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Letter to the Editor (Case report)

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Successful treatment with azacitidine in VEXAS syndrome with prominent myofasciitis

Rheumatology key message

- Azacitidine may be effective in patients with VEXAS syndrome.

Dear Editor, The recently defined VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome summarizes late-onset inflammatory conditions such as Sweet's syndrome with overlapping haematological features due to somatic variants in *UBA1* [1]. To date, data on effective therapies other than glucocorticoids are scarce.

Our patient first presented with non-pruritic tender lesions (Fig. 1A and B) at age 60. The histopathologically confirmed neutrophilic dermatosis was not responding to a wide range of treatments, including hydroxychloroquine, methotrexate, ciclosporin, azathioprine, infliximab, adalimumab, ustekinumab, and apremilast. Only prednisolone was effective, but high doses were needed to prevent relapse. Ten years later, the patient was admitted with limb swelling and myalgias accompanied by pronounced fatigue and recurrent fevers. Physical examination revealed massive limb oedema leading to weight gain of 25 kg (Fig. 1C). Laboratory exams showed anaemia (haemoglobin min. 5.9 g/dl), thrombocytopenia (min. 90 G/l), and undulating white blood cell counts (3.2–14.7 G/l within a day) with neutrophilia (73–96%) and lymphopenia (2–21%). CRP and erythrocyte sedimentation rate as well as values for IL-6, IL-2 receptor, and ANA were increased. Creatine kinase levels and myositis-specific autoantibodies were normal. Muscle MRI demonstrated oedema and contrast enhancement (Fig. 1E–H). Muscle biopsy showed infiltrates of neutrophils, macrophages, and T lymphocytes in the muscle and adjacent fascia (Fig. 1I–L), consistent with acute myofasciitis. Due to increasing transfusion requirements, a bone marrow examination was performed, revealing myelodysplastic syndrome (MDS) and vacuolization of erythroblasts. In summary, a malignancy-associated Sweet's syndrome was diagnosed according to common criteria [2].

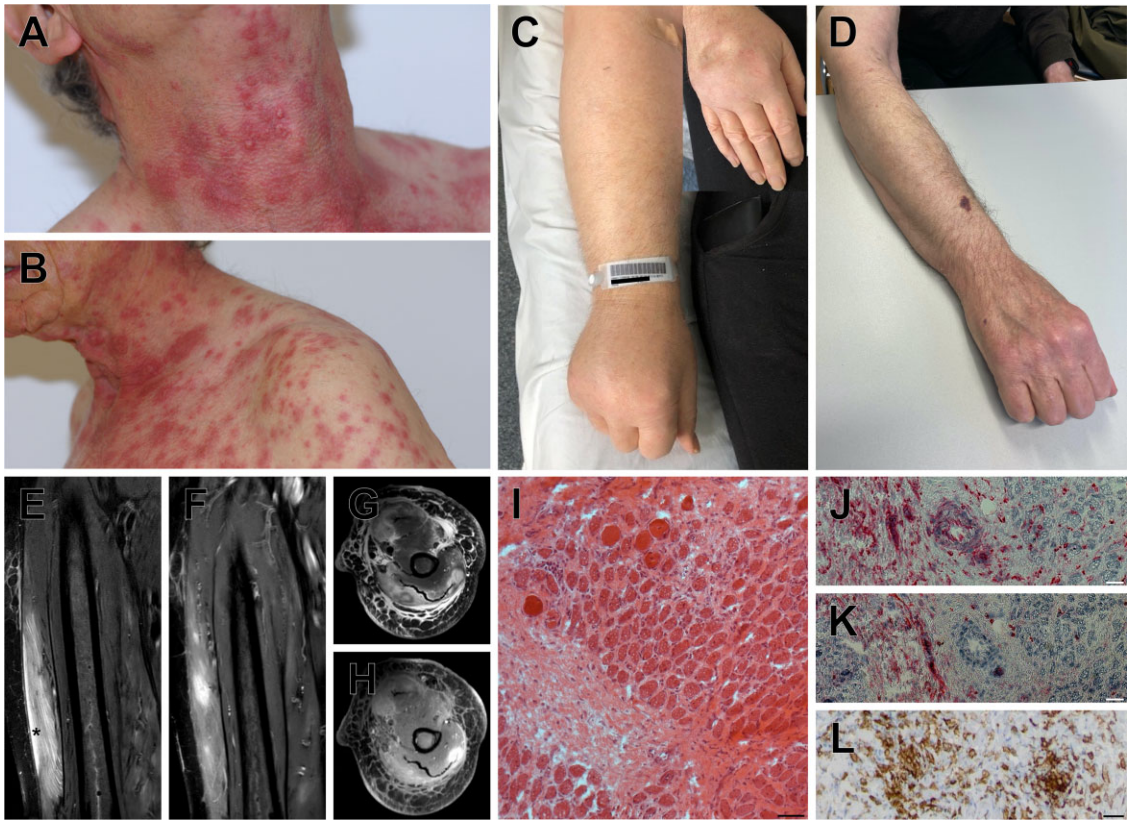
The patient was initially treated with prednisolone, which reduced fevers and decreased inflammatory markers, but resulted in relapse when tapered below 20 mg/day. Similarly, both colchicine (1.5 mg/day) and subcutaneous anakinra (100 mg/day) were not effective and had to be stopped due to side effects. Given the patient was refractory to treatment, the diagnoses made so far were re-evaluated; as we became aware of VEXAS syndrome [1], genetic testing was initiated. The detection of the somatic variant c.121A>C, leading to p.Met41Leu substitution in *UBA1* (NM_003334.4) eventually confirmed VEXAS syndrome. Variant allele fractions (VAF) determined by next generation sequencing (NGS) were 76% in peripheral blood and 29% in muscle. By performing NGS in FACS-sorted specific cell populations from bone marrow, we detected VAF of 3%, 17%, and 96% in $CD3^+$ T lymphocytes, $CD19^+$ B lymphocytes, and $CD15^+$ granulocytes, respectively.

Due to the MDS and the need for weekly blood transfusions, treatment with azacitidine was initiated and prednisolone was slowly tapered off. After receiving three cycles of azacitidine (75 mg/m^2/day subcutaneously), cytopenia improved and fever no longer occurred. The oedema receded completely (Fig. 1D) and both myalgia and fatigue improved. Furthermore, the patient maintained transfusion independence to date. For the first time in >10 years, a prednisolone dose of <10 mg/day was sufficient.

Our patient suffering from Sweet's syndrome accompanied by acute myofasciitis with capillary leak syndrome expands the phenotype of VEXAS syndrome. We assume that the mosaicism found in the muscle biopsy may be explained by neutrophil infiltration in muscle and fascia. As already indicated by Sanger sequencing in Beck *et al*. [1], we could confirm high VAF in neutrophils by NGS in FACS-sorted populations. Contrary to the aforementioned work, we also detected low VAF in B and T cells, which could, however, also be explained by a low level of contamination.

Patients with chronic relapsing Sweet's syndrome and accompanying MDS usually need high doses of prednisolone to prevent relapse [3]. In these patients, treatment with azacitidine, a DNA methyl-transferase inhibitor that paradoxically can also induce Sweet's syndrome, resulted in remission of MDS and Sweet's syndrome in individual cases [3–5]. Furthermore, azacitidine was efficient in other autoimmune disorders associated with MDS [6] and, interestingly, some response to this drug has recently also been reported in VEXAS syndrome [7]. We hereby provide further data on treatment with azacitidine in VEXAS syndrome with prominent myofascitis. Although prednisolone resulted in a prompt amelioration of symptoms, only azacitidine was finally able to maintain a complete haematological response and optimal symptom control. Importantly, treatment with the IL-1

Fig. 1 Clinical manifestations of VEXAS syndrome



(**A**, **B**) Papules and erythematous nodules on the patient's neck (**A**) and upper body (**B**). (**C**, **D**) Right arm at first presentation (**C**) and after treatment with azacitidine (**D**). (**E**, **F**) Coronal, T2-weighted (**E**) and gadolinium-enhanced, fat-suppressed, T1-weighted MRI (**F**) images showing hyperintensity and contrast enhancement in multiple muscles, accentuated in the right vastus lateralis with prominent fascial hyperintensity (*). (**G**, **H**) Axial, fat-suppressed, T2-weighted MRI sequence (**G**) demonstrates perifascial fluid and diffuse hyperintensity of the right biceps and triceps brachii with strong contrast in gadolinium-enhanced, fat-suppressed, T1-weighted image (**H**). (**I**) Muscle biopsy of the right triceps brachii muscle reveals fibrosis with an interstitial and invading inflammatory infiltrate in muscle and fascia, demonstrated with haematoxylin and eosin staining. (**J–L**) Immunohistochemical study showed diffuse $CD68^+$ macrophage (**J**), $CD8^+$ lymphocyte (**K**), and $CD11c^+$ neutrophil (**L**) infiltration. (**I–L**) Original magnification $\times$10, scale bars 40 μm.

receptor antagonist anakinra was not sufficient, providing evidence that, at least in this case, a cell-directed approach is likely to be more useful. We assume that treatment with azacitidine resulted in a proper differentiation and functional recovery of the haematopoietic cells harbouring *UBA1* variants in our patient, thus improving cytopenia and reducing secondary inflammatory responses.

In conclusion, our case strengthens the link between adult patients with complex and seemingly unrelated inflammatory conditions and causative somatic variants. Given the high mortality rate and the predisposition to haematological malignancies in VEXAS syndrome [1], high-risk therapies such as allogeneic bone marrow transplantation should be considered in select patients. The present case underlines the need for multidisciplinary patient care in autoimmune diseases. We encourage screening for *UBA1* variants in patients with late-onset inflammatory conditions, especially in those with overlapping haematological features and atypical or refractory courses.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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