Challenges in the Diagnosis and Treatment of VEXAS Syndrome- Two case reports

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INTRODUCTION

VEXAS (**V**acuoles, **E**1 enzyme, **X**-linked, **A**utoinflammatory, **S**omatic) syndrome is a recently discovered adult-onset syndrome that links haematological and autoimmune symptoms. It typically affects older males and occurs due to a mutation in the UBA1 gene. We describe 2 cases at our institution.

CASE 1

A 70-year-old man, with relapsing polychrondritis as well as a history of interstitial lung disease. He was on immunosuppression including prednisolone and methotrexate when he developed macrocytic anaemia, thrombocytopenia, as well as Sweet syndrome.

In the setting of refractory polychrondritis, difficult steroid wean and worsening cytopenias, a bone marrow biopsy was performed, and the morphology was suggestive of VEXAS with myeloid vacuolization (Figure 1). This was confirmed on molecular testing with mutation in *UBA1* gene.

He was treated with prednisolone and tocilizumab and continued to have aggressive flares of polychondritis and Sweet syndrome. Azacitidine was delivered with the aim to target the *UBA1* mutant clone. Profound thrombocytopenia limited the use of ruxolitinib. There was no clinical improvement; he died due to infection 12 months following the diagnosis of VEXAS.

CASE 2

A 76-year-old gentleman with seronegative inflammatory arthritis causing severe pain was commenced on methotrexate and prednisolone.

Five months following the diagnosis of inflammatory arthritis, he developed an unprovoked deep-vein-thrombosis. Following this, his health declined with macrocytic anaemia, despite cessation of methotrexate as well as bilateral pleural effusions requiring chest drains.

In early 2022, a bone marrow biopsy was performed, and this showed Myelodysplastic syndrome (MDS) with multilineage dysplasia. Cytoplasmic vacuolation was noted in the erythroid precursors (Figure 2). Molecular testing confirmed *UBA1* variant and *DNMT3A* variant with a variant allele frequency of 44%.

As the MDS was in the R-IPSS low risk category, he was managed conservatively. He subsequently developed cholecystitis and sepsis, leading to death 4 months after the diagnosis of VEXAS.

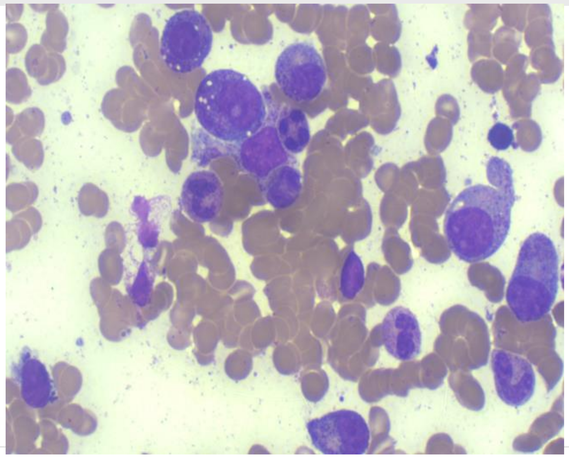


Figure 1: Bone marrow aspirate demonstrating vacuolization within myelocytes and evidence of neutrophil dysplasia (X60 objective)

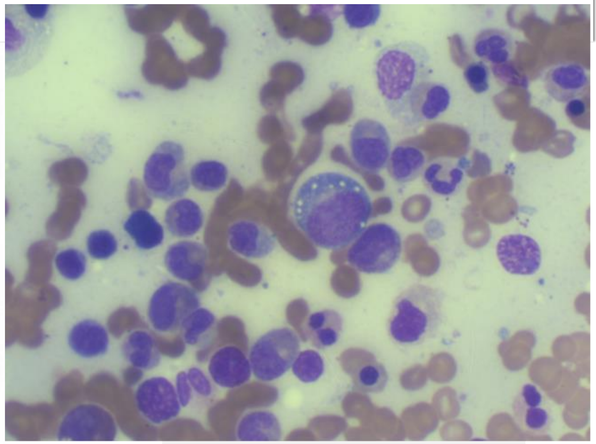


Figure 2: Bone marrow aspirate demonstrating erythroid vacuolisation and marked erythroid and granulocytic dysplasia (X60 objective)

CONCLUSION

These cases highlight the non-haematological clinical features and therapeutic challenges that are associated with VEXAS syndrome, including pleural effusions, thrombosis and Sweet syndrome.

The co-existence of other somatic mutations with *UBA1*, such as *DNMT3A* has been reported in 9.2%-22% of cases and is of unclear significance.

This may represent coincidental age-related clonal haematopoiesis. Earlier diagnosis and close collaboration within a multi-disciplinary team is crucial.

REFERENCE

Vitale, A., Caggiano, V., Bimonte, A. *et al.* VEXAS syndrome: a new paradigm for adult-onset monogenic autoinflammatory diseases. *Intern Emerg Med* **18**, 711–722 (2023). https://doi.org/10.1007/s11739-023-03193-z