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A PATIENT WITH VEXAS SYNDROME PRESENTING WITH COMPLETE OPHTHALMOPLEGIA

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ABSTRACT

Introduction: VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently identified, somatic mutation-driven, autoinflammatory syndrome primarily affecting older males. In VEXAS, somatic *UBA1* mutations drive the clonal expansion of bone marrow-derived myeloid cells that infiltrate and initiate inflammation across the body, leading to diverse symptomology. Due to both the relative novelty of its discovery and rarity of its incidence, unique presentations and their management are vital in our continued understanding of the disease.

Case description: We present a case of a 69-year-old male with no notable medical history who initially presented with episcleritis progressing to complete ophthalmoplegia. CT findings showed marked proptosis of the left eye and thickening of the lateral rectus. Over the subsequent months he presented to hospital repeatedly with worsening fibrotic lung disease. Eventually, after developing pancytopenia, a bone marrow biopsy showed histological features of VEXAS and the diagnosis was confirmed through genetic testing.

Discussion: This case reveals a novel presentation of VEXAS and demonstrates the rapid progression to multi-organ disease possible in VEXAS. In this case, diagnostic auto-antibody panels all tested negative, and the patient was initially treated with high-dose steroids for suspected ANCA-negative vasculitis. Multiple unsuccessful attempts were made to wean and replace steroids with disease-modifying antirheumatic drugs. Following genetic confirmation of VEXAS, tocilizumab therapy was initiated.

Conclusion: Due to the rapidly progressive nature of VEXAS and associated high mortality, early diagnosis is critical. This case highlights the importance of considering a bone marrow biopsy for suspicion of VEXAS when presented with an autoantibody-negative, multi-organ, autoinflammatory syndrome.

KEYWORDS

VEXAS syndrome, autoinflammatory disease, autoimmune disease, chronic disease, somatic mutation disease

LEARNING POINTS

- VEXAS syndrome can initially present with ocular symptoms without systemic manifestations.
- VEXAS syndrome should be considered in the context of a rapidly progressive multi-organ autoinflammatory syndrome.
- VEXAS syndrome should be considered in the context of disease-modifying antirheumatic drug resistant inflammatory disease.

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INTRODUCTION

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a progressive, systemic, autoinflammatory syndrome that typically affects older males[1,2]. VEXAS syndrome is driven through the acquisition of *UBA1* mutations in haematopoietic progenitors leading to the clonal expansion of circulating autoinflammatory myeloid cells and subsequent multi-organ inflammation[3]. Frequently, *UBA1* mutations are observed to co-occur against a background of developing myeloid neoplasms such as myelodysplastic neoplasms and acute myeloid leukaemia or lymphoid neoplasms, such as multiple myeloma. However, in a significant proportion of patients no concurrent driver mutation is observed[4].

The circulating nature of bone marrow-derived myeloid cells means that VEXAS syndrome presents with diverse clinical manifestations. Across the largest single cohort studied, patients presented with weight loss (55%), skin lesions (84%), fevers (65%), pulmonary symptoms (49%), chondritis (36%), ocular symptoms (40%), thrombophilia (35%) and lymphadenopathy 35%)[5]. Ocular manifestations of VEXAS typically include periorbital oedema (14%), episcleritis (9%), scleritis (9%) and uveitis (7%)[6]. Diagnostic bloods frequently show a macrocytic anaemia alongside a significantly elevated C-reactive protein and erythrocyte sedimentation rate. Bone marrow biopsies will typically show evidence of increased vacuolation in erythroid and myeloid precursors. We present a case of a patient whose first presentation was that of complete ophthalmoplegia of the left eye.

CASE DESCRIPTION

We present the case of a 69-year-old male with a past medical history of hypertension and a moderate smoking history, who initially presented to ambulatory care via his ophthalmology team. He presented to the acute eye clinic with a painful, red left eye, was diagnosed with episcleritis and prescribed diclofenac. He re-presented four days later with complete ophthalmoplegia, proptosis and ptosis of the left eye. He reported that following his initial consultation his eye began to swell and after 24 hours it was completely closed. His visual acuity had decreased from 0.00 to 0.2, his colour vision was reduced, and he had conjunctival chemosis and signs of optic nerve compromise.

He was admitted under the medical team and an urgent CT scan was arranged. This revealed thickening of the lateral rectus muscle, as well as inflammation of the retro-orbital fat suspicious of an inflammatory process as the cause of his ocular symptoms.

On further interrogation of systemic symptoms, the patient reported exertional breathlessness for the preceding three months with night sweats, diarrhoea, weight loss and a new widespread macular rash. A CT scan of his thorax and abdomen showed inflammatory changes in the lung bases and non-specific splenomegaly. Blood tests revealed elevated inflammatory markers and D-dimers. His autoimmune, complement levels, IgG subtypes and antineutrophil cytoplasmic antibodies (ANCA) screen were all normal. His biochemistry showed an acute kidney injury with an estimated glomerular filtration rate of 48.

The initial working diagnosis was ANCA-negative vasculitis. He was treated with high-dose methylprednisolone for three days which significantly improved all his symptoms. He was then stepped down to oral prednisolone and discharged on a steroid reducing regimen. At follow-up four weeks later, his symptoms remained well controlled, and he was started on methotrexate 25 mg weekly as a steroid sparing agent. Despite this, he was unable to wean below 15 mg of prednisolone due to increasing breathlessness at this dose.

His exercise tolerance remained significantly impaired to around 50–60 yards despite the continued higher doses of steroids. A CT pulmonary angiography and an echocardiogram both showed no acute cause for his breathlessness other than some emphysematous changes



Figure 1. Axial slice of a head CT scan showing proptosis of the left eye and thickening of the lateral rectus muscle with associated stranding of the orbital fat surrounding the muscle.

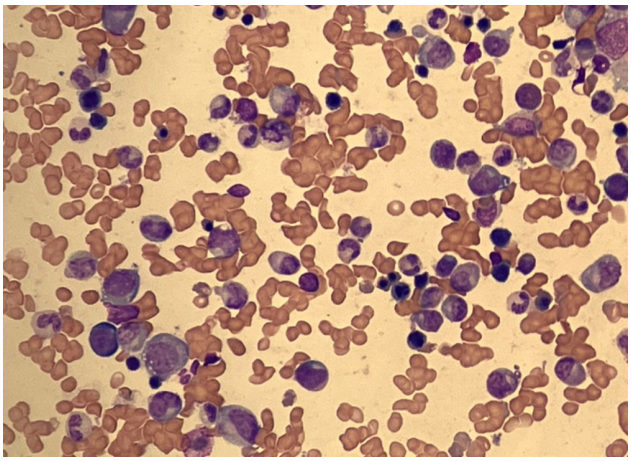


Figure 2. Bone marrow histology showing hypercellularity with left shifted granulopoiesis and mild dyshaemopoietic features in the erythroid lineage with no increase in blasts. Vacuolation is present in maturing granulocytic cells.

in his lungs. His breathlessness was felt to be secondary to deconditioning due to vasculitis and weight gain from long-term steroid use, so a rehabilitation regime was planned.

While undergoing rehabilitation it was first noted that the patient's mean corpuscular volume (MCV) was increasing. This was felt to be due to methotrexate and he was advised to increase his folic acid to three times a week. Due to ongoing breathlessness and the rising MCV, methotrexate was thought to not be beneficial and was changed to leflunomide. Establishing treatment on leflunomide was disrupted due to repeated hospital admissions for community-acquired pneumonia and exacerbations of COPD.

Despite the leflunomide, he was still unable to wean off his prednisolone due to breathlessness so leflunomide was replaced with mycophenolate. Following this change, he underwent lung function testing which showed a restrictive pattern of pathology with an FEV1 of 55.7% predicted and FVC 59.8% predicted, giving a ratio of 71.3%, with fine crepitations auscultated bilaterally. His BMI at this time was 35 with a 10 kg weight gain since steroids started.

After establishment on mycophenolate the patient again required multiple hospital admissions due to pneumonia and SARS-CoV-2 infection. Lung imaging during these admissions showed worsening lung fibrosis and bronchiectasis. He was then admitted with sepsis of unknown origin during which he developed severe pancytopenia requiring multiple blood transfusions. Following resolution of the infection the pancytopenia persisted, and a bone marrow biopsy was arranged.

The bone marrow biopsy showed vacuolated granulocytic cells with no increase in blasts in the aspirate; trephine showed no significant dysplasia. The SNP array showed no abnormality but on molecular assessment a pathogenic *UBA1* variant (c.121A>G (p.Met41Val)) was found with a variant allele frequency of 74.5%, confirming VEXAS syndrome, alongside a TET2 variant of uncertain significance with a variant allele frequency of 46.6%. Unfortunately, prior to starting tocilizumab the patient again developed severe pneumonia and was discharged on long-term-oxygen therapy to a hospice. Following his recovery he was able to begin treatment with tocilizumab.

DISCUSSION

Due to the relative recency of the discovery of VEXAS and the rarity of the disease itself, we continue to make significant advancements in our understanding of VEXAS through the identification of novel presentations in individual cases. The reported high mortality rate of VEXAS syndrome means that early recognition is vital to starting early treatment. In this case we report on a 69-year-old who initially presented with an acute red eye before quickly developing complete ophthalmoplegia with few other notable preceding symptoms. Ophthalmoplegia is a rarely reported ocular manifestation of VEXAS syndrome seen in only seven other reported cases of VEXAS syndrome. The pathological mechanism of ophthalmoplegia in these cases varies from myositis of the extra-ocular muscles themselves[7], to nerve sheath inflammation[8], to inflammatory infiltration causing compartment syndrome and compression of the oculomotor nerves[4,9].

All seven historical reports describe cases of 60–90-year-old males with autoantibody-negative, systemic inflammatory syndromes. In four of these cases patients had months to years of preceding symptoms including intermittent pyrexia with pulmonary disease[4], intermittent pyrexia with rash[5], polymyalgia and polyarthritis[6], and recurrent venous thrombosis[7]. In the other three cases that noted ophthalmoplegia as a presenting symptom, as in the case we report here, there was a long delay between the first presentation and a VEXAS diagnosis[8-10]. While the threshold for an invasive procedure such as a bone marrow biopsy should remain high, in all these cases the symptoms reported are not typically emblematic of any other rheumatological disease and an earlier biopsy may have been justified. Together, these cases highlight the importance of exploring VEXAS as a differential in instances of ophthalmological inflammation accompanied by systemic symptoms. These cases also call attention to having a high degree of suspicion for VEXAS syndrome in male patients who have a diagnosis of an autoantibody-negative, inflammatory disease who do not respond to steroid sparing agents. With the development of ultra-sensitive genetic testing of peripheral blood, minimally invasive testing of VEXAS should soon be accessible for an earlier diagnosis.

Notably, in this case the bone marrow biopsy showed a *UBA1* mutant variant allele fraction (VAF) of 74.5% which is markedly higher than the median reported VAF in larger cohort VEXAS studies (26%, 44%). This is comparable to the autosomal VAF of driver mutations in myelodysplastic syndrome (MDS)[1,2]; however, there was no evidence of accompanying myelodysplastic syndrome. In the seven identified cases of VEXAS syndrome with ophthalmoplegia, MDS was also not reported. A *TET2* variant of uncertain significance was also reported in this patient with a VAF of 46.6%, which is most likely to represent a benign germline variant and there were no other putative pathogenic variants identified. *TET2* is a canonical driver of both clonal haematopoiesis and MDS. In our case the *UBA1* mutation must be subclonal to the *TET2* mutation; however, there is not enough evidence available to suggest how these mutations may influence the fitness and phenotype of myeloid cells. A question remains in VEXAS patients without MDS of how *UBA1* mutant clones are able to reach such large sizes and how clinical manifestations correlate with the timing and development of these mutant clones.

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