Letter to the Editor
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The First Korean Case of VEXAS Syndrome Caused by a *UBA1* Somatic Variant

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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 systematic 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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Table 1. Clinical characteristics of patients with VEXAS syndrome

Study	Present study	Georgin-Lavialle, *et al.* [4]	Beck, *et al.* [1]
Patiant (N)	1	116	25
Male sex	Yes	95.7%	100.0%
Age at onset (yr, range)	66	71 (66–76)	64 (45–80)
Somatic *UBA1* variant			
p.Met41Thr	-	44.8%	60.0%
p.Met41Val	-	30.2%	20.0%
p.Met41Leu	Somatic (VAF, 48.8%) in whole blood	18.1%	20.0%
Splice site	-	6.9%	0.0%
Clinical findings			
Fever	Recurrent fever of unknown origin	64.6%	92.0%
Skin involvement	Panniculitis, erythematous nodules in upper extremities	83.6%	88.0%
Ear/nose chondritis	No	36.2%	64.0%
Lung involvement	Micronodular infiltration	49.1%	72.0%
Thromboembolism	Unprovoked pulmonary thromboembolism	35.3%	44.0%
Gastrointestinal involvement	Diarrhea	13.8%	NA
PNS involvement	Polyneuropathy	14.6%	NA
Vacuoles in bone marrow aspirates	Yes	NA	100.0%
MDS	Mild dysplastic changes in erythroid precursors and megakaryocytes	50.0%	24.0%
MGUS	IgM, lambda type	10.3%	20.0%
Laboratory findings			
Hyperferritinemia	Remarkable (1,540 ng/mL)	NA	NA
CRP	hs-CRP 140 mg/L	61 (30–128) mg/L	73 (18–128) mg/L
Rheumatoid factor	Positive (83 IU/mL)	NA	NA

Abbreviations: VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic; NA, not available; VAF, variant allele frequency; GI, gastrointestinal; PNS, peripheral nervous system; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; CRP, C-reactive protein; hs-CRP, high-sensitivity CRP.

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

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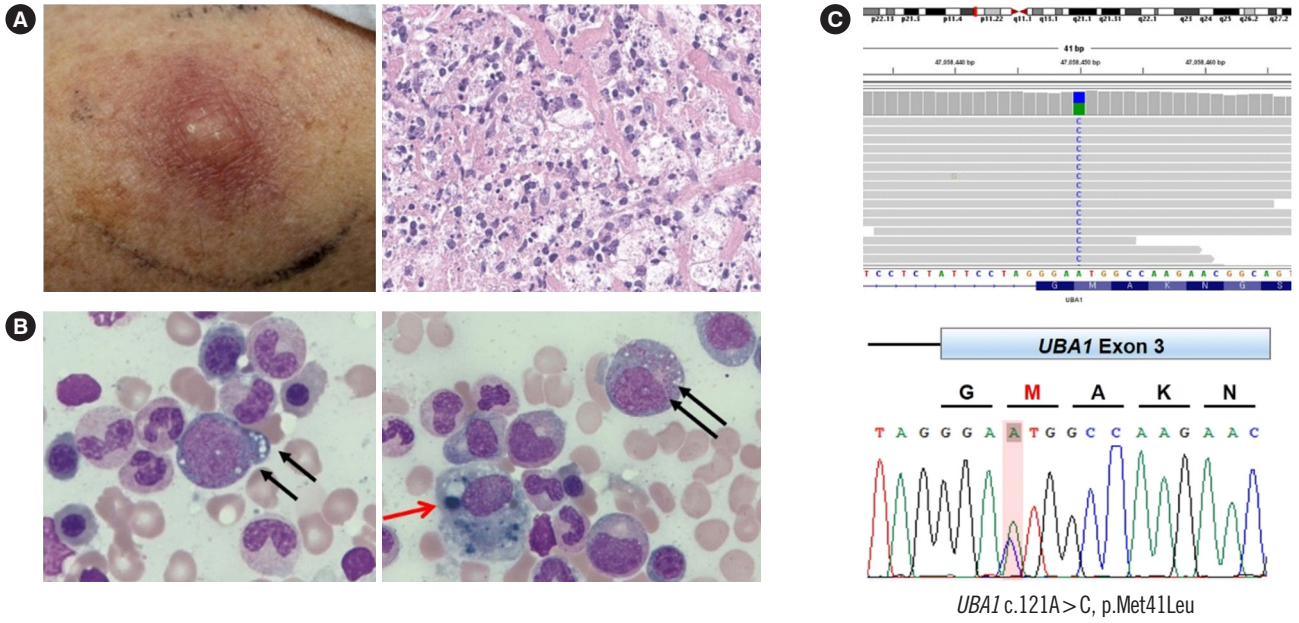

Fig. 1. Histological and molecular findings in the present case of VEXAS syndrome. (A) Skin manifestation of multiple nodular regions in the upper extremities. Skin biopsy findings indicating superficial and deep perivascular lymphohistiocytic infiltration with abundant neutrophils (hematoxylin and eosin stain, ×400). (B) BM aspirate smear findings showing hemophagocytic histiocytes (red arrow) and mild dysplastic features and typical multiple vacuoles (black arrow) in myeloid precursors (Wright–Giemsa stain, ×1,000). (C) Exome sequencing revealed no pathogenic germline variants; however, somatic variants in *UBA1* (NM_153280.3: c.121A>C, p.Met41Leu) with a variant allele frequency of 48.8% were detected and confirmed using Sanger sequencing.
Abbreviations: VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic; BM, bone marrow.

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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