VEXAS syndrome: a dermatological perspective

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Abstract

VEXAS (**V**acuoles, **E1** enzyme, **X**-linked, **a**utoinflammatory and **s**omatic mutation) syndrome is a genetically-defined disorder identified in 2020, describing patients with inflammatory syndromes associated with haematological dysfunction. It is a severe, treatment-resistant condition, with estimated mortality between 40 to 63%. A wide range of cutaneous manifestations have been described. Here, we report on two patients with treatment-resistant neutrophilic dermatosis and myelodysplastic syndrome, who were subsequently diagnosed with VEXAS syndrome. Our cases highlight the need for dermatologists' awareness of this novel condition and to initiate early referral to haematologists for appropriate multidisciplinary care.

Key words: Myelodysplastic Syndromes, Sweet Syndrome, Genetic Skin Diseases, UBA1 Protein, X-linked

Introduction

VEXAS (Vacuoles, E1 Enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a recently identified condition describing patients with adult-onset, treatment-resistant, autoinflammatory manifestations with associated haematological abnormalities. These patients have a myeloid lineage restricted somatic mutation in the *UBA1* gene that is located on the X-chromosome. This mutation results in the activation of the innate immune pathways and leads to systemic inflammation.[1] Clinical features include recurrent fevers, progressive haematological abnormalities (cytopaenias with bone marrow dysplasia displaying vacuolation of myeloid and erythroid precursors), chondritis, alveolitis, and thromboembolic disease.[1,2] The first presentation of VEXAS may be to the dermatologist, as cutaneous manifestations have been reported in up to 89% of patients, particularly neutrophilic dermatoses and vasculitis.[3] Here we report on two patients with treatment-resistant Sweet syndrome and myelodysplastic syndrome who were both later found to have the unifying diagnosis of VEXAS syndrome.

Case 1

A 63-year-old male presented in 2018 with a three-year history of erythematous papules and pustules on the torso and limbs, arthralgia, mouth ulcers and anterior uveitis. Bone marrow aspirate and trephine biopsy (BMAT) five months prior for investigation of pancytopaenia demonstrated mild hypercellularity in keeping with a reactive marrow and erythroid hypoplasia. Previous treatment had included prednisolone, methotrexate and infliximab for an initial diagnosis of Behçet disease which was then revised to Sweet syndrome. His medical history was significant for unprovoked deep venous thrombosis and pulmonary embolus on rivaroxaban, chronic dyspnoea and a 40-pack year history of smoking.

On admission, he was febrile (38.1°C) with extensive violaceous papules and plaques on the trunk and limbs (Figure 1a-d). Investigations revealed macrocytic anaemia with haemoglobin 108g/L (normal 130-180) and mean cell volume 105fL (normal 80-96), mild neutrophilia with white cell count 8.9×10^9/L (normal 4.0-11.0) and neutrophils 7.9×10^9/L (normal 2.0-7.5), elevated C-reactive protein (CRP 98mg/L, normal <5) and elevated erythrocyte sedimentation rate (ESR 91mm/hr, normal <13). An autoimmune screen revealed positive antinuclear antibody (ANA titre 640, normal < 80) but negative double-stranded DNA antibody, extractable nuclear antigen antibody (ENA) and anti-neutrophil cytoplasmic antibody (ANCA). Complement C3, complement C4 and serum protein electrophoresis were all normal. Full body computed tomography (CT) /positron emission tomography (PET) scan did not reveal any malignancy.

Skin biopsies showed a neutrophilic infiltrate in the upper dermis with oedema, red cell extravasation, and limited leukocytoclasis, consistent with a neutrophilic dermatosis. There was also some inflammation in a vessel in the deep dermis suggesting vasculitis (Figure 1e-g). A repeat BMAT showed myelodysplasia (MDS) with hypercellularity, moderate dysmegakaryopoiesis, mild dyserythropoiesis and vacuolation of myelocytes. Targeted next generation sequencing (NGS) of 26 genes recurrently mutated in haematological malignancy did not detect any mutations, and cytogenetics were normal.

He was managed with prednisolone 50mg daily (0.5mg/kg/day), colchicine 500mcg three times daily and dapsone 25 mg daily with initial good clinical response. There were multiple attempts to reduce the prednisolone dose over the following 4 years, resulting in skin flares at doses below 10 mg a day. Unfortunately, he developed haemolysis with dapsone and colitis with colchicine which required cessation of both agents. Treatment of the underlying MDS with six cycles of low-dose cytarabine did not result in any skin improvement. He remains on mycophenolate mofetil 1.5g twice daily and prednisolone 10mg daily, with intermittent higher prednisolone doses for skin flares. Following the recent publication by Beck *et. al*[1], Sanger sequencing of *UBA1* (NM_003334.3) was performed on the bone marrow aspirate sample which detected the c.122T>C; p.(Met41Thr) variant previously described in the context of VEXAS syndrome.

Case 2

A 59-year-old male presented in 2017 with a 3-year history of intermittent pruritic eruption on the trunk and limbs. Episodic flares of the cutaneous eruption correlated with bouts of severe generalised fatigue, dyspnoea and migratory inflammatory arthritis affecting his knees, ankles, feet and hands, which were severe to the point of immobility during flareups.

Examination revealed widespread, erythematous to violaceous papules and nodules with no ulceration or purpura (Figure 2a,b). Investigations revealed normal full blood count, blood film, biochemistry, renal and liver function. ESR was persistently elevated (79-100mm/hr) and pANCA was weakly positive. CT chest to pelvis showed no malignancy. Skin biopsies showed variable papillary dermal oedema, neutrophilic infiltrate extending from the dermis to also involve the subcutis, with prominent leukocytoclasia but absence of vasculitis (Figure 2c-e). This supported a clinicopathological diagnosis of Sweet syndrome. BMAT did not show evidence of myelodysplastic or myeloproliferative disorder and NGS panel showed no abnormalities.

He was commenced on prednisolone 25mg daily and colchicine 500mcg three times a day with good response. Unfortunately, his skin flared when a prednisolone wean was attempted. Steroid-sparing treatment with dapsone and colchicine were not tolerated due to dyspnoea, diarrhoea and fatigue. The differential diagnosis of seronegative rheumatoid neutrophilic dermatosis was considered, and methotrexate 10mg/week was trialled for 4 months with no benefit. He remained prednisolone-dependent at doses between 10-25mg daily over a period of 4 years. The disease course was notable for recurrent respiratory decompensation, presumed secondary to lower respiratory tract infections, as well as deep venous thrombosis and pulmonary embolus, necessitating treatment with rivaroxaban.

In 2021, worsening macrocytic anaemia (Hb 98g/L, MCV 116fL) prompted repeat BMAT which showed MDS with sideroblasts and multilineage dysplasia, including vacuolated erythroid and myeloid precursors. Cytogenetics were normal. Considering the haematological findings and the clinical picture of an autoinflammatory syndrome, he underwent *UBA1* Sanger sequencing and the c.121A>C; p.(Met41Leu) variant was detected, consistent with a diagnosis of VEXAS.[1] Targeted NGS performed on bone marrow aspirate at the same time as testing for VEXAS, again, did not detect additional acquired mutations in this patient.

Discussion

The acronym "VEXAS" has been given to this syndrome to describe its hallmark features. **V**acuoles are present in myeloid and erythroid progenitor cells. There is a mutation in the **E1** enzyme that is encoded by the *UBA1* gene on the **X**-chromosome. This mutation activates innate immune pathways, resulting in **a**utoinflammatory disease that presents late in life due to a **s**omatic mutation.[1,4] The phenotype of VEXAS syndrome is varied but systemic inflammation is most common, predominantly affecting the lungs, blood vessels, cartilage and skin.[3] Many patients present with refractory constitutional symptoms, inflammatory arthritis and relapsing polychondritis, or haematologic conditions such as MDS (the bone marrow changes are often subtle) or multiple myeloma.[1] Dermatologic manifestations have been reported in up to 89% of cases, presenting as neutrophilic dermatoses, cutaneous vasculitis and periorbital angioedema.[5] Zakine *et al.*[6] found that 63% of patients initially present with cutaneous manifestations.

Our cases demonstrate these characteristic features, with both patients presenting with treatment-refractory neutrophilic dermatosis ("Sweet syndrome"). Case 1 also demonstrated histopathological evidence of vasculitis, and both cases had associated autoimmune

inflammatory symptoms and developed MDS. The protracted course to diagnosis for both of these patients highlight the need for a high degree of diagnostic suspicion for the treating physician in order to request appropriate genetic testing.

Unfortunately, management of such cases still remains a challenge due to a paucity of highly effective therapies. Most patients require ongoing high-dose glucocorticosteroids with poor responses to steroid sparing agents.[1] Reports on treatment options for patients with VEXAS syndrome are currently limited to retrospective case reports or series.[3]

Bourbon *et al.*[7] retrospectively examined therapeutic approaches for 11 patients with VEXAS syndrome using time-to-next steroid-sparing agent as a marker of efficacy. In this cohort, the best outcomes were observed with JAK inhibitors (next treatment not reached, median follow up 25.1 months), azacitidine (21.9 months) and ciclosporin (12.7 months), although most treatment strategies were only transiently effective for cutaneous lesions, and had limited effect on cytopaenias or myelodysplastic changes.[7] The high mortality associated with VEXAS is likely a combination of long delay to definitive diagnosis, progression of haematological dysfunction and prolonged use of high-dose corticosteroids, leading to complications such as infection and steroid-induced bone fractures.[1,5] Loschi *et al.*[8] reported on a patient who cleared the *UBA1* mutation from the bone marrow following allogeneic haematopoietic stem cell transplant (AlloHSCT) and was cured of VEXAS syndrome. While AlloHSCT might offer a cure, it is a high-risk procedure complicated by significant treatment-related mortality and morbidity, including graft versus host disease.[9] Therefore, not all patients with VEXAS syndrome can be considered suitable candidates for this therapeutic option. Further prospective trials are required to evaluate the optimal management for VEXAS, including the timing of AlloHSCT.

Conclusion

The contribution of somatic mutations in inflammatory skin conditions has previously been poorly understood. The discovery of VEXAS syndrome provides insight into the shared genetic aetiology of inflammatory conditions and provides a unifying diagnosis for patients.
Whilst the elucidation of VEXAS syndrome is an exciting one, ongoing characterisation and evaluation of treatment options is needed for this newly defined disorder. Our cases highlight the need for dermatologists to be aware of and consider VEXAS syndrome in patients with treatment-resistant, corticosteroid-dependent neutrophilic dermatoses associated with autoimmune inflammatory features and haematological abnormalities.

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Figure 1 Case 1: Erythematous plaques on (a) arm and (b) back, (c) violaceous papule, (d) oedematous ulcerated Sweet-like nodule; (e) Histopathology demonstrating a neutrophilic infiltrate, lymphocytes and red cell extravasation (HE, ×200) (f) infiltrate consisting of neutrophils and lymphocytes with focal leukocytoclasis (×400) and (g) focal changes suggestive of vasculitis (×400)

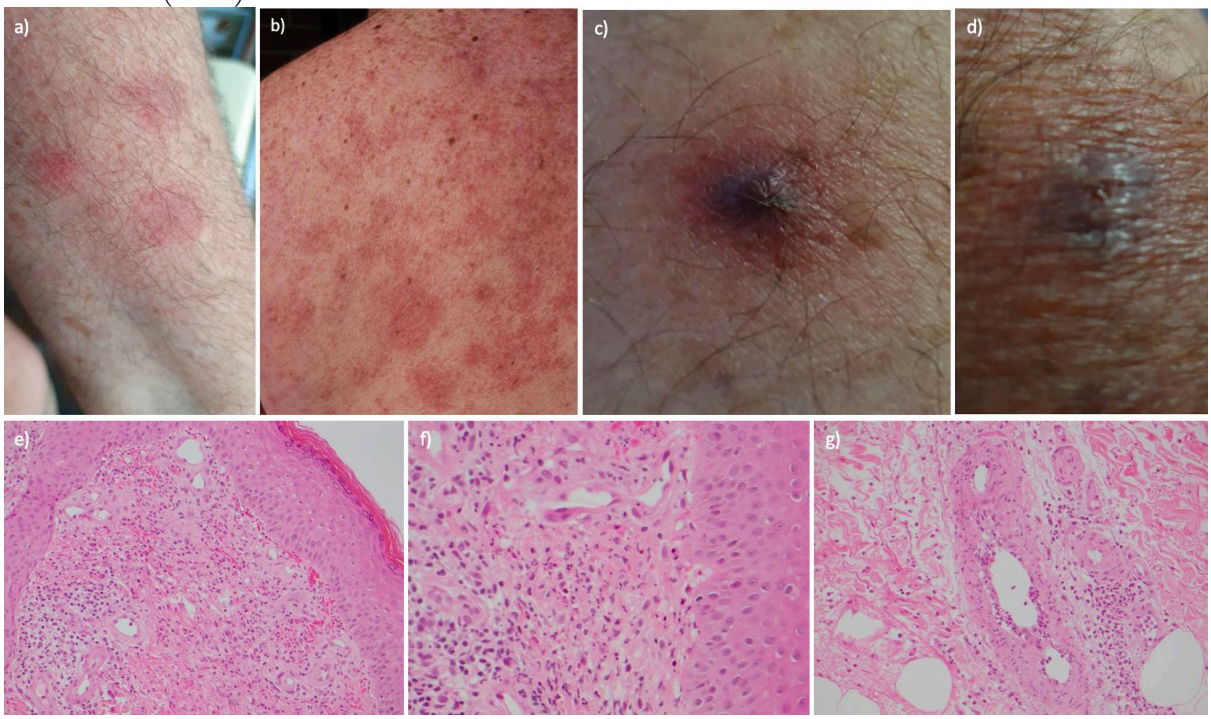

Figure 2 Case 2: Erythematous papules and nodules on the (a) upper limb and (b) back; (c) Histopathology demonstrating inflammatory infiltrate extending from the dermis to the subcutis (HE, ×20) (d) papillary dermal oedema, neutrophilic infiltrate with prominent leukocytoclasia but no vasculitis (HE, ×100) (e) involvement of the subcutis (HE, ×200)