VEXAS Syndrome—Diagnostic Clues for the Dermatologist and Gaps in Our Current Understanding: A Narrative Review

Lowell T. Nicholson[1], Edward W. Cowen[2], David Beck[3], Marcela Ferrada[4] and Lauren M. Madigan[1]

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome is a newly recognized, acquired autoinflammatory disorder with broad systemic implications and a poor global prognosis. Because cutaneous lesions are present in the majority of those affected, it is necessary that dermatologists are equipped to recognize this important disease. Through identification, there is a greater opportunity for disease stratification, surveillance for systemic involvement, and selection of the best available therapies. As our understanding of this disease develops, dermatologists should also play a role in addressing the knowledge gaps that exist.

Keywords: Autoinflammatory, Genetics, Hematologic malignancy, Neutrophilic dermatosis, VEXAS

JID Innovations (2024);**4:**100242 doi:10.1016/j.xjidi.2023.100242

INTRODUCTION

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a newly defined disorder characterized by systemic inflammation, hematologic abnormalities, cutaneous lesions, and acquired pathologic genetic alterations affecting ubiquitination. This syndrome results from somatic variants in the *UBA1* gene, which is located on the X chromosome and encodes for a major ubiquitin-activating ("E1") enzyme (Beck et al, 2020). In VEXAS syndrome, these specific variants within myeloid and erythroid precursors result in decreased ubiquitylation, hyperactivation of innate immune pathways, myeloid dysplasia (including vacuolization), and a systemic autoinflammatory disease (Beck et al, 2020). VEXAS syndrome tends to have a refractory treatment course and can be deadly, with a mortality rate of up to 40% reported in the initial cohort (Beck et al, 2020). Since its initial description, additional cases and developing national registries have further expanded the clinical spectrum of this severe, refractory illness. Cutaneous disease is a prominent finding and dermatologists should be aware of the clinical features, as well as the systemic manifestations of the disease, in order to make this challenging diagnosis. Currently, no formal diagnostic criteria are available for VEXAS syndrome. As such, this manuscript outlines a series of "clues" which, when present in the appropriate context, warrant additional testing (including evaluation for pathologic *UBA1* variants).

[1]*Department of Dermatology, University of Utah, Salt Lake City, Utah, USA;* [2]*Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Health, Bethesda, Maryland, USA;* [3]*Department of Medicine, New York University Grossman School of Medicine, New York City, New York, USA; and* [4]*Rheumatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Health, Bethesda, Maryland, USA*

Correspondence: Lauren M. Madigan, Department of Dermatology, University of Utah, 4A330 30 North 1900 East, Salt Lake City, Utah 84132, USA. E-mail: lauren.madigan@hsc.utah.edu

Abbreviation: DMARDs, disease-modifying antirheumatic drugs; ISR, injection site reactions; IVIG, intravenous Ig; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic

Received 19 June 2023; revised 25 September 2023; accepted 2 October 2023; corrected proof published online XXX

Cite this article as: JID Innovations 2024;4:100242

DIAGNOSTIC CLUE NUMBER 1: MORPHOLOGY

Across several retrospective cohorts, the incidence of skin involvement in VEXAS syndrome consistently exceeds 80% and is often a presenting sign of disease (Beck et al, 2020; Georgin-Lavialle et al, 2022; van der Made et al, 2022; Zakine et al, 2021). Dermatologists are therefore uniquely poised to facilitate identification of affected patients and manage the cutaneous features. The most common cutaneous manifestations observed in VEXAS syndrome are neutrophilic dermatitis, chondritis, and vasculitis/vasculopathy (Figure 1). Patients with neutrophilic dermatitis typically present with erythematous to violaceous, indurated or edematous plaques—which may appear arcuate—involving the face, trunk, and extremities, similar to classic Sweet syndrome (Alhomida et al, 2021; Beck et al, 2020; Cordts et al, 2022; Hage-Sleiman et al, 2021; Khosravi-Hafshejani et al, 2022; Koster and Warrington, 2021; Lacombe et al, 2022; Lacombe et al, 2021a; Loschi et al, 2022; Raaijmakers et al, 2021; Sterling et al, 2022; Zakine et al, 2021). In the initial National Institute of Health cohort published by Beck et al, 32% of patients carried a diagnosis of Sweet syndrome before VEXAS diagnosis (Beck et al, 2020). Less commonly, patients may present with subcutaneous nodules, which are clinically and histopathologically consistent with erythema nodosum (Beck et al, 2020; Dehghan et al, 2021; Georgin-Lavialle et al, 2022; Lacombe et al, 2022).

Chondritis occurs in 36−60% of patients and provides an important clinical clue to a diagnosis of VEXAS syndrome (Beck et al, 2020; Georgin-Lavialle et al, 2022; van der Made et al, 2022). This typically presents with erythema, swelling, and pain of the cartilaginous portion of the ear and nose (Beaumesnil et al, 2022; Beck et al, 2020; Bert-Marcaz et al, 2022; Euvrard et al, 2021; Ferrada et al, 2021; Goyal et al, 2022; Islam et al, 2022; Koster et al, 2021; Koster and Warrington, 2021; Shaukat et al, 2022; Tsuchida et al,

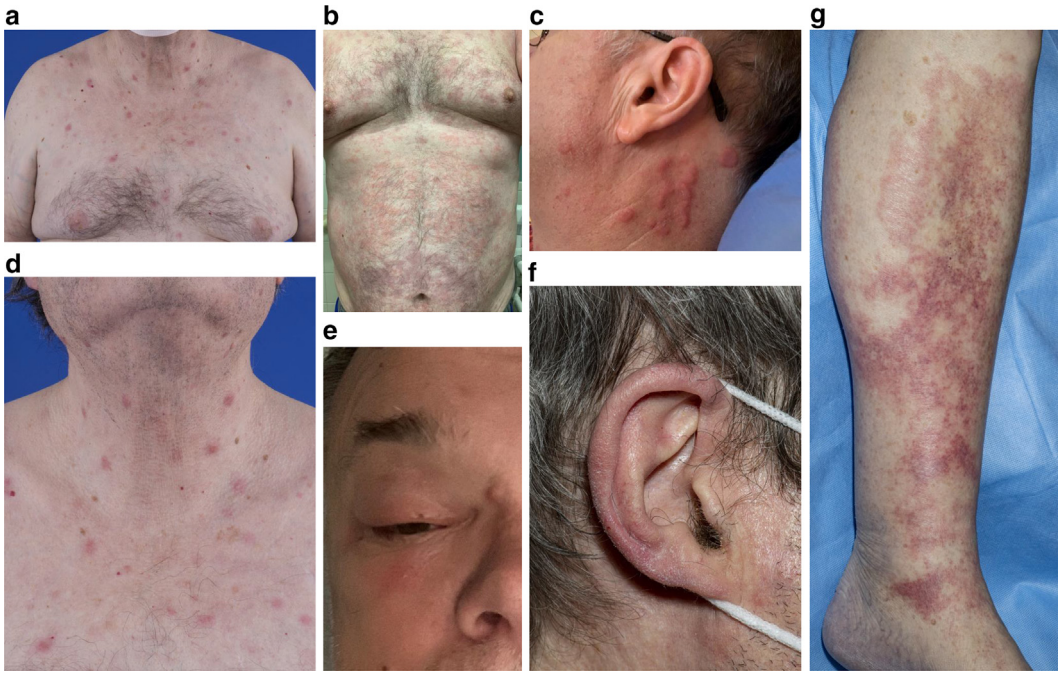

Figure 1. Cutaneous manifestations of VEXAS syndrome. (**a**–**d**) Edematous pink papules and plaques on the trunk and neck consistent with neutrophilic dermatitis; (**e**) periocular edema and erythema; (**f**) erythema and swelling of the auricle consistent with chondritis; (**g**) palpable purpura on the leg consistent with vasculitis.

2021)—though at least one case with associated lobular inflammation has been published (Beaumesnil et al, 2022). Involvement of the tracheobronchial cartilage may occur (Beaumesnil et al, 2022; Tsuchida et al, 2021) and chondritis with concurrent genital and oral mucosal ulceration may lead to an initial diagnosis of mouth and genital ulcers-inflamed cartilage syndrome (Diarra et al, 2022; Matsumoto et al, 2022). In evaluating patients with chondritis, the presence of macrocytic anemia provides an important clue to the diagnosis of VEXAS syndrome. In a cohort of 92 patients diagnosed with relapsing polychondritis, 7.6% were found to have a pathologic *UBA1* variant. A simple algorithm based on the presence of male sex, mean corpuscular volume > 100 fl, and a platelet count $< 200 \times 10^3$/μl discriminated patients with chrondritis with VEXAS from those without a *UBA1* variant with a sensitivity of 100% and a specificity of 96% (Ferrada et al, 2021).

Vasculitis, and/or vasculopathy, is also commonly reported with an incidence of 25.9% among the largest retrospective cohort published to date (Georgin-Lavialle et al, 2022). However, prevalence estimates remain imprecise given limitations in reporting and the possibility of overestimation (Zakine et al, 2023). As such, additional centralized review will be necessary to characterize this further. Involvement of all vessel sizes has been described, though cutaneous small vessel vasculitis appears to be most common (Barba et al, 2021; Beck et al, 2020; Georgin-Lavialle et al, 2022; Koster et al, 2021; Muratore et al, 2022). Morphologies include palpable purpura, as well as livedo racemosa, nodules, and ulceration in the setting of medium and large vessel involvement (Ferrada et al, 2021; Lacombe et al, 2022; Pàmies et al, 2022; Zakine et al, 2021). Notably, although cutaneous morphology may mimic polyarteritis nodosa—with 12% of the initial cohort carrying this diagnosis—mesenteric vasculitis is typically absent in patients with VEXAS (Beck et al, 2020; Koster and Warrington, 2021). Potential associations with antineutrophilic cytoplasmic antibody vasculitis and IgA vasculitis have also been suggested (Koster et al, 2023; Muratore et al, 2022; Pàmies et al, 2022). It should be noted that intense neutrophilic inflammation, such as that seen in neutrophilic dermatitis, can result in a neutrophilic vascular reaction. As such, the distinction between neutrophilic dermatitis and vasculitis and/or vasculopathy requires careful clinicopathologic correlation.

Although the cutaneous lesions in VEXAS may be morphologically indistinguishable from classic Sweet syndrome, vasculitis, and relapsing polychondritis, the co-occurrence of more than one of these "typical" cutaneous morphologies in an older male patient should raise suspicion for VEXAS syndrome and prompt testing for pathogenic *UBA1* variants should be performed (Figure 2). Notably, multiple cutaneous morphologies may appear simultaneously (Figure 3) or present over the course of years, highlighting the importance of continued surveillance (Sakuma et al, 2021).

Additional physical examination clues include the presence of periorbital edema, which may be bilateral or unilateral (Beck et al, 2020; Ferrada et al, 2021; Georgin-Lavialle et al, 2022; Islam et al, 2022; Koster and Warrington, 2021; Lacombe et al, 2021b; Takahashi et al, 2021; van der Made et al, 2022). This feature is relatively common among patients with VEXAS, with an incidence ranging between 8%–33% (Beck et al, 2020; Ferrada et al, 2021; Georgin-Lavialle et al, 2022; Koster and Warrington, 2021; Lacombe et al, 2021b; van der Made et al, 2022). Peripheral edema may

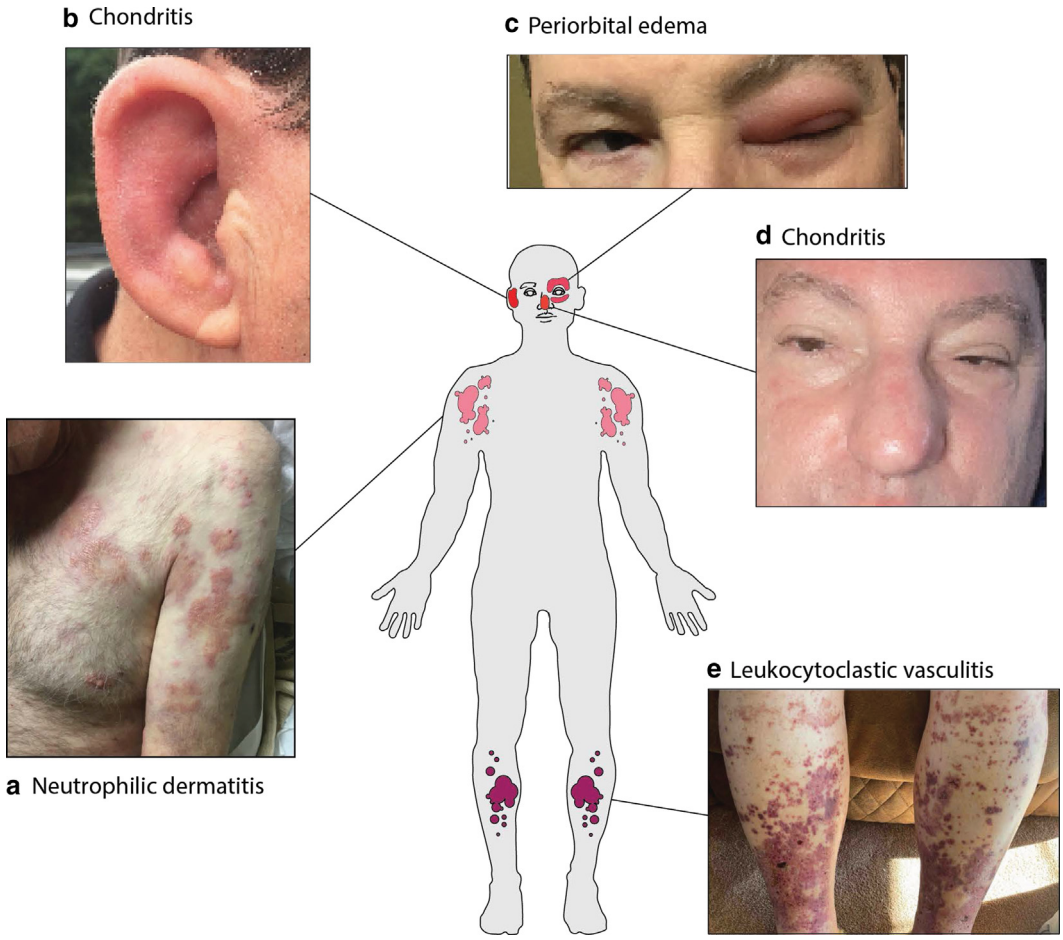

Figure 2. Co-occurrence of multiple "typical" cutaneous manifestations of VEXAS syndrome in an older male patient. (**a**) Edematous pink papules and larger edematous pink plaques scattered on the chest and upper arm; (**b**) erythema and swelling of the ear with notable sparing of the earlobe; (**c**) erythema and edema involving the periocular area; (**d**) erythema and swelling of the cartilaginous portion of the nose; (**e**) solitary and coalescing purpuric papules, some with overlying hemorrhagic bullae, and symmetrically distributed on the lower legs.

also be present. Prominent injection site reactions (ISR) were observed in 62% of patients receiving anakinra in the initial cohort, as well as 9% of all patients in a multi-institutional French cohort (Beck et al, 2020; Georgin-Lavialle et al, 2022). Although ISR are common with anakinra administration in general, additional case series and reports have confirmed an elevated risk of severe ISR in the VEXAS population (Ciprian, 2022; Lötscher et al, 2021; Muratore et al, 2022; van der Made et al, 2022).

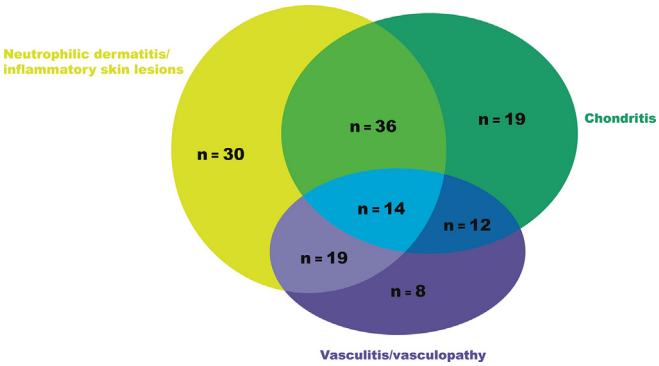

Figure 3. Venn diagram showing the relative number of the three reported "typical" cutaneous manifestations of VEXAS syndrome, as well as reported cases of morphological overlap.

Since the initial description of VEXAS syndrome in 2020, the spectrum of cutaneous manifestations described has expanded to include papular, eczematous, nodular, urticarial, pustular, polycyclic, and targetoid morphologies (Delplanque et al, 2021; Georgin-Lavialle et al, 2022; Goyal et al, 2022; Koster and Warrington, 2021; Loschi et al, 2022; Lötscher et al, 2021; Mohammed et al, 2023; Poulter et al, 2021; Tsuchida et al, 2021). Rarer presentations include a desquamative morbilliform eruption (Euvrard et al, 2021), extensive fibrosis and joint contractures (following severe peripheral edema) (Magnol et al, 2021), and cases of VEXAS syndrome presenting with urticarial lesions, painful lymphadenitis, and skin papules clinically and histologically resembling Kikuchi-Fujimoto disease (Fan et al, 2021; Lee et al, 2021; Ylmaz et al, 2022). Secondary skin sequelae have also been reported including digital necrosis due to mixed cryoglobulinemia (Koster et al, 2021).

DIAGNOSTIC CLUE NUMBER 2: UNIQUE DEMOGRAPHIC ATTRIBUTES OF VEXAS SYNDROME

As an acquired somatic disorder, VEXAS characteristically presents later in life with a median age at diagnosis of

~65–70 years of age (Beck et al, 2020; Georgin-Lavialle et al, 2022; van der Made et al, 2022). This relatively late presentation is distinct from other autoinflammatory and autoimmune syndromes that manifest at a younger age. This unique feature was demonstrated in two cohorts of patients with relapsing polychondritis, in which the average age of symptom onset in patients with a pathologic *UBA1* variant was 56 years and 66 years, respectively, in comparison to a median age of 37 years and 44 years in patients without a *UBA1* variant (Ferrada et al, 2021; Khitri et al, 2022). As such, the pretest probability of *UBA1* testing is highest among patients aged >40 years.

The *UBA1* gene resides on the X-chromosome, thus VEXAS is an X-linked disorder and was initially characterized only in men (Beck et al, 2020). As such, male gender remains an important clue in identifying patients most at risk for this disease, and the onset of new autoinflammatory features in an adult male should prompt consideration of testing. Nonetheless, this disease can occur in women with an estimated prevalence of 1:26,238 for females aged >50 years based on a single-center regional cohort of individuals with predominantly European ancestry (Beck et al, 2023). Women with conditions that result in the absence of a functional X chromosome—though rare—were identified relatively early within VEXAS cohorts. These conditions included acquired monosomy X (Barba et al, 2021; Khitri et al, 2022) and Turner syndrome (Stubbins et al, 2022). Recently, additional cases of affected women with *UBA1* pathogenic variants who lack aneuploidy have also been reported, though the mechanism for disease presentation in these cases is less clear (Beck et al, 2023; Poulter et al, 2022).

VEXAS was initially characterized in a group of 25 adult men (Beck et al, 2020), though there may be important differences in disease presentation in different demographic populations. As of June 2023, 167 distinct morphologic images of the skin and eyes had been published (Afsahi et al, 2023; Alhomida et al, 2021; Argobi, 2022; Balu et al, 2023; Beaumesnil et al, 2022; Beck et al, 2020; Beecher et al, 2022; Bert-Marcaz et al, 2022; Ciprian, 2022; Collantes-Rodríguez et al, 2023; Cordts et al, 2022; Dehghan et al, 2021; Euvrard et al, 2021; Ferrada et al, 2021; Goyal et al, 2022; Hage-Sleiman et al, 2021; Himmelmann and Brücker, 2021; Islam et al, 2022; Khosravi-Hafshejani et al, 2022; Koster et al, 2021; Koster and Warrington, 2021; Lacombe et al, 2022; Lacombe et al, 2021a; Legeas et al, 2023; Loschi et al, 2022; Lötscher et al, 2021; Magnol et al, 2021; Martin-Nares et al, 2022; Matsubara et al, 2022; Matsuki et al, 2022; Matsumoto et al, 2022; Mohammed et al, 2023; Neupane et al, 2022; Nguyen et al, 2022; Oganesyan et al, 2021; Pàmies et al, 2022; Raaijmakers et al, 2021; Ribereau-Gayon et al, 2022; Shaukat et al, 2022; Shimizu et al, 2022; Skowron et al, 2023; Staels et al, 2021; Sterling et al, 2022; Stiburkova et al, 2023; Takahashi et al, 2021; Topilow et al, 2022; Tozaki et al, 2022; Tsuchida et al, 2021; Valor-Méndez et al, 2023; van der Made et al, 2022; van Leeuwen-Kerkhoff et al, 2022; Varadarajan et al, 2023; Vitale et al, 2023; Yamaguchi et al, 2023; Yildirim et al, 2023; Yoon et al, 2023; Zakine et al, 2023; Zakine et al, 2021; Zeisbrich et al, 2023), however only six of these images, obtained from two adult male patients, demonstrate morphology in richly pigmented skin (Fitzpatrick skin type V or VI) (Ciprian, 2022; Neupane et al, 2022). Given that VEXAS syndrome is caused by an acquired somatic variant, we suspect the lack of clinical images in other ethnic and racial settings represents ascertainment bias. It will be important to expand the spectrum of skin presentations in the literature in diverse skin types and genetic backgrounds to accurately portray potential cutaneous disease variability.

DIAGNOSTIC CLUE NUMBER 3: THE PRESENCE OF ADDITIONAL ORGAN INVOLVEMENT

Hematologic abnormalities characterized by cytopenias, particularly macrocytic anemia as discussed previously, are a major risk of VEXAS syndrome. Vacuolization of myeloid and erythroid precursors within the bone marrow is highly sensitive, but not 100% specific for VEXAS, because it may be seen in other settings, such as nutritional deficiency and malignancy (Beck et al, 2020; Ferrada et al, 2021). Patients with VEXAS are also predisposed to progressive marrow dysplasia and 11%–55% meet criteria for myelodysplastic syndrome (Bourbon et al, 2021; Georgin-Lavialle et al, 2022; Koster et al, 2021; van der Made et al, 2022). Other clonal disorders, such as myeloma, monoclonal gammopathy of uncertain significance, and monoclonal B-cell lymphocytosis may occur (Beck et al, 2020; Koster et al, 2021; Obiorah et al, 2021). Secondary hemophagocytic lymphohistocytosis and systemic amyloidosis have also been reported (Delplanque et al, 2021; Euvrard et al, 2021; Grey et al, 2021; Kao et al, 2022; Staels et al, 2021; van der Made et al, 2022). Thrombosis develops in ~40% (10%–65% across series) and may manifest in the skin with thrombophlebitis symptoms, acute unilateral edema and/or pain (Beck et al, 2020; Georgin-Lavialle et al, 2022; Groarke et al, 2021; Koster and Warrington, 2021; Oo et al, 2022).

Constitutional symptoms are exceedingly common in VEXAS with the majority of patients experiencing significant fatigue and/or noninfectious fevers that often present concurrently with cutaneous lesions (Beck et al, 2020; Georgin-Lavialle et al, 2022; Koster et al, 2021). The breadth of additional organ involvement in VEXAS syndrome is wide (Table 1). From the initial disease description, it was apparent that chondritis, pulmonary and ocular disease were relatively common in the syndrome (Beck et al, 2020; Georgin-Lavialle et al, 2022; Koster and Warrington, 2021; Lee et al, 2021; Martin-Nares et al, 2022; Takahashi et al, 2021). A large multicenter case series of 116 French patients was subsequently published by Georgin-Lavialle *et al* that further expanded the spectrum of organ involvement to include the presence of lymphadenopathy, gastrointestinal, and cardiovascular dysfunction (Beck et al, 2020; Georgin-Lavialle et al, 2022). In addition, a possible case of VEXAS-related endocarditis was described among a cohort of Japanese patients with chondritis, though this association remains unclear (Tsuchida et al, 2021). Musculoskeletal disease is also common, with 28% of the French cohort (Georgin-Lavialle et al, 2022) endorsing arthralgias and additional reports describing severe erosive disease mimicking rheumatoid arthritis (Lacombe et al, 2021a) and acute myofasciitis (Cordts et al, 2022). Neurologic disease, renal dysfunction, and

Table 1. Clinical Manifestations of VEXAS Syndrome Stratified by Incidence

Relative incidence		
Expected (estimated incidence > 75%)	Constitutional	Fatigue Noninfectious fever Night sweats Weight loss
	Cutaneous lesions	Neutrophilic dermatitis Vasculitis (small > medium and large vessel) Injection site reaction Edema Less common morphologies: panniculitis, urticarial, and targetoid, morbilliform
	Hematologic abnormalities	Cytopenia (macrocytic anemia, and thrombocytopenia) Vacuolization of myeloid precursors in the bone marrow Myelodysplastic syndrome Less common presentation: myeloma, monoclonal gammopathy of uncertain significance, and monoclonal B-cell lymphocytosis
Common (estimated incidence 30–75%)	Chondritis	Nasal chondritis Auricular chondritis Less common: other sites
	Musculoskeletal	Arthralgias Inflammatory arthritis Myalgias Less common presentation: myofasciitis
	Pulmonary	Pulmonary infiltrates Pleural effusions Less common presentation: bronchiolitis obliterans
	Ocular	Uveitis Scleritis Episcleritis Less common presentation: iritis, pseudomembranous conjunctivitis, optic perineuritis, proptosis, and orbital mass
	Lymph node	Lymphadenopathy Less common presentation: necrotizing lymphadenitis
	Thrombosis	
	Cardiovascular	Pericarditis Myocarditis Aortitis and arterial aneurysms
	Neurologic	Sensory neuropathy Multiple mononeuropathy Sensorineural deafness Less common presentation: acute-onset chronic inflammatory demyelinating polyneuropathy, aseptic meningitis, and encephalitis
	Gastrointestinal	Hepatosplenomegaly Abdominal pain and diarrhea Colitis Less common presentation: gastrointestinal bleeding and perforation/obstruction
Uncommon (est. incidence <30%)	Cardiac	Pericarditis Myocarditis Cardiomyopathy
	Arterial	Aortitis Arterial aneurysm
	Renal	Renal insufficiency Proteinuria Interstitial nephritis
	Genitourinary	Orchitis Epididymitis Prostatitis

genitourinary complications have also been reported (Table 1) (Beck et al, 2020; Georgin-Lavialle et al, 2022; Grayson et al, 2021; Ronsin et al, 2022; Tsuchida et al, 2021).

The expanding spectrum of systemic disease speaks to the role of the *UBA1* gene in regulating global inflammation and additional disease manifestations are likely to be described. As such, careful attention to any new or evolving symptoms in patients affected by this syndrome is critical.

DIAGNOSTIC CLUE NUMBER 4: HISTOPATHOLOGY

Skin histopathology in VEXAS to date has largely focused on neutrophilic dermatitis, leukocytoclastic vasculitis, and/or leukocytoclasia as the predominant findings (Figure 4) (Beck

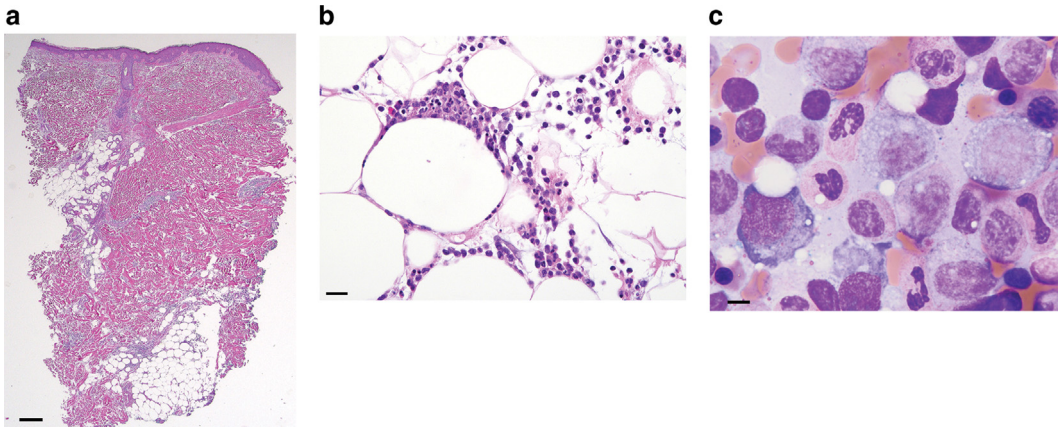

Figure 4. Histopathologic findings in VEXAS syndrome. (**a**) Superficial and deep perivascular and perieccrine neutrophilic inflammation, skin biopsy, H&E stain, ×40, Bar = 125 μm; (**b**) neutrophilic infiltration of the subcutis with immature cells, fragmented nuclei, and karyorrhexis, skin biopsy, H&E stain, ×100, Bar = 50 μm; (**c**) bone marrow aspirate showing characteristic cytoplasmic vacuolation of myeloid cells, H&E stain, ×600, Bar = 10 μm; other reported hematologic findings (not pictured here) include macrocytosis, bone marrow hypercellularity, and varying degrees of dysplasia.

et al, 2020; Khosravi-Hafshejani et al, 2022; van der Made et al, 2022; Zakine et al, 2023). Notably, the same loss-of-function *UBA1* variant present in the bone marrow has been identified in dermal infiltrates (Lacombe et al, 2022; Zakine et al, 2021). This finding suggests that the robust inflammatory infiltrate observed in cases of neutrophilic dermatitis directly results from the mutant myeloid clone, rather than a nonspecific manifestation of immune stimulation. Other less common histopathologic findings include large- and medium-vessel vasculitis, interstitial edema, and mixed dermal and perivascular inflammatory infiltrates (Khosravi-Hafshejani et al, 2022; Sterling et al, 2022; Zakine et al, 2021). The histiocytoid variant of Sweet syndrome or neutrophilic dermatitis has also been demonstrated in several patients (Himmelmann and Brücker, 2021; Sterling et al, 2022).

Although most cases clinically characterized by edematous dermal plaques correlate with tissue neutrophilia histologically, Ribereau-Gayon *et al* reported two patients with VEXAS syndrome presenting with widely distributed edematous plaques, including facial involvement, with features suggestive of tumid lupus on skin biopsy (lymphocytic inflammatory infiltrate with dermal mucin) (Ribereau-Gayon et al, 2022). Similarly, Khosravi-Hafshejani et al reported a single case with a Jessner-like lymphocytic infiltrate (without evidence of neutrophilic infiltration or vasculitis) (Khosravi-Hafshejani et al, 2022), and Valor-Méndez et al described a case in which initial histopathology demonstrating lymphohistocytic inflammation and small vessel vasculitis lead to the incorrect diagnosis of subacute lupus erythematosus (Valor-Méndez et al, 2023).

The true incidence of vasculitis among patients with VEXAS remains undetermined. Zakine et al performed a nationwide, centralized review of skin pathology samples on behalf of the National French VEXAS Study Group. Although a clinical suspicion of vasculitis was present in 17% of cases, and 22% of initial pathologic reports favored leukocytoclastic vasculitis, no patients were ultimately determined to have true cutaneous small vessel vasculitis by investigators (Zakine et al, 2023). Researchers in the United States subsequently performed a single center review of 14 patients with confirmed VEXAS syndrome. In this cohort, neutrophilic inflammation predominated as anticipated (25% characterized as neutrophilic urticarial dermatosis, 15% as neutrophilic dermatosis, and 10% as neutrophilic panniculitis). Twenty five percent of cases were reported as either cutaneous small vessel vasculitis or urticarial vasculitis; however, histopathology slides were not available for review at the time of the study (reported to be confirmed by the institution at the time of initial diagnosis) (Hines et al, 2023).

Our understanding of clonal versus nonclonal cutaneous manifestations also remains uncertain. Although independent researchers confirmed the presence of the *UBA1* mutant clone in neutrophilic infiltrates (as described initially by Zakine et al), they failed to identify this in other morphologic and histologic presentations of disease, including vasculitis (Lacombe et al, 2022; Zakine et al, 2021). Whether this indicates that these morphologies are paraclonal or simply do not contain enough myeloid cells to detect *UBA1* variation remains to be determined.

DIAGNOSTIC CLUE NUMBER 5: POOR RESPONSE TO THERAPY

There is no uniformly effective therapy for VEXAS syndrome and treatment refractory inflammation is a hallmark of the disease (Beck et al, 2020). High-dose glucocorticoids improve cutaneous lesions and other inflammatory symptoms in the short term, but recurrence after steroid tapering is nearly universal (Beck et al, 2020; Bourbon et al, 2021; Georgin-Lavialle et al, 2022). Adjunctive therapy is frequently required, and treatment resistance often necessitates the use of multiple treatments concurrently.

In the initial cohort described by Beck et al, most patients had been treated with at least two traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, mycophenolate mofetil, azathioprine, hydroxychloroquine, cyclophosphamide, dapsone, cyclosporine, or sulfasalazine, and two biologic and/or targeted therapies, such as anti-TNF-therapy (adalimumab, infliximab, etanercept, and golimumab), anti—IL-1 therapy (anakinra and

canakinumab), anti-Th17 therapy (secukinumab and ustekinumab), Jak inhibitors (tofacitinib and baricitinib), tocilizumab, rituximab, abatacept, or intravenous Ig (IVIG), without adequate disease control (Beck et al, 2020). The refractory nature of VEXAS syndrome-related inflammatory disease has since been reproduced by additional studies (Beck et al, 2020; Bourbon et al, 2021). To date, a wide variety of steroid-sparing therapies have been employed, including traditional DMARDs, biologic and targeted synthetic DMARDs, cellular signaling pathway inhibitors, and chemotherapeutic agents. Lack of response to one or more frequently effective therapies for isolated cutaneous vasculitis, chondritis or neutrophilic dermatosis should prompt consideration of VEXAS syndrome, particularly in older men at greatest risk of this disease.

There is limited evidence to suggest a single, superior steroid-sparing treatment for VEXAS syndrome. Bourbon et al used "time to next treatment" as a surrogate marker to measure clinical efficacy (Bourbon et al, 2021). In this small series of 11 patients, the median time to next treatment was 21.9 months for azacytidine, 12.7 months for cyclosporine, 8 months for tocilizumab, 7.4 months for methotrexate, and 3.4 months for adalimumab. The median time to next treatment was not reached for Jak inhibitors, although the duration of follow-up was limited (Bourbon et al, 2021). Other case series have also reported clinical responses after treatment with azacytidine (Comont et al, 2022; Cordts et al, 2022; Mekinian et al, 2022; Raaijmakers et al, 2021), tocilizumab (Goyal et al, 2022; Kirino et al, 2021; Kunishita et al, 2022), and IL-1 receptor antagonists (anakinra and canakinumab) (Campochiaro et al, 2022; Collantes-Rodríguez et al, 2023), all of which may be considered in the appropriate patient. Case reports also suggest potential efficacy for abatacept (Pathmanathan et al, 2022) and IVIG combined with secukinumab (Magnol et al, 2021). In contrast, limited or temporary improvement and complete lack of efficacy has also been described with these same agents (Alhomida et al, 2021; Beck et al, 2020; Dehghan et al, 2021; Koster et al, 2021; Pàmies et al, 2022; Takahashi et al, 2021). Notably, intestinal perforation during tocilizumab treatment has occurred (van der Made et al, 2022).

Jak inhibitors have also shown potential efficacy with ruxolitinib demonstrating superior disease control to other Jak inhibitors (including tofacitinib, baracitinib, and upadacitinib) in a recent multicenter retrospective investigation of 30 patients (Heiblig et al, 2022). Despite promising results in studies to date, additional data are needed regarding the efficacy and safety of Jak inhibition in patients with VEXAS, because cytopenias, infection, and thrombotic complications were observed (Heiblig et al, 2022).

Bone marrow transplantation is the only current potentially curative treatment for VEXAS syndrome. Loschi et al describe a single patient who experienced resolution of all systemic and cutaneous symptoms after allogenic hematopoietic stem cell transplant and Diarra et al retrospectively identified 6 patients with VEXAS syndrome who had undergone allogeneic hematopoietic stem cell transplantation, of whom 3 were still in remission after sufficient follow-up (Diarra et al, 2022; Loschi et al, 2022). More recently, van-Leeuwen-Kerkhoff et al have reported treating a single patient without myelodysplastic syndrome with allogenic hematopoietic stem cell transplant who was able to be tapered off all immunosuppression within 3.5 months and was still alive after 9 months (van Leeuwen-Kerkhoff et al, 2022).

Notably, patients in these studies suffered numerous treatment complications, which may ultimately limit its widespread use because patients with VEXAS are often older patients who at higher risk with multiple comorbidities. A separate cohort of 4 patients who received transplant from the United Kingdom was notable for a 50% mortality rate and only a 25% event-free survival at the time of publication (Hines et al, 2023). Reduced conditioning allogeneic stem cell transplant may be a feasible approach and preliminary data from an ongoing phase 2 clinical trial (NCT05027945) is promising (Mangaonkar et al, 2023).

Improved stratification of higher versus lower risk VEXAS by genotype or disease clustering will be critical to identify patients who would benefit from more aggressive, early intervention. Georgin-Lavialle et al performed an unsupervised hierarchical analysis of 116 patients, which identified following three disease clusters with prognostic differences: (i) patients with mild-moderate disease, (ii) those with underlying myelodysplastic syndrome and a higher mortality rate, and (iii) those with more prominent constitutional symptoms. They also identified genotype-specific features which seem to correlate with morbidity and mortality (Georgin-Lavialle et al, 2022). Another multivariable analysis of 83 patients found that ear chondritis was associated with increased survival, whereas transfusion dependence and the p.Met41Val variant were independently associated with decreased survival. In vitro models demonstrated that p.MetVal variants support less *UBA1b* translation compared with p.Met41Leu or p.Met41Thr, providing a possible explanation for the observed mortality difference (Ferrada et al, 2022). Although this work requires additional confirmation, it is a step toward more tailored therapy for those severely affected by this heterogeneous disease.

CONCLUSION

Dermatologists should be at the forefront of the recognition and diagnosis of VEXAS syndrome. Although formal diagnostic criteria have yet to be developed, dermatologists should consider *UBA1* testing in adults aged >40 years, particularly male, with characteristic cutaneous lesions, hematologic abnormalities, and/or features of autoinflammation. Genetic testing is now commercially available and can be performed using blood, bone marrow, or tissue specimens. Clinicians may also consider adding confirmed patients to the Autoinflammatory Disease Alliance registry, which aims to expand our understanding of VEXAS syndrome by collecting additional demographic, genetic, clinical, and therapeutic data. In areas where resources are limited, the further development of diagnostic criteria will be beneficial to allow for case identification in the absence of mutational testing. Any new criteria should, and will, be subject to validation. We hope that increased awareness of this rare condition will lead to earlier identification of cases, selection of appropriate therapy, and ultimately a reduction in morbidity and mortality.

ORCIDs
Lowell T. Nicholson: http://orcid.org/0000-0003-1582-3627
Edward W. Cowen: http://orcid.org/0000-0003-1918-4324
David Beck: http://orcid.org/0000-0002-5884-6231
Marcela Ferrada: http://orcid.org/0000-0003-3256-3273
Lauren M. Madigan: http://orcid.org/0000-0001-5659-5734

CONFLICT OF INTEREST
The authors state no conflict of interest.

ACKNOWLEDGMENTS
No external funds were received for this work. Written consent has been obtained from all patients whose images are included in the manuscript.

AUTHOR CONTRIBUTIONS
Conceptualization: LTN, LMM; Supervision: LMM; Visualization: LTN; Writing - Original Draft Preparation: LTN, LMM; Writing - Review and Editing: LTN, EWC, DB, MF, LMM

REFERENCES

Afsahi V, Christensen RE, Alam M. VEXAS syndrome in dermatology. Arch Dermatol Res 2023;315:161–4.

Alhomida F, Beck DB, George TI, Shaffer A, Lebiedz-Odrobina D, Kovacsovics T, et al. Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome-clinical presentation of a newly described somatic, autoinflammatory syndrome. JAAD Case Rep 2021;14:111–3.

Argobi Y. VEXAS syndrome with cutaneous nodules. Dermatol Reports 2022;14:9414.

Balu B, Ding Y, Junkins-Hopkins JM. VEXAS syndrome: diagnostic clues for dermatologists. Int J Dermatol 2023;62:e484–6.

Beaumesnil S, Boucher S, Lavigne C, Urbanski G, Lacombe V. Ear, nose, throat, and bronchial involvements in VEXAS syndrome: specifying the spectrum of clinical features. JAMA Otolaryngol Head Neck Surg 2022;148:284–6.

Barba T, Jamilloux Y, Durel CA, Bourbon E, Mestrallet F, Sujobert P, et al. VEXAS syndrome in a woman. Rheumatology (Oxford) 2021;60:e402–3.

Beck DB, Bodian DL, Shah V, Mirshahi UL, Kim J, Ding Y, et al. Estimated prevalence and clinical manifestations of UBA1 variants associated with VEXAS syndrome in a clinical population. JAMA 2023;329:318–24.

Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. N Engl J Med 2020;383:2628–38.

Beecher MB, Tong JY, Halliday LA, Hissaria P, Selva D. Recurrent orbital inflammation associated with VEXAS syndrome. Orbit 2022:1–4.

Bert-Marcaz C, Briantais A, Faucher B, Corazza G, Ebbo M, Attarian S, et al. Expanding the spectrum of VEXAS syndrome: association with acute-onset CIDP. J Neurol Neurosurg Psychiatry 2022;93:797–8.

Bourbon E, Heiblig M, Gerfaud Valentin M, Barba T, Durel CA, Lega JC, et al. Therapeutic options in VEXAS syndrome: insights from a retrospective series. Blood 2021;137:3682–4.

Campochiaro C, Tomelleri A, Cavalli G, De Luca G, Grassini G, Cangi MG, et al. Successful use of cyclosporin A and interleukin-1 blocker combination therapy in VEXAS syndrome: a single-center case series. Arthritis Rheumatol 2022;74:1302–3.

Ciprian G. Adverse reaction to COVID-19 mRNA vaccination in a patient with VEXAS syndrome. Cureus 2022;14:e23456.

Collantes-Rodríguez C, Jiménez-Gallo D, de la Varga-Martínez R, Mora-López F, Garrastazul-Sánchez MP, Linares-Barrios M. Vexas syndrome successfully treated with canakinumab. J Dtsch Dermatol Ges 2023;21:69–70.

Comont T, Heiblig M, Rivière E, Terriou L, Rossignol J, Bouscary D, et al. Azacitidine for patients with vacuoles, E1 Enzyme, X-linked, Autoinflammatory, Somatic syndrome (VEXAS) and myelodysplastic syndrome: data from the French VEXAS registry. Br J Haematol 2022;196:969–74.

Cordts I, Hecker JS, Gauck D, Park J, Härtl J, Günthner R, et al. Successful treatment with azacitidine in VEXAS syndrome with prominent myofasciitis. Rheumatology (Oxford) 2022;61:e117–9.

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;398:621.

Delplanque M, Aouba A, Hirsch P, Fenaux P, Graveleau J, Malard F, et al. USAID associated with myeloid neoplasm and VEXAS syndrome: two differential diagnoses of suspected adult onset Still's disease in elderly patients. J Clin Med 2021:10.

Diarra A, Duployez N, Fournier E, Preudhomme C, Coiteux V, Magro L, et al. Successful allogeneic hematopoietic stem cell transplantation in patients with VEXAS syndrome: a 2-center experience. Blood Adv 2022;6:998–1003.

Euvrard R, Fournier T, Georgescu D, Bourbon E, Sujobert P, Lega JC, et al. VEXAS syndrome-related AA amyloidosis: a case report. Rheumatology (Oxford) 2021;61:e15–6.

Fan BE, Cao L, Gallardo CA, Lee SMS, Koh LW, Goh LL, et al. Myeloid and lymphoid vacuolation in VEXAS syndrome. Am J Hematol 2021;96:1056–7.

Ferrada MA, Savic S, Cardona DO, Collins JC, Alessi H, Gutierrez-Rodrigues F, et al. Translation of cytoplasmic UBA1 contributes to VEXAS syndrome pathogenesis. Blood 2022;140:1496–506.

Ferrada MA, Sikora KA, Luo Y, Wells KV, Patel B, Groarke EM, et al. Somatic mutations in UBA1 define a distinct subset of relapsing polychondritis patients with VEXAS. Arthritis Rheumatol 2021;73:1886–95.

Georgin-Lavialle S, Terrier B, Guedon AF, Heiblig M, Comont T, Lazaro E, et al. Further characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients. Br J Dermatol 2022;186:564–74.

Goyal A, Narayanan D, Wong W, Laga AC, Connell NT, Ritter SY, et al. Tocilizumab for treatment of cutaneous and systemic manifestations of vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome without myelodysplastic syndrome. JAAD Case Rep 2022;23:15–9.

Grayson PC, Patel BA, Young NS. VEXAS syndrome. Blood 2021;137:3591–4.

Grey A, Cheong PL, Lee FJ, Abadir E, Favaloro J, Yang S, et al. A case of VEXAS syndrome complicated by hemophagocytic lymphohistiocytosis. J Clin Immunol 2021;41:1648–51.

Groarke EM, Dulau-Florea AE, Kanthi Y. Thrombotic manifestations of VEXAS syndrome. Semin Hematol 2021;58:230–8.

Hage-Sleiman M, Lalevée S, Guermouche H, Favale F, Chaquin M, Battistella M, et al. Dominance of an UBA1 mutant clone over a CALR mutant clone: from essential thrombocytemia to VEXAS. Haematologica 2021;106:3245–8.

Heiblig M, Ferrada MA, Koster MJ, Barba T, Gerfaud-Valentin M, Mékinian A, et al. Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study. Blood 2022;140:927–31.

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;8:002484.

Hines AS, Mohandesi NA, Lehman JS, Koster MJ, Cantwell HM, Alavi A, et al. Cutaneous involvement in VEXAS syndrome: clinical and histopathologic findings. Int J Dermatol 2023;62:938–45.

Islam S, Cullen T, Sumpton D, Damodaran A, Heath D, Bosco A, et al. VEXAS syndrome: lessons learnt from an early Australian case series. Intern Med J 2022;52:658–62.

Kao RL, Jacobsen AA, Billington CJ Jr, Yohe SL, Beckman AK, Vercellotti GM, et al. A case of VEXAS syndrome associated with EBV-associated hemophagocytic lymphohistiocytosis. Blood Cells Mol Dis 2022;93:102636.

Khitri MY, Guedon AF, Georgin-Lavialle S, Terrier B, Saadoun D, Seguier J, et al. Comparison between idiopathic and VEXAS-relapsing polychondritis: analysis of a French case series of 95 patients. RMD Open 2022;8.

Khosravi-Hafshejani T, O'Connor M, To F, Sreenivasan G, Shojania K, Au S. The spectrum of skin disease in VEXAS syndrome: a report of a novel clinico-histopathologic presentation. J Eur Acad Dermatol Venereol 2022;36:e435–7.

Kirino Y, Takase-Minegishi K, Tsuchida N, Hirahara L, Kunishita Y, Yoshimi R, et al. Tocilizumab in VEXAS relapsing polychondritis: a single-center pilot study in Japan. Ann Rheum Dis 2021;80:1501–2.

Koster MJ, Ghaffar U, Kermani TA, Patnaik MM, Go RS, Mangaonkar AA, et al. Antineutrophil cytoplasmic antibody-associated vasculitis and VEXAS syndrome: comment on the article by Muratore et al. Arthritis Rheumatol 2023;75:1490. –2.

Koster MJ, Kourelis T, Reichard KK, Kermani TA, Beck DB, Cardona DO, et al. Clinical heterogeneity of the VEXAS syndrome: a case series. Mayo Clin Proc 2021;96:2653–9.

Koster MJ, Warrington KJ. VEXAS within the spectrum of rheumatologic disease. Semin Hematol 2021;58:218–25.

Kunishita Y, Kirino Y, Tsuchida N, Maeda A, Sato Y, Takase-Minegishi K, et al. Case report: tocilizumab treatment for VEXAS syndrome with relapsing polychondritis: a single-center, 1-year longitudinal observational study in Japan. Front Immunol 2022;13:901063.

Lacombe V, Beucher A, Urbanski G, Le Corre Y, Cottin L, Croué A, et al. Distinction between clonal and paraclonal cutaneous involvements in VEXAS syndrome. Exp Hematol Oncol 2022;11:6.

Lacombe V, Kosmider O, Prévost M, Lavigne C, Urbanski G. Severe joint involvement in VEXAS syndrome: a case report. Ann Intern Med 2021a;174:1025–7.

Lacombe V, Prevost M, Bouvier A, Thépot S, Chabrun F, Kosmider O, et al. Vacuoles in neutrophil precursors in VEXAS syndrome: diagnostic performances and threshold. Br J Haematol 2021b;195:286–9.

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:e304–6.

Legeas C, Saucereau J, Saraux A, Schoenlaub P. VEXAS syndrome: a first case without any haematological abnormalities. Joint Bone Spine 2023;90:105473.

Loschi M, Roux C, Sudaka I, Ferrero-Vacher C, Marceau-Renaut A, Duployez N, et al. Allogeneic stem cell transplantation as a curative therapeutic approach for VEXAS syndrome: a case report. Bone Marrow Transplant 2022;57:315–8.

Lötscher F, Seitz L, Simeunovic H, Sarbu AC, Porret NA, Feldmeyer L, et al. Case report: genetic double strike: VEXAS and TET2-positive myelodysplastic syndrome in a patient with long-standing refractory autoinflammatory disease. Front Immunol 2021;12:800149.

Magnol M, Couvaras L, Degboé Y, Delabesse E, Bulai-Livideanu C, Ruyssen-Witrand A, 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:e314–5.

Mangaonkar AA, Langer KJ, Lasho TL, Finke C, Litzow MR, Hogan WJ, et al. Reduced intensity conditioning allogeneic hematopoietic stem cell transplantation in VEXAS syndrome: data from a prospective series of patients. Am J Hematol 2023;98:E28–31.

Martin-Nares E, Vargas-Serafín C, Delgado-de la Mora J, Montante-Montes de Oca D, Grayson PC, Larios E, et al. Orbital and periorbital inflammation in VEXAS syndrome. Scand J Rheumatol 2022;51:338–41.

Matsubara A, Tsuchida N, Sakurai M, Maeda A, Uchiyama Y, Sasaki K, et al. A case of VEXAS syndrome with Sweet's disease and pulmonary involvement. J Dermatol 2022;49:e177–8.

Matsuki Y, Kawai R, Suyama T, Katagiri K, Kanazawa N, Inaba Y. A case of VEXAS syndrome with myositis possibly associated with macrophage activation syndrome. J Dermatol 2022;49:e441–3.

Matsumoto H, Asano T, Tsuchida N, Maeda A, Yoshida S, Yokose K, et al. Behcet's disease with a somatic UBA1 variant:expanding spectrum of autoinflammatory phenotypes of VEXAS syndrome. Clin Immunol 2022;238:108996.

Mekinian A, Zhao LP, Chevret S, Desseaux K, Pascal L, Comont T, et al. A Phase II prospective trial of azacitidine in steroid-dependent or refractory systemic autoimmune/inflammatory disorders and VEXAS syndrome associated with MDS and CMML. Leukemia 2022;36:2739–42.

Mohammed TO, Alavi A, Aghazadeh N, Koster MJ, Olteanu H, Mangaonkar AA, et al. E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome: a presentation of two cases with dermatologic findings. Int J Dermatol 2023;62:e313–5.

Muratore F, Marvisi C, Castrignanò P, Nicoli D, Farnetti E, Bonanno O, et al. VEXAS syndrome: a case series from a single-center cohort of Italian patients with vasculitis. Arthritis Rheumatol 2022;74:665–70.

Neupane K, Jayarangaiah A, Zhang Y, Kumar A. VEXAS syndrome with progression of MDS to MDS/MPN overlap syndrome. BMJ Case Rep 2022;15.

Nguyen JK, Routledge D, van Der Weyden C, Blombery P, Angel CM, Johnson D, et al. VEXAS syndrome: a dermatological perspective. Australas J Dermatol 2022;63:488–92.

Obiorah IE, Patel BA, Groarke EM, Wang W, Trick M, Ombrello AK, et al. Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. Blood Adv 2021;5:3203–15.

Oganesyan A, Jachiet V, Chasset F, Hirsch P, Hage-Sleiman M, Fabiani B, et al. VEXAS syndrome: still expanding the clinical phenotype. Rheumatology (Oxford) 2021;60:e321–3.

Oo TM, JTJ Koay, Lee SF, Lee SMS, Lim XR, Fan BE. Thrombosis in VEXAS syndrome. J Thromb Thrombolysis 2022;53:965–70.

Pàmies A, Ferràs P, Bellaubí-Pallarés N, Giménez T, Raventós A, Colobran R. VEXAS syndrome: relapsing polychondritis and myelodysplastic syndrome with associated immunoglobulin A vasculitis. Rheumatology (Oxford) 2022;61:e69–71.

Pathmanathan K, Taylor E, Balendra J, Lim A, Carroll G. VEXAS syndrome: favourable clinical and partial haematological responses to subcutaneous abatacept therapy with 30-month follow-up. Rheumatology (Oxford) 2022;61:e174–7.

Poulter J, , UKGCA/VEXAS Consortium, Morgan A, Cargo C, Savic S. A high-throughput amplicon screen for somatic UBA1 variants in cytopenic and giant cell arteritis cohorts. J Clin Immunol 2022;42:947–51.

Poulter JA, Collins JC, Cargo C, De Tute RM, Evans P, Ospina Cardona D, et al. Novel somatic mutations in UBA1 as a cause of VEXAS syndrome. Blood 2021;137:3676–81.

Raaijmakers MHGP, Hermans M, Aalbers A, Rijken M, Dalm VASH, van Daele P, et al. Azacytidine treatment for VEXAS syndrome. Hemasphere 2021;5:e661.

Ribereau-Gayon E, Heiblig M, Bourbon E, Sujobert P, Harou O, Theillac C, et al. Atypical extensive lupus tumidus-like eruption as an early presentation of VEXAS syndrome. Int J Dermatol 2022;61:e89–91.

Ronsin C, Benard L, Mourtada A, Perrin F, Boukerroucha Z. Acute tubulointerstitial nephritis revealing VEXAS syndrome. Kidney Int 2022;101:1295–7.

Sakuma M, Tanimura A, Yasui S, Ishiguro K, Kobayashi T, Ohshiro Y, 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:e356–9.

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;6:134–9.

Shimizu T, Ide H, Tsuji Y, Koga T, Kawakami A. VEXAS syndrome complicated with severe infection. Rheumatology (Oxford) 2022;61:e374–6.

Skowron F, Klepfisch L, Guillaume L, Godeneche J, Facile A, Gombert M, et al. VEXAS syndrome following COVID-19 mRNA vaccination. J Eur Acad Dermatol Venereol 2023.

Staels F, Betrains A, Woei-A-Jin FJSH, Boeckx N, Beckers M, Bervoets A, et al. Case report: VEXAS syndrome: from mild symptoms to life-threatening macrophage activation syndrome. Front Immunol 2021;12:678927.

Sterling D, Duncan ME, Philippidou M, Salisbury JR, Kulasekararaj AG, Basu TN. VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) for the dermatologist. J Am Acad Dermatol 2022.

Stiburkova B, Pavelcova K, Belickova M, Magaziner SJ, Collins JC, Werner A, et al. Novel somatic UBA1 variant in a patient with VEXAS syndrome. Arthritis Rheumatol 2023;75:1285–90.

Stubbins RJ, McGinnis E, Johal B, Chen LY, Wilson L, Cardona DO, et al. VEXAS syndrome in a female patient with constitutional 45,X (Turner syndrome). Haematologica 2022;107:1011–3.

Takahashi N, Takeichi T, Nishida T, Sato J, Takahashi Y, Yamamura M, et al. Extensive multiple organ involvement in VEXAS syndrome. Arthritis Rheumatol 2021;73:1896–7.

Topilow JS, Ospina Cardona D, Beck DB, Ferrada MA, McMahan ZH, Paik JJ. Novel genetic mutation in myositis-variant of VEXAS syndrome. Rheumatology (Oxford) 2022;61:e371–3.

Tozaki N, Tawada C, Niwa H, Mizutani Y, Shu E, Kawase A, et al. A case of VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory,

somatic) with decreased oxidative stress levels after oral prednisone and tocilizumab treatment. Front Med (Lausanne) 2022;9:1046820.

Tsuchida N, Kunishita Y, Uchiyama Y, Kirino Y, Enaka M, Yamaguchi Y, et al. Pathogenic UBA1 variants associated with VEXAS syndrome in Japanese patients with relapsing polychondritis. Ann Rheum Dis 2021;80:1057–61.

Valor-Méndez L, Sticherling M, Zeschick M, Atreya R, Schmidt FD, Waldfahrer F, et al. VEXAS syndrome mimicking lupus-like disease. Rheumatology (Oxford) 2023;62:e271–2.

van der Made CI, Potjewijd J, Hoogstins A, Willems HPJ, Kwakernaak AJ, de Sevaux RGL, et al. Adult-onset autoinflammation caused by somatic mutations in UBA1: a Dutch case series of patients with VEXAS. J Allergy Clin Immunol 2022;149:432–9.e4.

van Leeuwen-Kerkhoff N, de Witte MA, Heijstek MW, Leavis HL. Case report: up-front allogeneic stem cell transplantation in a patient with the VEXAS syndrome. Br J Haematol 2022;199:e12–5.

Varadarajan A, Verghese RM, Tirlangi PK, Dass J, Soneja M, Seth T. VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic). Qjm 2023;116:313–5.

Vitale A, Caggiano V, Bimonte A, Caroni F, Tosi GM, Fabbiani A, et al. VEXAS syndrome: a new paradigm for adult-onset monogenic autoinflammatory diseases. Intern Emerg Med 2023;18:711–22.

Yamaguchi H, Kobayashi D, Nakamura G, Aida R, Horii Y, Okamoto T, et al. Acute heart failure due to left common iliac arteriovenous fistula: a case of VEXAS syndrome. Mod Rheumatol Case Rep 2023;7:327–33.

Yildirim F, Erdogan M, Yalcin Mutlu M, Akkuzu G, Ozgur DS, Karaalioglu B, et al. VEXAS syndrome with severe multisystem involvement: rapid recovery after splenectomy. Int J Rheum Dis 2023;26:559–62.

Ylmaz U, Güner S, Eşkazan T, Demiröz AS, Kurtuluş G, Bahar F, et al. Kikuchi Fujimoto disease as the presenting component of VEXAS syndrome: a case report of a probable association. Clin Rheumatol 2022;41:3589–92.

Yoon JG, Lee S, Kim S, Kim MJ, Chang YH, Park JK, et al. The first Korean case of VEXAS syndrome caused by a UBA1 somatic variant. Ann Lab Med 2023;43:217–20.

Zakine È, Papageorgiou L, Bourguiba R, Mekinian A, Terrier B, Kosmider O, et al. Clinical and pathological features of cutaneous manifestations in VEXAS syndrome: A multicenter retrospective study of 59 cases. J Am Acad Dermatol 2023;88:917–20.

Zakine E, Schell B, Battistella M, Vignon-Pennamen MD, Chasset F, Mahévas T, et al. UBA1 variations in neutrophilic dermatosis skin lesions of patients with VEXAS syndrome. JAMA Dermatol 2021;157:1349–54.

Zeisbrich M, Schindler V, Krausz M, Proietti M, Mrovecova P, Voll RE, et al. [Macrocytic anemia and polychondritis: VEXAS syndrome]. Z Rheumatol 2023.