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Review

Review Article on Vexas Syndrome

Dr. Padige Srivarsha*[1], R. Bhargav[2], A. Alekhya[3], M. Nikhitha[4], M. Sushma[5]

[1]Assistant Professor, Department of Pharmacy Practice, Malla Reddy College of Pharmacy.
[2,3,4,5]Pharm –D 4th year, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Telangana-500100

*Author for Correspondence: Dr. Padige Srivarsha
Email: nampellyraaziivvarma@gmail.com

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Abstract

VEXAS syndrome is a newly identified adult-onset autoinflammatory disorder caused by somatic mutations in the UBA1 gene. It is characterized by systemic inflammation and hematological abnormalities, including macrocytic anemia, thrombocytopenia, and bone marrow vacuolation, predominantly affecting older males. The disease presents with multisystem involvement such as fever, skin lesions, chondritis, and pulmonary manifestations, often mimicking other conditions.

Its pathogenesis involves impaired ubiquitination leading to excessive inflammatory responses. Diagnosis requires clinical evaluation supported by genetic testing. Current treatment mainly relies on corticosteroids, with emerging therapies such as JAK inhibitors and IL-6 inhibitors showing promise. Hematopoietic stem cell transplantation remains the only potential curative option. Overall, early diagnosis and targeted therapies are essential to improve outcomes in this complex and high-risk condition.

Keywords: UBA1 gene, auto inflammatory, glucocorticoids, emphasize, morbidity and mortality.

INTRODUCTION:

Somatic mutations in the UBA1 gene produce VEXAS syndrome, a refractory auto inflammatory illness in adults that manifests as hematologic and systemic inflammatory symptoms. With the exception of high-dose glucocorticoids, patients respond poorly to immune-suppressive therapies. Because of the syndrome's substantial morbidity and mortality, medical experts must give it careful consideration. VEXAS is a prototype for a new class of disorders, according to recent publications that emphasize novel genetic variations and possible therapeutic approaches [1].

Severe inflammatory and hematologic symptoms that can worsen quickly and be lethal are the hallmarks of VEXAS syndrome. Recurrent fevers, weight loss, and different types of vacuities are common symptoms,

along with hematological characteristics such myelodysplastic syndromes and macrocytic anemia [2]. UBA1 mutations affect the disease's expression, which affects the prognosis and thrombotic event risk. There are currently no established therapy reco mmendations for VEXAS syndrome, which emphasizes the need for improved knowledge and management strategies. Treatment alternatives are still being investigated by research, and a review of existing therapy approaches is essential for future advancements. First discovered in 2020, VEXAS syndrome is primarily found in elderly male patients and is associated with mutations in the UBA1 gene [3].

Vexas pattern, auto inflammatory condition caused by mutation in the UBA1gene.

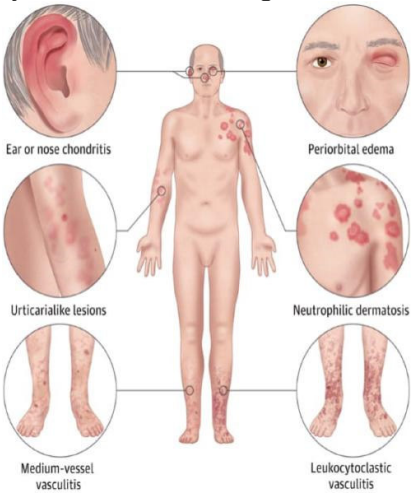


Figure 1: systemic involvement ranging from ear/nose chondritis and periorbital edema to various dermatological presentations such as neutrophilic dermatosis and vasculitis.

CHARACTERISTIC FEATURES OF VEXAS SYNDROME

1. VACUOLE:

Although vacuoles are useful organelles in bacteria, fungus, and plants, they may be a sign of disease in human cells. Cytoplasm vacuoles may be temporary or permanent, indicating long-term flaws. Only 24 out of 11c772 BM samples had them, making them uncommon in marrow myeloid and elytroid progenitor cells [4]. Myeloid neoplasm's, copper deficiency, and alcohol intoxication are examples of differential diagnosis. UBA1 variant sequencing should now be used in the assessment of individuals with cytoplasm vacuoles. Vacuoles are present in particular progenitor cells in VEXAS patients, and auto inflammatory symptoms and macrocytic anemia may be distinguishing characteristics. More research is necessary to determine the vacuoles' makeup, which is still unknown [5].

Breakdown of the components of the term "VEXAS"

- ***Vacuoles****: This refers to the presence of atypical vacuoles in the myeloid cells of affected individuals, as observed in laboratory analyses.*
- ***E1 enzyme****: The syndrome is associated with somatic mutations in the UBA1 gene, which encodes the E1 ubiquity-activating enzyme. These mutations are believed to contribute to the deregulation of the immune system.*
- ***X-linked****: The UBA1 gene is located on the X chromosome. The X-linked nature indicates that the syndrome primarily affects males, as they have only one X chromosome. Females, who have two X chromosomes, might have one unaffected copy that can compensate for the mutation.*
- ***Auto inflammatory****: VEXAS syndrome is classified as an auto inflammatory disorder, which means it involves the immune system mistakenly causing inflammation in the absence of infection.*
- ***Somatic****: Somatic mutations are those that occur in the body's non-reproductive cells and are not passed on to offspring.*

2. E1 Enzyme

The UBA1 gene encodes the enzyme responsible for ubiquity activation, known as the E1 enzyme, which

plays a vital role in the process of cellular ubiquitylation. Ubiquitination is a posttranslational modification of proteins that facilitates the degradation of improperly folded proteins, involving the sequential actions of ubiquity-activating (E1), conjugating (E2), and ligating (E3) enzymes. This process of ubiquitylation is critical for numerous cellular functions, including cell-cycle progression, response to DNA damage, and pathways related to immune signaling. Mutations in the UBA1 gene can lead to decreased levels of ubiquitination and promote activation of autoimmune pathways, resulting in signs of inflammation [6].

3. X-Linked

UBA1 can evade X chromosomal inactivation and is found on the X chromosome (Xp11.3). The fact that older men are more likely to have VEXAS syndrome suggests that the unmutated allele may protect women. Nonetheless, there have been a few documented female patients with either structural X chromosomal deletion or acquired X chromosome monosomy[7].

4. Auto inflammatory

Pulmonary infiltrates and vasculitis are examples of multiorgan autoinflammatory presentations.
The activation of several innate immune pathways w as also verified by transcriptomic analysis of the pati ent's peripheral blood.A higher percentage of spliced XBP1 in monocytes has also been reported, and it is hypothesized that the reduction in cytoplasmic ubiqui tylation brought on by the UBA1 mutation results in t he accumulation of unfolded proteins, which further activates the unfolded protein response and multiple i nflammatory pathways,neutrophil extracellular traps (NETs), neutrophils may potentially contribute to the worsening of the inflammatory response. In a zebra fish model where the UBA1 is form homolog was deleted, Beck et al. discovered increased gene expression of proinflammatory cytokines, indicating that UBA1 mutations may be linked to systemic inflammatory symptoms in VEXAS syndrome patients [8].

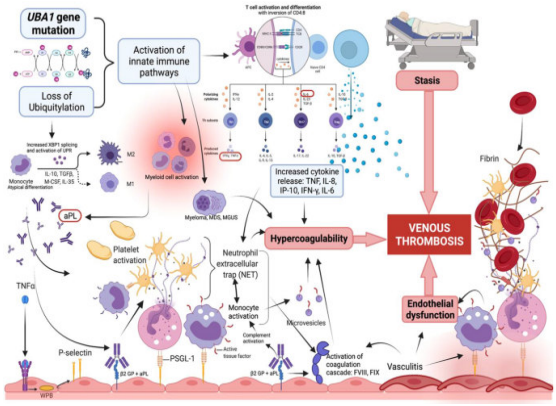
5. SOMATIC:

The UBA1 mutation in VEXAS syndrome is somatic, meaning it does not occur in all tissue cells. Sanger sequencing has a detection limit of 15-20% for somatic mutations. In other words, for a part of people, a more sensitive second-generation sequencing option is necessary to boost detection rates since variant allele frequencies (VAFs) below a threshold may be missed. However, it has been reported that high VAF of UBA1 detected by axon sequencing may be mistaken as germ line mutations associated with X-linked spinal muscular atrophy 2 (SMAX2). This could result in a biased diagnosis or affect the course of treatment. 25 Different tissue sequencing may be considered if the patient's clinical presentation does not match SMAX2 [9].

EPIDEMIOLOGY:

The prevalence of disease-causing UBA1 variations is roughly 1 in 13,591 people overall, according to a study analyzing genetic data from 163,096 participants, however the annual incidence of VEXAS is still unclear. In particular, the frequency increases to 1 in 4,269 among men over 50, while it is much lower for women in the same age range (1 in 26,238). Eleven people (two women and nine men) in the Kiesinger cohort were found to have pathogenic UBA1 mutations. These individuals all had inflammatory diseases that were consistent with VEXAS, including high rates of thrombocytopenia and macrocytosis [10]. A research examining genetic data from 163,096 participants found that the prevalence of disease-causing UBA1 variants is approximately 1 in 13,591 people overall; however, the annual incidence of VEXAS remains unknown. Specifically, in men over 50, the frequency rises to 1 in 4,269, although it is significantly lower for women in the same age group (1 in 26,238). Pathogenic UBA1 mutations were discovered in eleven members of the Kiesinger cohort, including two women and nine men. All of these people had inflammatory conditions that were typical of VEXAS, such as elevated levels of macrocytosis and thrombocytopenia [11].

PATHOPHYSIOLOGY:



Driver mutations improve survival across cell types in somatic mutations linked to cancers, increasing variant allele frequency (VAF) over generations. Multipotent hematopoietic progenitors undergo mutations in the context of VEXAS, but specific cell lines exhibit selective expression. While lymphoid progenitors preferentially express wild-type alleles because of negative clonal selection in mature lymphocytes, neutrophils and monocytes with high VAF show strong mutant allele propagation. Problems like lymphopenia result from this incompatibility with survival[12]. A case study showed that a UBA1 gene mutation outcompeted a patient with CALR-mutated essential thrombocythemia, suggesting that mutant UBA1 creates a favorable survival environment. Clonal haematopoiesis (CH) may be common in VEXAS, according to current research, but it is unclear how co-occurring CH alleles relate to clinical outcomes[12].

1. **Inflammatory profile** :

Uncertainty surrounds the mechanisms underlying inflammatory symptoms and progressive cytopenias in VEXAS. The unfolded protein response (UPR) and elevated inflammatory cytokines, such as interleukin (IL)-8, IP-10, and interferon gamma (IFNγ), are caused by somatic mutations that reduce UBA1 activity. Zebra fish with UBA1 mutations showed similar cytokine profiles. In certain auto inflammatory diseases, UPR activation sets off a type I interferon response that causes inflammatory states. Furthermore, there are instances of VEXAS-like syndromes without UBA1 mutations, indicating that mutations in other ubiquitylation process steps may result in comparable clinical outcomes. This has sparked interest in genetic analysis of related enzymes in subsequent studies [13].

2 . Bone marrow morphology/manifestations

The presence of cytoplasm vacuoles in myeloid and erythroid precursor cells, which are not specific to the syndrome but can also result from alcoholism, MDS, zinc toxicity, or copper deficiency, is a crucial finding in VEXAS syndrome. These vacuoles are uncommon and should prompt genetic testing for VEXAS syndrome if they are discovered in conjunction with inflammatory symptoms or suspected MDS. The significance of genetic testing when there is clinical suspicion is highlighted by the fact that some cases may show only slight morphologic alterations. Hyper cellular marrow with granulocytic hyperplasia, minimal dyspoiesis, a normal karyotype, and no increase in blasts without associated MDS are additional findings in VEXAS patients [14].

CLINICAL FEATURES:

VEXAS syndrome is a multi –system″hemato-inflammatory" disease. Its clinical manifestations are typically divided into inflammatory (rheumatologic) and hematological categories**.**

Because the UBA1 mutation occurs in myeloid precursor cells, the symptoms often mimic known autoimmune diseases but are distinguished by their severity and resistance to standard treat

1. **Constitutional and General Symptoms Recurrent fevers:** Present in 65%-100% of cases; frequently the first symptom. Weight loss and fatigue: Severe malaise and night sweats are typical. Glucocorticoid Dependence: A distinguishing clinical feature is that symptoms resolve quickly with high-dose steroids but return instantly when the dose is reduced.

2. Dermatological manifestations (~80% of individuals).

The skin is the most often infected organ. Manifestations include:

Neutrophilic Dermatosis: Similar to Sweet Syndrome (painful, erythematous plaques or nodules).

Leukocytoclastic Vacuities: Small-vessel inflammation resulting in palpable purpura.

Urticarial lesions are hives or "urticaria-like" rashes that can be persistent.

Panniculitis is inflammation of the fatty layer beneath the skin.

3. Hematological Features

Macrocytic Anemia: Nearly universal (>90%). Patients have a high Mean Corpuscular Volume (MCV) without B12/folate deficiency.

Bone Marrow Vacuoles: The "V" in VEXAS. Characteristic vacuoles are found in myeloid and erythroid precursor cells.

Thrombocytopenia: Low platelet counts, often worsening as the disease progresses.

Myelodysplastic Syndrome (MDS): About 25%–50% of patients develop clinical MDS or other plasma cell dyscrasias like Multiple Myeloma.

Thrombosis: High incidence of unprovoked Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE).

4. Musculoskeletal & Cartilage Involvement

Relapsing Polychondritis: Painful swelling and redness of the cartilage in the ears and nose. Unlike idiopathic polychondritis, VEXAS usually spares the joints of the mid-ear but involves the airway.

Inflammatory Arthritis: Polyarthritis or joint pain that can mimic Rheumatoid Arthritis but is usually seronegative.

5. Pulmonary & Ocular Manifestations

Lung Involvement (~50%): Includes neutrophilic alveolitis, pleural effusions, and "ground-glass opacities" on CT scans. It often presents as shortness of breath or a persistent cough.

Ocular Inflammation: Scleritis, episcleritis, and uveitis (red, painful eyes). Per orbital edema (swelling around the eyes) is a highly specific "red flag" for VEXAS**.**

Table 1: CLINICAL 'RED FLAG' [16]

ORGAN SYSTEM	KEY FINDINGS
Blood	Macrocytosis, low platelets, bone marrow vacuoles
Skin	Sweet-like syndrome, painful red nodules
Cartilage	Ear/Nose chondritis (swelling/redness)
Vessels	Recurrent blood clots (DVT/PE)
General	Male >50 years, fever, steroid-dependent

Clinical manifestations and multi system involvement

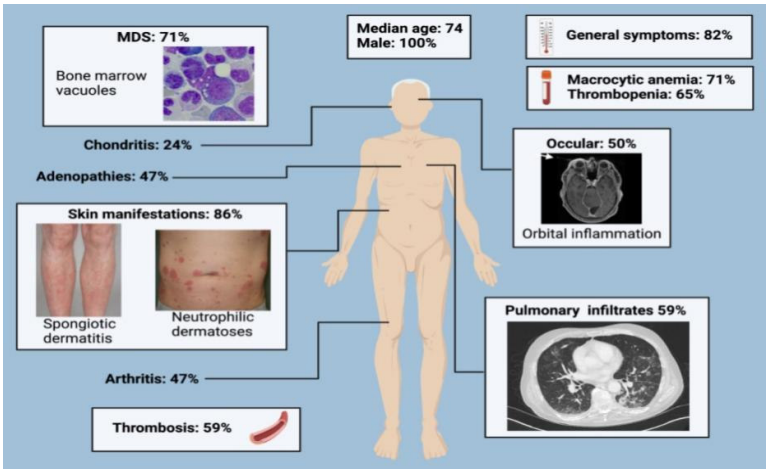


Figure 2: Key diagnostic markers, including bone marrow vacuoles, macrocytic anemia, and systemic involvement ranging from neutrophilic dermatoses to pulmonary infiltrates**.**

DIAGNOSIS:

Rheumatologists, geneticists, and other specialists use a combination of clinical evaluation, genetic testing, and laboratory assessments because there is no single test that can confirm a diagnosis of VEXAS (Vacuoles, E1 enzyme, X-linked, Auto inflammatory, and Somatic) syndrome. A multidisciplinary approach is frequently necessary due to the rarity and complexity of VEXAS.

Important elements of diagnosis consist of:

Clinical Evaluation: Physicians evaluate a patient's medical history and symptoms, including inflammatory skin lesions, blood abnormalities, and recurrent fevers. To find symptoms linked to VEXAS, a physical examination is performed.

Genetic Testing: Finding somatic mutations in the UBA1 gene, which codes for the E1 ubiquity-activating enzyme, is a crucial step in the diagnosis process. The diagnosis is confirmed by this mutation, which usually necessitates consultation with genetic experts.

Laboratory Evaluations: Blood tests assess markers such as erythrocyte count, C-reactive protein (CRP)

MANAGEMENT:

1. Supportive / Symptomatic

- Blood transfusions (anemia)
- Erythropoietin
- Infection prophylaxis
- Vaccinations (non-live preferred)
- Management of thromboembolism

2. Corticosteroids

- High-dose systemic steroids
- First-line for inflammation control
- Steroid-dependent disease common

3. Conventional Immunosuppressants (limited benefit)

- Methotrexate
- Azathioprine
- Mycophenolate mofetil
- Cyclophosphamide

4. Biologic / Targeted Therapies

- **IL-6 inhibitors**: Tocilizumab
- **TNF-α inhibitors**: Etanercept, Infliximab (variable response)
- **IL-1 inhibitors**: Anakinra (partial response)
- **JAK inhibitors**: Ruxolitinib, Tofacitinib (promising)

5. Hematologic Therapies

- Hypomethylating agents (Azacitidine)
- Lenalidomide (selected cases)
- Treatment of associated MDS / plasma cell disorders

6. Curative / Definitive Option:

- **Allogeneic hematopoietic stem cell transplantation (HSCT)**
  - Only potential cure
  - Selected fit patients

Steroids:

Despite the complexity of VEXAS syndrome and its relative resistance to multiple therapeutic agents, systemic corticosteroids remain a standard and effective therapy, albeit not curative . One of the two primary strategies for managing VEXAS focuses on inhibiting inflammatory signaling pathways and cytokines, a goal achieved through corticosteroid use [17]. Systemic corticosteroids are frequently administered empirically before the identification of the underlying UBA1 mutation and are considered a first-line treatment for managing the inflammatory symptoms and cytopenia associated with VEXAS syndrome [18] .

High dosages of corticosteroids (20 mg/day or more) can reduce systemic inflammation, according to research, but they frequently result in poor control and recurrence when tapered off. Steroids are not appropriate for long-term treatment since prolonged use might lead to consequences like cardiovascular problems and steroid dependence [19]. Oral prednisone was shown in a case study to alleviate symptoms in a patient who was not responding to steroid-sparing medications. Although they were less successful in treating hematologic problems, a cohort trial also demonstrated that high-dose corticosteroids successfully decreased inflammation in the majority of patients. Therefore, even if corticosteroids are essential for treating VEXAS syndrome, their long-term dangers call for the investigation of safer alternative treatments [20].

Ruxolitinib and Other JAK Inhibitors:

Janus kinase inhibitors (JAKi)—including ruxolitinib, baricitinib, upadacitinib, and

tofacitinib—have emerged as targeted therapeutic options for VEXAS syndrome by modulating the JAK–STAT signaling pathway**,** which plays a critical role in immune regulation and inflammatory responses[21]. Among the available agents**,** ruxolitinib**,** a selective JAK1 and JAK2 inhibitor**,** has demonstrated particularly notable efficacy. Its dose flexibility allows for individualized treatment based on patient response and tolerance. Furthermore, ruxolitinib has shown beneficial effects on cutaneous manifestations**,** especially when used in combination with **azacitidine**, suggesting a synergistic role in patients with concomitant hematological involvement [22].Despite their therapeutic promise, JAK inhibitors are associated with potential adverse effects, including **increased risk of thromboembolism and infections**, necessitating careful patient selection and monitoring. Overall, JAK inhibitors represent **a** promising therapeutic strategy for managing both the inflammatory and hematological manifestations of VEXAS syndrome, although further studies are required to better define their long-term safety and optimal use [23]

Abatacept:

Abatacept is a biologic disease-modifying antirheumatic drug (DMARD) that selectively inhibits **T-cell activation** by targeting co-stimulatory pathways essential for adaptive immune responses. It exerts its effect by binding to **CD80 and CD86** on antigen-presenting cells, thereby preventing their interaction with **CD28** on T cells and interrupting sustained T-cell–mediated inflammatory signaling [24]. Although evidence supporting the use of abatacept in **VEXAS syndrome** remains limited, emerging case-based reports suggest a potential therapeutic role in selected patients.

Pathmanathan *et al.* described the use of abatacept in a patient with VEXAS syndrome who exhibited **moderate-dose corticosteroid dependence** along with significant **systemic and hematological involvement** [20]. Prior to abatacept initiation, the patient had failed multiple immunomodulatory and immunosuppressive therapies, including **Golimumab, Etanercept, Adalimumab, Methotrexate, Azathioprine, and Ciclosporin**, without achieving steroid independence. Treatment with **Abatacept in combination with low-dose prednisone (5 mg/day)** resulted in a **sustained clinical response for 30 months**. While the improvement in hematologic and systemic manifestations was not complete, the response was **substantially superior** to that observed with previous therapeutic regimens, highlighting abatacept as a potential **steroid-sparing option** in refractory VEXAS syndrome [20].

IL-6 Inhibitors:

According to Tozaki et al., patients with VEXAS syndrome had higher serum levels of interleukin-6 (IL-6), indicating that IL-6 inhibitors like tocilizumab might be useful as a treatment. With oral prednisone and intravenous tocilizumab, they observed quick clinical improvement. Anti-IL-6 treatments help control inflammation and lower corticosteroid use, but many patients still experience progressive bone marrow loss, suggesting that IL-6 targeting by itself may not be sufficient to treat hematological problems. According to Kunishita et al., VEXAS patients with certain myelodysplastic syndrome (MDS) scores or severe inflammatory phenotypes may benefit more from the combination of glucocorticoids and tocilizumab[26]. Significant symptom improvements with weekly tocilizumab combined with corticosteroids allowed for transfusion independence and the discontinuation of corticosteroid medication. Patients with major inflammatory symptoms may benefit from IL-6 inhibitors, underscoring the significance of combination therapy for treating both hematological and inflammatory issues [25].

During the brief two-month follow-up period, siltuximab plus 10 mg of corticosteroids produced a partial response. Sarilumab also resulted in a partial reduction of corticosteroids; nevertheless, injection site reactions forced the termination of treatment. The patient's arthralgia, skin lesions, episcleritis, and auricular inflammation all flared up after stopping the medication, suggesting a return of symptoms . When thinking about this treatment option, careful patient selection and close monitoring for infections and gastrointestinal issues are crucial because bad reactions that force withdrawal can cause a quick recurrence of the illness [27].

Different TNF Inhibitors: Infliximab, Adalimumab and Etanercept:

The effectiveness of tumor necrosis factor-alpha (TNF-α) inhibitors, such as etanercept, adalimumab, and infliximab, as steroid-sparing medications for VEXAS syndrome is limited. Only one out of four patients responded favorably to adalimumab plus methotrexate treatment, according to a systematic study; the other patients did not respond, and one patient experienced pneumonia [23]. In a Canadian cohort, etanercept alleviated symptoms and decreased the dosage of corticosteroids, whereas infliximab was ineffective and stopped because of

rectal cancer. Adalimumab exhibited median efficacy duration of 3.4 months in three cases, but no favorable responses were observed in a Spanish cohort of thirty patients treated with anti-TNF drugs [28].

Stem Cell Transplantation:

For severe, refractory VEXAS syndrome, allogeneic hematopoietic stem cell transplantation (alloHCT) has demonstrated benefit, particularly in patients with hematologic involvement such as myelodysplastic syndromes (MDS). According to reports, many patients experience long-lasting remission following alloHCT, including improvements in inflammatory markers and bone marrow architecture. The therapeutic promise of alloHCT for VEXAS syndrome is highlighted by long-term follow-ups, which show that a significant number of patients can discontinue immunosuppressive medication and stay relapse-free [29]

Although allogeneic hematopoietic cell transplantation (alloHCT) for VEXAS syndrome has promising results, it is complicated by serious post-transplant problems, such as infections and graft-versus-host disease (GVHD), which call for close observation and supportive care. Immunosuppressive treatments like cyclophosphamide and tacrolimus are used as prophylaxis against GVHD, but they have hazards of their own, including drug-induced rashes and infections [30]. The prevalence of GVHD varies; mild occurrences are reported in some studies, whereas larger frequencies are reported in others. Furthermore, age and comorbidities limit eligibility for alloHCT, underscoring the need for better post-transplant care and wider access to treatment for better patient outcomes [31].

CHOP Therapy:

Traditionally, non-Hodgkin's lymphoma has been treated with CHOP therapy, which consists of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone. A single case report demonstrating a patient's notable improvement following CHOP therapy demonstrated its efficacy for VEXAS syndrome. However, more extensive research is required to assess CHOP's effectiveness in treating VEXAS syndrome because of the patient's numerous comorbidities. Additionally, two patients experienced remission with cyclophosphamide and methylprednisolone, but this combination was not appropriate for maintenance therapy due to the inability to lower steroid dosages [32].

Intravenous Immunoglobulins (IVIG):

By operating on a variety of intricate pathways in autoimmune, immunological-mediated, and inflammatory illnesses, IVIG therapy has the ability to modulate the immune system. This is mostly accomplished by interfering with the presentation of antigens, interacting with the complement system, cytokines, chemokines, and modifying the effector activities of T and B lymphocytes, natural killer cells, and T cells [33]. According to Magnol et al. innate immune involvement in VEXAS syndrome may indicate a positive reaction to IVIG infusion.If a patient was treated with a combination of IVIG and anti-IL17 medication after being first diagnosed with spondyloarthropathy (SpA) and then VEXAS syndrome. This allowed for a considerable reduction in the dosage of steroids and produced a maintained response with less chondritis, uveitis, IBD, or SpA flare-ups[34].

DISCUSSION:

Treatment for VEXAS syndrome must be individualized due to its variability. Comprehensive knowledge of certain UBA1 mutations and how they affect disease manifestation may help with prognostication and medication selection. Large-scale, multicenter clinical trials are desperately needed to methodically evaluate the safety and effectiveness of new treatments. In order to provide doctors with evidence-based advice for managing this complex illness, such trials should seek to establish standardized treatment procedures, ideal dose regimens, and monitoring measures. Furthermore, investigating combination treatments that target the hematologic and inflammatory components of VEXAS syndrome may yield synergistic therapeutic advantages.

CONCLUSION:

VEXAS syndrome represents a newly recognized, complex adult-onset autoinflammatory disorder that bridges the fields of hematology, rheumatology, immunology, and genetics. Caused by somatic mutations in the UBA1 gene**,** this syndrome is characterized by severe systemic inflammation, progressive hematologic abnormalities, and distinctive bone marrow findings such as cytoplasmic vacuoles. The disease predominantly affects older

males and is associated with significant morbidity and mortality, largely due to its refractory nature and diagnostic challenges.

This review highlights that **VEXAS syndrome is not a single-organ disease but a multisystem hemato-inflammatory condition**, often mimicking established autoimmune and myelodysplastic disorders. The overlapping clinical features—such as recurrent fevers, steroid dependence, neutrophilic dermatoses, chondritis, macrocytic anemia, thrombocytopenia, and thromboembolic events—frequently lead to delayed diagnosis. Recognition of clinical "red flags," combined with a high index of suspicion and confirmatory **genetic testing for UBA1 mutations**, is therefore critical for early and accurate diagnosis.

From a pathophysiological perspective, impaired ubiquitination due to dysfunctional E1 enzyme activity results in activation of innate immune pathways, unfolded protein response, and excessive cytokine production. This mechanistic insight explains both the inflammatory phenotype and the limited efficacy of conventional immunosuppressive therapies. While **systemic corticosteroids remain the cornerstone of symptom control**, their long-term use is hampered by toxicity and steroid dependence, underscoring the urgent need for effective steroid-sparing strategies.

Emerging targeted therapies, particularly **JAK inhibitors (notably ruxolitinib)**, IL-6 inhibitors, and selected biologics such as abatacept, have shown promising results in controlling inflammation and reducing steroid burden, although responses remain variable and hematologic improvement is often incomplete. **Allogeneic hematopoietic stem cell transplantation** currently stands as the only potentially curative option, especially for patients with severe or refractory disease and associated myelodysplastic syndromes, but its use is limited by age, comorbidities, and transplant-related risks.

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