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VEXAS SYNDROME IN A MOROCCAN PATIENT: THE STORY OF A TWO-YEAR DIAGNOSTIC LAG

Abire Allaoui[1], Lilia Zizi[1], Halima Hadri[2], Doha Kabil[1], Ahmed Aziz Bousfiha[3], Abdelhamid Naitlho[1], Mohamed Adnaoui[1]

[1] Internal Medicine Department, Mohammed VI University of Sciences and Health (UM6SS), Casablanca, Morocco
[2] Hematology Department, Mohammed VI University of Sciences and health (UM6SS), Casablanca, Morocco
[3] Laboratory of Clinical Immunology, Inflammation and Allergy, Faculty of Medicine and Pharmacy of Casablanca, Hassan II University of Casablanca, Casablanca, Morocco

Corresponding author's e-mail: lilia-zizi@hotmail.fr

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ABSTRACT

Background: VEXAS syndrome, also known as vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome, is a newly identified genetic condition characterised by a combination of autoinflammatory symptoms and myeloid dysplasia. The initial description was documented in 2020 and since then, there has been an increasing number of cases and series reported globally.

Case description: We present a case of VEXAS syndrome in an 88-year-old male patient. The patient has a p.Met41Val mutation in the UBA1 gene with notable skin, joint and lung involvement. As far as we know, this is the first documentation of VEXAS syndrome in Morocco and Africa. This condition may exhibit characteristics of recurrent fever, neutrophilic dermatitis, arthritis and chondritis, along with cytopaenias and myelodysplastic syndrome. The p.Met41Val mutation is known to be associated with severe clinical presentation and poor prognosis, with less chondritis involvement and more undifferentiated inflammatory syndrome, as seen in the described case.

Conclusions: VEXAS syndrome represents a prototype for a new classification of diseases, although it is still insufficiently identified in many underdeveloped countries, especially in Africa. It should be considered in elderly males with unexplained fever associated with systemic manifestations and worsening haematologic abnormalities.

KEYWORDS

VEXAS syndrome, myelodysplastic syndrome, autoinflammation, immune dysregulation, genetics

LEARNING POINTS

- This is the first documentation of VEXAS syndrome in Morocco and Africa, underscoring the technical challenges in the diagnosis of VEXAS disease in this part of the world.
- Fever and myelodysplastic syndrome in adults should suggest the diagnosis of VEXAS syndrome.
- A p.Met41Val mutation in the UBA1 gene is related to an increased mortality.

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INTRODUCTION/BACKGROUND

Myelodysplastic syndrome is frequently linked to autoimmunity and inflammation, to the point where it can be considered that myelodysplastic syndrome and autoimmune disorders are two sides of the same coin and share the same underlying mechanisms[1]. Dysregulation of the immunological environment and impaired levels of inflammatory cytokines, such as tumour necrosis factor-α, interferon-γ, interleukin (IL)-6, IL-8 and IL-17, appear to play a pivotal role in the pathogenesis of the disease[2]. In this context, VEXAS syndrome stands out as a notable example.

VEXAS syndrome stands for vacuoles, E1 enzyme, X-linked, autoinflammatory and somatic syndrome. This syndrome is a newly identified condition resulting from a mutation in the UBA1 gene, which causes an acquired autoinflammatory disease in adults. VEXAS was first reported in 2020 in 25 men with adult-onset inflammatory disease and myeloid dysplasia[1].

Clinical manifestations vary widely and are characterised by inflammatory and haematological involvement, defining a new category of haemato-inflammatory disease[2]. The most common signs include fever, skin lesions, arthritis, chondritis, cytopaenias (macrocytic anaemia, thrombocytopenia), infiltrative lung disease and venous thrombosis[3]. Systemic involvement is important because it makes other diagnoses such as polyarteritis nodosa, relapsing polychondritis or Sweet's syndrome more likely[3]. It causes significant morbidity and reduced life expectancy, and the standards of care remain undefined, but interest in this newly described disease is worldwide[2].

This article describes the first case of VEXAS syndrome reported in Morocco and Africa to the best of our knowledge; we searched in PubMed with the following search terms "VEXAS syndrome" + "Africa" – and found no reports. In this report, we underscored the impact of the clinician's flair and the crucial contribution of genetics to diagnosis.

CASE DESCRIPTION

We report the case of an 88-year-old patient initially admitted to intensive care for febrile respiratory distress. His medical history included high blood pressure and a COVID-19 infection the previous year. He is of Berber origin. The history of the disease dated back a few weeks, with the onset of an anaemic syndrome, bone pain and oedematous polyarthritis (RS3PE-like) in the context of a deteriorating general condition.

While in the hospital, he had recurrent febrile spikes with no individualised germ. He also had painful erythematous skin lesions *(Fig. 1)* and oedematous polyarthritis *(Fig. 2)*.

The biological workup showed macrocytic anaemia and lymphopenia. There was a significant inflammatory syndrome with a C-reactive protein of 240 mg/l, elevated ferritinaemia, hypoalbuminemia, hyper-alpha 1/alpha 2 proteins and polyclonal hypergammaglobulinemia on protein electrophoresis. All tests for infectious markers have shown negative results. The levels of C3 and C4 were within the normal range and the immunological testing, which included tests for anti-nuclear antibodies, rheumatoid factor, anti-citrullinated protein antibodies and anti-proteinase 3/MPO antibodies, yielded negative results. The levels of vitamins B9 and B12 were normal.



Figure 1. Erythematous skin lesions.



Figure 2. Oedematous polyarthritis (RS3PE-like).

A temporal artery ultrasound did not find signs of temporal arteritis. A thoracic-abdominal-pelvic computed tomography (CT) scan was performed to search for a possible neoplastic cause, finding diffuse interstitial lung disease *(Fig. 3)*. The 18F-FDG PET/CT images *(Fig. 4)* demonstrated intense FDG uptake in the bone marrow with bilateral basal pulmonary hypermetabolism associated with non-hypermetabolic pleurisy.

The patient was prescribed empirical anti biotherapy and corticosteroids, then he was released from the hospital.

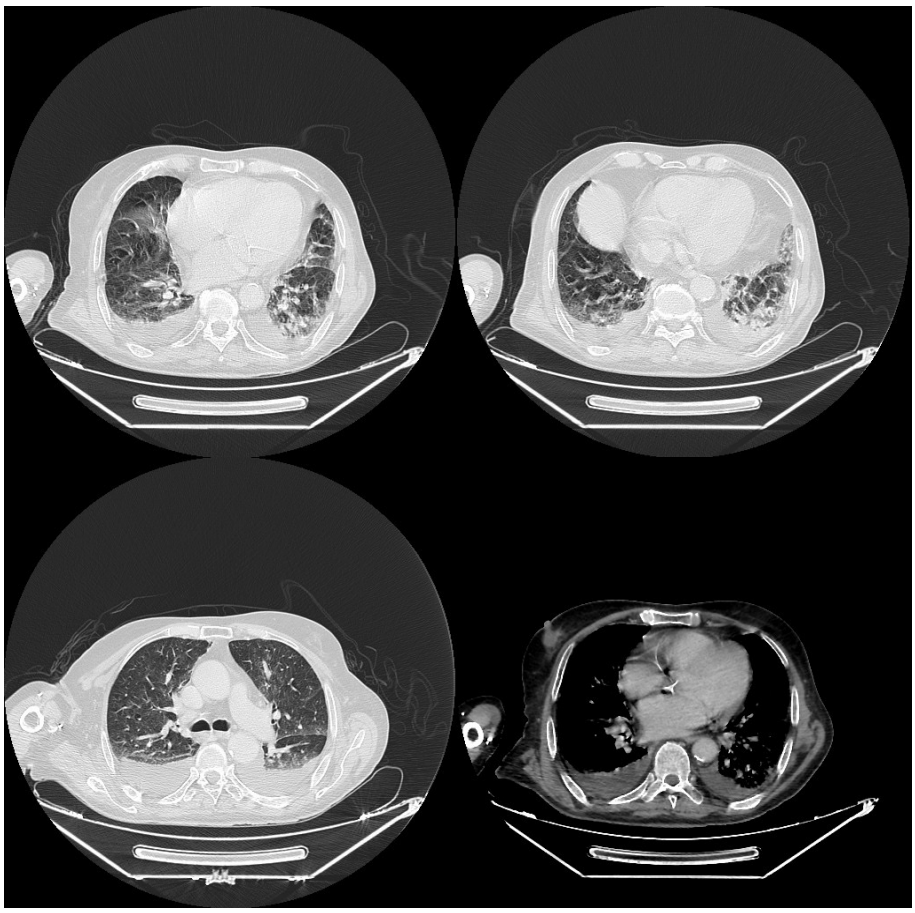


Figure 3. Left posterobasal pulmonary condensation, diffuse interstitial lung disease and bilateral pleural fluid effusion.

During the follow-up of 18 months, he had many flares (repeated fevers, cutaneous and joint inflammatory manifestations and persistent anaemia). He exhibited the clinical profile of VEXAS syndrome including being male, having an age of onset between the fifth and seventh decade, experiencing macrocytic anaemia and displaying systemic inflammatory characteristics. Since the genetic confirmation was delayed due to the non-availability of genetic tests in our settings, the patient was treated periodically with corticosteroids with a temporary improvement.

A bone marrow biopsy showed no tumour infiltration or granuloma, only generalised oedema congestive changes. No vacuoles were detected in the anatomopathological examination of the bone marrow. Nevertheless, the presence of cytopaenias, fever and skin lesions in addition to the persistent inflammatory syndrome indicated a potential diagnosis of VEXAS syndrome. Genetic analysis was finally carried out, and the sample was analysed abroad, revealing a mutation affecting methionine-41 of the UBA1 gene (c.121 A>G; p.Met41 valine [Val]), and we made a final diagnosis of VEXAS syndrome.

Currently, the patient consistently attends our clinic for routine examinations and is stabilised with corticosteroids and colchicine.



Figure 4. Homogeneous cerebral metabolism, absence of hypermetabolism in ENT mucosa, and cervical and mediastinal lymph nodes. Diffuse, homogeneous FDG uptake in the bone marrow with a maximum standardised uptake value of 5.99.

DISCUSSION

In October 2020, a group of researchers led by D.B. Beck identified and described a novel autoinflammatory syndrome, which they named VEXAS syndrome (vacuoles, E1

enzyme, X-linked, autoinflammatory, somatic syndrome)[3]. To identify this new disease, they used a technique not yet widely employed in genetics. Typically, new mutations are identified through exome analysis, preferably in a trio setting with the index case and its parents. In this study, the authors have employed a genotype-driven strategy to bypass the challenging analysis of phenotypes. They began by identifying genotypic communities within potentially relevant genes. In the original study, the authors focused on the ubiquitination genes, including UBA1, in US exome databases. They identified three patients with an acquired mutation inactivating the UBA1 gene. Once the mutation had been identified, they searched specifically for it in patients belonging to unidentified autoinflammatory disease cohorts. They found 25 patients whose phenotypic analysis showed similarities[3]. Numerous publications have followed the initial description of the disease worldwide[4], except for the African region. We report here the first Moroccan and African case of VEXAS syndrome in the area. The diagnosis delay was about two years.

The pathophysiological mechanism of VEXAS syndrome is based on altered ubiquitination[3], a protein activation process playing a central role in intracellular signalling and DNA repair, usually mediated by the enzymes E1 (of which there is only one sub-form), E2 and E3 (of which there are over 600 sub-forms)[3]. The formation of this E1 enzyme is usually ensured by the expression of the UBA1 gene, which has both nuclear and cytoplasmic expression. Mutation of the cytoplasmic isoform (UBA1b) leads to a ubiquitination defect in affected cells (unfolded protein response, autophagy dysregulation), as well as the appearance of cytoplasmic vacuoles typical of the disease[3].

Due to this intrinsic dysregulation, VEXAS patients display high levels of proinflammatory cytokines in their peripheral blood, including IL-1 and IL-18. This indicates the activation of the inflammasome and the dysregulation of myeloid cells. Gene expression studies show an increase in the activity of TNF and NF-κB signalling pathways, which may be responsible for promoting cell death and inflammation[5].

Three mutations have been identified in methionine-41 (p.Met41 Leu/Thr/Val), resulting in the expression of a non-functional isoform responsible for variable clinical phenotypes[5]. Our patient presented with a missense mutation p.Met41/Val, and he is more likely to have a more severe prognosis. Recent studies[4] have shown that patients with the p.Met41/Val mutation have a lower survival rate (approximately 76.7% after five years) compared to the group of patients with p.Met41Leu mutations.

Clinically, the patient exhibited two distinct features: joint manifestations resembling RS3PE arthritis and pulmonary infiltrates leading to severe respiratory distress, which was the main reason for his hospital admission. Joint involvement is frequent[5], with arthralgia and/or arthritis. Although it is often reported in the literature, it remains poorly described. Lung involvement is frequently observed in individuals with VEXAS syndrome. A meta-analysis included 269 patients with VEXAS syndrome. The most commonly described pulmonary manifestation was infiltrates (43.1%; n = 116), followed by pleural effusion (7.4%; n = 2,020) and idiopathic interstitial pneumonia (3.3%; n = 9)[6]. Pulmonary manifestations in VEXAS syndrome seem not to be severe and are responsive to corticosteroids[6].

Frequent cases of chondritis, particularly in the ears and nose, have been described in a third of VEXAS cases, but this feature was absent in our patient. This cartilage damage seems less associated with the UBA1 p.Met41Val mutation[5]. This case demonstrates a significant delay in diagnosis of almost two years, despite a high level of clinical suspicion for VEXAS syndrome. The delay can be attributed to the inadequate knowledge and expertise of our anatomopathologists and haematologists regarding this new condition, along with the lack of modern genetic testing. Furthermore, genetic testing is currently not included in health insurance coverage in our country.

CONCLUSION

VEXAS syndrome serves as a model for a novel category of illnesses, yet it remains insufficiently diagnosed in numerous developing nations, particularly in Africa. This is primarily attributed to the absence of accessible genetic testing and the limited awareness of this disease among internists, rheumatologists, haematologists and anatomopathologists. However, it is crucial to assess elderly male patients who have long-lasting or recurring fevers associated with different systemic symptoms and worsening blood abnormalities, a lack of response to treatment and a need for high doses of glucocorticoids, as they may potentially have VEXAS.

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