International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	VEXAS SYNDROME – A NEW CHALLENGE AT THE INTERFACE OF RHEUMATOLOGY AND HEMATOLOGY: A REVIEW PAPER
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3834
RECEIVED	04 August 2025
ACCEPTED	11 September 2025
PUBLISHED	16 September 2025
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VEXAS SYNDROME – A NEW CHALLENGE AT THE INTERFACE OF RHEUMATOLOGY AND HEMATOLOGY: A REVIEW PAPER

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ABSTRACT

Research Objectives: This review summarizes current knowledge on VEXAS syndrome—its genetics, pathophysiology, symptoms, diagnosis, treatment, and prognosis—highlighting its clinical relevance.
Methods: A focused literature review was conducted using PubMed and Google Scholar, emphasizing recent studies and relevant keywords related to VEXAS syndrome.
Key Findings: VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) is a newly identified, rare autoinflammatory disease caused by a somatic mutation in the UBA1 gene. It occurs almost exclusively in men and combines treatment-resistant inflammatory symptoms with bone marrow dysplasia, posing diagnostic and therapeutic challenges.
VEXAS has a non-specific clinical course, combining symptoms of autoinflammatory diseases (e.g., chondritis, fever, vasculitis) with hematologic features such as cytopenias, macrocytosis, and myelodysplastic syndromes (MDS). Diagnosis is often delayed and requires high clinical suspicion and genetic testing of bone marrow to detect UBA1 mutations.
There are no standardized treatment protocols; therapy usually includes glucocorticosteroids, immunosuppressants, and targeted agents. Allogeneic bone marrow transplantation may be an option in selected patients.
Conclusions: VEXAS syndrome lies at the intersection of rheumatology and hematology. Though recently discovered, its clinical importance is growing. Diagnosis demands a multidisciplinary approach and molecular testing. Further studies and patient registries are essential to improve care and understanding of the disease.

KEYWORDS

VEXAS, UBA1, Autoinflammatory Disease, Cytopenias, Targeted Therapy, MDS

CITATION

Joanna Kłosowska, Piotr Świerczek, Małgorzata Zach, Karolina Błądzińska, Maciej Błądziński, Kacper Szeląg, Antoni Kujawski, Paula Folta, Anna Opalińska, Cezary Lubas. (2025) VEXAS Syndrome – A New Challenge at the Interface of Rheumatology and Hematology: A Review Paper. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3834

Introduction

Autoinflammatory diseases are a diverse group of conditions characterized by recurrent episodes of inflammation without an autoimmune or infectious basis (Bruno et al., 2023). Myelodysplastic syndromes (MDS), on the other hand, are hematologic malignancies resulting from clonal disruption of hematopoiesis, leading to cytopenias and an increased risk of transformation into acute myeloid leukemia (Hagiya et al., 2024), (Beck et al., 2020). For a long time, these conditions were considered separately.

Recent genetic discoveries, particularly advances in sequencing techniques, have helped identify the molecular basis of many diseases, including complex or previously unrecognized ones (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.), (Ferrada et al., 2022). The discovery of somatic mutations in bone marrow stem cells has revolutionized disease classification by bridging the concepts of autoinflammation and hematologic disorders (Ferrada et al., 2022), (Loeza-Uribe et al., 2024).

VEXAS syndrome (derived from the acronym: V – Vacuoles; E – E1 enzyme; X – X-linked; A – Autoinflammatory; S – Somatic) is a newly identified disease entity. It was first described in December 2020 by a group of researchers including Beck and colleagues (Kobak, 2023). The discovery resulted from a genotype-to-phenotype approach, in which gene sequencing was performed in a population of individuals with unexplained chronic inflammation, leading to the identification of variants in the same *UBA1* gene (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.).

VEXAS is a newly defined adult-onset autoinflammatory syndrome characterized by treatment-refractory fever, arthritis, chondritis, vasculitis, blood count abnormalities such as cytopenias, vacuoles in hematopoietic precursor cells, and neutrophilic dermatitis and pneumonia (Kobak, 2023). It is considered the prototype of hematoinflammatory disease (Loeza-Uribe et al., 2024).

Methodology

This article employed a literature review methodology aimed at summarizing the current state of knowledge regarding VEXAS syndrome. The research material was collected from PubMed and Google Scholar databases, with a particular focus on studies published within the last five years. The search was conducted using keywords such as”VEXAS syndrome, ”“VEXAS syndrome treatment, ”“VEXAS syndrome blood, ”“VEXAS syndrome hematologic disease, ” and”VEXAS syndrome cases.” The selected studies addressed the genetics, pathophysiology, clinical manifestations, diagnosis, and treatment of the condition. The findings were synthesized to provide a comprehensive yet concise overview of available scientific evidence and to highlight gaps that warrant further investigation.

Genetic background and pathophysiology of VEXAS syndrome

VEXAS syndrome is the prototype of a new class of diseases (Grayson et al., 2021). It is an acquired (somatic) (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.), (Zeeck et al., 2022) autoinflammatory disorder (Ruffer & Krusche, 2023).

The molecular basis of this syndrome lies in somatic mutations in the *UBA1* gene. Since *UBA1* is located on the X chromosome, VEXAS predominantly affects men; in women, the presence of a normal allele on the second X chromosome typically protects against the disease. Women with VEXAS syndrome are extremely rare and usually have functional monosomy of the X chromosome, as seen in Turner syndrome (45, XO) or in age-related acquired X monosomy (Vitale et al., 2023).

The *UBA1* gene encodes the E1 enzyme, also known as ubiquitin-activating enzyme 1 (UBA1) (Gurnari et al., 2024). This enzyme plays a central role in the ubiquitination pathway—a process that modifies proteins and directs them toward degradation (Zeeck et al., 2022), (Jones et al., 2024). Most disease-defining mutations are located at position p.Met41, i.e., codon 41 of the *UBA1* gene (Ferrada et al., 2022), which serves as the translation initiation codon for the UBA1b isoform (Nakajima & Kunimoto, 2024). These mutations result in the loss of this normally active cytoplasmic isoform and the emergence of a new, enzymatically impaired isoform—UBA1c (Ferrada et al., 2022). The somatic mutation arises de novo in myeloid precursor cells within the bone marrow (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.). Impaired UBA1 function leads to clonal expansion of hematopoietic stem and progenitor cells and skews differentiation toward the myeloid lineage (Nakajima & Kunimoto, 2024). This leads to increased systemic inflammation and progressive bone marrow failure (Ferrada et al., 2022).

Clinical Picture

VEXAS syndrome is characterized by a wide range of clinical manifestations. Due to its X-linked genetic background, most cases occur in males. Symptoms typically develop in the fifth or sixth decade of life (Bruno et al., 2023), (Kobak, 2023), with a median age of onset between 66 and 67 years (Al-Hakim & Savic, 2023). Clinical symptoms span multiple medical specialties (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.).

General and inflammatory symptoms:

The hallmark symptom is fever of unknown origin (FUO), which is chronic and refractory to treatment (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.) (Jones et al., 2024). Additional general symptoms include weight loss and fatigue (Boyadzhieva et al., 2023), (Kobak, 2023), (Vitale et al., 2023).

Rheumatologic and autoinflammatory symptoms:

Cartilage inflammation—particularly of the auricular and nasal cartilages—is common. Joint pain and inflammation also occur, often affecting a single joint or a few joints. Other rheumatologic and autoinflammatory features may include tendonitis and myalgia (Bruno et al., 2023), (Al-Hakim & Savic, 2023), (Vitale et al., 2023).

Cutaneous and ocular manifestations:

Skin lesions are common and may include neutrophilic dermatoses such as Sweet's syndrome, erythema nodosum, rashes associated with cutaneous vasculitis, livedo reticularis, or hemorrhagic lesions (palpable purpura) (Loeza-Uribe et al., 2024). Periorbital swelling and inflammation are frequently observed (Baur et

al., 2023), (Beck et al., 2023). Ocular involvement is also reported and may manifest as scleritis or inflammatory eye disease affecting the epidermis (Al-Hakim & Savic, 2023), (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.).

Vasculitis:

Vasculitis involving small, medium, and large vessels has been described in patients with VEXAS syndrome (Sullivan & Koster, 2025). The clinical presentation may resemble polyarteritis nodosa (PAN), giant cell arteritis (GCA), leukocytoclastic vasculitis, or ANCA-associated vasculitis (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.).

Hematologic manifestations:

Macrocytic anemia is present in nearly all patients, occurring in 97% of cases in one cohort (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.), (Zeeck et al., 2022). Cytopenias typically progress over time and may range from moderate to severe, sometimes requiring blood transfusions (Koster et al., 2024), (Mascaro et al., 2023). Thrombocytopenia is also common (Ferrada et al., 2022). Leukopenia—particularly lymphopenia and monocytopenia—and, less commonly, neutropenia, are also observed (Koster et al., 2024).

Myelodysplastic syndrome (MDS) often coexists with VEXAS syndrome and is typically characterized by low-risk features and low blast counts, rarely progressing to more advanced forms (Bruno et al., 2023). A hallmark finding is cytoplasmic vacuolization in myeloid and erythroid precursors in the bone marrow, observed in more than 95% of VEXAS patients (Al-Hakim & Savic, 2023), (Sullivan & Koster, 2025).

VEXAS-associated MDS may differ from classical MDS (Kusne et al., 2024), (Baur et al., 2023). Unlike typical MDS, which is driven by clonal proliferation and characterized by excess blasts in the bone marrow, VEXAS syndrome is primarily driven by inflammation. Patients with VEXAS-associated MDS rarely exhibit additional mutations commonly found in conventional MDS. In some cases, pancytopenia and bone marrow dysplasia occur only during episodes of severe inflammation (Bruno et al., 2023), (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.).

Systemic manifestations:

Pulmonary involvement is a common feature of VEXAS syndrome. Pneumonia (Kobak, 2023), ground-glass pulmonary infiltrates (Bruno et al., 2023), and lung consolidations (Al-Hakim & Savic, 2023) have been reported. A serious and recurrent complication is venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) (Kusne et al., 2024).

Neurological symptoms are also possible, most commonly in the form of peripheral neuropathy. Gastrointestinal involvement has been described, including colitis and, in rare cases, bowel perforation. Lymphadenopathy—particularly bilateral hilar lymphadenopathy (BHL)—may also occur.

Cardiac manifestations, including myocarditis, pericarditis, and pericardial effusion, have been reported as well. Renal involvement is rare but can include interstitial nephritis and renal insufficiency (Baur et al., 2023), (Li et al., 2024).

Due to its wide range of clinical manifestations, VEXAS syndrome is sometimes referred to as a”great masquerader” (Gurnari et al., 2024). Accurate diagnosis requires high clinical suspicion and a multidisciplinary approach. The diagnostic process typically involves rheumatologists, hematologists, immunologists, geneticists, pathologists, and internists (Hagiya et al., 2024).

Diagnosis

The diagnosis of VEXAS syndrome—a newly recognized disease entity—is often challenging and may be delayed (Gurnari et al., 2024), (Hagiya et al., 2024). Currently, there are no established diagnostic criteria for VEXAS syndrome (Baur et al., 2023). Diagnosis relies on the careful interpretation of clinical symptoms and laboratory findings, with definitive confirmation provided by the identification of mutations in the *UBA1* gene (Vitale et al., 2023).

The key components that should raise suspicion and prompt further diagnostic workup for VEXAS syndrome include male sex and age typically over 50–60 years (Gurnari et al., 2024). Although rare, cases have also been reported in women—particularly those with monosomy X (Barba et al., 2021) - who present with the clinical features described above.

Complete blood counts often reveal cytopenias, especially macrocytic anemia, thrombocytopenia (Hagiya et al., 2024), and lymphopenia (Ruffer & Krusche, 2023). Bone marrow examination is a crucial diagnostic step (Vitale et al., 2023). Myelodysplastic syndrome frequently coexists with VEXAS syndrome (Gurnari et al., 2024).

A characteristic—though not specific but highly suggestive—finding is the presence of cytoplasmic vacuoles in myeloid and erythroid precursors (Hagiya et al., 2024). These vacuoles are observed in more than 95% of patients (Sullivan & Koster, 2025). While there is no universally accepted threshold for the number of vacuoles required for diagnosis, their presence, even in small numbers, should prompt further clinical evaluation (Hagiya et al., 2024). Some studies suggest that vacuolization in ≥10% of myeloid precursors may be associated with high sensitivity and specificity (Bruno et al., 2023), (Baur et al., 2023).

Definitive confirmation of VEXAS syndrome requires the identification of somatic mutations in the *UBA1* gene, located on the X chromosome (Gurnari et al., 2024). Methionine at codon 41 (p.Met41) is the most commonly affected site. Testing for *UBA1* variants is recommended in men with MDS and systemic inflammatory symptoms, and should also be considered in older men presenting with late-onset systemic inflammation, skin rashes, and blood count abnormalities (Hagiya et al., 2024).

Treatment

According to available sources, the treatment of VEXAS syndrome remains a significant clinical challenge, and the search for effective therapeutic options is ongoing (Loeza-Uribe et al., 2024), (Raaijmakers et al., 2021). Currently, there is no standardized treatment protocol (Alqatari et al., 2024). Patients often require multiple medications throughout the course of the disease (Al-Hakim & Savic, 2023).

Corticosteroids are commonly used as first-line therapy (Li et al., 2024). They can effectively reduce inflammatory activity (Kobak, 2023), but typically require high doses over extended periods. Relapses are common upon dose reduction, and long-term use is associated with substantial side effects (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.).

Conventional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, azathioprine, and cyclophosphamide, have shown limited efficacy (Bruno et al., 2023). In one reported case, methotrexate was found to be ineffective (Zeeck et al., 2022).

Targeted therapies, such as IL-1 and IL-6 pathway inhibitors (e.g., anakinra, canakinumab, tocilizumab), have been used with varying degrees of success. Some reports indicate limited or no response (Nakajima & Kunimoto, 2024) (Kosmider et al., 2024), while others describe partial or even complete responses (Alqatari et al., 2024).

Among JAK inhibitors, ruxolitinib appears to be more effective than other agents in this class, such as tofacitinib, baricitinib, or upadacitinib, for the treatment of VEXAS syndrome. Studies have shown that ruxolitinib can improve both clinical and hematological symptoms and reduce the need for corticosteroids (Heiblig et al., 2022).

Hypomethylating agents, such as azacitidine, have demonstrated efficacy in some cases—particularly in patients with coexisting MDS—likely by targeting the hematopoietic stem cell clone harboring the *UBA1* mutation. Cases of complete molecular remission following azacitidine therapy have been reported (Raaijmakers et al., 2021), (Alqatari et al., 2024), (Zhang et al., 2023).

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently considered the only potentially curative option for patients with VEXAS syndrome, particularly in severe cases. Retrospective studies have reported successful transplantation outcomes in some patients. However, due to disease-related factors, older age, comorbidities, and the inherent risks of transplantation, selecting appropriate candidates remains a significant challenge (Ferrada et al., 2022), (Hagiya et al., 2024), (Kosmider et al., 2024).

Prognosis

VEXAS syndrome is a chronic and relapsing disease that can follow a severe clinical course. Reported mortality is high—estimated at 27% in one study (Mads Nyhuus Bendix Rasch1, Fruzsina Szabados2, Jens Magnus Bernth Jensen3, 4, Kirstine Overgaard Nielsen3, Ellen & Margrethe Hauge1, 5 & Anne Troldborg1, 6, n.d.). The overall prognosis is generally poor due to progressive bone marrow failure, difficulty in controlling systemic inflammation, and the risk of life-threatening complications. (Li et al., 2024)

Although some therapies, such as azacitidine and allogeneic stem cell transplantation (allo-HSCT), offer hope for improved outcomes, allo-HSCT carries substantial risks. Even after transplantation, remission may be incomplete, and fatal complications can still occur (Saad et al., 2024).

Discussion and Conclusions

VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a recently described disease entity that combines features of autoinflammatory conditions and hematologic disorders. An acquired somatic mutation in the *UBA1* gene is a key element in its pathogenesis, leading to dysfunction of the ubiquitination pathway and chronic immune system activation.

The diagnosis of VEXAS poses a significant challenge due to its nonspecific clinical presentation, which may include treatment-refractory fever, chondritis, vasculitis, cytopenias, and features consistent with myelodysplastic syndromes (MDS). Bone marrow evaluation is essential to identify characteristic cytoplasmic vacuoles in myeloid and erythroid precursors, observed in approximately 95% of patients. Definitive diagnosis requires confirmation of a somatic *UBA1* mutation.

Treatment remains challenging and often ineffective with conventional immunosuppressive agents. There is growing interest in targeted therapies—such as IL-1 and IL-6 inhibitors and JAK inhibitors—which modulate overactive inflammatory pathways. Allogeneic hematopoietic stem cell transplantation is also being considered in selected cases.

VEXAS syndrome represents a significant new diagnostic and therapeutic challenge at the intersection of rheumatology and hematology. Raising awareness of the condition—particularly among clinicians evaluating middle-aged and older men with treatment-refractory systemic inflammation and coexisting hematologic abnormalities—is essential for early diagnosis and timely initiation of appropriate therapy, which may improve the typically unfavorable prognosis.

Given the rarity of the disease, its complex and variable phenotype, and the absence of standardized treatment protocols, there is an urgent need to develop clinical guidelines, establish patient registries, conduct prospective studies, and create interdisciplinary algorithms for diagnostic and therapeutic management. Collaborative efforts that combine the expertise of hematologists, rheumatologists, pathologists, geneticists, and other specialists are critical to providing optimal care for affected patients.

Acknowledgments: The authors declare no competing interests.

Author's contribution:

Data collection: Joanna Kłosowska, Piotr Świerczek, Małgorzata Zach, Karolina Błądzińska, Maciej Błądzieński, Paula Folta, Kacper Szeląg, Antoni Kujawski, Anna Opalińska, Cezary Lubas

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All authors have read and agreed with the published version of the manuscript.

Funding Statement: The study did not receive special funding.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Conflict of Interest Statement: The authors declare no conflict of interest.

Declaration of generative AI and AI- assisted technologies in the writing process:

While preparing this work the authors have used ChatGPT for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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