INTERNATIONAL JOURNAL OF
PHARMACEUTICAL AND HEALTHCARE INNOVATION
journal homepage: www.ijphi.com

OPEN ACCESS

Review Article

Understanding Insights and Treatment Options for VEXAS Syndrome

Navaneeth Krishna B*

PG scholar, Department of Pharmacy Practice, Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India. 574143.

Article Info

Article history:

Manuscript ID:

IJPHI0406172024
Received: 1- June -2024
Revised :12-june-2024
Accepted: 19-june-2024
Available online: June 2024

Keywords:
VEXAS syndrome, monogenic disorder, inflammation,

Hematologic abnormalities, therapeutic considerations.

Corresponding Author:

navaneethkrishnabhat@gmail.com

Abstract

The VEXAS syndrome, stemming from somatic mutations within the UBA1 gene, is a recently recognized monogenic condition with notable implications for inflammatory and hematologic disorders in adults. This article scrutinizes the pathophysiology, clinical manifestations, and therapeutic considerations associated with VEXAS syndrome, accentuating its intricate nature. By examining existing literature and clinical evidence, the article elucidates the genetic mechanisms that underlie autoinflammatory symptoms in affected individuals. The challenges in diagnosis are emphasized, stressing the importance of efficacious treatment approaches to address the complex interplay between inflammation and hematologic irregularities. Furthermore, the article investigates recent findings regarding genetic variations, disease advancement, and potential therapeutic targets, presenting encouraging avenues for enhancing the management of VEXAS syndrome. Serving as a prototype for a novel category of monogenic disorders, VEXAS syndrome underscores the necessity for further investigation to enrich our comprehension of its pathogenesis and optimize patient care in rare and complex inflammatory conditions. This all-encompassing analysis aims to establish a groundwork for forthcoming research endeavors and clinical methodologies, ultimately propelling progress in the realm of rare inflammatory conditions and enhancing outcomes for individuals impacted by VEXAS syndrome.

INTRODUCTION

VEXAS syndrome is an infrequent and serious autoimmune disease that was first recognized in 2020[1]. It is caused by somatic mutations in the UBA1 gene, which encrypts for the master enzyme of cellular ubiquitylation. Patients with VEXAS syndrome develop inflammatory and hematologic symptoms, including systemic inflammation involving the skin, lungs, blood vessels, and cartilage [1]. They also agonize from a spectrum of hematologic problems, including macrocytic anaemia, thrombocytopenia, thromboembolic disease, and progressive bone marrow failure, which can progress to hematologic malignancy. Myeloid-driven autoinflammation and progressive bone marrow failure lead to substantial disease and mortality [2]. VEXAS syndrome characteristically affects older adults, primarily males, with signs and symptoms of the condition developing in a person's fifties, sixties, or seventies. The name VEXAS is an abbreviation based upon key features of the syndrome: Vacuoles are seen in myeloid and erythroid progenitor cells from bone marrow aspirates. E1 enzyme refers to the ubiquitin activating enzyme encoded by UBA1, which is an X-linked gene. Mutations in UBA1 are lineage constrained to myeloid cells and result in autoinflammatory disease [1]. Currently, there are no consistently effective therapies for VEXAS syndrome. However, based on the current understanding of the pathophysiological mechanisms of VEXAS syndrome, two therapeutic strategies have been proposed: eradicating UBA1 mutations and blocking the inflammatory cascade response

HISTORY

VEXAS syndrome is a rare disease that affects both the immune system and the blood cells. It is also remarkable for how it was discovered using a ‘genotype-first’ method. This opens up new possibilities for finding new genetic diseases [3].

Most genetic diseases that cause inflammation are inherited from parents and start early in life. They are found by looking at the symptoms that run-in families. VEXAS syndrome is different. It was found in 2020 by looking at the genes of 2,560 patients. Three of them had a change in a gene called UBA1 that helps cells recycle proteins. This change caused similar problems in their blood cells and organs. They were mostly older men. Some of them had been diagnosed with other diseases before, like MDS or SAID. Later, 25 men with the same change and problems were reported [3].

VEXAS syndrome changes how we think about genetic diseases that cause inflammation. Most of them are inherited from birth. VEXAS syndrome is not. It happens when the UBA1 gene changes later in life, only in some blood cells. This change is enough to cause the disease, no matter how many cells have it [4]. This can only be seen by using new ways of

looking at genes. VEXAS shows how these new ways can help us find more diseases in the future.

ETIOLOGY

The phenomenon of somatic mutations occurring over time is well recognized, with outcomes varying from the build-up of harmless allele variants to the development of tumors and clinical diseases [6]. In the case of VEXAS syndrome, an inactivating mutation is acquired in the UBA1 gene, which is linked to the X chromosome [7]. The UBA1 gene encodes for the primary E1 activating enzyme in humans, which is accountable for more than 90% of ubiquitin activation, intracellular protein degradation dependent on ubiquitylation, and cellular homeostasis. The UBA1 gene can be expressed in two ways: as UBA1a, a nuclear isoform that starts at p.Met1, or as UBA1b, a shorter cytoplasmic isoform that starts at p.Met[8].

CLINICAL PRESENTATION

VEXAS is a serious and advancing disease that exhibits characteristics of both rheumatologic and hematologic conditions. It causes systemic inflammation that affects the skin, lungs, blood vessels, and cartilage, often leading to a range of clinical diagnoses such as Sweet syndrome, relapsing polychondritis, polyarteritis nodosa, and giant cell arteritis. Furthermore, VEXAS patients experience a variety of hematologic issues, including macrocytic anemia, thrombocytopenia, thromboembolic disease, and progressive bone marrow failure, which can develop into a hematologic cancer. There's a noted increased risk of hematologic cancer, particularly myelodysplastic syndrome (MDS), in many rheumatologic diseases. Conversely, MDS has been linked to several autoimmune syndromes. The existence of VEXAS syndrome could potentially clarify some of these historical clinical correlations [1,9,10,11].

PATHOGENESIS

In certain somatic mutations, such as those found in cancer, a driver mutation provides a survival advantage across all cell types, leading to an increased variant allele frequency (VAF) observed across successive cell generations [5]. In VEXAS syndrome, although the mutation is known to occur in multipotent hematopoietic progenitors, there seem to be selective pressures that restrict the expression of the mutated allele to specific cell lines only. For instance, in myeloid progenitors with a VAF of 80%, there was a VAF of over 80% in neutrophils and monocytes. Similarly, in megakaryocyte-erythrocyte progenitors with a VAF of over 65%, there was a VAF of over 90% in megakaryocytes. This indicates the propagation of mutant alleles through positive selection pressure [4].

Contrastingly, in lymphoid progenitors where the mutant allele VAF was over 75%, the derived B and T lymphocytes contained almost exclusively wild-type alleles. Interestingly, these distribution patterns remain consistent regardless of the VAF in the hematopoietic progenitor cells [4].

The absence of the mutant allele in mature lymphocytes suggests that its presence is not compatible with survival in these cell types.

This negative clonal selection pressure is highlighted by the development of lymphopenia as part of the disease. However, it's worth noting that lymphopenia in VEXAS might also be a result of frequent corticosteroid use. The reason why mature myeloid cells favor the mutant allele while lymphocytes exclusively select against it is not yet understood, and further research is needed to understand the mechanisms of this process [12]. In a particularly interesting case study, a patient initially had a CALR-mutated essential thrombocythemia (ET), which was later out-competed by a separate UBA1 gene mutation (pMet41Leu), leading to eventual UBA1 clonal dominance and resolution of the ET. CALR mutations are effective driver mutations in myeloproliferative neoplasms, and the positive selective pressure of the UBA1 mutation in this patient underscores the strength of the mutant UBA1 survival advantage, raising questions about how this is achieved. One possibility is that the mutant UBA1 alleles create an autoinflammatory microenvironment that predisposes these myeloid lineages to survival. Ongoing studies suggest that clonal hematopoiesis (CH) alleles are more commonly seen in VEXAS than previously thought, but the precise effects of co-occurring CH and mutated UBA1 on clone survival and disease outcomes are yet to be fully characterized [13].

DIAGNOSIS

Currently, there are no established national or international guidelines for the screening and treatment of patients with VEXAS. These patients often rely on steroids, and we've observed positive outcomes with the addition of tocilizumab therapy. Given the complexity and diversity of VEXAS, it's crucial for physicians to be aware and consider this diagnosis. Patients may consult with doctors across various medical specialties before receiving a correct diagnosis. It's particularly important for doctors to consider VEXAS in patients over 40 years old who present with inflammatory and/or thrombotic symptoms, especially if they also have macrocytic anaemia or myelodysplasia[14].

TREATMENTS

VEXAS syndrome is a complex condition and currently, there are no standardized treatment guidelines. However, several therapeutic strategies have been explored:

- Corticosteroids: These are frequently used to alleviate inflammation.
- Immunosuppressants: These medications are used to decelerate the immune system's response.
- Bone Marrow Transplant: This is an option if the patient's bone marrow is showing signs of failure. It can also help lessen the severity of certain autoimmune conditions.
- Tocilizumab: This has demonstrated positive outcomes when used as an additional therapy.
- Janus Kinase Inhibitors (JAKi): These have shown potential, but there might be an increased risk for venous thromboembolisms.
- Azacytidine: This has proven to be somewhat effective.

- Allogeneic Stem Cell Transplantation: This is a potentially curative approach, but it carries high risks.

It's important to note that the disease and treatment-associated adverse events remain a challenge. The choice of treatment should be individualized, and clinical trials are needed for the development of treatment algorithms [15].

PROGNOSIS

Individuals diagnosed with VEXAS syndrome face an increased likelihood of developing specific blood-related cancers, particularly hematologic malignancies such as myelodysplastic syndrome (MDS) and plasma cell dyscrasias. Most instances of MDS associated with VEXAS syndrome are typically classified as low-risk. However, there are occasional occurrences where the disease progresses to a more severe state, marked by elevated blasts and transformation into acute myeloid leukemia (AML) [16].

The challenges in addressing VEXAS syndrome lie in the identification of effective medical treatments. Current therapeutic strategies involve the use of corticosteroids, immunosuppressants, and, in some cases, resorting to a bone marrow transplant. Despite these interventions, effectively managing the disease and navigating through adverse events linked to both the condition and its treatments remain formidable obstacles. A crucial focus area for improvement involves finding solutions that strike a delicate balance between targeting the syndrome effectively and minimizing complications associated with its treatment. Enhancing overall care and outcomes for individuals grappling with VEXAS syndrome hinges on advancements in this nuanced approach to treatment [2,16].

RISK ASSESSMENT

The risk assessment for VEXAS syndrome entails assessing the possibility of thrombosis, both arterial (AT) and venous (VTE), which are frequently seen during the course of the disease and may affect as many as 50% of patients. Furthermore, it has been determined that male sex, a mean corpuscular volume >100fL, or a platelet count <200 x 10^9/L are predictive factors for VEXAS syndrome. Individuals diagnosed with VEXAS syndrome frequently exhibit systemic inflammation, encompassing symptoms like neutrophilic dermatosis, chondritis, and vasculitis. The syndrome is linked to significant morbidity and death rates, and since its symptoms are usually resistant to therapy, it is necessary to look into more potent forms of treatment. Furthermore, the association between hematologic malignancies, particularly myelodysplastic syndromes (MDS), and VEXAS syndrome underscores the importance of conducting comprehensive risk assessments and employing appropriate treatment techniques to address this correlation effectively [17,18].

DIET

A holistic approach is crucial for addressing VEXAS syndrome, with a particular emphasis on nutrition in promoting overall health and well-being. The dietary guidelines for VEXAS syndrome are continuously developing due to

its recent identification; however, adhering to a nutritious and well-balanced diet is beneficial in symptom management and overall health enhancement. The inclusion of foods with anti-inflammatory properties, such as fruits, vegetables, nuts, seeds, and oily fish abundant in antioxidants, omega-3 fatty acids, and phytonutrients, can assist in diminishing bodily inflammation. Furthermore, the consumption of healthy fats like avocados, olive oil, and nuts can promote cardiovascular health and supply vital nutrients. Optimal hydration is essential for supporting bodily functions, underscoring the significance of adequate water intake and the avoidance of sugary drinks. A comprehensive diet encompassing a diverse range of nutrients, such as vitamins, minerals, proteins, and carbohydrates, is crucial for overall health and immune system functionality. Given the intricate nature of VEXAS syndrome and its effects on inflammatory and hematologic systems, consulting a registered dietitian or healthcare professional for personalized dietary advice tailored to individual health requirements and symptoms is recommended. While specific dietary strategies for VEXAS syndrome may evolve alongside ongoing research, emphasizing a well-rounded and nutrient-dense diet can bolster the health and well-being of individuals managing this intricate condition. [18-19].

CONCLUSION

VEXAS syndrome is considered a prototype for a novel class of diseases. It is vital for physicians across various specialties to be aware of and consider this diagnosis, as patients may seek consultation from different medical disciplines before receiving an accurate diagnosis. It's important to note that the information is based on the current understanding of VEXAS syndrome and may evolve as more research is conducted.

Conflict of interest: None.

Financial support: None.

Ethics statement: None

REFERENCES

1. Grayson PC, Patel BA, Young NS. VEXAS syndrome. Blood, J Am Soc Hematol. 2021;137(26):3591-4.
2. Cleveland Clinic. VEXAS Syndrome. [Internet]. Cleveland Clinic; [updated 2022; cited 2023]. https://my.clevelandclinic.org/health/diseases/24826-vexas-syndrome.
3. Zhang Y, Dong X, Wang H. VEXAS Syndrome—Review. Glob Med Genet. 2023;10(03):133–43.
4. Poulter JA, Savic S. Genetics of somatic auto-inflammatory disorders. Semin Hematol. 2021;58(4):212–7.
5. 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.
6. Mustjoki S, Young NS. Somatic mutations in “benign” disease. N Engl J Med. 2021;384(21):2039-52.
7. Patel BA, Ferrada MA, Grayson PC, Beck DB, et al. VEXAS syndrome: An

inflammatory and hematologic disease. In: Semin Hematol. 2021;58(4):201-3.
8. Callis J. The ubiquitination machinery of the ubiquitin system. Arabidopsis Book Am Soc Plant Biol. 2014;12.
9. Noronha QW, Fathima T, Bhat R, Shabaraya AR. Current and Emerging Pharmacotherapies for Zika Virus: A Comprehensive Review. Indian J Pharm Drug Stud. 2022;1(3):97-101.
10. Lee SJ, Park JK, Lee EY, Joo SH, Jung KC, Lee EB, et al. Certain Autoimmune Manifestations Are Associated With Distinctive Karyotypes and Outcomes in Patients With Myelodysplastic Syndrome. Medicine. 2016;95(13).
11. Bhat R, Shanbhag P. Long Non-Coding RNAs in Kidney Injury: A Comprehensive Review. J Prev Diagn Manag Hum Dis. 2024;4(2):39-52.
12. Hage-Sleiman M, Lalevée S, Guermouche H, Favale F, Chaquin M, Battistella M, et al. Dominance of an UBA1 mutant clone over a CALR mutant clone: from essential thrombocytemia to VEXAS. Haematologica. 2021;106(12):3245–8.
13. Kusne Y, Fernandez J, Patnaik MM. Clonal hematopoiesis and VEXAS syndrome: survival of the fittest clones?. In: Semin Hematol. 2021;58(4):226-9.
14. Kobak S. VEXAS syndrome: Current clinical, diagnostic and treatment approaches. Intractable Rare Dis Res. 2023;12(3):170-9.
15. Boyadzhieva Z, Ruffer N, Kötter I, Krusche M. How to treat VEXAS syndrome: a systematic review on effectiveness and safety of current treatment strategies. Rheumatology. 2023;62(11):3518–25.
16. Malcovati L. VEXAS: walking on the edge of malignancy. Blood. 2023;142(3):214–5.
17. Bhat R, Saleem FM, Shabaraya AR. Assessing Self-Medication Practices: A Cross-Sectional Study on Implications and Challenges. Indian J Pharm Drug Stud. 2024;3(1):24-8.
18. Al-Hakim A, Savic S. An update on VEXAS syndrome. Expert Rev Clin Immunol. 2022;19(2):203–15.
19. Kreutzinger V, Pankow A, Boyadzhieva Z, Schneider U, Ziegeler K, Stephan LU, et al. VEXAS and Myelodysplastic Syndrome: An Interdisciplinary Challenge. J Clin Med. 2024;13(4):1049.