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

Abbreviations used:

CT:	computed tomography
IL:	interleukin
VEXAS:	vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic

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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 discomfort, and fever of up to 39.2 °C, which resolved after treatment with clindamycin and vancomycin. Serologic tests for mumps, Lyme disease, Babesia, Ehrlichia, Epstein-Barr virus, cytomegalovirus, and tuberculosis were negative.

Two weeks later, he experienced swelling and erythema of the right ear (Fig 1, *A*), left eye, and multiple small and large joints. CT of the face revealed evidence of idiopathic orbital myositis (Fig 1, *B*). Positron emission tomography-CT demonstrated diffuse heterogeneous fluorodeoxyglucose uptake in the bone marrow (Fig 1, *C*) and progression of the bilateral pulmonary apical ground-glass opacities. The bone marrow biopsy was normocellular, remarkable for occasional morphologic atypia in the myeloid, erythroid, and megakaryocytic lineages (Fig 1, *D* to *F*) and vacuoles in erythroid and myeloid precursors (Fig 1, *G* to *J*). Karyotype and 95-gene myeloid next-generation sequencing were unremarkable. Taken together with the normal cytogenetics and sequencing results, the mild morphologic atypia was not believed to be sufficient for a diagnosis of myelodysplastic syndrome.

Although the patient's symptoms improved with high-dose prednisone, recrudescence of symptoms occurred with tapering. Several months later, he experienced the sudden onset of widely disseminated, indurated, erythematous papules and polycyclic plaques (Fig 2, *A* to *D*), with fever and joint pain. Punch biopsy of the skin revealed dermal edema and a dense neutrophilic infiltrate (Fig 2, *E* to *F*), consistent with Sweet syndrome.

Because of his unusual constellation of symptoms, genetic testing was performed. Sequencing from peripheral blood leukocytes revealed a somatic mutation in the *UBA1* (p.Met41Thr) gene, consistent with VEXAS syndrome.

Despite trials of methotrexate and mycophenolate mofetil, the patient remained dependent on high doses of systemic corticosteroids. His hemoglobin level declined to 7.7 g/dL, and he required multiple transfusions. Weekly injections of tocilizumab (162 mg/0.9 mL) were initiated and daily oral prednisone (40 mg) was continued. Tocilizumab was selected as therapy on the basis of the observation that patients with VEXAS have elevated levels of IL-6 and tocilizumab is a competitive inhibitor of the binding of IL-6 to its receptor (IL-6R). At the time when the treatment was initiated, evidence for the efficacy of this treatment was not available in the literature, but data have subsequently been published by Kirino et al,[4] Bourbon et al,[5] and Heiblig et al.[6]

The patient's skin lesions cleared within 6 weeks from initiation of tocilizumab, with only residual postinflammatory hyperpigmentation. Repeat chest CT demonstrated resolution of the ground-glass opacities. His hemoglobin improved to 10.3 g/dL. He experienced cessation of his fevers, and his shortness of breath improved. These improvements were maintained while prednisone was tapered from 40 mg by 2.5 mg every 2 weeks and ultimately discontinued. At the time of this report, the patient was stable on weekly injections of tocilizumab (162 mg/0.9 mL) alone.

DISCUSSION

VEXAS is a newly discovered, autoinflammatory disease characterized by a myriad of systemic symptoms, including relapsing polychondritis, cytopenias, 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.[3]

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 response to subcutaneous injections, with complete clearance of cutaneous lesions and independence from transfusion, despite tapering of prednisone.

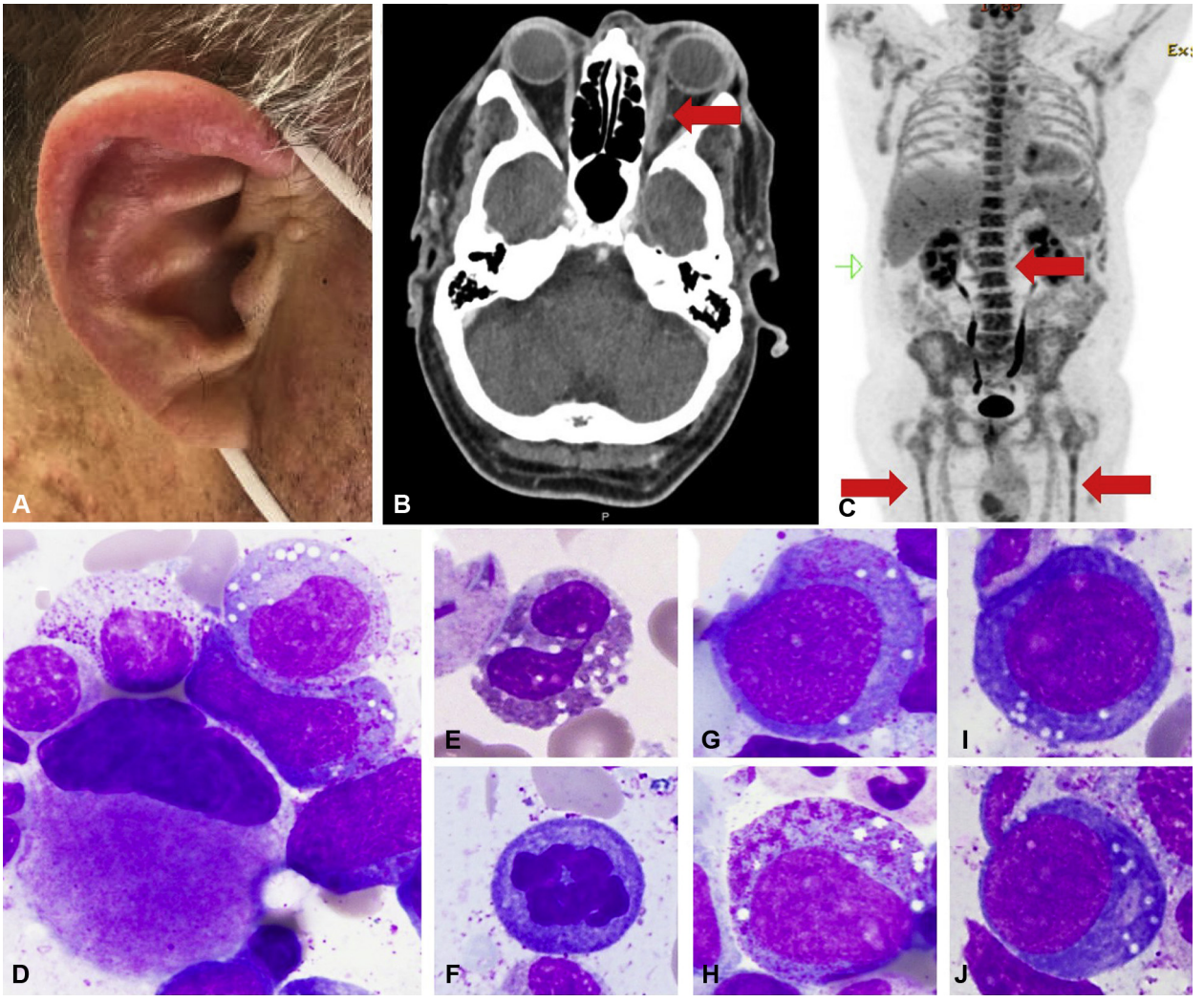

Fig 1. Radiographic and bone marrow findings in vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome. **A,** Erythema and swelling on the cartilaginous portion of the right ear. **B,** Axial computed tomography section of the face demonstrated asymmetric enlargement of the left medial rectus muscle with periorbital edema, consistent with an idiopathic orbital myositis (*red arrow*). **C,** Coronal positron emission tomography-computed tomography image demonstrated diffusely increased fluorodeoxyglucose uptake in the bone marrow (*red arrows*). **D** to **J,** Bone marrow smear demonstrated morphologic atypia in (**D**) megakaryocytic, (**E**) granulocytic, (**F**) and erythroid lineages, with **(G, H)** cytoplasmic vacuoles in myeloid and **(I, J)** erythroid progenitors. (Wright-Giemsa stain; original magnification: ×1000.)

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.[8]

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

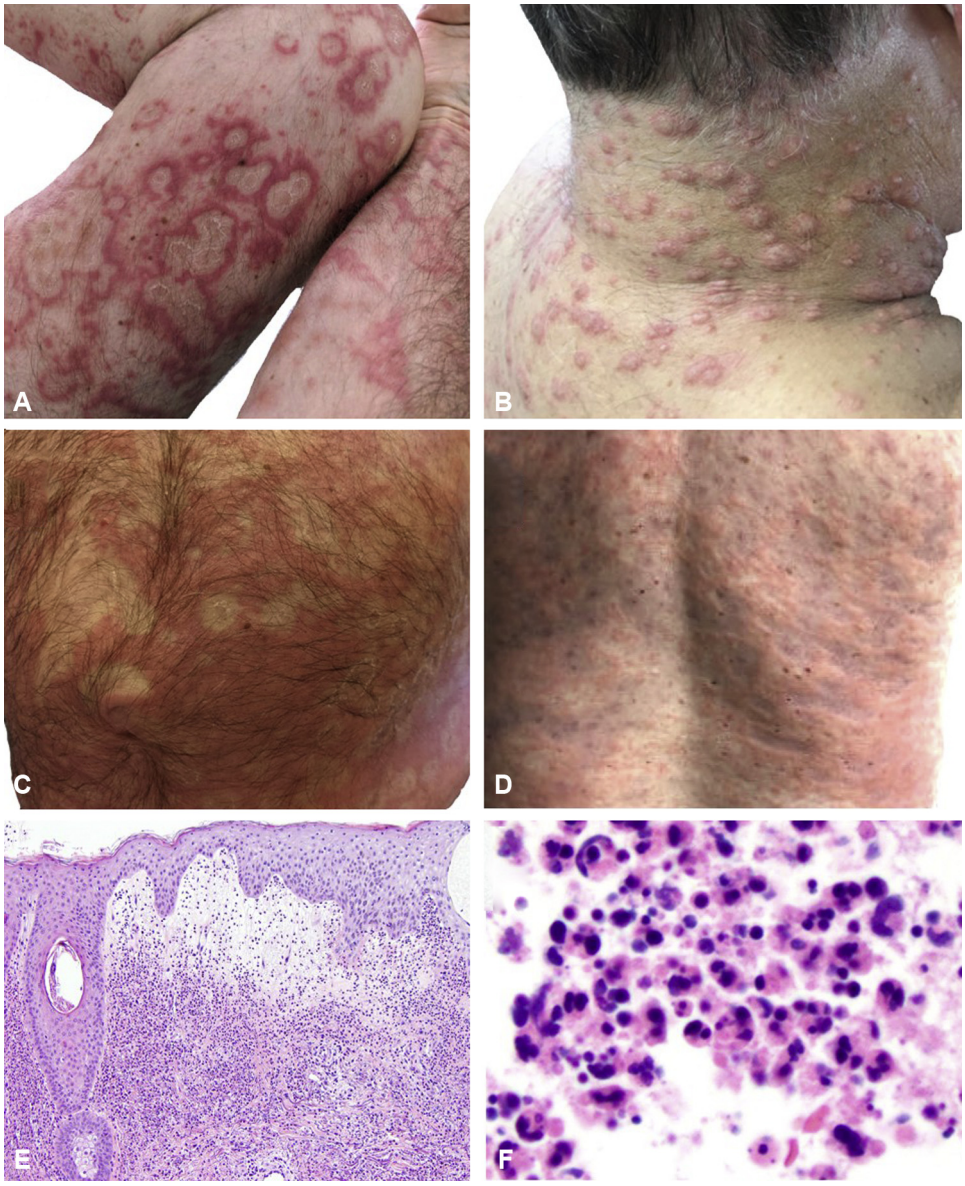

Fig 2. Cutaneous manifestations in vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome. **A,** A polycyclic erythematous indurated eruption was present on the patient's extremities. **B,** Numerous indurated, erythematous, papular lesions were seen on the patient's neck and back. **C,** 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.)

offer an excellent therapeutic option for patients with VEXAS, including those without concomitant myelodysplastic syndrome.

Conflicts of interest

None disclosed.

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