VIEWPOINT

VEXAS syndrome: a diagnostic puzzle

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ABSTRACT
The VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is an adult-onset systemic autoinflammatory condition that is caused by an acquired deficiency of the UBA1 gene in hematopoietic progenitor cells. The clinical spectrum of the VEXAS syndrome currently comprises a broad range of phenotypes such as vasculitis, relapsing polychondritis and Sweet’s syndrome. In the past, VEXAS patients have left clinicians puzzled and the true nature of this disease has not been captured until late 2020. This viewpoint describes the relevant clinical features of the VEXAS syndrome and reviews different approaches to establish the diagnosis. Finally, future directions within the field of systemic inflammatory diseases caused by somatic mutations are being discussed.

“Normals” teach us rules; “outliers” teach us laws.
— Siddhartha Mukherjee
Clinician scientist & Pulitzer prize-winning author

Somatic mutations have been recognised for decades as the cause of cancer and constitutional genetic diseases. However, their role in systemic inflammatory conditions has been less prominent until Beck et al. recently demonstrated that lineage-restricted somatic mutations in UBA1 can cause an adult-onset autoinflammatory disease referred to as the ‘VEXAS syndrome’ (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic). Their discovery disrupted the field of rheumatology by endorsing the perspective that this disease mechanism provides since somatic mutations have been ‘hiding in plain sight’. Subsequently, ‘haematoinflammatory diseases’ have been defined as a new entity.

Additionally, the VEXAS syndrome also teaches a valuable lesson for clinicians who encounter ‘outliers’, patients who challenge our current understanding of physiology, during their everyday practice.

‘CASES ARE NOT SCIENCE’ BUT NEITHER ARE THEY FICTION
Clinicians occasionally face patients who present with atypical clinical features or unusual responses to ‘standard treatment’. Jumping to conclusions is often tempting in these situations and the deliberate evaluation of disconfirming evidence is challenging. In the past, the VEXAS syndrome has left clinicians puzzled: All of us might have concluded that neutrophilic dermatosis (ND) represents a peculiar disease manifestation of relapsing polychondritis (RP) in older males. Just an ‘outlier’ from the average range, which nonetheless belongs to this condition, one might have thought. However, ‘every outlier represents an opportunity to refine our understanding of illness’, as Siddartha Mukherjee outlines in his ‘Laws of Medicine’. While detailed descriptions of single clinical cases played a prominent role in the early times of medicine, they play a minor role in modern evidence-based medicine where randomised controlled trials and meta-analyses provide the highest level of evidence. These approaches dramatically contributed to medical progress without a doubt. They clearly enable predictions for the average patient but may not be applicable to ‘outliers’. Colleagues might argue that ‘cases are not science’ but one might reply that neither are they fiction. This is especially true from the perspective of clinicians who work on a case-by-case basis in their daily routine. Many of us have seen these patients, older males with severe inflammation and multiorgan involvement, but we failed to capture the nature of this disease. Patients who do not fit into our current conceptions of normalcy remind us that medicine still involves imperfect models of physiology. The quest to understand the differences between ‘inliers’ and ‘outliers’ constitutes a path, which ultimately leads to the secrets of medicine.

Ironically, a genotype-first approach, which is blind to the notion of ‘outliers’, led to the initial recognition of the stereotypical VEXAS syndrome phenotype and expanded the disease spectrum in a subsequent observational study.

THE VEXAS SYNDROME: ANOTHER GREAT MIMICKER
‘Great mimickers’ such as syphilis have been known since the early days of medicine. However, the evolution of modern
rheumatology has recently supplemented this list (eg, IgG4-related disease). The inherent systemic nature of rheumatological conditions truly poses a considerable challenge to clinicians.

The clinical spectrum of the VEXAS syndrome currently comprises a broad range of phenotypes including vasculitis\(^1\) (giant cell arteritis, polyarteritis nodosa, ANCA-associated vasculitis, Behçet’s syndrome), RP\(^1\) \(9\) \(10\), Sweet’s syndrome (SwS)\(^1\) \(11\) \(12\), myositis\(^1\) \(13\), lupus-like disease\(^1\) \(14\), tubulointerstitial nephritis\(^1\) \(15\), and haemophagocytic lymphohistiocytosis.\(^1\) \(16\)

The clinical heterogeneity of the VEXAS syndrome certainly undermines early disease recognition and treatment initiation. However, focusing on the key features of this condition will support the diagnostic process.

The reliable diagnosis of the VEXAS syndrome appears to be of relevance for clinicians of multiple disciplines since the prevalence in males older than 50 years of age has been estimated 1 in 4269.\(^6\) The VEXAS syndrome seems to be a relatively common disease that also ‘hides in plain sight’ and many of us will have encountered these patients in our clinical career.

RAISING THE CLINICIAN’S SUSPICION AND CHALLENGING ESTABLISHED DIAGNOSES

When to consider the VEXAS syndrome? Diagnostic guidelines for the VEXAS syndrome have not been established yet. Although the VEXAS syndrome can present with a broad range of clinical findings, there is a stereotypical nature to this condition—as far as we know. Currently, clinicians should consider the VEXAS syndrome in every male older than 50 years of age who presents with systemic inflammation, multiorgan involvement and cytopenia.\(^1\) \(7\) \(17\) However, this condition may represent a ‘late stage’ since Beck et al\(^6\) recently identified a patient with a pathogenic variant prior to disease onset. Whether broad genetic testing of cohorts (possibly selected by artificial intelligence approaches based on patient charts and laboratory results) will translate into daily practice remains of great interest. The relatively specific features of the VEXAS syndrome may allow a sufficient selection of individuals.

The retrospective evaluation of cohorts based on the hallmark features led to the diagnosis of VEXAS in a substantial number of cases.\(^7\) \(18\) However, the diagnosis of the VEXAS syndrome also relies on the clinician’s suspicion in daily practice. Since VEXAS patients may fulfill classification criteria of various systemic inflammatory conditions, we must challenge diagnoses such as ‘refractory giant cell arteritis’ or ‘atypical polyarteritis’ in light of the recent discovery. The diagnosis of VEXAS will not have been established when these patients are admitted to our facilities. Instead, we have to remind and challenge ourselves to capture the true nature of these conditions. Does giant cell arteritis really present with a rash? Is the lung actually a classic target of polyarteritis?

GUIDANCE FOR THE CLINICIAN: SOLVING THE PUZZLE BY STRUCTURED ORGAN ASSESSMENT

Establishing the diagnosis of the VEXAS syndrome can be difficult but structured organ assessment provides guidance when considering differentials. Specifically, the haematopoietic system, skin, lung and cartilage represent the most prominent target organs of the condition (see figure 1).

The VEXAS syndrome (almost) always presents with progressive bone marrow (BM) dysfunction. Evaluation of the complete blood count will certainly demonstrate macrocytic anaemia (MCV>100 fL) as a result of inflammation and/or malignant haematological condition.\(^1\) \(19\) Anaemia may be severe with a need for transfusions in up to two-thirds of the patients.\(^1\) \(19\) Additionally, thrombocytopenia (up to two-thirds) and lymphopenia (up to 80%) may also develop.\(^19\) In this context, BM evaluation is frequently performed in the course of the disease due to progressive cytopenia. Vacuolisation of myeloid and

Figure 1 Diagnostic process of the VEXAS syndrome: (A) Clinical features of the VEXAS syndrome including (B) red flags. Created with BioRender.com. CRP, C-reactive protein. MDS, myelodysplastic syndrome. VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.
The lung represents another target organ and may be affected in at least half of the VEXAS patients. Pulmonary involvement may present with mild or unspecific symptoms such as fever. Chest computed tomography typically includes ground glass opacities and consolidations. On the other hand, pulmonary fibrosis seems to be rare in VEXAS. Bronchoalveolar lavage (BAL) analysis showed predominant lung infiltration of macrophages. In line with findings from histopathological studies of skin lesions, the presence of a corresponding \textit{UBA1} mutation in the BAL has also been confirmed in one patient supporting the notion of direct organ damage by aberrant myeloid clones. As for multiple other rheumatological conditions, failure of antibiotics or diuretics may indicate non-infectious inflammation in these cases.

Chondritis develops in a subset of VEXAS (RP-VEXAS) patients and may resemble idiopathic RP (iRP). Nose chondritis appears to be more common in iRP, while fever, skin lesions, pulmonary involvement and MDS should prompt diagnostic consideration of the VEXAS syndrome. A simple algorithm has been developed to identify RP-VEXAS patients based on sex (male), MCV (>100 fL) and platelet count (<200/µL).

Taken together, the discovery of the VEXAS syndrome significantly affects the diagnostic workup of multiple conditions whereas sex, age and refractory multiorgan disease constitute ‘red flags’ (figure 1). The diagnosis of myeloid neoplasia should include an evaluation of rheumatological features and BM vacuolisation. Patients with suspected SwS or refractory pulmonary infiltrates should also undergo haematological and rheumatological assessments. Finally, VEXAS-RP patients can be distinguished from iRP patients with a clinical algorithm.

The diagnosis of the VEXAS syndrome is exclusively based on the detection of pathogenic \textit{UBA1} variants from peripheral blood. The by far most frequent mutations involve p.Met41 substitutions of \textit{UBA1} exon 3 (usually p.Met41Thr, p.Met41Val, p.Met41Leu). Further mutations affect the splice acceptor site of \textit{UBA1} exon 3. However, previously unknown \textit{UBA1} mutations have been recently discovered and thus, expanding the genotype known to cause the VEXAS syndrome. Clinicians should be aware that a high variant allele frequency (VAF) can be subject to misinterpretation leading to the wrong notion of a hemizygous state and may require sequencing of additional tissues.

The \textit{UBA1} VAF represents a surrogate marker of clonal burden in the VEXAS syndrome and was thought to be associated with disease severity and treatment response. However, multiple studies failed to confirm this notion and molecular investigations have linked genotype-dependent residual \textit{UBA1b} translation to clinical phenotype and disease severity instead. For example, the p.Met41Val variant was associated with decreased survival in this context. On the other hand, increased survival rates were observed for the p.Met41Leu variant.

Currently, the treatment of VEXAS patients is very challenging as the clinical course is often characterised by relapsing and refractory conditions. Therapeutic strategies either ‘target the clone’ (eg, hypomethylating agents, allogeneic stem cell transplantation) or ‘block the cytokine storm’ (eg, glucocorticoids, Janus kinase inhibitors). In addition, supportive measures such as transfusions and infection prophylaxis should be evaluated. However, optimal management of the VEXAS syndrome is still unclear and the available data is based on case series as summarised in a recent systematic review that provides an overview on this issue.
FUTURE DIRECTIONS

The increased recognition of the VEXAS syndrome will enhance disease understanding and may further expand the current phenotype. Targeted and automated evaluation of cohorts with high pretest probability has not been established in routine practice but may represent a valuable approach in the future. For example, deep learning has already been applied in the VEXAS syndrome for the analysis of peripheral blood smears. Meanwhile, clinicians rely on their own suspicion to diagnose the VEXAS syndrome. The targeted re-evaluation of BM or other tissue specimens in individual cases or cohorts with features suggestive of VEXAS syndrome (eg, SwS, polychondritis, inflammatory MDS) will eventually identify additional patients (box 1).

Further systemic inflammatory diseases caused by somatic mutations will certainly be identified in the near future and will lead to the distinction of current entities since multiple rheumatological conditions are solely defined and diagnosed based on clinical features. Therefore, it may be useful to reopen old (unsolved) cases and reassemble the diagnostic puzzle with new pieces.

REFERENCES


