnosis of congenital skin-limited Langerhans cell histiocytosis was established.

By the age of two months lesions had resolved without treatment (Figure 7), but the follow up examination showed the recent development of an orange abdominal plaque with positive Darier sign —urtication after stroking the lesion— (Figure 8). A new biopsy showed oval cells with abundant amphophilic cytoplasm, round central nuclei, and fried egg appearance (Figure 9). They exhibited strong immunoreactivity for CD117 (c-kit) and tryptase, confirming the clinical diagnosis of mastocytoma. Langerhans cell histiocytes were not observed.



**Figure 7.** Spontaneous resolution of the nodule on the eyelid by the age of two months. **Figure 8.** Orange plaques on the abdomen and left forearm (see the peau d'orange appearance and Darier's sign in the later).



**Figure 9.** Hematoxylin and eosin. Dermal mast cells infiltrate, with oval abundant amphophilic cytoplasm, round central nuclei and fried egg appearance (10x).

By the age of eight months, a new yellow peau d'orange plaque was observed on his left forearm, again clinically concordant with mastocytoma. Serum tryptase was 5.95 ng/mL (increased tryptase level when greater than or equal to 20 ng/mL). Cytomegalovirus IgM antibodies were positive. Congenital infection was excluded by determining cytomegalovirus IgM antibodies and C-reactive protein in the blood taken for heel prick test at birth. Control serology and urine C-reactive protein were negative too. Physical examination and complementary studies (full blood count, coagulation, liver and kidney function) every 6 months have not shown relapse. Mastocytomas are still present after 2-years of follow-up.

## Discussion

Langerhans cells are antigen-presenting dendritic cells derived from bone marrow and generally localized in epidermis and lymph nodes. Langerhans cell histiocytosis is a proliferation of clonal cells more consistent with immature myeloid dendritic cells precursors (CD207 or langerin +) than epidermal Langerhans cells [1], which involve different organs with a broad clinical spectrum from isolated skin lesions to multisystem life-threatening disease [2]. Common (almost 60%) oncogenic somatic BRAF-V600E mutations support the consideration of this disease as a neoplasm [3]. Moreover, a recent report shows that BRAF-V600E expression in circulating blood cells is associated with disease severity and increased risk of recurrence when mutated in tissue [4]. An alternative hypothesis states that Langerhans cell histiocytosis is a reactive disease in the setting of immature dysregulation leading to an aberrant reaction between Langerhans cells and lymphocytes [5]. It could be triggered by viruses (human herpesvirus type 6, cytomegalovirus, Epstein-Barr virus). This point was the reason why

congenital cytomegalovirus infection was studied in our patient. However, other studies have not confirmed the viral association [6-8].

The morphology and evolution of our patient's lesions, as generalized papules and nodules, which tend to ulcerate and resolved without treatment, was previously called "congenital self-healing reticulohistiocytosis." This term is no longer used owing to documented cases that have evolved to multisystem disease years after resolution, which make long-term follow-up required [9]. Nevertheless, neonates with isolated skin involvement usually have a favourable prognosis [10].

Mastocytomas are a common type of cutaneous mastocytosis, which generally appear in the first year of life and resolve during childhood. They present as orange to yellow papules or plaques with positive Darier sign (urtication after stroking a lesion).

Mast cells originate in the bone marrow and mature through activation of the receptor CD117 (KIT), a transmembrane receptor with intrinsic tyrosine kinase activity. Gain of function mutations in c-Kit (mostly D816V) are capable of inducing neoplastic transformation of mast cells [11] and other different lineages, leading to mastocytosis, gastrointestinal stromal tumors (GISTs), and less commonly, melanoma and acute myeloid leukemia.

The association of mastocytosis and histiocytosis is not frequent [12-19]. Patients with coexisting mastocytosis and histiocytosis or coexisting histiocytic and mast cell infiltration are showed in Table 1. Mitsuya et al. described the infiltration of mast cells and Langerhans cells in the same lesion in a 2-year-old boy, diagnosed with mastocytosis with prominent Langerhans cell infiltration [12]. In the same way, significant mast cell infiltration in Langerhans cell histiocytosis has been documented; one case was congenital and self-healing [13, 14]. Tran et al. reported a coexisting mastocytoma with a prominent admixed infiltrate of CD68, xanthomatous histiocytes, and Touton-type giant cells [15]. In addition, there are four documented cases of coexistence of urticaria pigmentosa and juvenile xanthogranuloma in the literature [16, 17, 18, 19]. Tsutsui et al. propose that the increase in mast cells is responsible for the differentiation of histiocytes to dermal dendrocytes in coexisting urticaria pigmentosa and juvenile xanthogranuloma [16]. In our case, dermal mastocytosis appeared once nodules of Langerhans cell histiocytosis were apparently resolved.

## Conclusion

Association of mastocytosis and histiocytosis, both bone-marrow-derived cells, is not frequent and the occurrence of mastocytomas and Langerhans cell histiocytosis present in our patient has never been described. Mastocytomas shows an indolent clinical course with spontaneous recovery and neonates with isolated cutaneous Langerhans cell histiocytosis have usually a favorable prognosis. It could be hypothesized that both clonal disorders could have a common origin, but the current knowledge about their pathogeny reveals different mutations, BRAF-V600E in LCH and c-Kit in mastocytosis.

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