VEXAS syndrome: a report of three cases

Sirs,

The recently described VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) presents as a late adult-onset autoinflammatory disease often accompanied by haematological manifestations (1). The genetic background of VEXAS are somatic mutations in UBA1, an X-linked gene encoding enzyme initiating ubiquitination (2). The mutations result in decreased cellular ubiquitiation activity and lead to hyperactivation of innate immune pathways.

We present cases of three patients with VEXAS syndrome recently diagnosed at our institution. The first patient was a 76-year-old male patient with a five-month history of symmetric peripheral polyarthritis accompanied by episodes of pruritus and skin rash. Laboratory tests revealed a significantly elevated CRP (83.5 mg/l) with negative rheumatoid factors and anti-citrullinated protein antibodies. A diagnosis of seronegative rheumatoid arthritis was made and the patient was started on methotrexate (MTX) 15 mg/week in combination with low dose methylprednisolone, which lead to a resolution of peripheral arthritis. Three months later the patient developed macrocytic anaemia (haemoglobin (HGB) 108 g/l; mean corpuscular volume 104 fl) with normal folate and vitamin B12 serum levels, which was attributed to treatment with MTX. After treatment cessation arthritis remained in remission, however, progressive weight loss was noted by the patient and his anaemia was worsening (HGB 79 g/l). A persistent elevation of CRP up to 124 mg/l without fever or other clinical signs of infection was also present. A PET-CT scan showed vasculitis of the proximal aorta. During the diagnostic work-up the patient reported a new onset of right eye pain and painful swelling of ear and nose cartilage, and a diagnosis of sclero-uveitis and polychondritis was made. The presence of several seemingly unrelated inflammatory manifestations in an elderly male patient raised the suspicion of possible VEXAS syndrome. Identification of UBA1 monogenic somatic mutation (p.Met41Thr) confirmed the diagnosis.

The second case was a 74-year-old male with undiagnosed generalised skin rash persisting for 10 months and a history of an episode of polychondritis 6 months prior to admission. On presentation, the patient had elevated CRP (63 mg/l), mild leukopenia and macrocytic anaemia (HGB 79 g/l). The autoantibody screen was negative. Skin biopsy confirmed the diagnosis of neutrophilic dermatosis. Chest CT scan showed ground-glass opacities in both lungs. Bone marrow biopsy results were consistent with myelodysplastic syndrome. UBA1 monogenic somatic mutation p.Met41Leu was identified.

The third case was a 68-year-old male with a 6-month history of febrile episodes and 4-month history of generalised skin rash and relapsing polychondritis originally considered to be a paraneoplastic syndrome associated with seminoma. After orchiectomy, his rash did not resolve and episodes of polychondritis continued. Furthermore, the patient developed macrocytic anaemia and episcleritis. Suspicion of VEXAS syndrome was confirmed by the presence of UBA1 monogenic somatic mutation (p.Met41Thr). Methotrexate (15 mg weekly) had to be added to a medium dose of prednisone to induce remission and taper the dose of prednisone to 5 mg daily.

All our patients expressed multiple inflammatory manifestations exceeding the typical clinical phenotypes associated with the referred rheumatic diagnoses, and all had additional haematological abnormalities. This constellation prompted a search for a unifying diagnosis that could explain each of the signs and symptoms, which ultimately raised the suspicion of the recently described VEXAS syndrome.

VEXAS syndrome is caused by impaired cellular ubiquitylation activity, which contributes to the clinical heterogeneity of clinical manifestations (Table I). The disease should be suspected in older patients presenting with a combination of inflammatory and haematologic signs and symptoms, especially in patients with relapsing polychondritis (3, 4). Originally reported in males, it can affect both genders (4, 5). The optimal therapy of VEXAS syndrome is not yet known, but the beneficial role of various immunosuppressants including azacytidine and janus kinase inhibitors has been reported (6).

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Table I. Summary of the demographics, genetic and clinical characteristics comparing our patient with published cohorts

	Our patients	Beck *et al.* (1)	Bourbon *et al.* (6)	Ferrada *et al.* (3)	Tsuchida *et al.* (4)
Male gender, n (%)	3 (100%)	25 (100%)	11 (100%)	13 (100%)	8 (100%)
Median age at onset, years (range)	74 (68-76)	64 (45-80)	66 (47-83)	62 (48-71)	72 (66-81)
UBA1 mutations, n (%)	p.Met41Thr 2 (67%) p.Met41Leu 1 (33%)	p.Met41Thr 15 (60%) p.Met41Val 5 (20%) p.Met41Leu 5 (20%)	p.Met41Thr 5 (46%) p.Met41Val 3 (27%) p.Met41Leu 1 (9%) splice motif mutation 2 (18%)	p.Met41Thr 8 (62%) p.Met41Val 2 (15%) p.Met41Leu 3 (23%)	p.Met41Thr 3 (37.5%) p.Met41Val 2 (25%) p.Met41Leu 3 (37.5%)
Clinical features					
Arthritis, n (%)	1 (33%)	not reported	11 (100%)	6 (46%)	2 (25%)
Fever, n (%)	1 (33%)	23 (92%)	10 (91%)	13 (100%)	6 (75%)
Skin involvement, n (%)	3 (100%)	22 (88%)	11 (100%)	11 (85%)	7 (88%)
Pulmonary, n (%)	1 (33%)	18 (72%)	5 (46%)	10 (77%)	not reported
ENT chondritis, n (%)	3 (100%)	16 (64%)	5 (46%)	13 (100%)	8 (100%)
Vasculitis. n (%)	3 (100%)	4 (16%)	7 (64%)	not reported	not reported
Ophthalmologic, n (%)	2 (67%)	not reported	5 (46%)	not reported	3 (38%)
Haematologic, n (%)	macrocytic anaemia 2 (67%) MDS 1 (33%)	macrocytic anaemia 24 (96%) MDS 6 (24%) Multiple myeloma or MGUS 5 (20%)	macrocytic anaemia 7 (64%) MDS 6 (54%)	MDS 3 (23%) MGUS 1 (8%) multiple myeloma 1 (8%)	macrocytic anaemia 7 (88%) MDS 4 (50%)

ENT: ear nose throat; MDS: myelodysplastic syndrome; MGUS: monoclonal gammopathy of undetermined significance: UBA: ubiquitin-associated domain.