Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome—clinical presentation of a newly described somatic, autoinflammatory syndrome

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Key words: autoinflammation; genetics; MDS; myelodysplastic syndrome; neutrophilic dermatitis; Sweet syndrome; VEXAS.

INTRODUCTION

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a newly described, acquired autoinflammatory syndrome that can often follow a severe and fatal course. This disorder is characterized by a somatic loss of function mutation affecting the *UBA1* gene, resulting in the activation of the innate immune system and widespread systemic inflammation. Patients frequently present with cutaneous involvement, including neutrophilic dermatitis, vasculitis, and chondritis. The following case summarizes the characteristic features of this disease and highlights the importance of dermatology in recognizing patients with this condition, particularly given its progressive—and often refractory—nature.

Abbreviation used:

VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic

CASE REPORT

A man in his 60s presented with a generalized eruption associated with recurrent fever, polyarthritis, macrocytic anemia, and leukopenia. He had been evaluated by hematology, and initial bone marrow biopsy was notable for hypercellularity and mild reticulin fibrosis with normal karyotype and microarray results. The rheumatology department was consulted for diffuse synovitis, with laboratory test results notable for elevated inflammatory markers, low positive rheumatoid factor (15 IU/mL), and negative cyclic citrullinated peptide and antinuclear antibodies. Cutaneous examination revealed multiple edematous, erythematous plaques on the trunk and extremities (Fig 1). A punch biopsy demonstrated an abundance of neutrophils and nuclear debris that filled the papillary dermis with papillary dermal edema (Fig 2). Tissue cultures were negative. He was subsequently diagnosed with Sweet syndrome with suspected autoimmune myelofibrosis. Treatment with oral prednisone was initiated at 0.8 mg/kg/d with complete resolution of symptoms.

Over the subsequent months, attempts to decrease oral prednisone dose were made using several steroid-sparing agents, including colchicine, supersaturated potassium iodide (SSKI), dapsone, adalimumab, etanercept, abatacept, tocilizumab, anakinra, tofacitinib, and intravenous immunoglobulin. Despite these interventions, disease recurrence—characterized by cutaneous lesions, fevers, and arthralgias with intermittent dyspnea—occurred each time the prednisone dose was decreased below 25 mg to 35 mg daily. Skin lesions were consistent with neutrophilic dermatitis without clinical features of chondritis or vasculitis. Infectious complications

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Funding sources: None.
IRB approval status: Not applicable.

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JAAD Case Reports 2021;14:111-3.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.06.010

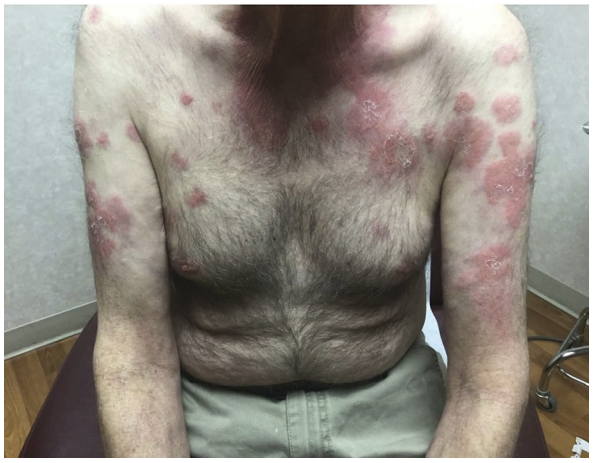

Fig 1. Multiple edematous, erythematous plaques on the trunk and extremities.

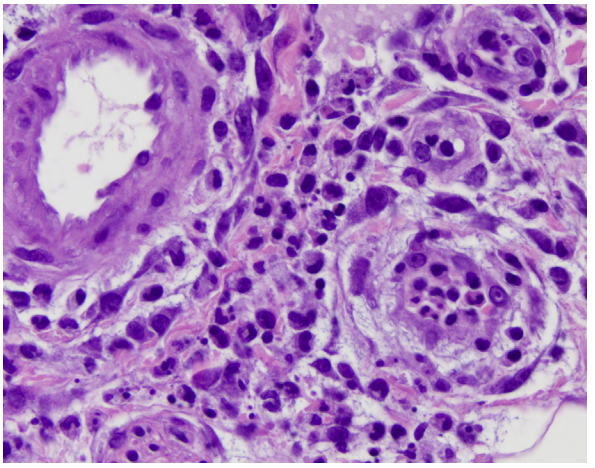

Fig 2. Punch biopsy from the skin of the upper arm demonstrating an abundance of neutrophils and nuclear debris that fills the dermis and subcutaneous fat. Note the absence of vasculitis. (Hematoxylin-eosin stain; original magnification: ×40.)

(including pneumonia and diverticulitis) also occurred, requiring treatment. A repeat bone marrow biopsy demonstrated hypercellularity, ring sideroblasts, and vacuolated erythroid and myeloid precursors (Fig 3). Following a recent publication by Beck et al,[1] collaboration with the National Institutes of Health was pursued. Genomic sequencing revealed a somatic mutation in *UBA1* c.121 A>C (p.Met41Leu). He was subsequently diagnosed with VEXAS syndrome and is currently under consideration for alternative treatment modalities, including allogeneic transplantation.

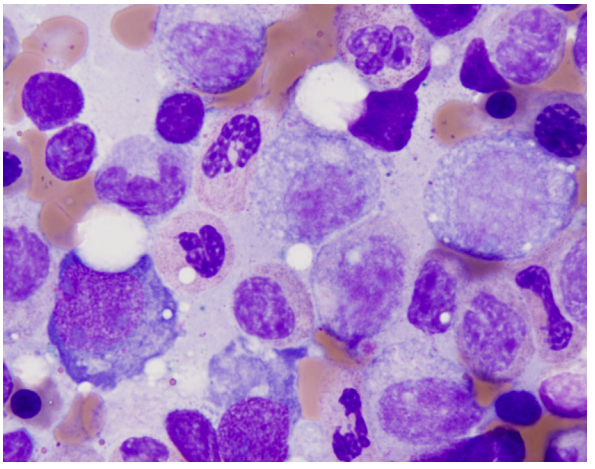

Fig 3. Cytoplasmic vacuoles were present in proerythroblasts and myeloid precursor cells in the bone marrow aspirate smear. (Wright-Giemsa stain; original magnification: ×200.)

DISCUSSION

In a recent publication,[1] a novel autoinflammatory disorder termed VEXAS syndrome was described in a cohort of 25 adult men. This treatment-resistant, often fatal syndrome is characterized by recurrent fever, cytopenias, dysplastic bone marrow with vacuolated myeloid and erythroid precursors, and cutaneous and pulmonary inflammation.[1] Cutaneous features were present in 88% of patients in the initial cohort and included neutrophilic dermatitis, vasculitis, and chondritis, with many carrying a diagnosis of relapsing polychondritis, Sweet syndrome, polyarteritis nodosa, or giant cell arteritis prior to sequencing. All patients were found to have an acquired loss of function somatic mutation affecting methionine-41 in *UBA1*, a gene encoding ubiquitin-activating enzyme 1, which resides on the X chromosome. Disease-causing mutations result in the loss of the normal, cytoplasmic isoform of *UBA1* and a decrease in cytoplasmic ubiquitylation, a type of posttranslational modification crucial for intracellular signaling and protein degradation. This results in increased activation of the innate immune system and widespread systemic inflammation, driven by mutant myeloid cells.[1]

Although the characterization of VEXAS syndrome is ongoing, the original cohort was similarly responsive only to systemic corticosteroids, despite the use of alternative agents. This disorder may follow a fatal course, with 40% of the cohort dying from disease-related causes (eg, respiratory failure, progressive anemia, complications from long-term steroid use). Further research is needed to explore bone marrow transplantation or gene-editing therapies as potential treatment modalities.[1]

Here, we presented a case of neutrophilic dermatitis in an adult man with recurrent fever, polyarthritis, and anemia exclusively responsive to systemic corticosteroids. *UBA1* mutation, characteristic of VEXAS syndrome, was confirmed in him via sequencing. Dermatologists should be aware of this newly described disorder and consider it in adult men with features of autoinflammation, hematologic abnormalities (eg, cytopenias, myeloid dyspoiesis), and characteristic cutaneous lesions (eg, neutrophilic dermatitis, chondritis, vasculitis). Recognition of the accompanying systemic manifestations, demographic features, and the refractory nature of the disease is essential as no specific morphologic discriminators have yet been identified. Early recognition and diagnosis may lead to a better prognosis and targeted treatments in the near future.

Dr Beck is supported by the Intramural Research Program of the National Genome Research Institute.

Conflicts of interest

None disclosed.

REFERENCE

1. Beck DB, Ferrada MA, Sikora KA, et al. Somatic mutations in *UBA1* and severe adult-onset autoinflammatory disease. *N Engl J Med*. 2020;383(27):2628-2638.