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Vexas Syndrome: A Newly Discovered Hemato-inflammatory Disease

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Abstract

VEXAS syndrome is a recently described hemato-inflammatory disease. It is an acronym from the syndrome's key characteristics: vacuoles in bone marrow biopsies, low levels of ubiquitin activating enzyme (E1 enzyme), X-linked, autoinflammatory, somatic. It results from a somatically acquired mutation affecting methionine 41 of the E1-ubiquitin ligase UBA1, leading to the expression of a catalytically impaired isoform that drives inflammation. As this gene is located on the X chromosome, only men appear to be affected by this syndrome. Patients have severe inflammatory symptoms that affect multiple organs. Clinical features bridge rheumatological, dermatological, ophthalmological, respiratory, and hematological conditions. There is an association between severe autoinflammatory manifestations and myeloid dysplasia.

Keywords: Hemato-inflammatory Disease; Autoinflammatory Manifestations; Myeloid Dysplasia; Vexas Syndrome; Inflammatory Cytokines

Abbreviations: MDS: Myelodysplastic Syndrome; DNMTI: DNA Methyltransferase Inhibitors; IL: Interleukin; ESA: Erythropoietin Stimulating Agents; JAKi: JAK Inhibitors

Introduction

VEXAS syndrome is an acquired, late onset autoinflammatory disorder that was identified in 2020. VEXAS is an acronym from the syndrome's key characteristics: vacuoles, E1 ubiquitin activating enzyme, X-linked, autoinflammatory, somatic [1]. VEXAS syndrome is rare. The estimated prevalence of VEXAS syndrome in an overall cohort of 163,096 patients within a Pennsylvania health-care system was 1 in 13,591 [2].

Genetics

VEXAS syndrome is caused by somatically acquired mutations in UBA1 gene located on the X chromosome. UBA1 codes for the main E1 activating enzyme, in humans, which is responsible for over 90% of the activation of ubiquitin, ubiquitylation-dependent intracellular protein degradation and cell homeostasis [1]. The codon 41 in UBA1 represents a mutational hotpot, where methionine -41 (p. Met41) is replaced by valine, threonine, or leucine [3], leading to the expression of a novel, catalytically impaired isoform (UBA1c) [4]. Other rarer described mutations are missense variants such as the p. Ser65Phe, and splice acceptor site mutations. Both common missense and splice site variants are responsible for a decrease in the cytoplasmic level of UBA1 protein [3].

Almost all pathogenic mutations in the UBA1 gene lead to loss of the cytoplasmic form of UBA1 (UBA1b) [1] in the blood cells. Mutations were found in more than half of the hematopoietic stem cells, including peripheral-blood myeloid cells but not lymphocytes or fibroblasts [4]. Peripheral-blood cells with impaired isoform showed decreased ubiquitylation. The innate immune pathways are abnormally activated [4]. As a consequence, there is hyperproduction of inflammatory cytokines such as TNF, IL-1, IL-6, IL-8, IFN-γ–induced protein 10, and IFN-γ, which are elevated in patients' sera, even during clinically quiescent periods [4]. These high levels of proinflammatory cytokines cause systemic inflammation with multi-organ involvement and associated aberrant bone marrow status [1].

Clinical presentation

VEXAS syndrome defines a new disease category – the hemato inflammatory disorders. It was identified only in men at a median age of 50 to 60 years, all of whom were clinically affected [3]. This suggests that the additional allele in women protects against the effects of the mutant allele [4]. VEXAS syndrome is rare in women, of milder degree, and shows a "pseudoautosomal" character requiring somatic double hits (e.g., Turner syndrome, acquired X deletions, or somatic X-skewing) [3].

The various clinical manifestations of VEXAS are broadly divided into inflammatory or hematological [3].

Common inflammatory and autoimmune features [3]

a. Constitutional symptoms such as noninfectious fever and weight loss in up to two third of cases.

b. Skin: the most involved organ, in up to 90% of cases. Patients can develop neutrophilic dermatosis, leukocytoclastic vasculitis and septal panniculitis. Cutaneous manifestations may be directly caused by the actual UBA1-mutant clone (clonal) or resulting from the downstream effects of the inflammatory cytokines (paraclonal).

c. Lung: the second most frequently involved organ. Up to 70% of patients may present with dyspnea and cough as a result of several pleuropulmonary disorders. Radiologic features included ground-glass opacities (87%), consolidations (49%), reticulation (38%), septal lines (51%), and pleural effusion (53%). VEXAS showed good responses to glucocorticoids treatment with a low incidence of pulmonary fibrosis.

d. Relapsing episodes of **ear, nose, and peripheral joint** chondritis are common [3].

Hematological features

a. Cytopenias: macrocytic anemia is almost universal and lymphopenia [3].

b. Macrophage activation syndrome and / or hemophagocytic lymphohistiocytosis and monoclonal B cell lymphocytosis have been reported [5].

c. MDS is the most frequent hematological neoplasm in VEXAS. Thrombocytopenia and neutropenia are more common in cases with concomitant myelodysplastic syndrome (MDS) [3]. Transition to MDS occur with acquisition of mutations in classical myeloid genes belonging to DTA triad (DNMT3A, TET2, ASXL1), which are observed in the aging BM [3].

d. Progression to hematological malignancies, such as acute myeloid leukemia or chronic myelomonocytic leukemia, is rare [1].

e. The full spectrum of plasma cell dyscrasias ranging from monoclonal gammopathy of undetermined significance to multiple myeloma in up to 25% of cases with VEXAS [3].

f. The presence of vacuoles greater than or equal to 10% of myeloid precursors in the BM has been associated with a reliable sensitivity and specificity of VEXAS diagnosis. Although no specific threshold for diagnosis is set. The use of hematopathology alone for diagnosis is limited by the presence of minimal BM changes in other studies [3].

g. The pathogenesis of such hematopathological manifestations seems multifactorial, probably mediated partly by chronic hyperinflammation and partly by the transition to clonal hematological disease and neoplasia [3].

h. Thrombotic events have been reported in as high as 55% of cases. Thromboembolism is typically present in the venous circulation with an increased likelihood for recurrence. Thrombosis is likely related to chronic hypercytokinemia and the resultant inflammation and endothelial dysfunction [3].

i. Concomitant lupus anticoagulant is present in up to half of the patients and is associated with recurrence of thrombotic events [3].

Treatment and risk stratification of VEXAS syndrome

VEXAS is a markedly heterogeneous disease. VEXAS causes significant morbidity and reduced life expectancy, but the optimum standard of care remains undefined [6].

Therapeutic options in patients manifesting with mild disease and no risk factors includes supportive and preventative measures such as prophylactic antibiotic/antivirals in the context of recurrent significant underrecognized infections. Vaccinations could be considered in lymphopenic patients. Long-term anticoagulation reduces the risk of typically unprovoked VTEs complications. This needs to be balanced against the risk of bleeding, especially gastrointestinal bleeds if the patient is on non-steroidal anti-inflammatories or steroids. Patients with mild disease and no risk factors should be a focus for optimizing medical management [1].

Medical management

The thrombopoietin receptor agonist eltrombopag and erythropoietin stimulating agents (ESA) are used to improve VEXAS-associated cytopenia. ESAs are used in low-risk MDS. ESAs are found to be 70% effective if used when serum levels of erythropoietin are <100 U/L.

Therapeutic options in patients manifesting mostly with inflammatory and rheumatological disease, include anti-IL1 (anakinra & canakinumab), anti-IL6 (tocilizumab) and JAK inhibitors (e.g., baricititinib & ruxolitinib). High-dose systemic corticosteroids are highly effective at controlling inflammatory symptoms, but their use is limited by toxicity. Steroids should be reduced, even to cessation as much as possible. Steroid-sparing agents should be provided [1].

Therapeutic options in patients manifesting with hematological manifestations, include the JAKi and the DNA methyltransferase inhibitors (DNMTI) e.g., azacitidine and decitabine. JAKi is an option for their effect on cell counts and transfusion dependence. DNMTI has shown efficacy in MDS-associated inflammation and is commonly used in MDS for pre-treatment prior to HSCT [1].

Therapeutic options in patients with poorly controlled or high-risk disease, e.g., patients with p. Met41Val mutation or

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transfusion dependence are allogeneic hematopoietic stem cell transplants. Although Allogeneic hematopoietic stem cell transplant is a potentially curative option in these patients [1], VEXAS-specific selection criteria and the ideal conditioning regimen need to be developed [6].

Conclusion

VEXAS is a markedly heterogeneous disease. The optimum standard of care remains undefined. Drugs used in the treatment of VEXAS syndrome depend on whether patients with VEXAS syndrome are manifesting primarily with inflammatory or hematological disease. There is currently no published data about the efficacy of the different therapeutic options proposed to these patients.

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