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Title	VEXAS-associated myelodysplastic syndromes
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Abstract

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome was first described by David Beck and colleagues in December 2020.[1] It was shown to be associated with hematological disorders, in particularly myelodysplastic syndrome (MDS).

Herein, we are going to report a patient suffered from VEXAS syndrome and MDS.

A 73 years old gentleman presented with fever, generalized pruritic erythematous papules, polyarthritis and relapsing polychondritis in early 2017. A skin biopsy was performed which the histology showed interstitial neutrophilic and granulomatous dermatitis. Patient was treated with high dose prednisolone in April 2017. The skin lesions showed initial improvement but worsen again whenever prednisolone dose was being tapered, and therefore, cyclosporin was added. He was admitted for pyrexia of unknown origin (PUO), relapse of polychondritis and pancytopenia (haemoglobin 7.9g/dL, white blood cell 2.8 x 10^9/L, platelet 77 x 10^9/L) in November 2017. A bone marrow exam was performed which showed hypercellular marrow with dysmegakaryopoiesis, mild dyserythropoiesis and subtle dysgranulopoiesis, compatible with myelodysplastic syndrome with multilineage dysplasia (MDS-MLD). Patient received extensive work up for PUO including Gallium scan, skin biopsy and bronchoscopy which were all not revealing. Subsequently a PET/CT was performed and showed multiple miliary lung nodules in bilateral lung fields. Patient was given empirical anti-tuberculosis treatment. He then received regular azacitidine infusion since April 2018. His disease was under stable control since then and all the immunosuppressants can be tapered off. In view of his typical presentation of severe adult-onset autoinflammatory disease and MDS in elderly male, his bone marrow slide was reviewed which demonstrated vacuoles in the erythroid and granulocytic precursor cells.

VEXAS syndrome is caused by a somatic missense mutation in codon 41 of ubiquitin-like modifier activating enzyme 1 (UBA1), an X-linked gene which encodes the enzyme that initiates ubiquitination. Reduction in ubiquitylation leads to the accumulation of unfolded proteins and activation of autoimmune pathways, leading to an uncontrollable inflammatory response.

VEXAS syndrome is a disease with multisystem involvement with hematological manifestations including macrocytic anemia, bone marrow vacuoles, thrombotic events, MDS and multiple myeloma.[2] The characteristic vacuolation is commonly found in myeloid and erythroid precursors on bone marrow specimens although absent of vacuoles does not exclude the diagnosis.

To date, treatment for VEXAS is not standardized with majority of the patients requiring use of immunosuppressant like high-dose steroid. The use of azacitidine was shown to be able to improve autoinflammatory symptoms allowing a reduction or discontinuation of steroid.[3] The treatment responses observed in our patient is in line with the literature. Hypomethylating agents were believed to have immunomodulatory effects by reducing the proliferative capacity of regulatory T cells. A concomitant reduction of pro-inflammatory T-helper cells, Th1 and Th17 after azacitidine treatment was also observed.[4] Further study to elucidate the pathophysiological mechanism between these two syndrome and evaluation on therapeutic options is warranted.

Reference:

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