Diagnostic Snapshot

Convergence of Hematology and Rheumatology: A Case Study

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Author's disclosure of conflict of interest is found at the end of this article.

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https://doi.org/10.6004/jadpro.2023.14.2.8

Abstract

Advanced practitioners may frequently encounter patients who have a hematologic and rheumatologic diagnosis. These patients are usually managed by multiple specialists, including hematologists, rheumatologists, and dermatologists, given their broad symptomatology. Genetic testing may provide the answer to the constellation of symptoms and refractory symptoms that these patients exhibit.

HISTORY

MG is a 55-year-old male with a past medical history that is significant for type 2 diabetes mellitus, hypothyroidism, and auricular chondritis (Figure 1).

CHIEF COMPLAINT

He presented to the emergency room with reports of fevers up to 100.8°F, significant fatigue, and weakness.

DIAGNOSTIC STUDIES

Laboratory findings revealed a white blood cell count of 4.6 K/uL, hemoglobin of 6.6 g/dL, mean corpuscular volume (MCV) of 111.9 fl, and platelets of 135,000 K/uL. A comprehensive metabolic panel was unremarkable except for an elevated total protein level of 8.5. There was no evidence of hemolysis. An abdominal ultrasound was normal with no evidence of hepatosplenomegaly. MG underwent esophagoduodenoscopy and colonoscopy with no evidence of bleeding, dysplasia, or malignancy. A bone marrow biopsy was performed and revealed a hypercellular marrow with myeloid predominant trilineage hematopoiesis, left shifted granulopoiesis, and dysmegakaryopoiesis with 4% blasts. He had a normal flow cytometry and cytogenetics. A myelodysplastic syndromes (MDS) fluorescence in situ hybridization (FISH) panel and myeloid molecular profile were both negative. MG received one unit of packed red blood cells and was discharged home.

FURTHER ASSESSMENTS

One month after discharge, MG was seen at the hematology clinic with complaints of worsening fatigue, left ear pain and inflammation, arthralgias, as well as painful nodular skin lesions throughout both upper and lower extremities. The laboratory evaluation revealed a hemoglobin level of 6.9 g/dL with an MCV of 101 fl and platelet count of 87,000 K/uL.

MG was given another unit of packed red blood cells and was directed to see a dermatologist to evaluate his skin lesions. A biopsy of a nodular skin lesion revealed leukocytoclastic vasculitis. He was then referred to rheumatology who, given findings of ear chondritis, polyarthritis, and uveitis, diagnosed MG with relapsing polychondritis.

MG was prescribed high-dose steroids and after a few weeks had an improvement in auricular chondritis and resolution of his skin lesions. However, he became transfusion dependent, which prompted a repeat bone marrow biopsy that revealed myeloid hyperplasia, erythroid hypoplasia, megakaryocytic dysplasia with vacuolization, and no significant increase in blasts. A sequence analysis revealed a somatic mutation affecting methionine-41 (p.Met41Thr) *UBA1*.

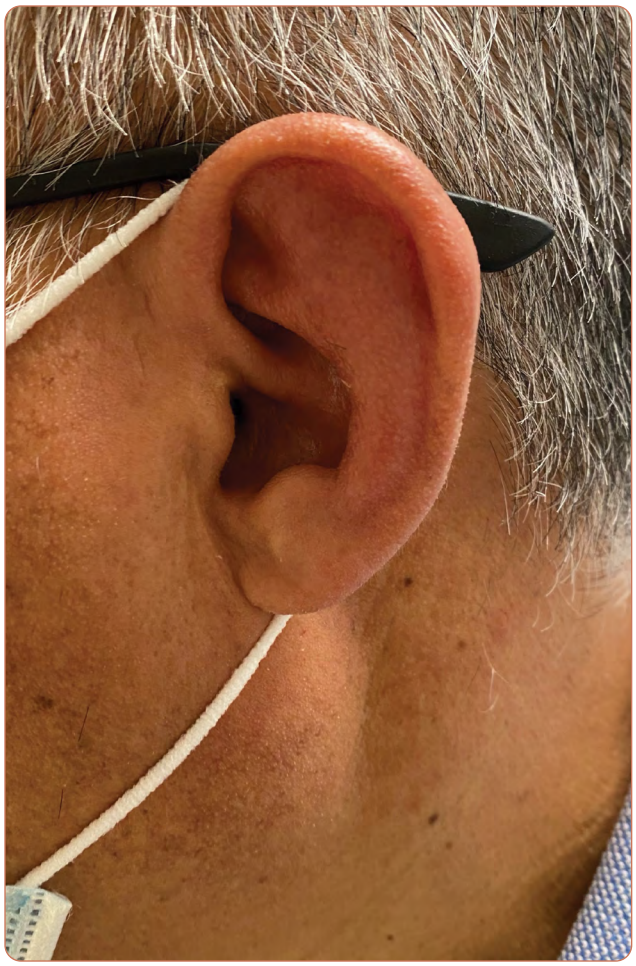

Figure 1. Left auricular chondritis.

DIFFERENTIAL DIAGNOSIS

WHAT IS THE CORRECT DIAGNOSIS FOR MG?

A ☐ Myelodysplastic syndromes

B ☐ Relapsing polychondritis

C ☐ VEXAS syndrome

SEE BACK FOR ANSWER ▶

WHAT IS THE CORRECT DIAGNOSIS FOR MG?

A Myelodysplastic syndromes

B Relapsing polychondritis

C VEXAS syndrome (correct answer)

A Myelodysplastic syndromes. Myelodysplastic syndromes is a heterogeneous group of hematologic neoplasms classically described as a clonal disorder of hematopoietic stem cells leading to dysplasia and ineffective hematopoiesis in the bone marrow (Dotson & Lebowicz, 2022). Clinical signs include abnormally low blood cell counts, fatigue, weakness, easy bruising or bleeding, and frequent infections. MG had evidence of dysplasia in the bone marrow, which explains his anemia and thrombocytopenia, as well as his fatigue. However, MDS does not explain the findings of inflammation that MG presented with.

B Relapsing polychondritis. Relapsing polychondritis is a rare autoimmune rheumatic disorder that is traditionally classified as a systemic vasculitis. It is characterized by inflammation of the cartilage, and typical presenting features include chondritis of the nasal bridge, auricular chondritis, ocular inflammation, and involvement of the bronchial tree (Kingdon et al., 2018). MG's clinical picture is consistent with relapsing polychondritis as he had auricular chondritis, conjunctivitis, and evidence of vasculitis. Although a systemic inflammatory condition may cause anemia and thrombocytopenia, it does not explain MG's findings of dysplasia seen in the bone marrow.

C VEXAS syndrome (correct answer). VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a novel disorder that was identified in patients with adult-onset inflammatory syndromes, often accompanied by MDS. During late adulthood, patients develop symptoms in multiple organs, including fevers; cytopenias; neutrophilic, cutaneous, and pulmonary inflammation; chondritis and vasculitis; vacuoles in myeloid and erythroid precursor cells; and dysplastic bone marrow (Beck et al., 2020). MG's clinical picture is consistent with VEXAS syndrome as evidenced by the findings of chondritis, vasculitis, cytopenias/MDS, vacuoles in marrow, and *UBA1* mutation. The co-occurrence of MDS and relapsing polychondritis can be best explained by VEXAS syndrome.

DISCUSSION

In December 2020, a multidisciplinary group of clinicians at the National Institutes of Health (NIH) published an article about a new, adult-onset syndrome that links seemingly unrelated hematologic and autoimmune symptoms, which they termed VEXAS. VEXAS was identified after a clinical geneticist, David Beck, MD, PhD, started to look for gene mutations within the ubiquitin pathway, a set of enzymes that adds a small regulatory protein called ubiquitin to other proteins to mark that protein for one of several fundamental tasks in the cell, including protein degradation, shuttling to a different part of the cell, and folding or altering ubiquitin's interactions with other proteins (Beck et al., 2020). This led to the first three patients with a genetic variant in the *UBA1* gene. These three patients turned out to be older men with an inflammatory condition and bone marrow failure. Until that moment, there had been a clinical association between disorders of the bone marrow and systemic inflammatory features, but there wasn't a biological explanation for both. VEXAS syndrome seems to connect hematology and rheumatology. Since the publication in 2020, over 100 patients with VEXAS syndrome have been identified (Templé & Kosmider, 2022). Given its recent discovery, the prevalence of this syndrome is unknown at this time.

MANAGEMENT

MG was diagnosed with VEXAS syndrome, as he had findings of myeloid vacuolization, evidence of systemic inflammation, and *UBA1* mutation. Until recently, MG was thought to have two completely different diseases; however, this discovery shows us that there is a relationship between them that is based on genetics. MG was treated with high-dose steroids with improvement in his

inflammatory symptoms, but no improvement was noted in his blood counts. MG's care was transferred to one of the MDS experts at our institution, but unfortunately he developed a cerebrovascular accident that precluded him from receiving further treatment.

Currently, there are multiple ongoing trials to evaluate the most effective therapeutic options for these patients, as they do not seem to respond to conventional treatments. There is no standard-of-care treatment for VEXAS syndrome, and most patients are typically dependent on steroids for relief of their inflammatory symptoms. Some retrospective studies have shown encouraging results for treatments with azacitadine (Vidaza, Onureg), a hypomethylating agent. Encouraging results were also seen with ruxolitinib (Jakafi), a JAK2 inhibitor (Templé & Kosmider, 2022). However, none of these treatments have been shown to eradicate the *UBA1* clone. One promising and possible curative option is allogeneic stem cell transplant, but more research needs to be done. Given the poor prognosis of VEXAS patients, it is important that better therapeutic options are found and that these patients be managed by a multidisciplinary team including a hematologist and rheumatologist.

Disclosure

The author has no conflict of interest to disclose.

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