Aortic-renal aneurysm in a patient with VEXAS syndrome treated with Tocilizumab

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Submitted: 03/01/2026

Accepted: 16/01/2026

Abstract

VEXAS syndrome is an adult-onset autoinflammatory disease caused by somatic mutations in the *UBA1* gene and is characterized by overlapping rheumatologic and hematologic clinical features. The most common clinical manifestations include recurrent fever, arthralgia/arthritis, pulmonary involvement, skin lesions, vasculitis, and/or thromboembolic events. Aortic–renal aneurysm in VEXAS syndrome is a rare entity and is associated with poor prognosis. Herein, we describe a 69-year-old male patient with VEXAS syndrome complicated by an aortic–renal aneurysm who responded well to tocilizumab treatment.

Keywords: VEXAS syndrome, aneurysm, tocilizumab, treatment

Introduction

VEXAS syndrome is a hemato-inflammatory condition caused by somatic mutations in the *UBA1* gene, which encodes the major E1 enzyme that initiates ubiquitylation[1]. Ubiquitylation is essential for various cellular processes, such as cell cycle progression, DNA damage response, and inflammatory signaling pathways. Dysregulation of the ubiquitin–proteasome system results in susceptibility to infections, lymphoproliferative disorders, autoinflammatory diseases, and malignancies. VEXAS syndrome often manifests with overlapping rheumatologic and hematologic clinical features[2]. It usually affects middle-aged and older individuals, predominantly men, and the true prevalence of the syndrome in the general population is not yet known[3]. The most common clinical features include recurrent fever, arthralgia/arthritis, pulmonary involvement, skin lesions, vasculitis, and/or thromboembolic events. VEXAS syndrome may mimic known rheumatologic diseases or coexist with them. Because it can present with clinical findings seen in many different rheumatologic conditions, misdiagnosis was common before it was defined. Patients previously diagnosed with vasculitis, connective tissue disease, and/or autoinflammatory disease have been found to have VEXAS syndrome in light of recent data.

Case Report

A 69-year-old male patient presented to our rheumatology clinic with recurrent fever, fatigue, weight loss, swelling of the left eyelid, skin lesions, dry cough, and pain, swelling, and limited movement in the left wrist and metacarpophalangeal (MCP) joints. His medical history revealed no chronic illnesses or medication use, and he had never smoked. On physical examination, vital signs were stable. Arthritis of the left wrist and the 2nd, 3rd, and 4th MCP joints was observed, along with erythema nodosum–like skin lesions on the upper and lower extremities. Laboratory evaluation revealed elevated acute-phase reactants: C-reactive protein (CRP) 89 mg/L (normal 0–5), erythrocyte sedimentation rate (ESR) 95 mm/h, and serum amyloid A (SAA) 15 mg/dL (normal <0.50). Complete blood count showed mild pancytopenia and macrocytic anemia. Serological tests, including rheumatoid factor (RF), antinuclear antibody (ANA), extractable nuclear antigen (ENA) profile, antineutrophil cytoplasmic antibody (ANCA), anti-cyclic citrullinated peptide antibody (anti-CCP), lupus anticoagulant (LA), anticardiolipin antibody (ACA) IgG/IgM, and anti–beta-2 glycoprotein I antibody IgG/IgM, were all negative. Familial Mediterranean fever (FMF) mutation analysis and other autoinflammatory disease genetic panels were also negative. No infectious focus was detected following consultation with an infectious disease specialist. Radiologic examinations were performed. Thoracic CT revealed a 4.5-mm solid nodule in the posterobasal segment of the right lung, along with peribronchovascular and septal thickening and ground-glass opacities. A chest diseases consultation was obtained, and bronchoscopy with bronchoalveolar lavage (BAL) was performed to evaluate for infection or malignancy. Bronchoscopy revealed no pathological findings; no malignant cells were observed in BAL fluid, and cultures, including acid-fast bacilli (AFB), showed no growth. PET-CT demonstrated increased FDG uptake in the subcutaneous tissues of both lower extremities. Skin biopsy from these lesions was consistent with lymphoplasmacytic dermatitis. Orbital MRI revealed an inflammatory process with contrast enhancement extending along the left temporal muscle fibers into the subcutaneous tissues of the left preseptal orbital area and partially into the retro-orbital region, accompanied by mild proptosis of the left globe. Brain MRI was normal. Based on advanced age, male sex, fever, skin lesions, pancytopenia, macrocytic anemia, and musculoskeletal involvement, VEXAS syndrome was suspected. Genetic consultation was obtained, and *UBA1* mutation analysis identified a pathogenic *UBA1* (Met41Thr) variant consistent with VEXAS syndrome. Bone marrow biopsy performed by a hematologist revealed minimal megakaryocytic dysplasia. Treatment with methylprednisolone 32 mg/day was initiated. One month later, the patient's symptoms

resolved, and laboratory parameters normalized. Over the subsequent three months, the methylprednisolone dose was tapered to 4 mg/day. At the fourth month of follow-up, the patient presented with sudden-onset abdominal pain, bloating, nausea, and fatigue. Physical examination revealed diffuse abdominal tenderness. Laboratory tests showed CRP 138 mg/dL, ESR 67 mm/h, SAA 52.20 mg/dL, and D-dimer 1.41 µg/mL. Abdominal ultrasonography revealed a saccular aneurysm with a thrombosed component in the abdominal aorta at the level of the renal artery. CT angiography demonstrated an aneurysmal dilatation measuring 35 mm in length and 52 mm in maximal diameter, with mildly lobulated contours and a mural thrombus up to 10 mm in thickness. Hypodense wedge-shaped areas and focal cortical thinning suggestive of chronic infarction were noted in the left kidney. PET-CT showed intense FDG uptake (SUV 8.1) in the aneurysmal segment of the abdominal aorta and renal artery, supporting an inflammatory etiology consistent with vasculitis. High-dose methylprednisolone (1 mg/kg/day) was initiated; however, acute-phase reactants remained elevated. Tocilizumab (TCZ) 162 mg subcutaneously once weekly was subsequently started. Due to rapid aneurysm progression and high rupture risk, endovascular repair was successfully performed without complications. One month later, the patient's symptoms resolved, and inflammatory markers normalized. Over the following months, corticosteroids were tapered to 8 mg/day. At six months of follow-up, the disease remained stable, and rheumatology outpatient follow-up continues.

Discussion

Herein, we report an aortic–renal aneurysm in a 69-year-old male patient with VEXAS syndrome; to our knowledge, this is the first such case reported in the literature. The precise mechanisms by which *UBA1* mutations drive inflammation remain unclear. Increased inflammation in VEXAS syndrome is driven by mutant myeloid cells that survive despite harboring somatic mutations. Patients exhibit highly activated inflammatory pathways involving tumor necrosis factor, interleukin-6, and interferon-γ. Activation of multiple cytokine cascades results in elevated acute-phase reactants, a hallmark laboratory finding in VEXAS syndrome[4]. VEXAS syndrome typically affects middle-aged and older men, and its true prevalence remains unknown[5]. Hematologic features include progressive abnormalities such as macrocytic anemia, thrombocytopenia, myeloid dysplasia, and bone marrow vacuolization restricted to myeloid and erythroid precursor cells. Common clinical manifestations include recurrent fever, arthralgia/arthritis, pulmonary involvement (neutrophilic alveolitis), skin lesions, various forms of vasculitis (e.g., PAN, GCA), and thromboembolic events[6]. Currently, no standardized treatment protocols exist for VEXAS syndrome. In the absence of randomized controlled trials,

management is based on clinical experience with autoinflammatory diseases and recently published case series[7]. The disease often demonstrates resistance to multiple therapeutic agents and is associated with high mortality[8]. Most patients require long-term glucocorticoid therapy at doses ≥10 mg/day, with difficulty tapering. Limited responses to conventional and biologic DMARDs highlight the need for alternative treatment strategies. Given the elevated IL-6 and CRP levels observed in VEXAS patients, tocilizumab may be effective for certain disease manifestations, although it does not halt disease progression[9]. In our patient, TCZ was selected as the first biologic agent due to marked inflammatory activity, vascular involvement, and its established efficacy in giant cell arteritis. Complete clinical, laboratory, and radiologic responses were achieved, and TCZ enabled reduction of glucocorticoid dosage to a moderate level (8 mg/day). Data regarding TCZ efficacy in VEXAS syndrome remain limited[10]. Recent results from the international AIDA Network VEXAS registry demonstrated variable responses to biologic therapies[11]. Johansen et al. reported that IL-6 receptor inhibition with TCZ effectively controlled inflammation and reduced prednisone requirements in VEXAS patients[12].

In conclusion, we describe a patient with VEXAS syndrome complicated by an aortic–renal aneurysm who responded well to tocilizumab. Rheumatologists should consider VEXAS syndrome in elderly male patients presenting with recurrent fever, arthritis, vasculitis, macrocytic anemia, and steroid-refractory disease. While the optimal treatment strategy remains unclear, corticosteroids, biologic and targeted DMARDs, chemotherapeutic agents, and bone marrow transplantation have shown potential benefit[13,14,15]. Close collaboration between hematologists and rheumatologists is essential to improve diagnosis, phenotyping, and management of VEXAS syndrome.

Tables and Figures

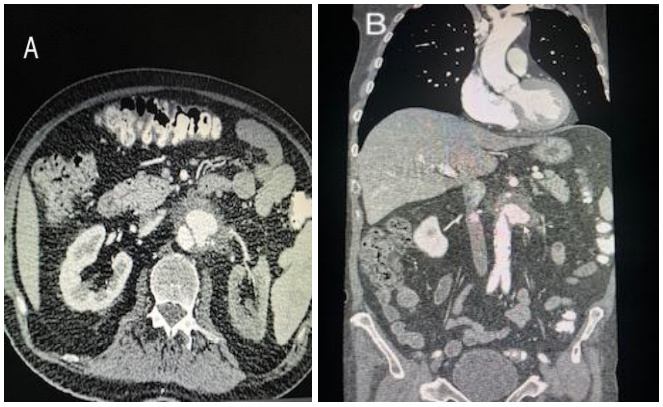

Figure 1 (Panel A / Panel B) - Abdominal CT-angiography showed aneurysmal dilatation in sections passing through the abdominal aorta at the level of the renal artery

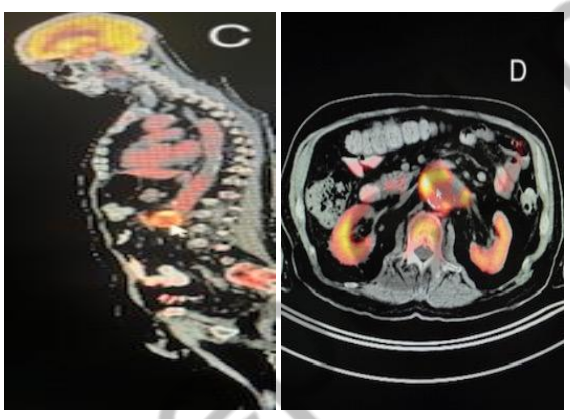

Figure 2 (Panel C / Panel D) - PET-CT showed aneurysmal expansion at the level of the abdominal aorta and renal artery with widespread FDG uptake (SUV: 9.1)

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