CASE REPORT

Ninety-year-old man with hypereosinophilia, lymphadenopathies and pruritus

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SUMMARY

We report a case of a 90-year-old man with hypereosinophilia, lymphadenopathies and skin lesions, namely lichenification and pruritus. An aetiological investigation was performed, and a bone marrow (BM) biopsy and aspirate showed a hypercellular marrow with hypereosinophilia without dysmorphia or abnormal elements, and the BM and inguinal node's immunophenotyping denied any presence of abnormal lymphoid cell population. The inguinal node biopsy revealed a multinodular proliferation of large cells S100 and CD1a⁺, and a diagnosis of Langerhans cell histiocytosis was made. The hypereosinophilia and skin lesions were managed with corticotherapy with substantial improvement of cutaneous lesions and lymphadenopathies and normalisation of eosinophil count. Finally, to define if it is a single or multisystem disease, a skin biopsy will be necessary.

BACKGROUND

Langerhans cell histiocytosis (LCH) is a disease that affects mostly the paediatrics age, with an incidence in adults around one case per million,^{1 2} aiming mainly younger adults.^{3–5} Besides this, LCH has a heterogeneous clinical presentation, encompassing a single-organ involvement with benign prognosis to a multisystemic disease with severe organ dysfunction.^{6–9} Reports of skin involvement and hypereosinophilia are rare in adult,^{10 11} which make the diagnosis and treatment more difficult and appealing. In this report, we present a case of LCH in a 90-year-old patient with hypereosinophilia, lymphadenopathies and skin lesions.

CASE PRESENTATION

A 90-year-old man, with good performance status and autonomous in the activities of daily living, had been well until 1 month before our evaluation when he started having generalised skin pruritus. During these period, he was seen in two dermatology consultations, in which initially he was diagnosed as having scabies and was medicated with benzyl benzoate, desloratadine and cutaneous methylprednisolone and then with levocetirizine and Nutratopic cream for hives, without any improvement in both situations. Two weeks later, his symptoms worsened, and he went to the emergency department (ED). The patient did not have fever or abdominal and urinary symptoms. He also denied introduction of any drug recently. Last trip was to Southwest Asia 2 years ago. Medical

history: diabetes mellitus type 2, hypertension, dyslipidaemia, Heart failure (HF) New York Heart Association Class I, iatrogenic hypothyroidism (secondary to amiodarone, suspended about a half year before), carpal tunnel syndrome and osteo-articular pathology. Usual medication: pantoprazole 20 mg once a day; lisinopril 5 mg once a day; furosemide 40 mg once a day; bisoprolol 2.5 mg once a day; sitagliptin 25 mg once a day; simvastatin 10 mg once a day; hydroxyzine 25 mg three times a day.

On examination at ED, he had lichenification and scaly skin with itchy lesions, namely in the abdomen and upper limbs (figure 1). He also had painless lymphadenopathies (inguinal and right supraclavicular) with 1 cm of larger diameter, without adherence. He denied B symptoms. The vital signs were normal, as were the remainder of the general examination. Haemoglobin was 12.1 g/dL, white cell count was elevated ($16.9 \times 10^9/\text{dL}$; neutrophils $4.5 \times 10^9/\text{dL}$ and eosinophils $6.25 \times 10^9/\text{dL}$; platelet count were normal; blood levels of electrolytes revealed slight hyperkalaemia (5.69 mmol/L). Renal function test revealed prerenal acute kidney injury (urea 78 mg/dL and creatinine 2.24 mg/dL). Liver function, urinalysis and C reactive protein (CRP) were normal, and a chest radiograph revealed cardiomegaly and slight right deviation of trachea without evidence of condensation. A diagnostic procedure was performed.

INVESTIGATIONS

An aetiological investigation was obtained in outpatient, namely white cell count with differential count, IgE assay 1210 UI/mL (reference value (RV) <100) and stool ova and parasites test (negative for *Salmonella*, *Shigella* and *Campylobacter*), autoimmunity tests (rheumatoid factor, ANAs, ENAs, AMA, c-ANCA, p-ANCA, antimicrobial and anti-PR3: all negative), BM examination and pelvic–abdominal–thorax CT. The CT documented, among other changes, kidneys with signs of atrophy and axillary and inguino-cruial lymphadenopathies (right iliofemoral lymph node 23×28 mm). For that reason, a right iliofemoral node biopsy was performed. Two days after, the patient had fever with purulent exudate in the right inguinal region and was admitted in ED with anaemia (haemoglobin 10.1 g/dL) and leucocytosis (leucocytes $25.7 \times 10^9/\text{L}$, neutrophils $20 \times 10^9/\text{L}$, eosinophils $0.72 \times 10^9/\text{L}$, creatinine 1.79 mg/dL and CRP 18.8 mg/dL). Liver function tests and electrolytes were normal. Exudate and blood cultures were

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Figure 1 Lichenification and scaly lesions: (A) abdomen; (B) palm of the left hand.

performed. The patient was hospitalised and started on empirical antibiotics with amoxicillin/clavulanic acid 1000/200 mg ev and hydrocortisone ev 100 mg three times a day.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of lymphadenopathies, eosinophilia and skin lesions is extensive. We can subdivide, briefly, the causes of lymphadenopathy in seven categories, namely infectious diseases (parasitic, viral or bacterial); immunological, such as rheumatoid arthritis, systemic lupus erythematosus (SLE); drug hypersensitivity (allopurinol, primidone, etc); haematological (Hodgkin's lymphoma, non-Hodgkin's lymphomas, hairy cell leukaemia, malignant histiocytosis) or metastatic; lipid storage (eg, Gaucher's disease); endocrine (hyperthyroidism) and others, such as Castleman's disease, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Rosai-Dorfman disease and LCH.¹² On the other hand, eosinophilia may be primary, associated with haematological disorders such as leukaemia and myeloproliferative disorders, secondary or idiopathic (hypereosinophilic syndrome).¹³ The most common cause worldwide is allergic, and in these spectrum fits the DRESS syndrome characterised by fever, rash, eosinophilia, atypical lymphocytosis, lymphadenopathy, and signs and symptoms related to end-organ involvement (typically heart, lungs, spleen, skin and nervous system).¹³ Other common causes include infections (typically parasitic), autoimmune disorders (Churg-Strauss syndrome, SLE, polyarteritis nodosa, scleroderma), solid tumours (melanoma, adenocarcinomas, etc), endocrinopathies such as hypocortisolism,¹³ and finally, the pruritus and the skin's lichenification. The clinical history should rule out any substances that can cause skin lesions, such as drugs or food, as well as environmental or occupational exposure.¹⁴ Aetiological investigation of secondary causes of pruritus, such as thyroid, haematological, kidney and liver disorders and diabetes mellitus are necessary to complement the evaluation and narrow the differential diagnosis.¹⁴

TREATMENT

A conservative treatment approach was decided on. The infection was treated with antibiotic and daily dressing. The skin lesions and hypereosinophilia were treated with corticotherapy, initially hydrocortisone ev and then prednisolone orally.

OUTCOME AND FOLLOW-UP

Further evaluation of skin (eg, biopsy) will be necessary to determine if the disease is limited to lymph node or if there is a multisystem involvement to address appropriate treatment. After 1 month, an evaluation was made, and the patient reported

Figure 2 Improvement of skin lesions after 1 month of corticotherapy. Note the disappearance of the scaly skin on the palm of the left hand.

substantial improvement of the pruritus with disappearance of the scaly lesions (figure 2). A follow-up evaluation will be made on haematology department.

DISCUSSION

In this case, a 90-year-old man with acute onset of lymphadenopathies, skin lesions (pruritus and lichenification) and eosinophilia with a high IgE make atopic or allergic diseases likely, but the absence of exposure discard this hypothesis. Besides this, DRESS syndrome should be included in the differential diagnosis, but although four diagnostic criteria were present (fever, eosinophilia, lymphadenopathy and signs of end-organ involvement, namely acute kidney injury), the absence of exposure to new medication recently makes this diagnosis unlikely. Finally, but not least, the aetiological investigation also makes unlikely any autoimmune or endocrine diseases. Therefore, a bone marrow (BM) and lymph node evaluation should be imperative for the diagnosis. Although the BM evaluation and immunophenotyping of inguinal node did not show any disease, a lymph node biopsy revealed a multinodular proliferation of large cells S100 and CD1a⁺ (figure 3), and a diagnosis of LCH was made.

LCH, formerly known as histiocytosis X, is a group of disorders subdivided in three categories, according to Histiocyte Society: dendritic cell histiocytosis, in which LCH belongs; macrophage-related disorders and malignant histiocytosis.⁸ Although already being accepted that LCH is characterised by a clonal proliferation of bone marrow-derived Langerhans-like cells,⁸ the true origin of pathological cell in LCH is still in discussion and the aetiology remains unclear.^{3 7 15} As an aetiological

Figure 3 Histopathological examination of lymphatic lymph node (A) multinodular proliferation of histiocytic infiltrate (left side), with eosinophilic cytoplasm and nuclei irregular (H&E, 20× magnification). Immunohistochemistry positive for the antigen CD1a (B) and CD68 (C), specific markers of Langerhans cell histiocytosis.

cause, dysregulation, inflammation and malignancy (eg, oncogenic BRAF V600E mutation present in half of patients^{16 17}) had been reported in previous studies.

LCH is a disease that affects mostly the paediatric age, with an incidence in adults around one case per million,^{1 2} affecting mainly younger ones.^{3–5 18} Besides this, LCH has a heterogeneous clinical presentation, encompassing a single organ involvement with benign prognosis to a multisystemic disease with severe organ dysfunction.⁶ In fact, the Histiocyte Society classifies the haematopoietic system, spleen and liver as ‘risk organs’, since they confer an adverse prognosis.^{4 5 18 19}

The clinical presentation of cutaneous LCH is highly diversified,^{20 21} and the true incidence is still unknown with some research advocating that it is often the first symptom of multi-systemic LCH.^{11 22 23} The overlap of the cutaneous presentation makes the diagnosis difficult,^{10 21 22} and that is what had happened in our clinical case, in which a diagnosis of scabies and hives was made previously. Besides cutaneous LCH, osteolytic bone lesions are common, namely in axial bone skeleton with infiltration of the skull in one-third of cases. Another atypical feature of multi-systemic LCH is pulmonary involvement in which about 90% of the patients are smokers.^{19 24–26}

The diagnosis is histologically suggestive by the identification of cells with eosinophilic cytoplasm and nuclei irregular in tissue biopsy.²⁷ The finding of Birbeck granules by electron microscopy is pathognomonic for LCH and the presence of CD1a⁺ and CD207⁺ antigens can confirm the diagnosis.^{10 15 27} Initial workup include blood tests (full blood count, liver and renal function test, and bone profile),⁸ and chest and skeletal radiograph survey which reveal interstitial pattern lesion and osteolytic lesion (usually affecting long bones), respectively.^{5 8 28} Further evaluation with CT scan and lung biopsy (when lung involvement is suspected), hormonal study (to assess the hypothalamic–pituitary axis) and bone marrow biopsy are necessary to complement the aetiological investigation.^{7 9 18 29}

Due to the rarity of the disease and the protocols being directed towards the paediatric age, treatment in adulthood is not yet fully defined.^{1 11 19 25} In a single-organ disease, watchful waiting and local treatment are the mainstay approach. In this spectrum, patients with bone disease are treated with bone curettage or corticotherapy²⁵ and in pulmonary LCH, smoking cessation is frequently the only, and perhaps curative, therapeutic intervention.^{19 30} Localised skin lesions can be treated by surgical

Learning points

- ▶ Skin involvement and hypereosinophilia are a rare presentation of Langerhans cell histiocytosis (LCH).
- ▶ In LCH, the involvement of haematopoietic system, spleen and liver, known as ‘risk organs’, predicts worse prognosis.
- ▶ The treatment in adults remains a challenge due to the rarity of the disease and to the protocols that are directed towards the paediatric age.
- ▶ New targeted therapies are under investigation, namely imatinib (tyrosine kinase inhibitor), vemurafenib (BRAF V600E inhibitor), pioglitazone (peroxisome proliferator-activated receptor gamma agonist), etoricoxib (cyclooxygenase-2 inhibitor) and trofosamide (alkylating medium), which can improve the overall survival.

excision or with topical therapies with corticosteroid or immunotherapy (tacrolimus, imiquimod).^{9 31 32}

On the other hand, in systemic disease, the first-line therapy is not still well established because of the lack of clinical trials, with some physicians advocating chemotherapy with vinblastine plus prednisone, while others with arabinoside or cladribine.³³ Systemic therapy for severe skin LCH includes single or combination regimens with oral methotrexate, thalidomide or interferon-alpha.^{22 34}

New therapies are being developed and some have already demonstrated the possibility of cure such as haematopoietic stem cell transplantation,²⁴ while others are under investigation, namely imatinib (tyrosine kinase inhibitor), vemurafenib (BRAF V600E inhibitor), pioglitazone (peroxisome proliferator-activated receptor gamma agonist), etoricoxib (cyclooxygenase-2 inhibitor) and trofosamide (alkylating medium).^{25 35}

This case of skin involvement and hypereosinophilia reports an unusual presentation of LCH in adults and may result in misdiagnosis. Therefore, the physicians should take into account the differential diagnosis and consider the treatment options mentioned.

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