VEXAS syndrome diagnosis starting from ultrasound findings: a case report

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Abstract

VEXAS syndrome is a recently described condition characterized by systemic inflammation, predisposition to hematologic malignancy and a high rate of venous thrombosis. Here we report the case of an elderly male with erythema nodosum-like lesions, ankle arthralgia, and general symptoms. B-mode and Doppler ultrasound of the subcutis diagnosed superficial thrombophlebitis of the lower limbs, which turned out to be the manifestation of a paucisymptomatic VEXAS syndrome. VEXAS should be considered in any patient who presents with unexplained superficial thrombophlebitis, macrocytic anemia and unexplained systemic inflammation.

Keywords: VEXAS syndrome; ultrasound; superficial thrombophlebitis; macrocytic anemia

Introduction

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently described autoinflammatory condition determined by mutations in the UBA1 (ubiquitin activating enzyme 1) gene [1,2]. Biologic and conventional synthetic disease-modifying antirheumatic drugs were reported to be ineffective for long-term disease control [2,3]. Glucocorticoids are the only class of medication that can reduce the inflammatory process, with the burden of long-term toxicity [3]. VEXAS patients present a high rate of venous thrombosis due to systemic inflammation, including superficial thrombophlebitis (STP) [3]. In most cases, surgical biopsy of the affected vein is needed to exclude potential differential diagnoses [4]. We present the case of a patient where the presence of STP was the clue for the diagnosis of VEXAS syndrome.

Case report

A 68-year-old Caucasian male, with a history of well-controlled primary arterial hypertension, was referred for a 2-month history of ankle arthralgia, fatigue, and weight loss of 10 kg. Physical examination revealed painful, erythema nodosum-like lesions located in the calves, hands, and forearms (fig 1). Laboratory evaluation revealed marked inflammatory syndrome and macrocytic anemia, without vitamin B12 and folate deficiency (Hemoglobin 8.6 g/dL, C-reactive protein 12.6 mg/dL, Erythrocyte sedimentation rate >140 mm/h, Ferritin 1670 ng/mL).

B-mode and Doppler ultrasound (US) of the subcutis was performed (GE Logiq™ E 10 machine, 18 MHz hockey-stick transducer). The diagnosis of EN was ruled out, but thickened walls in many superficial non-varicose veins with thrombosed areas (with no color Doppler signal) were found in the calves (fig 2, video on the journal site). Deep vein thrombosis was excluded. A biopsy of one of the affected veins showed diffuse transmural inflammatory infiltrate associated with luminal narrowing (fig 3a,b).
Abdominal US, thoraco-abdominopelvic contrast-enhanced computed tomography, upper and lower gastrointestinal endoscopy, and tumor markers were all within normal limits, and Trousseau syndrome was excluded. An extensive screening for hereditary thrombophilias, antiphospholipid syndrome, autoimmune diseases, sarcoidosis, and tuberculosis was performed with no particular pathological results. Furthermore, classification criteria for adult-onset Still disease and haemophagocytic syndrome were not met.

In the diagnostic workup of macrocytic anemia, a bone marrow aspirate was carried out and myelodysplastic syndrome (MDS) or plasma cell dyscrasia was excluded. The presence of vacuolization of myeloid and erythroid precursors (fig 3c) raised suspicion of VEXAS syndrome. UBA1 gene mutations were tested using Next Generation Sequencing (NGS) and the 122T>C (p.Met41Thr) mutation was identified, which confirmed the diagnostic suspicion.

Treatment with oral prednisone, 25 mg/day, was started, which led to the complete resolution of skin rash, arthralgia, and systemic symptoms. Methotrexate 15 mg/week was added for the purpose of tapering the glucocorticoid doses. Anticoagulation with rivaroxaban 10 mg/day was recommended. Three months after the diagnosis, the patient was asymptomatic, and excepting the macrocytic anemia, all laboratory data were within normal range.

Discussion

VEXAS syndrome is a hematological and autoinflammatory disease first described by Beck et al in 2020 using the ‘genotype-first’ approach [1]. UBA1 codes the E1 activating enzyme, which is responsible for ubiquitination-dependent protein degradation and cell homeostasis [2]. To date, 97 case reports regarding VEXAS patients were published on PubMed. Currently, there are neither diagnostic criteria nor guidelines for selecting patients for whom genetic testing is recommended [5,6].

Although some patients may be initially diagnosed with relapsing polychondritis, systemic or cutaneous vasculitis, MDS, Sweet’s syndrome, the presence of atypical manifestations, refractoriness to standard therapy, and an ongoing need for glucocorticoids should raise the suspicion of VEXAS syndrome [5,6,7]. Thus, male patients older than 50 years with a combination of rheumatologic,
hematologic, dermatologic, or pulmonary symptoms, along with macrocytic anemia, thrombocytopenia, and elevated inflammatory markers should undergo targeted bone marrow aspiration [6,7]. The worsening of cytopenias can anticipate MDS and support the need to repeat bone marrow aspirates [7,8].

Ultimately, the definitive diagnosis of the VEXAS syndrome is exclusively based on the detection of pathogenic UBA1 variants [7,9].

Patients with VEXAS syndrome manifest a high rate of thrombotic events (up to 50% in all reported cases), typically in the venous circulation, with an increased likelihood of recurrence, even under anticoagulant treatment [2,3,10]. Elevated factor VIII, lupus anticoagulant and enhanced neutrophil extracellular trap formation might be involved in this process [3].

Starting our diagnostic workup with US combined with the biopsy of the nodular lesion has brought us several advantages. Firstly, we were able to correctly identify the nature of nodular lesions, excluding panniculitis and confirming STP (nodular) in non-varicose veins. Secondly, we were able to narrow down differential diagnoses to three main types of conditions: malignancies, thrombophilia, and systemic or cutaneous vasculitis. Furthermore, in the given clinical setting, we could rule out conditions in which venous involvement represents a distinctive feature, namely, antiphospholipid syndrome, thromboangitis obliterans, and Behçet syndrome (BS). Although our patient did not meet the diagnostic criteria for BS, there are noteworthy similarities between the two conditions, particularly regarding the venous inflammation (venulitis) [10,11]. If this hypothesis holds true, it suggests that US findings in the superficial veins could potentially be useful in the diagnosis of VEXAS syndrome.

Given the systemic inflammation and associated hypercoagulability, antithrombotic prophylaxis should be considered in all patients with VEXAS syndrome, especially in patients with known prothrombotic risk factors and high-risk situations [3,7].

To the best of our knowledge, this is the first case of VEXAS syndrome, where the US and biopsy findings guided the clinician in the diagnostic work-up.

In conclusion, patients with unexplained SVT who present with extensively thickened venous walls and STP on US, should guide the clinician to consider VEXAS syndrome as a differential diagnosis.

References