Cutaneous Langerhans cell histiocytosis with subsequent development of haematological malignancies.

Report of two cases

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SUMMARY

Adult cutaneous Langerhans cell histiocytosis (LCH) is a rare disease. We report two cases illustrating the variability of the clinical presentation and the response to treatment. In both cases a remission was achieved: in one case a partial remission with psoralen plus UVA irradiation (PUVA) and methotrexate plus topical corticosteroid ointment; in the other case by treatment with thalidomide. Despite a therapeutic response, both patients later developed haematological malignancies: a chronic myelo-monocytic leukaemia and an acute lymphatic leukaemia. In conclusion, patients with adult cutaneous LCH should be monitored carefully so that a secondary malignancy is not overlooked.

KEY WORDS

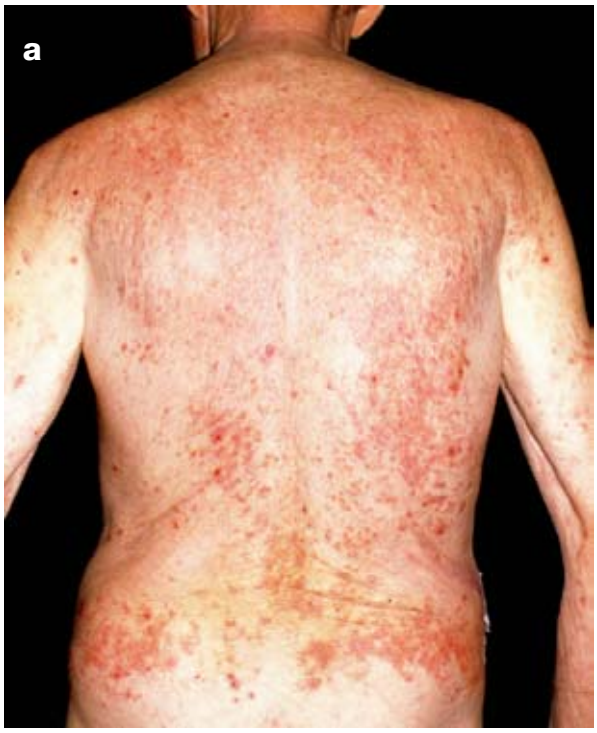
histiocytosis, Langerhans cell, pathology, course, treatment, secondary malignancies

Introduction

Cutaneous histiocytoses are rare diseases with a broad spectrum of clinical presentations, age-distribution and prognosis. A major obstacle to a full understanding is the word „histiocyte“, a cell that does not exist. Histiocytes are cells that either differentiate into monocytes/ macrophages or into dendritic cells, the Langerhans cells: either a veiled cell or an interdigitating dendritic cell, a follicular dendritic cell, a plasmocytic dendritic cell, or a dermal dendrocyte (1). An excellent review by Luz et al on non-Langerhans cell histiocytes appeared recently (2).

In 1953 Lichtenstein et al. proposed the term histiocytosis X as a unifying concept for Abt-Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma of bone (3). In 1987 the Histiocyte Society replaced the „X“ by Langerhans cell histiocytosis (LCH) (4). The incidence of LCH is 2 to 4 per million. Several clinical variants are known.

The Abt-Letterer-Siwe type occurs mostly in preschool age and typically shows a multisystemic involvement. The Hand-Schüller-Christian type develops during pre-school or primary school age and is characterized by a triad of bony lesions, diabetes insipidus, and exophthalmus. About 10% of patients are older than 30 years. The eosinophilic granuloma type shows bone lesions and sometimes diabetes insipidus as well. The Hashimoto-Pritzker type of congenital self-healing histiocytosis is part of the spectrum (5).



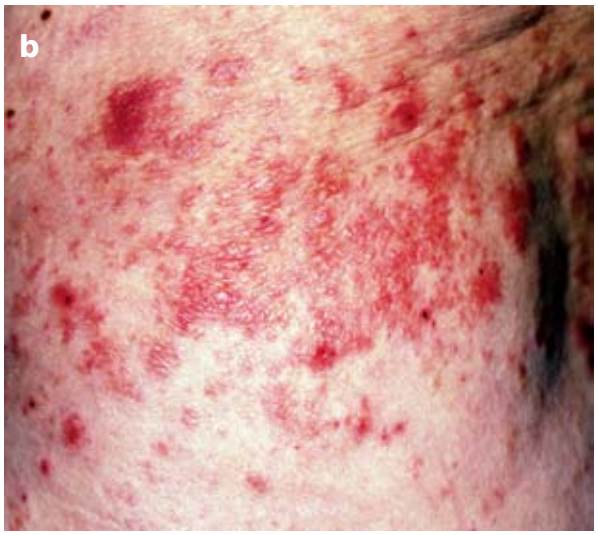
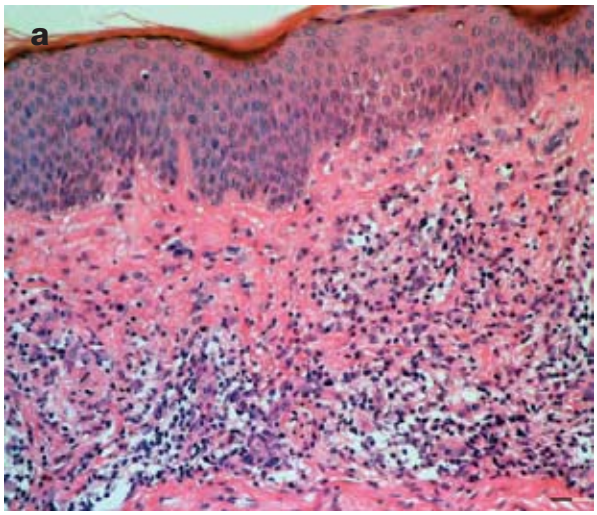


Figure 1. Adult cutaneous Langerhans cell histiocytosis (case #1). a) Overview: disseminated erythematous papules. b) Detail.

Pure cutaneous adult LCH is extremely rare (6). We report on two adult cases of disseminated LCH, their course and treatment. Despite a favourable clinical response to treatment both patients subsequently developed haematological malignancies which needed an aggressive chemotherapy. The second case has been partly reported before, but the focus in the previous article was on thalidomide therapy (7).



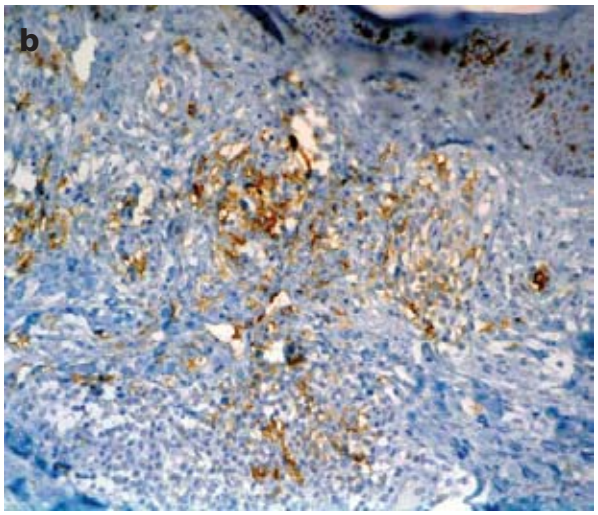


Figure 2a. Adult cutaneous Langerhans cell histiocytosis – histopathology. Hematoxylin-eosin stain shows a mixed inflammatory dermal infiltrate with variable density, composed of lymphocytes, monocytic cells, some neutrophils, plasma cells and eosinophils (objective x 20).

Figure 2b. Adult cutaneous Langerhans cell histiocytosis – histopathology. Immunostaining for CD1a shows small nodules of positively stained dermal cells as found as in cutaneous Langerhans cell histiocytosis (Immunoperoxidase, Objective x40)

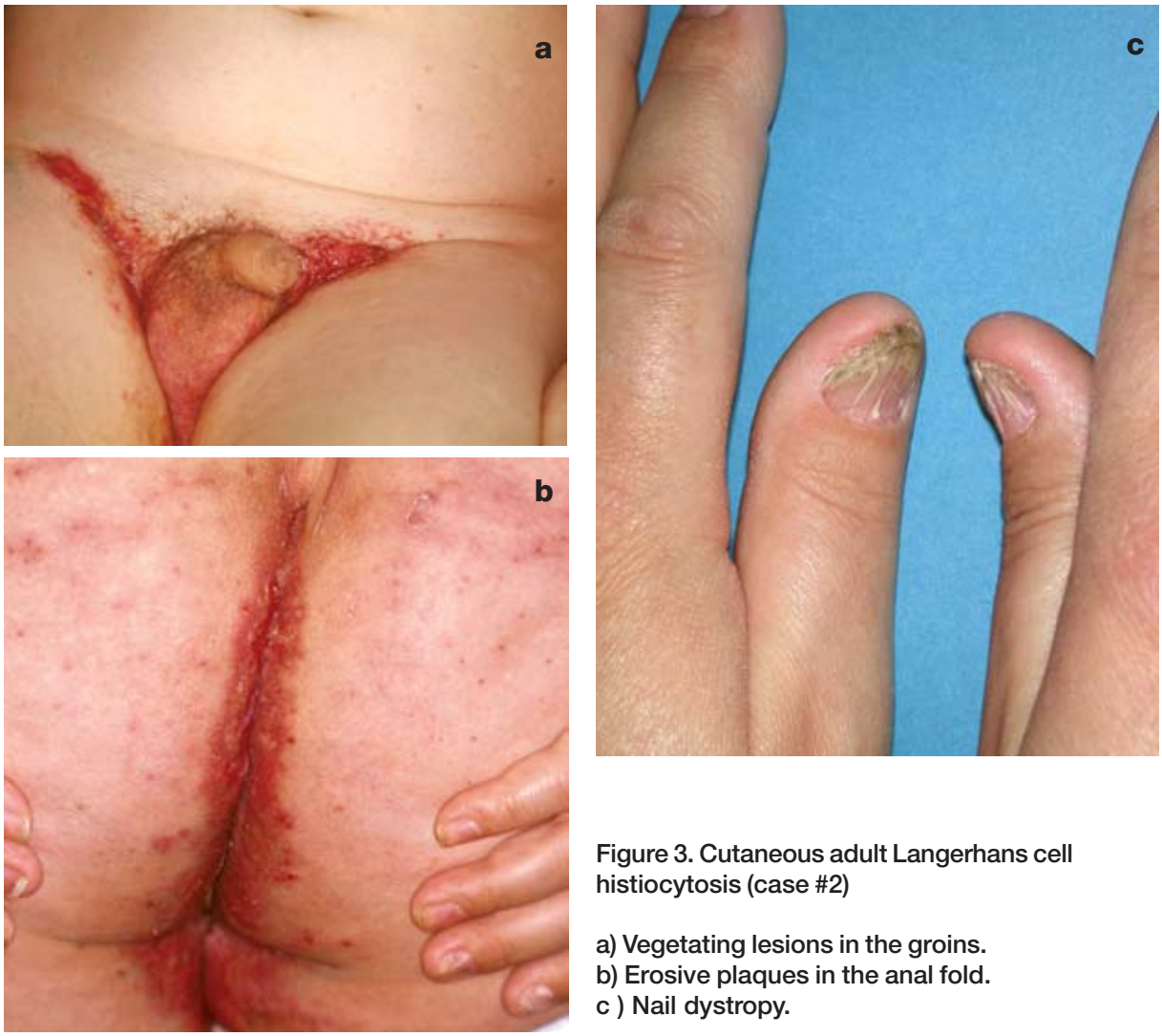


Figure 3. Cutaneous adult Langerhans cell histiocytosis (case #2)

a) Vegetating lesions in the groins.
b) Erosive plaques in the anal fold.
c) Nail dystropy.

Case reports

Case 1

A 73-year-old Caucasian male patient with pruritic skin lesions on his trunk not responsive to topical corticosteroids was referred to the Department of Dermatology Dresden-Friedrichstadt. He had a history of prostate cancer that was surgically removed.

On examination we observed multiple, disseminated lichenoid papules 3-5 mm in diameter on the trunk and thighs, excoriation and postinflammatory hyperpigmentation. The hair and nails, as well as scalp, palms and soles were not involved.

A skin biopsy revealed a superficial dermal, perivascular lymphocytic infiltrate without any indication of vasculitis or lymphoma.

Laboratory investigations including blood cell counts, antinuclear antibody screening, TPHA, and hepatitis serology were within normal limits, except for a slight monocytosis.

Based on the working diagnosis „lichenoid dermatosis" we initiated a combined treatment with oral prednisolone 60 mg daily and cream-PUVA irradiation (cumulative UVA dosage 21 J) resulting in rapid improvement. About six weeks later a severe, highly pruritic relapse occurred necessitating a hospitalization (Figure 1).

A second skin biopsy revealed a superficial and deep perivascular lymphocytic infiltrate with monocytes, mast cells and eosinophils. In addition there was a broad bandlike infiltrate composed of medium to large sized cells with eosinophilic cytoplasm and large bean-shaped nuclei (Figure 2a). Immunostainings were positive for S100 and CD1a and indicated a Langerhans cell-phenotype (Figure 2b).

Laboratory investigations at this stage disclosed a mild lymphopenia (14%), eosinophilia (18%), mono-

cytosis (22%), hypergammaglobulinaemia (21.4%), as well as normal values of liver and kidney tests, microbiology, C-reactive protein, prostate-specific antigen, and IgE.

Imaging investigations including sonography, chest X-ray, abdominal computer tomography, and whole body bone scintigraphy were normal except for symptomless liver cysts.

The diagnosis of disseminated cutaneous Langerhans cell histiocytosis was thus confirmed.

Treatment and course: We introduced oral methotrexate 15mg/week with folic acid substitution on the following day. In addition a cream-PUVA therapy was performed (cumulative UVA dosage 18 J). Betamethasone 0.1% ointment was applied once daily, in part under occlusion. After a partial response, the methotrexate dose was reduced to 10 mg/week. The treatment was well tolerated. During a five month follow-up a partial remission was observed. Later on, however, he developed a chronic myelo-monocytic leukaemia. A palliative therapy with idarubicine (zavedos) was started. Twelve months later the patient died during an acute blast crisis.

Case 2

A 38-year-old male patient was presented to the Department of Dermatology and dermatological Allergology, University of Jena, because of a six month history of painful genitoanal ulcerating lesions. Diabetes mellitus was diagnosed one year before and autoimmune thyreoiditis five years earlier.

On examination we observed hypertelorism, exophtalmus, and gynecomastia. Ulcerated malodorous plaques, covered with slough were located in the groins and perianal region (Figures 3a and b). The buccal mucosa showed some localized indurations and two small ulcerations. Fingernails were partly dystrophic with subungual hyperkeratosis, distal splitting, and onycholysis (Figure 3c).

The skin biopsy revealed in upper and mid dermis a dense perivascular and interstitial infiltrate with large histiocytic cells with eosinophilic cytoplasm, bean-shaped nuclei and some mitoses. Immunostaining revealed positivity for S100 and CD1a, while electron-microscopy showed typical Birbeck granules. A bone marrow biopsy was normal.

Abdominal sonography showed hepatomegaly and steatotic hepatitis, while Chest X-ray, cranial magnetic resonance imaging and positron emission spectroscopy did not detect abnormalities.

The diagnosis of adult cutaneous Langerhans cell histiocytosis was confirmed.

Treatment and course: Treatment with 2-chlor-2-desoxyadenosin (cladribine) 10 mg i.v. per day for five days was initiated on a monthly basis for half a year. The treatment was well tolerated. A partial remission was achieved with healing of the buccal mucosa ulcers. However, the inguinal and perianal ulcerations did not improve. Thereafter, thalidomide 200 mg p.o. per day was introduced. Four weeks later a clinical remission began to appear. After 3 months, the ulcerations in the groins and anal fold had healed, leaving a scar. The only adverse effect was fatigue, no polyneuropathy was observed. After 3 months the thalidomide dosage was reduced to 100 mg daily and was continued for a total of 9 months. No relapse was observed during a 12 month follow-up, but the patient developed a non-Hodgkin lymphoma with bone-marrow involvement, stage IV (8). The International Prognostic Index (IPI) (9) was "1" corresponding to low-risk lymphoma. The patient was treated with 6 cycles of CHOP (cyclophosphamide, doxorubicine, vincristine, and prednisone) which resulted in a complete remission. Nine months later he developed an acute lymphatic leukaemia (B-ALL). The patient is on a waiting list for bone marrow transplantation.

Discussion

Adult cutaneous LCH is a very rare clonal disease (1, 2). Key micromorphologic features of LCH are large cells with eosinophilic cytoplasm and kidney -shaped nuclei that express S100 and CD1a. Birbeck granules are present in varying amounts (1). Investigations with a panel of markers for Langerhans cell differentiation showed that the cells accumulating in skin, lymph node or bony lesions are immature to a varying degree (5,10,11). It has been assumed that LCH is characterised by precursors myeloid blood cells. Indeed, serum levels of early haematopoietic cytokines such as fms-like tyrosine kinase and macrophage colony-stimulating factor are raised in LCH (10).

The murine c-fms (Csf1r) gene encodes the macrophage colony-stimulating factor receptor, which is essential for macrophage development. It is expressed at a low level in haematopoietic stem cells and is switched off in all non-macrophage cell types (12).

In large studies the most common skin lesions are papules on the trunk that can ulcerate, and a seborrheic eczema-like erythematous scaling on the scalp. Ulcerations in the flexures, groins and perianal region are more common in adult patients (13). Areas of purpura may be seen. Nail involvement is thought to be a sign of unfavourable prognosis (14). Peridontal involvement affecting the lower molar areas is the most common oral manifestation (15).

We described two male patients aged 73 and 38 years, respectively, that illustrate the variable clinical manifestation of adult cutaneous LCH. In both cases histopathology from skin lesion confirmed the diagno-

sis. There is no standard treatment as no prospective randomized placebo-controlled double-blind trial is available. These diseases are rare, and a general recommendation is to start with the simplest therapy and progress to systemic or more aggressive treatment (6, 10, 16). Some reports stressed the usefulness of PUVA, corticosteroids, isotretinoin, interferon alfa, or thalidomide (1, 5, 6, 10, 16). Indeed, the second patient was additionally treated with thalidomide and a partial remission was obtained, thus confirming previous positive reports (16).

Chemotherapeutic agents also have been used in cases of widespread disease. Cladribine (2-chlorodeoxyadenosine), 6-mercaptopurine, etoposide, low dose methotrexate (10, 17, 18) or topical mustard (19) have been used successfully and particularly in adults.

Disseminated cutaneous LCH itself is treatable, but may precede other malignancies as shown in our two cases (19, 20). Therefore we recommend a close follow-up of LCH patients even after complete remission, to ensure an early diagnosis and treatment in the case of malignant evolution.

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