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

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ABSTRACT
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 corticosteroids are considered the mainstay of treatment (2). However, numerous side effects limit their long-term use. Anti-interleukin-5 (IL-5) monoclonal agents, such as mepolizumab, have shown to be an effective alternative treatment for HES (2).

In this report, we present the case of idiopathic HES with marked cutaneous involvement reminiscent of eosinophilic cellulitis (Wells’ syndrome), showing complete recovery with the combination therapy of dapsone 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 (figure A). A complete blood count showed hypereosinophilia at an absolute eosinophil count of 6,9 x 10^9/L. Skin biopsies revealed a prominent dermal eosinophilic infiltrate with flame figures that was 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 ranging from 1.3 to 9.9 x 10^9/L (figure B). Skin biopsies were repeated
during a cutaneous relapse in 2011 which revealed an eosinophil-rich dermal
infiltrate and flame figures without vasculitis (figure C). Perilesional direct
immunofluorescence 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 x 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. Histopathological 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 and had a normal comprehensive
metabolic panel. Serum immunoglobulins, immunoglobulin E measurement as well
as tryptase level were all within normal limits. Antinuclear antibody titer,
antineutrophilic cytoplasmic antibodies, hepatitis B and C, human
immunodeficiency virus serologies and other infections (including parasites) were
negative. Serum protein electrophoresis and immunofixation failed to demonstrate
a monoclonal spike. Molecular genetic studies were all negative, including FIP1L1-
PDGFRA and BCR-ABL1 fusion genes, JAK2 V617F mutation as well as FGFR1,
*PDGFRB* and receptor gamma and beta gene rearrangements. Flow cytometry did not 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 internal malignancy or lymph nodes. The persistent blood hypereosinophilia over several years, the bone marrow eosinophilia as well as the pulmonary involvement with a negative thorough etiologic work-up 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 ten-year period. In 2006, minocycline (100 mg twice daily) was given for a few months, and in 2008, tetracycline (1500 mg per day divided in three 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 hypereosinophilia and the disappearance of cutaneous lesions. In the first eight months of therapy, she had two cutaneous relapses of neutrophilic dermatosis-like plaques on her abdomen, back and right lower limb without systemic symptoms. Skin biopsies revealed persistent eosinophils at one site and another biopsy showed prominent neutrophilic infiltrate. Oral dapsone was then reintroduced at a lower dose of 100 mg daily, showing no recurrence after 11 months of follow-up.
HES are a spectrum of disorders defined by hypereosinophilia and variable organ involvement. The skin may be affected predominantly (3). Cutaneous manifestations are non-specific, 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 that typically presents with cellulitis-like plaques that can last weeks or years and heal without scarring (4). Hypereosinophilia may be present, but no other organ is involved beside the skin as opposed to HES. However, there is significant overlap between the two 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 interleukin that positively influences the maturation, differentiation, mobilization, and survival of eosinophils (6). Mepolizumab is a humanized immunoglobulin G1 anti-IL5 monoclonal antibody that binds IL-5 with high affinity and specificity to prevent from associating with the IL-5 eosinophilic receptor (7). It is FDA-approved treatment for HES at a dose of 300 mg subcutaneous every 4 weeks. In our patient who had no significant organ damage, mepolizumab at a lower dose of 100 mg subcutaneous every 4 weeks was chosen, as reported in successfully treated 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 intravenous) (9).

Furthermore, a prospective study on patients with allergic asthma treated with mepolizumab (750 mg intravenous) has shown that eosinophils in the bronchial mucosa can remain activated despite treatment since 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 disease combining 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 an interesting option in patients with predominant cutaneous involvement.
Figure A: Erythematous vesicular plaques on patient’s right wrist at initial presentation in 2005.

Figure B: Cutaneous relapse presenting as large necrotic plaques on patient’s left arm that was treated with oral prednisone in 2006. At this point of time, the patient had no long-term treatment.

Figure C: Skin biopsy of an ulcerated papule on patient’s right axilla revealed an eosinophil-rich dermal infiltrate and flame figures during a relapse in 2011.
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