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Letter
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Recovery of Bone Marrow Function in VEXAS Syndrome-potential Role for Romiplostim

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VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently reported late-onset hematoinflammatory disorder occurring predominantly in older men, due to acquired mutations in the X-linked *UBA1* gene.[1] An emerging category of hematoinflammatory disorders are broadly defined as diseases caused by somatic mutations restricted to the blood, but results in systemic inflammation with multiorgan involvement and are associated with abnormal and/or premalignant bone marrow (BM) changes.[2] The inflammatory manifestations are driven in part by activation of the NLRP3 inflammasome and release of proinflammatory cytokines such as interleukin (IL)-1β, IL-18, and IL-6.[3] The hematological manifestations include vacuoles in erythroid and myeloid precursors, macrocytosis, and multilineage cytopenias. Most patients are diagnosed with clonal cytopenia of unknown significance, with 31%–50% of cases also fulfilling diagnostic criteria for myelodysplastic syndrome (MDS).[4,5] Typical inflammatory manifestations include fever, weight loss, skin lesions, lung disease, joint involvement, and inflammatory eye disease, while VEXAS can clinically mimic inflammatory syndromes such as Sweet's syndrome (acute febrile neutrophilic dermatosis), relapsing polychondritis, and polyarteritis nodosa.[4,5]

The best characterized and, to date, most common pathogenic variants lead to substitution of methionine at position 41, (*UBA1* p.Met41 [p.Met41Leu/Thr/Val]), which is the start codon for translation of the cytoplasmic, enzymatically active, isoform of UBA1 (UBA1b). Consequently, there is loss of intracellular homeostasis due to dysregulated ubiquitination. The mutation is found in multipotent hematopoietic progenitors, with putative selection pressure conferred by the mutation driving a high variant allele fraction (VAF) in myeloid cells, while lymphocytes generally do not survive with the mutation.[6]

VEXAS syndrome is associated with significant morbidity, and for the 32% of patients who develop transfusion dependence, the risk of mortality is increased by 4.5-fold.[4] Presently, the only potentially curative treatment is allogenic hematopoietic stem cell transplantation (ASCT), with numerous other medical therapies used for symptomatic control only. Here, we describe a case of VEXAS syndrome, P22 from the original cohort published in 2020,[1] who has undergone spontaneous resolution of their trilineage cytopenia and inflammatory manifestations, despite the persistence of the pathogenic *UBA1* mutation.

The patient is a 76-year-old male who initially presented with macrocytic anemia 10 years earlier. The anemia was later found to be part of his VEXAS syndrome, subsequently diagnosed in 2020. He had a difficult clinical course due to trilinage cytopenia and a variety of inflammatory complications, including suspected polymyalgia rheumatica and relapsing polychondritis (Figure 1). He was not deemed suitable for ASCT due to initial uncertainty about the diagnosis and the presence of significant comorbidities. His treatment has largely been supportive and aimed at controlling inflammatory complications and cytopenia. He became transfusion dependent in June 2015 and subsequently developed severe thrombocytopenia. His anemia and thrombocytopenia were initially presumed to be immune-mediated and he was therefore treated with intravenous immunoglobulin and later rituximab, without success. He had a nondiagnostic BM examination on several occasions. Retrospective investigations showed the presence of the pathogenic *UBA1* Met41Leu mutation with similar VAFs in all BM samples.

In 2020, he was briefly treated with eltrombopag, which was ineffective and subsequently commenced on the thrombopoietin receptor agonist (TPO-RA), romiplostim, for thrombocytopenia. He continues to receive monthly romiplostim (Suppl. Figure S1). The full blood count before his final transfusion in November 2021 showed a hemoglobin (Hb) of 110 g/L, platelets (PLT) 80×10^9/L, mean corpuscular volume (MCV) 114, lymph 0.67×10^9/L. Over subsequent months, these have

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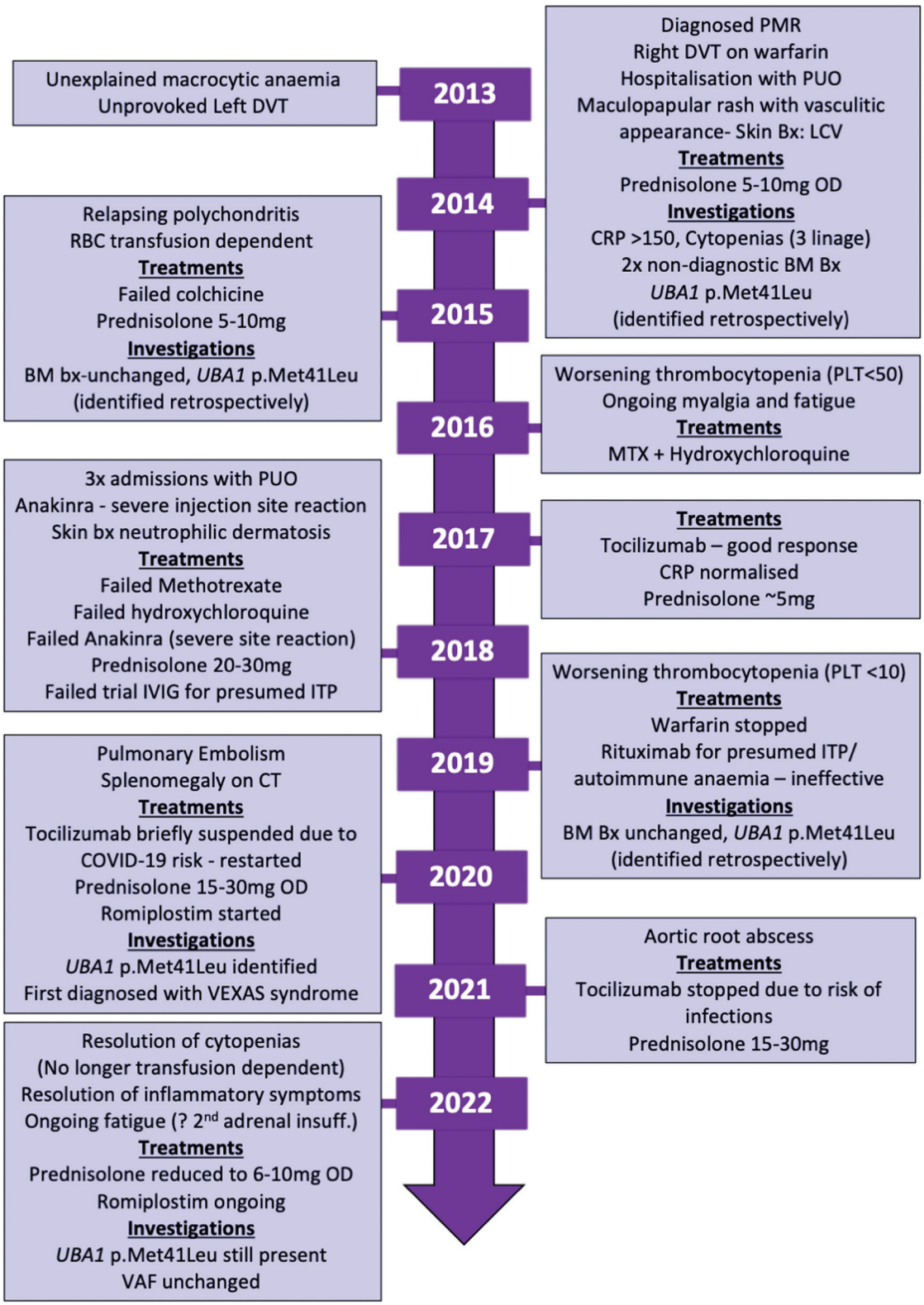


Figure 1. Summary of clinical progress and treatment responses. Timeline of symptoms and complications development, investigations, and treatment responses. BM = bone marrow; Bx = biopsy; CRP = C-reactive protein; CT = computer tomography; DVT = deep vein thrombosis; LCV = leukocytoclastic vasculitis; PLT = platelets; PMR = polymyalgia rheumatica; PUO = pyrexia of unknown origin; RBC = red blood cells.

spontaneously improved to normal levels (Hb 156, PLT 188, and lymph 1.10), although the MCV remains elevated at 110 (Suppl. Figure S1). The patient's inflammatory symptoms are well-controlled despite his prednisolone being weaned down to its current level of 6 mg/day. Further reduction is limited by the patient complaining of severe fatigue. A synacthen test indicated that this is likely due to secondary adrenal insufficiency, but since the test was done while the patient was still receiving 6 mg of prednisolone (<5 mg daily is required for the test to be fully valid), the diagnosis remains unconfirmed. The patient's

latest C-reactive protein (CRP) readings (November 2022 and January 2023) demonstrate well-controlled inflammation with CRP <5 mg/L. These results, along with the clinical picture, confirm that the patient is currently in remission while not receiving any active anti-inflammatory treatment.

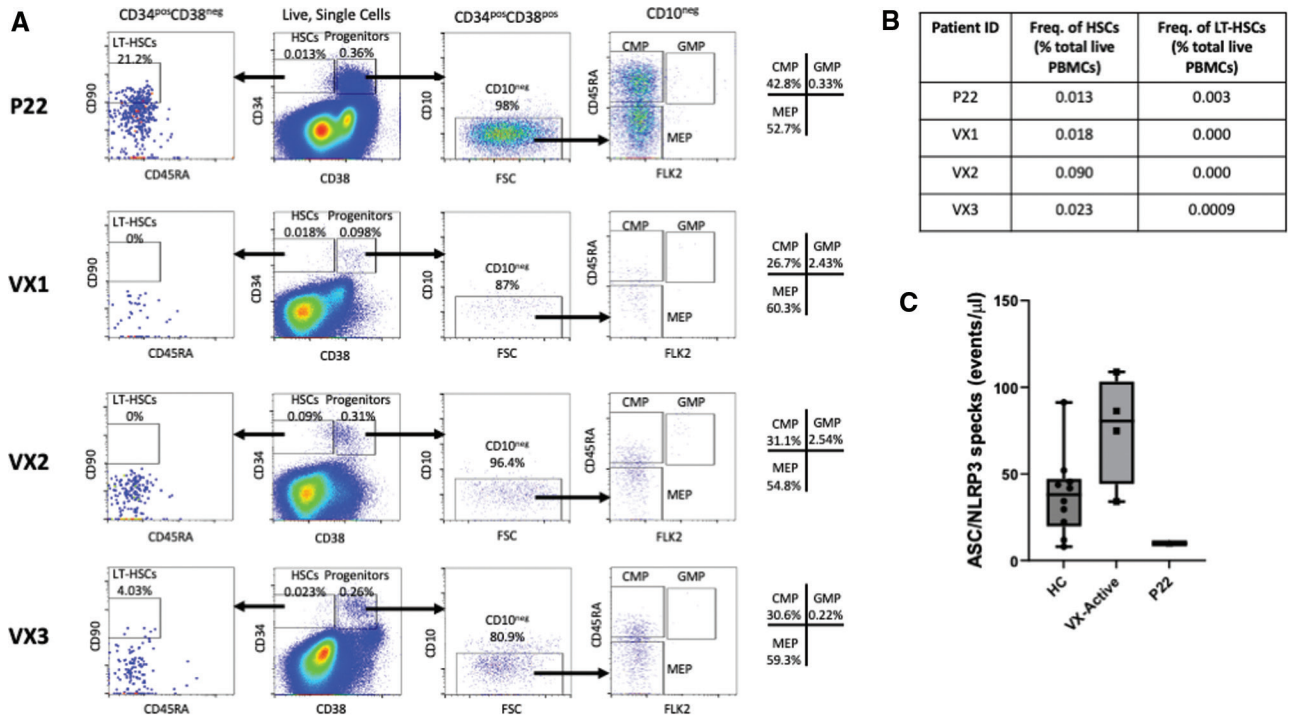
We initially postulated that the resolution of his condition was due to spontaneous clearance of the *UBA1* Met41Leu clonal cells, but longitudinal testing of whole blood DNA showed the presence of the same pathogenic UBA variant with an unchanged VAF. Additional genetic tests (whole genome sequencing) did not reveal the emergence of any novel mutations, such as *JAK2 V617F* mutations, which might be postulated to rescue the phenotype.

To further test if there were any significant differences that might provide some insight into why his hematopoiesis has recovered, we used cell surface marker analysis to investigate the hematopoietic stem and progenitor cell (HSPC) compartment. We compared this case to patients with ongoing manifestations of VEXAS, including macrocytic anemia and thrombocytopenia (VX1, VX2, and VX3); peripheral blood mononuclear cells isolated from the patient (P22) following symptom reversion showed similar frequencies of progenitors ($CD34^+CD38^+$) and hematopoietic stem cell (HSC) enriched fractions ($CD34^+CD38^-$). However, there was a marked difference in the frequency of long-term HSCs ($CD34^+CD38^-CD90^+CD45RA^-$), with P22 being 21.2% compared with 0%–4% in the other patients' samples (Figure 2A and 2B).

To determine if there was any evidence of ongoing subclinical inflammation, we compared proinflammatory cytokine profile and the status of the NLRP3 inflammasome activation between the index patient, P22, and 4 other VEXAS patients, matched for sex and age (69–75 years), with active disease (VX-active) who were treated with similar doses of corticosteroids (between 10 and 15 mg prednisolone daily). Patient 22 had a 7.7-fold reduction in levels of extracellular ASC/NLRP3 protein specks—a readout for NLRP3 inflammasome activation—compared with the 4 active VEXAS patients' sera (mean VX-active group = 76.05 events/µL [range, 34.06–108.93 events/µL], while P22 had only 9.84 events/µL) (Figure 2C). Reductions in IL-6, IL-18, IL-8, IL-23, and MCP-1 levels were detected in P22 compared with VEXAS-active patients (Suppl. Figure S2).

Here, we present a case of a patient with VEXAS syndrome, who appears to have undergone remarkable recovery of BM function, with resolution of the inflammatory complications coinciding with the initiation of romiplostim for his thrombocytopenia. Further investigations have shown that this recovery occurred despite the pathogenic *UBA1* variant still being detectable, but was associated with an increased frequency of long-term HSCs and complete resolution of inflammation. As we did not carry out a simultaneous measurement of the VAF in sorted HSPCs at the time, we cannot distinguish whether the increased HSPC fraction carries the *UBA1* mutation, so this may represent a resurgence of nonmutant HSPCs in response to Romiplostin.

Given the timing of his recovery, we wondered what role romiplostim might have played in the process. Endogenous TPO and its receptor c-MPL are regarded as the main drivers of HSC survival, as evidenced by various murine models.[7,8] Furthermore, children with functional mutations in TPO or c-MPL tend to develop progressive multilineage cytopenias associated with reduction of HSPCs.[7] It has recently been shown that IFN-γ inhibits the stimulation of c-MPL by TPO, possibly through the formation of a TPO:IFN-γ heterodimer.[7] The same study showed that the TPO-RA, eltrombopag, was able to evade this inhibitory mechanism and successfully stimulate



Patient ID	Freq. of HSCs (% total live PBMCs)	Freq. of LT-HSCs (% total live PBMCs)
P22	0.013	0.003
VX1	0.018	0.000
VX2	0.090	0.000
VX3	0.023	0.0009

Figure 2. Biological response to romiplostim. (A) Viably frozen PBMCs from 4 patients were thawed and stained with the following antibodies: CD34 PE (clone 561, Biolegend), CD38 FITC (clone HIT2, BD Biosciences), CD90 APC (clone 5E10, BD Biosciences), FLK2 BV650 (clone 4G8, BD Biosciences), CD10 APC-Cy7 (clone HI10a, Biolegend), CD45RA V450 (clone HI100, BD Biosciences), and 7AAD (Thermo-Fisher). Samples were analyzed on a MoFlo Astrios (Beckman Coulter). (C) In-house flow cytometry assay, for quantification of ASC/NLRP3 protein specks in sera. Briefly, 100 µL of patients' sera was incubated in Phycoerythrin conjugated anti-ASC (TMS-1) Antibody (653904, BioLegend) and APC-conjugated NLRP3 Antibody (IC7578A, BioTechne) for 1 hour at room temperature, shaking. Totally 50 µL of sample was measured by using a Cytoflex S Flow Cytometer, gating for events 1 µM in size, using Flow Cytometry Submicron Particle Size Reference beads (F13839, Thermo-Fisher Scientific). Results were analyzed using CytExpert software and presented as ASC positive events per microliter. Data are represented in a box and whisker plot of ASC/NLRP3 protein specks. PBMC = peripheral blood mononuclear cells.

the c-MPL receptor. Although only licensed for thrombocytopenia, the 2 TPO-Ras, romiplostim and eltrombopag, have both been shown to restore trilineage hematopoeisis in aplastic anemia (AA) refractory to immunosuppression.[9,10] Patients with AA show paradoxically elevated levels of endogenous TPO, reinforcing the suggestion that these synthetic agents can evade an underlying inhibitory mechanism.[11] IFN-γ levels are known to be increased in VEXAS findings, which have been supported by pathogenic *UBA1* mutations in zebrafish models, and it is plausible that romiplostim has bypassed this mechanism of hematopoetic suppression, thereby allowing restoration of multiple cell lineages.[1] Although this is a plausible explanation for how romiplostim might act to fully restore hematopoiesis, we have no explanation of what mechanisms might be responsible for resolution of the inflammatory complications. Although associations between autoinflammatory complications and MDS have been recognized for a long time, the precise biology underpinning this relationship remains uncertain. For example, it is unclear whether the inflammatory BM milieu, irrespective of the underlying cause, drives the acquisition of somatic mutations leading to MDS, or whether autoinflammatory manifestations are driven by the MDS-causative mutations. In the latter case, any treatment resulting in the cure of MDS would also lead to resolution of the inflammation. In the case described, restoration of BM function, which coincided with use of romiplostim and with resolution of inflammatory complications, was of particular note given the persistence of the pathogenic *UBA1* mutation. It would be premature to recommend routine use of romiplostim in VEXAS based on this anecdotal evidence, but our findings are sufficiently interesting to consider testing the utility of romiplostim in VEXAS in the context of a clinical trial.

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AUTHOR CONTRIBUTIONS

AA and SS wrote the first draft of the article. AA, JT, FN, JM, RA, and JP processed the samples and conducted laboratory experiments and analyzed the data. RO, CC, and SS provided clinical details and care of the patient. MFM, DK, and SS provided funding and overall supervision of the study. All authors read and approved the article.

DISCLOSURES

DK is a Scientific Editor for HemaSphere. The remaining authors have no conflicts of interest to disclose.

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