A Case of VEXAS Syndrome

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ABSTRACT

Introduction: VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a rare disease caused by somatic mutations in the *UBA1* gene, first identified in 2020. Prevalence is unclear, and there are no established treatment guidelines, highlighting the need for disease recognition.

Case presentation: An 82-year-old man presented with hypoxic respiratory failure, fever, rash, and pancytopenia. After an extensive workup, he was diagnosed with VEXAS syndrome based on bone marrow biopsy and genomic testing.

Discussion: VEXAS syndrome results from dysregulation in the ubiquitylation pathway, causing autoinflammatory and hematologic symptoms. Diagnosis is challenging due to variable presentation. Bone marrow biopsy and genomic testing for *UBA1* mutation are crucial for diagnosis. Treatment focuses on controlling inflammation with steroids and IL-6 receptor antagonists such as tocilizumab.

Conclusions: We present this case to raise awareness of this recently established condition. Further understanding will aid in optimizing management and improving clinical outcomes.

INTRODUCTION

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic)—a rare systemic inflammatory disease first identified by Beck et al in 2020—is caused by somatic mutations in the *UBA1* gene in hematopoietic precursor cells.[1] Mutations in *UBA1* result in defects in the E1 enzyme, causing defective protein degradation, clonal hematopoiesis, and widespread autoinflammation. This leads to multisystem involvement characterized by overlapping hematologic and rheumatologic findings, especially in older men.[2]

DNA sequencing is used to identify the *UBA1* mutation to support the diagnosis; however, diagnosis is often delayed because of the wide spectrum of presenting symptoms and perplexing laboratory findings. The condition's low prevalence is partly due to underrecognition and underreporting. Management of VEXAS syndrome is challenging because of limited treatment options and requires a multidisciplinary approach.

Herein, we present a case of VEXAS syndrome in an 82-year-old man who presented with respiratory failure, pancytopenia, and systemic symptoms.

CASE PRESENTATION

An 82-year-old man with a medical history of lower extremity deep vein thrombosis, splenic infarct, chronic macrocytosis, monoclonal gammopathy of undetermined significance, iron deficiency anemia, chronic kidney disease, and osteoporosis presented to the emergency department with fevers and shortness of breath. Two years prior, he had been started empirically on steroid therapy and intermittent tocilizumab for suspected giant cell arteritis (GCA) because of jaw claudication, headache, elevated C-reactive protein, and intermittent fevers. A temporal artery biopsy at that time was nonconclusive and a positron emission tomography scan was negative for large-vessel vasculitis. He continued steroid therapy but discontinued tocilizumab as the diagnosis of GCA was questioned.

On admission, the patient was febrile, hypoxic (requiring 6 L

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Figure 1. Hematoxylin and Eosin-Stained Bone Marrow Core Biopsy

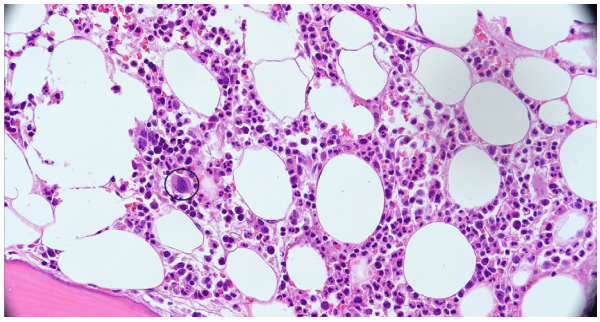
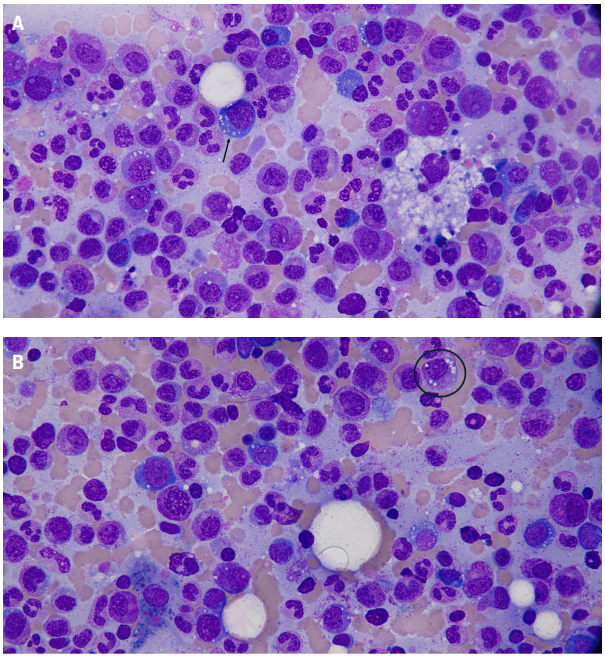


Image demonstrates a hypercellular marrow with an elevated myeloid: erythroid ratio and mild megakaryocyte atypia (black circle).

Figure 2. Wright-Giemsa-Stained Bone Marrow Aspirate



Images demonstrate a myeloid-predominant marrow with prominent cytoplasmic vacuolization in myeloid and erythroid precursors. Scattered hemophagocytic histiocytes are present.

oxygen via nasal cannula), and had acute kidney injury, thrombocytopenia, and anemia. He also had a morbilliform rash on his chest, back, and lower extremities. On hospital day 3, pancytopenia developed, with a white blood cell count (WBC) of 3.5×10^3/uL, hemoglobin (Hgb) 6.9 g/dL, and platelets (PLTs) of 160×10^3/uL (reference ranges: WBC, 4.0-15.0; Hgb, 13.7–17.5 g/dL; PLTs 165–366 K/μL). He was admitted to the intensive care unit (ICU) for acute hypoxic respiratory failure and started on intravenous antibiotics for possible pneumonia; however, the infectious workup was negative. His steroid dose was increased to 100 mg daily. A computed tomography scan of the chest ruled out pulmonary embolism and showed variable infiltrates. Bronchoscopy revealed acute alveolar hemorrhage. Prior antinuclear antibodiy (ANA) screens had been negative, but ANA titer on this admission was borderline positive at 1:80.

The patient's hospital course was complicated by intermittent worsening of acute respiratory failure when steroids were tapered, requiring multiple transfers to the ICU. Dermatology was consulted for the rash, which became diffusely red on the bilateral lower extremities, torso, and upper extremities. Hematoxylin-eosin-stained skin biopsy revealed scattered dyskeratotic keratinocytes and a sparse superficial perivascular infiltrate of lymphocytes, neutrophils, and some eosinophils.

During hospitalization, the patient also developed shingles, likely because of his immunocompromised state while on high-dose prolonged steroids, and was treated with acyclovir. Hematology was consulted, and a bone marrow biopsy was performed. Hematoxylin-eosin-stained bone marrow core biopsy and clot sections revealed a hypercellular (90%) marrow with megakaryocyte atypia characterized by small, simplified forms (Figure 1). Plasma cells were not numerically increased and were polytypic by in situ hybridization for kappa and lambda light chains. The Wright-Giemsa-stained bone marrow aspirate demonstrated an increased myeloid-to-erythroid ratio of 18.2. There was no increase in blasts. Early myeloid and erythroid precursors showed frequent cytoplasmic vacuolization (Figures 2A and 2B). Rare hemophagocytosis was observed. Cytogenetic analysis performed on bone marrow demonstrated a normal karyotype. Next generation sequencing revealed a pathogenic *UBA1* mutation (c.121A>G, p.Met41Val) at a variant allele frequency of 70.1%. No other definitively pathogenic variants were identified. Taken together, the clinical, morphologic, and molecular findings were consistent with a diagnosis of VEXAS syndrome. Hematology and rheumatology collaborated with the National Institutes of Health for a treatment plan, and the patient was placed on high-dose steroid taper and started on tocilizumab infusions. He was discharged on day 37 with supplemental oxygen. Four months after discharge, ruxolitinib (a JAK2 kinase inhibitor) was added.

Seven months after discharge, the patient continued to tolerate tocilizumab infusions. He had been on steroids for the past 2 years and was unable to wean off. He also was treated with acyclovir and atovaquone to prevent opportunistic infections while on steroids. He reported progressively worsening vision, retinal disease, and cataracts. Additionally, he developed steroid-induced diabetes and myopathy. His overall strength had not fully recovered to prediagnosis levels, although some stabilization and improvement were noted.

DISCUSSION

This case underscores the debilitating nature of VEXAS syndrome, a progressive systemic inflammatory disease predominantly affecting men older than 50 years.[2] As a recently recognized diagnosis,

its true prevalence remains uncertain. A review of health records from more than 160 000 adults by the National Heart, Lung, and Blood Institute estimated a prevalence of 1 in 4269 men older than 50.[3] A PubMed search identified only 109 reported cases globally in the past 5 years—and 25 in the United States—highlighting the need for further research to define prevalence and improve recognition.

Pathophysiology

VEXAS syndrome results from somatic mutations in the *UBA1* gene, which encodes the E1 ubiquitin-activating enzyme essential for the ubiquitin-proteasome system. The mutations impair protein degradation, leading to accumulation of misfolded proteins and chronic immune activation.[1,4] Mutated hematopoietic stem cells undergo clonal expansion, producing peripheral blood cytopenias and characteristic marrow changes.[1,5,6] Elevated cytokines—particularly interleukin-6 (IL-6)—further amplify inflammation.[7] Clinical manifestations reflect this interplay of clonal hematopoiesis and immune dysregulation, with systemic symptoms and organ involvement.[5,8] Rare dermatologic conditions such as Sweet syndrome and Kikuchi-Fujimoto disease may occur.[1,4] Additional mutations in genes like *DNMT3A* or *TET2* have been reported.[5]

Clinical Presentation

VEXAS syndrome exhibits heterogeneous features, including systemic inflammation, hematologic abnormalities, and cutaneous lesions.[2] Early symptoms may include fever, fatigue, and myalgia, with involvement of the skin, cartilage, joints, lungs, and blood vessels.[2] Common inflammatory features resemble conditions such as Sweet's syndrome, relapsing polychondritis, and polyarteritis nodosa.[1] Macrocytic anemia and other cytopenias are also prevalent.[9]

A literature review of US cases revealed presentations ranging from neutrophilic dermatitis to mediastinal lymphadenopathy and hematologic issues.[10] Notably, isolated dermatologic disease does not exclude VEXAS, emphasizing the need for genetic testing when clinical suspicion exists. The syndrome may also predispose to hematologic malignancies, including plasma cell neoplasia and myelodysplastic syndrome, though this association requires further study.[6]

Diagnosis and Treatment

Diagnosis requires correlation of clinical findings with bone marrow morphology and molecular testing. Bone marrow typically shows hypercellularity with cytoplasmic vacuoles in myeloid and erythroid precursors. Detection of a pathogenic *UBA1* variant—usually with a variant allele frequency greater than 20%—lends confidence to the diagnosis.[1]

There are no standardized treatment guidelines. Current management focuses on controlling inflammation with high-dose corticosteroids and IL-6 receptor antagonists such as tocilizumab.[11] IL-6 receptor antagonists are favored in cases with persistent inflammation but no significant transfusion-dependent cytopenias, while corticosteroids are tapered.[11] JAK inhibitors (ruxolitinib, tofacitinib) have been used in refractory cases, whereas conventional immunosuppressants (methotrexate, azathioprine, mycophenolate) are generally ineffective.[1,12] Allogeneic hematopoietic stem cell transplantation has shown success in some patients.[13,14]

Further research is necessary to optimize treatment and improve outcomes. Future strategies may include therapies targeting the ubiquitination pathway or gene editing, and clinical trials are crucial for developing evidence-based treatment algorithms.[11,12] Supportive care for complications—such as infections, cytopenias, and thrombosis—is essential, and lifelong anticoagulation therapy required for patients at risk of recurrent thrombosis.[11]

Mortality often results from respiratory failure, severe anemia, or treatment-related adverse effects.[1] This case illustrates the importance of considering VEXAS syndrome in patients with unexplained systemic inflammation, particularly when symptoms persist despite immunosuppressive therapy.

CONCLUSIONS

This case of VEXAS syndrome in a patient with pulmonary, dermatologic and hematologic manifestations demonstrates the disease's clinical complexity. Diagnosis was confirmed bone marrow biopsy showing vacuolated myeloid precursors and identification of a pathogenic *UBA1* mutation in hematopoietic cells. The underlying defect in the ubiquitination pathway drives immune dysregulation and system inflammation, explaining the broad spectrum of symptoms. Given the limited therapeutic options and recent recognition of the syndrome, further research is critical to improve outcomes. Increased awareness and early detection may help prevent disease progression and reduce morbidity and mortality.

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