Mini-Review

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A neurologist's guide to VEXAS syndrome: Differentiating somatic autoinflammation from autoimmune mimics

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SUMMARY: This review characterizes VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) as a prototype of adult-onset autoinflammation that challenges traditional autoimmune paradigms. Driven by constitutive activation of innate myeloid cells *via* Ubiquitin-Like Modifier Activating Enzyme 1 (UBA1) mutations, VEXAS affects the nervous system in approximately 6–10% of cases. We identify the peripheral nervous system as the primary target (70%), typically manifesting as refractory axonal polyneuropathy, while central involvement may present as neutrophilic meningoencephalitis. Crucially, we highlight the "hematologic paradox"—hyperinflammation co-occurring with macrocytic anemia rather than thrombocytosis—as the key biomarker distinguishing VEXAS from vasculitic mimics, necessitating early genetic sequencing for targeted clone suppression.

Keywords: VEXAS syndrome, UBA1, neuroinflammation

1. Introduction

Adult-onset neuroinflammation is framed through the lens of autoimmunity, where a breach in adaptive immune tolerance leads to T-cell or antibody-mediated attacks against specific neural antigens. VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome challenges this established paradigm. It represents a distinct category of autoinflammatory disease driven not by antigen recognition, but by the constitutive, innate activation of myeloid cells due to somatic mutation (*1,2*).

The discovery of somatic mosaicism confirmed that acquired mutations may drive this adult-onset disease, which may exhibit with neurological symptoms that mimic traditional inflammatory disorders (*3*). Neurologists may misdiagnose VEXAS as 'atypical vasculitis' and initiate lymphocyte–depleting therapies that are mechanistically ineffective against an innate myeloid clone.

Given the rarity of typical diagnostic clues in neurological presentations, VEXAS remains critically underdiagnosed (*1*). This mini-review addresses the need to provide neurologists with a specific diagnostic framework in order to identify these patients (*4*). Rather than an exhaustive systematic analysis, this article provides a focused conceptual synthesis and clinical perspective. By defining the specific clinical and hematological signatures of this UBA1–driven disease, we propose a stepwise diagnostic algorithm to distinguish neuro VEXAS syndrome from its autoimmune and rheumatological mimics (*5*).

2. Scope of the review

This mini–review synthesizes literature published between January 2020 and December 2025, coinciding with the initial description of VEXAS syndrome. To ensure clinical relevance, we prioritized the analysis of primary data from large, multi–center retrospective cohorts and mechanistic studies over isolated case reports. The thematic scope focuses on defining neurological phenotypes, genotype-phenotype correlations, and treatment outcomes. Emphasis was placed on studies elucidating the "hematological paradox" and the distinction between clonal inflammation and classical autoimmunity. The final synthesis integrates these findings to establish a practical diagnostic framework for the practicing neurologist.

3. Genetic abnormalities and pathophysiological mechanism

The primary molecular mechanism underlying VEXAS

syndrome is a disruption in the ubiquitin-proteasome system. This dysfunction stems from the Ubiquitin-Like Modifier Activating Enzyme 1 (UBA1) gene, which is responsible for producing the E1 enzyme—a critical component in flagging aberrant proteins for elimination (*2*). Somatic mutations in VEXAS are predominantly restricted to codon 41 (p.Met41). These mutations specifically disrupt the production of the cytoplasmic variant, UBA1b, but leave the nuclear variant, UBA1a, unaffected (*1*). This isoform causes a severe impairment of cytoplasmic ubiquitination capacity, leading to the accumulation of pathogenic protein aggregates, while DNA repair and other nuclear functions remain relatively intact (*6,7*).

Consequently, this proteostatic dysfunction triggers an active maladaptive stress response. The accumulation of ubiquitination-deficient proteins triggers the Unfolded Protein Response (UPR), a conserved stress pathway intended to restore homeostasis (*8*). In myeloid cells, however, this stress response results in constitutive, antigen-independent activation of the NLRP3 inflammasome. Unlike autoimmune responses which require specific antigen recognition, VEXAS myeloid clones are intrinsically driven to a hyper-inflammatory state solely by proteostatic stress. Consequently, these macrophages exhibit sustained, constitutive activation, explaining why therapies targeting antigen presentation are ineffective (*9*). As a result, a hyper-inflammatory phenotype characterized by the dysregulated secretion of IL–1β, IL-6, and tumour necrosis factor–alpha (TNFα), drives systemic manifestations and neuroinflammation, in the absence of infection or other triggers (*10,11*) (Figure1).

On a cellular level, the UBA1 mutation exerts a differential effect across cell lines. Lymphocytes are highly sensitive to ubiquitin deficiency; they cannot sustain the metabolic stress of the UPR and undergo rapid apoptosis, resulting in the profound lymphopenia seen in more than 90% of patients (*12*). Conversely, myeloid cells are resistant to this apoptotic signal. Adaptive responses lead to sequestering defective proteins into cytoplasmic vacuoles, thus entering a state of senescent hyperinflammation (*13*). The precise mechanism by which UBA1–mutated clones breach the blood-brain barrier (BBB) is not yet fully understood (*14*). Contemporary evidence suggests that CNS involvement is not exclusively attributed to cytokine-induced endothelial activation; an active cellular (mainly neutrophilic) invasion analogous to the syndrome's cutaneous lesions (neutrophilic dermatosis) constitutes an additional contributor (*15,16*). Moreover, UBA1-mutated neutrophils exhibit delayed apoptosis and prolonged survival that sustain their accumulation in tissues (*1,13*). Histopathological analysis of skin tissues frequently reveals perivascular infiltrates of mature neutrophils admixed with $CD163^{+}$ myeloid precursors (*15*). We hypothesize that a similar 'neuro-neutrophilic' mechanism may drive the CNS pathology, where long-lived myeloid clones cross the BBB, resulting in neutrophilic pleocytosis and parenchymal damage distinct from the lymphocytic inflammation seen in autoimmune CNS disorders (*17,18*).

While the loss of the UBA1b isoform is the unifying mechanism, the clinical trajectory is heavily influenced by the specific amino acid substitution at codon 41. Current literature stratifies risk based on the specific amino acid substitution (*1,6*). The p.Met41Val (Valine) variant drives the most aggressive hematologic

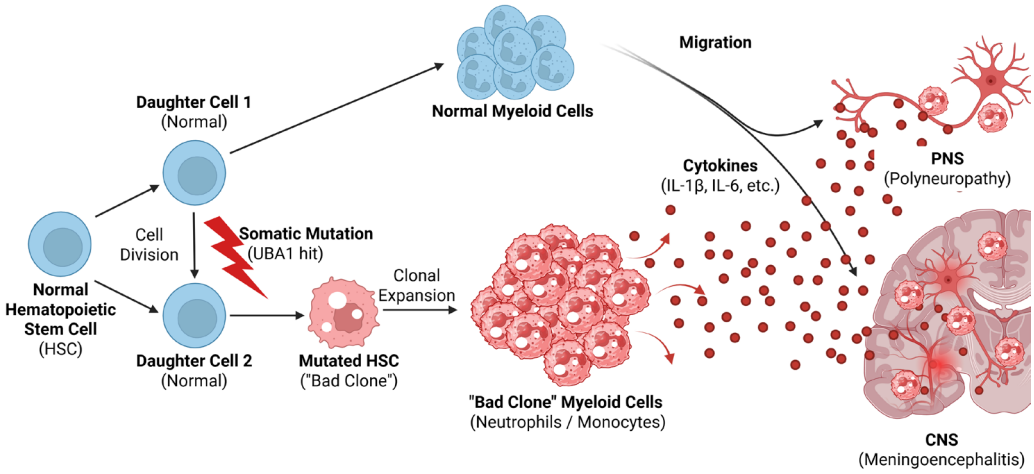

Figure 1. Pathogenesis of Somatic Mosaicism in Neuro–VEXAS. Schematic illustration of the pathogenic clonal expansion. A single hematopoietic stem cell (HSC) acquires a somatic UBA1 mutation, leading to the expansion of inflammatory myeloid cells (neutrophils and monocytes, red). These pathogenic clones hyper–secrete proinflammatory cytokines (*e.g.*, IL–1β, IL–6) and migrate into neural tissue. The diagram illustrates the dual impact on the nervous system: invasion of the Central Nervous System (CNS) resulting in meningoencephalitis, and infiltration of the Peripheral Nervous System (PNS) causing the prevalent vasculitic polyneuropathy. *Note*: This figure was created using BioRender.com. *Abbreviations*: CNS, Central Nervous System; HSC, Hematopoietic Stem Cell; IL, Interleukin; PNS, Peripheral Nervous System; UBA1, Ubiquitin–like modifier activating enzyme 1.

phenotype, correlating with transfusion dependence and significantly reduced overall survival (5–year survival ~50%) (*6,19*). Consequently, Valine positivity serves as a critical prognostic marker for early mortality, necessitating aggressive hematologic intervention (*e.g.*, transplantation). However, no data currently confirm that Valine carriers are at higher risk for neurological manifestations (*20*). In contrast, the p.Met41Leu (Leucine) and p.Met41Thr (Threonine) variants are associated with superior survival but are strongly linked to cutaneous neutrophilic dermatosis (Sweet Syndrome) (*19*). Nevertheless, caution is needed to avoid mistaking the 'mild' mortality profile of Leucine for a lack of neuro-inflammatory risk; these patients may remain prone to tissue infiltration despite preserved marrow function.

In summary, the specific UBA1 mutations dictate a unique pathophysiology where intrinsic myeloid activation drives both systemic hyperinflammation and simultaneous bone marrow stress. This sets the biological foundation for the 'hematologic paradox', establishing a direct causal link between the somatic clonal expansion in the marrow and the subsequent aggressive infiltration of the central and peripheral nervous systems.

4. Neurological manifestations of VEXAS syndrome

Diagnosing VEXAS syndrome depends on identifying a hallmark triad of symptoms that allows distinction from systemic autoimmune disorders and vasculitides. A male adult with neurologic defects and refractory macrocytosis, chondritis, and an abnormal bone marrow biopsy is a classic case for a VEXAS diagnosis. The patient typically presents with refractory macrocytosis (MCV > 100 fL) which may be thought to result from myelodysplastic syndromes (MDS), which is different than the normocytic anemia typical in cases of chronic disease seen in patients with autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) (*15*). Inflammation of the auricular and nasal cartilage (chondritis) occurs in 50-60% of patients, presenting as saddle-nose deformity that can mimic relapsing polychondritis (*6*). Bone marrow biopsy reveals vacuolization of myeloid and erythroid precursor cells, the characteristic sign of the disease often underreported by pathologists unless specifically prompted (*1,19*).

Neurological evaluation frequently reveals involvement of the peripheral nervous system (PNS), affecting approximately 70% of patients with neurological manifestations (*20*). The pathologic process occurs due to a neutrophilic vasculitis of the vasa nervorum; thus, there is an ischemic damage to the nerves. This will produce clinical symptoms that resemble those found in Polyarteritis Nodosa (PAN), or ANCA–associated vasculitis. These symptoms are those of a length dependent, axonal sensorimotor polyneuropathy (*ie*: progressively distal weakness, and progressive distal sensory loss). While this is the classic presentation for these patients, a significant proportion of patients present with a mononeuritis multiplex (*17,21*).

With regards to cranial neuropathies, the facial and vestibulocochlear nerves are preferentially affected. Cranial involvement is often contiguous to chondritis; inflammation of the ear cartilage or nasal structures extends locally to entrap or inflame adjacent nerves. Consequently, the sudden onset of facial palsy or sensorineural hearing loss in a middle–aged man or older with presumed Relapsing Polychondritis (RP) should prompt screening for UBA1 mutations (*22*). Notably, unlike Guillain–Barré syndrome or chronic demyelinating distal polyneuropathy, neuropathy in VEXAS is primarily axonal and is often refractory to intravenous immunoglobulin. Treatment necessitates suppression of the myeloid clone (*23*).

CNS manifestations are present in approximately 10–30% of cases and although less frequent than PNS involvement, they are commonly severe and indicative of advanced disease stage (*6,19,20*). Unlike the lymphocyte–predominant type of inflammation seen in paraneoplastic syndromes or autoimmune encephalitis, VEXAS produces a neutrophilic meningoencephalitis. The patients usually begin by presenting with symptoms of a subacute decline in cognition and/or mental status and also develop seizures. Lumbar punctures performed on these patients will often show evidence of neutrophilic pleocytosis as well as increased levels of cerebrospinal fluid (CSF) protein and normal levels of glucose; this allows for distinguishing from those encephalitides that are caused by viruses or autoimmunity, where the pleocytosis is characterized by an elevation in the number of lymphocytes (*18,24*).

Rarely, VEXAS syndrome may present pseudotumoral CNS involvement; however, evidence for this phenotype is currently limited to isolated case reports, and clinicians should interpret this association with caution. A recent study reported an individual with significant central nervous system (CNS) lesions that demonstrated ring enhancement and were producing mass effect. The clinical presentation of this case of tumefactive demyelination mimicked that of high-grade glioma and primary CNS lymphoma on initial imaging studies; therefore, a brain biopsy was performed to rule out neoplastic glial cells and confirm the presence of neutrophils instead of lymphocytes (*25*). Neurological symptoms of the disease can also involve the orbits; and thus cause orbital myositis, or dacryoadenitis. The patient develops double vision (diplopia), swelling of the eye (proptosis) and paralysis of one or more of the eye muscles (ophthalmoplegia), and this can mimic the symptoms of IgG4–Related Disease or Tolosa–Hunt Syndrome, especially in the case of the RP phenotype (*19*). In addition, the patient could have various other symptoms such as focal brain stem dysfunction; these include ataxia, multidirectional nystagmus and cranial neuropathy of one or more cranial nerves, which is due

to neutrophilic rhombencephalitis, either isolated or associated with an episode of meningitis (*20*).

Cerebrovascular consequences of the autoinflammatory syndrome may be equally devastating (*26*). Inflammation and activation of the coagulation cascade, anemia and anti–phospholipid antibodies may predispose to thrombosis (*27*). Moreover, the senescent, hyper–inflammatory myeloid clones may infiltrate cerebral vessels, leading to localized vessel wall inflammation and constriction mediated by hyperactive neutrophils, resulting in encephalopathic changes or lacunar events (*28*). While true CNS vasculitis affecting large or small vessels is uncommon compared to PNS involvement, it constitutes a documented phenotype of the syndrome, specifically identified in vasculitis-focused cohorts (*23*). Stroke in VEXAS patients is usually attributed to lacunar infarcts, and the syndrome is associated with cerebral small vessel disease (*29*). Cerebral venous thrombosis has been reported in a minority of VEXAS cases (*30*), though this is currently based on single case observations rather than large cohort data.

Magnetic resonance imaging (MRI) findings are nonspecific and highly variable, displaying T2/FLAIR hyperintensities in the periventricular white matter and brainstem which represent sites of active neutrophilic invasion (*14,31*). The imaging technique 18F–fluorodeoxyglucose (FDG)–PET/CT has emerged as the superior modality for visualizing sites of active inflammation (*32*). Intense, symmetric tracer uptake in the ear and nose cartilage is typical for the disease. Patchy vascular uptake is also frequently demonstrated (*19*). FDG–PET evaluation has been suggested for patients with unexplained encephalopathy and a negative MRI evaluation in search of subclinical systemic inflammation that may lead to VEXAS diagnosis (*16*).

Ultimately, whether manifesting as meningoencephalitis, cranial neuropathy, or axonal polyneuropathy, these neurological deficits are direct extensions of the underlying myeloid clonality. Therefore, diagnostic suspicion must be immediately elevated when severe neuro-inflammatory syndromes are paradoxically coupled with macrocytosis or progressive cytopenias, rather than the reactive thrombocytosis typical of classical autoimmune mimics.

5. Differential diagnosis and mimics

VEXAS syndrome patients are frequently misdiagnosed as people with a primary rheumatologic disorder. A major driver of this misdiagnosis is that these patients often fulfill the classification criteria for Polyarteritis Nodosa (PAN), RP or Giant Cell Arteritis (*6,14,19*). In addition, VEXAS patients frequently exhibit non-pathogenic autoantibodies, such as anti-nuclear antibodies and lupus anticoagulant, leading to misdiagnoses such as SLE or primary antiphospholipid syndrome in the setting of stroke. However, these serologies often represent a dysregulated immune milieu rather than a primary autoimmune diathesis (*27*). Additionally, approximately 50% of patients will meet criteria for MDS during the disease course (*33*). Unexplained neurological deterioration may serve as the primary catalyst for genetic investigation, ultimately unmasking the somatic mutation in cases that otherwise lack classic diagnostic triggers (*25*).

One of the most significant clinical characteristics that distinguish VEXAS from other autoimmune vasculitis syndromes is that systemic inflammation and bone marrow failure occur together. Typical systemic vasculitides (like PAN or GCA) have a reaction to the systemic inflammation of the bone marrow causing it to produce an acute phase response and thus thrombocytosis and leukocytosis will result. In contrast, VEXAS is defined by a fundamental uncoupling of the inflammatory response: the somatic mutation drives profound systemic inflammation (elevated CRP/ferritin) while simultaneously impairing hematopoiesis, resulting in progressive bone marrow failure (cytopenias) rather than the reactive thrombocytosis seen in classic vasculitis (*34*). The pattern of hyper-inflammation paired with marrow failure is a reliable distinguishing feature. In a patient diagnosed with refractory PAN and exhibiting macrocytic anemia and/or thrombocytopenia, the diagnosis warrants re-evaluation for the possibility of a UBA1-driven myeloid neoplasia (*35*).

VEXAS diagnosis and differentiation from other emerging somatic syndromes is particularly difficult in the setting of negative UBA1 testing. While VEXAS typically follows a chronic course, somatic NLRC4 mutations present as a hyperacute, IL–18–driven 'cytokine storm' with fulminant Macrophage Activation Syndrome (*36*). Conversely, somatic NLRP3 mosaicism mirrors VEXAS chronicity but manifests as aseptic meningitis and sensorineural hearing loss without the characteristic macrocytosis; these low-level clones often require Next-Generation Sequencing (NGS) for detection (*37*). Finally, phenotypes indistinguishable from VEXAS may stem from somatic mutations in OTULIN or SHARPIN. These disorders share the somatic clonal ubiquitin–defect mechanism and neurological overlaps, representing the essential next step in the diagnostic algorithm for the 'UBA1–negative' patient (*38,39*).

To prevent delayed diagnosis and the futile use of broad immunosuppression, clinicians must consider VEXAS syndrome earlier in the diagnostic process. A high index of suspicion for UBA1 mutations is required when adult-onset neuroinflammation presents with specific "red flags". Common misdiagnoses—such as unclassifiable systemic vasculitis (particularly mimicking PAN or GCA), atypical autoimmune encephalitis, or idiopathic myelitis—should be critically re-evaluated if they occur in a male patient over 50 years of age who is refractory to standard therapy (*40*). The most definitive early red flag prompting immediate genetic sequencing

is the presence of unexplained cytopenias—specifically macrocytic anemia or thrombocytopenia—occurring concurrently with systemic inflammation, sharply contrasting with the reactive thrombocytosis expected in classical autoimmune disorders (*33*).

Considering the existence of numerous potential mimics and the paucity of UBA–1 genetic testing in clinical practice, an appraisal of diagnostic algorithms for adult-onset vasculitis and neurological manifestations may help guide clinical practice. While neuroimaging is frequently nonspecific, it remains essential for excluding structural mimics (*e.g.*, malignancy). In patients presenting with neurological symptoms indicating vasculitic process of the PNS or CNS and concomitant hematologic abnormalities (notably macrocytic anemia and thrombocytopenia), bone marrow aspiration and biopsy should be considered in the diagnostic approach, in concert with vascular imaging and electrophysiological evaluation (Figure 2) (*40*).

6. Management implications

It must be emphasized that current therapeutic strategies for VEXAS syndrome are provisional and based entirely on retrospective cohorts and case series, as no randomized controlled trials (RCTs) have yet been published. The therapeutic strategy for VEXAS requires a careful trade–off between controlling disease activity and minimizing the toxicity of immunosuppression. While high-dose corticosteroids (0.5–1 mg/kg) typically yield rapid improvement in neurological symptoms, this initial success is rarely durable. A defining feature of the syndrome is severe steroid dependency; attempts to taper the dosage below 15–20 mg/day almost always precipitate a relapse (*19,41*).

With regards to steroid sparing agents, in the case of VEXAS, Janus kinase (JAK) inhibitors have emerged as superior treatment options to TNF and IL–1 blockade. JAK inhibitors act by suppressing the JAK–STAT pathway, thereby severing downstream signaling of IL–6 and type I/II interferons. This mechanism is very effective at reducing the cytokine peak and the hyperinflammatory state that the aberrant myeloid clone

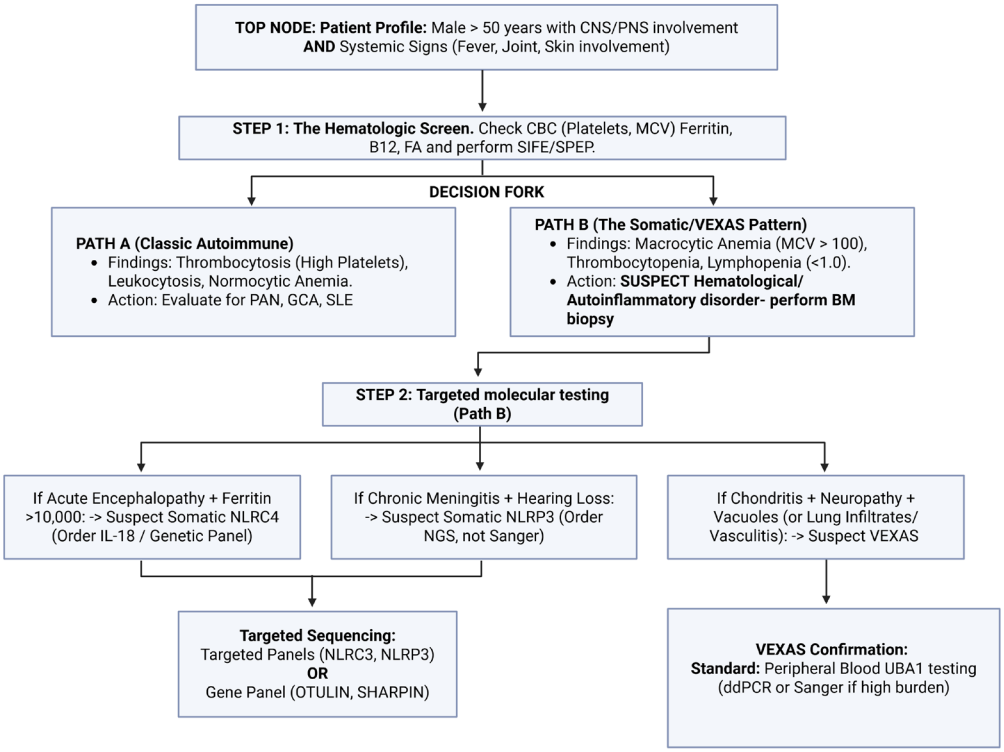

Figure 2. Proposed Diagnostic Algorithm for Suspicion of Somatic Autoinflammation with Neurological manifestations. This flowchart illustrates a stepwise approach for evaluating adult males (> 50 years) with undefined neuroinflammation. The algorithm centres on the "Hematologic Screen" (Step 1) as the primary discriminator between autoimmune mimics (Path A) and somatic clonal disorders (Path B). Path A (Autoimmune) is suggested by reactive thrombocytosis and leukocytosis, while Path B (Somatic/VEXAS) is identified by the "hematologic paradox" of systemic inflammation coexisting with signs of marrow failure (macrocytic anemia, thrombocytopenia). Step 2 directs specific molecular testing based on distinct phenotypic clusters: acute encephalopathy with extreme hyperferritinemia (NLRC4), chronic meningitis with sensorineural hearing loss (NLRP3), or the classic VEXAS triad (UBA1). *Note*: This figure was created using BioRender.com. *Abbreviations*: BM, Bone marrow; CBC, Complete blood count; CNS, Central nervous system; ddPCR, Droplet digital polymerase chain reaction; FA, Folic acid; GCA, Giant cell arteritis; IL, Interleukin; MCV, Mean corpuscular volume; NGS, Next–generation sequencing; NLRC3, NLR family CARD domain containing 3; NLRC4, NLR family CARD domain containing 4; NLRP3, NLR family pyrin domain containing 3; OTULIN, OTU deubiquitinase with linear linkage specificity; PAN, Polyarteritis nodosa; PNS, Peripheral nervous system; SHARPIN, SHANK–associated RH domain interactor; SIFE, Serum immunofixation electrophoresis; SLE, Systemic lupus erythematosus; SPEP, Serum protein electrophoresis; UBA1, Ubiquitin–like modifier activating enzyme 1.

has caused, yet it does not eliminate the underlying clonal proliferation (*42*). Studies have demonstrated that the JAK1/2 inhibitor Ruxolitinib results in superior response rates compared to TNF and IL–1 inhibitors, serving as the steroid-sparing treatment of choice (*33,42*). Systemic symptoms (fever, chondritis) typically resolve within weeks of JAK inhibition, however, established axonal polyneuropathy may show limited reversibility, reflecting permanent axonal loss rather than active inflammation (*23*). Therefore, while robust retrospective cohort data establish JAK inhibitors as highly effective for symptom control, they are not disease–modifying; they suppress proinflammatory signal transduction pathways but fail to eradicate the underlying UBA1–mutated clone (*43*). Currently, based on small cohort experiences, allogeneic hematopoietic stem cell transplantation remains the only truly disease–modifying and potentially curative option for patients with high–risk genotypes (*p*.Met41Val) or transfusion dependence (*13*). In the long term, neurological outcomes are intrinsically linked to the successful management of the underlying hematologic disorder. Rapid diagnosis and the immediate deployment of targeted therapies are essential strategies to optimize clinical response and prevent the morbidity caused by chronic steroid exposure (*41,42*).

7. Limitations

The retrospective nature of existing cohorts currently limits our understanding of neuro-VEXAS. Most data are derived from hematology referral centers, potentially introducing a reporting bias in cases of milder neurological deficits (*19,20*). Furthermore, true mutation prevalence in the group of seronegative CNS vasculitis remains unknown, as UBA1 sequencing testing is uncommon in these cases and not yet a standard practice (*3*). Long–term longitudinal data of VEXAS patients, especially regarding neurological symptoms and related disability, and their outcomes following treatment are currently lacking (*42*). Finally, the diagnostic algorithm proposed herein is derived from retrospective phenotypic patterns. Its clinical utility requires validation in prospective studies, particularly in tertiary centers with a sufficient volume of VEXAS cases, to establish its value in real-world neurological practice.

8. Conclusions

VEXAS syndrome has redefined the landscape of adult–onset neuroinflammation, exposing somatic clonal evolution as a driver of disease distinct from classical autoimmunity. By recognizing its distinct haematological features, clinicians may bypass futile empiric immunosuppression and prioritize high–yield molecular testing. Ultimately, the shift from treating 'atypical autoimmunity' to targeting innate clonal drivers may enable prevention of irreversible neurological injury in people with VEXAS syndrome.

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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; 383:2628-2638.
2. Groarke EM, Turturice B, Patel BA, Quinn KA, Fike A, Grayson PC. VEXAS syndrome: A comprehensive review of pathogenesis, clinical spectrum, and therapeutic strategies. The Lancet. 2026; 407:637-648.
3. Sullivan MM, Koster MJ. Is it VEXAS or is it vasculitis? Clinical and Experimental Rheumatology. 2025; 43:749-755.
4. Diprose WK, Jordan A, Anderson NE. Autoinflammatory syndromes in neurology: When our first line of defence misbehaves. Pract Neurol. 2022; 22:145-53.
5. Dong G, Liu J, Jin W, *et al*. UBA1–depleted neutrophils disrupt immune homeostasis and induce VEXAS–like autoinflammatory disease in mice. Journal of Clinical Investigation. 2025; 135:e193011.
6. Ferrada MA, Sikora KA, Luo Y, *et al.* Somatic mutations in *UBA1* define a distinct subset of relapsing polychondritis patients with VEXAS. Arthritis & Rheumatology. 2021; 73:1886-95.
7. Narendra VK, Das T, Wierciszewski LJ, *et al*. Independent mechanisms of inflammation and myeloid bias in VEXAS syndrome. Nature. 2025; 649:1273-1281.
8. Singh A, Chaudhary R. VEXAS syndrome: A newly identified X-linked hematoinflammatory disorder – A comprehensive overview of its genetic, molecular, inflammatory, and clinical landscape. Journal of Autoimmunity. 2025; 154:103425.
9. Vergneault H, Picard C, Georgin-Lavialle S. Break down the barriers of auto-inflammation: How to deal with a monogenic auto-inflammatory disease and immuno-haematological features in 2022? Immunology. 2023; 168:1-17.
10. Zakine E, Schell B, Battistella M, *et al*. *UBA1* variations in neutrophilic dermatosis skin lesions of patients with VEXAS syndrome. JAMA Dermatol. 2021; 157:1349.
11. Shaukat F, Hart M, Burns T, Bansal P. UBA1 and DNMT3A mutations in VEXAS syndrome: A case report and literature review. Modern Rheumatology Case Reports. 2022; 6:134–9.
12. Templé M, Duroyon E, Croizier C, *et al*. Atypical splice-site mutations causing VEXAS syndrome. Rheumatology. 2021; 60:e435-7.
13. Diarra A, Duployez N, Fournier E, *et al*. Successful allogeneic hematopoietic stem cell transplantation in patients with VEXAS syndrome: A 2-center experience. Blood Advances. 2022; 6:998-1003.
14. Koster MJ, Lasho TL, Olteanu H, *et al*. VEXAS syndrome: Clinical, hematologic features and a practical approach to diagnosis and management. American J Hematol. 2024; 99:284-99.
15. 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 Advances. 2021; 5:3203-15.
16. Sterling D, Duncan ME, Philippidou M, Salisbury JR, Kulasekararaj AG, Basu TN. VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) for the dermatologist. Journal of the American Academy of Dermatology. 2023; 89:1209-14.
17. Staels F, Betrains A, Woei-A-Jin FJSH, *et al*. Case Report: VEXAS syndrome: From mild symptoms to life-threatening macrophage activation syndrome. Front Immunol. 2021; 12:678927.
18. Campochiaro C, Belizaire R. NK cell exhaustion in VEXAS: Another piece in the puzzle. Blood. 2025; 146:1877–8.
19. 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; 186:564-74.
20. Bert-Marcaz C, Fortanier É, Briantais A, *et al*. Neurological manifestations in patients with VEXAS syndrome. J Neurol. 2025; 272:181.
21. Murai Y, Watanabe R, Tsurumoto T, *et al*. VEXAS syndrome with eosinophilia and pathologically mimicking histiocytosis: A case report. Modern Rheumatology Case Reports. 2025; 9:rxaf064.
22. Gupta K, El-Ghazali S, Kubba F. A rare case of VEXAS syndrome. Rheumatology Advances in Practice. 2026; 10:rkaf135.
23. Muratore F, Marvisi C, Castrignanò P, *et al*. VEXAS syndrome: A case series from a single-center cohort of Italian patients with vasculitis. Arthritis & Rheumatology. 2022; 74:665-70.
24. Al-Hakim A, Goldberg S, Gaillard S, Heiblig M, Beck DB, Savic S. Clinical features in VEXAS syndrome: A systematic review. Rheumatology. 2025; 64:5217-29.
25. Eatz T, Gultekin SH, Chandhok NS, O'Phelan KH, Koch S. VEXAS syndrome-associated tumefactive demyelination. J Neurol. 2025; 272:506.
26. Kusne Y, Fernandez J, Patnaik MM. Clonal hematopoiesis and VEXAS syndrome: Survival of the fittest clones? Seminars in Hematology. 2021; 58:226–9.
27. Guédon AF. VEXAS syndrome: From a vascular perspective. Blood. 2024; 143:2118-20.
28. Tan IJ, Ferrada MA, Ahmad S, *et al*. Skin manifestations of VEXAS syndrome and associated genotypes. JAMA Dermatol. 2024; 160:822.
29. Costa A, Pilo F, Pettinau M, *et al*. VEXAS syndrome: Is it more a matter of inflammation or hematopoietic clonality? A case series approach to diagnosis, therapeutic strategies and transplant management. Ann Hematol. 2025; 104:253-262.
30. Zisapel M, Seyman E, Molad J, *et al*. Case report: Cerebral sinus vein thrombosis in VEXAS syndrome. Front Med. 2024; 11:1377768.
31. Satoh K, Tsujimoto Y, Kasugai D, *et al*. Clinical features and treatments of VEXAS syndrome in critical care: A scoping review. Crit Care. 2025; 29:154.
32. Lacombe V, Beucher A, Urbanski G, *et al.* Distinction between clonal and paraclonal cutaneous involvements in VEXAS syndrome. Exp Hematol Oncol. 2022; 11:6.
33. Koster MJ, Kourelis T, Reichard KK, *et al*. Clinical heterogeneity of the VEXAS syndrome. Mayo Clinic Proceedings. 2021; 96:2653-9.
34. Gurnari C, Pascale MR, Vitale A, *et al*. Diagnostic capabilities, clinical features, and longitudinal *UBA1* clonal dynamics of a nationwide VEXAS cohort. American J Hematol. 2024; 99:254-62.
35. Kucharz E. VEXAS syndrome: A new discovered systemic rheumatic disorder. Reumatologia. 2023; 61:123-9.
36. Canna SW, De Jesus AA, Gouni S, *et al.* An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. Nat Genet. 2014; 46:1140-6.
37. Nakanishi H, Kawashima Y, Kurima K, *et al*. *NLRP3* mutation and cochlear autoinflammation cause syndromic and nonsyndromic hearing loss DFNA34 responsive to anakinra therapy. Proc Natl Acad Sci USA. 2017; 114:E7766-E7775.
38. Damgaard RB, Walker JA, Marco-Casanova P, *et al.* The deubiquitinase OTULIN is an essential negative regulator of inflammation and autoimmunity. Cell. 2016; 166:1215-1230.e20.
39. Cai J, Lin Y, Zhou B, Xiao F, Xu G, Lu J. SHARPIN contributes to sevoflurane-induced neonatal neurotoxicity through up-regulating HMGB1 to repress M2 like-macrophage polarization. Metab Brain Dis. 2024; 39:841-53.
40. Vitale A, Caggiano V, Bimonte A, *et al*. VEXAS syndrome: A new paradigm for adult-onset monogenic autoinflammatory diseases. Intern Emerg Med. 2023; 18:711-22.
41. Corty RW, Brogan J, Byram K, Springer J, Grayson PC, Bick AG. VEXAS-defining *UBA1* somatic variants in 245,368 diverse individuals in the NIH *All Of Us* cohort. Arthritis & Rheumatology. 2024; 76:942-8.
42. Heiblig M, Ferrada MA, Koster MT, *et al.* Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: A retrospective multicenter study. Blood. 2022; 140:927-31.
43. Palandri F, Tiribelli M, Breccia M, *et al*. Ruxolitinib rechallenge in resistant or intolerant patients with myelofibrosis: Frequency, therapeutic effects, and impact on outcome. Cancer. 2021; 127:2657-65.

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