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VEXAS Syndrome: An Overlooked Threat

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Autoinflammatory diseases comprise diverse conditions resulting from innate immune system abnormalities. The term describes a broad range of diseases that may manifest with various symptoms across multiple systems. Although the differential diagnosis is complex, the underlying etiology is not impossible to diagnose since autoinflammatory diseases are frequently hereditary; however, several of these diseases are associated with somatic mutations. In this context, Beck et al.[1] identified an adult-onset multisystemic autoinflammatory condition in 2020. A genotype-driven approach detected acquired mutations in the *UBA1* gene as the underlying cause of inflammation in patients who presented with symptoms such as fever, skin lesions, pulmonary infiltrates, nasal or auricular chondritis, venous thromboembolism, or macrocytic anemia. These patients frequently responded to glucocorticoid therapy and met the diagnostic criteria for relapsing polychondritis, Sweet's syndrome, or myelodysplastic syndromes (MDS). This disorder was named as the vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome.[1]

VEXAS syndrome is a late-onset, severe autoinflammatory disorder resulting from somatic mutations in the *UBA1* gene of hematopoietic stem/progenitor cells. The *UBA1* gene encodes the E1 enzyme, which is essential for cellular ubiquitination. Ubiquitination, a type of posttranslational modification, causes the degradation of misfolded proteins. Impaired ubiquitination leads to a proinflammatory hematopoietic milieu and systemic inflammation.[2] Males are mostly affected by VEXAS syndrome because the *UBA1* gene, which is found on the X chromosome, can evade X chromosomal inactivation.[3] Only a few female patients with acquired mosaic X chromosome monosomy or constitutional X chromosome deletion have been reported in the literature.[4] Because *UBA1* gene mutations are somatic, the disease is not hereditary. Over time, these mutations accumulate, causing a delayed onset disease.[2] The estimated prevalence of the disease among men over 50 was 1 in 4269.[5]

VEXAS syndrome induces a multisystem inflammatory response, which may involve the blood, skin, lungs, musculoskeletal system, blood vessels, and eyes (Figure 1). Patients mainly present to the rheumatology, hematology, and dermatology departments with skin lesions, recurrent fever, pulmonary manifestations, arthritis, systemic vasculitis, relapsing polychondritis, ocular manifestations, and weight loss. Thrombocytopenia, leukopenia, thrombosis, and macrocytic anemia are frequent signs of hematological disease.[6,7] A bone marrow aspiration may identify cytoplasmic vacuoles in myeloid and erythroid precursor cells, which is the characteristic which forms the basis for its nomenclature.[1] Reports of the disease's progression to MDS is common and they can occur even during the diagnostic stage.[7] Levels of inflammatory markers including C-reactive protein, erythrocyte sedimentation rate, and ferritin are typically elevated.[6] VEXAS syndrome manifests as a severe and fulminant disease and has been associated with high rates of morbidity and mortality. Significant clinical variability is caused by somatic mutations in the *UBA1* gene, some of which are associated with worse prognoses and more severe disease.[8]

All VEXAS syndrome patients have acquired mutations in the *UBA1* gene, which is believed to be the gold standard for diagnosing this illness.[1] Cytoplasmic vacuolation of myeloid and erythroid precursors on the bone marrow aspirate is a characteristic finding that is observed in nearly all patients. However, cytoplasmic vacuoles can also be detected in various other conditions and may be absent in certain VEXAS cases. Vacuoles are therefore neither pathognomonic, nor is their absence exactly definitive in ruling out the diagnosis.[2] Because VEXAS syndrome is rare and has a diverse clinical presentation, it is frequently misdiagnosed. Before making the diagnosis of VEXAS, the most frequently made diagnoses include relapsing polychondritis, Sweet's syndrome, polyarteritis nodosa, and MDS.[1,9] Although all diagnostic algorithm proposals based on clinical and laboratory features are useful in identifying individuals who should be screened

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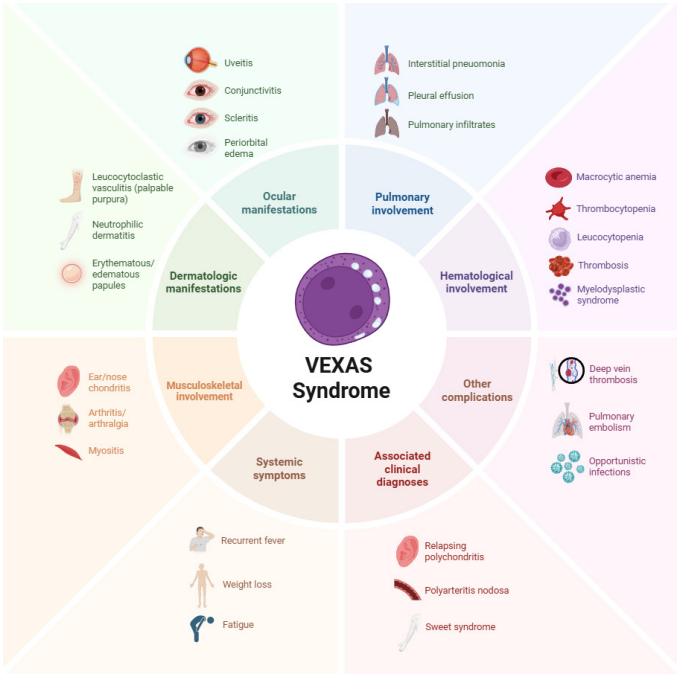

FIG. 1. Clinical spectrum of the VEXAS syndrome.
VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome.

for the *UBA1* gene, their applicability is limited in settings where genetic testing is not appropriate. Artificial intelligence (AI)-based diagnostic models should be crucial in forecasting the diagnosis and prognosis of VEXAS in the future, given the growing application of AI in healthcare and the anticipated increase in the number and characteristics of patients with this newly identified disease.

VEXAS syndrome is challenging to treat, and there are currently no established standard treatment algorithms for it. In VEXAS syndrome, glucocorticoids serve as the initial therapy for managing elevated disease activity and systemic inflammation. Although patients often respond to glucocorticoids, many require long-time, high-dose corticosteroids, as discontinuation or tapering frequently leads to disease relapse. Because of the significant toxicity linked to their prolonged administration, the therapeutic goal is to taper the glucocorticoid dosage while preserving disease control.[10] In this regard, emerging medical treatment options have demonstrated potential in lowering disease activity and mitigating glucocorticoid dependence. Azacitidine, a hypomethylating chemotherapeutic agent, has been proven to produce long-term clinical and genetic remission by eliminating UBA1-mutated cells.[11] Given that azacitidine is the standard treatment for MDS, it may also be a suitable therapeutic option for VEXAS syndrome patients with concomitant MDS.[10] JAK inhibitors are considered a promising therapeutic option in VEXAS syndrome, as they help regulate inflammatory symptoms and lessen the need for corticosteroids.[12] Among various JAK inhibitors, ruxolitinib is more effective in achieving clinical and hematological responses.[10,13] Another therapeutic target may be interleukin-6-mediated inflammation. Tocilizumab and sarilumab have been reported to effectively impede disease activity and progression while enabling a reduction in glucocorticoid dosage.[12] Despite the frequent proposals for anti-IL-1 and anti-tumor necrosis factor medicines, their overall effectiveness was shown to be inferior to that of the aforementioned therapy choices.[12] While non-invasive treatments are considered effective in lowering disease activity and reducing glucocorticoid dosage, it should be noted that none of them offer a cure, with the exception of azacitidine, which targets mutated UBA1 clones in the bone marrow.[11,12] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative technique that is relatively invasive. Allo-HSCT has been linked to significantly high rates of complete response and overall survival.[14]

Patients with VEXAS syndrome are reported to experience severe complications as the disease progresses. Three factors can be utilized to evaluate the origin of these adverse events: uncontrolled disease activity, advanced age of the patients, and treatment-related side effects. Given all these features, the overall susceptibility to infections is elevated in VEXAS patients. Severe opportunistic infections during immunosuppressive treatment are among the main causes of morbidity and mortality.[12] Cytopenia and thrombosis are other frequently reported adverse effects during follow-up and may be associated with the aforementioned three characteristics.[10,15] Acute and chronic graft-versus-host disease is a serious complication of allo-HSCT in VEXAS patients.[14] Overall, physicians should recognize that these patients are at a high risk of adverse events and need close monitoring during therapy.

Although the current literature appears to provide guidance on the efficacy and safety of therapeutic alternatives employed for VEXAS syndrome, there is currently insufficient data to establish a standard treatment algorithm for the disease. Most of our current clinical knowledge about this disease is derived from low-grade evidence studies, such as case reports and case series. Globally, prospective and retrospective cohort studies have begun to emerge from national and international VEXAS cohorts;[6,12,15] however, it is evident that well-designed clinical trials and evidence-based medical studies, such as systematic reviews, are necessary to advance our understanding of the management of this disease in the future.

In conclusion, VEXAS syndrome is a late-onset autoinflammatory disorder caused by somatic mutations in the *UBA1* gene, that presents with systemic inflammation and diverse multisystem manifestations. VEXAS should be suspected and genetic testing should be initiated when patients exhibit symptoms such recurrent fever, skin involvement, lung signs, arthritis, and hematological abnormalities. Given the variability in clinical presentation, diagnosing VEXAS may be challenging. Optimizing patient outcomes requires the creation of a customized treatment plan. A standardized treatment algorithm for VEXAS syndrome is yet to be established and needs more evidence from prospective clinical trials and evidence-based studies.

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