CASE REPORT

Tocilizumab for treatment of cutaneous and systemic manifestations of vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome without myelodysplastic syndrome

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INTRODUCTION

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a newly described, adult-onset, autoinflammatory disorder caused by somatic mutations in the X-linked UBA1 gene. This syndrome is characterized by fevers, cytopenias, peripherally circulating myeloid and erythroid precursors with cytoplasmic vacuoles and dysplastic changes, pulmonary inflammation, chondritis, vasculitis, and joint pain and swelling.1,2 Nearly all patients with VEXAS present with cutaneous manifestations of the disease, most commonly a robust neutrophilic dermatosis.3

VEXAS was first described in December 2020 by Beck et al.1 UBA1 encodes the enzyme that initiates ubiquitin signaling; mutations impair the activation of ubiquitin and result in defective hematopoiesis. Myeloid progenitors with the UBA1 mutation are believed to trigger an inflammatory response, resulting in the various manifestations of the syndrome. Gene expression profiling of neutrophils and monocytes from affected patients demonstrates activation of inflammatory signatures, including tumor necrosis factor, interleukin 6 (IL-6), and interferon γ.1

Systemic corticosteroids and supportive care are the first-line treatment for the inflammatory symptoms and cytopenias of VEXAS. However, identification of nonsteroidal therapies is necessary for long-term management. The steroid-sparing treatments that have been reported in the literature with some success are methotrexate, mycophenolate, azathioprine, cyclophosphamide, and cyclosporine.4 Targeted agents, including anti–IL-1 therapy (anakinra and canakinumab), IL-6 blockade (tocilizumab), tumor necrosis factor α blockade (adalimumab, infliximab, and etanercept), and Janus kinase inhibitors, have been proposed as possible treatments for VEXAS.4,5 Several additional therapeutic options have been reported in the literature for patients with concomitant myelodysplasia. These options include azacitidine,5 hypomethylating agents, lenalidomide,6 and allogeneic bone marrow transplantation.7

Here we present the case of a patient with the hallmark characteristics of VEXAS, caused by a pathogenic mutation in the UBA1 (p.Met41Thr) gene, who was treated successfully with weekly tocilizumab.

Abbreviations used:
CT: computed tomography
IL: interleukin
VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic
injections of tocilizumab. This regimen allowed him to become transfusion independent, cleared his skin lesions, and facilitated tapering of systemic corticosteroids.

**CASE REPORT**

A 64-year-old man with a history of prostate cancer presented with asymptomatic anemia (hemoglobin 11.7 g/dL) and 3 years of persistent cough. Computed tomography (CT) of the chest demonstrated subtle ground-glass opacities in the lung apices, considered to be inflammatory. The erythrocyte sedimentation rate was elevated to 116 mm/h and the C-reactive protein level was elevated to 10.3 mg/dL. Tests for HIV, complement and immunoglobulin deficiency, antineutrophil cytoplasmic antibody, antinuclear antibody, rheumatoid factor, and myositis antibody panel were unremarkable.

He subsequently developed fever and swelling of the right leg, which was diagnosed as cellulitis and treated with cephalexin and doxycycline. Despite the resolution of erythema, fevers up to 38.3 °C persisted. Two weeks later, he re-presented with bilateral parotid swelling, bilateral testicular discom-fort, and fever of up to 39.2 °C, which resolved after treatment with clindamycin and vancomycin.

Seroologic tests for mumps, Lyme disease, Babesia, Ehrlichia, Epstein-Barr virus, cytomegalovirus, and babesiosis, fevers, pulmonary infiltrates, and a striking neutrophilic dermatosis. There is evidence that the dermal infiltrates in the VEXAS cutaneous lesions are derived from the pathologic myeloid clone, suggesting that therapies targeting the pathologic clone may be critical for the long-term management of cutaneous involvement.5

Although prednisone and other systemic corticosteroids are necessary for initial disease control, transitioning to steroid-sparing therapies is necessary. Tocilizumab was selected for use in this patient given our understanding of the mechanistic basis of VEXAS. The patient had excellent cutaneous and hematologic clearance of cutaneous lesions and independence from transfusion, despite tapering of prednisone.
Tocilizumab is currently in use for a variety of other inflammatory conditions, including cytokine release syndrome caused by cellular therapy, giant cell arteritis, rheumatoid arthritis, systemic sclerosis–associated lung disease, and severe COVID-19. Significant side effects of tocilizumab may include reactivation of tuberculosis; infection with opportunistic bacteria, fungi, and viruses; and intestinal perforation. Of note, there are 2 reports of intestinal perforation in patients with VEXAS receiving tocilizumab.

In summary, a diagnosis of VEXAS should be strongly considered in any patient with neutrophilic dermatosis, relapsing polychondritis, cytopenias, vacuoles in the erythroid and myeloid precursors, recurrent fevers, and other autoinflammatory symptoms. Although treatment with tocilizumab has been reported in the literature in a handful of patients with VEXAS, the response has been variable. This patient had an excellent response to tocilizumab, despite failure of standard immunosuppressants, including methotrexate and mycophenolate. Tocilizumab may...
offer an excellent therapeutic option for patients with VEXAS, including those without concomitant myelodysplastic syndrome.

Conflicts of interest
None disclosed.

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Fig 2. Cutaneous manifestations in vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome. A, A polycyclic erythematous indurated eruption was present on the patient's extremities. B, Numerous indurated, erythematous, papular lesions were seen on the patient's neck and back. C, Confluent geographic erythematous indurated plaques were present on the abdomen, with areas of sparing. D, Erythematous urticarial plaques on a background of dusky erythema were present on the patient's lower back. E, Punch biopsy of the trunk demonstrated marked papillary dermal edema with a diffuse neutrophilic infiltrate, consistent with Sweet syndrome. F, There were innumerable neutrophils with karyorrhectic debris throughout the infiltrate. (E and F, Hematoxylin-eosin stain; original magnifications: E, ×200; F, ×400.)
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