

A Case of Cutaneous Mastocytosis in a Child with Prominent Langerhans Cell Infiltration

Juniku Mitsuya, M.D.,* Hiroyuki Hara, M.D., Ph.D.,† Naozumi Fukuda, M.D.,*
and Tadashi Terui, M.D., Ph.D.*

**Department of Dermatology, Nihon University School of Medicine, Itabashi-ku, Tokyo, Japan,*

†Department of Functional Morphology, Nihon University School of Medicine, Itabashi-ku, Tokyo, Japan

Abstract: We recently encountered a 2-year-old boy with slightly infiltrative brown papules on the face, trunk, and extremities. Stroking of one of the papules produced an urticarial wheal (positive Darier's sign). Histopathologic tests revealed a dense infiltration of mast cells containing numerous granules and showing metachromasia under Toluidine blue staining. Immunohistochemical tests revealed that these cells were positive for CD68 and for c-kit. In addition, dermal dendritic cells that were positive for S100 and CD1a immunostaining were intermingled with the mast cells. We confirmed through electron microscopy that the dermal dendritic cells that were observed adjacent to the infiltration of mast cells had Birbeck granules in their cytoplasm, namely Langerhans cells. However, because of the greater numbers of mast cells than Langerhans cells, and because of the absence of both monomorphic LC proliferation and systemic symptoms of Langerhans cell histiocytosis, the present case favors a diagnosis of cutaneous mastocytosis in a child with Langerhans cell infiltration.

Both mastocytosis and Langerhans cell histiocytosis (LCH) are proliferative processes that can have similar cutaneous manifestations such as infiltrated plaques and nodules. Darier's sign can often help clinically distinguish mastocytosis from LCH, yet several cases of mast-cell-rich LCH have been reported to show a positive Darier's sign; this condition has been called urticating histiocytosis or urticating Hashimoto-Pritzker LCH (1,2). Here, we describe a 2-year-old boy who clinically presented with multiple red-brown macules showing a positive Darier's sign. Histologic findings showed a predominant

infiltrate of mast cells with some intermingled Langerhans cells.

CASE REPORT

A 2-year-old Japanese boy was referred to our dermatology clinic for evaluation of multiple red-brown papular lesions. Several of these lesions first appeared on the trunk when he was 8 months old. They gradually increased in number, and new lesions appeared on his face and extremities over time. A physical examination at

Address correspondence to Hiroyuki Hara, M.D., Ph.D., Department of Functional Morphology, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan, or e-mail: hhara@med.nihon-u.ac.jp.



Figure 1. A 2-year-old boy with slightly raised brown-red macules and papules on the back.

the time of presentation revealed slightly raised red-brown papules scattered on the face, trunk, and extremities (Fig. 1). Most lesions measured < 10 mm in diameter each. Stroking the papules on the back produced an urticarial wheal within a few minutes (positive Darier's sign). The patient was otherwise in good health.

The results of a routine hematologic examination were within normal limits. No evidence of eosinophilia was observed. The serum level of histamine was 0.20 ng/mL (normal range; 0.11–0.50); serum tryptase levels were not measured, however. Chest radiograph were normal.

Punch biopsy was performed on one of the papular lesions on the back.

Histopathologic examination of the biopsy tissue showed increased melanin content in the basal cells of the epidermis. Some eosinophils, histiocytes, and dense closely packed cuboidal cells with basophilic cytoplasm were infiltrated in the upper dermis (Fig. 2). We performed additional tests on the cuboidal cells to determine their identity. We found that their cytoplasm showed metachromasia under Toluidine blue staining (Fig. 3), and that it was strongly reactive to antibodies against KP 1 (CD 68; Dako, Glostrup, Denmark) and c-kit (Dako); this evidence indicates that the cuboidal cells were mast cells (Fig. 4).

We also observed that some cells intermingled with the mast cells were labeled positive for S100 protein (Dako) and CD1a (Novocastra Laboratories Ltd.,

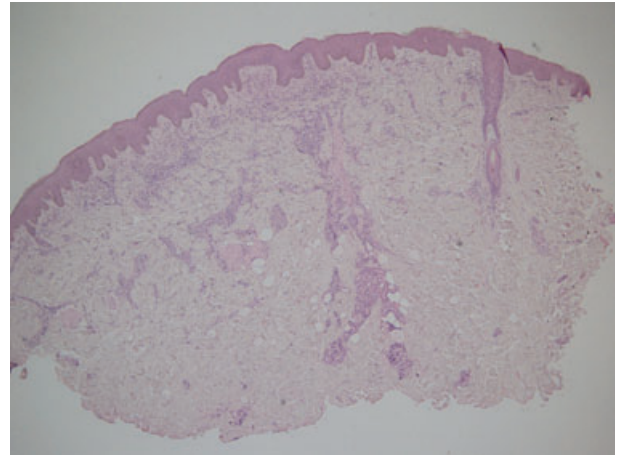


Figure 2. Skin biopsy specimen from the back, showing an intact epidermis overlying a dense dermal infiltrate in the upper dermis (hematoxylin-eosin stain; $\times 40$).

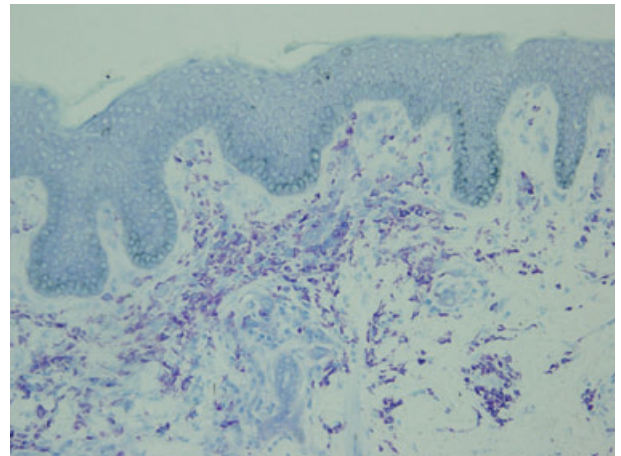


Figure 3. Mast cells with metachromatic granules in the dermis (toluidine blue; $\times 200$).

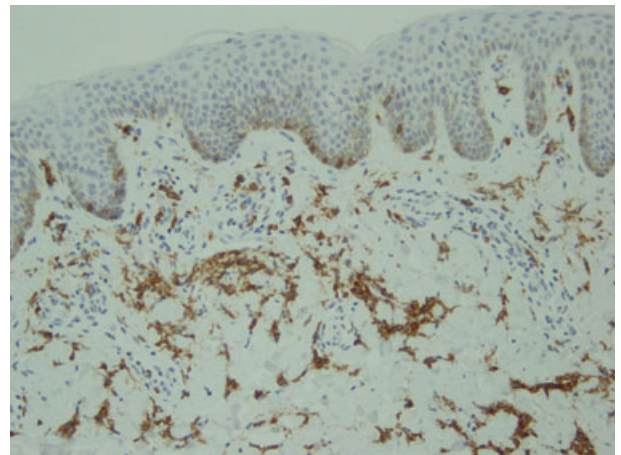


Figure 4. Mast cells stained strongly for c-kit (c-kit; $\times 200$).

Newcastle-Upon-Tyne, UK). All S100- and CD1a-positive cells consisted of dendritic cells in the epidermis or dendritic or round cells in the dermis, indicating that all were Langerhans cells (Fig. 5). The mast cell count was up to 42 cells per high-power field, whereas the Langerhans cell count was up to 16 cells per high-power field. An

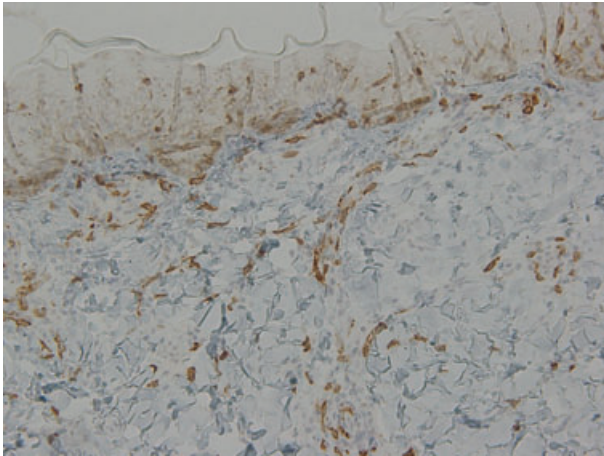


Figure 5. Histiocytes stained somewhat less strongly for CD1a (CD1a; $\times 200$).

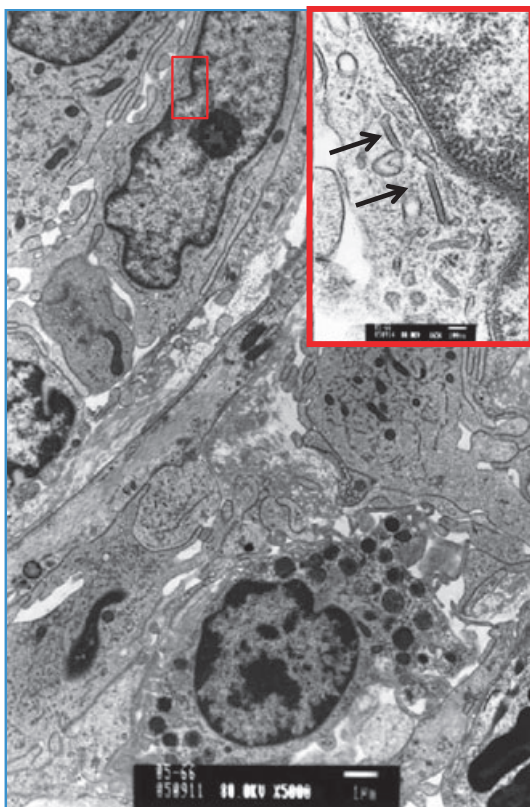


Figure 6. Electron-microscopic examination revealed Langerhans cells with Birbeck granules adjacent to mast cells ($\times 8,000$). *Inset:* High-power view of Birbeck granule ($\times 65,000$).

electron-microscopy study showed that the mast cells contained characteristic granules composed of lamellae and electron-dense finely granular material. In addition, dermal dendritic cells with numerous Birbeck granules in their cytoplasm were observed adjacent to the mast cells (Fig. 6).

The patient was treated with cyproheptadine, an oral antihistaminic agent. The lesions became soft and flat 1 year after the start of this treatment.

DISCUSSION

Both mastocytosis and Langerhans cell histiocytosis (LCH) result from an abnormal proliferation of bone-marrow-derived cells, which can involve multiple organ systems. Both of these cutaneous disorders typically affect infants and children and have a tendency to regress with age. Mastocytosis is one of a rare heterogeneous group of disorders involving an abnormal increase of mast cells in one or more organ systems. Most pediatric patients suffer from cutaneous mastocytosis (CM), whereas adults usually have systemic mastocytosis (3). Cutaneous mastocytosis is divided into maculo-papular CM (MPCM = urticaria pigmentosa, UP), diffuse cutaneous mastocytosis (DCM), and solitary mastocytoma of the skin (3). Langerhans cell histiocytosis can be localized to a single site, multiple sites within a single system, usually bone, or more disseminated and multisystem. In multisystem disease, the skin, bone, liver, spleen, and bone marrow are the preferential sites of involvement (4). Systemic involvement requires systemic management, whereas those with localized lesions can be treated with a topical medications or observational approach (5).

In this case, histochemical, immunohistochemical, and electron-microscopic techniques all revealed an infiltration of closely packed mast cells intermingled with Langerhans cells. We diagnosed our patient with MPCM with infiltrates of Langerhans cells. We diagnosed based on the following: (i) clinically, the patient did not have signs of multisystem LCH, (ii) histopathology showed predominately dense infiltrates of mast cells with only a small minority Langerhans cells, and an absence of a monomorphic LC proliferation was observed. Three previous cases (1,2,6) in which an infiltration of both mast cells and Langerhans cells were observed are summarized in Table 1. Although other conditions exhibiting a positive Darier's sign and increased numbers of mast cells may sometimes be confused with mastocytosis, Foucar et al (1) made a diagnosis of urticating histiocytosis in the absence of monomorphic mast cell proliferation or systemic symptoms of mastocytosis. Butler et al (2) described a case of urticating Hashimoto-Pritzker LCH

TABLE 1. *Reported Cases with an Infiltration of Both Mast Cells and Langerhans Cells*

Case no.	Age	Gender	Clinical features	Histopathology	Giemsa	Toluidine blue	CD1a	S-100	Diagnosis
1 (1)	13 yrs	F	Extensive skin lesions on the face, trunk, and extremities with positive Darier's sign.	Numerous mast cells present in the dermis with a marked infiltration of Langerhans cells.	+	Unexamined	+	+	Urticating histiocytosis
2 (2)	2 mos	M	Erythematous urticarial plaques involving the cheeks, chest back, and extremities. Red-brown papules on the ankles, feet, and left axillae with positive Darier's sign.	Polymorphous infiltrates of mononuclear cells, neutrophils, eosinophils, and mast cells involving the papillary dermis. Collection of CD1a positive Langerhans cells within the epidermis.	Unexamined	+	+	+	Urticating Hashimoto-Pritzker Langerhans cell histiocytosis
3 (6)	83 yrs	M	Inguinal intertrigo-like lesions bilaterally with positive Darier's sign.	A mixed infiltration of mast cell and histiocytes in the dermis predominated by the latter.	+	+	-	-	Inguinal mastocytosis with histiocyte infiltration
Our case	2 yrs	M	Multiple red-brown, maculo-papular lesions on the face, trunk, and extremities with positive Darier's sign.	Langerhans cells intermingled with massive mast cells in the dermis.	+	+	+	+	Cutaneous mastocytosis with Langerhans cell infiltration

that met the following diagnostic criteria: (i) the papules developed within the first 2 months of life, (ii) the papules resolved after 3–4 months, (iii) no extracutaneous involvement, and (iv) no recurrence. Their most striking histologic feature was a collection of LC within the epidermis and a polymorphous infiltrate of mononuclear cells, neutrophils, eosinophils, and mast cells. The concluded mast cells may be a prominent component of the LCH. Enginger et al (6), in contrast, diagnosed an 83-year-old inguinal mastocytosis associated with histiocytic infiltrate. Although the cells of which the infiltrate was composed were negative for CD1a and S100, Birbeck granules were observed in their cytoplasm by electron microscopy and the numbers of mast cells were greater than those of histiocytes.

Although it is very difficult to divide a line between these two entities, namely, mastocytosis with Langerhans cells infiltrates and LCH with mast cells infiltrates, we favor a diagnosis of mastocytosis with Langerhans cells infiltrates in our case. As only a few cases had been reported that both mast cells and Langerhans cells were infiltrated, additional reports are required to establish the phenomenon that Langerhans cell infiltrates can be seen in mastocytosis.

REFERENCES

1. Foucar E, Piette WW, Tse DT et al. Urticating histiocytosis: a mast cell-rich variant of histiocytosis X. *J Am Acad Dermatol* 1986;14:867–873.
2. Butler DF, Ranatunge BD, Rapini RR et al. Urticating Hashimoto-Pritzker Langerhans cell histiocytosis. *Pediatr Dermatol* 2001;18:41–44.
3. Valent P, Akin C, Escribano L et al. Standards and standardization in mastocytosis: consensus statement on diagnostics treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37:435–453.
4. Jaffe R, Weiss LM, Facchetti F. Tumours derived from Langerhans cells. In: Swerdlow SH, Campo E, Harris NL et al., eds. *WHO classification of tumours of haematopoietic and lymphoid tissues*. Lyon: International Agency for Research on Cancer, 2008:358–360.
5. Caputo R, Gelmetti C. Langerhans cell histiocytosis. In: Wolff K, Goldsmith LA, Katz SI et al., eds. *Fitzpatrick's dermatology in general medicine*. New York: McGraw-Hill, 2008:1414–1418.
6. Enginger V, Bedane C, Pistorius MA et al. Inguinal mastocytosis with histiocytic infiltrate. *Ann Dermatol Venerol* 1995;122:536–539.