

Lymphocyte-variant hypereosinophilic syndrome presenting as chronic dermatitis and responding to mycophenolic acid



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INTRODUCTION

Hypereosinophilic syndrome (HES) is a group of rare blood disorders characterized by persistent peripheral blood eosinophilia (eosinophil count of $1.5 \times 10^9/L$ or greater) and evidence of end-organ involvement. HES is a diagnosis of exclusion, and clonal eosinophilia and reactive eosinophilia must first be ruled out. Confirmation of HES relies on assessing blood and bone marrow morphology, cytogenetics, flow cytometry, and T-cell clonality. HES can present with primarily cutaneous findings.¹

Lymphocyte-variant HES (L-HES) is a distinct subtype, characterized by aberrant clonal T-cell populations that produce eosinophil-promoting cytokines.² Currently, the first-line treatment for L-HES is systemic steroids.³ However, a recent study showed that L-HES is more steroid resistant than other forms of HES, with an odds ratio of steroid response of only 0.34 compared with idiopathic HES.⁴

At present, there is no standard therapy for steroid-refractory L-HES. Mepolizumab, an anti-interleukin (IL) 5 monoclonal antibody, is the only agent shown to be an effective steroid-sparing agent in a randomized clinical trial of patients with HES.⁵ Interferon α , cyclosporine, imatinib, methotrexate, alemtuzumab, hydroxyurea, cyclophosphamide, fludarabine, and Janus kinase (JAK) inhibition have all been reported in small numbers of patients, with varying degrees of efficacy.^{3,6} In contrast, patients with myeloid HES, in which malignant

Abbreviations used:

HES:	hypereosinophilic syndrome
IL:	interleukin
JAK:	Janus kinase
L-HES:	lymphocyte-variant hypereosinophilic syndrome
MFA:	mycophenolic acid
MMF:	mycophenolate mofetil

myeloid clones express platelet-derived growth factor, often respond to imatinib therapy.¹

We present a case of L-HES showing skin presentation, chronicity of clinical course, and successful treatment with mycophenolic acid (MFA). To our knowledge, this represents the first case in which cutaneous manifestations and eosinophilia have been successfully managed with MFA.

CASE REPORT

A woman in her late 70s was referred for a dermatology consultation with a 20-year history of periodic pruritic and erythematous eruptions on the flanks that had been diagnosed as atopic dermatitis but was resistant to topical corticosteroids (Fig 1). She was healthy otherwise, with no personal or family history of atopy, and was not taking any medications.

She had large erythematous plaques on the flanks bilaterally. There was no lymphadenopathy or organomegaly. Skin biopsy showed superficial

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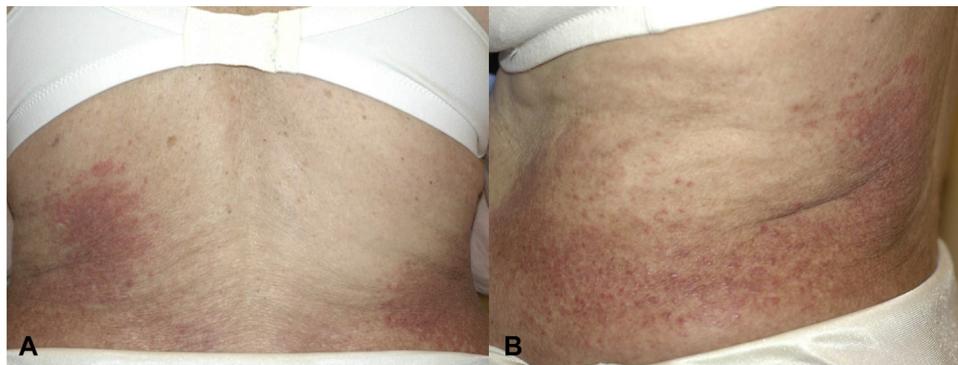


Fig 1. Images of the trunk at presentation showing erythematous papules coalescing into plaques on (A) the back and (B) the flanks.



Fig 2. Image of the palms at 2 years after presentation showing papules and pustules on the palmar surface of left hand.

perivascular dermatitis with vascular thrombosis and eosinophilia that was nondiagnostic.

Over the next 2 years, she developed generalized cutaneous eosinophilic disease involving the palmar surfaces, neck, arms, and thighs (Fig 2). Topical corticosteroids, narrowband UVB therapy, and pimecrolimus were tried with minimal benefit. Blood work three years after presentation showed eosinophilia, with an eosinophil count of $1.0 \times 10^9/L$. Renal and hepatic profiles, coagulation, C-reactive protein level, and erythrocyte sedimentation rate were normal. Repeat skin biopsy showed numerous eosinophils and spongiotic dermatitis, but this was nondiagnostic. Acitretin and methotrexate were tried with minimal effect.

Seven years after presentation, the patient's eosinophil count increased to $2.1 \times 10^9/L$. Strongyloides serology and stool ova and parasite test results were negative. Peripheral blood immunophenotyping showed 95% T cells and a markedly increased CD4:CD8 ratio at 20:1. Of her lymphocytes, 25% (normal, <2%) were aberrant CD3⁻CD4⁺ lymphocytes, although T-cell receptor polymerase chain reaction results were negative for clonality. Results of fluorescence in situ hybridization for platelet-

derived growth factor receptor α and β were negative. Bone marrow biopsy showed marked eosinophilia (18% of nucleated cells) without evidence of lymphoma or mastocytosis. Serum immunoglobulin E was elevated at 14 829 $\mu g/L$ (normal, <470 $\mu g/L$), and IL-5 was 6.0 pg/mL (normal, <3.5 pg/mL).

The patient received a diagnosis of L-HES. She had transient improvement with prednisone 50 mg/day, but her skin rash returned on the trunk, arms, and legs when she tapered to less than 30 mg/day. Mycophenolate mofetil (MMF) was added, but she developed gastrointestinal intolerance. Pegylated interferon $\alpha 2a$ 180 μg administered subcutaneously weekly was initially very effective and well tolerated, but the disease relapsed after 4 months of therapy. She was then switched to MFA 720 mg 2 times per day for its better gastrointestinal adverse-effect profile, with excellent clinical response. Throughout this time, her eosinophilia normalized while she was receiving systemic therapy (Fig 3). For a period of 2 months, she chose to discontinue the MFA due to several episodes of loose stools. Subsequently, she experienced a flare of symptoms involving erythematous papules on her lower back and arms. She restarted MFA, and her skin cleared within several weeks. She continued to be in sustained remission for 3 years until dying of unrelated causes 12 years after presentation.

DISCUSSION

L-HES was first described by allergists and dermatologists examining patients with erythroderma and idiopathic eosinophilia, who noted that a proportion of these patients harbored clonal populations of T cells producing IL-5.⁷ The diagnosis is based primarily on flow cytometry and T-cell clonality analysis in the appropriate clinical context. The most well-known immunophenotype is CD3⁻CD4⁺,

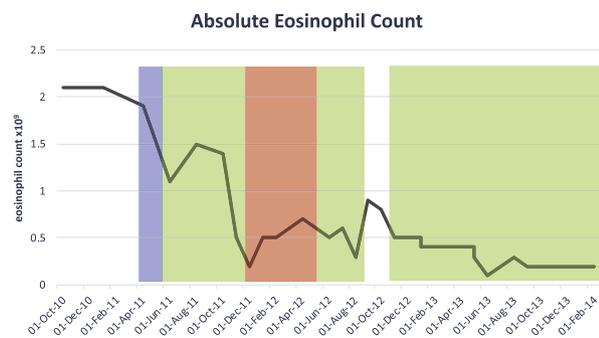


Fig 3. Graphic representation of disease time course. Absolute eosinophil count is depicted in relation to time and therapy. White, no treatment; blue, treatment with high-dose prednisone; red, treatment with interferon α ; green, treatment with mycophenolate.

followed by $CD3^+TCR^{\alpha/\beta+}CD4^-CD8^-$ and $CD3^+CD4^+CD7^-$.

In the largest published series of patients with $CD3^-CD4^+$ L-HES, 17 of 21 patients (81%) had skin involvement.² This included cutaneous features presenting with pruritus, dermatitis, urticarial eruptions, or angioedema with a delay in diagnosis varying from 0 to 18 years. Many patients had a history of atopic dermatitis and elevated levels of immunoglobulin E, suggesting that L-HES should be considered in the differential diagnosis for any patient with marked eosinophilia and chronic dermatitis. Consistent with this, our patient had a 20-year history of recalcitrant dermatitis, with subsequent development of eosinophil-rich papulopustular palmar eruptions 2 years after presentation and peripheral eosinophilia 7 years after presentation, leading to the diagnosis of L-HES.

MMF is a prodrug of MFA that reversibly inhibits inosine monophosphate dehydrogenase to prevent de novo purine synthesis. Because B- and T-lymphocyte proliferation depends on the inosine monophosphate dehydrogenase pathway, dividing lymphocytes are selectively inhibited.⁸ Activating mutations in the signal transducer and activator of transcription 3 pathway have recently been described in L-HES, and a response to JAK inhibition has been noted, suggesting that JAK inhibition may

be another therapeutic option if treatment with MFA fails.^{9,10}

To our knowledge, there is only 1 prior case report of HES responding to MMF in the literature. The patient presented with a 9-year history of itch with progressive lymphadenopathy and was believed to have peripheral T-cell lymphoma/mycosis fungoides that behaved like L-HES.⁶ Initiation of MMF led to normalization of eosinophil count and complete remission of clinical symptoms.

Although further studies to evaluate therapeutic choices in L-HES are certainly necessary, we suggest that MMF/MFA may be a cost-effective and safe steroid-sparing treatment for this uncommon condition.

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