

VEXAS syndrome: A review on clinical manifestations

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ABSTRACT**Background**

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently identified progressive, adult-onset, inflammatory disorder. Somatic mutations in the Ubiquitin-like modifier activating enzyme 1 (UBA1) gene at methionine-41 (p. Met41) were found in the patients. Clinical presentations are not limited to hematological and immunological systems; all organ systems are affected by VEXAS syndrome. The aim of this review is to summarise the scientific evidence accrued from the research studies on VEXAS syndrome, highlighting the clinical features and involvements of different organ systems.

Conclusion

Although the primary manifestations affect the immunological and haematological systems, they gradually affect different other organ systems. Distinct clinical features necessitate ruling out the other possibilities that will be helpful for early diagnosis. More research should be carried out by the global research community in a collaborative manner for a better understanding and early diagnosis of the syndrome.

Keywords

Infiltrates, inflammatory, manifestations, mutation, patients, syndrome, UBA1 gene, vasculitis

Background

The term VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome was first introduced by Beck *et al.* in 2020. Somatic mutations in the Ubiquitin-like modifier activating enzyme 1 (UBA1) gene at methionine-41 (p. Met41) were detected in hematopoietic progenitor cells of patients admitted with systemic inflammatory manifestations [1]. The diagnosis of VEXAS syndrome typically occurs between the ages of 43 and 87, suggesting that the condition tends to manifest later in life or remains undetected [2].

The clinical presentation of VEXAS syndrome is diverse and extends beyond hematologic manifestations. The syndrome is characterized by fever, tiredness, chondritis, relapsing polychondritis (RP), and various forms of vasculitis. Dermatologic manifestations include erythema nodosum, cardiovascular manifestations, pulmonary infiltrations, musculoskeletal symptoms, arthritis and myositis, and gastrointestinal, renal, and nervous system involvement is frequently observed [3–6]. In this context, the purpose of this review is to summarise the scientific evidence accrued from the research studies on VEXAS syndrome, highlighting the clinical features and involvements of different organ systems.

Clinical features

VEXAS syndrome is a debilitating and progressive disorder characterised by the simultaneous involvement of multiple organ systems. Its primary clinical presentations include systemic inflammatory symptoms and haematological abnormalities. The spectrum of clinical indications associated with VEXAS syndrome has progressively broadened since its initial documentation in 2020, in correlation with the escalating number of reported cases. The clinical presentations of VEXAS can resemble various systemic rheumatologic disorders that are commonly associated with myelodysplastic syndromes (MDS). These disorders include small vessel vasculitides, rheumatoid arthritis, seronegative spondyloarthritis, Sweet syndrome, RP, polyarteritis nodosa, and even Behcet's disease [1, 7]. The initial stage of the phenomenon exhibits varying durations, after which more symptoms become observable [8].

Immunological characteristics

In VEXAS patients, a transcriptome study of the peripheral blood has revealed a gene expression pattern that is indicative of the activation of various innate immune mechanisms. In-depth analysis reveals that monocytes and neutrophils exhibit pronounced activation of inflammatory pathways, characterized by elevated expression levels of tumor necrosis factor (TNF), interleukin (IL)-6, IL-8, and interferon (INF)- γ . In VEXAS patients, there is evidence of proinflammatory neutrophil activation, as indicated by the presence of mutant neutrophils that retain their phagocytic function but have an increased propensity for spontaneous

neutrophil extracellular trap creation. The unfolded protein response and integrated stress response pathways were found in myeloid cells, albeit with limited scope [1, 9].

The presence of p.Met41 mutations has been observed to result in a reduction of cytoplasmic UBA1 function. This is achieved through the production of a catalytically defective isoform known as UBA1c. Upon examination of mutant monocytes, it was revealed that the levels of the catalytically competent UBA1b isoform were lowered, although measurable levels of UBA1c were present. This resulted in a subsequent drop in ubiquitylation activity. In contrast, Beck *et al.* and Onuora *et al.* found that peripheral T cells, which only possess the UBA1 mutation in a restricted number of instances, did not show any differences in competent UBA1 isoforms when compared to normal individuals [1, 10–12].

Hematological findings

MDS in patients diagnosed with VEXAS syndrome is well documented. According to Georgin-Lavialle *et al.*, within a study cohort consisting of 116 VEXAS patients, MDS constituted 50% [13]. Pancytopenia and myelodysplasia were reported when severe systemic inflammation worsened. However, these conditions were no longer present after the resolution of the symptoms [14]. This suggests an association between bone marrow dysplasia, cytopenia, and the VEXAS syndrome in the context of severe systemic inflammation. The presence of mutations in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene has been observed in a subset of individuals diagnosed with VEXAS syndrome. These mutations have been implicated in the development of hematologic malignancies, including MDS, in patients with VEXAS syndrome. [9, 14–16].

Obiorah *et al.* reported that macrocytic anaemia was present in all 16 patients, even though their levels of vitamin B12, folate, and copper were within the normal range. Additionally, thrombocytopenia was detected in 8 patients. The majority of patients (80%) had absolute lymphopenia, while half of the patients showed monocytopenia. In contrast, neutropenia was less prevalent, affecting just 2 patients (13%). Circulating immature granulocytic precursors was observed in 11 patients. Cytoplasmic vacuoles and neutrophils with reduced granules and segments were observed in the peripheral smears, and in one instance, the presence of a pseudo-Pelger–Huët-like abnormality was reported [17]. Groarke *et al.* reported the presence of vacuolated monocytes in a total of nine patients [18].

The inflammatory milieu induced by VEXAS may facilitate the development of mutant clones and secondary MDS, or VEXAS itself may contribute to the promotion of MDS. There is also a proposition that the DNMT3A mutation, which exhibits a tight association with MDS, could potentially enhance the proliferation of VEXAS clones and, as previously noted, induce more pronounced inflammatory signs [19, 20].

Individuals with the UBA1 mutation have an increased vulnerability to MDS and other hematologic cancers in

comparison to individuals without this mutation [21]. Consequently, these individuals are more inclined to necessitate regular clinical monitoring. Two investigations have revealed substantial DNMT3A clones in individual patients with MDS. The variable allele frequency (VAF) for these clones was found to be 43% and 24% in the respective patients. Smaller clones were also observed in other MDS patients, specifically in partial tandem duplication (PTD) of the KMT2A (MLL) gene (MLL-PTD).

However, the clinical significance of these smaller clones remains uncertain. The molecular profile observed in VEXAS MDS patients differs from that typically observed in classical MDS. In typical MDS, mutations in myeloid neoplasia genes are frequently observed, vast clones are present, and numerous genes are often implicated. Additional investigations into the clonal genetic composition among individuals diagnosed with VEXAS will offer a valuable understanding of the involvement of inflammation in the pathophysiology of MDS [22, 23].

Thrombotic complications

Thrombotic events have the potential to manifest during the early stages of VEXAS syndrome. In the initial documentation of VEXAS syndrome, venous thromboembolism (VTE) was observed in 44% of the patients [1]. Obiorah *et al.* observed a greater prevalence of thrombotic complications in a majority of the patients (63%) and noted instances of relapse during anticoagulation therapy [17]. The incidence of venous thrombosis was found to be significantly higher compared to arterial thrombosis, with rates of 34.4% and 1.6%, respectively [24].

The dysregulation of ubiquitination, resulting from somatic mutations in UBA1, has been suggested as a significant factor contributing to thrombosis in VEXAS patients. Inflammation, unusual release of cytokines, and the formation of neutrophil extracellular traps (NETs) are the consequences that lead to activate platelets and alter normal hemostasis, dysfunction of endothelial cells, and facilitate the coagulation cascade [17, 24, 25]. So, the utilisation of immunomodulation and immunosuppression could be contemplated as a potential approach for mitigating thrombotic occurrences.

Khider *et al.* failed to identify any UBA1 mutations in a sample of 97 males aged 50 years and older who experienced an initial unprovoked thrombotic event. So, considering UBA1 mutations as a part of routine examination in aged individuals who showed the first unprovoked thrombotic events may be clinically insignificant [25]. Hage-Sleiman *et al.* documented the case of a 67-year-old male suffering from essential thrombocythemia for a duration of 10 years who had a Calreticulin (CALR) mutation. Skin infiltration of non-blastic tumour cells, commonly known as myelodysplasia cutis, was observed. Additionally, the patient was found to have an ad UBA1 mutation. Mutations in UBA1 may confer a significant selection advantage, enabling them to surpass CALR mutant clones. Nonetheless, it is important to note

that this discovery may be coincidental or influenced by the administration of hydroxyurea and thalidomide. Therefore, it is imperative to gather additional observations in order to validate the claim [26].

Vasculitis

VEXAS syndrome frequently presents with vasculitides as a prevalent symptom. The most prevalent manifestation observed is leukocytoclastic vasculitis, which belongs to the category of small-vessel vasculitis [6, 20, 27].

The histopathological examination of skin biopsy specimens obtained from 80–90% of cases showed this specific type of vasculitis. Most patients exhibited angiocentric segmental inflammatory infiltrations, often characterised by the presence of neutrophils and fibrinoid necrosis. In addition to leukocytoclastic vasculitis, IgA vasculitis and antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis were also observed. Still, more research is required to confirm the relationship between these diseases and the pathophysiology of the VEXAS syndrome. In a recent study, nine cases of medium-sized vasculitis were observed [28]. Ramon *et al.* reported that a total of seven patients were diagnosed with polyangiitis nodosa. The occurrence of large vessel vasculitis seems to be infrequent, primarily documented in the context of giant cell arteritis [29].

Polychondritis

Polychondritis, also known as localised chondritis, is a prevalent manifestation of VEXAS syndrome. Auricular or nasal chondritis was reported in approximately 60% of patients, and surprisingly, a majority of them had already fulfilled the diagnostic criteria for RP prior to the confirmation of the VEXAS diagnosis [3, 28].

In many cases, the chondritis observed in individuals diagnosed with VEXAS syndrome exhibits similarities that make it difficult to differentiate from RP. The investigation aimed to assess the prevalence of the UBA1 mutation among individuals diagnosed with recurrent polychondritis. The findings exhibit considerable variability, spanning from 7% to 73% [13, 30, 31]. The cause of the observed heterogeneity in this context remains inadequately comprehended, while it is plausible that the investigations involved patients with RP, and racial disparities have also been proposed as a contributing factor [5, 32].

According to Ferrada *et al.*, considering a decision tree algorithm with high accuracy that takes into account factors such as male gender, mean corpuscular volume greater than 100 fL, and platelet counts less than 200 k/ μ L may lead to a strong recommendation for genetic testing for the UBA1 mutation in order to provide further clarification on the VEXAS condition.

In contrast to individuals with RP lacking the UBA1 mutation, the cohort of patients exhibiting VEXAS syndrome consisted only of males who experienced the onset of the disease throughout the fifth decade of life or beyond. These individuals were presented with symptoms such as

chondritis of the ear, fever, cutaneous manifestations, deep venous thrombosis, and pulmonary infiltrations. Khatri *et al.* observed the same findings, including an increased prevalence of fever (60%), skin lesions (82%), and lung infiltrates (46%). The levels of acute phase reactants were high, and the patients had haematological abnormalities. The absence of chondritis of the airways or costochondritis in the VEXAS patients is a notable observation. The prognosis of the VEXAS subgroup patients was worse, with a reduced response rate to drug therapy, and the mortality rate was five times greater than in patients with RP without the UBA1 mutation [3].

Systemic symptoms

The most prevalent symptom observed in a significant number of patients (74% of cases) was recurrent fever. The presence of additional symptoms such as weight loss, reduced appetite, weariness, and increased levels of acute-phase reactants were also present [33].

Cutaneous manifestations

Skin involvement was a prevalent manifestation observed in the majority of VEXAS syndrome patients. This dermatological manifestation exhibited considerable heterogeneity among patients, approximately 84% of the affected population. Neutrophilic dermatitis, vasculitis, erythematous papules, erythema nodosum, urticaria, periorbital edoema (rarely characterised as nummular and violaceous), and injection-site reactions (particularly following anakinra administrations) were observed, with decreasing frequency. [33, 34]. Patients also presented with eczematous rash and hard, painful infiltrates with symptoms resembling Sweet syndrome [34].

A skin biopsy revealed leukocytoclastic vasculitis involving small to medium arteries, characterised by mixed infiltrations of agranulocytes (lymphocytes) and granulocytes (neutrophils and eosinophils). In certain instances, solitary cell-type infiltrates were seen. Occasionally, patients with VEXAS exhibit dermal infiltrates characterised by monocytic or histiocytoid cells, whereas cutaneous pathology may reveal the presence of lymphocytic vasculitis. The presence of cutaneous nodules accompanied by lymphocytic infiltration, without any indication of neutrophils, eosinophils, or vasculitis, has also been seen. [35].

Zakine *et al.* conducted a study on sequencing and analysis techniques to identify the UBA1 mutation using skin samples obtained from VEXAS patients. Mutations were present in myeloid cells as well. The authors concluded that dermal infiltration is likely attributable to the clonal growth of UBA1 mutant cells rather than being driven by an inflammatory context [34, 36].

Lacombe *et al.* reported that UBA1 mutations were observed in the skin of patients with neutrophilic dermatosis, but on the other hand, cutaneous leukocyte fragmentation vasculitis and spacer lipofuscinosis cases lacked the mutation. So, it

was postulated that UBA1 mutant clones are either absent in non-neutrophilic dermatitis or below the detectable limit. This phenomenon gives rise to various treatment possibilities, including the elimination of the UBA1 mutation or the inhibition of the inflammatory response [37].

Patients with skin lesions necessitate the consideration of VEXAS as a potential differential diagnosis by dermatologists. Consequently, early initiation of genetic testing is crucial to aid in the diagnosis of VEXAS, thereby facilitating prompt and accurate identification of the condition.

Panniculitis and cholesterol emboli in medium-vessel arteries are additional histological manifestations that have been documented by several researchers [2, 15, 31, 36–41]. A considerable number of cells within the infiltrate had positive staining for a cluster of differentiation 68 (CD68), indicating the presence of myeloperoxidase-positive "histiocytoid" myeloid progenitor cells. These cells bear a resemblance to the ones identified in Sweet syndrome, as reported by Sterling in 2022 [34]. The utilisation of paired sequencing analysis has indicated that the cutaneous infiltrates originate from the identical diseased myeloid clone with the UBA1 mutation detected in the bone marrow [36].

Musculoskeletal symptoms

A retrospective study by Ferrada *et al.* showed that among a total of 92 participants who were diagnosed with RP, a p.Met41 mutation on the UBA1 gene was identified in 7 (7.6%) patients. Interestingly, no one diagnosed with VEXAS-associated RP (VEXAS-RP) exhibited symptoms of airway chondritis or costochondritis. The mortality rate was higher among individuals diagnosed with VEXAS-relapsing polychondritis (VEXAS-RP) compared to those without UBA1 mutations, with rates of 27% and 2%, respectively. Individuals with VEXAS-RP exhibited a high prevalence of increased acute phase reactants and hematologic abnormalities. The study offered an algorithm designed to differentiate between patients diagnosed with VEXAS-RP and those diagnosed with RP but without VEXAS. The algorithmic tree consists of a male gender node at the first level, followed by a second node representing mean corpuscular volume greater than 100 fL, and finally, a third node representing platelet count less than 200 k/ μ L.

All patients who met the criteria of the three nodes were accurately diagnosed as VEXAS-RP, while three patients with RP were erroneously classified as having VEXAS-RP. Hence, the algorithm demonstrated a sensitivity of 100% and a specificity of 96% [3].

Subsequently, a retrospective analysis was conducted to compare a cohort of 95 patients diagnosed with VEXAS-RP to a group of 40 patients diagnosed with idiopathic RP. The findings of this study corroborated previous observations that male gender, advanced age, and the occurrence of fever, skin manifestations, ocular involvement, pulmonary infiltration, and heart inflammatory conditions were more prevalent among individuals with VEXAS-RP [5].

The severity of myositis can be significant, as evidenced by pathological observations that reveal myofascitis characterized by the presence of perimysial, epimysial, and fascial macrophagic CD68-positive inflammation. Additionally, histological analysis has identified considerable necrotizing myopathy in individuals diagnosed with VEXAS. Significant intramuscular vacuoles that lacked red rims were observed. The presence of macrophagic infiltrations and necrotizing myopathy was noticeable [8]. Sterling *et al.* reported the observation of intramuscular vacuoles in certain instances [34].

The presence of ocular myositis and its association with chondritis, systemic inflammation, and arthritis suggests the emergence of a novel phenotype within the disease. Reports documented Lymphadenopathy was prevalent in 35% of individuals. It was specifically observed in lymph nodes located in the hilar and mediastinal regions but also manifested in cervical, axillary, abdominal, and inguinal sites. Enlargement of the spleen was seen in 13.8% of the patients [13].

Cardiac manifestations

Al-Hakim *et al.* reported that approximately 10% of patients exhibited cardiac symptoms, specifically myocarditis and pericarditis [42]. Myocarditis has the potential to progress into cardiomyopathy. The occurrence of vasculitis in the coronary arteries can induce ischemic heart disease. It is necessary to consider the possibility of arterial involvement (10.3%) in cases of aortitis (1.7%), aneurysms (3.4%), and vasculitis that was negative for anti-neutrophil cytoplasmic antibodies (ANCA). Approximately one-third of patients have reported instances of venous and arterial thrombosis occurring in different regions, with 60% of these cases observed during the first two years following the onset of symptoms [13].

The incidence of VTE is reported to range from 10% to 56% in various situations [18]. Obiorah *et al.* identified a total of nine patients diagnosed with VEXAS who also presented with VTE. Among these cases, two patients had elevated levels of factor VIII, a known factor linked with an elevated risk of venous thrombosis due to its role in promoting thrombin generation. Additionally, one patient had an elevated blood level of factor IX [17].

In contrast to VTE, arterial thrombosis has a lower prevalence, with fewer than 10% of instances being documented [18]. Considering the observed incidence of venous thrombosis, it was proposed to consider the possibility of VEXAS syndrome in male individuals presenting with unprovoked VTE accompanied by systemic inflammatory symptoms as well as macrocytic anaemia or thrombocytopenia [25].

An analysis of the transcriptome in VEXAS neutrophils indicates an upregulation of gene networks related to proinflammatory cytokines, including tumour necrosis factor, IL-6, and INF- γ . Furthermore, there was an increase in the activity of gene networks associated with complement,

coagulation, hypoxia, JAK/STAT signalling, and reactive oxygen species, all of which are pertinent to thromboinflammation [1, 18].

Neutrophils obtained from patients with VEXAS showed an excessive and spontaneous production of NETs, even without any external stimulus. NETs are a distinct kind of cell death with inflammatory properties, distinguished by the extracellular liberation of DNA in the form of a mesh-like structure. NETs facilitate thrombogenesis by serving as a scaffold for platelet adhesion, presenting coagulation factors, and promoting fibrin production.

Although there are various factors contributing to VTE, it is advisable to consider administering anti-thrombotic prophylaxis to all VEXAS patients, particularly those with further high-risk pro-thrombotic factors, including immobilisation or recent surgery. Subsequent research is required to emphasise the most appropriate preventive measures, taking into account the elevated bleeding risk in these individuals, which can be partially attributed to thrombocytopenia and the use of non-steroidal anti-inflammatory drugs (NSAIDs) for managing the condition [18].

Pulmonary manifestations

Pulmonary manifestations are frequently observed in VEXAS syndrome [43]. Evidence suggests approximately half of the patients exhibit pulmonary infiltrates. Individual cases of bronchiolitis obliterans, pulmonary vasculitis, bronchiectasis, and alveolar haemorrhage are well documented [42, 43]. The prevalence of lung involvement in patients was high, affecting approximately half of the individuals. The most commonly observed illness symptoms in the lungs include pulmonary infiltrates and pleural effusion. Fibrosis, bronchiolitis obliterans, and vasculitis cases are also reported [1, 13, 41].

Gastrointestinal manifestations

The occurrence of gastrointestinal involvement is infrequent, affecting 13.8% of the patient population. The prevailing manifestations were abdominal pain (8.6%), followed by diarrhea (6.9%). Additionally, a smaller proportion of patients had ulcerative lesions accompanied by gastrointestinal bleeding (0.9%). In rare instances, digestive perforation or blockage was observed [13]. Jejunum perforation has been seen in patients undergoing treatment with the anti-IL-6 agent tocilizumab and was also reported [31].

Renal system manifestations

Georgin-Lavialle *et al.* reported that renal involvement was evident in 9.5% of the patient population. The presence of proteinuria, erythrocyturia with dysmorphic erythrocytes, and a gradual deterioration in renal function resulting in kidney dysfunction was observed in VEXAS patients [13]. The existence of endotheliitis, along with medium-sized vessel vasculitis and interstitial infiltration of

myeloperoxidase and CD68 positive myeloid cells, was reported by van der Made *et al.* [31]

Nervous system manifestations

The nervous system manifestations include headaches, cerebrovascular accidents, and meningitis. Involvement of the peripheral nervous system, sensory neuropathy (5.2%), and multiple mononeuropathy (2.6%) were observed [13]. An instance of chronic inflammatory demyelinating polyradiculoneuropathy was reported too. Nerve biopsies revealed demyelination, characterised by thin myelin sheaths along with a concentric proliferation of the glial cells (Schwann cells) and loss of axons [44].

A study by Martín-Nares showed approximately 40% of the VEXAS patients had ocular manifestations. Episcleritis, uveitis, scleritis, orbital mass, and blepharitis were predominant. Inflammation in the orbital and periorbital regions is also mentioned [45]. Orbital inflammation was accompanied by conjunctival chemosis and an edematous eyelid [46].

Conclusion

VEXAS syndrome is a recently identified refractory adult-onset inflammatory syndrome that mostly affects adult males. Although the primary manifestations are associated with immunological and haematological abnormalities, they gradually affect different organ systems like the musculoskeletal, cardiovascular, respiratory, gastrointestinal, renal, nervous, and reproductive systems. Thrombotic events, vasculitis, and polychondritis are observed in the patients. Distinct clinical features necessitate ruling out the other possibilities that will be helpful for early diagnosis. There is no doubt that further investigations should be carried out by the global research community in a collaborative manner for a better understanding and early diagnosis of the syndrome.

Abbreviations

Anti-neutrophil cytoplasmic antibodies (ANCA), Calreticulin (CALR), cluster of differentiation 68 (CD68), DNA (cytosine-5)-methyltransferase 3A (DNMT3A), interferon (INF)- γ , interleukin (IL), methionine-41 (p. Met41), myelodysplastic syndromes (MDS), neutrophil extracellular traps (NETs), non-steroidal anti-inflammatory drugs (NSAIDs), partial tandem duplication (PTD) of the KMT2A (MLL) gene (MLL-PTD) relapsing polychondritis (RP), tumor necrosis factor (TNF), Ubiquitin-like modifier activating enzyme 1 (UBA1), variable allele frequency (VAF), venous thromboembolism (VTE), VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), VEXAS-relapsing polychondritis (VEXAS-RP)

Authors' contribution

- a. Study planning: BR
- b. Review of literature: BR, JO, NF

- c. Manuscript writing: BR, JO, NF
- d. Manuscript revision: BR, JO, NF
- e. Final approval: BR, JO, NF
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