

CLINICAL REPORT

Clinical Spectrum of Cutaneous Langerhans' Cell Histiocytosis Mimicking Various Diseases

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Langerhans' cell histiocytosis summarizes a spectrum of diseases on the basis of histogenetic criteria. These are characterized by an accumulation of cells with Langerhans' cell phenotype in one or multiple organs. Up to 50% of patients with either single or multi-organ manifestation of Langerhans' cell histiocytosis initially present with cutaneous symptoms. Nevertheless, cutaneous Langerhans' cell histiocytosis is rare and heterogeneous in its clinical features and therefore prone to misdiagnosis. We report on five patients, two infants and three adults, suffering from cutaneous Langerhans' cell histiocytosis, either singly or as part of multi-organ disease. The different skin features morphologically mimicking other entities are shown and the differential diagnoses are discussed. The correct diagnosis in all presented cases is based on immunohistological examination, showing a histiocytic infiltrate positively staining with anti-S100 antibodies, CD1a and – apart from one case – with CD207 (langerin). Key words: Langerhans' cell; histiocytosis; immunohistology; skin infants; adults

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The class of the Langerhans' cell histiocytosis (LCH) summarizes a disease triad previously called histiocytosis X, consisting of eosinophilic granuloma (benign variant, usually localized to the bone), Letterer-Siwe disease (skin lesions, hepatosplenomegaly, lymphadenopathy, bone marrow infiltration) and Hand-Schüller-Christian disease (diabetes insipidus, exophthalmus and eosinophilic granuloma of the bone), self-healing LCH, Hashimoto-Pritzker disease, pure cutaneous histiocytosis, Langerhans' cell (LC) granulomatosis, type II histiocytosis and non-lipid reticuloendotheliosis (generic name) on the basis of histogenetic criteria (1, 2). The terms selfhealing LCH, Hashimoto-Pritzker disease and pure cutaneous histiocytosis characterize benign variants of LCH with solitary or multiple skin lesions appearing in different age groups. All these entities, based on the sites of involvement and extent of disease, are characterized by an accumulation, respectively proliferation of cells with the phenotype of LCs, that may involve one or mul-

tiple organ systems, such as bone, lung, hypothalamus, posterior pituitary gland, lymph nodes, liver, mucous membranes and the skin. LCs, which are dendritic cells of bone marrow origin, acquire their typical phenotype within the epidermis. They are responsible for processing and presenting antigens to T lymphocytes. As LCs physiologically belong to the immune system of the skin, it is not surprising that skin manifestations are frequently seen, whenever cells of that phenotype tend to proliferate in one or multiple organs. From a large cohort of 314 patients with LCH studied in the Mayo Clinic, 77 patients had skin or mucous membrane affections (3). According to other authors, up to 50% of patients with LCH will initially present with a rash (4). Unfortunately, cutaneous LCH either as a single organ disease or as part of a multisystem disease presents a broad spectrum of symptoms and thus is often misdiagnosed.

CASE REPORTS

Case 1

A 1-day-old boy was presented to our department because of a skin lesion on the left foot, that had been observed immediately after birth. Dermatological examination revealed a softly palpable, crust-covered tumour measuring 1 cm in diameter on the left ball of the first toe. Also a flaccid blister surrounded by small vesicles and yellowish papules was localized on the left medial forefoot (Fig. 1). The bacterial culture revealed growth of *Staphylococcus aureus*. Direct immunofluorescence was negative for herpes simplex virus type 1 and 2. Histopathological examination showed a dense dermal infiltrate of large cells with pale cytoplasm and reniform nucleus, staining positive for S100, CD1a and CD207 (langerin). Thus the diagnosis of LCH was established. Apart from the skin other organ manifestations of LCH could be excluded. Under application of local antiseptics the lesions disappeared, 1 year later only residual scars could be observed. The spontaneously healing lesion, fulfilling the histological criteria of LCH, was thus characterized as congenital self-healing LCH.

Case 2

At the age of 12 months, a girl developed a generalized pustular eruption, initially diagnosed as superinfected



Fig. 1. Lesions on the plantar region of the forefoot in a newborn boy (case 1).

chickenpox in a children's clinic. Despite antibiotic treatment purulent lesions persisted which led to hospitalization under suspicion of an immunodeficiency syndrome. Chest X-ray revealed diffuse striation of the lung. Computed tomography (CT) of the chest showed multiple lung cysts and honeycombs (up to 2.5 cm in diameter) with accentuation in the upper lobes and peribronchial striation. Progressive deterioration of the skin lesions led to the first consultation at our department in January 1996. The girl (then aged 21 months) presented with generalized disseminated, partially crusted papules and pustules, eczematous lesions in the retroauricular region and on the scalp, and ulcerated nodes of the lower legs. The distal parts of fingers and toes were distended and of lilac colour, the nail plates showed deformation, thickening, hyperkeratosis and onychorrhexis as well as onycholysis with greenish black discoloration (Fig. 2). Bacteriological and fungal cultures of skin and nail swabs were negative. Histopathologic examination of skin biopsies revealed the same features as described in case 1, thus LCH was diagnosed. Apart from skin and lung involvement no other organ manifestations could be detected. Under chemotherapy with intravenous vinblastine (6 mg/m² body surface once a week) and oral prednisone (40 mg/m² body surface daily) over a period of 6 weeks according to the LCH-II Protocol (Gadner H, Vienna, Austria) improvement of skin and nails could be observed. Maintenance chemotherapy at 3-weekly intervals (vinblastine 6 mg/m² body surface on the first day of each cycle, prednisone 40 mg/m² body surface on days 1–5, 6-mercaptopurine 50 mg/m² body surface daily) led to a complete resolution of the skin manifestations and to an improvement of lung and nail affection. Due to a progression of lung manifestation and mouth mucosa affection induction chemotherapy had to be repeated in July 1997. Oral administration of cyclosporin A (5 mg/kg body weight) was added from November 1997 to December 2000. Under this regimen



Fig. 2. Papulo-nodular lesions on the distal parts of the left leg and fingers of a 21-month-old girl (case 2).

pulmonary disease remained stable and no further skin manifestations have emerged up to now.

Case 3

An 89-year-old man developed an asymptomatic singular node localized on the right flank. Histological examination after excision biopsy showed a subepidermal tumour, honeycombed with leukocytes, with central necrosis. Adjacent to the necrotic area histiocytic cells with pale cytoplasm, lymphocytes and multiple eosinophils could be identified. S100 and CD1a staining of the histiocytes were positive (Fig. 3a and b). CD207 labelling was not done in this case. Thus the node was diagnosed as eosinophilic granuloma of the skin. After excision of the node no relapse has been observed up to now.

Case 4

A 69-year-old woman had a 4-year history of persisting asymptomatic erythematous lesions in the anogenital region, which had not responded to prior treatment attempts with external antimycotics or glucocorticosteroids, applied by non-resident colleagues. In April 1995, she presented to our department with a pale red, infiltrated erythema with marginal flat papules localized in the perianal region and on the labia majora (Fig. 4). A skin biopsy showed the typical pattern of LCH. After exclusion of extracutaneous manifestation, radiation therapy (8×200 cGy) was performed, which resulted in complete clearance. In the following 5 years neither relapse nor recurrence in other localization could be observed.

In March 2000 the patient was hospitalized in a Swiss hospital due to pneumonia. Despite antibiotic treatment the inflammatory parameters (C-reactive protein, leukocytes) remained elevated. High resolution CT of the chest in January 2001 revealed a reticulonodular

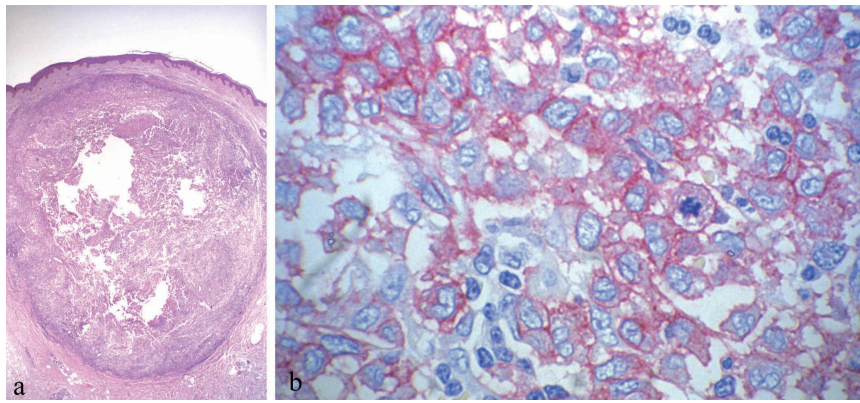


Fig. 3. (a) Low power view of an eosinophilic granuloma of the skin (case 3). (b) High magnification showing aggregated CD1a-positive cells with high mitotic activity.

and a partially striated lung structure with consolidated areas in subpleural localization. Cytological examination after pulmonary washing showed squamous epithelia, columnar epithelia with cilia, sporadically siderophages, lymphocytes, neutrophil leukocytes and erythrocytes. In the specimen many macrophages and especially multinuclear macrophages could be identified, but histiocytes typical for LCH have not been found. Immunocytochemistry revealed areas with >3% S100-positive histiocytes besides areas with only a few isolated positive cells; CD1a antigen staining failed. A definite cytological diagnosis could therefore not be provided, a possible lung manifestation of LCH was neither confirmed nor excluded by the Swiss colleagues. A therapeutic attempt with oral prednisone (initially

40 mg daily) was started at the end of January 2001. Unfortunately, the patient died in February 2001 due to cardiovascular disease. Autopsy was refused by her relatives.

Case 5

In May 1999, a 66-year-old woman presented to our department with disseminated, partially confluent red or lilac papules and nodules and isolated pinhead-sized red-brown macules mainly localized on the trunk and proximal extremities (Fig. 5a). Several nodules showed a haemorrhagic crust in the centre. According to the patient's report the first lesions had appeared 2 months prior to consultation and had been localized on the upper trunk. Medical history revealed a myelomonocytic leukaemia, diagnosed in February 1999. Due to progressing leukocytosis in April 1999 the patient had been treated orally with hydroxyurea. Under suspicion of leukaemic cutaneous infiltrates a skin biopsy was taken, but histological examination showed a dense infiltrate of histiocytes with reniform nuclei extending from the basal epidermis to the deep reticular dermis. The histiocytes stained positive for CD1a and S100 antigen, sporadically positive for lysozyme and negative for CD68 antigen, thus confirming the histological diagnosis of LCH. Langerin (CD207), however, was not expressed. A lung involvement could be excluded by chest X-ray. We did not perform further staging because of the poor condition of the patient's general health. To improve the severe stigmatizing skin lesions, a PUVA bath therapy (four times a week) was initiated but had to be stopped after 2 weeks because of a progression of the myelomonocytic leukaemia with deterioration of the patient's general condition and worsening of the skin lesions. A second skin biopsy, taken 5 weeks after the first one, showed a perivascular infiltrate of blast-like cells with great variety in shape and size of the nuclei in the reticular dermis (Fig. 5b). The majority of these cells stained positive for CD68 and lysozyme.

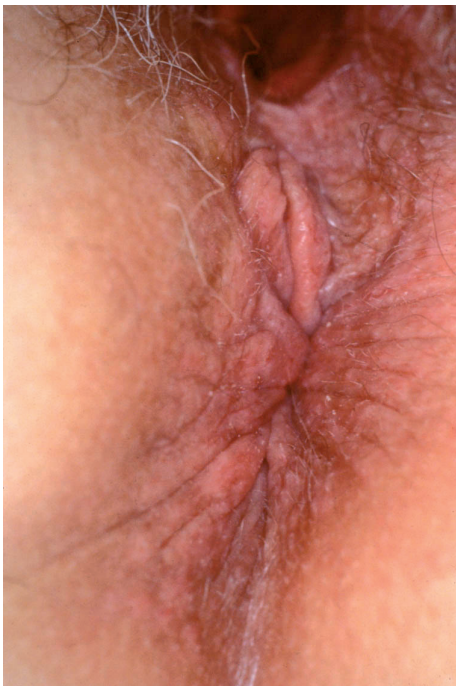


Fig. 4. Infiltrated erythema with flat papules in the anogenital region of a 69-year-old woman (case 4).

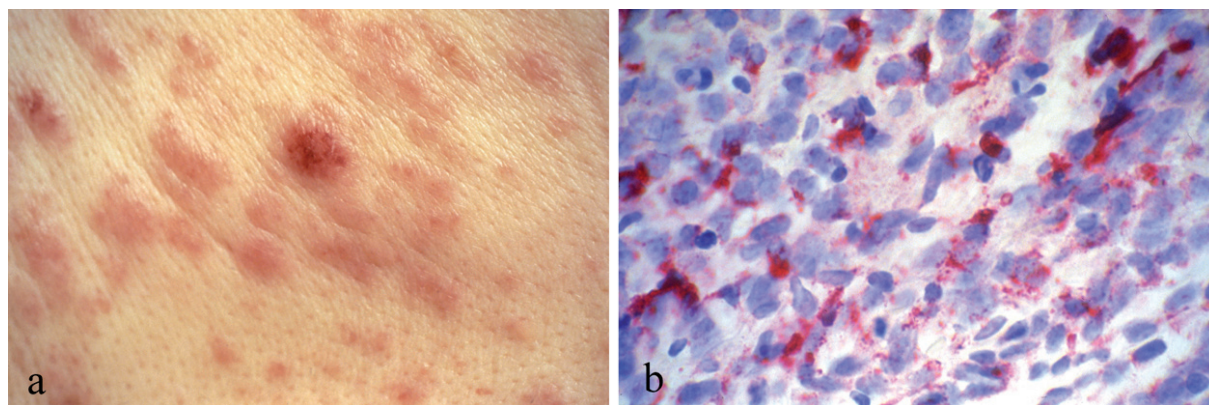


Fig. 5. (a) Close-up of disseminated, partially haemorrhagic papules in a woman suffering from myelomonocytic leukaemia (case 5). (b) CD68- positive immunophenotype of the cutaneous infiltrate biopsied in July 1999.

Only singular histiocytic cells with reniform nuclei, staining positive for S100 and CD1a antigen, could be identified. Despite chemotherapy with vincristine (2 mg absolute) the patient's general condition worsened and she died due to a blast crisis in August 1999.

DISCUSSION

The presented cases reflect the astonishing variety of cutaneous manifestations of either single or multiple organ LCH in patients of different age groups. Due to the diversity of the clinical presentation and the morphological similarity to other entities, cutaneous LCH is a diagnostic challenge.

Cutaneous LCH may appear as localized (as in cases 1, 3 and 4) or as disseminated lesions (as in cases 2 and 5). In case 1 the cutaneous lesions were restricted to the plantar region and consisted of a soft tumour besides a blister with satellite papules and pustules. Therefore our differential diagnoses included localized infectious diseases such as impetigo contagiosa or herpes simplex manifestation. Blisters in plantar localization may also be a symptom of hereditary epidermolyses, e.g. epidermolysis bullosa simplex. Histopathology and clinical features (congenital or perinatal appearance and spontaneous involution) suggested congenital self-healing histiocytosis as diagnosis, first described by Hashimoto & Pritzker (5) and later confirmed by Ikeda et al. (6). The solitary node on the flank of the 89-year-old man reminded us of pseudolymphoma, sarcoidosis or a cutaneous metastasis. Immunohistological examination characterized the lesion as eosinophilic granuloma of the skin. Eosinophilic granuloma may involve all organs but has a predilection for flat bones. In the fourth case an example of external genital involvement in an elderly woman has been shown, which could be misdiagnosed as extramammary Paget's disease, allergic contact dermatitis, atopic dermatitis, or candidiasis (7). Sole cutaneous involvement of the genitalia is rare and only reported in elderly female patients. Sometimes

multisystem manifestation may follow seemingly solitary cutaneous LCH, as supposed in case 4.

In cases 2 and 5, however, cutaneous LCH presented as generalized eruption, which resulted in a completely different spectrum of differential diagnoses.

The papulopustular eruption in the 12-month-old girl had initially been misdiagnosed as chickenpox before the patient was referred to our department. A similar case of a 4-month-old boy has been reported by Johno et al. (8). The coincidence of the varicella-like eruption with symptoms (nail changes, scaly erythema) that do not match the suspected diagnosis and the atypical course should arouse doubts regarding the diagnosis. Scaly erythema, as in the presented case occurring in the retroauricular region (case 2), are frequently found in LCH. The lesions resemble seborrhoeic dermatitis and appear in the predilection sites of seborrhoeic dermatitis. Dermatophytosis should be considered as further differential diagnosis, but also as potential concomitant infection (9). In the same case cutaneous symptoms coincided with nail and nail bed alterations, similar to candida paronychia or onychomycosis. Nail lesions are not commonly reported in LCH and, if occurring, include a diversity of symptoms such as longitudinal grooving, purpuric striae, hyperkeratosis, subungual pustules, onycholysis, paronychia and elkonyxis (10).

In the fifth case a rash occurred in a woman suffering from myelomonocytic leukaemia. For obvious reasons cutaneous infiltration due to leukaemia was considered as the most probable diagnosis. Nevertheless the reniform aspect of the nuclei as well as the positivity for S100 and for CD1a antigen in the absence of CD68 clearly pointed to LCH. On the other hand, considering the lack of expression of langerin (CD207), the LCH differentiation was incomplete in this case. In addition, it was rapidly transient and already gone at the time of the second biopsy (Fig. 5b). There is no consensus yet as to whether such phenomena should be classified within the spectrum of LCH, or whether they should

be distinctly interpreted as an LCH-like episode of myelomonocytic leukaemia. In analogy, indeterminate cell histiocytosis (ICH) is regarded by some authors as a dedifferentiated member of the LCH family, by others as a separate entity. While S100 and CD1a antigen are present in ICH, langerin (CD207) is absent. This fact explains the absence of Birbeck granules because their formation is induced by the endocytic receptor langerin (11).

The controversial opinions about the classification of the mentioned 'incomplete' LCH-like entities mainly result from the uncertainty about the pathogenesis of LCH. Its reactional or neoplastic nature is still debated. According to Baikian et al. (12) and Egeler et al. (13) the association with myelomonocytic leukaemia suggests a common cytogenetic origin. The latter hypothesis is supported by the detection of clonal histiocytes in the LCH lesions by Willman et al. (14).

The diverse cutaneous or mucocutaneous lesions, either as curable single organ disease or as part of multisystem manifestation, are often the keys to the correct identification of LCH or LCH-like infiltrates. Inversely, these polymorphic lesions in infants and adults are also prone to be mistaken for a broad spectrum of more common diseases, a pitfall that can easily be avoided by a simple skin punch biopsy. In each of the presented cases, the diagnosis was established by pathognomonic dermatohistological features. According to the writing group of the Histiocyte Society the diagnosis of LCH requires the finding of Birbeck granules in lesional cells by electron microscopy and/or the expression of T6-antigenic determinants (positive staining with CD1a antibodies) on the surface of lesional cells (1). Anti-S100, langerin (CD207), CD68 and factor XIIIa (15) may be further helpful markers if LCH is suspected and has to be distinguished from other types of histiocytoses. LCs usually label for S100 and CD207, not for CD68 and factor XIIIa. The identification of Birbeck granules by electron microscopy has become dispensable today, especially since CD207 antibodies are available for immunohistochemistry on paraffin sections (16, 17).

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