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CASE REPORT

Concurrent inhibited erythropoiesis in a case of VEXAS syndrome

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Abstract

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a rare disease described by Beck et al. in 2020. Here we report a case of VEXAS syndrome with progressive worsening of pancytopenia. This patient demonstrated inhibited erythropoiesis along with normal granulopoiesis and megakaryopoiesis in the bone marrow. A diagnosis of myelodysplastic syndrome (MDS) was ruled out, while the patient presented with pure red cell aplasia (PRCA), a manifestation not previously described in the context of VEXAS syndrome. Therefore, VEXAS syndrome may also present with PRCA-like erythroid hypoplasia, which may aid in the better recognition of this disease.

Background

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a rare disease described by Beck et al. in 2020 [1]. The hallmark of VEXAS syndrome is mutations in the *UBA1* (Ubiquitin Like Modifier Activating Enzyme 1) gene, identified in all patients. *UBA1* encodes the master enzyme responsible for cellular ubiquitylation and mutations in *UBA1* lead to reduced ubiquitylation activity and autoinflammatory disorders [2]. Common symptoms include fever, skin lesions, Sweet's syndrome/ neutrophilic dermatosis, and auricular as well as nasal chondritis [3]. Vacuoles were typically observed in the myeloid and erythroid progenitors in the bone marrow of nearly all cases. VEXAS syndrome is closely associated with hematological abnormalities [4]. Approximately 25-55% of patients with VEXAS syndrome were diagnosed with myelodysplastic syndrome (MDS) [1, 5, 6]. Here, we report a case of VEXAS syndrome with progressive worsening of pancytopenia. He had concurrent inhibited erythropoiesis but normal granulopoiesis and megakaryopoiesis, resembling pure red cell aplasia (PRCA) - a manifestation not previously described in the context of VEXAS syndrome.

Case description

A 55-year-old male with a one-year history of skin lesions presented to our hospital in July 2020. The patient had developed scattered skin lesions, including papules, erythematous plaque, and petechiae, on the trunk and limbs since 2019. He had been treated with prednisone, at an unknown dose, for half a year with a diagnosis of vasculitis by a local hospital. Upon admission to our hospital, a complete blood count showed a white blood cell count of 1.87×10^9/L, a neutrophil count of 0.81×10^9/L, and a lymphocyte count of 0.85×10^9/L. Hemoglobin and platelet levels were within normal range. Flow cytometry analysis of peripheral blood indicated 21.35% abnormal T large granular lymphocytes (T-LGL) with an immunotype of $CD3^{pos}$, $CD57^{pos}$, $CD8^{pos}$, $perforin^{pos}$, and $granzymeB^{pos}$. Clonal rearrangement of T-cell receptor gamma (TCRγ) was positive. However, since the absolute count of T-LGL was less than 0.5×10^9/L, a diagnosis of large granular lymphocyte leukemia was not established. The patient was managed with a watch-and-wait strategy. During this time, he was given topical medication to alleviate skin symptoms.

In March 2022, the patient was readmitted to our hospital due to recurrent fever, with the highest temperature reaching 38.5 °C, and the persistence of skin lesions (Fig. 1A, B).

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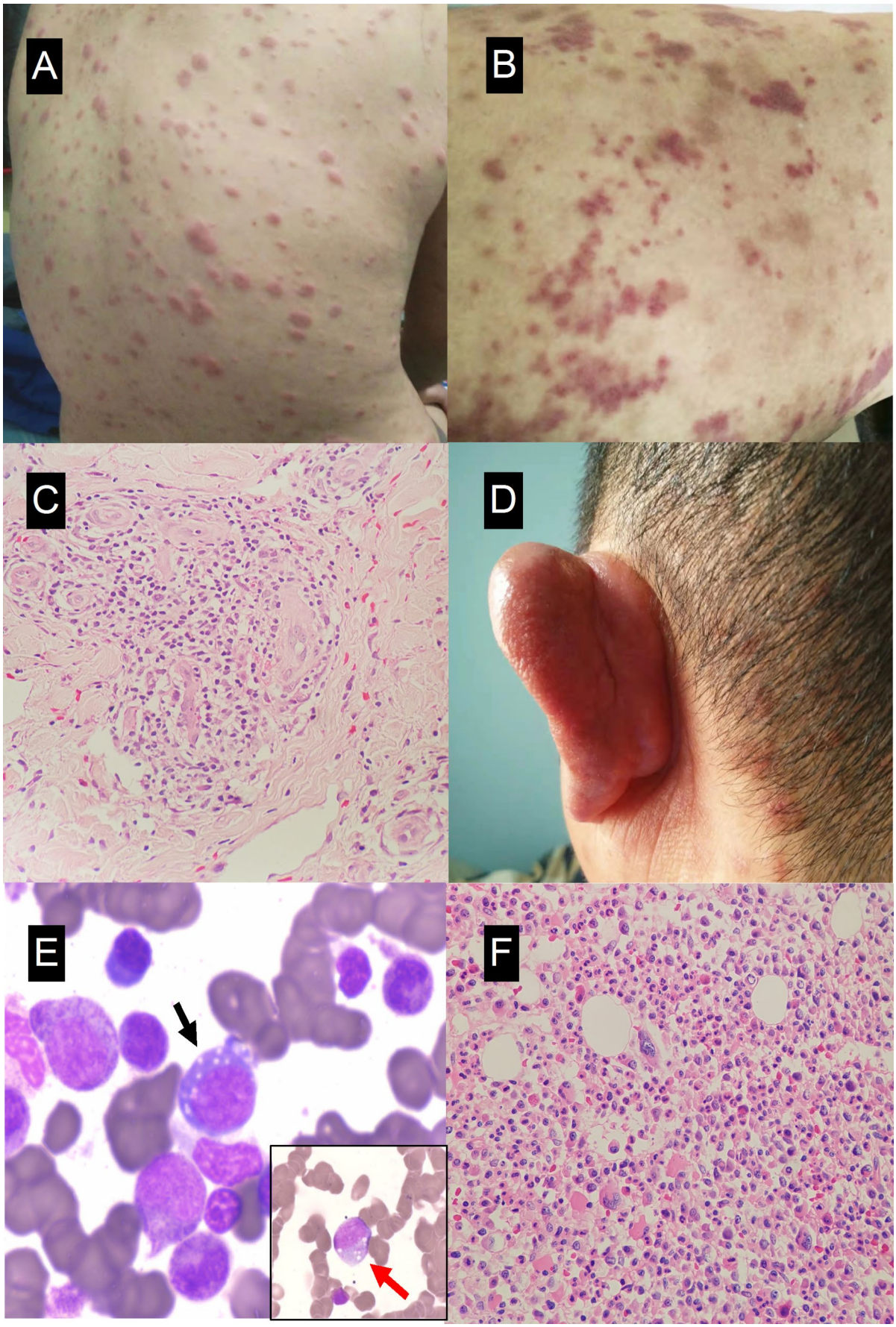
A
B
C
D
E
F

Fig. 1 Skin lesions on the back (**A**) and the lower limb (**B**). Skin biopsy pathology of the lower limb (400×) (**C**). Ear chondritis (**D**). Bone marrow aspiration showed vacuoles in erythroid (black arrow) and myeloid precursors (red arrow) (1000×) (**E**). Bone marrow biopsy showed reduced erythroid precursors and active granulopoiesis as well as megakaryopoiesis (400×) (**F**)

Steroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics were used to control fever. No evidence of infection was found and standard antibiotic therapy failed to control the fever effectively. A complete blood count revealed a white blood cell count of 1.23×10^9/L, a neutrophil count of 0.56×10^9/L, and a lymphocyte count of 0.52×10^9/L. Hemoglobin was 106 g/L, and macrocytic anemia was identified, with a mean corpuscular volume (MCV) of 107.8 fL and a mean corpuscular hemoglobin (MCH) of 35.9 pg. The absolute reticulocyte count was 0.0372×10^9/L. The platelet count was between normal range. Bone marrow aspiration showed erythroid hypoplasia (G = 72%, E = 11%, G/E = 6.55, megakaryocyte number was 11). A skin biopsy from the left lower limb demonstrated small lymphocyte hyperplasia, predominantly normal T lymphocytes (Fig. 1C). Fever frequency gradually reduced, and the watch-and-wait strategy was continued.

In May 2024, the patient's skin lesions worsened, and he experienced recurrent fever again. He also reported a consistent decrease in hemoglobin and platelet levels during follow-up (**Online Resource 1**), along with the new onset of ear chondritis (Fig. 1D). A complete blood count showed a white blood cell count of 1.48 × 109/L, a neutrophil count of 0.68 × 10^9/L, and a lymphocyte count of 0.60 × 109/L. The hemoglobin level was 69 g/L, and the platelet count was 63 × 109/L. The absolute reticulocyte count was 0.0289 × 10^12/L. Macrocytic anemia persisted, with an MCV of 119.9 fL and an MCH of 40.4 pg. Vitamin B12, folate, and ferritin were within normal range. Anti-nuclear antibody (ANA) test was positive (1:1000). Except this, other antibodies were all negative. A bone marrow test revealed more severe erythroid hypoplasia (G = 74%, E = 7.5%, G/E = 9.87) with active granulopoiesis and megakaryopoiesis (Megakaryocyte number was 187). No precursors dysplasia or excess blasts were discovered. Cytoplasmic vacuoles were found in the myeloid and erythroid lineages (Fig. 1E). Bone marrow biopsy showed 90% cellularity with an increased G/E ratio. Erythroid precursors were rare and active granulopoiesis and megakaryopoiesis were detected (Fig. 1F). The karyotype was normal. The percentage of T-LGL in peripheral blood was 19.44%. C reactive protein (66.50 mg/L, normal range 0-8 mg/L) and IL-6 (9.37pg/ml, normal range < 5.3pg/ml) were above normal value. No hepatomegaly or splenomegaly was identified by ultrasound. To further clarify the diagnosis, next-generation sequencing (NGS) for myeloid neoplasms was performed (panel shown in **Online Resource 2**). Mutations in *UBA1* ((NM_003334): c.122T > C; p.M41T)) with the variant allele frequency (VAF) of 78.10% and *DNMT3A* ((NM_022552): c.2645G > A; pR882H) with the VAF of 39.40% were identified. Considering all the tests, the patient was diagnosed with VEXAS syndrome with inhibited erythropoiesis resembling PRCA. He was prescribed disease controlling drugs including cyclosporin, thalidomide and prednisone but he refused all the medications. Now he is dependent on red blood cell transfusion and waiting for allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Discussion and conclusions

There have been no reports of VEXAS syndrome presenting with inhibition of erythropoiesis resembling PRCA since the syndrome was first described. The classical *UBA1* mutation, was identified in this patient. Consistent with previous studies [7, 8], granulocytic hyperplasia and a left shift, as well as an increased myeloid to erythroid ratio, were also observed in the bone marrow of our patient. Vacuoles were also present in the bone marrow of this patient. Along with other evidence such as fever, skin lesions, cytopenia and ear chondritis, this led to a definitive diagnosis of VEXAS syndrome. This patient exhibited pancytopenia with a low reticulocyte count, yet no morphologically abnormal cells or excess blasts were identified in the bone marrow. Instead, the patient displayed only inhibited erythropoiesis. The diagnosis of MDS was not established. The presence of monoclonal LGL cells, along with erythroid hypoplasia, initially resulted in a suspected diagnosis of T-LGL leukemia combined with PRCA. Ultimately, the patient was diagnosed with VEXAS syndrome.

Aberrant cytokine production and activated immune pathways due to *UBA1* deficiency may affect the physiological erythropoiesis. In addition, T-LGL leukemia has been reported to co-occur with PRCA in 29–42% of Asian patients [9, 10]. In this case, it is difficult to rule out the possibility that the inhibited erythropoiesis was partly caused by monoclonal T-LGL cells, although a definitive diagnosis of T-LGL leukemia was not established.

In addition to *UBA1*, the most common mutation (p. Arg882His) of *DNMT3A* was also identified [11]. In a French multicenter study, *DNMT3A* was identified in 11/75 patients of VEXAS syndrome [12]. It has been reported that *DNMT3A* early doubled the risk of death although the exact mechanisms remain unknown [13].

Patients with VEXAS syndrome were generally associated with poor outcomes. The presence of the p.M41T mutation is linked to a better 5-year survival rate (83%) compared to p.M41V (76.7%) and worse compared to p.M41L (100%)

[12]. Currently, no consistently effective treatment exists for VEXAS syndrome. Allo-HSCT, which can replace the abnormal hematopoietic system, is a promising option with the potential for durable remission [14]. This patient refused to take any medications, making allo-HSCT the only therapeutic option for him.

In conclusion, we reported a case of VEXAS syndrome of progressive worsening of pancytopenia. He also demonstrated inhibited erythropoiesis along with normal granulopoiesis and megakaryopoiesis in the bone marrow. He was diagnosed with PRCA rather than MDS which was more common. Refusing all the medications, he is currently awaiting allo-HSCT therapy. Therefore, in addition to MDS, VEXAS syndrome can also present with PRCA-like erythroid hypoplasia, which may aid in the better recognition of this disease.

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Author contributions F.K.Z. designed the research. L.X.X. and W.R.L. performed the research, analyzed the data and wrote the paper. Y.L., J.G.X. and Z.Q.L. contributed essential data collection. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval The study was approved by the Ethics Committee and Institutional Review Board of Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College and was in line with the principles of the Declaration of Helsinki.

Consent to participate Written informed consent was obtained from the patient.

Competing interests The authors declare no competing interests.

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