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Case Report

Somatic Mutation in *UBA1* and ANCA-associated Vasculitis

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome was recently discovered in 25 men with late-onset severe and refractory inflammatory syndromes and associated hematologic abnormalities. Various diseases have been described, such as relapsing polychondritis, myelodysplastic syndrome, polyarteritis nodosa, and giant cell arteritis. The disorder originates from a somatic mutation in *UBA1*, an X-chromosome gene encoding the ubiquitin-activating enzyme 1.[1] Myelodysplastic syndrome has been previously reported concomitantly with systemic vasculitides,[2] but only a few cases have been described with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV).[3,4] A shared genetic contribution was thus far unknown. Here, we report the first case, to our knowledge, of refractory granulomatosis with polyangiitis (GPA) with overlapping myelodysplasia and a mosaic mutation in *UBA1*. Ethics approval for this case report was waived by our institution's ethics committee. The patient's written informed consent was obtained.

In April 2019, a 68-year-old man was referred to our clinic for ongoing constitutional symptoms. Medical history was significant for past cocaine use that was discontinued more than 30 years ago, as well as resolved hepatitis B and C infections. Complete blood count revealed a hemoglobin of 60 g/L without macrocytosis, leukopenia, or thrombocytopenia. Other laboratory results were significant for microscopic hematuria, elevated serum creatinine (250 μmol/L), and elevated C-reactive protein (CRP; 300 mg/L). Kidney biopsy was consistent with pauci-immune glomerulonephritis. Multiple subpleural pulmonary nodules (6–9 mm in diameter) with nodular ground glass opacities, nasal septum perforation, and signs of chronic sinusitis were detected on imaging studies. A bone marrow biopsy was unremarkable at that time, showing only hypercellularity. Thorough rheumatological serologies were negative, including ANCA, rheumatoid factor, cryoglobulins, antinuclear antibodies, and extractable nuclear antigen antibodies. Serum complement levels (C3 and C4) were normal and viral loads were undetectable for both hepatitis B and C. The clinical presentation was in keeping with severe ANCA-negative GPA with an initial Birmingham Vasculitis Activity Score (BVAS version 3) of 24, and the patient fulfilled the American College of Rheumatology classification criteria for GPA.[5]

Over the course of the disease, several relapses were characterized by marked increases in creatinine and CRP, and reappearance of microscopic hematuria and anemia, with failure to taper glucocorticoids (GCs) below 20 mg/day of oral prednisone. The patient was refractory to remission-induction therapy with cyclophosphamide (CYC; 12.5 mg/kg intravenously every 2–3 weeks for 4 months); he then received a combination of CYC and rituximab (RTX) infusions (1000 mg on Days 1 and 15). He relapsed during maintenance therapy with RTX alone (1000 mg every 4 months), then combined with oral mycophenolate mofetil (2000 mg/d).

In November 2020, while on prednisone 20 mg daily, the patient developed severe constitutional symptoms, macrocytic anemia (hemoglobin 55 g/L and mean corpuscular volume 116 fL), mild leukopenia (white blood cell count 2.3 × 10^9/L), and thrombocytopenia (platelets 120 × 10^9/L). His CRP level was again elevated (60 mg/L). A bone marrow biopsy showed multilineage dysplasia (> 10%), 2% blasts, and presence of cytoplasmic vacuoles in granulocytes and erythroid progenitors; cytogenetic analysis was normal. During this disease relapse, his BVAS was calculated at 7. Over the course of his disease or relapses, he never presented signs of auricular or nasal chondritis, cutaneous manifestations, or thromboembolic events.

Given treatment failure and co-occurrence of hematologic abnormalities, a *UBA1* gene test (blood sample) was ordered in November 2020 and showed a somatic pathogenic variant for *UBA1* c.122T>C, p.(Met41Thr) with an allele frequency of 85%.

Intravenous tocilizumab was initiated in November 2020, and prednisone increased to 30 mg/day. GCs were then gradually tapered to 20 mg after 1 month, then decreased by 5 mg every 2 weeks. As of March 2021, the patient remains on a low dose of prednisone (5 mg/d) and is in complete remission (BVAS of 0). Time will tell if the patient remains in sustained remission, as the disease is known to be refractory to steroid-sparing agents.[1]

In conclusion, we describe a case of ANCA-negative GPA with co-occurrence of myelodysplasia and a somatic mutation affecting the *UBA1* gene. To our knowledge, this is the first reported case of apparent VEXAS syndrome associated with AAV. This case report highlights the highly variable initial presentation described in association with VEXAS syndrome, despite patients sharing a common genotype. The increased awareness of this syndrome will hopefully help find suitable treatment options for these patients in which mortality is high.

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The authors declare no conflicts of interest.

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