

Unravelling VEXAS syndrome: An overview of the enigmatic autoimmune condition

Roy B^{1*}, Yi YY²

***Corresponding author:**

Dr. Bedanta Roy,
Associate Professor, Department of Physiology, Faculty of
Medicine, Quest International University, Ipoh, Perak,
Malaysia

Email: bedanta.roy@gmail.com [ORCID](#)

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VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome was first identified in 25 males in 2020. It was found to be linked to myeloid dysplasia and inflammatory illnesses that started in adults [1]. The acronym VEXAS is derived from the key characteristics of the syndrome. Myeloid and erythroid progenitor cells isolated from bone marrow of the affected showed cytoplasmic vacuoles inside the cell. The ubiquitin-activating enzyme, located on the X chromosome and encoded by UBA1, is called the E1 enzyme. Autoinflammatory disease and progressive bone marrow failure arise from mutations in UBA1, found in myeloid cells in the affected individuals. This disease is typically present in adulthood and results from somatic mutations in the blood [2]. This ailment has been reported to primarily affect men, and women are believed to be safeguarded by the unmutated allele [1].

The UBA1 gene is sequenced to make a molecular diagnosis of VEXAS syndrome. The three most prevalent mutations affect methionine 41 of exon 3. These mutations are denoted as UBA1: p.M41T (c.122T>C), p.M41V (c.121A>G), and p.M41L (c.121A>C). Subsequently, several new variants have been documented that involve Splice region mutations at exon 3 (c.118-2A>C and c.118-1G>C) [3] and (c.118-9_118-2del). Furthermore, a codon 56 mutation (c.167C>T) has been described, with patients showing milder clinical conditions [1].

The VEXAS syndrome may be able to explain some of these antecedent clinical relationships. Patients with progressive hematologic abnormalities who do not respond effectively to treatment should be evaluated for VEXAS. Additionally, it has been demonstrated that diagnosing VEXAS syndrome in patients with recurrent polychondritis symptoms and a mean corpuscular volume >100 fL or a platelet count of 200×10⁹/L is highly accurate and reliable [4].

The likelihood of recovery from the syndrome VEXAS is comparatively low because it resists the conventional therapeutic strategy. No standardised treatment is now available; instead, various therapeutic approaches are adopted for the treatment. 40% of the patients died from disease-related causes or treatment toxicity, as most received concurrent glucocorticoids and multiple steroid-sparing drugs [1].

However, azacitidine, a demethylating drug that works most effectively in individuals with concurrent myelodysplastic syndrome (MDS), has shown positive results [5]. Additionally, a multicenter, retrospective study involving a cohort of 30 patients supports using JAK pathway inhibitors as a potential and optimistic therapeutic strategy. Ruxolitinib was found to be more efficient than other JAK inhibitors due to its target specificity and inhibitory action on JAK1 and JAK2, which significantly increased haemoglobin and platelet levels, as well as showing a decrease in corticosteroid dependence in patients after a 6-month course of JAK inhibitors. However, despite the use of these medications, the UBA1 clone can still be identified through sequencing in follow-up samples [6, 7]. Therefore, the only curative option for VEXAS syndrome is allogeneic bone marrow transplantation. The effectiveness of this therapy has undergone rigorous scrutiny. Still, the high death rate has made it necessary to carefully balance the risks and advantages before starting this therapeutic option. VEXAS syndrome can be confirmed through molecular testing of the UBA1 gene and clinical manifestations. Effective treatment options for VEXAS syndrome remain limited. Allogeneic bone marrow transplantation has been proposed as a curative option, especially when medical therapy cannot eradicate UBA1 clones. Further research and collaborative efforts are needed to deepen our understanding of the underlying pathophysiology and develop efficacious treatments to optimise outcomes for affected individuals.

Dr. Bedanta Roy
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Yang Yun Yi
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Disease, infection, management, transmission, virus

Abbreviations

Acquired immunodeficiency syndrome (AIDS), Centers for Disease Control and Prevention (CDC), cytomegalovirus (CMV), Expanded Access-Investigational New Drug (EA-IND), Food and Drug Administration (FDA), Intravenous vaccinia immune globulin (VIGIV)

Availability of data and materials

Not applicable.

Competing interests

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Author information

Dr. Bedanta Roy, Associate Professor, Department of Physiology, Faculty of Medicine, Quest International University, Ipoh, Perak, Malaysia [ORCID](#)

Yang Yun Yi, MBBS student, Faculty of Medicine, Quest International University, No. 227, Plaza Teh Teng Seng (Level 2), Jalan Raja Permaisuri Bainun, 30250 Ipoh, Perak Darul Ridzuan, Malaysia [ORCID](#)

References:

1. Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, *et al.* Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. *N Engl J Med* 2020;383:2628–38. <https://doi.org/10.1056/NEJMoa2026834>
2. Levy-Lahad E, King M-C. Hiding in plain sight - somatic mutation in human disease. *N Engl J Med* 2020;383:2680–2. <https://doi.org/10.1056/NEJMe2030754>
3. Bourbon E, Heiblig M, Gerfaud Valentin M, Barba T, Durel C-A, Lega JC, *et al.* Therapeutic options in VEXAS syndrome: insights from a retrospective series. *Blood* 2021;137:3682–4. <https://doi.org/10.1182/blood.2020010177>
4. Ferrada MA, Sikora KA, Luo Y, Wells KV, Patel B, Groarke EM, *et al.* Somatic mutations in UBA1 define a distinct subset of relapsing polyarthritides patients with VEXAS. *Arthritis Rheumatol* 2021;73:1886–95. <https://doi.org/10.1002/art.41743>
5. Comont T, Heiblig M, Rivière E, Terriou L, Rossignol J, Bouscary D, *et al.* Azacitidine for patients with Vacuoles, E1 Enzyme, X-linked, Autoinflammatory, Somatic syndrome (VEXAS) and myelodysplastic syndrome: data from the French VEXAS registry. *Br J Haematol* 2022;196:969–74. <https://doi.org/10.1111/bjh.17893>
6. Heiblig M, Ferrada MA, Koster MJ, Barba T, Gerfaud-Valentin M, Mékinian A, *et al.* Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study. *Blood* 2022;140:927–31. <https://doi.org/10.1182/blood.2022016642>

7. Roy B. Investigating treatment strategies for VEXAS syndrome: Deciphering the possibilities for therapeutic intervention. *MGM J Med Sci* 2023;10:595.
https://doi.org/10.4103/mgmj.mgmj_185_23