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Case Report

VEXAS Syndrome: A Prototype for Hemato-Inflammatory Diseases?

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Abstract

VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a rare disease caused by somatic mutations in hematopoietic progenitor cells in the UBA1 gene, resulting in decreased ubiquitylation, impaired hematopoiesis and systemic inflammation. We present the case of a male affected by relapsing polychondritis with parallel onset of macrocytic anemia, admitted because of fever, headache, chest pain, left hemisoma hypoesthesia, bilateral hearing loss and conjunctivitis. The investigations suggested a reactivation of relapsing polychondritis, with prevailing neurological symptoms. The bone marrow biopsy showed myelodysplastic syndrome. We suspected VEXAS syndrome and the UBA1 mutation was found. A good clinical response to steroid with refractoriness to several drugs other than glucocorticoids, was observed. When a JAK inhibitor was added, rheumatologic manifestations, but not cytopenia improved.

Keywords: *VEXAS; Hemato-Inflammatory Diseases*

Abbreviation

RP: Relapsing Polychondritis

Learning Points:

- In patients with treatment-refractory inflammatory disease associated with progressive hematologic disorders, a diagnosis of VEXAS should be considered and somatic mutations in hematopoietic progenitor cells in the UBA1 gene should be sought.
- VEXAS is a prototype of hemato-inflammatory diseases characterized by a genetic link between clonal hematopoiesis and systemic inflammation.
- Growing clinical interest will increase awareness of VEXAS, possibly leading to syndrome's pathogenesis and appropriate therapeutic strategies.

Introduction

Hemato-inflammatory diseases characterized by a genetic link between clonal hematopoiesis and systemic inflammation have recently received growing interest [1-5]. VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a rare adult disease, first reported in 2020 [6,7], caused by somatic mutations in hematopoietic progenitor cells in the X-linked gene UBA1, resulting in decreased ubiquitylation, impaired hematopoiesis and systemic inflammation.

More frequently hematologic manifestations include macrocytic anemia, thrombocytopenia, thromboembolic disease, myelodysplastic syndrome and multiple myeloma, while rheumatologic manifestations are relapsing polychondritis (RP), Sweet syndrome and polyarteritis nodosa. RP is a systemic autoimmune disease characterized by recurrent episodes of inflammation of cartilaginous and proteoglycan-rich tissues [8].

Here we report the case of a patient affected by RP with macrocytic anemia who subsequently was diagnosed as having VEXAS syndrome.

Case Description

A 62-year-old male had a diagnosis of RP on the basis of fever, weight loss and non-productive cough with pulmonary infiltrates, associated with nasal and laryngotracheal chondritis, costochondral and costovertebral arthritis, episcleritis, urticarial papules and aortitis. The transbronchial biopsy showed inflammatory lymphocytic infiltrates and signs of organizing pneumonia. An oral steroid treatment was started and any attempts to reduce steroid by immunosuppressive therapy resulted in the development of infectious complications. In parallel with the onset of RP, a macrocytic anemia developed with normal laboratory tests and bone marrow biopsy (BMB). A DNMT3A mutated gene, predisposing to clonal hematopoiesis, was reported and mild thrombocytopenia developed.

At the age of 65 years the patient was admitted to the Internal Medicine ward because of the acute onset of fever associated with headache, chest pain, left hemisoma hypoesthesia, bilateral hearing loss and conjunctivitis. At laboratory neutrophilic leukocytosis, macrocytic anemia, thrombocytopenia and increased PCR, with slightly modified PCT but normal lactates and increased Serum Amyloid A (SAA) protein (day 1) were present. Chest X-ray, abdominal ultrasound, brain CT and EEG were all normal, with negative blood and urine cultures, suggesting a systemic reactivation of RP. Treatment with intravenous methylprednisolone, ampicillin, meropenem and acyclovir was administered, with clinical improvement (day 8). Steroid therapy was stepped down, antibiotic therapy was discontinued and infection prophylaxis was started. The patient underwent weekly administration of erythropoietin and red blood cell transfusions. A BMB was repeated, showing trilinear maturation disorder, consistent with myelodysplastic syndrome, and neutrophil vacuoles. We suspected VEXAS syndrome and the somatic mutation in UBA1 (M41T) was found.

On day 21st, after the reduction of 10 mg/day of methylprednisolone, fever and dyspnea relapsed, with peripheral arterial oxygen desaturation and negative chest X-ray. PCR and SAA increased in association to hematological worsening. The increase of steroid dosage improved clinical and laboratory changes. On day 32nd the patient developed pneumonia with septic shock, with neutrophilic dermatitis and severe anemia, requiring blood cells transfusion, and thrombocytopenia. Fluid challenge, norepinephrine, oxygen were given and empirical antibiotic therapy was started. Steroid therapy was maintained for 10 days and then given orally. On day 48th the patient was discharged with a slow steroid decalage and persistence of normal inflammatory markers, improvement of anemia and thrombocytopenia and no relapse of systemic symptoms. Six months after discharge the patient complained a right popliteal deep vein thrombosis. The JAK inhibitor baricitinib was added to the patient's therapy, in order to reduce steroid dosage with a favourable effect on the rheumatologic manifestations, but not on cytopenia.

Discussion

The patient we described had representative features of VEXAS syndrome, characterized by efforts in treating RP with myelodysplastic syndrome. The diagnosis of RP, still based on clinical grounds, was made mainly on the basis of nasal chondritis, costochondral inflammatory non-erosive polyarthritis with typical chest pain and ocular inflammation. During hospitalization neurological symptoms, probably linked to nervous system vasculitis, and sensorineural hearing loss, also usually described in RP, developed. As reported in literature, patients with RP who also have diagnosis of VEXAS have some peculiar clinical manifestations [9]. In particular, inflammatory pulmonary infiltrates and deep vein thrombosis have been described, as in our patient [10,11]. Moreover, neutrophil vacuoles, found in BMB, are reported in myelodysplastic syndrome in VEXAS [12].

A good clinical response to steroid with refractoriness to drugs other than glucocorticoids represents another typical feature of VEXAS. Studies, aimed to find effective steroid-sparing drugs, especially azacitidine and JAK inhibitors [13], including baricitinib, are ongoing.

Conclusion

This case report would like to raise awareness among clinicians on hemato-inflammatory diseases with a genetic link [6], such as VEXAS syndrome. VEXAS syndrome is a rare severe disease, recently described, whose diagnosis should be considered in patients with treatment-refractory inflammatory disease (especially RP, Sweet syndrome and polyarteritis nodosa) associated with progressive hematologic alterations. Further studies are needed to identify the syndrome's pathogenesis, in order to design appropriate therapeutic strategies.

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