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– CASE REPORT –

# Unmasking VEXAS Syndrome: A Diagnostic Dilemma

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***Abstract***

***Background:*** *VEXAS syndrome is caused by a somatic mutation in the UBA1 gene, required for the ubiquitination of proteins. Patients may present with an array of complications, which may be associated with autoimmune disease, clonal hematopoiesis or monoclonal gammopathy, along with systemic inflammation.*

***Case report:*** *We report a case of a 44-year-old male, who was initially diagnosed with autoimmune disease, found to have myelodysplastic syndrome/myeloproliferative syndrome (MDS/MPN) on work up, and on further evaluation, revealed a UBA1 mutation on next-generation sequencing to establish the diagnosis of VEXAS syndrome. The patient was treated with azacitidine and corticosteroids, resulting in complete resolution of symptoms.*

***Conclusion:*** *Persistent inflammation in VEXAS syndrome may lead to a range of complications. Timely diagnosis is of utmost importance as mortality associated with the syndrome complications is very high.*

***Keywords****: Myelodysplastic syndrome, VEXAS syndrome, inflammation, UBA1 mutation, bone marrow transplant.*

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## Introduction

VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, auto-inflammatory, Somatic) was initially identified by Dr. David Beck and associates in 2020. [1] The presence of a somatic mutation in the ubiquitin-like modifier-activating enzyme 1 (UBA1) on the X chromosome causes defective ubiquitination, leading to inhibition of the ubiquitination-proteasome pathway, one of the pathways responsible for the degradation of abnormal or ageing proteins. Persistent accumulation of these proteins causes endoplasmic reticulum stress and cellular stress, leading to activation of the inflammatory pathway responsible for disease symptoms.[2] The use of the other pathways, the autophagy-lysosomal pathway, to compensate for the degradation of abnormal or ageing proteins is overwhelmed, leading to dysfunction and further accumulation of the protein.[3] Mutations in the hematopoietic precursor lead to vacuolization in the erythroid and myeloid precursors, which, on bone marrow examination, is a characteristic feature of the disease. The disease has a high preponderance towards males at the age of 50 years; however, a case report in a 40-year-old is also documented. [4]

The genetic changes that occur in the disease include a mutation in the UBA1 gene, which encodes the E1 enzyme that initiates ubiquitination. The mutation occurs at codon 41 of the gene, and pMet41Thr is the commonest variant, in which Methionine is replaced by Threonine. Mutations can be missense, and however, splice-site mutations are also observed. Three isoforms of the UBA1 protein exist, with UBA1b being the most observed isoform. The absence of UBA1b leads to increased production of UBA1c, which has lower catalytic activity, resulting in defective ubiquitination.[5]

Dermatological manifestations such as neutrophilic dermatosis, papules, plaques, erythema nodosum, and panniculitis are often seen as presenting complaints. Other manifestations include ocular, respiratory, haematological, musculoskeletal, and thromboembolic symptoms, as well as constitutional symptoms.[6] Patients with VEXAS syndrome have a high propensity for clonal hematopoiesis and include a spectrum of disorders, but not limited to monoclonal gammopathy, myelodysplastic syndrome, cytopenias, increasing morbidity and mortality. Here, in our case report, a 44-year-old gentleman presented complaints of skin rashes, later diagnosed to have MDS/MPN NOS and subsequently was found to have VEXAS syndrome.

## Case presentation

A 44-year-old male presented with recurrent high-grade fever, weight loss of 5 kg over 6 months and a painful erythematous skin rash on the forearm and recurrent oral ulcers along with redness and pain in the right eye. There was no history of any chronic illness, and no significant family history was reported. On examination, the patient was pale and febrile. Multiple erythematous tender nodules were seen on the forearm, and there was splenomegaly of 5 cm from the left mid-clavicular line. Skin biopsy of the nodule showed subcutaneous lobular panniculitis, while laboratory evaluation showed macrocytic anaemia, high erythrocyte sedimentation rate (ESR), positivity of antinuclear antibody (ANA) and HLA-B51. Based on these findings, the patient was diagnosed with Behçet's syndrome according to the international study group criteria. [7] The patient was started on prednisolone, methotrexate, and azathioprine, which mildly improved the patient's symptoms. A year later, he again presented in the outpatient department (OPD) in view of persistent fever, generalised swelling and fatigue, dyspnea, modified medical research council (MMRC) grade III with history of packed red blood cells (PRBC) transfusion in every 45 days for past 5 months. Laboratory investigations revealed bicytopenia with leucocytosis. Bone marrow findings showed hypercellular proliferative marrow with multilineage dysplasia, along with vacuolization in the erythroid and myeloid lineages, as shown in image 1.

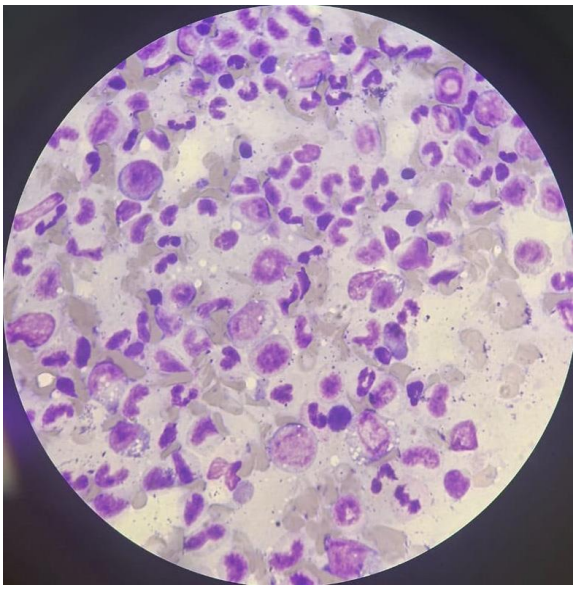

***Image 1.*** *Bone marrow showing Erythroid and myeloid precursors vacuolization*

The MDS fluorescent in situ hybridisation (FISH) panel was normal; karyotyping showed 46XY. Immunohistochemistry (IHC) showed positivity for CD34 and CD117. Myeloid panel detected no mutations. Patient was diagnosed with MDS/MPN not otherwise specified (MDS/MPN NOS). High-resolution computed tomography (HRCT) showed bilateral consolidation requiring a month-long intensive care unit (ICU) admission in view of sepsis and septic shock with multiple transfusions. Due to persistent fever and increased inflammatory markers along with splenomegaly, the patient was diagnosed with secondary hemophagocytic lymphohistiocytosis (HLH). He was started on corticosteroids, etoposide (weekly), and azacitidine, with a good initial response, no longer requiring blood transfusions. Meanwhile, whole-exome sequencing revealed a UBA1 mutation suggestive of VEXAS syndrome. Patient received 4 cycles of azacytidine and etoposide and was maintained on the low dosage of corticosteroid therapy (10mg) due to recurring dermatological symptoms. Presently, the patient is transfusion independent, and his recent blood workup is shown in Table 1.

***Table 1.*** *Patient's blood work up timeline*

| Parameter/ Year-wise Blood work up | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 |
|---|---|---|---|---|---|---|
| Hemoglobin(HB ) g/dl | 7.3 | 6.5 | 9.8 | 9.6 | 10.0 | 9.0 |
| TLC/µl | 15000 | 14000 | 8300 | 7000 | 6500 | 5799 |
| Platelets/µl | 11000 | 25000 | 153000 | 200000 | 170000 | 120000 |
| CRP (mg/L) | 88 | 80 | 50 | 30 | 10 | <10 |
| Ferritin mg/dl | 1215 | 4840 | 3460 | 1200 | 1300 | 800 |
| MCV(Fl) | 121 | - | - | - | - | 101 |

## Discussion

VEXAS syndrome is a heterogeneous disease and often presents with complaints related to the presence of autoimmune disease or haematological abnormalities. The syndrome has a predilection for males over 50 years of age; however, a few cases in females have also been

reported, probably due to X-chromosome inactivation. American and European males are mainly affected, and few case reports from the Asian region are available. Poor response to treatment of autoimmune disease with progressive cytopenia raises suspicion of the disorder.[5] Dermatological manifestations are observed in nearly 80% of patients with VEXAS syndrome, as in our case, the patient had an erythematous skin lesion on the forearm, which was found to have panniculitis on biopsy, and had an initial response to corticosteroids, methotrexate, and Azathioprine, but skin lesions reappeared along with the progressive cytopenia.[5,8] Any cytopenia with an underlying immune disorder is likely considered immune-mediated, and remission in the primary disease often brings count recovery. In our patient, relapse of dermatological manifestations and new onset cytopenia prompted us to consider bone marrow examination, which showed dysplasia along with vacuolization in the erythroid and myeloid precursors, prompting us to investigate the possible presence of VEXAS syndrome. The clinical exome sequencing reveals a UBA1 mutation at codon 41, changing the amino acid Methionine to Threonine. This mutation is among the most common observed in VEXAS syndrome, and other mutations include the replacement of methionine by Valine or Leucine.[9] Replacement of Threonine is classified as classical VEXAS syndrome, observed in 60% of cases, while replacement with Leucine is considered a good prognostic factor. [10] All three mutations have a specific syndromic predisposition. In our case, there is an increased risk of inflammatory eye disease as our patient had ocular hyperemia and pain in the right eye; however, our patient had MDS/MPN NOS, which was more frequently seen with a mutation involving Valine in place of Methionine. [10] Chondritis is one of the most common symptoms of VEXAS syndrome, observed in 60-100% of patients, and symptoms often start with auricular or nasal chondritis, but our patient had an initial dermatological rash on the forearm.[11]

Peripheral blood examination of our patient showed macrocytic anaemia, a finding replicated in our study and in other studies, along with monocytopenia, seen in approximately 50% of individuals.[12] Though these findings are not characteristics of VEXAS syndrome, they hint towards the possibility of VEXAS syndrome. Bone marrow findings of the presence of myeloid and erythroid precursors vacuolization does not only happen in VEXAS syndrome and a few mineral deficiencies, such as copper deficiency, along with other causes like zinc excess, Pearson's syndrome and acute alcohol intoxication.[13] The clinical correlation between high-grade inflammation and supporting symptoms and marrow findings helps in reaching a diagnosis. VEXAS syndrome has a propensity for disease transformation to acute leukaemia and hence mandates early diagnosis and treatment. [14] HLH is a condition of hyperinflammation and is found in a few case reports of VEXAS syndrome. In our patient, we have given intravenous Etoposide and Dexamethasone, which have decreased fever episodes and improved cytopenias.[15] Treatment of VEXAS syndrome is necessary to tackle the ongoing unopposed inflammation with improvement of cytopenia via growth factors and chemotherapy if associated with MDS or disease transformation. Our patient received 4 cycles of azacitidine along with Etoposide( for HLH), which improved the patient's general condition.

## Conclusion

VEXAS syndrome is a heterogeneous disease which needs early diagnosis, multidisciplinary care and molecular diagnosis. Treatment is mainly based on corticosteroids and hypomethylating agents, along with supportive management of the underlying complication.

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Ethics Statement and Conflict of Interest Disclosures

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Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by the participant in this study.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interests: The authors declared that they have no competing interests.

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