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UNMASKING VEXAS SYNDROME: A RARE CASE WITH CRESCENTIC GLOMERULONEPHRITIS

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ABSTRACT

Introduction: VEXAS (vacuoles, E1-enzyme, X-linked, autoinflammation, and somatic) syndrome is a newly recognized autoinflammatory hematologic condition due to mutations in the *UBA1* gene. This case demonstrates its clinical variability, such as neutrophilic dermatosis, pulmonary disease, and a rare presentation with acute kidney injury and glomerulonephritis.

Case description: A 77-year-old man with a history of benign prostatic hyperplasia, osteoarthritis, and patent foramen ovale presented with fatigue, night sweats, weight loss, and recurrent rashes, diagnosed as neutrophilic dermatosis. Laboratory results were pancytopenia and nephrotic-range proteinuria, and imaging revealed mediastinal lymphadenopathy and pulmonary ground-glass opacities. Bone marrow biopsy showed hypercellularity with vacuolization of myeloid and erythroid precursors. Renal biopsy revealed proliferative necrotizing and crescentic glomerulonephritis. Genetic analysis confirmed the UBA1 p.Met41Val mutation, diagnosing VEXAS syndrome. Treatment with corticosteroids, tocilizumab, and mycophenolate mofetil initially improved the symptoms, but steroid dependence continued. Severe pancytopenia necessitated changing to azacitidine after a year, and the patient was assessed for stem cell transplantation. His course was additionally complicated by neutrophilic pulmonary alveolitis.

Conclusion: VEXAS syndrome presents with recurring fever, arthritis, pulmonary and cutaneous involvement, and cytopenias. Diagnosis needs to be entertained in the context of cryptic cytopenias and antineutrophil cytoplasmic antibodies (ANCA)-negative vasculitis. Renal involvement is atypical, especially in ANCA negative cases. Treatment continues to remain difficult, with the initial first-line therapy as high-dose glucocorticoids, with the alternative options being Janus kinase inhibitors, interleukin-6 inhibitors, and stem cell transplant. The case highlights the value of identifying both characteristic and atypical presentations of VEXAS syndrome. Prompt genetic testing is essential in diagnosis, and management entails a multidisciplinary strategy.

KEYWORDS

VEXAS syndrome, autoimmune, pancytopenia, haemato-inflammatory

LEARNING POINTS

- VEXAS (vacuoles, E1-enzyme, X-linked, autoinflammation, and somatic) syndrome should be considered in patients with unexplained cytopenias, systemic inflammation, or atypical vasculitis.
- VEXAS syndrome is caused by a mutation of the UBA1 p.Met41Val gene.
- VEXAS syndrome usually presents itself as glomerulonephritis in antineutrophil cytoplasmic antibodies (ANCA) positive patients. However, it can be rarely present in ANCA negative patients too.

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INTRODUCTION

This case report highlights the clinical heterogeneity of VEXAS (vacuoles, E1-enzyme, X-linked, autoinflammation, and somatic) syndrome and the challenges that can be encountered while treating the patient. The case described below has some classic signs of VEXAS syndrome, such as neutrophilic dermatosis secondary to vasculitis and pulmonary involvement with neutrophilic alveolitis. However, the presence of acute kidney injury along with glomerulonephritis, which is an uncommon finding in VEXAS syndrome, underlines how variability in the size of the vessels involved can lead to an atypical presentation[1,2]. Because of this ambiguity in presentation VEXAS syndrome must be on the differential when we assess a patient with hematologic and/or inflammatory disorders.

CASE DESCRIPTION

We report the case of a 77-year-old fit Caucasian male who presented with worsening fatigue, night sweats, weight loss, and recurrent rashes, confirmed via biopsy as neutrophilic dermatosis. His past medical history was positive for benign prostatic hypertrophy, tubular adenomas, patent foramen ovale with aortic aneurysm and osteoarthritis, managed with meloxicam. The patient had no history of major interventions, and physical examination was unremarkable except for the rash mentioned above.

Laboratory findings revealed pancytopenia. Due to his worsening symptoms, he was admitted and rapidly progressing acute kidney injury was noted. Initial studies showed nephrotic-range proteinuria and a markedly elevated C-reactive protein (CRP) of 196 mg/l. A computed tomography scan of the chest revealed mediastinal lymphadenopathy and bilateral pulmonary ground-glass opacities. Bone marrow biopsy *(Fig. 1)* showed hypercellularity with vacuolization of myeloid and erythroid precursors and a mildly elevated M:E ratio. Renal biopsy showed proliferative necrotizing and crescentic glomerulonephritis *(Fig. 2)*. The erythrocyte sedimentation rate (ESR) and CRP were markedly elevated, rheumatoid factor was 181.9 U/ml, IgA was 623 mg/dl, there was no detectable M-spike on serum protein electrophoresis. antineutrophil cytoplasmic antibodies (ANCA), proteinase 3, myeloperoxidase, antinuclear antibodies (ANA), SSA, and SSB were all negative, with no evidence of vasculitis on magnetic resonance angiography of the chest and abdomen. The differential for pancytopenia included haematological malignancy, medication side effect (the patient was on meloxicam since 2019), infections (workup for parvovirus, hepatitis B, hepatitis C, human immunodeficiency virus was negative) and connective tissue disorders (sarcoid, vasculitis, VEXAS syndrome). Negative ANA made rheumatoid arthritis, systemic lupus erythematosus, and adult-onset Still's disease less likely. The clinical presentation, along with the lab findings, raised suspicion for VEXAS syndrome. The diagnosis of VEXAS syndrome was confirmed by testing for the UBA1 mutation, which revealed a p.Met41Val mutation.

The patient was initially treated with corticosteroid pulses, tocilizumab, and mycophenolate mofetil, with an excellent response. There was rapid improvement in cytopenias, renal function, proteinuria, and constitutional symptoms, which returned close to his prior baseline *(Table 1)*. However, prednisone could not be tapered off. Over a year later, the patient developed severe pancytopenia. A repeat bone marrow biopsy remained consistent with VEXAS syndrome, showing no genetic alteration other than the known UBA1 mutation. Mycophenolate was switched to azacitidine, and the patient underwent a stem cell transplant evaluation. His course was complicated by dyspnoea on exertion, requiring hospitalization, which led to a diagnosis of neutrophilic pulmonary alveolitis *(Fig. 3)*.

The patient undergoes regular follow-up to assess his cell count, CRP, ESR, and renal function. He has good adherence to medication; however, an inability to taper prednisone remains a concern.

DISCUSSION

In the first report of VEXAS syndrome, by Beck et al., the discovery of VEXAS syndrome was an incidental finding, with previous cases being diagnosed and managed

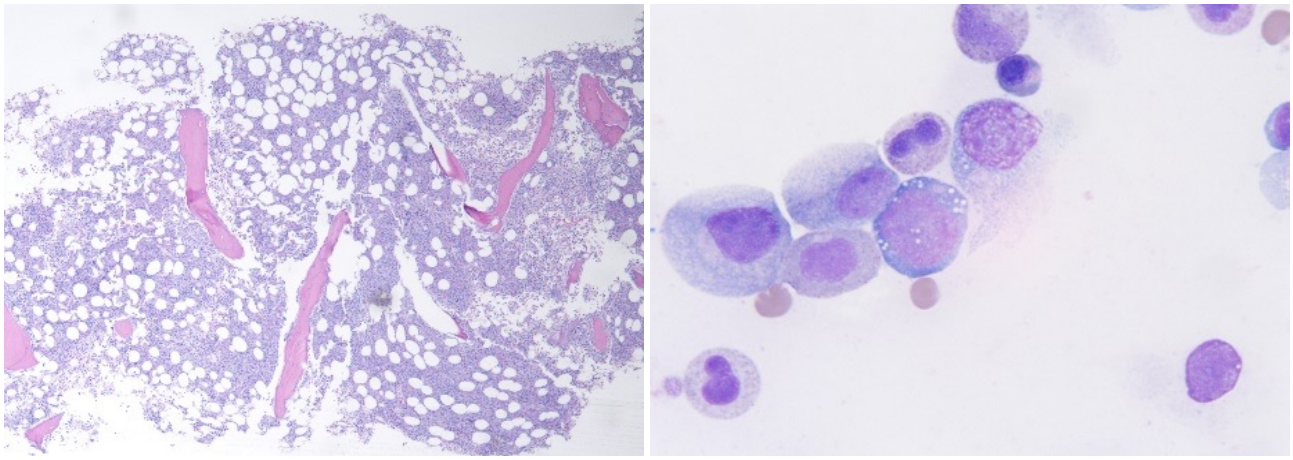


Figure 1. Bone marrow biopsy showing hypercellularity with vacuolization of myeloid and erythroid precursors and mildly elevated myekoid to erythroid ratio.

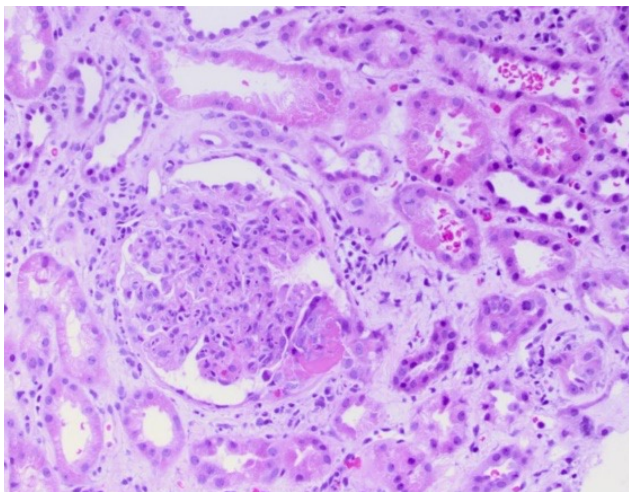


Figure 2. Renal biopsy showing proliferative necrotizing and crescentic glomerulonephritis.

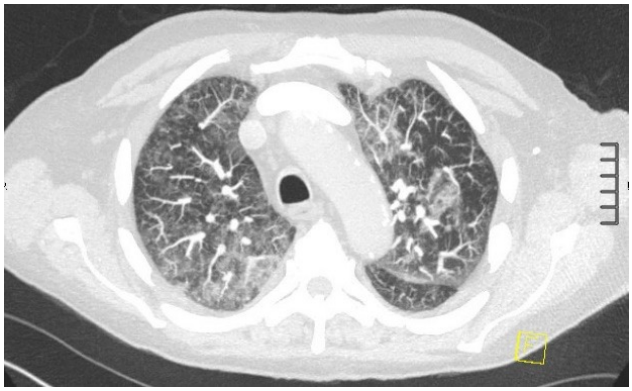


Figure 3. Computed tomography scan showing neutrophilic alveolitis.

as myelodysplastic syndromes (MDS) or systemic inflammatory and autoimmune diseases[3].

While it was initially believed that VEXAS syndrome is a rare disease, a recent large retrospective cohort study done in individuals with European ancestry estimates the prevalence to be around 1 in 14,000. Interestingly, the study also revealed that multiple individuals carrying the mutation did not have any manifestations during the study. However, they did go on to eventually exhibit signs and symptoms of the disease.

VEXAS syndrome can be described as a haemato-inflammatory disease. Clinical manifestations are diverse and include recurrent fever, arthritis, chondritis, unprovoked thrombosis, pulmonary and dermatologic manifestations, along with hematologic abnormalities such as thrombocytopenia and macrocytic anaemia[2,4].

Renal involvement is an important aspect of our case. Renal involvement remains an underreported aspect of VEXAS syndrome despite an estimated prevalence rate of 9.5-25%[2]. Renal pathology in VEXAS syndrome commonly presents as acute kidney injury, followed by nephrotic syndrome and, rarely, chronic kidney disease. The most widely reported histopathological finding is acute interstitial nephritis, followed by reports of pauci-immune glomerulonephritis and secondary amyloidosis[5]. Patients with VEXAS syndrome who present with glomerulonephritis are often ANCA positive. Glomerulonephritis in an ANCA-negative patient with VEXAS syndrome is rare but has been reported previously[6]. Hence, it is important to screen for renal involvement in patients diagnosed with VEXAS syndrome.

There is no clear data on management, and therapy is primarily based on small-scale retrospective studies. Initial high-dose glucocorticoids are effective first-line therapy, but there are significant concerns of long-term toxicity and steroid dependence in most cases[7]. Janus kinase (JAK) inhibitors and interleukin (IL)-6 inhibitors have shown promising results in multicentric retrospective cohort studies, but these results are yet to be confirmed via prospective trials[8]. Stem cell therapy has also been used in a few cases of refractory cytopenia and recalcitrant inflammatory disease and has been associated with durable correction of UBA1 mutation in bone marrow[9].

The primary takeaway from this case is understanding the typical as well as atypical presentation of VEXAS syndrome. It is important to have high clinical suspicion for VEXAS syndrome in cases of unprovoked thrombosis, recurrent chondritis and cases of ANCA-negative vasculitis. From a hematologic standpoint, VEXAS syndrome must be included in cases of unexplained cytopenias. Diagnosis can be confirmed through the detection of UBA1 mutation in genetic testing. A bone marrow biopsy must be pursued to look for concurrent MDS. Therapy involves initial high-dose glucocorticoids during the initiation phase and JAK inhibitors or IL-6 inhibitors during the maintenance phase with attempts to taper steroids. In cases of refractory cytopenia and recalcitrant inflammatory disease, stem cell therapy can be considered.

Test	At presentation	After steroids	At admission for pulmonary alveolitis
WBC ($\times 10^3/\mu l$)	5.2	1.6	2.1
RBC ($\times 10^6/\mu l$)	2.1	2.44	2.12
Hb (g/dl)	6.9	8.9	7.2
Hct (%)	21.5	26.8	22.10
Platelets ($\times 10^3/\mu l$)	133	109.8	104.2
CRP (mg/l)	196	4.8	>300
Creatinine (mg/dl)	3.83	1.24	1.44
ANC ($\times 10^3/\mu l$)	0.74	1.06	1.24

Table 1. Labs before and after steroids were started.

Abbreviations: WBC, white blood cells; RBC, red blood cells; Hb, haemoglobin; Hct, haematocrit; CRP, C-reactive protein; ANC, absolute neutrophil count.

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