Eosinophilic cellulitis (Wells syndrome) successfully treated with mepolizumab

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INTRODUCTION
Eosinophilic cellulitis (Wells syndrome [WS]) is a rare inflammatory skin disorder of unknown etiology. It is characterized by first edematous and later indurated plaques with eosinophilic infiltration of the dermis. In 1971 G.C. Wells first described the disease as recurrent granulomatous dermatitis with eosinophilia. To date, approximately 150 cases are reported. Trigger factors like insect bites, medications, infections, malignant tumors, or myeloproliferative disorders are discussed, but the exact etiology and pathogenesis of the disease are still unknown. We report a case of WS associated with bronchial asthma and successfully treated with mepolizumab, an anti–interleukin-5 humanized antibody.

CASE REPORT
A 33-year-old man presented with multiple, edematous, erythematous and greenish, sharply demarcated, indurated plaques with violaceous borders of 3 to 30 cm diameter on the back, trunk, and upper limbs recurring for 6 months (Fig 1). He further reported a 1-year history of bronchial asthma. Clinical differential diagnoses of the skin manifestations included eosinophilic cellulitis, morphea, disseminated granuloma anulare, the spectrum of figurate erythemas, and the different forms of urticarial rashes.

Laboratory results showed massive eosinophilia of 10.5 g/L (normal range [NR], <0.4 g/L) in the peripheral blood and highly elevated levels of eosinophilic cationic protein (297 µg/L; NR, <11.3). The patient reported no allergies. His total IgE was only minimally elevated (105 kU/L; NR, <100) and serologic testing for specific IgE antibodies against common allergens was negative as were serologic analyses for parasitic infections. Results were negative for antinuclear antibodies and antineutrophil cytoplasmic antibodies. Lymphoproliferative and myeloproliferative diseases could be molecularly excluded (no JAK2 V617F mutation, no FIP1L1-PDGFRα translocation, and no T-cell receptor-αβ and T-cell receptor-γδ rearrangement in the peripheral blood) as a possible reason for the eosinophilia.

A pulmonary function test found obstruction (forced expiratory volume in 1 minute, <75%), a computed tomography scan of the chest did not show any abnormalities. Histologic examination of a lesional skin biopsy found superficial and deep perivascular and diffuse interstitial infiltration with mostly eosinophilic granulocytes and interspersed lymphocytes and histiocytes (Fig 2). The finding of flame figures was remarkable (Fig 2, arrowheads). Based on the clinical presentation and the characteristic histologic pattern, a diagnosis of WS was made. The patient was first treated with systemic glucocorticosteroids (prednisolone), which led to prompt clearing of the skin symptoms. However, every attempt at tapering of this therapy caused immediate relapse of the disease at a dosage of about

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ABBREVIATIONS USED
CSS: Churg-Strauss syndrome
WS: Wells syndrome

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548
12.5 mg/d of prednisolone. Because of the associated asthma with peripheral eosinophilia and promising reports of interleukin (IL)-5 blockade in the treatment of eosinophilic asthma,\textsuperscript{3,4} a therapy with mepolizumab (100-mg subcutaneous injection every 4 weeks) was started. Prednisolone was tapered to 6.25 mg daily and discontinued at the time of the first injection of mepolizumab. After 2 months of therapy, the lesions had resolved completely (Fig 3) and the asthmatic complaints had improved markedly. During follow-up for 12 months the patient remained disease free and without any side effects under continuous treatment.

**DISCUSSION**

WS is a rare relapsing eosinophilic dermatitis with variable clinical appearance.\textsuperscript{1} During the acute phase, tender urticarial plaques, vesicles, bullae or nodules, and, at later stages, indurated morphealike lesions are described that resolve without scarring. In half of the patients, skin symptoms are accompanied by peripheral blood eosinophilia. Characteristic histopathologic findings include eosinophilic granulomatous infiltration of the dermis and formation of flame figures without signs of vasculitis. Such flame figures can also be observed in other skin diseases associated with eosinophilic infiltrates such as Churg-Strauss syndrome (CSS), cutaneous eosinophilic vasculitis, insect bite reactions, cutaneous parasitic infections, and bullous pemphigoid. Most commonly, WS is treated successfully with topical and systemic corticosteroids but often relapses upon tapering. Alternative treatment options based on a few case reports include cyclosporine, dapsone, local/oral tacrolimus, and antihistamines.\textsuperscript{2}

Associations between WS and other eosinophilic diseases and the possibility of its progression to CSS (eosinophilic granulomatosis with polyangiitis) have been discussed, as CSS shows similar blood (elevated IgE, eosinophilia, elevated eosinophilic cationic protein) and histologic findings.\textsuperscript{5-7} Our patient presented with characteristic signs of WS but also suffered from asthma, which was indicative of CSS. Importantly, no signs of vasculitis could be detected in the histopathology, and the patient did not fulfill the American College of Rheumatology criteria for the diagnosis of CSS.\textsuperscript{8}

Recently, treatment with mepolizumab, an IgG\textsubscript{1}\textk anti–IL-5 antibody, was shown to be highly effective in patients with CSS, resulting in more weeks in remission and allowing for reduced steroid use than did placebo.\textsuperscript{9} Blockade of IL-5 is also found to be an effective treatment strategy for eosinophilic asthma.\textsuperscript{3,4} Besides mepolizumab, one other humanized antibody (reslizumab, an IgG\textsubscript{4}\textk antibody) that also binds to IL-5 and interferes with its binding to the IL-5 receptor has been approved by regulatory authorities. An antibody targeting the IL-5 receptor \(\alpha\) subunit (benralizumab) is currently under regulatory review. IL-5 is mainly produced by T helper cell–2
lymphocytes and stimulates the production, maturation, migration, activation, and survival of eosinophils. Its blockade leads to an often dramatic decrease in circulating eosinophils and has a slightly less pronounced effect on the reduction of tissue eosinophilis. Most common adverse events include parasitic infections and allergic reactions.

This report shows that anti-IL-5 antibodies can also be a very effective means in the treatment of WS and might be worth of consideration as a future treatment option in recalcitrant patients.

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