Rapid cutaneous remission response to tofacitinib and systemic corticosteroids in VEXAS syndrome with a novel UBA1 mutation

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Key words: neutrophilic dermatoses; tofacitinib; UBA1; VEXAS.

INTRODUCTION

Vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic (VEXAS) syndrome is a late-onset, X-linked autoinflammatory disorder caused by somatic mutations in the *UBA1* gene within hematopoietic progenitor cells. Clinically, it is characterized by fever, neutrophilic dermatoses, relapsing polychondritis, pulmonary inflammation, thromboembolic events, and often macrocytic anemia. VEXAS syndrome is a rare disease that presents a significant diagnostic challenge and a lack of effective management recommendations.[1] We report a diagnostically challenging presentation of VEXAS syndrome in an elderly man with an unreported somatic UBA1 mutation and were successfully treated with tofacitinib.

Abbreviations used:

AHSCT:	allogeneic hematopoietic stem cell transplantation
mNGS:	metagenomics next-generation sequencing
VEXAS:	vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic

CASE REPORT

An 80-year-old Chinese male presented to our clinic with a 10-month history of episodic fever, migratory erythematous plaques with pustules, and scaling and neutrophilia. Also, the patient developed cough and dyspnea and chest computed tomography showed interstitial pneumonia complicated with pneumocystis jirovecii and cytomegalovirus infection identified by mNGS (metagenomics next-generation sequencing). Antimicrobial therapy improved pulmonary symptoms with residual interstitial lung changes. The patient demonstrated initial improvement of cutaneous lesions with systemic corticosteroid therapy, but experienced disease relapse upon corticosteroid tapering.

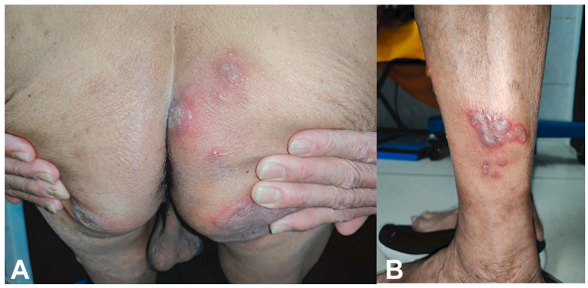

Fig 1. Clinical images. **A, B,** pustular erythematous plaques on the buttocks and lower limb.

Physical examination demonstrated pustular erythematous plaques involving face, scalp, extremities, trunk and buttocks (Fig 1). Laboratory work-up showed elevated leukocytes (12.3-26.5 $\times$ 10^9/L), no significant abnormalities in hemoglobin or platelet counts, elevated CRP (104 mg/L), and ESR (30 mm/h); ANA, ANCA, and antidesmoglein antibodies were negative. Malignancy screening and bone marrow examination were unremarkable.

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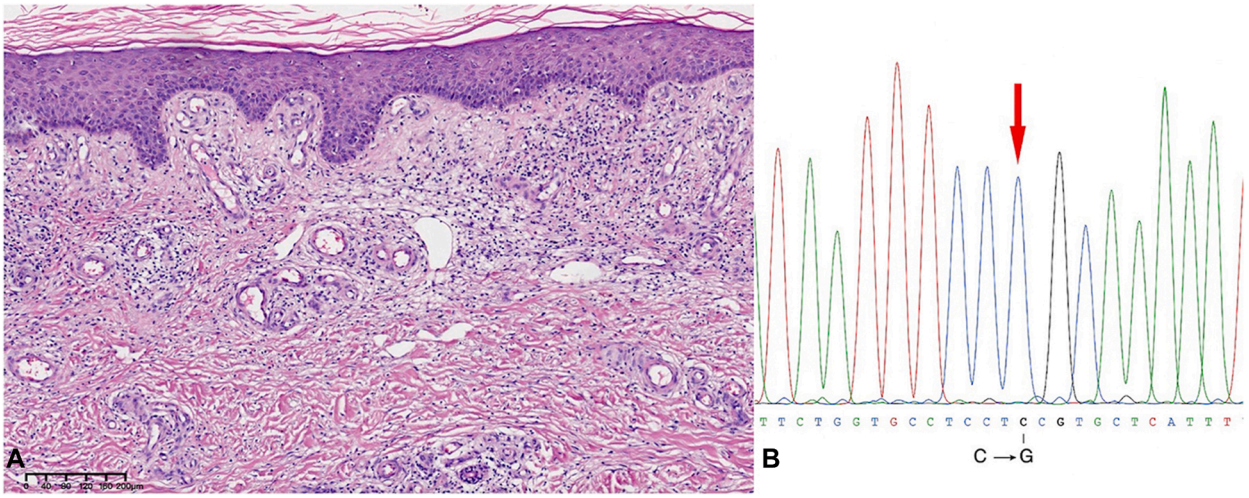

Fig 2. A, Histopathology demonstrates papillary dermal edema, superficial dermal vascular proliferation, and dense neutrophilic infiltrates surrounding vessels and between collagen bundles throughout the dermis (hematoxylin-eosin stain; bar = 200 μm). **B,** Peripheral blood whole-exome sequencing identified a somatic UBA1 mutation (c.1702C>G, p.Leu568Val), confirming the diagnosis of VEXAS syndrome. The *red arrow* marks the c.1702C>G somatic variant in UBA1(p.Leu568Val). *VEXAS*, Vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic.

Histopathologic examination of skin revealed dense dermal neutrophilic infiltrates and papillary dermal edema (Fig 2, *A*). Peripheral blood whole-exome sequencing revealed a somatic UBA1 mutation: c.1702C>G, p.Leu568Val (L568V), located within a conserved functional domain (Fig 2, *B*). Predictive modeling (SIFT/PolyPhen-2) indicates that this mutation is likely to result in deleterious effects. Based on the history, clinical examination, histologic findings, and UBA1 gene mutation, the patient was diagnosed as VEXAS syndrome. The variant on this patient has not been previously reported in VEXAS.

Due to treatment with corticosteroids, cyclosporine, and mycophenolate mofetil led to only partial responses, the patient was started on tofacitinib 10 mg/day in combination with low-dose methylprednisolone (12 mg/day). Surprisingly, his skin lesions showed significant improvement and neutrophils decreased from 30.96 to 12.81 $\times$ 10^9/L within 72 hours. After a 7-month follow-up period, with methylprednisolone tapered to 4 mg/d in combination with tofacitinib, the patient maintained complete resolution of skin lesions and demonstrated improvement in pulmonary condition.

DISCUSSION

VEXAS syndrome is a late-onset, X-linked autoinflammatory disorder caused by somatic mutations in the *UBA1* gene within hematopoietic progenitor cells.[2] The intricate interplay between genetic mutations and dysregulated inflammatory responses contributes to the complex and severe clinical manifestations. The syndrome induces a broad range of inflammatory responses affecting various organs and systems, leading to symptoms such as fever, neutrophilic dermatoses, relapsing polychondritis, pulmonary inflammation, thromboembolic events, and often macrocytic anemia.[3] UBA1 mutations disrupt ubiquitination and innate immune regulation, leading to systemic autoinflammation.[4] While most reported cases involve p.Met41 variants, emerging data suggest that non-M41 mutations may present with distinct, sometimes milder, phenotypes.[3]

Some cases had no prior rheumatologic or hematologic diagnoses associated with VEXAS.[5] Our case report a noncanonical UBA1 p.Leu568Val somatic mutation associated with a VEXAS phenotype dominated by neutrophilic dermatoses and leukocytosis, without hematologic cytopenias. This case adds to the growing evidence that mutation-specific clinical profiles exist and reinforces the value of genotype-phenotype correlation in diagnosis and management.

Currently, VEXAS syndrome lacks standardized treatment protocols.[6] In VEXAS syndrome, corticosteroids remain the initial treatment choice in over 80% of reported cases. However, they frequently cause symptom recurrence during dose tapering and carry significant adverse effects with long-term high-dose use. Other therapies include IL-6/IL-1/TNF inhibitors,

Janus kinase inhibitors, azacitidine, and allogeneic hematopoietic stem cell transplantation (AHSCT). Among these, Janus kinase inhibitors were effective for some features of systemic inflammatory disease, particularly skin involvement.[7]

Due to economic considerations, tofacitinib was selected in this case and achieved rapid, durable remission in our patient and may be especially suitable in milder, hematologically spared presentations. This underscores the importance of personalized treatment based on genetic and phenotypic heterogeneity. However, given the prothrombotic risk associated with both VEXAS and Janus kinase inhibition, close monitoring is essential.

Given the under-recognition of VEXAS in Asian populations and the expanding spectrum of pathogenic UBA1 variants, clinicians should consider somatic sequencing in elderly men with refractory neutrophilic dermatoses—even in the absence of classical hematologic abnormalities, including macrocytic anemia, thrombocytopenia, and vacuolization of myeloid and erythroid precursors in the bone marrow. Early diagnosis may facilitate tailored therapy and improve outcomes.

Conflicts of interest

None disclosed.

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