Dear Editor,

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome was first characterized in 2020 as an adult-onset inflammatory disorder caused by a myeloid-restricted acquired mutation in the ubiquitin-like modifier activating enzyme 1 gene UBA1 [1]. As UBA1 is located on chromosome X, most patients are male; women with VEXAS often have acquired monosomy X or Turner syndrome [2, 3]. VEXAS syndrome has a wide range of clinical manifestations, including recurrent fever, chondritis, skin manifestations, lung infiltrates, thrombosis, and hematologic abnormalities, and can occasionally progress into MDS (Table 1) [1, 4]. VEXAS syndrome should be suspected in patients who present with systemic autoinflammatory or autoimmune syndromes, including relapsing polychondritis, Sweet syndrome, or polyarteritis nodosa [5]. We report the first case of a Korean male patient with VEXAS syndrome who presented with a treatment-refractory fever of unknown origin. Informed consent was appropriately obtained from the patient, and the Institutional Review Board of Seoul National University Hospital, Seoul, Korea, approved the study (2006-083-1132).

A 66-year-old male patient with diabetes mellitus, hypertension, and chronic kidney disease presented with recurrent fevers in December 2018. His initial complete blood count (CBC) showed leukocytosis (white blood cells, 14.8×10^9/L) and anemia (Hb, 101 g/L). His high-sensitivity C-reactive protein (hs-CRP) level was elevated at 140 mg/L (reference: <5 mg/L). The lambda-type IgM fraction was increased on serum immunofixation electrophoresis, suggesting monoclonal gammopathy of undetermined significance (MGUS). Bone marrow (BM) examination showed normocellular marrow (cellularity, 40%–65%) and a normal karyotype (46,XY).

In 2019, he developed intermittent fevers along with a new erythematous, tender, papular skin rash in both the upper and lower extremities. His hs-CRP and serum ferritin levels were remarkably elevated (60.9 mg/L and 1,540 µg/L, respectively [reference: 21.8–274.7 µg/L]), and his rheumatoid factor was positive (83 IU/mL). Chest computed tomography (CT) showed multiple micronodules; a whole-body positron emission tomography scan showed multiple hypermetabolic lesions in the skin and skeletal muscles. Skin biopsy revealed perivascular lymphohistiocytic infiltration with abundant neutrophils (Fig. 1A). Neutrophilic dermatosis, such as Sweet syndrome due to pre-
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Clinical MDS or adult-onset Still’s disease, was suspected. He was treated with high-dose corticosteroids. Methotrexate was added as a steroid-sparing agent. Pancytopenia (white blood cells, 1.0×10^9/L; Hb, 73 g/L; platelets, 17×10^9/L) was noticed during follow-up. Considering the potential BM suppression by methotrexate, the drug was replaced with tocilizumab. His CBC and hs-CRP levels gradually normalized, but ferritin levels (2,449 µg/L) remained elevated.

A few months later, the patient developed acute shortness of breath. Chest CT showed pulmonary embolism in the right upper and bilateral focal segmental regions. There were immature myeloid precursors, such as myelocytes, on peripheral blood smears. BM examination revealed various cellularity and hemophagocytic histiocytes, suggesting macrophage activation syndrome. Erythroid precursors and megakaryocytes revealed mild dysplastic changes, and some vacuoles were observed in myeloid and erythroid precursors, suggesting VEXAS syndrome with myelodysplastic features (Fig. 1B). Whole-exome sequencing (WES) using whole blood DNA revealed a known UBA1 somatic variant (c.121A>C, p.Met41Leu), which was confirmed using Sanger sequencing (Fig. 1C). No additional pathogenic germline or somatic variants were detected. While standard therapy for VEXAS syndrome has yet to be defined, therapeutic options may include corticosteroids in combination with disease-modifying antirheumatic drugs or immunosuppressants and allogeneic hematopoietic stem cell transplantation [6]. Given the patient’s old age, BM transplantation could not be considered. The patient was symptomatically managed with corticosteroids and tocilizumab, with no recurrent fever or other symptoms, in line with a previous report’s findings [7].

The only confirmatory diagnostic test of VEXAS syndrome is the detection of somatic variant in UBA1 [5]. UBA1 is involved in clinical MDS or adult-onset Still’s disease, was suspected. He was treated with high-dose corticosteroids. Methotrexate was added as a steroid-sparing agent. Pancytopenia (white blood cells, 1.0×10^9/L; Hb, 73 g/L; platelets, 17×10^9/L) was noticed during follow-up. Considering the potential BM suppression by methotrexate, the drug was replaced with tocilizumab. His CBC and hs-CRP levels gradually normalized, but ferritin levels (2,449 µg/L) remained elevated.

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in the termination of intracellular inflammatory signaling. Frequent hotspot regions, such as methionine 41 and serine 56 residues, and splice-site variants result in impaired UBA1 isoforms [8, 9]. The p.Met41Leu variant detected in our case occurred in the most frequent site and is associated with better prognoses [4]. Co-occurring variants in other genes, such as DNMT3A, TET2, CSF1R, GNA11, and EZH2, which are associated with increased risks of progression to MDS, were not detected [10]. WES or panel sequencing using peripheral blood or BM should be an appropriate approach for VEXAS syndrome considering the co-occurring variations.

In summary, our patient showed a long diagnostic odyssey because of the complex clinical manifestations of VEXAS syndrome. Since the syndrome may be underdiagnosed in Korea, we encourage the assessment of UBA1 somatic variants, particularly in male or highly suspicious female patients who display clinical features of combined autoinflammatory disorders and hematologic abnormalities in advanced age.

**AUTHOR CONTRIBUTIONS**

Yoon JG, Park JK, Shin DY, and Moon J conceived and designed the study. Yoon JG, Lee S, Kim S, Kim MJ, and Chang YH collected and interpreted the data. Yoon JG, Park JK, Shin DY, and Moon J wrote the manuscript. All authors participated in the coordination and discussion; they accept responsibility for the entire content of this manuscript and have approved the submission.

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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**ORCID**

Jihoon G. Yoon  
https://orcid.org/0000-0002-4401-7803

Seungbok Lee  
https://orcid.org/0000-0002-3145-8714
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