Review

DOI: 10.5582/irdr.2023.01020

VEXAS syndrome: Current clinical, diagnostic and treatment approaches

Senol Kobak*

Department of Internal Medicine and Rheumatology, Istinye University Faculty of Medicine, Liv Hospital, WASOG Sarcoidosis Clinic, Istanbul,Turkey.

SUMMARY VEXAS syndrome, is a hemato-inflammatory chronic disease characterized with predominantly rheumatic and hematologic systemic involvement. It was first described in 2020 by a group of researchers in the United States. VEXAS syndrome is a rare condition that primarily affects adult males and is caused by a mutation in the UBA1 gene located on the X chromosome. Its pathogenesis is related to the somatic mutation affecting methionine-41 (p.Met41) in UBA1, the major E1 enzyme that initiates ubiquitylation. Mutant gene lead to decreased ubiquitination and activated innate immune pathways and systemic inflammation occur. The specific mechanism by which the UBA1 mutation leads to the clinical features of VEXAS syndrome is not yet fully understood. VEXAS is a newly define adult-onset inflammatory syndrome manifested with treatment-refractory fevers, arthritis, chondritis, vasculitis, cytopenias, typical vacuoles in hematopetic precursor cells, neutrophilic cutaneous and pulmonary inflammation. Diagnosing VEXAS syndrome can be challenging due to its rarity and the overlap of symptoms with other inflammatory conditions. Genetic testing to identify the UBA1 gene mutation is essential for definitive diagnosis. Currently, there is no known cure for VEXAS syndrome, and treatment mainly focuses on managing the symptoms. This may involve the use of anti-inflammatory medications, immunosuppressive drugs, and supportive therapies tailored to the individual patient's needs. Due to the recent discovery of VEXAS syndrome, ongoing research is being conducted to better understand its pathogenesis, clinical features, and potential treatment options. In this review article, the clinical, diagnostic and treatment approaches of VEXAS syndrome were evaluated in the light of the latest literature data.

Keywords VEXAS syndrome, clinical, diagnositc, treatment, approaches

1. Introduction

In December 2020, a revolutionary study was shared with scientific community, which sheds light on the pathogenesis of some diseases and has strong evidence of gene-disease relationship (*1*). Using a genotype-driven approach, the authors identified a disorder that connects seemingly unrelated adult-onset inflammatory syndromes, named the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome. The recurrent and acquired somatic mutations were found in UBA1, a gene encoding the ubiquitin-activating enzyme 1, which is necessary for the initiation of ubiquitylation (*2*). UBA1 is expressed as two isoforms (nuclear and cytoplasmic) differing in translation start site; nuclear UBA1a initiated at p.Met1 and cytoplasmic UBA1b initiated at p.Met41 (*3*). Ubiquitylation is a type of post-translational modification of proteins that is regulate the intracellular signaling and protein degradation through the proteasome or the autophagy-lysosome system (*4*). Loss of cytoplasmic UBA1 function and disruption of ubiquitylation process involving also myeloid lineage cells leading to uncontrolled inflammation resulting in a late-onset, treatment refractory inflammatory syndrome with associated hematologic abnormalities (*5*).

The possible role of various genes in the pathogenesis of rheumatological diseases has been investigated (*6*). As a result of genetic studies, monogenic (autoinflammatory) and/or polygenic (autoimmune) rheumatological diseases have been defined (*7*). Autoimmunity and autoinflammation were considered as "double-edged knife"; an one end of the "knife" are the various autoantibodies produced by B-cells and the other end are monogenic autoinflammatory diseases (*8*). Connective tissue diseases (ex. SLE) are the representative autoimmune diseases that depends on acquired immunity, whereas FMF are the representative of the autoinflammatory diseases in which the innate immunity

have important role (*9*). While the "borders" are so clearly have been drawn in rheumatology, some diseases have features belonging to both disease groups (*10*). With the definition of VEXAS syndrome, some "boundaries" in rheumatology knowledge have been crossed and the "walls" have been broken. This syndrome involving the clinical pictures of autoimmune and autoinflammatory diseases both opened new era in our knowledge.

Herein we review the genetic, immunological, clinical and treatment aspects of a newly defined VEXAS syndrome.

2. Focus on somatic mutations in rheumatology practice

It is well known that different genes play an important role in the pathogenesis of rheumatic diseases. Increased expression and/or gene polymorphisms of some genes have been shown to determine disease susceptibility, clinical course, and sometimes prognosis of the diseases (*11*). Rheumatological diseases can be polygenic and/or monogenic, and sometimes they can carry the characteristics of both groups (*12*). In general, the "borders are well drawn" in rheumatology and the diseases are well defined in terms of genetics. Autoimmune diseases are characterized by the synthesis of different B-lymphocyte-derived autoantibodies as a result of autoreactive T-cell activation triggered by an unknown antigen. It has been reported that many genes may be responsible for the pathogenesis of these diseases, not a single gene (*13*). It is well established that autoimmune diseases have common mechanisms and are caused by both genetic and non-genetic risk factors. One novel risk factor that can contribute to autoimmunity is somatic mutations, in a role parallel to their role in cancer (*14*). On the other hand, the development of autoinflammatory diseases has been described as a result of mutations in a single gene, the most striking example of which is FMF (*15*). Genetic mutations in the germline define an increasing list of heritable, monogenic autoinflammatory diseases that typically manifest early in life. In contrast to germline mutation, changes in DNA that occur after the first zygotic division are called somatic mutations (*16*).

Unlike germinal mutations, somatic mutations are genomic alterations that are not transmitted to offspring. Its may occur during life, from early embryogenesis through adulthood (*17*). Somatic mutations are usually restricted to specific tissue types, and may play a causal and important role in non-heritable rheumatological diseases, especially conditions that start in advanced stage of life (*18*). Using sequencing technology it is possible to detect somatic mutations in various tissue types, especially blood (*19*). While somatic mutations are well defined in malignant hematological diseases, its role in rheumatological diseases is not clearly yet (*20*). Although rare, some autoimune and autoinflammatory rheumatic diseases associated with somatic mutation have been described (Table 1).

Schnitzler syndrome is a rare adult-onset autoinflammatory disease characterized with chronic urticarial rash, recurrent fever, arthralgia or arthritis, monoclonal gammopathy of undetermined significance (MGUS), and marked systemic inflammation (*21*). The

Table 1. Somatic mutations in rheumatic diseases

Disease	Gene	Chromosome	Mechanism	Clinical findings	Treatment
VEXAS syndrome	UBA1	Chr. X	LOF	recurrent fever, polychondritis, vasculitis, arthritis, macrocytic anemia	CSs Tocilizumab JAKi Azacytidine ASCT
MDS/BD	NR	Crh.8	trisomy	oral/genital ulcers, rash, fever and intestinal involvement	DMARDs chemoterapeutic drugs
ECD	MAPK/BRAF	Crh.7	GOF	central diabetes insipidus, restrictive pericarditis, perinephric fibrosis, and sclerotic bone lesions	BRAF inhibitors
TRAPS	TNFRSF1A	Chr.12	GOF	recurrent fever; abdominal, chest, and muscle pain; red and swollen eyes; and a typical rash lasting for more than one week.	IL-1 blockers (ANK, CKM) TNFA inh.(ETN) IL-6 inh (TCZ)
NLRP3-AID	NLRP3	Chr. 1	GOF	fever, urticaria,arthritis sensorineural hearing loss, central nervous system involvement	IL-1 blockers (ANK, CKM)
ALPS	FAS	Chr. 10	LOF	lymphadenopathy and splenomegaly, hypergammaglobulinemia, haemolytic anaemia, idiopathic thrombocytopenia and neutropenia	CSs IS drugs splenectomy
Felty s/m	STAT 3	Chr .7	GOF	splenomegaly, anemia, neutropenia, thrombositopenia	DMARDs, splenectomy IL-1 blockers
Schnitzler syndrome	MYD88	Chr.1	GOF	chronic urticarial rash, recurrent fever, arthralgia or arthritis, monoclonal gammopathy of undetermined significance (MGUS)	(ANK, CKM)

AID: NLRP3-associated inflammatory disease; ALPS: autoimmune lymphoproliferative syndrome; ANK:anakinra; ASCT: allogeneic hematopoietic stem cell transplantation; CKM:canakinumab; CSs:corticosteroids; DMARDs:disease modifying anti-rheumatic drugs; ECD: Erdheim-Chester disease; ETN:etanercept; GOF: gain-of-function; IL-1:interleukine-1; JAKi: janus kinase inhibitors; LOF: loss-of-function; MAPK: mitogen activated protein kinase; MDS: myelodysplastic syndrome; NLRP3- TRAPS: tumour necrosis factor receptor-associated periodic syndrome; TCZ: tocilizumab; TNFA: tumor necrosis factor alpha; VEXAS: vacuoles, E1enzyme, X-linked, autoinflammatory, somatic.

inflammasome related IL-1 overproduction is a result of a somatic mosaic gain of function mutation of NLRP3 (nucleotide-binding oligomerization domain [NOD]-like receptor [NLR] family pyrin domain containing 3) gene. Somatic NLRP3 mosaicism was found also in patients with Schnitzler-like syndromes. Patients with IgGκ variant Schnitzler syndrome and severe clinical phenotype showed myeloid lineage restrict somatic NLRP3 mosaicism. Mutated NLRP3 gene (c.1906C >G p.Q636E) resulted in cell death in a monocyte cell line, and adaptor molecule apoptosis-associated speck-like protein containing a CARD (ASC)-dependent activation of nuclear factor (NF)-κB (*22*). This resulted in inflammasome activation and overproduction of predominantly IL-1 cytokine. There are report that some patients with Schnitzler syndrome have MYD88 gene somatic mutations, which is considered an independent risk factor for Waldenström's macroglobulinemia (WM) (*23*). That data may be useful to guide clinical monitoring since a significant proportion of patients with Schnitzler syndrome might develop lymphoproliferative malignancy.

The autoimmune lymphoproliferative syndrome (ALPS), which is the first identified non-malignant autoimmune disease caused by a somatic mutation, is characterized with persistent lymphadenopathy and splenomegaly, hypergammaglobulinemia, haemolytic anaemia, idiopathic thrombocytopenia and neutropenia (*24*). The cause of ALPS was found to be somatic FAS mutations in hematopoietic precursor stem cells, an accumulation of double-negative T cells, and hypergammaglobulinemia. Savola *et al.* reported somatic mutations in immune- related genes in mature expanded CD8+ T-cell populations in RA patients (*25*). They conclude that this mutations were associated with autoimmunity or cell survival. The same authors showed the somatic STAT3 mutations in Felty's syndrome shares molecular markers with large granular lymphocyte (LGL). The authors conclude that this findings provided molecular evidence for the hypothesis that Felty's syndrome and LGL leukemia are actually the same disease (*26*). Monogenic autoinflammatory diseases are group of familial and sporadic autosomal dominant diseases characterized by gain-of-function mutations in NLRP3, leading to increased inflammasome activity (*27*). Some NLRP3 mutations are closely related to disease severity, while other are associated with heterogeneous clinical presentations, due to various genetic or environmental factors. Sporadic NLRP3-AID may be due to de novo germline or acquired somatic mutations (*28*). While NLRP3 somatic mutations have mostly been described in childhood patients these mutations may also cause adult-onset disease. Using conventional Sanger sequencing, a large international study investigators identified that 30% of neonatal-onset multisystem inflammatory disorder (NOMID) cases are due to mosaicism (*29*). Sporadic NOMID clinical features is shown to be more aggressive and severe than familial form.

Erdheim-Chester disease (ECD) is a rare histiocytosis characterized with systemic inflammatory features involving skin, lung, aorta, bone, central nervous system and the retroperitoneum (*30*). Typical findings of ECD include central diabetes insipidus, restrictive pericarditis, perinephric fibrosis, and sclerotic bone lesions. Somatic mutations activating the MAPK pathway are found in more than 80% of patients with ECD, mainly the BRAF activating mutation, followed by MAP2K1 (*31*). Multisystem or refractory ECD patents have benefitted from highly effective therapy with BRAF and MEK inhibitors.

Recently the trisomy 8 mosaicism (T8m) was reported in patients with Behçet disease (BD). T8m has a highly variable phenotype, and it may also be associated with haematological disorders, such as MDS. It was reported that Behçet-T8m patients have mostly oral/genital ulcers, rash, fever and intestinal involvement (*32*). In recent years our knowledges about somatic mutations associated with various rheumatological diseases are increased. Somatic mutations seen in autoimmune and autoinflammatory diseases may also act as a "bridge" in terms of inflammation and malignancy development. The newly described VEXAS syndrome is not only a disease that culminates this relationship, but also a new beginning in this regard.

3. Genetic and immunological aspect of VEXAS syndrome

VEXAS syndrome is adult onset hematoinflammatory disease caused by somatic mutations in the gene UBA1, the majör E1 enzyme that initiates ubiquitylation. Ubiquitylation is a post-translational modification that triggers proteasomal degradation (*33*). It is essential for various cellular processes such as cell cycle progression, DNA damage response, and inflammatory signaling pathways (*34*). Dysregulation of the ubiquitin-proteasome system results in susceptibility to infection, lymphoproliferative disorders, autoinflammatory diseases and malignancy (*35*). Ubiquitylation is initiated by the attachment of a single ubiquitin molecule to a target protein through a three-step process performed by the concerted actions of ubiquitin activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and substrate specific ligases (E3). Ubiquitin-like modifier-activating enzyme 1 (UBA1), the major E1 enzyme, has two isoforms: UBA1a and UBA1b (*36*). UBA1a is the long isoform and is localized in the nucleus, whereas UBA1b is the short isoform and is localized in the cytoplasm without a nuclear localization signal.

The major cause of the VEXAS syndrome is a depletion of cytoplasmic UBA1 which resultant decreased ubiquitylation activates the unfolded protein response and type I interferon production (*37*). Increase

inflammation in the VEXAS syndrome is driven by mutant myeloid cells which can survive with this somatic mutation. Patients with VEXAS syndrome have highly activated inflammatory pathways including tumor necrosis factor, interleukin-6, and interferon-γ, which a finding that is consistent with severe myeloid inflammation (*38*). Activation of multiple cytokines cascades result in the elevated acute phase reactants (C-reactive protein and erythrocyte sedimentation rate) levels in the sera which is the characteristic laboratory findings in VEXAS patients (*39*). The changes were also seen in B-lymphocytes repertoar, atypical differentiation of B-cells with loss of immature B cells and increase of monocyte populations (*40*). This increase inflammatory responses in VEXAS syndrome may also aggravated by activation of neutrophils with preserved phagocytic activity and formation of neutrophil extracellular traps (NETs) (*41*).

4. Clinical features of VEXAS

VEXAS syndrome is an adult-onset inflammatory syndromes often manifest with overlapping rheumatologic and hematologic clinical features. Typically, this condition predominantly affects middle-aged and older men, occurring in the fifth and seventh decade of their lives. The exact prevalence of the syndrome in the population is still unknown. Initially, it was thought to be exclusive to males due to the involvement of the X chromosome (UBA1 gene). However, female cases with inherited or acquired monosomy of the X chromosome have also been reported (*42,43*).

VEXAS is a heterogeneous syndrome that can manifest with various hematological and rheumatic manifestations (*44*). The hematological features often include progressive abnormalities like macrocytic anemia, thrombocytopenia, myeloid dysplasia, and bone marrow vacuolization affecting myeloid and erythroid precursor cells (*45*). The most common clinical features comprise recurrent fever, arthralgia/arthritis, pulmonary involvement, skin lesions, various types of vasculitis, and/or thromboembolic events (*46*). From a rheumatologist's perspective, VEXAS syndrome can mimic known rheumatologic diseases or coexist with them (*47,48*) (Table 2). Since the recognition of this syndrome, many rheumatologists have reviewed their previous diagnoses. VEXAS can present with clinical findings seen in various rheumatological diseases, leading to misdiagnoses before its definition. Notably, patients previously diagnosed with vasculitis, connective tissue disease, and/or autoinflammatory disease were later identified to have VEXAS syndrome based on recent data (*49*). Interestingly, VEXAS patients may also partially meet established diagnostic or classification criteria for several known clinical conditions (*50*).

Given its heterogeneity, VEXAS syndrome exhibits a wide range of clinical findings. Numerous rheumatology centers have reported their cases since the disease's recognition (Table 3). In the first original VEXAS study by Beck *et al*. among 25 patients 18 (72%) had pulmonary involvement, 16 (64%) had ear and nose chondritis, four patients had vasculitis (3PAN, 1GCA) (*1*). Subgroups of participants met or partially met established diagnostic or classification criteria for a number of clinical conditions (ex. PAN, GCA, relapsing polychondritis). Coster *et al.* reported the clinical features and outcomes of 9 patients with VEXAS syndrome followed at Mayo Hospital (*51*). Vasculitis was observed in 4 patients (cutaneous, renal peritubular capillaritis, cryoglobulinemia and large vessel vasculitis involving abdominal aorta). Reccurent ear and nose chondritis was present in 5 of 9 patients; ocular inflammation was observed in 4 patients (2 with uveitis and 2 with episcleritis). All patients with ear and nose chondritis, ocular inflammation, and vasculitis had the p.Met41Thrn mutation. Ciferska *et al.* reported 3patients newly diagnosed as VEXAS syndrome in their rheumatology center (*52*). All 3 patients are elderly man, the median age of the patients are 72.6 years old. The patients have been diagnosed with a different rheumatic disease (1 seronegative RA, 1 relapsing polychondritis, 1 paraneoplastic s/m) before VEXAS diagnosis. All 3 patients expressed multiple inflammatory manifestations exceeding the typical clinical phenotypes associated with the referred rheumatic diagnoses, and all had additional haematological abnormalities. Khitri *et al.* compared the clinical characteristics, the laboratory features and the outcomes between idiopathic-relapsing polychondritis (I-RP) and VEXAS-relapsing polychondritis (VEXAS-RP) (*53*). They found that VEXAS-RP characterized by high prevalence of male sex, fever, skin lesion, ocular involvement, pulmonary infiltration, heart involvement, older age and hematological abnormality. Staels *et al.* reported two VEXAS patients; one characterized by recurrent rash and symmetric polyarthritis, and another who was initially diagnosed with idiopathic multicentric Castleman disease and developed macrophage activation syndrome as a complication of the VEXAS syndrome

Table 2. Rheumatic manifestations of VEXAS syndrome

Clinical Manifestations	Associated Conditions
Recurrent fever	Coexistance with:
Relapsing polychondritis	- Systemic lupus erythematosus
Polyarteritis nodosa	- Still disease
Giant cell arteritis	- Vasculitides
Arthralgia	- Relapsing polychondritis
Inflammatory asymetric mono/oligoarthritis	- Macrophage activation syndrome
Neutrophilic alveolitis	- Spondylarthritis
Venous thrombosis	- Hematological malignancy
Lymphadenopathy	
Scleritis/episcleritis/uveitis/retinal vasculitis	
Sweet syndrome	
AA amyloidosis	

Table 3. Published studies in the literature showed the main characteristics of patients with VEXAS syndrome

Features	Beck *et al.* *Ref (1)*	van der Made *et al.* *Ref (56)*	Muratore *et al.* *Ref (57)*	Khitri *et al.* *Ref (53)*	Ferrada *et al.* *Ref (60)*	Tsuchida *et al.* *Ref (59)*	Bourbon *et al.* *Ref (58)*	Ciferska *et al.* *Ref (52)*	Koster *et al.* *Ref (51)*
Gender (M/F), *n* (%)	25 (100%)	12 (100%)	7 (100%)	53 (96%)	13 (100%)	8 (100%)	11 (100%)	3 (100%)	9 (100%)
Median age at onset, years	64 (45–80)	67 (55–79)	64 (46–76)	66 (61–72)	62 (48–71)	72 (66–81)	66 (47–83)	74 (68–76)	70 (65–72.5)
Fever, *n* (%)	23 (92%)	11 (92%)	7 (100%)	33 (60%)	13 (100%)	6 (75%)	10 (91%)	1 (33%)	8 (88%)
Artralgia/Arthritis, *n* (%)	NR	4 (33%)	NR	36 (67%)	6 (46%)	2 (25%)	11 (100%)	1 (33%)	5 (55%)
Vasculitis, *n* (%)	4 (16%)	2 (16%)	7 (100%)	3 (6%)	NR	NR	7 (64%)	3 (100%)	4 (44%)
Eyes involvement, *n* (%)	NR	5 (42%)	NR	30 (57%)	NR	3 (38%)	5 (46%)	2 (67%)	4 (44%)
Skin involvement, *n* (%)	22 (88%)	10 (83%)	5 (71%)	44 (82%)	11 (85%)	7 (88%)	11 (100%)	3 (100%)	NR
Pulmonary, *n* (%)	18 (72%)	8 (67%)	6 (85%)	13 (46%)	10 (77%)	NR	5 (46%)	1 (33%)	NR
Chondritis, *n* (%)	16 (64%)	6 (50%)	1 (14%)	52 (98%)	13 (100%)	8 (100%)	5 (46%)	3 (100%)	5 (55%)
Hematologic, *n* (%)	macrocytic anaemia 24 (96%), MDS 6 (24%), MM or MGUS 5 (20%)	Macrocytic anemia 11 (%) MDS 6 (%)	Macrocytic anemia 6 (%)	MDS 41 (75%)	MDS 3 (23%) MGUS 1 (8%) MM 1 (8%)	macrocytic anaemia 7 (88%), MDS 4 (50%)	macrocytic anaemia 7 (64%), MDS 6 (54%)	macrocytic anaemia 2 (67%) MDS 1 (33%)	macrocytic anemia 9 (100%) MM 1 (%) MDS 1 (%)
UBA mutation, *n* (%)	p.Met41Thr 15 (60%) p.Met41Val 5 (20%) p.Met41Leu 5 (20%)	p.(Met41Thr), 12 (%)	p.Met41Thr	NR	p.Met41Thr 8 (62%) p.Met41Val 2 (15%) p.Met41Leu 3 (23%)	p.Met41Thr 3 (37.5%) p.Met41Val 2 (25%) p.Met41Leu 3 (37.5%)	p.Met41Thr 5 (46%) p.Met41Val 3 (27%) p.Met41Leu 1 (9%)	p.Met41Thr 2 (67%) p.Met41Leu 1 (33%)	p.Met41Thr 9 (100%)
CRP (median) (mg/L)	73 (18–128)	185 (61–407)	152 (41–250)	69 (30–107)	17.7 (9.6–99.5)	NR	114 (16.7-205)	73 (63-89)	NR
ESR (median) mm/h	97 (64–124)	111 (71–130)	94 (50–137)	NR	66.5 (42–110)	NR	NR	NR	NR

CRP:C-reactive protein; ESR: erythrocyte sedimentation rate; MDS: myelodysplastic syndrome; MGUS: monoclonal gammopathy of undetermined significance: UBA: ubiquitin-associated domain; NR:not reported.

(*54*). The latter patients was treated with anti-IL6 therapy (siltuximab) leading to a regression of systemic symptoms. Oganesyan *et al.* described the 76 years old male patients with recurrent fevers, joint inflammation, elevated levels of acute-phase reactants, macrocytic anaemia and skin lesions, who was diagnosed with VEXAS syndrome (*55*). The patient have been treated with anakinra (anti-IL1R antagonist) first, but did not result in any clinical or biological response. Prednisolone (1 mg/kg per day) was started and rapidly both clinical and biological complete remission within the week was done. Van der Made *et al*. reported 12 patients with VEXAS syndrome who had previously been registered as having unclassified autoinflammation (*56*). All patients were male and the median age were 67 years old (range 47–79 years). The patients presented with systemic symptoms, elevated inflammatory parameters, and multiorgan involvement. The newly reported features of VEXAS from this study included interstitial nephritis, cardiac involvement, stroke, and intestinal perforation related to treatment with tocilizumab. Despite different types of treatment were initiated, most patients became treatment-refractory, with a high mortality rate of 50%. Sharma *et al.* reported the coexistence of VEXAS syndrome and SLE in 70 years-old male (*47*). He was initiated on monthly intravenous immunoglobulin and clinical and laboratory regression was achieved. Recently Muratore *et al*. retrospectively evaluated the clinical records of 147 consecutive male patients followed up in their vasculitis clinic from 2013–2022. The authors identified seven patients (one with AAV) with vasculitis and concomitant features of VEXAS syndrome (*57*). Bourbon *et al.* identified 19 male patients with myeloid dysplasia and autoinflammatory disease such as relapsing polychondritis or Sweet syndrome. Among these 19 patients, 11 (57.9%) had a mutation of UBA1 gene (*58*). The median age at disease onset was 66 years (range, 47–83 years). As expected, most patients had fever (91%), skin involvement (100%), and arthritis or arthralgia (100%). All patients had an elevated serum concentrations of C-reactive protein, and most of them (64%) had macrocytic anemia. Tsuchida *et al.* reported the association of VEXAS syndrome and relapsing polychondritis (RP) in Japanese patients (*59*). UBA1 was examined in 13 of the 14 patients; 73% (8/11) of the male patients had somatic UBA1 variants. The authors concluded that genetic screening for pathogenic UBA1 variants should be considered in patients with RP, especially male patients with skin lesions. Ferrada *et al.* reported the prevalence of somatic mutations in UBA1 in patients cohort with RP (*60*). Seven of 92 patients with RP (7.6%) had UBA1 mutations (VEXAS-RP). Patients with VEXAS-RP were all male, were on average ≥ 45 years of age at disease onset, and commonly had fever, ear chondritis, skin involvement, deep vein thrombosis, and pulmonary infiltrates. Mortality was greater in VEXAS-RP than in RP (23% *vs.* 4%).

Table 4. Proposed algorithm to identify patients with VEXAS syndrome

Demographic	Clinical	Coexistence with	Laboratory Findings	Genetic Findings
Age: older age group	Unexplained recurrent fever	Relapsing polychondritis resistant to treatment and/or with a different clinical course	Increase serum cytokines (IL-1, IL-6, IL-17, TNF-alpha)	UBA1 mutation
Gender: predominantly male	Recurrent polychondritis (ear-nose)	Treatment-resistant vasculitis, which is beyond the classical knowledge	Unexplained very high CRP/ESR	
Population: Caucasian	Inflammatory arthritis: usually involving large joints of the lower extremities	Spondylarthritis or connective tissue diseases (ex. SLE)	Macrocytic anemia	
	Vasculitis: in the presence of simultaneous involvement of vessels of different diameters	Hematological malignancy (MDS) with signs of autoimmune disease	Presence of typical vacuoles in bone marrow biopsy	
	Eye involvement: treatment-resistant scleritis/episcleritis/retinal vasculitis			
	Severe, treatment-resistant skin lesions(inc. leucocytoclastic vasculitis and Sweet s/m)			
	Lung involvement, neutrophilic alveolitis			
	Kidney involvement, interstitial nephritis			

CRP:C-reactive protein; ESR:erythrocyte sedimentation rate; IL-1:interleukine-1; IL-6:interleukine-6; IL-17:interleukine-17; MDS: myelodisplastic syndrome; SLE:systemic lupus erythematosus;TNF-alpha:tumor necrosis factor-alpha; UBA1: Ubiquitin-like modifier-activating enzyme 1.

Georgin-Lavialle *et al.* reported the characteristics of one hundred and sixteen patients with VEXAS syndrome from a French multicentre registry between November 2020 and May 2021 (*61*). The main clinical features of VEXAS syndrome were found to be skin lesions (83%), noninfectious fever (64%), weight loss (62%), lung involvement (50%), ocular symptoms (39%), relapsing chondritis (36%), venous thrombosis (35%), lymph nodes (34%) and arthralgia (27%). The studies report that VEXAS syndrome may mimicking and/or coexist with any type of vasculitis (*62,63*). Watanabe *et al.* reviewed the literature data to delineate the clinical characteristics of vasculitis associated with VEXAS syndrome (*64*). The authors reported 23 patients with VEXAS-vasculitis. Among 23 patients, 2 (9%) had LVV, 9 (39%) had medium vessel vasculitis, and 12 (52%) had small vessel vasculitis. The median age of the patients were 66.4 years old (range 50–87). The AutoInflammatory Disease Alliance (AIDA) international Registry for VEXAS syndrome included 113 Centers from 23 Countries in 4 continents, is designed for the retrospective and prospective collection of real-life data (*65*). The aim of this registry is to collect the demographic, genetic, clinical, laboratory and treatment data starting since the disease. The rheumatology community awaits the results of this registry with impatience, curiosity and excitement.

In conclusion, rheumatologists should consider the possibility of VEXAS syndrome in the following situations: *i*) elderly men, particularly those in their fifth decade of life or older; *ii*) patients presenting with clinical features of adult-onset autoinflammation accompanied by multiorgan involvement including recurrent fever, skin inflammation, asymmetrical mono/oligoarthritis, relapsing polychondritis with pulmonary involvement, any type of vasculitis, and MDS-like features observed in peripheral blood (Table 4).

Moreover, it is essential to be aware that VEXAS patients often prove to be treatment-refractory, despite attempts with multiple drugs. Given the overlapping clinical features with other rheumatologic diseases, keeping VEXAS syndrome in mind will facilitate accurate diagnosis and appropriate management for these patients. Early recognition of VEXAS can help improve patient outcomes and quality of life by tailoring treatment strategies to address the unique challenges posed by this heterogeneous syndrome.

5. VEXAS syndrome: more questions than answers

VEXAS syndrome is a recently defined disease with several uncertainties and unknown aspects, making each new case report invaluable and significant in shaping future research. As more cases are reported, we gain insights into the heterogeneous and complex nature of VEXAS syndrome (*66*). Despite its seemingly benign appearance, VEXAS is a condition associated with high morbidity and mortality due to its involvement across multiple body systems (*67*). It serves as a "bridge" between autoimmunity, autoinflammation, and carcinogenesis, with the prognosis heavily influenced by hematological involvement and/or the development of malignancy. From a rheumatological standpoint, it is essential to re-evaluate older age patients for the possibility of VEXAS, even if they were previously diagnosed with vasculitis, autoinflammatory diseases, or recurrent polychondritis according to the ACR/EULAR classification criteria (*68*). Another unresolved area pertains to identifying risk factors that influence

the disease's course, prognosis, and the development of malignancy in VEXAS syndrome. It can manifest with mild symptoms or life-threatening clinical presentations. To pave the way for future randomized prospective studies on VEXAS, it is crucial to establish clear and defined diagnosis/classification criteria for the disease. This will enable the recognition of distinct disease phenotypes and, more importantly, the determination of treatment options and protocols. The advancement of new genetic methods, including next-generation sequencing, will not only aid in diagnosing VEXAS but also uncover numerous other rheumatological diseases associated with somatic mutations. This promising avenue of research holds the potential to revolutionize our understanding and management of various rheumatologic conditions.

6. Treatment

Currently, there are no established treatment protocols for this newly defined disease in the medical literature. As randomized controlled trials have not yet been conducted, the treatment of VEXAS syndrome is primarily based on the collective clinical experience gained from treating autoinflammatory diseases and the information available from recently reported VEXAS case series (*69,70*).

As mentioned earlier, VEXAS syndrome has shown resistance to multiple therapeutic agents, resulting in high mortality rates. The disease's complexity, involving multiple mechanisms, may contribute to its relative resistance to various target-specific anti-rheumatic agents, with the exception of systemic glucocorticoids (*71*). The one approach that has been considered based on the increased serum IL-6 levels and significantly elevated CRP levels observed in VEXAS patients is the use of tocilizumab. Tocilizumab may be considered as a drug of choice for some manifestations of the syndrome; however, it does not appear to alter the disease's progression (*72*). There are various report of tocilizumab use in patients with VEXAS syndrome. Goyal *et al.* reported the efficacy of tocilizumab for treatment of cutaneous and systemic manifestations of VEXAS syndrome (*73*). Despite treatment with methotrexate and mycophenolate mofetil, the patient remained dependent on high doses of systemic corticosteroids. Weekly injections of tocilizumab were initiated and daily oral prednisone was continued. At 6.month of tocilizumab treatment the patient complaints disappear almost totally. Kunishita *et al.* reported the efficacy and safety of tocilizumab (TCZ) and CSs in 3patients with VEXAS syndrome (*74*). One-years follow-up showed that the combination of TCZ and glucocorticoids allowed the patients to continue treatment for at least one year without significant disease progression. Glucocorticoids were able to be reduced from the start of TCZ. Indeed, Janus kinase inhibitors (JAKi) have shown promise as potential treatment options for VEXAS syndrome. JAK inhibitors work by blocking intracellular signaling pathways activated by cytokine receptors, leading to decreased gene activation and subsequent immune responses. Several studies and case reports have suggested that JAK inhibitors could be clinically effective in managing VEXAS (*75-78*). Heiblig *et al.* reported the efficacy of JAKi in 30 patients with VEXAS syndrome (*79*). The authors describe more significant treatment efficacy with the JAK1/2 inhibitor ruxolitinib compare with other JAKi. Rates of clinical remission favored ruxolitinib over other JAK inhibitors at 67% *vs.* 38% at month 1, 83% *vs.* 18% at month 3, and 87% *vs.* 11% at month 6. There was also a marked steroid dose reduction of 83.6% with ruxolitinib and 75% with other JAK inhibitors.

Indeed, in some patients with VEXAS syndrome, benefits from intravenous immunoglobulin (IVIG) administration have been reported. IVIG is a treatment approach that involves infusing a solution containing pooled immunoglobulins obtained from the plasma of healthy donors. It is known for its immunomodulatory and anti-inflammatory effects. Magnol *et al.* reported a case previously diagnosed with spondyloarthritis and VEXAS syndrome (*80*). Despite treatment with cDMARDS and bDMARDs(anti-TNF-inhibitor) and tDMARDS (baricitinib), the patients symptoms have been continued. Intravenous immunoglobuline and IL-17 inhibitor have been started and the patients complaints disappear. The treatment of VEXAS syndrome can be particularly challenging due to the varying clinical presentations and the limited response of certain manifestations to targeted therapies like biologic disease-modifying antirheumatic drugs (b/tDMARDs). While b/tDMARDs may show some efficacy in managing milder skin or rheumatic manifestations of the disease, they may not be as effective in addressing the hematological features associated with VEXAS. One such approach that has shown promise in some cases is the use of azacytidine, a hypomethylating agent. Azacytidine is commonly used in the treatment of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) and has demonstrated potential in managing VEXAS-related hematological abnormalities (*81-83*). Based on a French nationwide registry of 116 patients with VEXAS, Comont *et al.* report the efficacy and safety of azacitidine in 11 patients with VEXAS concomitant with MDS (*84*). Clinical response of VEXAS to azacitidine was achieved in five patients (46%), suggesting that azacitidine can be effective in selected patients with VEXAS and associated MDS. For severe cases of VEXAS syndrome with widespread multi-systemic involvement, including severe hematological abnormalities, bone marrow transplantation may be considered as a curative therapeutic option (*85*). Diarra *et al.* reported successful allogeneic hematopoietic stem cell transplantation(ASCT) in 4patients with VEXAS syndrome (*86*). Three patients are in durable complete remission after ASCT. One unfortunately

died post-ASCT. The authors suggest that ASCT could be a curative option in patients with VEXAS syndrome and severe manifestations. Given the lack of established treatment guidelines, managing VEXAS syndrome remains a significant challenge for healthcare professionals. Continued research, case reports, and clinical experience will be critical in shaping the development of effective treatment strategies to improve the prognosis and quality of life for individuals affected by this complex and potentially life-threatening condition.

7. Conclusions

It is clear that somatic mutations in rheumatic diseases are more likely to have more severe functional effects than germinal mutations, since they do not undergo purifying selection of the whole organism.

VEXAS syndrome, which is caused by myeloid-restricted somatic missense mutations in UBA1, may cause severe inflammatory conditions that manifest in adulthood. The presence of recurrent fever, relapsing polychondritis, arthritis, vasculitis, macrocytic anemia, elderly male, and symptoms refractory to traditional steroid-sparing agents should prompt rheumatologists to consider VEXAS as a possible diagnosis. The treatment of VEXAS syndrome is not known yet, the beneficial role of corticosteroids, b/tDMARDs (tocilizumab, JAKi)), various chemotherapeutics (azacytidine) and bone marrow transplantion has been reported. More genetic studies and close collaboration between hematologists and rheumatologists are needed to identify and characterize the clinical phenotypes and treatment approaches of VEXAS syndrome.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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; 383:2628-2638.
2. Poulter JA, Collins JC, Cargo C, De Tute RM, Evans P, Ospina Cardona D, Bowen DT, Cunnington JR, Baguley E, Quinn M, Green M, McGonagle D, Beck DB, Werner A, Savic S. Novel somatic mutations in UBA1 as a cause of VEXAS syndrome. Blood. 2021; 137:3676-3681.
3. Komander D, Rape M. The ubiquitin code. Annu Rev Biochem. 2012; 81:203-229.
4. Beck DB, Werner A, Kastner DL, Aksentijevich I. Disorders of ubiquitylation: Unchained inflammation. Nat Rev Rheumatol. 2022; 18:435-447.
5. Craney A, Rape M. Dynamic regulation of ubiquitin-dependent cell cycle control. Curr Opin Cell Biol. 2013; 25:704-710.
6. Gerussi A, Soskic B, Asselta R, Invernizzi P, Gershwin ME. GWAS and autoimmunity: What have we learned and what next. J Autoimmun. 2022; 133:102922.
7. Gaggiano C, Vitale A, Tufan A, *et al.* The autoinflammatory diseases alliance registry of monogenic autoinflammatory diseases. Front Med (Lausanne). 2022; 9:980679.
8. Hocking AM, Buckner JH. Genetic basis of defects in immune tolerance underlying the development of autoimmunity. Front Immunol. 2022; 13:972121.
9. Efthimiou P, Petryna O, Nakasato P, Kontzias A. New insights on multigenic autoinflammatory diseases. Ther Adv Musculoskelet Dis. 2022; 14:1759720X221117880.
10. MacLauchlan S, Fitzgerald KA, Gravallese EM. intracellular sensing of DNA in autoinflammation and autoimmunity. Arthritis Rheumatol. 2022; 74:1615-1624.
11. Mikhaylenko DS, Nemtsova MV, Bure IV, *et al.* Genetic polymorphisms associated with rheumatoidarthritis development and antirheumatic therapy response. Int J Mol Sci. 2020; 21:4911.
12. Ishigaki K. Beyond GWAS: From simple associations to functional insights. Semin Immunopathol. 2022; 44:3-14.
13. Reed JH. Transforming mutations in the development of pathogenic B cell clones and autoantibodies. Immunol Rev. 2022; 307:101-115.
14. Rosen A. Immunoediting in autoimmune rheumatic diseases. Trans Am Clin Climatol Assoc. 2022; 132:34-43.
15. Ozen S. Update in Familial Mediterranean fever. Curr Opin Rheumatol. 2021; 33:398-402.
16. Ren P, Dong X, Vijg J. Age-related somatic mutation burden in human tissues. Front Aging. 2022; 3:1018119.
17. Evans MA, Walsh K. Clonal hematopoiesis, somatic mosaicism, and age-associated disease. Physiol Rev. 2023; 103:649-716.
18. Abbasi A, Alexandrov LB. Significance and limitations of the use of next-generation sequencing technologies for detecting mutational signatures. DNA Repair (Amst). 2021; 07:103200.
19. Gniadecki R, Iyer A, Hennessey D, Khan L, O'Keefe S, Redmond D, Storek J, Durand C, Cohen-Tervaert JW, Osman M. Genomic instability in early systemic sclerosis. J Autoimmun. 2022; 131:102847.
20. Gaulin C, Kelemen K, Arana Yi C. Molecular pathways in clonal hematopoiesisfrom the acquisition of somatic mutations to transformation into hematologic neoplasm. Life (Basel). 2022; 12:1135.
21. Gusdorf L, Lipsker D. Schnitzler syndrome: a review. Curr Rheumatol Rep. 2017; 19:46.
22. de Koning HD. Schnitzler's syndrome: lessons from 281 cases. Clin Transl Allergy. 2014; 4:41.
23. Treon SP, Xu L, Yang G *et al.* MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med. 2012; 367:826-833.
24. Del-Rey M, Ruiz-Contreras J, Bosque A, Calleja S, Gomez-Rial J, Roldan E, Morales P, Serrano A, Anel A, Paz-Artal E, Allende LM. A homozygous Fas ligand gene mutation in a patient causes a new type of autoimmune lymphoproliferative syndrome. Blood. 2006; 108:1306-1312.
25. Savola P, Kelkka T, Rajala H, *et al.* Somatic mutations in clonally expanded cytotoxic T lymphocytes in patients with newly diagnosed rheumatoid arthritis. Nat Commun. 2017; 8:15869.
26. Savola P, Brück O, Olson T, Kelkka T, Kauppi MJ, Kovanen PE, Kytölä S, Sokka-Isler T, Loughran TP, Leirisalo-Repo M, Mustjoki S. Somatic *STAT3* mutations

in Felty syndrome: an implication for a common pathogenesis with large granular lymphocyte leukemia. Haematologica. 2018; 103:304-312.
27. Papa R, Caorsi R, Volpi S, Gattorno M. New monogenic autoinflammatory diseases: 2021 year in review. Immunol Lett. 2022; 248:96-98.
28. Louvrier C, Assrawi E, El Khouri E. NLRP3- associated autoinflammatory diseases: henotypic and molecular characteristics of germline versus somatic mutations. J Allergy Clin Immunol. 2020; 145:1254-1261.
29. Omoyinmi E, Melo Gomes S, Standing A. Brief report: Whole-exome sequencing revealing somatic NLRP3 mosaicism in a patient with chronic infantile neurologic, cutaneous, articular syndrome. Arthritis Rheumatol. 2014; 66:197-202.
30. Alcedo PE, Gutierrez-Rodrigues F, Patel BA. Somatic mutations in VEXAS Syndrome and Erdheim-Chester disease: Inflammatory myeloid diseases. Semin Hematol. 2022; 59:156-166.
31. Abla O, Weitzman S. Treatment of Langerhans cell histiocytosis: Role of BRAF/MAPK inhibition. Hematology Am Soc Hematol Educ Program. 2015; 2015:565-570.
32. Ogawa H, Kuroda T, Inada M, Yamamoto M, Enomoto H, Kishima Y, Yoshida K, Ito H, Ogawa H, Nakamura H. Intestinal Behçet's disease associated with myelodysplastic syndrome with chromosomal trisomy 8--a report of two cases and a review of the literature. Hepatogastroenterology. 2001; 48:416-420.
33. Oh E, Akopian D, Rape M. Principles of ubiquitin-dependent signaling. Annu Rev Cell Dev Biol. 2018; 34:137-162.
34. Rape M. Ubiquitylation at the crossroads of development and disease. Nat Rev Mol Cell Biol. 2018; 19:59-70.
35. Aksentijevich I, Zhou Q. NF-kappaB pathway in autoinflammatory diseases: dysregulation of protein modifications by ubiquitin defines a new category of autoinflammatory diseases. Front Immunol. 2017; 8:399.
36. Schulman BA, Harper JW. Ubiquitin-like protein activation by E1 enzymes: The apex for downstream signalling pathways. Nat Rev Mol Cell Biol. 2009; 10:319-331.
37. Lacombe V, Prevost M, Bouvier A, Thépot S, Chabrun F, Kosmider O, Lacout C, Beucher A, Lavigne C, Geneviève F, Urbanski G. Vacuoles in neutrophil precursors in VEXAS syndrome: diagnostic performances and threshold. Br J Haematol. 2021; 195:286-289.
38. Arlet JB, Terrier B, Kosmider O. Mutant UBA1 and severe adult-onset autoinflammatory disease. N Engl J Med. 2021; 384:2163.
39. Grayson PC, Patel BA, Young NS. VEXAS syndrome. Blood. 2021; 137:3591-3594.
40. Huang H, Zhang W, Cai W, Liu J, Wang H, Qin T, Xu Z, Li B, Qu S, Pan L, Huang G, Gale RP, Xiao Z. VEXAS syndrome in myelodysplastic syndrome with autoimmune disorder. Exp Hematol Oncol. 2021; 10: 23.
41. Stubbins RJ. Lost in translation: Cytoplasmic UBA1 and VEXAS syndrome. Blood. 2022; 140:1455-1457.
42. Stubbins RJ, McGinnis E, Johal B, Chen LY, Wilson L, Cardona DO, Nevill TJ. VEXAS syndrome in a female patient with constitutional 45,X (Turner syndrome). Haematologica. 2022; 107:1011-1013.
43. Barba T, Jamilloux Y, Durel CA, Bourbon E, Mestrallet F, Sujobert P, Hot A. VEXAS syndrome in a woman. Rheumatology (Oxford). 2021; 60:e402-e403.
44. Grayson PC, Beck DB, Ferrada MA, Nigrovic PA, Kastner DL. VEXAS syndrome and disease taxonomy in rheumatology. Arthritis Rheumatol. 2022; 74:1733-1736.
45. D'Angelo G. Hematopoietic cells vacuolation, not always a reactive event. The VEXAS syndrome. Int J Lab Hematol. 2023; 45:e15-e16.
46. Uchino K, Kanasugi J, Enomoto M, Kitamura F, Tsuchida N, Uchiyama Y, Maeda A, Kirino Y, Matsumoto N, Takami A. VEXAS syndrome. Int J Hematol. 2022; 116:463-464.
47. Sharma A, Naidu G, Deo P, Beck DB. VEXAS syndrome with systemic lupus erythematosus: Expanding the spectrum of associated conditions. Arthritis Rheumatol. 2022; 74:369-371.
48. Delplanque M, Aouba A, Hirsch P, *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; 10:5586.
49. Oganesyan A, Jachiet V, Chasset F, Hirsch P, Hage-Sleiman M, Fabiani B, Duriez P, Georgin-Lavialle S, Delhommeau F, Hakobyan Y, Fain O, Mekinian A; on behalf MINHEMON. VEXAS syndrome: Still expanding the clinical phenotype. Rheumatology (Oxford). 2021; 60:e321-e323.
50. Pyo JY, Ahn SS, Song JJ, Park YB, Lee SW. The reclassification of patients with previously diagnosed eosinophilic granulomatosis with polyangiitis based on the 2022 ACR/EULAR criteria for ANCA-associated vasculitis. J Rheumatol. 2023; 50:213-218.
51. Koster MJ, Kourelis T, Reichard KK, *et al.* Clinical heterogeneity of the VEXAS syndrome: A case series. Mayo Clin Proc. 2021; 96:2653-2659.
52. Ciferska H, Gregová M, Klein M, Šenolt L, Soukupová Maaloufová J, Pavelka K, Mann H. VEXAS syndrome: A report of three cases. Clin Exp Rheumatol. 2022; 40:1449.
53. Khitri MY, Guedon AF, Georgin-Lavialle S, *et al*. French VEXAS group and MINHEMON. Comparison between idiopathic and VEXAS-relapsing polychondritis: Analysis of a French case series of 95 patients. RMD Open. 2022; 8:e002255.
54. Staels F, Betrains A, Woei-A-Jin FJSH, Boeckx N, Beckers M, Bervoets A, Willemsen M, Neerinckx B, Humblet-Baron S, Blockmans DE, Vanderschueren S, Schrijvers R. Case report: VEXAS syndrome: From mild symptoms to life-threatening macrophage activation syndrome. Front Immunol. 2021; 12:678927.
55. Oganesyan A, Hakobyan Y, Terrier B, Georgin-Lavialle S, Mekinian A. Looking beyond VEXAS: Coexistence of undifferentiated systemic autoinflammatory disease and myelodysplastic syndrome. Semin Hematol. 2021; 58:247-253.
56. 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; 149:432-439.e4.
57. Muratore F, Marvisi C, Castrignanò P, Nicoli D, Farnetti E, Bonanno O, Longo R, Zaldini P, Galli E, Balanda N, Beck DB, Grayson PC, Pipitone N, Boiardi L, Salvarani C. VEXAS syndrome: A case series from a single-center cohort of Italian patients with vasculitis. Arthritis Rheumatol. 2022; 74:665-670.
58. Bourbon E, Heiblig M, Gerfaud Valentin M, Barba T, Durel CA, Lega JC, Barraco F, Sève P, Jamilloux Y, Sujobert P. Therapeutic options in VEXAS syndrome: insights from a retrospective series. Blood. 2021; 137:3682-3684.
59. Tsuchida N, Kunishita Y, Uchiyama Y, Kirino Y, Enaka M, Yamaguchi Y, Taguri M, Yamanaka S, Takase-Minegishi K,

Yoshimi R, Fujii S, Nakajima H, Matsumoto N. Pathogenic *UBA1*variants associated with VEXAS syndrome in Japanese patients with relapsing polychondritis. Ann Rheum Dis. 2021; 80:1057-1061.
60. Ferrada MA, Savic S, Cardona DO, *et al.* Translation of cytoplasmic UBA1 contributes to VEXAS syndrome pathogenesis. Blood. 2022; 140:1496-1506.
61. Georgin-Lavialle S, Terrier B, Guedon AF, *et al.* French VEXAS group; GFEV, GFM, CEREMAIA, MINHEMON. 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; 186:564-574.
62. Itagane M, Teruya H, Kato T, Tsuchida N, Maeda A, Kirino Y, Uchiyama Y, Matsumoto N, Kinjo M. Clinical images: VEXAS syndrome presenting as treatment-refractory polyarteritis nodosa. Arthritis Rheumatol. 2022; 74:1863-1864.
63. Matsumoto H, Asano T, Tsuchida N, *et al.* Behçet's disease with a somatic UBA1 variant:Expanding spectrum of autoinflammatory phenotypes of VEXAS syndrome. Clin Immunol. 2022; 238:108996.
64. Watanabe R, Kiji M, Hashimoto M. Vasculitis associated with VEXAS syndrome: A literature review. Front Med (Lausanne). 2022; 9:983939.
65. Vitale A, Caggiano V, Della Casa F, *et al.* Development and implementation of the AIDA international registry for patients with VEXAS syndrome. Front Med (Lausanne). 2022; 9:926500.
66. 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-e373.
67. Vergneault H, Picard C, Georgin-Lavialle S. Break down the barriers of auto-inflammation: How to deal with a monogenic auto-inflammatory disease and immuno-haematological features in 2022? Immunology. 2023; 168:1-17.
68. Lacombe V, Kosmider O, Prévost M, Lavigne C, Urbanski G. Severe joint involvement in VEXAS syndrome: A case report. Ann Intern Med. 2021; 174:1025-1027.
69. McHugh J. Pathogenic UBA1 variants define a subset of relapsing polychondritis. Nat Rev Rheumatol. 2021; 17:312.
70. Luzzatto L, Risitano AM, Notaro R. Mutant UBA1 and severe adult-onset autoinflammatory disease. N Engl J Med. 2021; 384:2164.
71. Zakine E, Schell B, Battistella M, *et al.* UBA1 Variations in neutrophilic dermatosis skin lesions of patients with VEXAS syndrome. JAMA Dermatol. 2021; 157:1349-1354.
72. Kirino Y, Takase-Minegishi K, Tsuchida N, Hirahara L, Kunishita Y, Yoshimi R, Nakajima H. Tocilizumab in VEXAS relapsing polychondritis: A single-center pilot study in Japan. Ann Rheum Dis. 2021; 80:1501-1502.
73. Goyal A, Narayanan D, Wong W, Laga AC, Connell NT, Ritter SY, Cobos G. 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; 23:15-19.
74. Kunishita Y, Kirino Y, Tsuchida N, Maeda A, Sato Y, Takase-Minegishi K, Yoshimi R, Nakajima H. 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.
75. Guilpain P. JAK inhibitors in autoinflammatory syndromes? The long road from drug development to daily clinical use. Rheumatology (Oxford). 2023; 62:1368-1369.
76. Heiblig M, Patel BA, Groarke EM, Bourbon E, Sujobert P. Toward a pathophysiology inspired treatment of VEXAS syndrome. Semin Hematol. 2021; 58:239-246.
77. Fu Y, Wu W, Chen Z, Gu L, Wang X, Ye S. Trisomy 8 associated clonal cytopenia featured with acquired auto-inflammation and its response to JAK inhibitors. Front Med (Lausanne). 2022; 9:895965.
78. Conway R. Ruxolitinib takes center stage for VEXAS syndrome. Blood. 2022; 140:807-808.
79. Heiblig M, Ferrada MA, Koster MJ, *et al.* Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: A retrospective multicenter study. Blood. 2022; 140:927-931.
80. Magnol M, Couvaras L, Degboé Y, Delabesse E, Bulai-Livideanu C, Ruyssen-Witrand A, Constantin A. VEXAS syndrome in a patient with previous spondyloarthritis with a favourable response to intravenous immunoglobulin and anti-IL17 therapy. Rheumatology (Oxford). 2021; 60:e314-e315.
81. Cordts I, Hecker JS, Gauck D, Park J, Härtl J, Günthner R, Hammitzsch A, Schoser B, Abeck D, Götze KS, Haack TB, Deschauer M, Moog P, Hemmer B. Successful treatment with azacitidine in VEXAS syndrome with prominent myofasciitis. Rheumatology (Oxford). 2022; 61:e117-e119.
82. Raaijmakers MHGP, Hermans M, Aalbers A, Rijken M, Dalm VASH, van Daele P, Valk PJM. Azacytidine treatment for VEXAS syndrome. Hemasphere. 2021; 5:e661.
83. Manzoni M, Bosi A, Fabris S, *et al.* Clinical, morphological and clonal progression of VEXAS syndrome in the context of myelodysplasia treated with azacytidine. Clin Hematol Int. 2022; 4:52-55.
84. Comont T, Heiblig M, Rivière E, *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; 196:969-974.
85. Al-Hakim A, Poulter JA, Mahmoud D, Rose AMS, Elcombe S, Lachmann H, Cargo C, Duncan CJA, Bishton M, Bigley V, Khan A, Savic S. Allogeneic haematopoietic stem cell transplantation for VEXAS syndrome: UK experience. Br J Haematol. 2022; 199:777-781.
86. Diarra A, Duployez N, Fournier E, *et al.* Successful allogeneic hematopoietic stem cell transplantation in patients with VEXAS syndrome: A 2-center experience. Blood Adv. 2022; 6:998-1003.

Received March 1, 2023; Revised July 30, 2023; Accepted August 15, 2023.

**Address correspondence to:*
Senol Kobak, Department of Internal Medicine and Rheumatology, Istinye University Faculty of Medicine, Liv Hospital, WASOG Sarcoidosis Clinic, Canan sokak No:5 Istanbul, Turkey.
E-mail: senolkobak@yahoo.com

Released online in J-STAGE as advance publication August 18, 2023.