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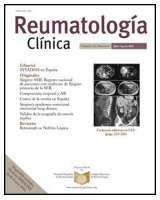

Letter to the Editor

Entities inside one another: VEXAS, a matryoshka-type disease

Unas entidades dentro de otras: VEXAS, una enfermedad tipo matrioska

Dear Editor,

Matryoshka are sets of wooden Russian dolls of decreasing size placed one inside another. Matryoshkas are also used metaphorically in medicine.[1] However, Alter[2] used the term "a matryoshka-doll type presentation," for the first time to refer to a clinically presenting autoimmune disease masking a clinically silent autoimmune disease.

Here, we report a patient with a matryoshka-doll type presentation with fever, lymphadenopathy and exanthema, who was diagnosed over the years of cryptogenic organizing pneumonia (COP), adult-onset Still's disease (AOSD), histiocytoid Sweet syndrome (HSS), cutaneous polyarteritis nodosa and myelodysplastic syndrome (MDS), masking a VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, genetic diagnosis made 2 years postmortem.

Case report

A 70-year-old man consulted in 2014 for high fever, cervical lymphadenopathy, chest pain and nonpruritic evanescent exanthema on the trunk of 1 year of evolution. On presentation, physical examination revealed inflammatory signs in the right arm, suggestive of cellulitis and inspiratory crackles. Laboratory analysis showed hemoglobin 12.5 g/dL, MCV (mean corpuscular volume) 100.9 fL, leucocytes 5.8 g/l (77N (neutrophils), 19 L (lymphocyte), 3M (monocytes)), and platelets 127 g/l. Further tests showed a marked elevation of acute-phase reactants: reactive C protein 26 mg/l, erythrocyte sedimentation rate (ESR) 80 mm, ferritin 5348 ng/ml, with normal or negative general biochemistry, urine sediment, antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF), angiotensin-converting enzyme, and complement. Biopsy of the skin lesions revealed leukocytoclastic vasculitis. Chest radiography revealed bilateral, patchy opacities. High-resolution computed tomography (CT) revealed peripheral and multifocal consolidations. Bronchoalveolar lavage (BAL) was performed to rule out infection. COP was diagnosed, and the patient improved with intermediate doses of steroids in a descending oral regimen. Several weeks later, after steroid tapering, the patient developed axillary lymphadenopathy, high fever, polyarthritis, and erythematous, raised, warm, erythematous skin lesions. A core needle lymph node biopsy revealed reactive lymphadenitis. 18F-FDG PET/CT scan was obtained without detection of vascular inflammation. Adult-onset Still's disease (AOSD) was suspected. At discharge, methotrexate was administered as a steroid-sparing agent. He again had leukocytes with a left shift, mild thrombocytopenia, and elevated CRP and ferritin levels, all normalizing with increasing steroids. Another skin biopsy was compatible with histiocytoid Sweet syndrome. One month later, he developed *Listeria monocytogenes* meningitis, and antimetabolites were suspended. At that time, he presented with mild anemia and thrombopenia (91,000 platelets), and a marrow aspirate was performed in February 2017 and also presented with myelodysplastic syndrome type multilineage dysplasia, with Y chromosome loss in the karyotype analysis. No vacuoles were observed. With the decrease of steroids below 20 mg/day of prednisone, the fever and skin lesions returned, and a third skin biopsy was performed, which revealed findings compatible with histiocytoid Sweet syndrome associated with cutaneous polyarteritis nodosa.

Steroids plus intravenous immunoglobulin, tocilizumab, rituximab, and adalimumab were administered without success. He required high doses of steroids and was admitted to several hospitals to control the fever. He developed complications due to immunosuppressive treatments, including diabetes, acute confusional syndromes, urinary infections, and *Pneumocystis jiroveci* pneumonia. Finally, the family decided to care for him at home, where he eventually died in 2020. Two years after death, DNA was extracted from a skin paraffin-embedded biopsy, and a genetic study was performed. A UBA1 somatic mutation was found: p.Met41Thr in exon 3, as a mosaicism, which has been previously described as causing VEXAS syndrome.

Discussion

Autoinflammatory syndromes result from a defective innate immune system. They are characterized by recurring or persistent episodes of multisystemic inflammation, unexplained fever, and elevated acute-phase reactants. Autoinflammatory syndromes can be inherited, acquired, or present in adulthood. Acquired autoinflammatory syndromes include adult-onset Still's disease, Schnitzler syndrome, and more recently VEXAS syndrome.[3]

VEXAS syndrome, first described in 2020 in 25 patients, is a monogenic inflammatory syndrome. Key features include treatment-refractory inflammatory syndrome, which develops in late adulthood; recurrent fever; chondritis; vasculitis; dysplastic bone marrow; and characteristic vacuoles in myeloid and erythroid precursor cells. Patients typically require high dose corticosteroids to control inflammatory symptoms and are refractory to other anti-inflammatory medications.[4]

This new disease entity, similar to a matryoshka doll, connects seemingly different inflammatory conditions and hematologic disorders (myelodysplastic syndrome or multiple myeloma). Notably, patients with VEXAS syndrome sometimes fulfill the corresponding

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classification criteria for Behçet disease, AOSD, giant cell arteritis, or polyarteritis nodosa.[5]

Skin manifestations are typical but nonspecific in VEXAS syndrome, including Sweet syndrome, erythema, nodules, papules, erythema nodosum, and panniculitis. The histological hallmark of skin lesions is neutrophilic dermatosis, often accompanied by leukocytoclastic vasculitis.[5,6] Cutaneous PAN and HSS were only reported to be associated with MDS by Pinal-Fernandez in 2013.[7] We believe that this patient would now be fit for VEXAS syndrome.

Our patient presented with COP at disease onset. Although lung infiltrates were described in 72% of the first 25 VEXAS syndrome patients,[8] pulmonary manifestations have been highlighted recently. Kouranloo et al.[9] reviewed 269 patients with VEXAS from all published articles until May 2022, and 56.1% of them had pulmonary involvement at presentation. The most frequently described pulmonary manifestation was infiltrates (43%), followed by pleural effusion (7.4%), and idiopathic interstitial pneumonia (3%). Other pulmonary manifestations included nonspecific interstitial pneumonia, bronchiolitis obliterans, pulmonary vasculitis, bronchiectasis, alveolar hemorrhage, pulmonary embolism, bronchial stenosis, and alveolitis. It is unclear whether respiratory manifestations are part of the primary disease or a co-existing condition. Borie et al.[10] reviewed 114 patients included in the French VEXAS cohort between November 2020 and May 2021. 51 patients had a chest CT scan available for review and 45 (39%) had pleuropulmonary abnormalities that were considered related to VEXAS. These 45 patients showed lung opacities, including ground-glass opacities (87%), consolidations (49%), reticulation (38%), septal lines (51%), and pleural effusion (53%). In addition, 20 patients showed a pattern suggestive of COP. Most patients showed improvement with prednisone but usually required >20 mg/day.

The presence of an atypical or refractory systemic disease should raise the suspicion of VEXAS, even in patients without hemopathies, which usually appear over the course of the disease. A matryoshka-doll type presentation is common, with autoinflammatory diseases masking this new syndrome. The diagnosis is genetic; therefore, it is possible to diagnose patients who have already died by retrieving and testing stored biopsies.

Conflict of interests

The authors state that they have no conflict of interests.

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