LETTER TO THE EDITOR

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A Case of VEXAS Syndrome Presenting with Unexplained Headache

Açıklanamayan Baş Ağrısı ile Başvuran Bir VEXAS Sendromu Olgusu

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To the Editor,

"Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic" syndrome (VEXAS) 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 hematological abnormalities, including cytopenia. 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 (CNS) [1,2,3,4].

We report the case of an 80-year-old man who was hospitalized for further evaluation of a 6-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, mean corpuscular volume of 89 fL, neutrophil count of 2700/mm^3, and platelet count of 34,000/mm^3. The patient's medical history included only diabetes mellitus and hypertension. An initial diagnostic workup failed to identify an explanation for the 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 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 3 months of treatment, his hemoglobin increased to 8.5 g/dL, the platelet count rose to 80,000/mm^3, and the corticosteroid dose was gradually tapered. Unfortunately, the patient died of pneumonia in the fifth month of follow-up.

Neurological involvement in VEXAS syndrome has been reported in approximately 10% of cases, with 70% involving the peripheral nervous system (PNS) and 30% involving the 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 of CNS involvement, abnormal findings are observed in imaging, nerve conduction studies, or cerebrospinal fluid (CSF) analysis [5]. Although we did not identify any radiological evidence of CNS involvement in our patient, the absence of CSF analysis constitutes a limitation in our interpretation. Nevertheless, the patient exhibited a marked response to corticosteroids, consistent with previous reports [5].

Hematological abnormalities in VEXAS syndrome most commonly include MDS, characterized by cytopenia and myeloid precursors with cytoplasmic vacuolization. In addition, plasma cell dyscrasias and both arterial and venous thrombotic events

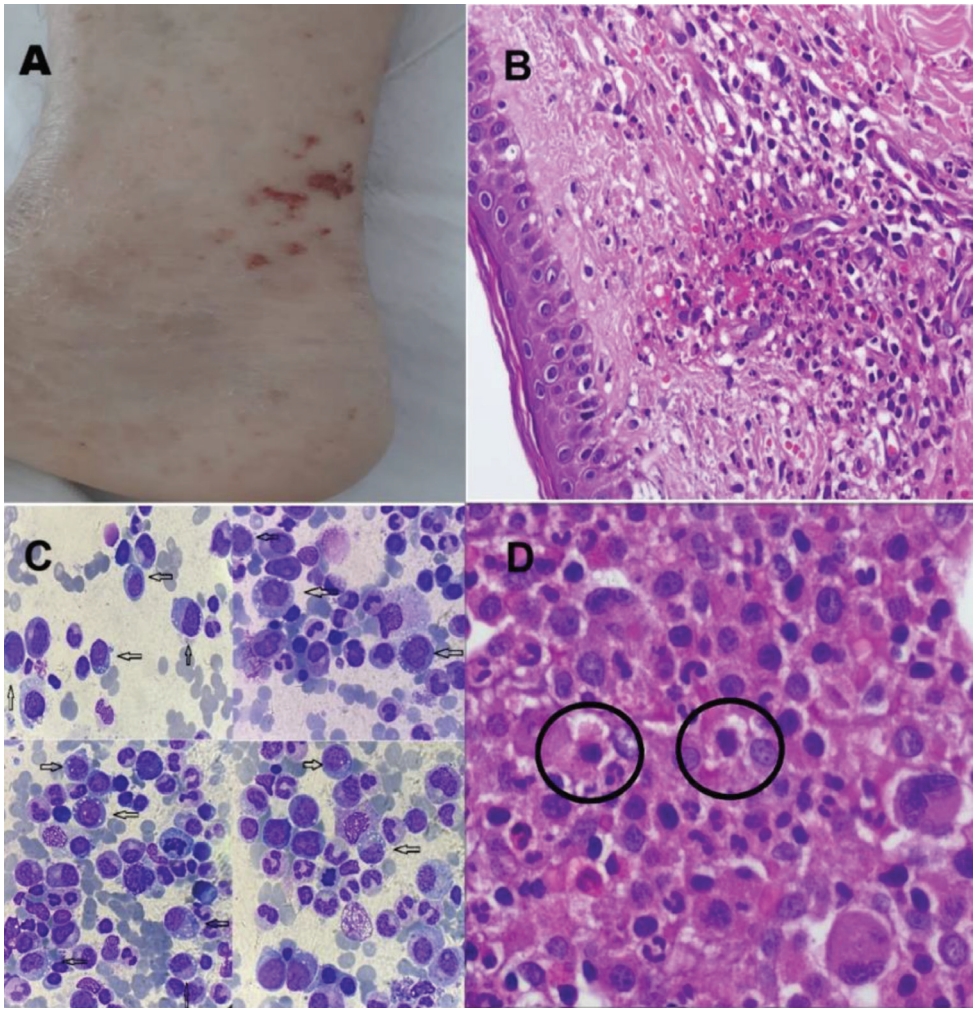

Figure 1. A) Irregularly bordered erythematous to violaceous maculopapular lesions with areas of hemorrhagic crusting and ulceration. B) Perivascular inflammation with neutrophilic infiltration, fibrin deposition, and nuclear debris (hematoxylin and eosin, 40^{x}). C) Bone marrow aspiration smear showing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

have been described [1,3,4,6]. The detection of vacuolated myeloid precursors in bone marrow aspiration smears is a key diagnostic feature, but histopathologic identification can be challenging and these myeloid precursors 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, interleukin-6 inhibitors, and interleukin-1 inhibitors. In selected refractory cases, allogeneic stem cell transplantation may be considered [7].

Keywords: VEXAS syndrome, Myelodysplastic syndrome, Autoinflammatory

Anahtar Sözcükler: VEXAS sendromu, Miyelodisplastik sendrom, Otoenflamatuvar hastalık

Ethics

Informed Consent: Written informed consent could not be obtained due to the patient's death; all data have been anonymized.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ü.A., F.N.A., Ş.Ö.K.; Concept: Ü.A., D.B., S.Ş.; Design: Ü.A., F.N.A.; Data Collection or Processing: Ü.A., D.B., S.Ş.; Analysis or Interpretation: Ü.A., D.B., S.Ş., Ş.Ö.K.; Literature Search: Ü.A., D.B., S.Ş.; Writing: Ü.A., F.N.A., D.B., S.Ş., Ş.Ö.K.

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