

Idiopathic hypereosinophilic syndrome with eosinophilic cellulitis-like cutaneous involvement treated with mepolizumab and dapson



Madeleine Lachance, MD,^a Jean Bernard, MD, FRCPC,^a Aubert Lavoie, MD, FRCPC,^b Éric Gagné, MD, FRCPC,^c and Pierre-Olivier Grenier, MD, FRCPC^a
Québec, Canada

Key words: anti-IL-5; eosinophilic dermatosis; hypereosinophilic syndrome; mepolizumab; Wells syndrome.

INTRODUCTION

Hypereosinophilic syndromes (HES) are a heterogeneous group of rare entities characterized by sustained blood eosinophilia with secondary tissue damage that can affect several organs, including the skin.¹ Systemic corticosteroid therapy is considered the mainstay of treatment.² However, numerous side effects limit its long-term use. Anti-interleukin (IL) 5 monoclonal agents, such as mepolizumab, have shown to be an effective alternative treatment for HES.²

In this report, we present a case of idiopathic HES with marked cutaneous involvement reminiscent of eosinophilic cellulitis (Wells syndrome), showing complete recovery with the combination therapy of dapson and mepolizumab.

CASE REPORT

A 40-year-old Caucasian woman without known medical history first presented to the dermatology clinic in 2005 with erythematous vesicular plaques on her right wrist and left concha (Fig 1). A complete blood count revealed hypereosinophilia at an absolute eosinophil count of $6.9 \times 10^9/L$. Skin biopsies revealed a prominent dermal eosinophilic infiltrate with flame figures consistent with eosinophilic cellulitis. Rapid improvement was observed after the initiation of prednisone.

Subsequently, she presented over the course of a 14-year period with highly polymorphic skin relapses for which no specific triggers were identified, affecting various anatomic sites accompanied by low-grade fever, general malaise, and eosinophilia

Abbreviations used:

HES: hypereosinophilic syndromes
 IL: interleukin

ranging from 1.3 to $9.9 \times 10^9/L$ (Fig 2). Skin biopsies were repeated during a cutaneous relapse in 2011, which revealed an eosinophil-rich dermal infiltrate and flame figures without vasculitis (Fig 3). A perilesional direct immunofluorescence test was negative. Ten years after the initial diagnosis, in 2015, she presented with a massive exudative pleural effusion. Her blood count at that time showed absolute eosinophil counts ranging from 1.3 to $1.5 \times 10^9/L$. No infectious or neoplastic causes were found, and she spontaneously recovered over a few weeks after therapeutic thoracentesis. She also underwent a below-knee amputation because of terminal ischemia of her left lower limb secondary to atherosclerotic disease. Histopathologic analysis did not demonstrate eosinophil-related endothelial damage.

In 2015, given the extracutaneous manifestations, full rheumatology and hematology workups were performed to rule out a secondary cause of eosinophilia. She had no lymphocytosis but rather had an unremarkable comprehensive metabolic panel. Serum immunoglobulins, immunoglobulin E measurement, as well as tryptase level were all within normal limits. Tests for antinuclear antibodies, antineutrophilic cytoplasmic antibodies, hepatitis B and C, human immunodeficiency virus, and other infections (including parasites) were

From the Department of Dermatology,^a Department of Immunology and Allergology,^b and Department of Pathology,^c Centre Hospitalier Universitaire de Québec, Université Laval, Québec.

Funding sources: None.

IRB approval status: Not applicable.

Correspondence to: Madeleine Lachance, MD, Department of Dermatology, Centre Hospitalier Universitaire de Québec, Université Laval, Hôtel-Dieu de Québec 11, Côte du Palais,

G1R 2J6 Québec, Québec, Canada. E-mail: madeleine.lachance.1@ulaval.ca.

JAAD Case Reports 2022;22:11-3.
 2352-5126

© 2022 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jcdr.2022.01.022>



Fig 1. Erythematous vesicular plaques on the patient's right wrist at initial presentation in 2005.



Fig 2. Cutaneous relapse presenting as large necrotic plaques on the patient's left arm and treated with oral prednisone in 2006. At this point of time, the patient had no long-term treatment.

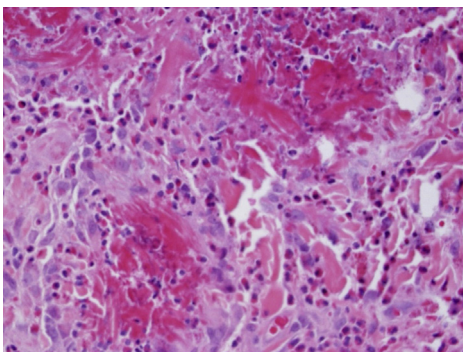


Fig 3. Skin biopsy of an ulcerated papule on the patient's right axilla revealed an eosinophil-rich dermal infiltrate and flame figures during a relapse in 2011.

negative. Serum protein electrophoresis and immunofixation failed to demonstrate a monoclonal spike. Molecular genetic studies were all negative, including *FIP1L1-PDGFR*A and *BCR-ABL1* fusion genes, *JAK2 V617F* mutation, as well as *FGFR1*, *PDGFRB*, and receptor gamma and beta gene

rearrangements. Flow cytometry failed to reveal a monoclonal lymphocytic population. IL-5 levels were not measured. A bone marrow aspiration and biopsy showed eosinophilia with normal cellularity according to her age. Echocardiogram was normal. Repeated computed tomography scans of the thorax, abdomen, and pelvis performed in 2012, 2015, and 2019 were negative for lymphadenopathy or internal malignancy. The blood hyper-eosinophilia persisting for several years, the bone marrow eosinophilia, as well as the pulmonary involvement with a negative thorough etiologic workup were highly suggestive of idiopathic HES.

Intermittent courses of prednisone 50 mg daily slowly tapered over a few weeks were given multiple times over a 10-year period. In 2006, minocycline (100 mg twice daily) was given for a few months, and in 2008, tetracycline (1500 mg per day divided into 3 doses) was tried for 10 days without improvement. Dapsone (100 mg twice daily) was subsequently initiated for 2 years but failed to prevent relapses. In 2019, mepolizumab was initiated at a dose of 100 mg subcutaneous monthly, resulting in the normalization of blood hyper-eosinophilia and the disappearance of cutaneous lesions. In the first 8 months of therapy, she had 2 cutaneous relapses of neutrophilic dermatosis-like plaques on her abdomen, back, and right lower limb in the absence of systemic symptoms. Skin biopsies revealed persistent eosinophils at one site and another biopsy showed a prominent neutrophilic infiltrate. Oral dapsone was then reintroduced at a lower dose (100 mg daily), showing no recurrence after 11 months of follow-up.

DISCUSSION

HES comprise a spectrum of disorders defined by hyper-eosinophilia and variable organ involvement. The skin may be affected predominantly.³ Cutaneous manifestations are nonspecific, including angioedema, urticaria, eczematous and lichenoid eruptions, prurigo-like lesions, as well as bullous lesions.³ Eosinophilic cellulitis (Wells syndrome) is a distinct eosinophilic dermatosis typically presenting with cellulitis-like plaques that can last for weeks or years and heal without scarring.⁴ Hyper-eosinophilia may be present, but no other organ is involved beside the skin as opposed to HES. However, there is significant overlap between the 2 entities, and cases of idiopathic HES presenting with skin manifestations reminiscent of eosinophilic cellulitis have been described, as shown in our patient.⁵

IL-5 is the most specific IL that positively influences the maturation, differentiation, mobilization, and survival of eosinophils.⁶ Mepolizumab is a

humanized immunoglobulin G1 anti-IL-5 monoclonal antibody that binds IL-5 with high affinity and specificity to prevent from associating with the IL-5 eosinophilic receptor.⁷ It is a Food and Drug Administration-approved treatment for HES at a dose of 300 mg subcutaneously every 4 weeks. In our patient who had no significant organ damage, mepolizumab at a lower dose of 100 mg subcutaneously every 4 weeks was chosen, because it had been reported to be successful in treating patients with eosinophilic cellulitis.⁸ The dose of 100 mg, also used in severe eosinophilic asthma, may be considered to treat selected patients with idiopathic HES showing predominant cutaneous manifestations without significant systemic involvement.

Interestingly, our patient presented mild cutaneous relapses after the initiation of mepolizumab. A skin biopsy performed during a cutaneous relapse showed the persistence of dermal eosinophils but also a predominant neutrophilic infiltrate, for which dapsone was chosen. Of note, in HES, tissue persistence of eosinophils has been reported even at high doses of mepolizumab (750 mg intravenously).⁹ Furthermore, a prospective study on patients with allergic asthma treated with mepolizumab (750 mg intravenously) showed that eosinophils in the bronchial mucosa can remain activated despite treatment, because they have persistent cellular activation markers and receptors related to the IL-5 cytokines. Thus, patients may still present clinical exacerbations despite a reduced number of circulating and tissue eosinophils.¹⁰

In conclusion, HES are a spectrum of diseases involving sustained hypereosinophilia and secondary organ damage. The initial presentation can rarely manifest as eosinophilic cellulitis-like plaques. The treatment of HES is challenging, and lower doses of

mepolizumab may be a relevant option in patients with predominant cutaneous involvement.

Conflicts of interest

None disclosed.

REFERENCES

1. Weller PF, Bublej GJ. The idiopathic hypereosinophilic syndrome. *Blood*. 1994;83(10):2759-2779.
2. Kuang FL, Klion AD. Biologic agents for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol Pract*. 2017;5(6):1502-1509. <https://doi.org/10.1016/j.jaip.2017.08.001>
3. Salomon G, Severino M, Casassa E, et al. Les manifestations cutanées du syndrome hyperéosinophilique sont polymorphes et difficiles à traiter: étude de cohorte rétrospective. *Ann Dermatol Venereol*. 2019;146(12):A292-A293.
4. Long H, Zhang G, Wang L, Lu Q. Eosinophilic skin diseases: a comprehensive review. *Clin Rev Allergy Immunol*. 2016;50(2):189-213. <https://doi.org/10.1007/s12016-015-8485-8>
5. Tsuji Y, Kawashima T, Yokota K, et al. Wells' syndrome as a manifestation of hypereosinophilic syndrome. *Br J Dermatol*. 2002;147(4):811-812. <https://doi.org/10.1046/j.1365-2133.2002.49093.x>
6. Sanderson CJ. Interleukin-5, eosinophils, and disease. *Blood*. 1992;79(12):3101-3109.
7. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med*. 2008;358(12):1215-1228. <https://doi.org/10.1056/NEJMoa070812>
8. Herout S, Bauer WM, Schuster C, Stingl G. Eosinophilic cellulitis (Wells syndrome) successfully treated with mepolizumab. *JAAD Case Rep*. 2018;4(6):548-550. <https://doi.org/10.1016/j.jidcr.2018.02.011>
9. Plötz SG, Simon HU, Darsow U, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med*. 2003;349(24):2334-2339. <https://doi.org/10.1056/NEJMoa031261>
10. Kelly EA, Esnault S, Liu LY, et al. Mepolizumab attenuates airway eosinophil numbers, but not their functional phenotype, in asthma. *Am J Respir Crit Care Med*. 2017;196(11):1385-1395. <https://doi.org/10.1164/rccm.201611-2234OC>