REVIEW

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) for the dermatologist

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In 2020, Beck et al[1] described a novel adult autoinflammatory syndrome entitled VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic), a newly-discovered disorder that connected previously unrelated inflammatory syndromes and a prototype for a new class of hematoinflammatory diseases.[2] Eighty-nine percent of published cases have documented skin involvement, but despite the high incidence and diagnostic accessibility of skin manifestations, there has been little focus on the dermatological features of VEXAS syndrome thus far. A PubMed search of all published case reports of VEXAS syndrome to date was performed, with inclusion of all cases confirmed by genetic sequencing, and this review summarizes the reported dermatological signs. There have already been 141 confirmed published cases since original publication, 126 of which had documented cutaneous signs.[1-34] A wide range of skin presentations are reported, including Sweet-like urticated and tender erythematous nodules, cartilaginous involvement with chondritis, cutaneous vasculitis, and periorbital angiodema.[1-34] Many patients had been diagnosed with Sweet syndrome, relapsing polychondritis, polyarteritis nodosa, or erythema nodosum.[1-34] Hallmarks of skin histopathology are a neutrophilic dermatosis with coexisting or exclusive leukocytoclastic vasculitis.[1] The new classification therefore helps link previously disparate inflammatory skin conditions into a unifying pathophysiological pathway. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2022.01.042.)

Key words: autoinflammatory; leukocytoclastic vasculitis; neutrophilic dermatosis; relapsing polychondritis; Sweet syndrome; VEXAS syndrome.

VEXAS syndrome is characterized by a dysregulated innate immune response, manifesting as an adult-onset, treatment-refractory, hyperinflammatory state.[3] The phenotype can be variable, as systemic inflammation occurs predominantly in the skin, lungs, blood vessels, and cartilage (Fig 1).[2] Hallmark features include the presence of fever, characteristic bone marrow vacuolation, elevated inflammatory markers, and cytopenias.[1] The dysplastic bone marrow can manifest with macrocytic anemia and thrombocytopenia and may evolve into a myelodysplastic syndrome (MDS).[1] Dermatologists may often be the first clinicians to suspect a diagnosis of VEXAS syndrome, as cutaneous signs can portend the evolution of the recognized systemic complications. Recalcitrant inflammation results in fever, fatigue, weight loss, lymphadenopathy, pulmonary infiltrates with neutrophilic alveolitis, pulmonary vasculitis, venous thromboembolism, inflammatory arthritis, synovitis, and serositis, alongside ophthalmic complications of uveitis and scleritis.[1,2] Disease-related mortality varies between 40% and 63% in different case series but is consistently high with substantial associated morbidity.[1,3]

MATERIALS AND METHODS

A PubMed search was performed using the search term "VEXAS Syndrome" to identify all published case reports to date. All cases with confirmatory genetic sequencing were included. Cutaneous involvement was ascribed through author-reported clinical description, confirmatory histopathological skin biopsy, or assigned clinical diagnosis.

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RESULTS

There have been 12 case series (n = 2-25), and 19 individual case reports of VEXAS syndrome published to date, totaling 141 published cases,[1-34] of which 126 (89%) had author-reported skin involvement (Supplemental Table I, available via Mendeley at https://doi.org/10.17632/h7pfnt3768.1).[1-34]

Pathophysiology

VEXAS syndrome presents in later life due to acquired nonsynonymous somatic mutations within hematopoietic progenitor cells, specifically at codon 41 (p.Met41) within the X-chromosomal *UBA1* gene.[1,2] *UBA1* encodes ubiquitin-activating enzyme 1, the master enzyme of cellular ubiquitination.[1] This ubiquitination is a type of posttranslational modification of proteins and controls multiple cellular functions including intracellular signaling, the proteasome system, and the autophagy-lysosomal system, and consequently has an essential role in regulating the innate immune response.[1]

Within the peripheral blood compartments, there was noted a discordance of the *UBA1* gene mutation between hematopoietic cell populations, with an absence among the lymphoid lineages but evident mutant myeloid cells (neutrophils and monocytes).[1] This suggests that the mutation may occur relatively late during the ontological development of white blood cells, or alternatively that mutant lymphocytes are negatively selected within the bone marrow, whereas mutant myeloid precursor cells survive.[1]

The condition is acquired and progressive, suggesting these mutated myeloid progenitor cells may be clonally selected and expand over time.[4] Since the original case series, 4 further pathogenetic somatic mutations within the same gene have been identified (c.118-1G>C, c.167C>T, c.118-2A>C and c.119-1G>C variants), all resulting in the VEXAS syndrome phenotype.[2,4,5]

CAPSULE SUMMARY

- VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) is a novel autoinflammatory syndrome.
- Dermatologic manifestations include erythematous nodules, vasculitis, and periorbital angioedema. Many patients were originally diagnosed with relapsing polychondritis, Sweet syndrome, or polyarteritis nodosa. Adult males may present with systemic symptoms, hematological dyscrasia, and a refractive neutrophilic dermatosis.

Epidemiology

The syndrome is pathogenic within single X-chromosome carriers, predominantly men in the 5th decade of life or later, with the additional X-allele in women appearing protective.[1]

Cutaneous features

Despite the high incidence and diagnostic accessibility of skin manifestations, there has been little focus on the cutaneous features of VEXAS syndrome thus far. Utility of the data presented is limited by the authors ascribing dermatological involvement through the various lenses of descriptive terms, clinical signs, histopathological features, or clinical diagnoses. However, a more recent case series of 8

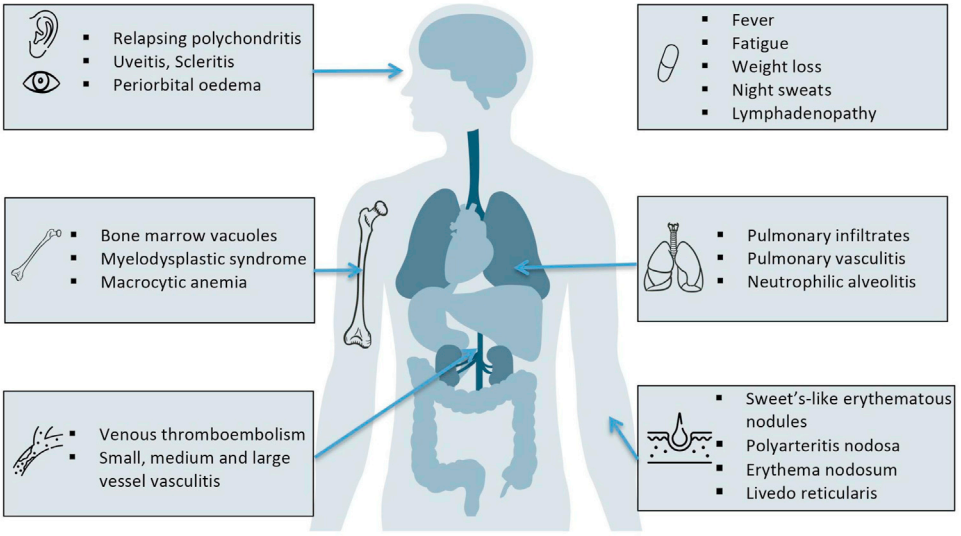

Fig 1. Clinical manifestations of VEXAS syndrome.

Abbreviations used:

MDS: myelodysplastic syndrome
VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic

patients by Zakine et al[7] better characterized the cutaneous features of VEXAS syndrome and found cutaneous signs were part of the initial presentation in 63% of patients. Similarly, other case series have found cutaneous signs to be the second most common clinical symptom after fever.[5]

Cutaneous manifestations usually presented with Sweet-like multiple, firm, tender, infiltrated erythematous or violaceous nodules affecting the trunk, limbs, and neck (Fig 2).[1-34] Some lesions arose initially as smaller edematous papules, which became fixed and progressive.[1-34] There was no associated pathergy or itch but prominent tenderness.[1-34]

Another reported manifestation was periorbital, nummular, violaceous edema, which was reported in 5% of confirmed VEXAS cases (Supplemental Fig 1).[1-34]

Thirty-six percent of VEXAS cases had a comorbid diagnosis of relapsing polychondritis, 19% with Sweet syndrome, 4% with erythema nodosum, 4% with polyarteritis nodosa, and 3% with livedo reticularis, with some patients having multiple diagnoses.[1-34] Cartilaginous involvement with aural and nasal chondritis was prominent and affected 49% of confirmed cases.[1-34]

A final relevant diagnostic clue for the dermatologist is the high reported incidence of severe localized skin reactions in VEXAS syndrome patients treated with the interleukin 1 receptor antagonist anakinra.[1,9] Sixty-two percent of the 13 patients treated by Beck et al[1] with anakinra developed pronounced delayed-onset erythematous, infiltrated plaques at the site of the injection.[9]

Histopathology

Hallmarks of reported skin histopathology from these Sweet-like lesions were a neutrophilic dermatosis with myeloid cell infiltration, with coexisting or exclusive leukocytoclastic vasculitis (Fig 3).[1] There was often a perivascular infiltrate throughout the dermis with associated moderate interstitial edema.[1-34] This inflammatory infiltration extended to the dermal vessels or even the entire dermis and subcutaneous fat in some case series.[7] Small vessel cutaneous, medium vessel polyarteritis nodosa as well as large vessel vasculitis have also all been reported.[1-34]

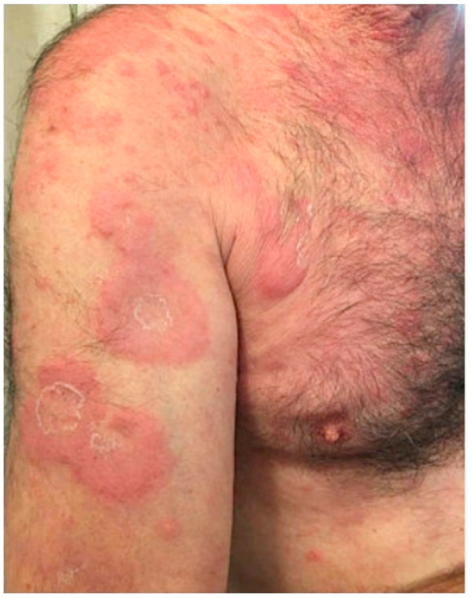

Fig 2. VEXAS syndrome. Multiple firm, tender, fixed, and progressive urticated erythematous nodules affect the trunk and limbs. Lesions are nonpruritic with some post-inflammatory epidermal desquamation.

In patients with comorbid MDS, many cells in the infiltrate were found to be CD68-positive, myeloperoxidase-positive "histiocytoid" myeloid precursor cells, as is characteristic of histiocytoid Sweet syndrome (Fig 3). Zakine et al7 noted the inflammatory infiltrate contained matured neutrophils, admixed with lymphoid cells and immature myeloid cells with indented nuclei (metamyelocytes and immature band neutrophils). The authors elegantly demonstrated through paired sequencing analysis that the dermal infiltrates in VEXAS syndrome are derived from the same pathological *UBA1*-mutated myeloid clone found in the bone marrow.[7] Therefore cutaneous inflammation appears to be driven by a clonal infiltration of affected myeloid cells, as opposed to a generalized proinflammatory milieu.[7]

Treatment

Further prospective evaluation of optimal treatment for VEXAS syndrome is still required. High-dose corticosteroids are effective, but the disease consistently relapses during tapering, and a wide spectrum of steroid-sparing agents have been tested.[5] Therapeutic targets against the affected clone, as previously described in MDS, could prove useful in targeting the organ-specific

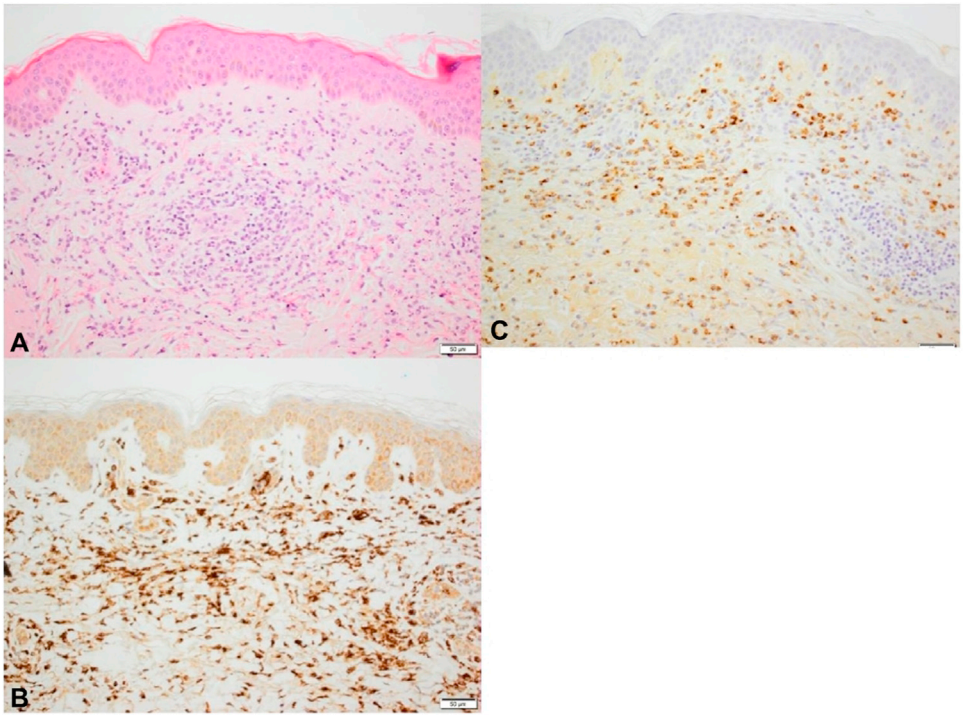

Fig 3. VEXAS syndrome histopathology. Biopsy taken from a Sweet-like erythematous nodule. (**A**) Leucocytoclastic vasculitis (hematoxylin-eosin stain; original magnification: ×100). (**B**) Leucocytoclastic vasculitis stained for the macrophage/histiocyte marker CD68 demonstrates many cells in the infiltrate are histiocytes (CD68 stain; original magnification: ×100). (**C**) Leucocytoclastic vasculitis stained for myeloperoxidase demonstrates these histiocytic cells are myeloperoxidase-positive as is characteristic of histiocytoid Sweet syndrome (myeloperoxidase stain; original magnification, ×100).

inflammation;[7,9] for example, hypomethylating agents such as 5-azacytidine have previously shown efficacy in Sweet syndrome associated with MDS.[5,9]

Bourbon et al[5] used the proxy of "time to next treatment" as a surrogate for drug efficacy in a case series of 11 patients. The median time to next treatment was 3.4 months for adalimumab (n = 3), 3.9 months for corticosteroids (n = 10), 7.4 months for methotrexate (n = 3), 8 months for tocilizumab (n = 4), 12.7 months for cyclosporine (n = 3), 21.9 months for azacytidine (n = 4), and was not reached for Janus Kinase inhibitors (ruxolitinib, n = 2; tofacitinib, n = 1).[5] Interestingly the Janus Kinase inhibitors provided dramatic regression of cutaneous symptoms within this small case series.[5] Due to the high associated disease mortality, future treatment options may explore gene editing therapies and bone marrow transplantation.[1]

DISCUSSION

The discovery of a potential shared genetic etiology that spans inflammatory skin conditions may provide insight into the mechanisms that foundationally underlie cutaneous inflammation.

Neutrophilic dermatoses are generally characterized by a dense infiltrate of mature polymorphonuclear cells to the affected tissue.[7] Approximately 20% of neutrophilic dermatoses occur within the context of an underlying myelodysplasia.[7] In classical Sweet syndrome, there is a dense dermal infiltrate of mature neutrophils.[8] This is distinct from histiocytoid Sweet syndrome whereby the cutaneous lesions are infiltrated by histiocytoid-like myeloperoxidase-positive immature myeloid cells at various differentiation stages.[7,8]

More recently, Delaleu et al[8] proposed that all MDS patients presenting with a histological picture of histiocytoid Sweet syndrome may be better considered as myelodysplasia cutis. This novel entity is used more specifically for MDS patients in which lesions show a "histiocytoid" histopathological pattern of infiltrating immature myeloid cells in the dermis, which have been shown to be of the same clonal origin as those in the bone marrow through mutational analysis.[8] The authors report this myeloperoxidase-positive immature myeloid infiltrate to be perivascular and periadnexal, without vessel wall necrosis or leukocytoclastic vascultis.[8]

VEXAS syndrome also shares the same clonal infiltrate affecting the skin and bone marrow, and lesions reminiscent of Sweet syndrome have been seen in 19% of confirmed VEXAS cases.[1-34]

However, the condition is discrete in that it refers specifically to a *UBA1* gene mutation of hematopoietic progenitor cells, and can be associated with a spectrum of cytopenias which may evolve into, but are not exclusively associated with, an MDS.[1] Reported incidence of myelodysplastic comorbid VEXAS syndrome varied between 25% (6/25; Beck et al[1]), 30% (3/10; Poulter et al[4]), and 55% (6/11; Bourbon et al[5]). Furthermore, other characteristic hallmarks are evident such as cytoplasmic vacuoles, a predilection for chondritis, and the more widespread systemic complications of the resultant recalcitrant inflammation.[1] However, the clinical appearances of VEXAS syndrome, myelodysplasia cutis, and histiocytoid Sweet syndrome may be difficult to distinguish on appearance alone. It is possible that while a subset of known patients with Sweet-like lesions, especially those with histiocytoid Sweet syndrome, and myelodysplasia will have VEXAS, other cases of Sweet-like lesions associated with MDS could be truly a paraneoplastic phenomenon without preferential trafficking of clonal myeloid cells into the skin.

VEXAS syndrome should therefore be considered in adult males affected by systemic symptoms such as fever and fatigue, presenting to the dermatologist with tender, purpuric, or erythematous infiltrated nodules, periorbital edema, chondritis, or a refractory vasculitis. Further suspicion should be raised if there is an abnormal blood film with cytopenias, high inflammatory markers, and a biopsy supportive of a neutrophilic dermatosis with or without leukocytoclastic vasculitis.[1,3] Such patients should be referred for consideration of bone marrow interrogation for characteristic vacuoles or definitive diagnosis via genetic sequencing.[1]

CONCLUSIONS

As more genetic data is acquired, further mutations underpinning novel autoinflammatory disorders may emerge. Hence recognized dermatoses may fit increasingly into new inflammatory syndromes with a common pathogenesis. It will therefore remain important for dermatologists to forge frameworks of multidisciplinary collaboration as commonalities between dermatological manifestations, hematological dysplasia, and hyperinflammatory states become more apparent. After all, as most dermatologists will tell you, it all comes out in the skin.

Conflicts of interest

None disclosed.

REFERENCES

1. Beck DB, Ferrada MA, Sikora KA, et al. Somatic mutations in *UBA1* and Severe adult-onset autoinflammatory disease. *N Engl J Med*. 2020;383(27):2628-2638. https://doi.org/10.1056/NEJMoa2026834
2. Grayson PC, Patel BA, Young NS. VEXAS syndrome. *Blood*. 2021;137(26):3591-3594. https://doi.org/10.1182/blood.2021011455
3. van der Made CI, Potjewijd J, Hoogstins A, et al. Adult-onset autoinflammation caused by somatic mutations in UBA1: A Dutch case series of patients with VEXAS. *J Allergy Clin Immunol*. 2022;149(1):432-439.e4. https://doi.org/10.1016/j.jaci.2021.05.014
4. Poulter JA, Collins JC, Cargo C, et al. Novel somatic mutations in UBA1 as a cause of VEXAS syndrome. *Blood*. 2021;137(26):3676-3681. https://doi.org/10.1182/blood.2020010286
5. Bourbon E, Heiblig M, Gerfaud Valentin M, et al. Therapeutic options in VEXAS syndrome: insights from a retrospective series. *Blood*. 2021;137(26):3682-3684. https://doi.org/10.1182/blood.2020010177
6. Ferrada MA, Sikora KA, Luo Y, et al. Somatic mutations in UBA1 define a distinct subset of relapsing polychondritis patients With VEXAS. *Arthritis Rheumatol*. 2021;73(10):1886-1895. https://doi.org/10.1002/art.41743
7. Zakine E, Schell B, Battistella M, et al. UBA1 Variations in neutrophilic dermatosis skin lesions of patients with VEXAS syndrome. *JAMA Dermatol*. 2021;157(11):1349-1354. https://doi.org/10.1001/jamadermatol.2021.3344
8. Delaleu J, Kim R, Zhao LP, et al. Clinical, pathological and molecular features of myelodysplasia cutis. *Blood*. 2021. https://doi.org/10.1182/blood.2021013967
9. Kulasekararaj AG, Kordasti S, Basu T, Salisbury JR, Mufti GJ, du Vivier AW. Chronic relapsing remitting Sweet syndrome - a harbinger of myelodysplastic syndrome. *Br J Haematol*. 2015;170(5):649-656. https://doi.org/10.1111/bjh.13485
10. Staels F, Betrains A, Woei-A-Jin FJSH, et al. Case report: VEXAS syndrome: from mild symptoms to life-threatening macrophage activation syndrome. *Front Immunol*. 2021;12:678927. https://doi.org/10.3389/fimmu.2021.678927
11. Obiorah IE, Patel BA, Groarke EM, et al. Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. *Blood Adv*. 2021;5(16):3203-3215. https://doi.org/10.1182/bloodadvances.2021004976
12. Koster MJ, Kourelis T, Reichard KK, et al. Clinical heterogeneity of the VEXAS syndrome: a case series. *Mayo Clin Proc*. 2021;96(10):2653-2659. https://doi.org/10.1016/j.mayocp.2021.06.006
13. Tsuchida N, Kunishita Y, Uchiyama Y, et al. Pathogenic *UBA1* variants associated with VEXAS syndrome in Japanese patients with relapsing polychondritis. *Ann Rheum Dis*. 2021. https://doi.org/10.1136/annrheumdis-2021-220089
14. Lacombe V, Prevost M, Bouvier A, et al. Vacuoles in neutrophil precursors in VEXAS syndrome: diagnostic performances and threshold. *Br J Haematol*. 2021;195(2):286-289. https://doi.org/10.1111/bjh.17679
15. Templé M, Duroyon E, Croizier C, et al. Atypical splice-site mutations causing VEXAS syndrome. *Rheumatology (Oxford)*. 2021;60(12):e435-e437. https://doi.org/10.1093/rheumatology/keab524
16. Lee SMS, Fan BE, Lim JH, Goh LL, Lee JSS, Koh LW. A case of VEXAS syndrome manifesting as Kikuchi-Fujimoto disease,

relapsing polychondritis, venous thromboembolism and macrocytic anaemia. *Rheumatology (Oxford)*. 2021;60(9):e304-e306. https://doi.org/10.1093/rheumatology/keab200

17. Sakuma M, Tanimura A, Yasui S, et al. A case of polychondritis-onset refractory organizing pneumonia with cytopaenia diagnosed as VEXAS syndrome: the disease course of 7 years. *Rheumatology (Oxford)*. 2021;60(10):e356-e359. https://doi.org/10.1093/rheumatology/keab349
18. Rieu JB, El Kassir A, Largeaud L, Dion J, Comont T, Mansat-De Mas V. Characteristic vacuolisation of granulocytic and erythroid precursors associated with VEXAS syndrome. *Br J Haematol*. 2021;194(1):8. https://doi.org/10.1111/bjh.17381
19. Takahashi N, Takeichi T, Nishida T, et al. Extensive multiple organ involvement in VEXAS syndrome. *Arthritis Rheumatol*. 2021;73(10):1896-1897. https://doi.org/10.1002/art.41775
20. Lacombe V, Kosmider O, Prévost M, Lavigne C, Urbanski G. Severe joint involvement in VEXAS syndrome: a case report. *Ann Intern Med*. 2021;174(7):1025-1027. https://doi.org/10.7326/L21-0023
21. Magnol M, Couvaras L, Degboé Y, et al. VEXAS syndrome in a patient with previous spondyloarthritis with a favourable response to intravenous immunoglobulin and anti-IL17 therapy. *Rheumatology (Oxford)*. 2021;60(9):e314-e315. https://doi.org/10.1093/rheumatology/keab211
22. Himmelmann A, Brücker R. The VEXAS syndrome: uncontrolled inflammation and macrocytic anaemia in a 77-year-old male patient. *Eur J Case Rep Intern Med*. 2021;8(4):002484. https://doi.org/10.12890/2021_002484
23. Barba T, Jamilloux Y, Durel CA, et al. VEXAS syndrome in a woman. *Rheumatology (Oxford)*. 2021;60(11):e402-e403. https://doi.org/10.1093/rheumatology/keab392
24. Fan BE, Cao L, Gallardo CA, et al. Myeloid and lymphoid vacuolation in VEXAS syndrome. *Am J Hematol*. 2021;96(8):1056-1057. https://doi.org/10.1002/ajh.26098
25. Oganesyan A, Jachiet V, Chasset F, et al. VEXAS syndrome: still expanding the clinical phenotype. *Rheumatology (Oxford)*. 2021;60(9):e321-e323. https://doi.org/10.1093/rheumatology/keab225
26. Grey A, Cheong P, Lee F, et al. A case of VEXAS syndrome complicated by hemophagocytic lymphohistiocytosis. *J Clin Immunol*. 2021;41(7):1648-1651. https://doi.org/10.1007/s10875-021-01070-y
27. Shaukat F, Hart M, Burns T, Bansal P. UBA1 and DNMT3A mutations in VEXAS syndrome. A case report and literature review. *Mod Rheumatol Case Rep*. 2022;6(1):134-139. https://doi.org/10.1093/mrcr/rxab021
28. Alhomida F, Beck DB, George TI, et al. Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome-clinical presentation of a newly described somatic, autoinflammatory syndrome. *JAAD Case Rep*. 2021;14:111-113. https://doi.org/10.1016/j.jdcr.2021.06.010
29. Dehghan N, Marcon KM, Sedlic T, Beck DB, Dutz JP, Chen LYC. Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome: fevers, myalgia, arthralgia, auricular chondritis, and erythema nodosum. *Lancet*. 2021;398(10300):621.
30. Lytle A, Bagg A. VEXAS: a vivid new syndrome associated with vacuoles in various hematopoietic cells. *Blood*. 2021;137(26):3690. https://doi.org/10.1182/blood.2021010714
31. Sharma A, Naidu G, Deo P, Beck DB. VEXAS syndrome with systemic lupus erythematosus: expanding the spectrum of associated conditions. *Arthritis Rheumatol*. 2022;74(2):369-371. https://doi.org/10.1002/art.41957
32. Ross C, Elfassy HL, Makhzoum JP. Somatic mutation in *UBA1* and ANCA-associated vasculitis. *J Rheumatol*. 2021;48(10):1626-1627. https://doi.org/10.3899/jrheum.210149
33. Euvrard R, Fournier T, Georgescu D, et al. VEXAS syndrome-related AA amyloidosis: a case report. *Rheumatology (Oxford)*. 2021;61(1):e15-e16. https://doi.org/10.1093/rheumatology/keab683
34. Huang H, Zhang W, Cai W, et al. VEXAS syndrome in myelodysplastic syndrome with autoimmune disorder. *Exp Hematol Oncol*. 2021;10(1):23. https://doi.org/10.1186/s40164-021-00217-2