



VEXAS syndrome

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VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a monogenic disease of adulthood caused by somatic mutations in *UBA1* in hematopoietic progenitor cells. Patients develop inflammatory and hematologic symptoms. Myeloid-driven autoinflammation and progressive bone marrow failure lead to substantial morbidity and mortality. Effective medical treatments need to be identified. Reports in the current issue of *Blood* describe novel *UBA1* genetic variants, treatment options, and insight into disease pathophysiology. VEXAS syndrome represents a prototype for a new class of diseases.

Introduction

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) was first reported in 2020 in 25 men with adult-onset inflammatory disease and myeloid dysplasia.¹ Using a genotype-first approach to disease discovery, acquired mutations were identified in all cases of VEXAS in the *UBA1* gene, which encodes for the master enzyme of cellular ubiquitylation.² These mutations were novel (ie, absent from public databases, including the Genome Aggregation Database). The name VEXAS is an acronym based upon key features of the syndrome. Vacuoles are seen in myeloid and erythroid progenitor cells from bone marrow aspirates. E1 enzyme refers to the ubiquitin activating enzyme encoded by *UBA1*, which is an X-linked gene. Mutations in *UBA1* are lineage restricted to myeloid cells and result in autoinflammatory disease. Finally, this disease presents late in life as the result of somatic mutations in blood.³

Clinical description of VEXAS syndrome

VEXAS is a severe, progressive disease with clinical features that bridge rheumatologic and hematologic conditions. Systemic inflammation involving the skin, lungs, blood vessels, and cartilage often leads to the assignment of various clinical diagnoses, including Sweet syndrome, relapsing polychondritis, polyarteritis nodosa, and giant cell arteritis. Additionally, patients with VEXAS suffer from a spectrum of hematologic problems, including macrocytic anemia, thrombocytopenia, thromboembolic disease, and progressive bone marrow failure, which can evolve to hematologic malignancy (Figure 1). An increased risk for hematologic malignancy, most notably myelodysplastic syndrome (MDS), has been reported in many rheumatologic diseases, and conversely, MDS has been associated with a variety of autoimmune syndromes.⁴⁻⁸ VEXAS syndrome may explain some of these historic clinical associations.

A diagnosis of VEXAS should be considered in patients with treatment-refractory inflammatory disease with associated progressive hematologic abnormalities. Among patients with a

clinical diagnosis of relapsing polychondritis, male sex plus a mean corpuscular volume >100fL or platelet count <200 × 10⁹/L predicted VEXAS syndrome with near-perfect accuracy.⁹

Bourbon et al,¹⁰ Gurnari et al,¹¹ Lytle et al,¹² and Poulter et al¹³ add to the evolving clinical understanding of the VEXAS syndrome. In aggregate, they detail an additional 24 cases of VEXAS. The identification of a substantial number of patients so quickly after the first report of the syndrome suggests an underappreciated prevalence of this disease. Similar to the initial publication,¹ cases were only identified in men with disease onset in the fifth decade of life or later. Systemic inflammation manifested as vasculitis, chondritis, and neutrophilic dermatosis, among other symptoms and signs. The clinical similarities to the initial description of patients with VEXAS may reflect the stereotypical nature of the syndrome or selection bias due to preferential screening of patients with autoinflammatory disease and myeloid dysplasia.

Genetic diagnosis of VEXAS syndrome

UBA1 is an X-linked gene that escapes X inactivation.¹⁴ To date, VEXAS has been reported exclusively in men, and women likely are protected by the unmutated allele. In the original description, all 25 men with VEXAS had missense mutations in codon 41 of *UBA1*.¹ These mutations were seen in hematopoietic progenitor cells in bone marrow and lineage restricted to myeloid cells in circulation. Bourbon et al¹⁰ and Poulter et al¹³ describe additional mutations in *UBA1* that do not involve codon 41. Two patients had a novel variant in the splice motif at the junction of intron 2 and exon 3 (C.118-1G>C), resulting in a *UBA1* protein lacking methionine 41. The authors speculate that this mutation likely leads to the formation of a catalytically inactive cytoplasmic isoform of *UBA1*, as previously described.¹ An additional novel variant (C.167C>T; p.Ser56Phe)¹³ in a single patient was also reported to be restricted to myeloid cells, leading to temperature-dependent impairment of the resulting isoform.

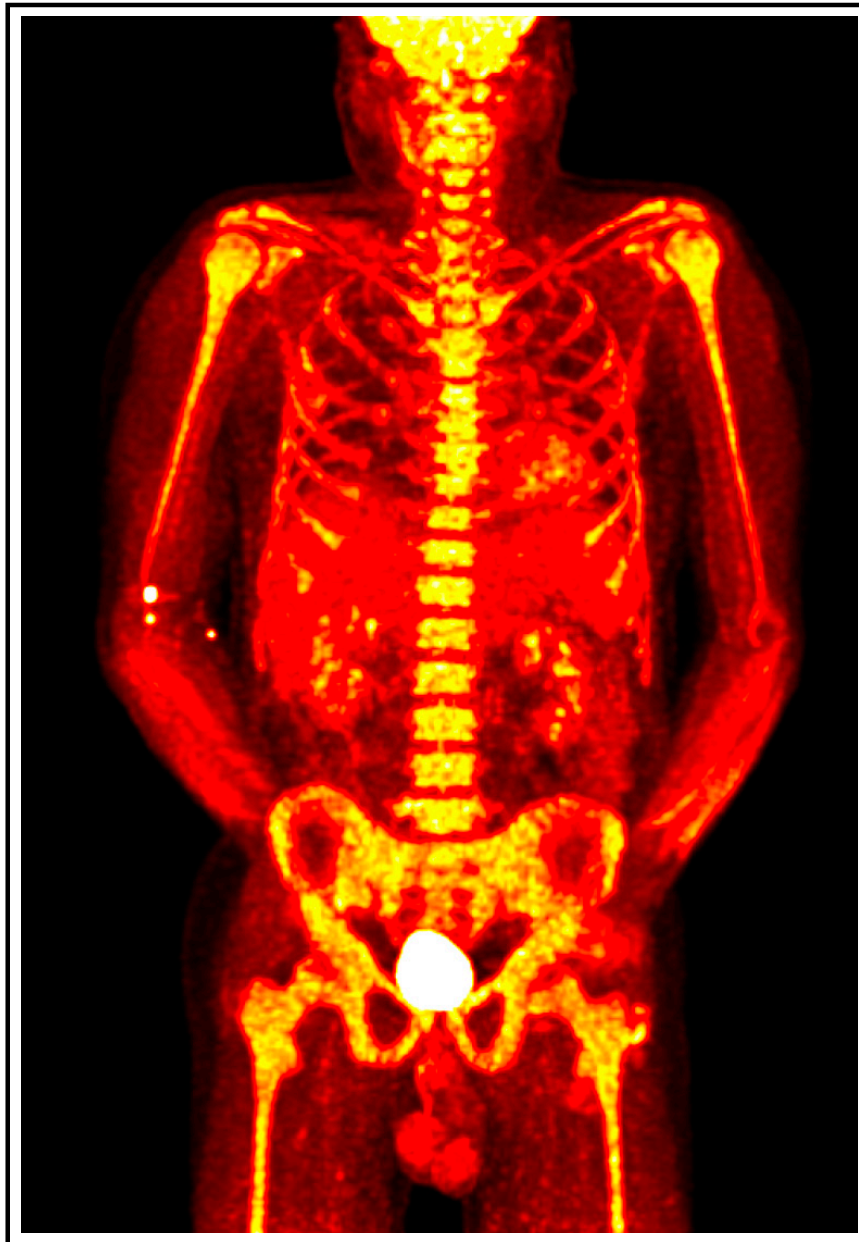


Figure 1. ^{18}F -fluorodeoxyglucose positron emission tomography in a patient with VEXAS syndrome demonstrating hypermetabolic activity in bone marrow (yellow). Somatic mutations in *UBA1* in hematopoietic cells lead to myeloid-driven inflammation that is often refractory to treatment in patients with VEXAS syndrome.

Vacuoles as a characteristic feature of VEXAS syndrome

Vacuoles are normal and functional intracellular organelles in plants, fungi, and bacteria,¹⁵⁻¹⁷ but cytoplasmic vacuoles in mammalian cells can indicate pathology.¹⁸ Vacuoles in affected cells can be transient or irreversible, and the latter implies a permanent intrinsic defect.^{18,19} Vacuoles are rare in marrow myeloid and erythroid precursor cells. Gurnari et al¹¹ screened 11c772 BM samples but found only 24 with cytoplasmic vacuoles. When cytoplasmic vacuoles are identified in these lineages on morphologic examination of marrow for cytopenia, the differential diagnosis includes alcohol intoxication,²⁰ copper deficiency/zinc toxicity,²¹⁻²³ and myeloid neoplasms.²⁴ Sequencing of *UBA1* variants now needs to be included

in the evaluation of an adult patient with cytoplasmic vacuoles in the marrow. Vacuoles in myeloid and erythroid precursors have been present in all patients with VEXAS thus far (in the initial report¹ and now by Bourbon et al,¹⁰ Gurnari et al,¹¹ Lytle et al,¹² and Poulter et al¹³) Cytoplasmic vacuoles are predominantly localized in promyelocytes, myelocytes, erythroid precursors, and blasts in the marrow from VEXAS patients.¹¹ Features that may aid in differentiating VEXAS from other etiologies of myeloid and erythroid precursor cell cytoplasmic vacuolization include presence of autoimmune-inflammatory manifestations, macrocytic anemia as a predominant cytopenia followed by thrombocytopenia, cytopathology with numerous coarse vacuoles in both myeloid and erythroid lineages, and normal copper levels. Exactly what vacuoles contain is not clear and needs further investigation.

VEXAS syndrome and hematologic malignancies

The association between autoinflammation and myeloid malignancies is well described in the literature,^{4,25} but VEXAS establishes a genetic link for the co-occurrence of these heterogeneous disorders. MDS has been diagnosed at a high frequency in patients with VEXAS, including 25% (6/25; Beck et al¹), 30% (3/10; Poulter et al¹³), and 55% (6/11; Bourbon et al¹⁰). The risk of developing MDS with acquired *UBA1* mutation appears to be much higher than observed with well-established clonal hematopoietic disease such as paroxysmal nocturnal hemoglobinuria (2% to 6% by 10 years).²⁶ *UBA1* is a key regulator of cellular protein degradation, a pathway not within the current list of genes associated with MDS.²⁷ Whether *UBA1* mutation represents a new driver clone for myeloid neoplasm or the occurrence of MDS in VEXAS is driven by other clones selected in chronic inflammatory microenvironment is not known. Two reports identified large DNMT3A clones in one patient each with MDS (43% variant allele frequency [VAF]¹ and 24%VAF,¹¹ respectively); smaller clones in MLL-PTD (3.45%), CSF1R (3.12%), and SF3B1 (1%) were present in other MDS patients,¹ but their clinical significance is unclear. The molecular landscape in VEXAS MDS is not typical of classical MDS, in which myeloid neoplasia gene mutations are common, large clones are present, and multiple genes are often involved.^{28,29} Further studies of the clonal genetic landscape in patients with VEXAS will provide insight into the role of inflammation in the pathophysiology of MDS.

In addition to MDS, acquisition of *UBA1* mutation predisposes to multiple myeloma (MM) or MM and MDS both. Lytle et al¹² presented a case of a 68-year-old male with a history of myeloma and relapsing polyarthritides whose bone marrow biopsy, which was performed for progressive pancytopenia, showed features that were diagnostic for both MDS with multilineage dysplasia and residual myeloma. As more patients are identified earlier in the VEXAS disease course, prospective follow-up should include enhanced screening for both of these malignancies.

Treatment of VEXAS syndrome

Understanding the molecular basis of a particular disease is an important first step toward developing more effective treatments. The VEXAS syndrome is associated with considerable morbidity and high mortality. Symptoms are typically refractory to treatment, and high-dose glucocorticoids are only temporizing and have substantial toxicity. Bourbon et al¹⁰ and Poulter et al¹³ emphasize the treatment-refractory nature of VEXAS, as most patients received several steroid-sparing agents in addition to concomitant glucocorticoids. Due to the retrospective study design, Bourbon et al¹⁰ evaluated “time to next treatment” as a proxy for effectiveness. The hypomethylating agent azacitidine was used for the longest median duration (21.9 months), but no improvement in cytopenia or myelodysplastic features on bone marrow was observed. Janus kinase inhibitors were effective for some features of systemic inflammatory disease, particularly skin involvement. Prospective evaluation of treatment efficacy is needed to define optimal clinical management. Nuances in clinical phenotype may inform treatment approaches in VEXAS. For example, hypomethylating agents might be preferentially

considered in a subset of patients with concomitant MDS. Animal models of VEXAS could enable preclinical research to better understand the pathophysiology of the disease and provide insight into novel therapeutic targets. A zebrafish model, replicating loss of the cytoplasmic isoform of *UBA1*, demonstrates upregulation of multiple inflammatory cytokines that are elevated in VEXAS (eg, tumor necrosis factor, interleukin-1 [IL-1], IL-6, and IL-8).¹ Development of an animal model in a higher organism poses some challenges, as the mutations associated with VEXAS syndrome are likely embryonic lethal. High-risk therapies such as allogeneic bone marrow transplantation should be considered in select patients with VEXAS syndrome given the clonal nature of the disease, persistent and progressive hyperinflammation from complex activation of multiple innate immune pathways, and predisposition to hematologic malignancies.

Future directions

The identification of the VEXAS syndrome serves as another link between clonal hematopoiesis and systemic inflammation.^{30,31} VEXAS may be a prototype for a new class of “hematoinflammatory diseases.” These diseases would be defined by somatic mutations in hematopoietic cells, systemic inflammation, and the potential to evolve into overt myelodysplastic, myeloproliferative, or lymphoproliferative disease. Acquired mutations in *STAT3* in lymphocytes underlie a proportion of patients with Felty syndrome and predispose to large granular lymphocyte leukemia.³² Somatic mutations in *BRAF* in histiocytes are causal in some patients with Erdheim-Chester disease and may lead to aortitis and myeloproliferative neoplasms.^{33,34} A series of lymphoma driver mutations transform B cells to produce pathogenic autoantibodies that predispose the development of cryoglobulinemic vasculitis in Sjogren syndrome, a disease associated with increased risk for non-Hodgkin lymphoma.³⁵ In the reports of Bourbon et al¹⁰ and Poulter et al,¹³ 8 of 19 patients and 8 of 18 patients, respectively, had myeloid dysplasia and autoinflammation without detectable mutations in *UBA1*, but further genomic studies may reveal additional novel acquired mutations in *UBA1*-mutation-negative patients.

Early observations in VEXAS syndrome and related diseases are helping to define the role somatic mutations play in complex, adult-onset diseases³³ and provide a framework for collaboration in the clinic and the research laboratory between hematologists and rheumatologists.

Authorship

Contribution: P.C.G., B.A.P., and N.S.Y. designed research, performed research, and wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Footnote

Submitted 25 March 2021; accepted 29 April 2021; prepublished online on *Blood* First Edition 10 May 2021. DOI 10.1182/blood.2021011455.

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