

Multisystemic Langerhans cell histiocytosis in an adult



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Key words: adult; *BRAF* mutation; Langerhans cell histiocytosis; multisystemic; pathogenesis; peroxisome proliferator-activated receptor.

INTRODUCTION

The etiology of Langerhans cell histiocytosis (LCH), a mix between immune dysregulation, inflammation, and malignancy, remains unclear.¹⁻⁴ In half of the patients, an oncogenic *BRAF* mutation is found.³ Because of the diversity of symptoms, the diagnosis of LCH, as defined by the Histiocyte Society, is often made with considerable delay. Multisystemic LCH, affecting 2 or more organ systems and “risk organs,” like the hematopoietic system, the spleen, liver, and central nervous system, implies a worse prognosis.^{1,3-6} To raise the awareness of multisystemic LCH, the case of an elderly patient is presented and a new therapeutic scheme with pioglitazone (peroxisome proliferator-activated receptor- γ [PPAR- γ] agonist), etoricoxib (COX-2 inhibitor), and trofosamide (alkylating medium) is described.

CASE PRESENTATION

A 77-year-old man presented with plaques and ulcerations in his armpits and groin, crusts and papules at the scalp, inflamed oral mucosa, hearing deficiency, otorrhea, and productive cough for 4 months (Fig 1). The patient had been a smoker (50 pack-years). During a dental extraction, a biopsy specimen from the jaw bone was taken, and immunohistochemical-positive CD1a⁺ and CD207⁺ stains proved the diagnosis of LCH (Figs 2-4).

The diagnosis of LCH with a *BRAF*-V600E mutation was proven by skin biopsy. Birbeck granules were not detected. In an ultrasound scan, enlarged lymph nodes were found cervically, axillarily, and inguinally. With normal liver function results, the

Abbreviations used:

CT:	computed tomography
LCH:	Langerhans cell histiocytosis
PPAR- γ :	peroxisome proliferator-activated receptor- γ

echographic structure of the liver was compatible with hepatic steatosis and not typical for LCH. A thoracic computed tomography (CT) scan showed pulmonary cystic nodules. Pulmonary function testing was without pathologic findings. No signs of diabetes insipidus were found: the patient did not suffer from polyuria or polydipsia. Blood count, thyroid-stimulating hormone, serum/urine osmolality, and a CT scan of the pituitary were inconspicuous. A CT scan showed involvement of the mastoid cells, which explained the otorrhea. A biopsy of the mastoid showed a co-expression of CD1a and S100 on Langerhans cells.

A multisystemic LCH with involvement of the lungs, bones, skin, and lymph nodes was diagnosed. A topical disinfectant (Octenisept, Schülke & Mayr GmbH, Norderstedt, Germany) and betamethasone cream were administered. We combined it with a systemic therapy (trofosamid 50 mg 3 times a day; and pioglitazon 15 mg and etoricoxib 30 mg once a day) starting in October 2015 and continuing currently.

DISCUSSION

LCH in adults is seen with an incidence of 8:100,000. We report on an elderly patient with multisystemic LCH, treated by a novel cytotoxic, anti-inflammatory, and antiangiogenic therapy.

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Fig 1. Clinical appearance.

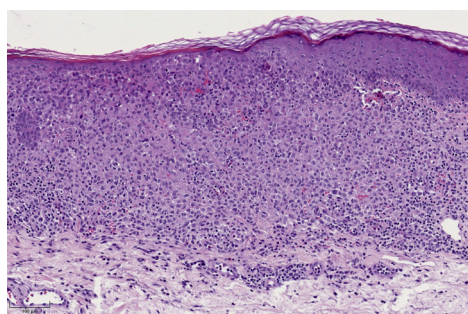


Fig 2. Hematoxylin eosin staining.

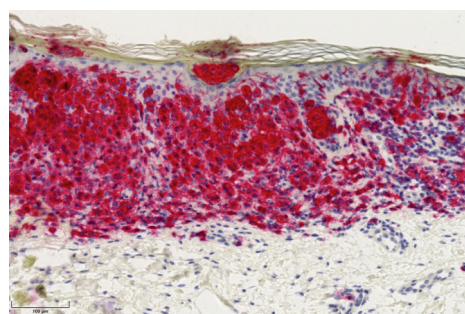


Fig 3. CD1a staining.

The finding of Birbeck granules by electron microscopy is pathognomonic for LCH. The presence of CD1a⁺ and CD207⁺ antigens can confirm the diagnosis.^{4,6} LCH can be diagnosed if at least 2 stains for ATPase, S-100 protein, α -D-mannosidase, or binding of peanut lectin on lesional cells are positive.⁶ Similar to our patient, in half of all LCH cases an oncogenic *BRAF* mutation is found.³ CD1a⁺ and CD207⁺ antigens were detected in our patient; Birbeck granules were not seen. Suffering from multisystemic LCH, our patient had osseous, pulmonary, cutaneous lesions together with an involvement of the lymph nodes:

Most LCH-related bone lesions are found in the skull, spine, or mandible.¹ Our patient had lesions in the mandible and in the mastoid cells. Infiltration of the skull is found in approximately 25% to 45% of the patients. The temporal bone is affected in up to 60%.⁷ Loosening of the teeth was caused by gingival and alveolar bone infiltration. Tooth extractions should be avoided in these patients.³ Bone lesions may be treated by surgery, intralesional injection of methylprednisolone, or radiotherapy.^{3,4}

Pulmonary involvement is an atypical feature of multisystemic LCH. This finding could be related to

smoking, as more than 90% of LCH patients are smokers, and cessation of smoking can be curative.^{3,7}

Cutaneous LCH is often the first symptom of multisystemic LCH. Scalp lesions with small papules and axillary and inguinal involvement were found in our patient.³ In skin lesions, the efficacy of topical corticosteroids has never been proven.

In 1 of 20 patients, mainly cervical lymph nodes are infiltrated.⁷ Our patient showed an echographic enlargement of cervical, axillary, and inguinal lymph nodes.

Multisystemic LCH necessitates systemic therapy, often vinblastine, 6 mg/m², and prednisone, 40 mg/m²/d. In case of progression after 6 weeks, patients should be treated for another 6 weeks or should be converted to a combination of 2-chlorordeoxadenosine and cytarabine.⁴

A hematopoietic stem cell transplant may offer a chance for a cure.¹ *BRAF* inhibitors like vemurafenib are new therapeutic options.³ An overexpression of prostaglandins and cyclooxygenase 2 in pathologic Langerhans cells is described. The activity of Langerhans cells is regulated by the PPAR- γ . These findings lead to a new therapeutic

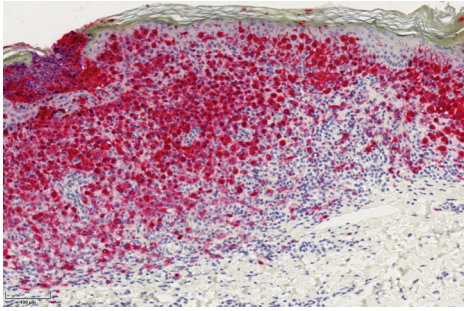


Fig 4. CD207 staining.

scheme with pioglitazone (PPAR- γ agonist), etoricoxib (COX-2 inhibitor), and trofosfamide (alkylating medium),^{8,9} which was applied in our patient. He tolerated the therapy without any side effects. During the progression of therapy, all skin lesions healed and the pulmonary and osseous manifestations have shown a remission at the last staging examinations.

LCH is a rare and serious disease often diagnosed late because of its manifold symptoms.^{3,10} The prognosis depends on the number of organs involved, the presence of organ dysfunction, and the patient's age. Often LCH follows a benign course, but some patients suffer from progressive disease with high mortality. These patients must be identified in time for treatment.

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