Review

Is it VEXAS or is it vasculitis?

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ABSTRACT

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently defined clinical entity caused by somatic mutations in UBA1*, a gene encoding the ubiquitin-activating enzyme 1, the major enzyme that initiates ubiquitylation. Dysfunction of the ubiquitin pathway results in a treatment-refractory autoinflammatory syndrome associated with haematologic abnormalities. Clinical features are heterogenous but small-, medium- and large-vessel vasculitis have been observed. This review will highlight vasculitic manifestations of VEXAS syndrome and provide recommendations on when to consider VEXAS syndrome among patients presenting with atypical, treatment-refractory, or recalcitrant vasculitic features.*

Introduction

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a newly identified disease caused by somatic alterations in the *UBA1* gene on the X chromosome, which consequently produces a refractory inflammatory state associated with haematologic disturbances. This condition was identified by the National Institutes of Health (NIH) in 2020, using a genotype-driven approach to identify non-synonymous missense mutations in codon 41 of the UBA1 gene resulting in shared clinical features and laboratory parameters. This novel approach allowed for identification of additional patients among existing NIH cohorts, and the index cohort description of 25 patients with VEXAS syndrome outlined its clinical heterogeneity (1). Of note, prior to correctly identifying VEXAS syndrome as the unifying cause of symptoms, 2 patients had been clinically diagnosed as polyarteritis nodosa (PAN), one with giant cell arteritis (GCA), and leukocytoclastic vasculitis had been observed in 28% of the initial cohort. With further case identification and cohort description, it is apparent that vasculitis is a common feature of VEXAS syndrome.

Given the unique clinical course, diminished response to commonly utilised immunosuppressives, and the glucocorticoid dependency observed in VEXAS syndrome, it is key for providers to be able to distinguish between primary vasculitic conditions and VEXAS syndrome. This review will highlight vasculitic manifestations observed in VEXAS syndrome and the key features that help distinguish this condition from other primary rheumatologic or vasculitic disorders.

Vasculitic features observed in VEXAS syndrome

The most common vasculitic feature observed in patients with VEXAS syndrome is cutaneous vasculitis. Small-vessel vasculitis, with histopathologic features consistent with leukocytoclastic vasculitis (LCV), has been reported in multiple cohorts with frequencies ranging from 19–40% (1-6). Urticarial vasculitis, lymphocytic vasculitis with urticaria, eosinophilic vasculitis, and type III cryoglobulinaemic vasculitis with associated digital gangrene have also been reported (2, 4, 6). Nodular-like skin lesions, with histopathologic features of septal panniculitis and medium-vessel vasculitis occur in 10% or fewer of cases (1, 3, 4, 6-8). Some investigators have suggested, however, that the frequency of LCV is overestimated. Zakine *et al*. evaluated 59 patients with VEXAS, in whom they observed leukocytoclasia in 63% of cases where perivascular and periadnexal lymphohistiocytic infiltrate were observed without frank vasculitis (9). Therefore, in circumstances where inflammatory cutaneous lesions are present, leukocytoclasia without overt vas-

culitis is also considered a suspicious feature of VEXAS syndrome.

Pulmonary findings are common in patients with VEXAS syndrome but confirmation of vasculitic involvement by pathology is notably less frequent because of a reduced number of patients undergoing pulmonary biopsy. When biopsies have been performed, a variety of vasculitic features have been described, including medium-vessel vasculitis involving bronchial arteries, lympho-histio-plasmacellular vasculitis of larger arterioles and eosinophilic capillarities (1, 6). Ground-glass opacities (47–87%) and pulmonary consolidations (49–74%) are non-specific but can raise the question of small-vessel pulmonary vasculitis (10, 11). When bronchoalveolar lavage is performed, neutrophilic alveolitis appears to be a frequent and distinguishing feature but diffuse alveolar haemorrhage is exceptionally rare (1, 10-12).

Ocular involvement can occur in approximately 40% of patients with VEXAS and includes both vasculitic and non-vasculitic features. The most frequent and distinctive non-vasculitic ocular VEXAS feature is periorbital oedema (8-12%), which can be unilateral or bilateral and is sometimes misdiagnosed as pre-septal cellulitis (13, 14). Dacryoadenitis and extra orbital myositis have further been described (15). Scleritis and episcleritis have been respectively reported in 8.5–38% and 8.5–12.5% of patients (13-15). Unilateral involvement is more common than bilateral, but regardless of laterality a common feature is a recurrent, relapsing course (15). Thus far, corneal melt and globe rupture have not been described, distinguishing these cases of scleritis and episcleritis from other ocular inflammatory diseases such as severe ANCA-associated vasculitis or rheumatoid arthritis associated ocular disease.

Neurologic manifestations are infrequent in VEXAS. While Georgin-Lavialle *et al*. have reported sensory neuropathy in 5.2% and multiple mononeuropathies in 2.6% of their 116 patient-cohort (13), nerve biopsies confirming vasculitic features have not been reported to date and therefore it remains uncertain whether the neuropathic features are due to vasculitic neuropathy or other etiologic mechanism. One case of presumed CNS vasculitis has been described based on multifocal cerebral white matter changes with gadolinium enhancement of distal vessel walls (16). Angiography did not show stenosis or occlusion of intracranial vessels; however, while treatment with glucocorticoids improved cognitive dysfunction no biopsy confirmation was performed and the patient passed prior to any repeat imaging.

Although small-vessel vasculitis and medium-vessel vasculitis are more frequent, large-vessel vasculitis has also been noted. In the index NIH VEXAS cohort, one patient had biopsy confirmation of temporal artery inflammation; however, characteristics of the biopsy specimen were not provided (1). In a cohort focused on the vasculitic manifestations of patients with VEXAS, a temporal artery biopsy from a patient with cranial symptoms was obtained and showed that neutrophils were the dominant inflammatory infiltrate; an atypical finding since GCA specimens more often are T lymphocyte and macrophage predominant (4). Periarterial thickening, particularly of the carotid arteries, has also been reported (4).

Distinguishing VEXAS fromother primary vasculitides

Due to the heterogeneity of presenting features, prior to correctly diagnosing as VEXAS, patients are often labelled as having one or more primary rheumatic disorder or vasculitide. However, for patients with VEXAS, the presentation features and response to therapy tend to be non-classical for such entities.

In the index NIH VEXAS cohort, 12% of patients were felt to fulfil classification criteria for polyarteritis nodosa (PAN) (1). Given the list of criteria used in the 1990 ACR classification for PAN (Table I) it is understandable why patients may be mislabelled as PAN (17). Particularly, since 36–54% of patient with VEXAS will have unintentional weight loss, 25–40% have a biopsy with small or medium-vessel vasculitis, 44% experience myalgia or musculoskeletal symptoms, 25% demonstrate an elevated creatinine, and 12% have testicular pain or tenderness (4, 5, 12, 13, 18). Livedo reticularis and racemosa are overall uncommon, but one cohort reported its presence in 38% (3/8) of patients with cutaneous features (9). Histopathologic evidence of medium vasculitis has primarily been reported as cutaneous while reports of mesenteric vasculitis are exceedingly rare (19). Distinct differences between classical PAN and VEXAS include a low rate of mononeuropathy, a lack of association with renovascular hypertension, and an absence of medium-vessel visceral arteriographic abnormalities.

VEXAS has been identified as a mimicker of ANCA-associated vasculitis (AAV) and in patients meeting classification criteria for AAV but with additional atypical features or non-classical response to standard of care therapies (7, 8, 12, 20-22). Although renal biopsies, when performed have shown pauci-immune glomerulonephritis in a few cases (21, 22), most have shown histopathologic features that would be considered unusual for AAV. Endothelialitis, intermediate-vessel vasculitis with interstitial nephritis, and renal peritubular capillarities are among the reported findings (6, 20). The majority of patients labelled as AAV with subsequent diagnosis of VEXAS in the literature have been ANCA-negative (6, 8, 12, 22). Among those with positive antibodies discordant features have been observed including c-ANCA with myeloperoxidase (MPO), or proteinase-3 (PR3) positive with negative c-ANCA (8, 23). In patients with concordant positive ANCA serologies (*i.e*. c-ANCA with PR3 or p-ANCA with MPO), titres have been more commonly low or modesta (7, 20, 21).

The updated 2022 ACR/EULAR classification criteria have placed a strong emphasis on ANCA serologies in the classification criteria for granulomatosis with polyangiitis (GPA) [positive c-ANCA or PR3, +5 points, with sum score ≥5 needed for classification] and microscopic polyangiitis (MPA) [positive p-ANCA or MPO, +6 points, with sum score ≥5 needed for classification] (24, 25). Therefore, it is possible for a patient with VEXAS with biopsy confirmed small- or medium-vessel vascu-

Table I. Comparison of disease features in classification criteria for primary vasculitides to VEXAS syndrome.

Polyarteritis nodosa[a]	VEXAS	Granulomatosis with polyangiitis	VEXAS	Giant cell arteritis[b]	VEXAS	Behçet's disease[c]	VEXAS	Cogan's syndrome	VEXAS
Weight loss > 4 kg	+++	Nasal involvement – crusting, ulcer, septal perforation (+3)	(-)	Age ≥ 50 years at time of diagnosis	+++	Ocular lesions (+2)	++	Sudden onset audiovestibular symptoms	++
Livedo reticularis	+	Cartilaginous involvement (+2)	+++	Morning stiffness in shoulders/neck (+2)	+	Genital aphthosis (+2)	±	(hearing loss, tinnitus, vertigo)	
Testicular pain or tenderness	+	Conductive of sensorineural hearing loss (+1)	+	Sudden visual loss (+3)	±	Oral aphthosis (+2)	±	Interstitial keratitis (Typical)	(-)
Myalgia, weakness, or leg tenderness	++	Positive c-ANCA/PR3 (+5)	±	Jaw or tongue claudication (+2)	±	Skin lesions (+1)	++	Uveitis / Scleritis / Episcleritis (Atypical)	++
Mono or polyneuropathy	+	Pulmonary nodules or masses on chest imaging (+2)	±	New onset temporal headache (+2)	±	Neurological manifestations (+1)	±		
Elevated BUN (> 40mg/dl) or creatinine (>1.5 mg/dl)	+	Granuloma on biopsy (+2)	(-)	Scalp tenderness (+2)	±	Vascular manifestations (+1)	++		
Hepatitis B virus	(-)	Nasal/paranasal inflammation on imaging (+1)	(-)	Abnormal temporal artery exam (+2)	±	Positive pathergy test (+1)	(-)		
Arteriographic abnormality (visceral)	(-)	Pauci-immune glomerulonephritis (+1)	±	ESR ≥ 50 mm/hr or CRP ≥ 10 mg/L (+3)	+++				
Biopsy of small or medium-sized artery containing polymorphonuclear cells	++	Positive p-ANCA/MPO (-1)	±	Positive temporal artery biopsy or halo sign on temporal artery ultrasound (+5)	±				
		Blood eosinophilia ≥ $1x10^9$/liter (-4)	(-)	Bilateral axillary involvement (+2)	(-)				
				FDG-PET avidity throughout the aorta (+2)	+				
For classification purposes a patient shall be said to have polyarteritis nodosa if at least 3 of the 10 criteria are present		A score of ≥5 is needed for classification of granulomatosis with polyangiitis		A score of ≥6 points is needed for the classification of giant cell arteritis		A score of ≥4 indicates Behçet's disease		No criteria score has been developed for Cogan syndrome	

+++: > 40%; ++: 20-40%; +10-20%; ±: 1-9%, (-): not reported.
[a]1990 American College of Rheumatology classification criteria.
[b]2022 American College of Rheumatology / European Alliance of Associations for Rheumatology classification criteria.
[c]2014 International Team for the Revision of the International Criteria for Behçet's Disease.

litis to be mis-classified as AAV even if they just have a positive ANCA serology and no associated negative point criteria. This is important because it would be unlikely for ANCA negative patients with VEXAS to fulfil criteria, particularly GPA, based on clinical or radiologic grounds alone. Even though auricular/nasal chondritis [+2 points, GPA] (36–64%) and sensorineural hearing loss [+1 point, GPA] (13-63%) are observed with frequency among VEXAS patients, sinonasal disease is notably uncommon (1, 4, 5, 13, 26). In addition, pulmonary features in VEXAS are typically ground glass opacities (74–87%) rather than nodules (25–47%), and cavitary masses [+2 points, GPA] have not been observed (10, 11). It is critical, therefore, for providers before considering use of GPA or MPA classification criteria to apply these only after carefully considering alternative diagnoses, particularly VEXAS, in order to avoid misclassification and delay in diagnosis.

Among patients with AAV and concomitant VEXAS or patients with VEXAS mimicking AAV, the lack of response to standard of care treatment is a unifying red-flag for considering alternative aetiologies as the cause of the patient's condition. Symptomatic improvement with clinical and biochemical response to prednisone doses of ≥20 mg/day but with loss of disease control when attempting to taper lower than 10-20 mg/day prednisone despite appropriate dosing and timing of rituximab, cyclophosphamide or the combination should strongly raise suspicion for VEXAS syndrome (7, 20-22).

Because of the age of onset of clinical symptoms of VEXAS occurring predominantly in patients 50 years or over, patients are often evaluated for the possibility of GCA. In the NIH index cohort, only 1/25 patients (4%) were diagnosed with GCA, for which the authors required a positive temporal artery biopsy (1). In a cohort of 89 patients with VEXAS, 14 presented with cranial symptoms (headache, vision changes, jaw pain) and overall, 22 patients were evaluated for GCA with temporal artery biopsy. Only 1 patient met ACR 2022 classification criteria for GCA (4). As previously mentioned, the temporal artery biopsy in the patient that met classification criteria for GCA was non-standard with predominant neutrophilic infiltrate. Most patients that have been listed as large-vessel vasculitis have been due to findings on advanced imaging, particularly PET-CT. Bixio *et al*. performed a systematic review of patients with VEXAS for which PET scanning was performed. Among the 27 patients in the literature and 8 patients

from their institution, large-vessel uptake was seen in 23% (27). For patients with abnormal uptake, the thoracic aorta, particularly the ascending, aortic arch and subclavian vessels were the most common locations of abnormality, but temporal artery and carotid uptake have less frequently observed (27). To date, histopathologic analysis from aortic resection surgery of patient with VEXAS and FDG-avid aortitis has not been reported; therefore, it is unknown if the inflammatory signal in the aorta shares a similar neutrophil signature as has been seen in the temporal artery.

The overall prevalence of large-vessel inflammation is unknown as other cohorts have reported aortitis in only 1.7% of cases (13). It is noteworthy that the majority of VEXAS patients reported with aortitis have had at least one or more atypical features that would be considered uncommon for GCA including cytopenias, chondritis, myelodysplastic syndrome, thrombophlebitis, and concomitant small-vessel vasculitis (27-30). Conversely, patients with classical GCA features are unlikely to have evidence of disease causing *UBA1* mutations, as was evidenced by the screening of 612 male patients with GCA without chronic cytopenia failing to find any occult VEXAS patients (23). Therefore, in patients with classical GCA features, the likelihood of VEXAS is low.

Given VEXAS syndrome can involve small, medium, or large vessels, it has been suggested that it should be considered within the spectrum of the variable-vessel vasculitides (4). As such, it is important to consider both the overlapping clinical features and the distinguishing characteristics between VEXAS and other variable-vessel vasculitis conditions such as Behçet's disease (BD) and Cogan syndrome. Unlike PAN, GCA, and AAV which have classification criteria, the International Criteria for Behçet's Disease (ICBD) has outlined diagnostic criteria for Behçet's disease (Table I) (31). In contrast to the International Society Group for Behçet's Disease from 1990 which required a mandatory criterion of recurrent (at least 3 episodes in any 12-month period) oral aphthosis, the ICBD does not have any single mandatory criterion (31, 32). This is pertinent to VEXAS because while oral and genital ulceration have been reported they are overall uncommon among described cohorts (33, 34). Conversely, ocular criteria for BD includes anterior or posterior uveitis, which has been reported in 6.8–38% of patients with VEXAS (13-15). The skin manifestations of VEXAS are most commonly neutrophilic dermatosis, as compared to the more common cutaneous features of BD which are pseudofolliculitis (2, 3, 5, 13). However, erythema nodosum with septal panniculitis on biopsy is a shared feature of both diseases and seen in 10-13% of patients with VEXAS (2, 13). Parenchymal neurologic manifestations associated with BD such as brainstem, cerebral, or spinal cord disease have not been observed in patients with VEXAS syndrome and non-parenchymal neurologic features, such as cerebral venous thrombosis, has only been described in VEXAS patients to date (35). Superficial thrombophlebitis and venous thromboembolism are common to both conditions; however, hepatic vein, superior and inferior vena cava occlusion are common locations of thrombus in BD but would be considered exceptional in VEXAS (13, 35, 36).

Cogan syndrome has not had a formal classification, or diagnostic criteria developed. Early descriptions of this variable-vessel vasculitis employed terminology of typical and atypical designations with the former including ocular findings of non-syphilitic interstitial keratitis (IK), and the latter with non-IK ocular inflammatory features such as uveitis, scleritis, or episcleritis (37). However, while this nomenclature is still used by some, it has not been universally accepted. Beyond ocular inflammation, the other main feature of Cogan syndrome is inner ear disease causing episodes of vertigo, tinnitus, and hearing loss (37, 38). The frequency of inner ear disease has not been systematically reported among VEXAS cohorts, but when described, sensorineural hearing loss has been observed in up to 29% of patients (39). Classical Meniere-like attacks, which are considered characteristic of Cogan syndrome, are not typical of VEXAS syndrome. Nevertheless, given the additional non-ocular and non-otologic features of Cogan syndrome include fever (27%), arthralgia (35%) and aortitis (12%), it is understandable how some providers might consider atypical Cogan syndrome in patients with VEXAS (38).

Figure 1 highlights the major similarities and differences between primary vasculitides and VEXAS syndrome.

When to consider VEXAS syndrome among patients with vasculitis

The main features for providers to be aware of in considering suspicion for VEXAS among patients with vasculitis are the epidemiologic features, concomitant haematologic parameters, and chronic glucocorticoid requirements. In contrast to the aforementioned primary vasculitic disorders, VEXAS syndrome is present near exclusively in male patients because of the location of the *UBA1* gene on the X chromosome. To date, only 13 female patients internationally have been diagnosed with somatic *UBA1* mutations causing symptomatic features of VEXAS syndrome; the majority of which have karyotype 45, XO (40-42). In addition, most patients demonstrating symptoms of VEXAS are over 40 years of age or older, with a mean age of symptom onset between 60–70 years (4, 13). The geographic and ethnic distributions of disease are not yet fully established but reports to date have described higher frequency among white males in Europe and North America, less frequently in Asia, and infrequently among Middle Eastern, African or African American populations (4, 13, 34, 43, 44).

Although patients with chronic rheumatic disease may have or develop cytopenic changes due to disease severity of medication side effects, the haematologic disturbances associated with VEXAS tend to be prevalent and prominent. While not all patients at initial symptom onset have non-nutritional macrocytosis or macrocytic anemia, during the course of disease it is near universal (45, 46). Thrombocytopenia is also frequent (45-69%) but generally not seen in isolation of anemia (47). Monocytopenia, which is observed in over 50% of patients with

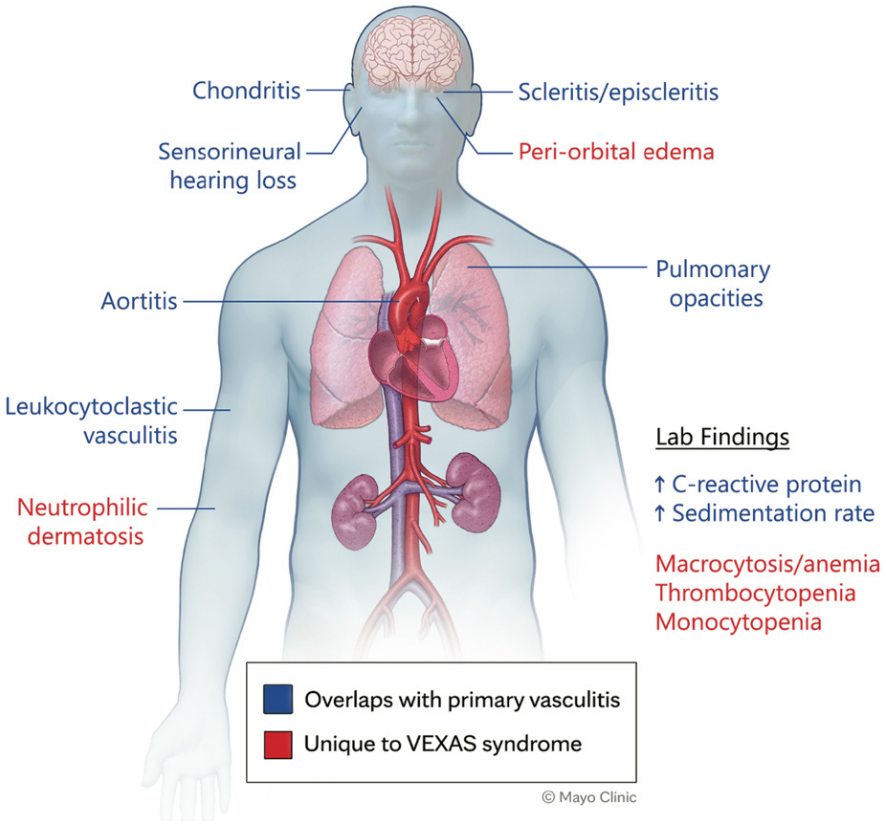

Fig. 1. Overlapping and distinctive features of VEXAS syndrome and primary vasculitis.
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VEXAS, can be a helpful distinguishing parameter as it can be appreciated early in the disease when compared to other cytopenias and is less commonly found among other rheumatic conditions or primary vasculitic diseases (32, 45, 46, 48). Other notable haematologic disturbances seen in association with VEXAS include plasma cell proliferative disorders (monoclonal gammopathy of uncertain significance, plasma cell myeloma; 10–25%) and myelodysplastic syndrome (20–60%) (45, 46). For patients presenting initially to rheumatology, bone marrow biopsies may not yet have been performed, particularly if the peripheral blood cytopenias are not profound. Among patients undergoing bone marrow aspirate and biopsy, findings commonly include hypercellularity, an increased myeloid to erythroid ratio, and megakaryocytic hyperplasia (46). Cytoplasmic vacuoles in erythroid and/or myeloid precursors, while not exclusive to VEXAS, are strongly indicative of this disease and are observed in more than 95% of patients with this condition (46).

Although the inflammatory features associated with VEXAS are heterogenous, a general theme is steroid-responsiveness to doses ≥15-20 mg/day of prednisone (or equivalent) but with relative lack of control of inflammatory features with most conventional and biologic disease-modifying anti-rheumatic drugs considered standard of care for the clinical entities patients with VEXAS may have been originally misclassified or misdiagnosed with (49). Among targeted rheumatologic agents, anti-IL6 and JAK inhibitor therapies have shown partial effect with clinical response seen at 6 months in 26–30% of patients (49). Durable glucocorticoid-free remission in VEXAS patients is often unachievable unless non-rheumatologic therapies are employed such as hypomethylating agents (azacitidine, decitabine) or allogeneic stem cell transplant (50, 51).

Identification of patients with new diagnoses of VEXAS syndrome is highest among cohorts where both inflammatory features and cytopenias are present. A general screen for VEXAS associated UBA1 mutations among patients with non-diagnostic cytopenias showed a low new capture rate of only 0.66% (23). When testing is applied to populations with myelodysplastic syndrome with systemic inflammatory features, rates of identification of new VEXAS diagnosis increase to 12–33% (52, 53). If parameters of chronic inflammation, steroid-dependency, and cytopenias are applied to patients with vasculitis, even higher rates of new VEXAS identification are seen. For example, Muratore and colleagues reviewed 147 patients in their vasculitis clinic to identify patients that fulfilled the following criteria: 1) recurrent fever and at least one of the following – skin involvement, pulmonary infiltrates, ear or nose chondritis, or venous thromboembolism; 2) a C-reactive protein level of >20 mg/L and at least one of the following – macrocytic anaemia, thrombocytopenia, neutropenia or a diagnosis of myelodysplastic syndrome and 3) failure to respond to at least one synthetic or biologic disease-modifying anti-rheumatic drug and needing ongoing glucocorticoid therapy (21). For patients fulfilling these criteria for whom UBA1 testing was completed, 60% were confirmed to have VEXAS syndrome as a cause of their refractory vasculitis.

In summary, rheumatologists in general and vasculitis providers in particular need to be aware that VEXAS syndrome can manifest with large-, medium-, or more commonly small-vessel vasculitis. Providers need to be familiar with the clinical and haematologic parameters that are suggestive of VEXAS and differentiate from other primary vasculitides to avoid misclassification or misdiagnosis. Expert recommendations for who and how to test for VEXAS have been described (47). An international consensus panel has been convened and formal recommendations on diagnosis and management are awaited. In the interim, male patients with 'recurrent,' 'relapsing,' 'recalcitrant,' or 'chronic' inflammation associated with one or more cytopenia or haematologic disturbance, and for whom traditional standard of care therapies are considered ineffective resulting in chronic steroid dependency should strongly trigger suspicion for VEXAS.

References

1. BECK DB, FERRADA MA, SIKORA KA *et al*.: Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. *N Engl J Med* 2020; 383(27): 2628-38. https://doi.org/10.1056/nejmoa2026834
2. HINES AS, MOHANDESI NA, LEHMAN JS *et al*.: Cutaneous involvement in VEXAS syndrome: clinical and histopathologic findings. *Int J Dermatol* 2023; 62(7): 938-45. https://doi.org/ 10.1111/ijd.16635
3. LACOMBE V, BEUCHER A, URBANSKI G *et al*.: Distinction between clonal and paraclonal cutaneous involvements in VEXAS syndrome. *Exp Hematol Oncol* 2022; 11(1): 6. https://doi.org/10.1186/s40164-022-00262-5
4. SULLIVAN M, MEAD-HARVEY C, SARTORI-VALINOTTI JC *et al*.: Vasculitis associated with VEXAS syndrome. *Rheumatology* (Oxford) 2024 Oct 11. https://doi.org/10.1093/rheumatology/keae550
5. TAN IJ, FERRADA MA, AHMAD S, FIKE A *et al*.: Skin manifestations of VEXAS syndrome and associated genotypes. *JAMA Dermatol* 2024; 160(8): 822-29. https://doi.org/10.1001/jamadermatol.2024.1657
6. VAN DER MADE CI, POTJEWIJD J, HOOGSTINS A *et al*.: Adult-onset autoinflammation caused by somatic mutations in UBA1: a Dutch case series of patients with VEXAS. *J Allergy Clin Immunol* 2022;149(1):432-9 e4. https://doi.org/10.1016/j.jaci.2021.05.014
7. AFSAHI V, CHRISTENSEN RE, ALAM M: VEXAS syndrome in dermatology. *Arch Dermatol Res* 2023;315(2):161-64. https://doi.org/10.1007/s00403-022-02340-4
8. MURILLO-CHAVEZ F, ANTIOCHOS B: VEXAS syndrome as a mimicker of ANCA-associated vasculitis. *Rheumatol Adv Pract* 2024; 8(4).. https://doi.org/10.1093/rap/rkae116
9. ZAKINE E, PAPAGEORGIOU L, BOURGUIBA R *et al*.: Clinical and pathological features of cutaneous manifestations in VEXAS syndrome: A multicenter retrospective study of 59 cases. *J Am Acad Dermatol* 2023; 88(4): 917-20. https://doi.org/10.1016/j.jaad.2022.10.052
10. BORIE R, DEBRAY MP, GUEDON AF *et al*.: Pleuropulmonary manifestations of vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome. *Chest* 2023; 163(3): 575-85. https://doi.org/10.1016/j.chest.2022.10.011
11. CASAL MOURA M, BAQIR M, TANDON YK *et al*.: Pulmonary manifestations in VEXAS syndrome. *Respir Med* 2023; 213: 107245. https://doi.org/10.1016/j.rmed.2023.107245
12. KOURANLOO K, ASHLEY A, ZHAO SS, DEY M: Pulmonary manifestations in VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome: a systematic review. *Rheumatol Int* 2023;43(6):1023-32. https://doi.org/10.1007/s00296-022-05266-2
13. GEORGIN-LAVIALLE S, TERRIER B, GUEDON AF *et al*.: Further characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients. *Br J Dermatol* 2022; 186(3): 564-74. https://doi.org/10.1111/bjd.20805
14. VITALE A, CAGGIANO V, MARTIN-NARES E *et al*.: Orbital/ocular inflammatory involvement in VEXAS syndrome: Data from the international AIDA network VEXAS registry. *Semin Arthritis Rheum* 2024; 66: 152430. https://doi.org/10.1016/j.semarthrit.2024.152430
15. ABUMANHAL M, LEIBOVITCH I, ZISAPEL M, EVIATAR T, EDEL Y, BEN CNAAN R: Ocular and orbital manifestations in VEXAS syndrome. *Eye* (Lond) 2024; 8(9): 1748-54. https://doi.org/10.1038/s41433-024-03014-3
16. LANGLOIS V, CURIE A, DEMAS A *et al*.: Central nervous system vasculitis in VEXAS syndrome: A rare involvemen. *Clin Neurol Neurosurg* 2024; 242: 108351. https://doi.org/10.1016/j.clineuro.2024.108351
17. LIGHTFOOT RW, JR., MICHEL BA, BLOCH DA *et al*.: The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990; 33(8): 1088-93. https://doi.org/10.1002/art.1780330805
18. KALANTARI K, SULLIVAN MM, HERNANDEZ LPH *et al*.: Acute kidney injury, an underrecognized feature of VEXAS syndrome. *Rheumatology* (Oxford) 2024 Aug 26. https://doi.org/10.1093/rheumatology/keae465
19. ITAGANE M, TERUYA H, KATO T *et al*.: Clinical images: VEXAS syndrome presenting as treatment-refractory polyarteritis nodosa. *Arthritis Rheumatol* 2022; 74(11): 1863-64. https://doi.org/10.1002/art.42257
20. KOSTER MJ, WARRINGTON KJ: VEXAS within the spectrum of rheumatologic disease. *Semin Hematol* 2021; 58(4): 218-25. https://doi.org/10.1053/j.seminhematol.2021.10.002
21. MURATORE F, MARVISI C, CASTRIGNANO P *et al*.: VEXAS syndrome: a case series from a single-center cohort of Italian patients with vasculitis. *Arthritis Rheumatol* 2022; 74(4): 665-70. https://doi.org/10.1002/art.41992
22. ROSS C, ELFASSY HL, MAKHZOUM JP: Somatic mutation in UBA1 and ANCA-associated vasculitis. *J Rheumatol* 2021; 48(10): 1626-27. https://doi.org/10.3899/jrheum.210149
23. POULTER J, CONSORTIUM UV, MORGAN A, CARGO C, SAVIC S: A high-throughput amplicon screen for somatic UBA1 variants in cytopenic and giant cell arteritis cohorts. *J Clin Immunol* 2022; 42(5): 947-51. https://doi.org/10.1007/s10875-022-01258-w
24. ROBSON JC, GRAYSON PC, PONTE C *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Arthritis Rheumatol* 2022; 74(3): 393-99. https://doi.org/10.1002/art.41986
25. SUPPIAH R, ROBSON JC, GRAYSON PC *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. *Ann Rheum Dis* 2022; 81(3): 321-26. https://doi.org/10.1136/annrheumdis-2021-221796
26. KOSTER MJ, KOURELIS T, REICHARD KK *et al*.: Clinical heterogeneity of the VEXAS syndrome: a case series. *Mayo Clin Proc* 2021; 96(10): 2653-59. https://doi.org/10.1016/j.mayocp.2021.06.006
27. BIXIO R, BINDOLI S, MORCIANO A *et al*.: The role of (18)FDG-PET imaging in VEXAS syndrome: a multicentric case series and a systematic review of the literature. *Intern Emerg Med* 2024; 19(8): 2331-45. https://doi.org/10.1007/s11739-024-03763-9
28. BORET M, MALFAIT T: Case report: diagnosis of VEXAS syndrome in a patient with therapy-resistant large vessel vasculitis. *Acta Clin Belg* 2024;79(2):143-47. https://doi.org/10.1080/17843286.2024.2312627
29. GRAMBOW-VELILLA J, BRAUN T, POP G, LOUZOUN A, SOUSSAN M: Aortitis PET imaging in VEXAS syndrome: a case report. *Clin Nucl Med* 2023; 48(2):e67-e8. https://doi.org/10.1097/rlu.0000000000004506
30. MIDTVEDT O, STRAY-PEDERSEN A, ANDERSSON H *et al*.: A man in his sixties with chondritis and bone marrow failure. *Tidsskr Nor Laegeforen* 2022; 142(4). https://doi.org/10.4045/tidsskr.21.0370
31. INTERNATIONAL TEAM FOR THE REVISION OF THE INTERNATIONAL CRITERIA FOR BEHÇET'S D: The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 2014; 28(3): 338-47. https://doi.org/10.1111/jdv.12107
32. CRITERIA FOR DIAGNOSIS OF BEHÇET'S DISEASE: International Study Group for Behçet's Disease. *Lancet* 1990; 335(8697): 1078-80.
33. DIARRA A, DUPLOYEZ N, FOURNIER E *et al*.: Successful allogeneic hematopoietic stem cell transplantation in patients with VEXAS syndrome: a 2-center experience. *Blood Adv* 2022; 6(3): 998-1003. https://doi.org/10.1182/bloodadvances.2021004749
34. MATSUMOTO H, ASANO T, TSUCHIDA N *et al*.: Behçet's disease with a somatic UBA1 variant: Expanding spectrum of autoinflammatory phenotypes of VEXAS syndrome. *Clin Immunol* 2022; 238: 108996. https://doi.org/10.1016/j.clim.2022.108996
35. ZISAPEL M, SEYMAN E, MOLAD J *et al*.: Case report: Cerebral sinus vein thrombosis in VEXAS syndrome. *Front Med* (Lausanne) 2024; 11: 1377768. https://doi.org/10.3389/fmed.2024.1377768
36. KUSNE Y, GHORBANZADEH A, DULAU-FLOREA A *et al*.: Venous and arterial thrombosis in patients with VEXAS syndrome. *Blood* 2024; 143(21): 2190-200. https://doi.org/10.1182/blood.2023022329
37. HAYNES BF, KAISER-KUPFER MI, MASON P, FAUCI AS: Cogan syndrome: studies in thirteen patients, long-term follow-up, and a review of the literature. *Medicine* (Baltimore) 1980; 59(6): 426-41.
38. GLUTH MB, BARATZ KH, MATTESON EL, DRISCOLL CL: Cogan syndrome: a retrospective review of 60 patients throughout a half century. *Mayo Clin Proc* 2006; 81(4): 483-88. https://doi.org/10.4065/81.4.483
39. FERRADA MA, SAVIC S, CARDONA DO *et al*.: Translation of cytoplasmic UBA1 contributes to VEXAS syndrome pathogenesis. *Blood* 2022; 140(13): 1496-506. https://doi.org/10.1182/blood.2022016985
40. BARBA T, JAMILLOUX Y, DUREL CA *et al*.: VEXAS syndrome in a woman. *Rheumatology* (Oxford) 2021; 60(11): e402-e3. https://doi.org/10.1093/rheumatology/keab392
41. BOURGUIBA R LV, JACHIET V, COMONT T *et al*.: Clinical and biological features of VEX-

AS syndrome in women: study of 9 French cases compared with 263 men. *Arthritis Rheumatol* 2025.
42. STUBBINS RJ, MCGINNIS E, JOHAL B *et al*.: VEXAS syndrome in a female patient with constitutional 45,X (Turner syndrome). *Haematologica* 2022; 107(4): 1011-13. https://doi.org/10.3324/haematol.2021.280238
43. KIRINO Y, TAKASE-MINEGISHI K, TSUCHIDA N *et al*.: Tocilizumab in VEXAS relapsing polychondritis: a single-center pilot study in Japan. *Ann Rheum Dis* 2021; 80(11): 1501-2. https://doi.org/10.1136/annrheumdis-2021-220876
44. TSUCHIDA N, KUNISHITA Y, UCHIYAMA Y *et al*.: Pathogenic UBA1 variants associated with VEXAS syndrome in Japanese patients with relapsing polychondritis. *Ann Rheum Dis* 2021; 80(8): 1057-61. https://doi.org/10.1136/annrheumdis-2021-220089
45. OBIORAH IE, PATEL BA, GROARKE EM *et al*.: Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. *Blood Adv* 2021; 5(16): 3203-15. https://doi.org/10.1182/bloodadvances.2021004976
46. OLTEANU H, PATNAIK M, KOSTER MJ *et al*.: Comprehensive morphologic characterization of bone marrow biopsy findings in a large cohort of patients with VEXAS syndrome: a single-institution longitudinal study of 111 bone marrow samples from 52 patients. *Am J Clin Pathol* 2024; 161(6): 609-24. https://doi.org/10.1093/ajcp/aqad186
47. KOSTER MJ, LASHO TL, OLTEANU H *et al*.: VEXAS syndrome: clinical, hematologic features and a practical approach to diagnosis and management. *Am J Hematol* 2024; 99(2): 284-99. https://doi.org/10.1002/ajh.27156
48. GUTIERREZ-RODRIGUES F, KUSNE Y, FERNANDEZ J *et al*.: Spectrum of clonal hematopoiesis in VEXAS syndrome. *Blood* 2023; 142(3): 244-59. https://doi.org/10.1182/blood.2022018774
49. HADJADJ J, NGUYEN Y, MOULOUDJ D *et al*.: Efficacy and safety of targeted therapies in VEXAS syndrome: retrospective study from the FRENVEX. *Ann Rheum Dis*. 2024; 83(10): 1358-67. https://doi.org/10.1136/ard-2024-225640
50. DIAS AL, GROARKE EM, HICKSTEIN D, PATEL B: Role of allogeneic hematopoietic cell transplantation in VEXAS syndrome. *Ann Hematol* 2024; 103(11): 4427-36. https://doi.org/10.1007/s00277-024-05942-2
51. MANGAONKAR AA, LANGER KJ, LASHO TL *et al*.: Reduced intensity conditioning allogeneic hematopoietic stem cell transplantation in VEXAS syndrome: Data from a prospective series of patients. *Am J Hematol* 2023; 98(2): E28-E31. https://doi.org/10.1002/ajh.26786
52. DELPLANQUE M, AOUBA A, HIRSCH P *et al*.: USAID associated with myeloid neoplasm and VEXAS syndrome: two differential diagnoses of suspected adult onset still's disease in elderly patients. *J Clin Med* 2021; 10(23). https://doi.org/10.3390/jcm10235586
53. ZHAO LP, SCHELL B, SEBERT M *et al*.: Prevalence of UBA1 mutations in MDS/CMML patients with systemic inflammatory and auto-immune disease. *Leukemia* 2021; 35(9): 2731-33. https://doi.org/10.1038/s41375-021-01353-8