VEXAS syndrome complicated with severe infection

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Key message: VEXAS syndrome can be complicated by severe infections, which should be given attention during treatment.

Dear Editor,

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently described adult-onset inflammatory disease caused by somatic mutations in Ubiquitin-like modifier activating enzyme 1 (*UBA1*) (1). The disease is characterised by fever, pancytopenia, chondritis, vasculitis, and neutrophilic dermatitis; however, more heterogeneous manifestations have recently been reported (2).

A 69-year-old Japanese man presented with acute onset polyarthralgia and fever in March 2015. A previous skin biopsy of his lower limbs in April 2014 showed evidence of cutaneous leukocytoclastic vasculitis. He had swelling and tenderness at several fingers, bilateral wrists and knee joints with elevated CRP (10.8 mg/dL) and rheumatoid factor (85.9 IU/ml). Antibodies for anti-cyclic citrullinated peptide, anti-nuclear, myeloperoxidase anti-neutrophil cytoplasmic (ANCA) and proteinase-3-ANCA were not detected. Two sets of blood cultures were negative and joint X-rays revealed no abnormalities. However, the musculoskeletal ultrasound revealed synovitis equivalent to PowerDoppler Grade 2 in several fingers and bilateral wrist joints. In addition, thoracoabdominal CT revealed consolidation in the right lower lobe; however, no bacteria were detected in bronchoalveolar lavage fluid. These findings prompted us to consider the possibility of rheumatoid vasculitis. After starting oral prednisolone (PSL) 40 mg/day, his symptoms improved. However, reducing his PSL to 7 mg/day relapsed his arthralgia and fever. Subsequently, he was given salazosulfapyridine, which was discontinued due

to severe drug rash after one week and we increased PSL dosage to 15 mg/day in November 2016. In July 2017, he was admitted to our hospital with lower leg cellulitis and sepsis from a post-insect bite on his right leg, which improved with antimicrobial therapy. He continued to have fever, arthralgia, recurrent mobile consolidation and ground-glass opacities in his lungs. In April 2018, multiple small erythematous patches appeared on the upper extremities. The skin biopsy taken at that time showed neutrophilic dermatosis, which was suspected as Sweet's disease (Figure 1A). He was given azathioprine (AZP) and colchicine; however, the recurrence symptoms did not improve. In January 2019, he was brought to our hospital for emergency treatment for loss of consciousness and convulsions while on PSL 9 mg/day and AZP 25 mg/day. Head contrast-enhanced magnetic response images showed a ring enhanced mass with extensive surrounding oedema in the left parietal lobe (Figure 1B). He was diagnosed with a brain abscess in the left parietal lobe caused by Nocardia, which required long-term antimicrobial therapy after abscess drainage. In May 2019, he presented with progressive pancytopenia, especially anaemia. Bone marrow examination indicated no specific findings suggestive of myelodysplastic syndromes. However, he was required to have blood transfusions. He then continued to have recurrent fever, arthralgia and consolidation in the lungs every few months. In April 2021, he developed infective endocarditis caused by E. coli with aortic valve aneurysm formation and perforation while taking PSL 12 mg/day. He underwent aortic valve replacement, recovering temporarily. However, he died in July 2021 due to complications with intestinal perforation from a sigmoid diverticulum and necrotising cholecystitis. His laboratory findings are shown in Supplementary Table S1. Although he was initially thought to have rheumatoid vasculitis, the clinical course was atypical. After his death, sanger sequencing analyses of peripheral

blood cells found a missense mutation p.Met41Thr in the *UBA1* gene (Figure 1C). In addition, a retrospective review of the bone marrow smear revealed cytoplasmic vacuoles in myeloid precursors (Figure 1D). These findings led to the diagnosis of VEXAS syndrome.

VEXAS syndrome was initially identified in 25 late adult men characterised by systematic inflammatory features with novel somatic mutations in *UBA1*. These cases often met clinical criteria for inflammatory diseases, such as relapsing polychondritis (RP) and Sweet's disease (1). He had no features indicative of RP; however, recent reports have shown that this syndrome is associated with more heterogeneous manifestations, such as rheumatic diseases (3, 4). He had several features that have been reported as VEXAS syndrome (2, 5); however, he also developed severe infections, including cellulitis, brain abscesses and infective endocarditis.

VEXAS syndrome is caused by an acquired somatic mutation in methionine 41 of *UBA1*, the major E1 enzyme that initiates ubiquitination (6). This mutation leads to the loss of normal cytoplasmic isoform of UBA1 protein, resulting in abnormal activation of innate immune response due to a cellular impaired ubiquitin-proteasome system. In addition, a recent report described two patients with genetic variants of proteasome subunit gene characterised by immunodeficiency and autoinflammatory features including neutrophilic dermatitis (7). Thus, the excessive signs of infection in this patient may be triggered by acquired immunodeficiency due to the impaired ubiquitin-proteasome system combined with treatment with immunosuppression agents. In fact, a case of VEXAS syndrome complicated with severe lung infection was recently reported (8). In conclusion, we present a fatal course of a patient with VEXAS syndrome complicated by severe infections. Notably, VEXAS syndrome itself may have caused the severe

infections due to aberrant immunity such as dysregulated neutrophil activation.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Acknowledgements

We thank Dr. Koji Ando (Nagasaki University) for providing with the bone marrow aspirate images.

Disclosure statement

All authors declare that they have no competing interests.

Data availability statement

Available with request.

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Figure legends

Fig. 1

Skin finding, head magnetic response (MR) images, Sanger sequencing analysis and bone marrow aspirate specimen.

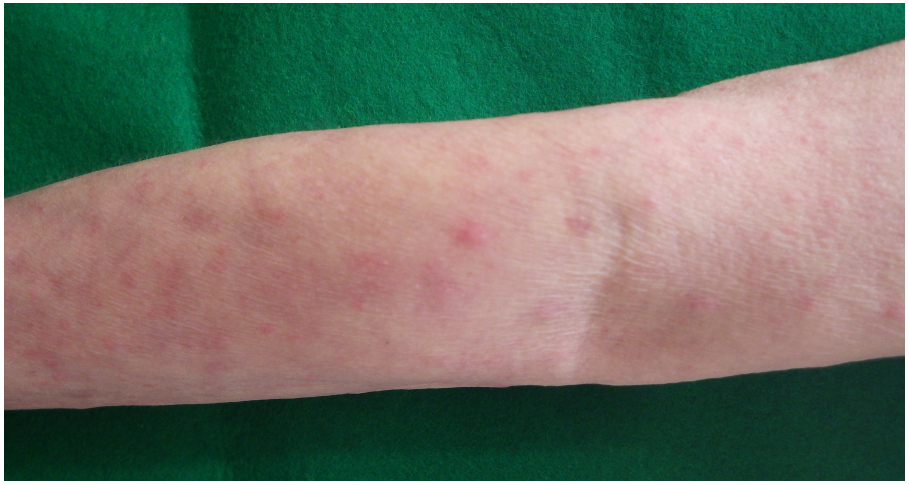
(A) Multiple small erythematous patches on the upper extremities.

(**B)** Head T1-weighted contrast-enhanced fat-suppressed spin-echo MR images showing a ring enhanced mass with extensive surrounding oedema in the left frontal lobe (white arrow).

(C) Sanger sequencing of a peripheral blood sample showing a mosaic mutation affecting methionine-41 (p.Met41Leu, c.121 A>C) of the *UBA1* gene exon 3 (lower panel). Upper panel showing a wild type sequence as reference sequence.

(D) Bone marrow aspirate showing cytoplasmic vacuoles in myeloid precursors.

A



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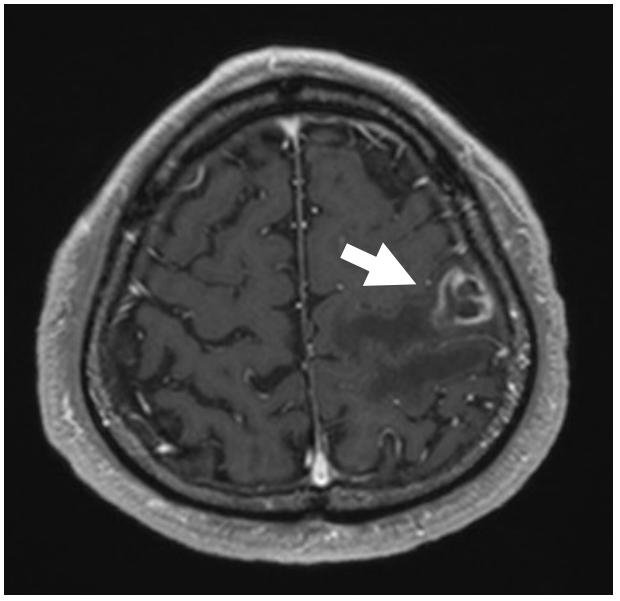

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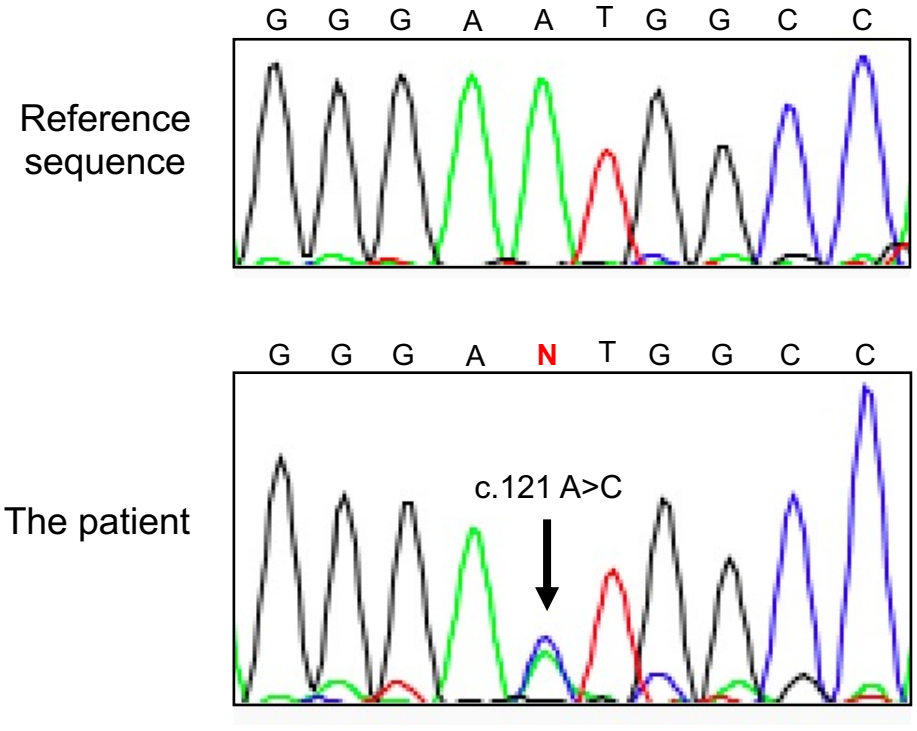
G G G A A T G G C C
Reference sequence
G G G A N T G G C C
c.121 A>C
The patient

D