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SHORT COMMUNICATION

VEXAS syndrome in a nutshell

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ABSTRACT

Introduction:

VEXAS is a multisystem autoinflammatory disorder caused by acquired somatic mutations in the ubiquitin-like modifier activating the X chromosome's enzyme 1 (UBA1) gene. VEXAS syndrome predominantly affects men, with the disease typically presenting with a progressive onset after age 50. Patients exhibit a wide range of clinical symptoms which involve skin, lungs, cartilage, and joints. Common systemic symptoms include recurring, unexplained fever episodes, general malaise, and fatigue. The care of VEXAS syndrome is challenging and necessitates a multidisciplinary approach from numerous specialized teams due to its heterogeneous manifestations. Although no standardised therapies are available for VEXAS patients, high-dose, long-term corticosteroid therapies and Janus kinase (JAK) inhibitors are used as therapeutic options.

Conclusion:

Clinicians should consider VEXAS syndrome in patients with unexplained systemic inflammatory symptoms, particularly when accompanied by peripheral cytopenia and other hematologic disorders.

Keywords

Autoinflammatory, manifestations, patients, symptoms, syndrome, ubiquitin-like modifier activating the enzyme 1 (UBA1), vacuole

Introduction

In 2020, a rare and severe multisystem autoinflammatory disorder with complex pathogenesis was first described by scientists as VEXAS syndrome (vacuole, E1 enzyme, X-linked, autoinflammatory, and somatic). Acquired somatic mutations in the ubiquitin-like modifier activating the enzyme 1 (UBA1) gene on the X chromosome cause this syndrome. [1] UBA1 initiates the protein ubiquitylation process, a post-translational modification (PTM) targeting proteins for various vital cellular processes, including degradation, signalling, localization, and protein-protein interactions. [2]

A crucial observation of bone marrow smears from VEXAS patients is the presence of cytoplasmic vacuoles within myeloid and erythroid precursor cells [1]. They are not pathognomonic for VEXAS syndrome since they can also be observed in copper deficiency, zinc toxicity, alcoholism, or myelodysplastic syndrome (MDS). [3] However, these findings are rare, and if they are detected in the presence of inflammatory symptoms, genetic analysis is strongly recommended to investigate the possibility of VEXAS syndrome. Also, clinicians should not rule out the possibility of VEXAS syndrome without a vacuole, as certain patients may not present with vacuoles on a bone marrow smear. [4]

VEXAS syndrome predominantly affects men, with the disease typically presenting with a progressive onset occurring after age 50, though it can affect women too. A study by Beck DB *et al*. has shown that within the initial cohort of 25 male patients, the female second X-chromosome allele has a protective influence against the pernicious impact of the mutated UBA1 allele [1]. More recent studies describing the VEXAS syndrome in women with monosomy X support this hypothesis. [5, 6]

Patients with VEXAS syndrome exhibit many clinical symptoms that can impact several organ systems, such as the skin, lungs, cartilage, and joints. Common systemic symptoms include recurring, unexplained fever episodes, general malaise, and fatigue. [1, 7] The VEXAS syndrome is characterised by cutaneous involvement, which manifests as neutrophilic dermatosis and a vasculitis rash [1, 8]. According to current research, 88% of patients reported cutaneous symptoms, with a significant number of people (45%) presenting the symptoms as the initial complication. [9] People with VEXAS syndrome typically experience pulmonary involvement, with the most common manifestations being pulmonary infiltration and venous thromboembolism. [1, 10] Less frequent symptoms include interstitial pneumonia and pleural effusion. [10]. Arthritis and chondritis are frequent features of the VEXAS syndrome. [8] Cytopenia and macrocytic anaemia are frequent haematological findings. [1, 9, 11] To rule out VEXAS syndrome, genetic testing should be undertaken for people whose aetiology of these manifestations is unknown.

The care of VEXAS syndrome is challenging and necessitates a multidisciplinary approach from numerous specialized teams due to its heterogeneous manifestations. To date, there are no standardized therapies for VEXAS patients. Generally, the current treatments have two objectives: to prevent systemic inflammation and to eradicate the UBA1-mutated population of hematopoietic cells. In addition, medications for managing the multi-organ manifestations are needed. Patients often respond to high-dose, long-term corticosteroid therapies. However, the side effects after dosage tapering are frequent. [12] This highlights the need for more effective therapy for the disease.

Janus kinase (JAK) inhibitors may be a therapeutic option for VEXAS patients, targeting multiple pathways activating systemic inflammation. Among the JAK inhibitors, the JAK1 and JAK2 inhibitor ruxolitinib was more effective in VEXAS syndrome treatment. Clinical and laboratory responses have been observed in approximately 50% of patients within one month, and the response rates exceeded 80% at the three-month assessment. [13]

Conclusion

Diagnosing VEXAS syndrome can be challenging since it is newly discovered, has overlapping clinical features with other autoinflammatory disorders, and requires high-cost genetic testing. Clinicians should consider VEXAS syndrome in patients with unexplained systemic inflammatory symptoms, particularly when accompanied by peripheral cytopenia and other hematologic disorders. Since the discovery of this syndrome, much ongoing research has aimed to elucidate further the molecular mechanisms linking the UBA1 gene to VEXAS syndrome, with the idea of improving the diagnosis, management, and treatment strategies for individuals affected by this rare condition to improve their quality of life.

Abbreviations

Janus kinase inhibitor (JAK), myelodysplastic syndrome (MDS), post-translational modification (PTM), ubiquitin-like modifier activating the enzyme 1 (UBA1), vacuole, E1 enzyme, X-linked, autoinflammatory and somatic (VEXAS).

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Competing interests

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