

Lymphocytic variant of hypereosinophilic syndrome

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Summary

Hypereosinophilia may be associated with any of several underlying diseases. Atopy or allergic drug reactions are the most common causes, but infections with bacteria and parasites should also be considered in the differential diagnosis. When thorough evaluation of a patient with chronic hypereosinophilia fails to reveal an underlying disease, the diagnosis of idiopathic hypereosinophilic syndrome (HES) should be considered. We report a patient with unexplained persistent hypereosinophilia associated with a chronic pruritic rash and an underlying diagnosis of HES (lymphocytic variant).

Hypereosinophilia is seen in a wide range of nonclonal and clonal disorders. In most cases it is reactive and associated with atopy, autoimmune conditions, infections or malignancies.¹ In rare cases, accumulation of eosinophils in peripheral blood and tissues can result either from an acquired abnormality of the haemopoietic myeloid stem cell (i.e. clonal), or from the production of eosinophilopoietic cytokines by nonmyeloid cells (i.e. nonclonal) when myeloid lineage is normal and the accumulation of eosinophils is a cytokine-driven process.^{1–3} Whatever its cause, eosinophil accumulation may have pathological consequences as a result of local release of toxic substances.

Report

A 55-year-old man was referred with a 5-year history of a pruritic rash and eosinophilia ($2.7\text{--}3.6 \times 10^9/\text{L}$; normal range $< 0.5 \times 10^9/\text{L}$). He had been diagnosed as having 'eczema' and treated with potent topical steroids with variable response. His personal medical, social and travel history were unremarkable, with no history of atopy, and there was no relevant family history. He was systemically well and not on any systemic medications.

On physical examination, a dry follicular papular rash was seen over the lower back and both axillae and both legs, with evidence of chronic lichenification (Fig. 1). Clinically, the appearance was not typical of eczema or systemic mastocytosis.

Laboratory investigations gave normal results for erythrocyte sedimentation rate and full blood count except for a high eosinophil count ($3.1 \times 10^9/\text{L}$). A blood film confirmed eosinophilia with no atypical cells. Serum IgE level was $19\,850\ \mu\text{g}/\text{mL}$ (normal $< 120\ \mu\text{g}/\text{mL}$) and hypergammaglobulinaemia without paraprotein. Serology testing for parasites (*Toxocara* and *Strongyloides*), human T-cell lymphotropic virus, and hepatitis B and C gave negative results. Rheumatoid factor was also negative.

Histological examination of a skin biopsy found epidermal hyperkeratosis, perivascular chronic inflammation and pigment incontinence with amorphous material in the dermis, in keeping with chronic lichenified eczema (Fig. 2a). Lichen amyloid deposition was identified by Congo red staining (Fig. 2b).

A bone marrow aspirate and trephine biopsy were normal except for increased mature eosinophils. There was no dysplasia. Lymphocytes were 13% of aspirated cells (normal range 20–30%). Molecular analysis was negative for *BCR-ABL1*, *JAK2 V617F* [ARMS (amplification refractory mutation system) PCR and pyrosequencing assay] and *FIP1L1-PDGFR* (nested reverse transcription PCR). Flow cytometry immunophenotyping of bone-marrow cells found an increase in

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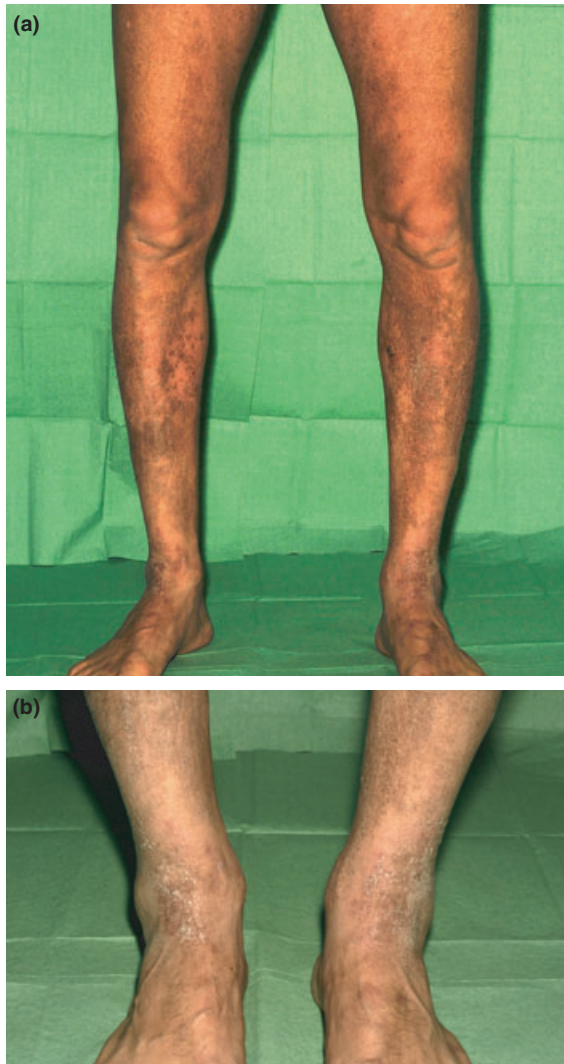


Figure 1 (a) Dry follicular papular rash over legs; (b) close-up view.

CD4-positive, CD2-positive T cells, most of which also expressed CD7.

A T-cell clone was identified by T-cell gene rearrangement studies on skin biopsy and peripheral blood (V γ 9). Computed tomography imaging of the entire body found borderline enlargement of nodes in both inguinal regions and axillae, which were considered to be unimportant.

A diagnosis of the lymphocytic variant of HES was made, based on exclusion of underlying possible causes and fulfilling the necessary criteria for this syndrome, as below. The patient responded well to a tapering dose of oral steroids in combination with ciclosporin, and had significant improvement with an 80% reduction in his

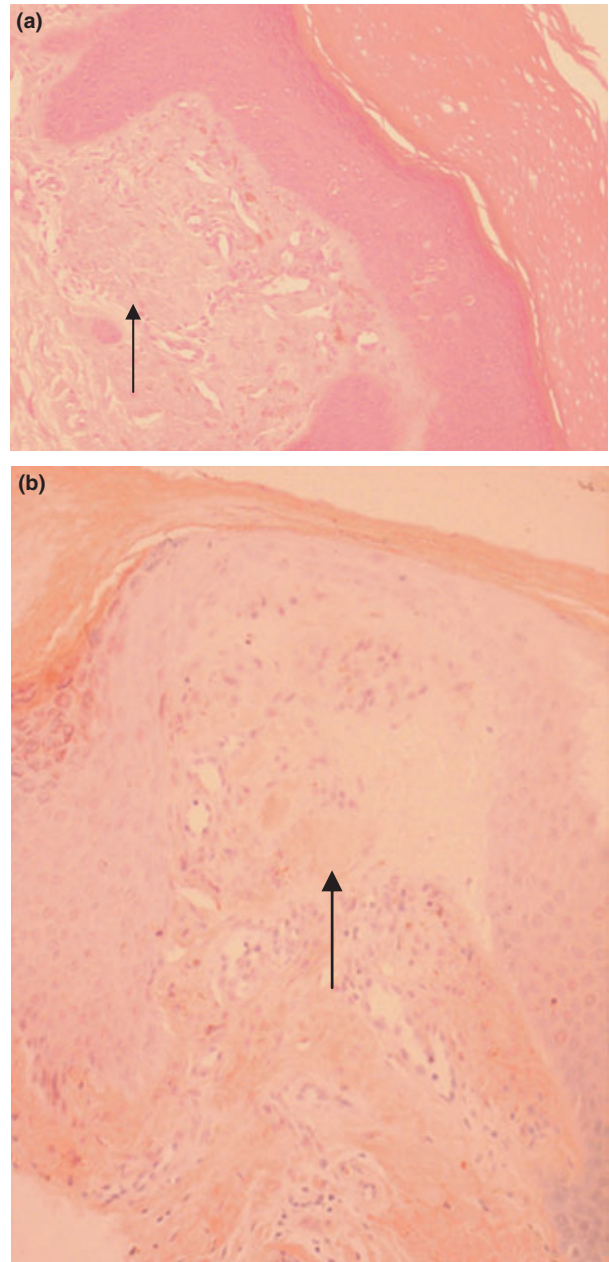


Figure 2 (a) Chronic lichenified eczema and lichen amyloid (arrow) in dermis (haematoxylin and eosin, original magnification $\times 40$). (b) Lichen amyloid (arrow) in dermis (Congo red, original magnification $\times 40$).

pruritic symptoms and no further progression of his rash.

The hypereosinophilic syndrome is a heterogeneous disorder diagnosed by the following criteria:^{1–5} (i) blood eosinophilia $> 1.5 \times 10^9/L$ (normal range $< 0.5 \times 10^9/L$) for > 6 consecutive months; (ii) absence of an

underlying cause of hypereosinophilia despite extensive investigation; and (iii) evidence of organ damage or dysfunction as a result of local release of toxic eosinophil contents.

The major tissue targets include the skin, heart and nervous system. Eosinophilic infiltration of other organs such as the lungs, liver, digestive system and kidneys may cause a variety of additional symptoms.^{1–4} Cutaneous features have been reported as angio-oedematous and urticarial lesions, or an erythematous dermatitis and erythematous, intensely pruritic papulonodular dermatitis.^{1,3}

There are two major variants of HES: myeloproliferative and lymphocytic. The clinical and biological features of the myeloproliferative variant are similar to those of myelogenous leukaemia and other myeloproliferative syndromes with chromosomal abnormalities, anaemia, thrombocytopenia and abnormal leucocyte alkaline phosphatase score.^{1–4}

The identification of an underlying T-cell clone by T-cell receptor gene rearrangement analysis or atypical phenotype, e.g. CD3⁺ CD4⁺ or less commonly CD3⁺ CD4⁺ CD8⁺, is indicative of the lymphocytic variant of HES.¹ Skin involvement, hypergammaglobulinaemia and increased levels of interleukin (IL)-5 and IgE in the absence of atopy are also suggestive of lymphocytic variant of HES, as in our patient. In the lymphocytic variant, clonal T lymphocytes induce nonclonal eosinophil proliferation through overproduction of eosinophilopoietic cytokines such as IL-3, IL-5 or granulocyte-macrophage colony-stimulating factor (GM-CSF).

In addition to the considerable clinical heterogeneity among patients who fulfil the diagnostic criteria of HES, there is also some variability in its prognosis, ranging from paucisymptomatic disease with prolonged survival to a rapidly fatal disease due to sudden severe heart failure or malignant transformation to lymphoma/leukaemia.¹ The aim of treatment is to inhibit eosinophilopoietic cytokine production (IL-5 and IL-3,

GM-CSF) by aberrant T cells and to control their expansion and prevent end-organ damage, thromboembolic events and malignant transformation.

Except for the myeloproliferative variant of HES (associated with the *FIP1L1-PDGFR* fusion gene), for which imatinib (a tyrosine kinase inhibitor) is considered the first-line therapy, current treatment options for patients with lymphocytic variant of HES include steroids and hydroxycarbamide, but many other agents such as ciclosporin and methotrexate have been successful in small numbers of patients.² The role of a trial of imatinib in this disease remains controversial. There have been several reports of response to imatinib even in patients negative for the *FIP1L1-PDGFR* fusion gene, especially in patients who are unresponsive to steroids.⁴ Newer treatments available include the anti-IL-5 monoclonal antibodies (e.g. mepolizumab), which have a selective role in eosinophil development and seem to contribute to the pathogenesis of HES.⁵ Mepolizumab is highly specific and binds with high affinity to free IL-5, thus preventing its interaction with the IL-5 receptor on the surface of eosinophils. Our case highlights the importance of investigating patients with unexplained persistent eosinophilia, and including this unusual syndrome in the differential diagnosis.

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