LETTER TO THE EDITOR
DOI: 10.4274/tjh.galenos.2025.2025.0080

A Case of VEXAS Syndrome Presenting with Unexplained Headache

Ataş Ü. Et al.: A New Case of VEXAS Syndrome and Headache

Ünal Ataş[1], Fadime Nurcan Alhan[1], Dilek Beypınar[2], Sevinç Şahin[2], Şakir Özgür Keşkek[3]

[1]Alanya Alaaddin Keykubat University, Alanya Training and Research Hospital, Department of Internal Medicine, Division of Hematology, Antalya, Türkiye
[2]Alanya Alaaddin Keykubat University, Alanya Training and Research Hospital, Department of Medical Pathology, Antalya, Türkiye
[3]Alanya Alaaddin Keykubat University, Alanya Training and Research Hospital, Department of Internal Medicine, Antalya, Türkiye

Ünal Ataş, M.D., Alanya Alaaddin Keykubat University, Alanya Training and Research Hospital, Department of Internal Medicine, Division of Hematology, Antalya, Türkiye
vrlunalatas@gmail.com

March 3, 2025
April 7, 2025

Letter to the Editor

VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) is a rare autoinflammatory disorder first described in 2020, caused by somatic mutations in UBA1, an X-linked gene encoding ubiquitin-like modifier activating enzyme 1 [1]. It is predominantly observed in older men and presents with a variety of systemic inflammatory manifestations and hematologic abnormalities, including cytopenias. The clinical spectrum of VEXAS syndrome includes fever, diverse skin lesions (papules, infiltrative plaques, nodules, livedo racemosa), neutrophilic dermatosis, small- and medium-vessel vasculitis, chondritis, arthritis or arthralgia, periorbital edema, uveitis, scleritis, pleural and peritoneal effusions, pulmonary infiltrates, and involvement of the gastrointestinal and central nervous systems [1-4].

We report the case of an 80-year-old male who was hospitalized for further evaluation of a six-week history of persistent headache that did not respond to analgesics, accompanied by maculopapular lesions primarily on the legs (Figure 1A). Laboratory investigations revealed hemoglobin of 7.4 g/dL, MCV of 89 fL, neutrophil count of 2700/mm³, and platelet count of 34,000/mm³. The patient's medical history included only diabetes mellitus and hypertension. Initial diagnostic workup failed to identify an explanation for his cytopenias. Neurological examination was unremarkable, and both computed tomography and magnetic resonance imaging showed no evidence of hemorrhage, ischemia, thrombosis, parenchymal lesions, leptomeningeal enhancement, or vasculitic changes in the intracranial, cervical, or temporal vascular structures. The patient also had unexplained pleural effusion and minimal ascites. During hospitalization, he developed arthritis in the right knee and epididymitis/orchitis. A skin biopsy was consistent with small-vessel neutrophilic/leukocytoclastic vasculitis (Figure 1B).

Bone marrow aspiration revealed myeloid precursor cells with cytoplasmic vacuoles (Figure 1C), while bone marrow biopsy demonstrated hypercellularity with trilineage dysplasia, a few myeloid precursors with poorly defined vacuoles (Figure 1D), and no excess blasts, consistent with myelodysplastic syndrome (MDS). Chromosomal analysis identified -Y [20], with no fluorescence in situ hybridization (FISH) findings suggestive of MDS. Next-generation sequencing confirmed the presence of the UBA1 c.121A>G (p.Met41Val) mutation, leading to the diagnosis of VEXAS syndrome and low-risk MDS. Methylprednisolone was initiated, resulting in significant improvement in the patient's vasculitic rash, arthritis, epididymitis/orchitis, and headache. After three months of treatment, hemoglobin increased to 8.5 g/dL, platelet count rose to 80,000/mm³, and the corticosteroid dose was gradually tapered. Unfortunately, the patient succumbed to pneumonia in the fifth month of follow-up.

Neurological involvement in VEXAS syndrome has been reported in approximately 10% of cases, with 70% affecting the peripheral nervous system (PNS) and 30% involving the central nervous system (CNS). While

polyneuropathies are the most common PNS manifestations, CNS involvement is highly heterogeneous, with headache being exceptionally rare (reported in only 2 out of 30 cases). In nearly all cases with CNS involvement, abnormal findings are observed in imaging, nerve conduction studies, or cerebrospinal fluid (CSF) analysis [5]. Although we did not identify radiological evidence of CNS involvement in our patient, the absence of CSF analysis remains a limitation in our interpretation. Nevertheless, the patient exhibited a marked response to corticosteroids, consistent with previous reports [5].

Hematologic abnormalities in VEXAS syndrome most commonly include MDS, characterized by cytopenias and myeloid precursors with cytoplasmic vacuolization. In addition, plasma cell dyscrasias and both arterial and venous thrombotic events have been described [1,3,4,6]. The detection of vacuolated myeloid precursors in bone marrow aspiration smears is a key diagnostic feature, yet histopathologic identification can be challenging and may be missed if not specifically sought.

Although high-dose glucocorticoids effectively control inflammatory symptoms, their long-term use is challenging due to significant adverse effects. Alternative treatment options include hypomethylating agents and targeted therapies such as JAK inhibitors, IL-6 inhibitors, and IL-1 inhibitors. In selected refractory cases, allogeneic stem cell transplantation may be considered [7].

Keywords: VEXAS syndrome, Myelodysplastic syndrome, Autoinflammatory

Conflicting Interest: The authors declared that they have no potential conflicts of interest.
Funding Disclosure: The authors declared that this study received no financial support.
Authorship Contributions: All authors contributed to the management of the patient and collected clinical information. All authors read, critically reviewed and approved the manuscript.

References

1. Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, Balanda N, Ross DL, Ospina Cardona D, Wu Z, Patel B, Manthiram K, Groarke EM, Gutierrez-Rodrigues F, Hoffmann P, Rosenzweig S, Nakabo S, Dillon LW, Hourigan CS, Tsai WL, Gupta S, Carmona-Rivera C, Asmar AJ, Xu L, Oda H, Goodspeed W, Barron KS, Nehrebecky M, Jones A, Laird RS, Deuitch N, Rowczenio D, Rominger E, Wells KV, Lee CR, Wang W, Trick M, Mullikin J, Wigerblad G, Brooks S, Dell'Orso S, Deng Z, Chae JJ, Dulau-Florea A, Malicdan MCV, Novacic D, Colbert RA, Kaplan MJ, Gadina M, Savic S, Lachmann HJ, Abu-Asab M, Solomon BD, Retterer K, Gahl WA, Burgess SM, Aksentijevich I, Young NS, Calvo KR, Werner A, Kastner DL, Grayson PC. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. *N Engl J Med*. 2020;383(27):2628-2638.
2. Zakine E, Schell B, Battistella M, Vignon-Pennamen MD, Chasset F, Mahévas T, Cordoliani F, Adès L, Sébert M, Delaleu J, Jachiet M, Lepelletier C, Lemaire P, Chauvel C, Dhouaieb B, Kim R, Cassius C, Georgin-Lavialle S, Mekinian A, Bagot M, Braun T, Rousset L, Begon E, de Masson A, Fenaux P, Clappier E, Bouaziz JD. UBA1 Variations in Neutrophilic Dermatosis Skin Lesions of Patients With VEXAS Syndrome. *JAMA Dermatol*. 2021;157(11):1349-1354.
3. Georgin-Lavialle S, Terrier B, Guedon AF, Heiblig M, Comont T, Lazaro E, Lacombe V, Terriou L, Ardois S, Bouaziz JD, Mathian A, Le Guenno G, Aouba A, Outh R, Meyer A, Roux-Sauvat M, Ebbo M, Zhao LP, Bigot A, Jamilloux Y, Guillotin V, Flamarion E, Henneton P, Vial G, Jachiet V, Rossignol J, Vinzio S, Weitten T, Vinit J, Deligny C, Humbert S, Samson M, Magy-Bertrand N, Moulinet T, Bourguiba R, Hanslik T, Bachmeyer C, Sebert M, Kostine M, Bienvenu B, Biscay P, Liozon E, Sailler L, Chasset F, Audemard-Verger A, Duroyon E, Sarrabay G, Borlot F, Dieval C, Cluzeau T, Marianetti P, Lobbes H, Boursier G, Gerfaud-Valentin M, Jeannel J, Servettaz A, Audia S, Larue M, Henriot B, Faucher B, Graveleau J, de Sainte Marie B, Galland J, Bouillet L, Arnaud C, Ades L, Carrat F, Hirsch P, Fenaux P, Fain O, Sujobert P, Kosmider O, Mekinian A; French VEXAS group; GFEV, GFM, CEREMAIA, MINHEMON. Further characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients. *Br J Dermatol*. 2022;186(3):564-574.
4. Beck DB, Bodian DL, Shah V, Mirshahi UL, Kim J, Ding Y, Magaziner SJ, Strande NT, Cantor A, Haley JS, Cook A, Hill W, Schwartz AL, Grayson PC, Ferrada MA, Kastner DL, Carey DJ, Stewart DR. Estimated Prevalence and Clinical Manifestations of UBA1 Variants Associated With VEXAS Syndrome in a Clinical Population. *JAMA*. 2023;329(4):318-324.
5. Bert-Marcaz C, Fortanier É, Briantais A, Faucher B, Bourguiba R, Swiader L, Schleinitz N, Corazza G, Jean R, Bigot A, Marianetti-Guingel P, Kostine M, Outh R, Dieudonné Y, Lazaro E, Vial G, Palat S, Frachet S, De Almeida Chaves S, Vinzio S, Sacré K, Robert M, Comont T, Dion J, Girardie P, Lacombe V, Langlois V, Jachiet V, Decker P, Moulinet T, Grosleron S, Broner J, Guilpain P, Samson

M, Terrier B, Georgin-Lavialle S, Attarian S, Mekinian A, Delmont E, Ebbo M; FRENVEX; MINHEMON; FILNEMUS. Neurological manifestations in patients with VEXAS syndrome. J Neurol. 2025 Feb 1;272(2):181.
6. Obiorah IE, Patel BA, Groarke EM, Wang W, Trick M, Ombrello AK, Ferrada MA, Wu Z, Gutierrez-Rodrigues F, Lotter J, Wilson L, Hoffmann P, Cardona DO, Patel N, Dulau-Florea A, Kastner DL, Grayson PC, Beck DB, Young NS, Calvo KR. Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. *Blood Adv*. 2021;5(16):3203-3215.
7. Boyadzhieva Z, Ruffer N, Kötter I, Krusche M. How to treat VEXAS syndrome: a systematic review on effectiveness and safety of current treatment strategies. *Rheumatol Oxf Engl*. 2023;62(11):3518-3525.

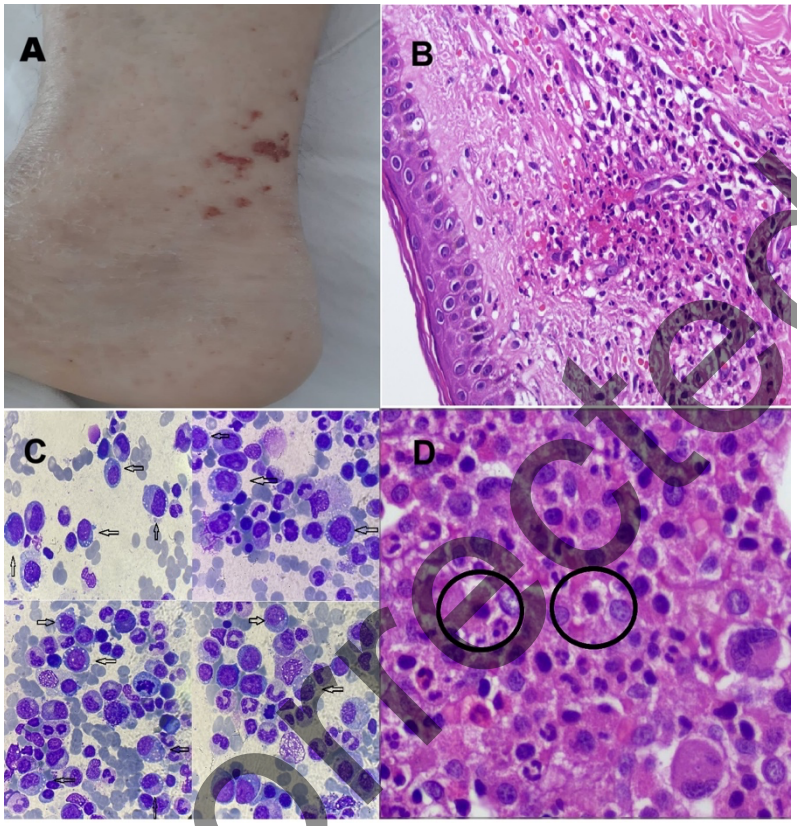

Figure 1. A) Irregularly bordered, erythematous to violaceous maculopapular lesions with areas of hemorrhagic crusting and ulceration; **B)** Perivascular inflammation with neutrophilic infiltration, fibrin deposition, and nuclear debris (Hematoxylin&Eosin,40x); **C)** Bone marrow aspiration smear showing myeloid precursor cells with cytoplasmic vacuoles (100x); **D)** Bone marrow biopsy demonstrating vacuolated myeloid cells (circles) (Hematoxylin & Eosin, 400x, original magnification).