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A Solitary Variant of Congenital Self-healing Reticulohistiocytosis: Solitary Hashimoto-Pritzker Disease

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Abstract: Four neonates had solitary, congenital, rapidly growing, spontaneously ulcerating tumors of the face, trunk, and extremities. No extracutaneous involvement was found, and all lesions spontaneously involuted. Mononuclear cells of the cutaneous infiltrate were Langerhans' cells. These findings expand the spectrum of congenital self-healing reticulohistiocytosis.

The Langerhans' cells (LC), dendritic cells primarily located in the epidermis and some other epithelia, can be regarded as members of the mononuclear-phagocyte system. One of their functions is to present selected antigens to T lymphocytes (1, 2). Disorders of Langerhans' cells have been difficult to study, since LC are not specifically identifiable in routine histologic material. Histiocytosis X (3) in all its forms and congenital self-healing reticulohistiocytosis (CSHR) (4–10) are the only two diseases identified to date as proliferations of the cells. Cutaneous lesions in both conditions usually are multiple. We observed four neonates with solitary, ulcerating, congenital tumors containing Langerhans' cells that subsequently have followed a benign course.

CASE REPORTS

Patient 1

A female child was the product of an uncomplicated pregnancy in a 31-year-old Hispanic woman, gravida 7, para 5, abortus 2. At birth she had a solitary 1-cm brown nodule on the right temple (Fig. 1). During the first week of life the lesion spontaneously ulcerated and crusted. Over the next six

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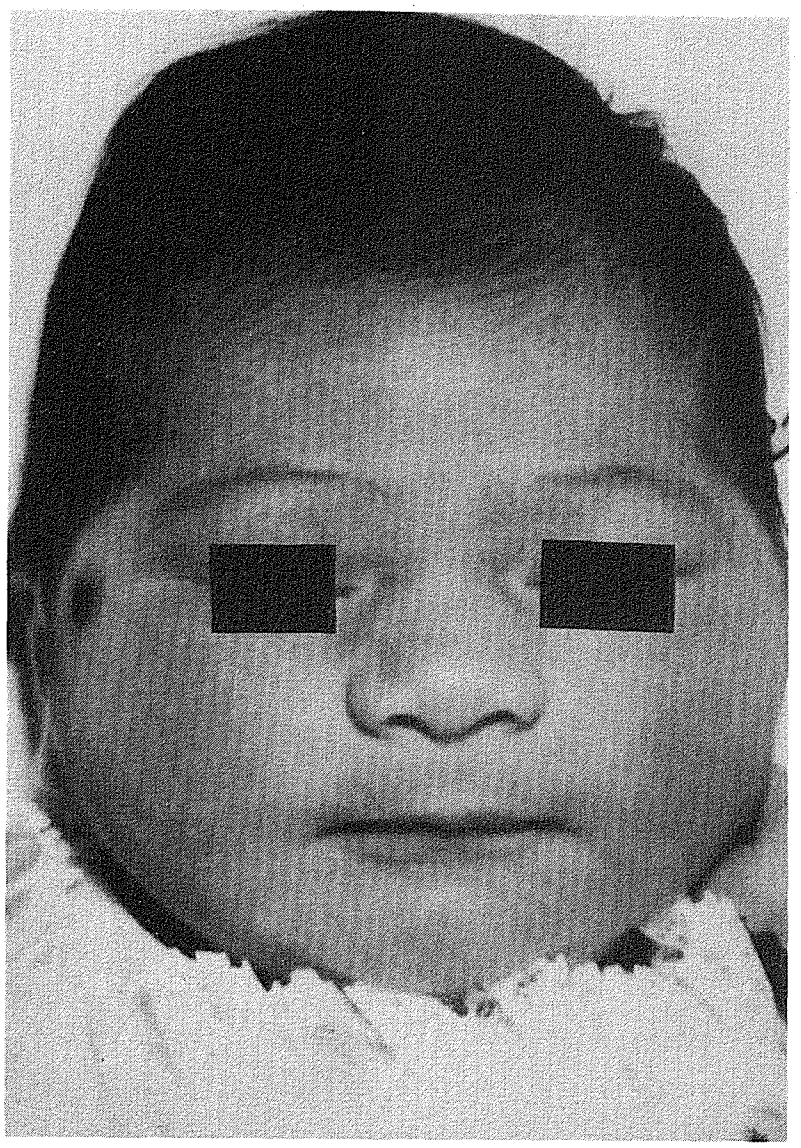


Figure 1. Patient 1. A 1-cm pigmented nodule on the temple at 1 day of age.

weeks the lesion grew to 2 cm in diameter and maintained a large central ulcer, despite several courses of oral antibiotics. At age 7 weeks, physical examination revealed a 2- × 2-cm, crusted, right temporal ulcer with raised borders (Fig. 2). Results of a complete blood cell count, urinalysis, liver-spleen scan, bone scan, skeletal survey, chest and skull films, and examination of bone marrow aspirate were normal. Results of routine serum chemical determinations, including cholesterol and triglycerides, also were normal. By 12 weeks the skin lesion had reached a diameter of 2.5 cm. By 18 weeks it had involuted completely, leaving an atrophic scar.

Patient 2

A 3510-g male child was born to a 19-year-old, black, gravida 2, para 2 woman whose pregnancy was significant only for recurrent urinary tract infections treated successfully with Keflex. In the delivery room, initial physical examination of the newborn showed a 1-cm, dry, crateriform nodule

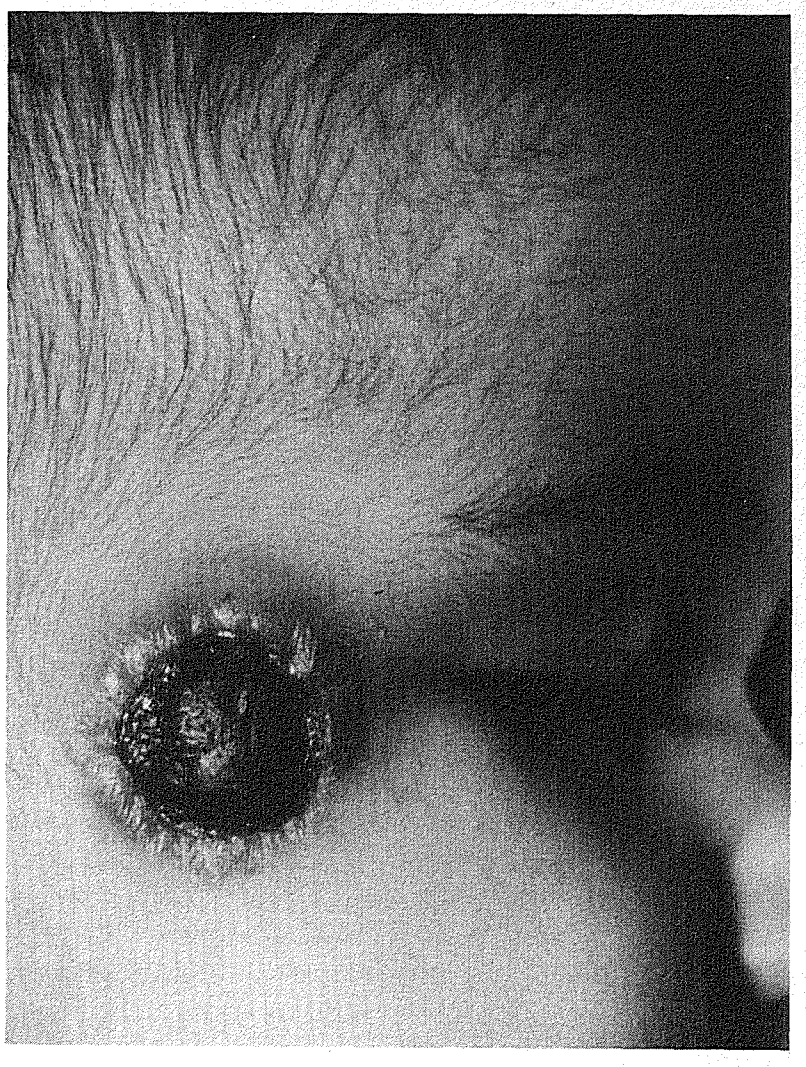


Figure 2. Patient 1. A 2-cm ulcerated nodule at age 7 weeks.

with central necrotic ulceration on the dorsum of the right foot (Fig. 3). Physical examination was otherwise normal. The skin lesion crusted and involuted at 2 weeks, and by 9 weeks consisted only of a small, flat, hyperpigmented 1-cm scar. The child's growth and development have been normal.

Patient 3

A 2-day-old male infant was seen by a consulting dermatologist for an ulcerated nodule on the hypothenar eminence of the right hand, present at birth (Fig. 4). Results of all clinical and laboratory studies after a biopsy diagnosis of Langerhans' cell tumor were negative. The lesion spontaneously cleared, leaving a small scar. The child is alive and well at 5 years of age.

Patient 4

A black male child, the product of an uncomplicated pregnancy and delivery, at birth had an erythematous, left inguinal cutaneous nodule measuring 1 × 2 cm. On day 2, superficial ulceration was

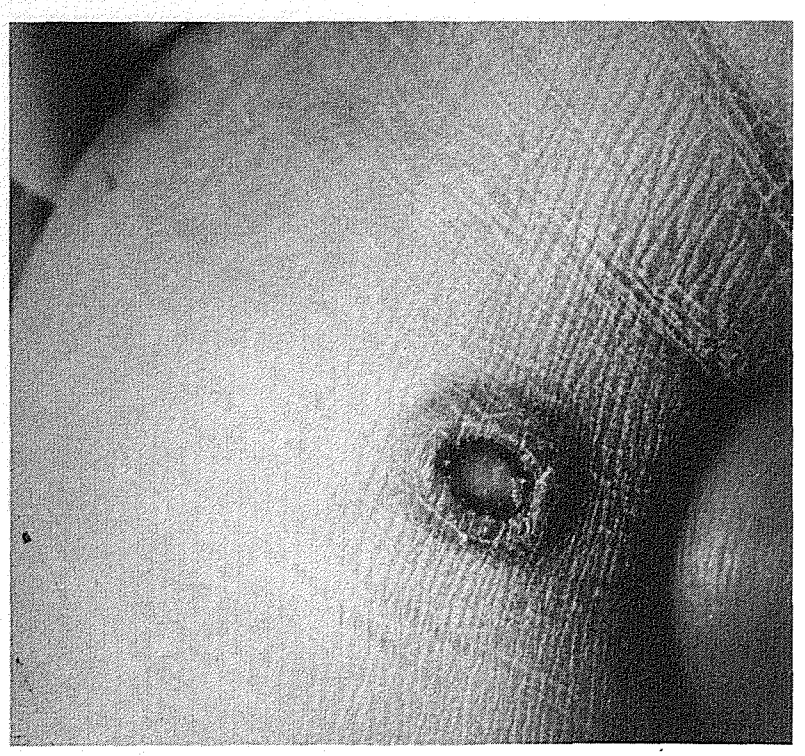
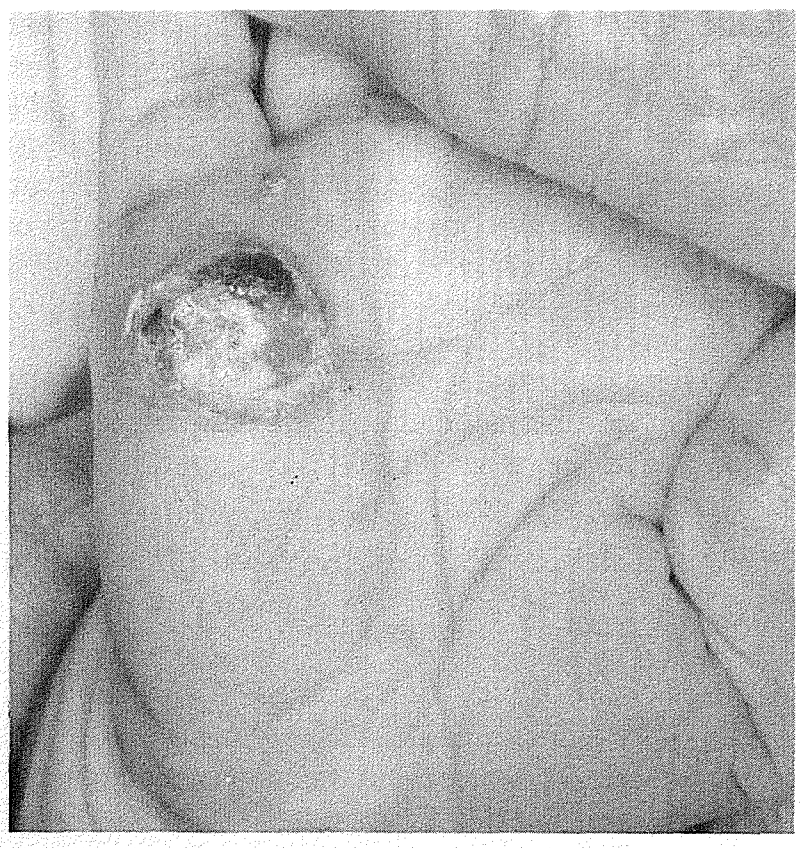


Figure 3. Patient 2. A 1-cm ulcerated nodule immediately after birth.

noted, which rapidly progressed to central necrosis. The remainder of the physical examination and results of routine laboratory studies (complete blood count, urinalysis, and chest radiograph) were unremarkable. The lesion involuted during the next 10 weeks and was undetectable on follow-up examination at age 1 year.

Figure 4. Patient 3. Ulcerated nodule of palm at age 2 days.

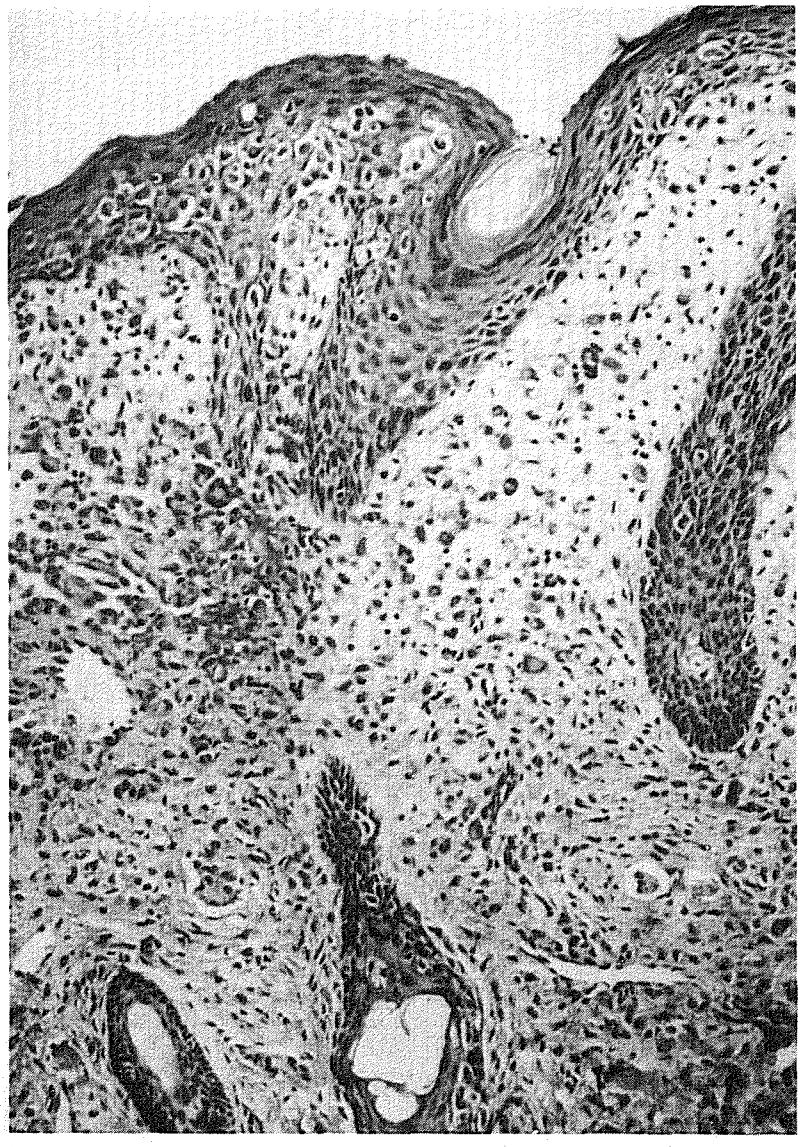


LABORATORY STUDIES

Light Microscopy

Biopsy specimens obtained at 6 and 8 weeks in patient 1 and within the first week of life in patients 2, 3, and 4 showed similar features. A dense, mononuclear infiltrate was present within the dermis to the level of the subcutaneous fat. Large mononuclear cells with abundant amphophilic cytoplasm dominated the infiltrate (Fig. 5). Nuclei were oval or reniform, and nucleoli were inconspicuous. Multinucleated giant cells with eosinophilic cytoplasm, present in all patients (Fig. 6), were abundant in patients 1, 2, and 4, and rare in patient 3. Epidermal erosion was present in all children, but large mononuclear cells in the epidermis were identified only in patients 1 and 3. Deep dermal necrosis and extravasation of red blood cells in the dermis were present in patients 1, 2, and 4. Eosinophils were abundant in patient 4 and rare in the others.

Figure 5. Patient 1. Dermal infiltrate of large mononuclear cells with irregular nuclei, extravasation of red blood cells, and involvement of the epidermis. (Hematoxylin and eosin; original magnification 63×.)



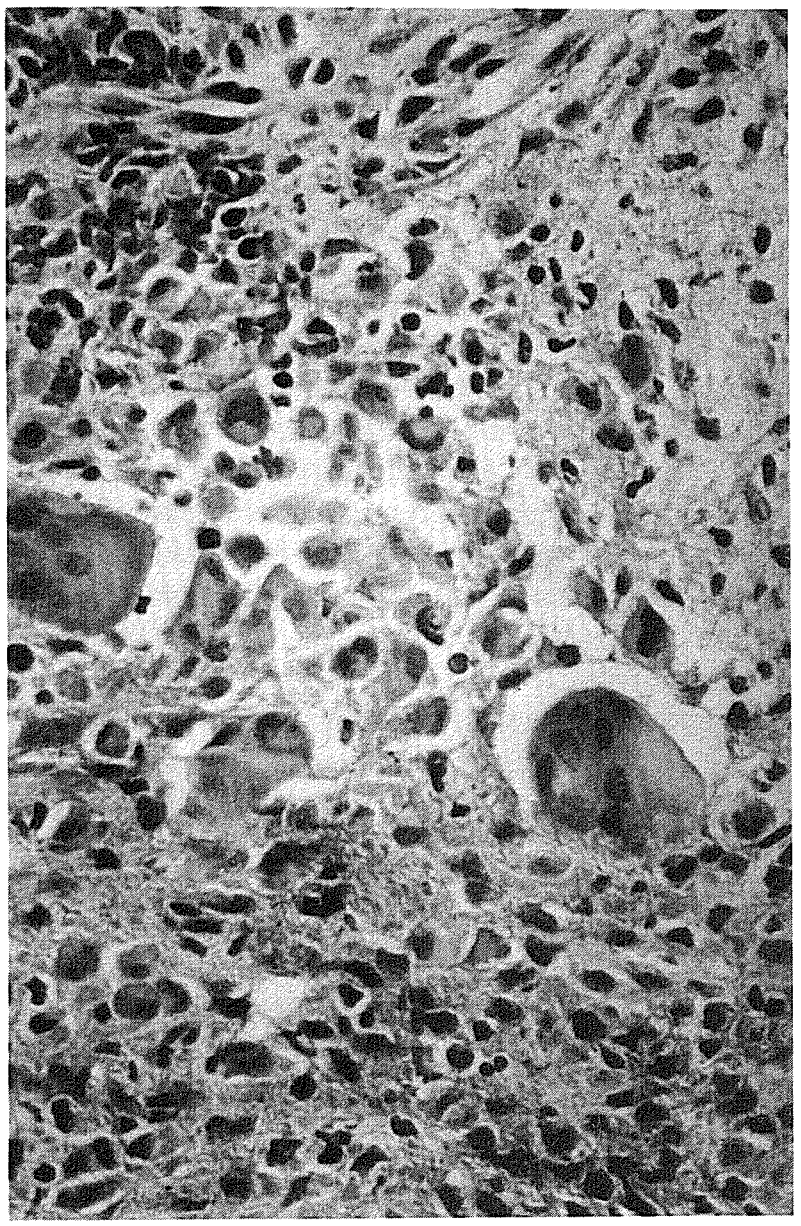


Figure 6. Patient 1. Large mononuclear cells, some with kidney-bean-shaped nuclei, and large multinucleated giant cells in the dermal infiltrate. (Hematoxylin and eosin; original magnification 100×.)

Immunoperoxidase Studies

Routinely processed, paraffin-fixed tissue from patients 1 and 4 were stained for the S-100 antigen and from patient 1 for lysozyme. In some areas, the majority of mononuclear cells in the dermis stained positively for S-100. Dendritic cells along the basal cell layer and in the stratum spinosum also were positive. There were no identifiable epidermotropic mononuclear cells in the small portion of epidermis on the sections stained for S-100. Adjacent sections stained for lysozyme showed strongly positive staining in the areas not stained for S-100, with only focal positive staining of occasional cells in the S-100–positive areas. No epidermal staining for lysozyme was found.

Fresh frozen tissue from patient 2 was examined by immunofluorescence and immunoperoxidase (ABC Vecta stain) techniques. The large dermal cells stained positively for OKT6, but were negative for OKT4. Immunoperoxidase studies of patient 3 were not done.

Electron Microscopy

Electron microscopic evaluation of biopsy material from patient 1 showed the large epidermotropic cells to contain Langerhans' (Birbeck) granules. Occasional myelin-like bodies were also found in the dermal infiltrating cells.

In patient 2, a range of cell types was noted in the dermis, including mature mononuclear phagocytes with clusters of phagosomes and lysosomes (30%); similar mononuclear cells without these organelles (30%); immature mesenchymal cells (30%); and mature lymphocytes (10%). A small percentage (less than 5%) of the mononuclear cells with and without phagosomes contained small numbers of Langerhans' cell (Birbeck) granules (Fig. 7). Lysosomes with a myelinated internal structure were rare.

In patient 3, electron microscopy readily demonstrated typical Langerhans' cell granules in cells of the mononuclear infiltrate. Electron microscopic studies were not performed on patient 4.

DISCUSSION

Langerhans' cells were first identified as dendritic cells in the epidermis by Paul Langerhans in 1868 (2). A century passed before their origin and functions were clarified. Katz et al (1) demonstrated that the cells originate from a mobile pool of bone marrow-derived precursor cells. In the epidermis, they represent 2% to 4% of the total epidermal cell population and occur in a suprabasal position. The cells are highly dendritic and form a continuous network, which plays a critical role in the afferent limb of the immune response. Langerhans' cells take up and present antigens entering the epidermis to T lymphocytes, initiating cutaneous cell-mediated immunity (2). With the advent of monoclonal antibody and immunoperoxidase technology, antigens have been identified on the Langerhans' cell surface that allow identification in histologic material. These antigens include S-100 and OKT6 (2). (Although less specific, S-100 staining can be performed on paraffin-fixed tissue.) As part of their immune function, Langerhans' cells also express HLA-DR (Ia) antigen (2).

In 1956 Basset and Turiaf (11) identified specific

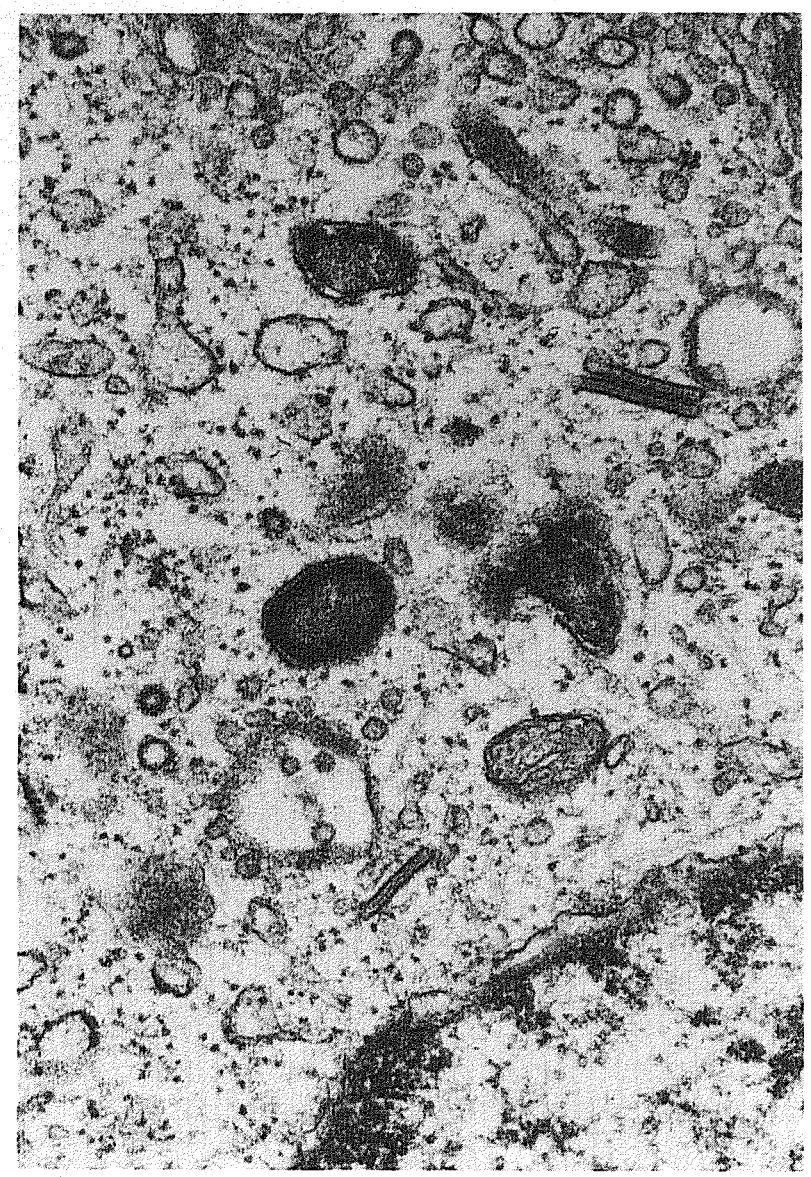


Figure 7. Patient 2. Electron micrograph of Langerhans' cell granules. (Original magnification 60,000×.)

intracytoplasmic, tennis-racket-shaped granules in a patient with histiocytosis X. In 1961 Birbeck et al (12) identified identical granules in the Langerhans' cells in normal epidermis. These findings were expanded, and Langerhans' cell (Birbeck) granules have been identified in all forms of histiocytosis X (3, 13).

Classically, histiocytosis X was divided into three diseases: Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma. Lichtenstein (14) in 1953 proposed that these were not three separate conditions, but rather a disease spectrum, which he called histiocytosis X. (The X referred to the unknown etiologic agent.) This concept persists to the present, and the electron microscopic findings mentioned above have supported this theory.

In 1973 a second disorder of Langerhans' cells, congenital self-healing reticulohistiocytosis (CSHR), was described by Hashimoto and Pritzker (4). The unique features of this disorder were presence at birth or perinatally of numerous cutaneous nodules, absence of internal involvement, and universal spontaneous and permanent healing. Several cases have since been described (4–10), allowing the following list of criteria to be proposed for this entity:

1. Congenital symptomless papulonodule(s)
2. Self-healing within a few months without recurrence
3. No systemic symptoms and no visceral lesions
4. Histopathology showing large mononuclear cells and multinucleated giant cells with ground-glass or foamy cytoplasm in the dermis and epidermis
5. Electron microscopy showing Birbeck granules and dense bodies (some with myelin-like lamination)
6. Immunoperoxidase staining positive for T6, HLA-DR(Ia), and S-100

The finding by electron microscopy of concentrically laminated dense core bodies and LC granules in the same cell has been proposed as a specific marker for CSHR (10).

We believe our four patients represent a clinical variant of Langerhans' cell proliferations most analogous to CSHR. All lesions were solitary, present at birth, larger than 1.5 cm or grew rapidly to greater than 1.5 cm, and ulcerated. Systemic involvement was not found. Biopsy of the lesions showed proliferation of large mononuclear cells in the dermis and epidermis, together with multinucleated giant cells with ground-glass or foamy eosinophilic cytoplasm. These findings have been observed in other Langerhans' cell proliferations (i.e., CSHR and granulomatous HX). Electron microscopy and immunoperoxidase techniques demonstrated markers specific for LCs in the infiltrating cells. The lesions spontaneously resolved within 18 weeks, and all patients have been free of disease for at least 6 months.

Evaluation of large numbers of patients with systemic Langerhans' cell proliferations (HX) showed that, in general, prognosis is dependent upon the age of onset, organ systems involved, and extent of organ involvement (15, 16). Even multifocal, multisystem disease may spontaneously regress, however (17, 18). In addition, low numbers of circulating suppressor T cells were detected in patients with systemic Langerhans' cell proliferations. Return to normal of this T cell abnormality, either spontaneously or by treatment with calf thymus gland extract, was associated with clinical remis-

sion (17, 19), leading various authors to propose that histiocytosis X is not a malignancy, but rather a reactive or immunologic disorder (17, 20). For the moment, at least, most LC proliferations should probably be regarded as paraneoplastic phenomena. In each instance, however, it is clearly desirable to determine the presence or absence of systemic disease. Therefore therapy should be expectant in children with no evidence of constitutional upset or vital organ dysfunction (17).

Conditions to consider in the clinical differential diagnosis of Langerhans' cell tumors include juvenile xanthogranuloma (JXG) and benign cephalic histiocytosis. Juvenile xanthogranuloma may be large, solitary, and present at birth (21). Ulceration is uncommon, and the hue in Caucasian skin is usually yellow to yellow-orange. Histologically, the typical wreathtype giant cells characteristic of JXG are not seen in Langerhans' cell proliferations. In addition, mononuclear cells in the epidermis are not a feature of JXG. Finally, Langerhans' cells have never been identified in JXG (22).

Benign cephalic histiocytosis (papular infantile xanthomatosis) is a benign eruptive disorder occurring in infants and young children (23). Small, erythematous papules, 1 to 5 mm, appear in a more or less symmetric distribution, particularly over the head and neck. With time, individual lesions accumulate cholesterol and neutral lipids, becoming yellow or yellow-orange, followed by slow involution. Headington et al (24) recently showed that the mononuclear cell infiltrate is S-100 positive OKT6 negative. They postulated that this may be a reactive or self-limited disorder of indeterminate cells. Langerhans' cell granules are rare within the mononuclear cells of the papillary dermal infiltrate in benign cephalic histiocytosis.

In summary, we followed four neonates with large, solitary, congenital tumors similar in clinical course and histopathology to the multiple lesions described by Hashimoto and Pritzker (4–10). Ulceration was followed by spontaneous regression without evidence of systemic disease. The oldest of these patients is alive and well five years after diagnosis. These findings expand the spectrum for LC proliferations. We wish to stress, however, that although self-healing Langerhans' cell proliferations can be suspected clinically, the cutaneous findings in those cases with systemic involvement may also be congenital, nodular, and ulcerative (18, 25). For this reason, a minimal systemic evaluation is advisable in all cases, including physical examination, complete blood cell count, liver function tests, skin biopsy with electron microscopic or special marker studies, and bone survey. Liver-spleen scan and bone marrow biopsy may also be considered. If extracutaneous involvement is not found with the features discussed above, spontaneous remission can be anticipated.

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REFERENCES

1. Katz S, Kunihiko T, Sachs D. Epidermal Langerhans' cells are derived from cells originating in bone marrow. Nature 1979;282:324–326.
2. Wolff K, Stingl G. The Langerhans' cell. J Invest Dermatol 1983;80:17–20.
3. Wolff H. Subtle clues to diagnosis of skin disease by electron microscopy. Am J Dermatopathol 1979;1: 77–81.
4. Hashimoto K, Pritzker M. Electron microscopic study of reticulohistiocytoma. Arch Dermatol 1973; 107:263–270.
5. Laugier P, Hunziker N, Laut J, et al. Reticulohistiocytose d'evolution benigne (type Hashimoto-Pritzker). Ann Dermatol Syph (Paris) 1975;102:21–35.
6. Mascaro J, Aliaga A, Mascaro-Galy C. Reticulose congenitale auto-involutive. Ann Dermatol Venereol 1978;105:223–227.
7. Rufli T, Fricker H. Kongenitale, selbstheilende Retikulohistiozytose. Z Hautkr 1979;54:554–558.
8. Bonifazi E, Caputo R, Ceci A, et al. Congenital self-healing histiocytosis. Arch Dermatol 1982;118:267–272.
9. Hashimoto K, Griffin D, Kohsbaki M. Self-healing reticulohistiocytosis. Cancer 1982;49:331–337.
10. Hashimoto K, Takahashi S, Lee R, et al. Congenital self-healing reticulohistiocytosis. J Am Acad Dermatol 1984;11:447–454.
11. Basset F, Turiaf J. Identification par la microscopie electronique de particules de nature probablement viral dans les lesions granulomateuses d'une histiocytose "X" pulmonaire. CR Acad Sci (Paris) 1956; 261:3701–3703.
12. Birbeck MS, Breathnach AS, Everall JD. An electron microscope study of basal melanocytes and high-level clear cells (Langerhans' cells) in vitiligo. J Invest Dermatol 1961;37:51–63.
13. Nezelof C, Basset F, Rousseau M. Histiocytosis X histogenetic arguments for a Langerhans' cell origin. Biomedicine 1973;18:365–371.
14. Lichtenstein L. Histiocytosis X. Arch Pathol 1953;-56:84–102.
15. Lahey ME. Histiocytosis X — an analysis of prognostic factors. J Pediatr 1975;87:184–189.
16. Greenberger JS, Crocker AC, Vanter G, et al. Results of treatment of 127 patients with systemic

histiocytosis (Letterer-Siwe syndrome, Schüller-Christian syndrome and multifocal eosinophilic granuloma). Medicine 1981;60:311–338.
17. Broadbent V, Daries EG, Heat D, et al. Spontaneous remission of multisystem histiocytosis-X. Lancet 1984;1:253–254.
18. Marsh WL, Lew SW, Heath VC, et al. Congenital self-healing histiocytosis-X. Am J Pediatr Hematol Oncol 1983;5:227–233.
19. Osband ME, Lipton JM, Lavin P, et al. Histiocytosis X. N Engl J Med 1981;304:146–153.
20. Pritchard J. Histiocytosis X. Natural history and management in childhood. Clin Exp Dermatol 1979;4:421–433.
21. Helwig EB, Hackrey VC. Juvenile xanthogranuloma (nevoxantho-endothelioma). Am J Pathol 1954;30: 625–626.
22. Rowden G, Conneley EM, Winkelmann RK. Cutaneous histiocytosis-X: the presence of S-100 protein and its use in diagnosis. Arch Dermatol 1983;119: 553–559.
23. Barsky BL, Lao I, Bursky S, et al. Benign cephalic histiocytosis. Arch Dermatol 1984;120:650–655.
24. Headington JT, Rassmussen J, Hashimoto K, et al. Papular infantile xathomatosis (abstr). Arch Dermatol 1984;120:1611.
25. Stateva S, Kiriakow I, Mustakov G. Kongenitale histiocytosis X. Hautarzt 1980;31:26–29.