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Review

VEXAS Syndrome – at Crossroads of Immunity and Mutation

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ABSTRACT

The newly identified refractory adult-onset autoinflammatory syndrome known as VEXAS (Vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic) is brought on by somatic mutations in the ubiquitin-like modifier-activating enzyme 1 (UBA1) gene in hematopoietic stem and progenitor cells that change the expression of the UBA1 isoform. As a result, patients have a variety of hematologic and systemic inflammatory symptoms. Except for high-dose glucocorticoids, patients currently respond poorly to immune suppressive medications, and no clear treatment guidelines exist. All medical disciplines need to treat patients with VEXAS syndrome seriously because of the high fatality rate. To better understand the targeted therapy and enhance the prognosis of VEXAS syndrome, this article seeks to discuss the essential characteristics, pathophysiology, and clinical symptoms of VEXAS syndrome.

KEYWORDS: Mutation, UBA1, Myelodysplastic syndrome. Thrombosis, Vasculitis, Vacuoles, Auto inflammation

INTRODUCTION

In the year 2020, 25 men were identified as having somatic mutations in UBA1 enzyme – specifically of Methionine–41strain. UBA1 is known to initiate the process of ubiquitylation in X chromosome. Described in the study, these patients were susceptible to developing a severe inflammatory condition in late adulthood with features such as vacuolated myeloid and erythroid precursor cells, cytopenia, pyrexia, myelodysplastic syndrome, vasculitis etc. Majority of these patients fulfilled the criteria for an inflammatory condition and/or a haematological derangement. These patients were driven through a genotypic analysis and the authors cemented a strong connection between these unrelated adult – onset inflammatory syndromes. The disease was termed as VEXAS Syndrome. VEXAS stands for – Vacuoles, E1 Enzyme, X–Linked autoinflammatory, somatic). All VEXAS cases were diagnosed to be having acquired somatic mutations in UBA1 gene[1].

There is substantially growing evidence in VEXAS syndrome, mainly because of a new interaction between marrow progenitors leading to systemic autoinflammation, and also the fact that the increasing prevalence of the condition is seemingly unparalleled for a novel diagnosis, especially in such a short period of time[2]. At current time the registry of Autoinflammatory Disease Alliance (AIDA) has identified VEXAS syndrome already[3].

EPIDEMIOLOGICAL CONSIDERATIONS

Estimation of considerable accuracy for prevalence of VEXAS syndrome is still in early stages of development. Beck *et al.*[4] estimated the prevalence of Pathognomic variants of UBA1 mutations. In his study, 11 participants developed the VEXAS specific somatic mutations of UBA1 gene out of 163,096 total study population. This gives a prevalence of 1:14,000 with male predominance. Newer and newer studies are proving the disease to be much more prevalent than previously thought of[5].

There is strong association with chromosome X as the mutation site for the disease. Male gender have a much higher percentage of developing the disease, especially of above 50 years of age[4].

A chromosome X genetic mutation is linked to the syndrome. It is obvious that men are more likely than women to have this autoinflammatory disease. Patients over 50 years old frequently have overt clinical symptoms of the condition. There haven't been many reports of female cases. In female patients, monosomy X, Turner syndrome, or somatic mosaicism are the causes of the condition[4].

The current state of research denotes that there are also newer variants of the mutation where there are instances of UB1 negative VEXAS mimicking disorders. Deep sequencing will be used to investigate sporadic, VEXAS-like cases using DNA collected from multiple cellular or tissue locations. To determine the best supportive and therapeutic alternatives for patients with different illness severity and prognosis, prospective studies are required. Also needed are VEXAS-specific hematopoietic stem cell transplant selection criteria[6].

Interestingly, none of the suggested typical inflammatory signs of VEXAS, such as Sweet's syndrome, RP, or PAN, had ever been associated with a patient. However, compared to the initial group, there was a comparable rate of pulmonary and haematological involvement. This was a groundbreaking discovery that demonstrated how the mutation might be acquired before the onset of clinical disease and confirmed the strong penetrance of the mutations[7].

According to the article, VEXAS prevalence is comparable to that of MDS (1 in 14,000) and Behcet disease (1 in 10,000), which offers a useful comparison when examining clinically complex cases[7,8,9].

A wider group of patients with clinical symptoms similar to those of the original three patients was found through further research and examination of different cohorts, and the illness was subsequently recognised as a brand-new clinical entity[2]. Since its discovery, more than 165 papers have been published that discuss the VEXAS syndrome, and numerous new instances have also been documented.

EPONYMOUS EXPLANATION

The term VEXAS is an acronym short for the terms

V → Vacuoles (Primarily based from myeloid precursors)

E → E1 Enzyme

X → X-Linked

A → Autoinflammatory

S → Somatic

The basis of the eponym formation is varied and consists of complex explanations, however we have tried to summarise them.

Vacuoles – The Characteristic Feature

Nearly all VEXAS syndrome patients exhibit the recognisable vacuolation of myeloid and erythroid progenitors on bone marrow samples. Eosinophils, monocytes, megakaryocytes, and plasma cells can also occasionally have vacuoles, although mature lymphocytes and fibroblasts typically don't, which may be connected to the location of the UBA1 somatic mutation. It is possible that the absence of vacuoles in the bone marrow smears of two individuals with atypical UBA1 splice site mutations does not rule out the diagnosis of VEXAS syndrome, though[1,10,11].

Therefore, when vacuolation of hematopoietic precursor cells is observed in patients, particularly in older men with systemic inflammatory manifestations, the UBA1 mutation should be further evaluated to aid in the diagnosis of VEXAS syndrome at the same time that other potential causes of vacuolation have been ruled out. Uncertainty exists regarding the Vacuolar contents and the mechanism of cell vacuolation in VEXAS syndrome patients[12].

The E1 Enzyme – UBA1 Gene

The ubiquitin-activating enzyme (E1 enzyme), which is essential for cellular ubiquitylation, is encoded by the UBA1 gene. The process of ubiquitination, which uses the enzymes ubiquitin-activating (E1), conjugating (E2), and ligating (E3) in succession, is used to degrade misfolded proteins. Numerous biological functions, including cell cycle progression, the response to DNA damage, and immunological signalling pathways, depend on ubiquitylation[13].

The X-Linked Inheritance

UBA1 can avoid X chromosome inactivation because it is situated on the X chromosome (Xp11.3). The fact that elderly men are more likely to develop VEXAS syndrome suggests that women may be shielded by the unmutated allele[14,15]. However, a small number of female individuals with acquired X chromosomal monosomy or X chromosome structural deletion have been documented[16,17].

The Autoimmunity of VEXAS Syndrome

Uncertainty exists regarding the mechanism by which UBA1 abnormalities cause a variety of autoinflammatory symptoms. Fever, ear and nose chondritis, dermatological symptoms, pulmonary infiltrates, and vasculitis are examples of multi-organ autoinflammatory signs. The patient's peripheral blood transcriptomic study further demonstrated the activation of numerous innate immune pathways[12].

An increased proportion of spliced XBP1 was also reported in monocytes, and neutrophils may also be involved in escalating the inflammatory response by encouraging the formation of neutrophil extracellular traps. It is hypothesised that the accumulation of unfolded proteins caused by the UBA1 mutation activates the unfolded protein response and multiple inflammatory pathways (NETs)[1,18].

The Somatic Mutation of UBA1

Since the UBA1 mutation in VEXAS syndrome is a somatic mutation, not all tissue cells have it. By Sanger sequencing, somatic mutations can be detected to a minimum of 15 to 20 percent.

Because the VEXAS syndrome UBA1 mutation is a somatic mutation, not all tissue cells have it. Sanger sequencing has a 15 to 20 percent minimum detection threshold for somatic mutations[19]. The numerous VAF of UBA1 uncovered by exon sequencing, however, has been reported to be mistaken for germline mutations connected to X-linked spinal muscular atrophy 2 (SMAX2), which may prejudice the diagnosis or potentially have an impact on the course of treatment[20].

THE GENETIC MAKEUP OF THE DISEASE

For more than 90% of the activation of ubiquitin, ubiquitylation-dependent intracellular protein degradation, and cell homeostasis in humans, UBA1 genes for the primary E1 activating enzyme. The gene can be produced as either UBA1a, a shorter cytoplasmic isoform that began at p.Met41, or UBA1b, a longer nuclear isoform, both of which are initiated at p.Met1[21,22].

The clinical appearance and severity of the ensuing disease are determined by the many mutations affecting Methionine-41, according to the publication by Ferrada *et al.*[23] using a retrospective case series from the USA and UK. It was proven by the researchers that these three replacement mutations did, in fact, result in residual synthesis of UBA1b to a larger extent than the six other options, indicating a threshold of UBA1b production that permits cell survival and disease manifestation. Results revealed that TTG generated less UBA1b than the other three, supporting the notion that there is a threshold, despite the fact that it also codes for a leucine and has some translational potential. This finding was further supported by a VEXAS patient identified with two novel mutations in exon 3 of UBA1: c.121 A > T, p.Met41LeuTTG (the only identified TTG case) which reduced UBA1b below the assumed disease-specific threshold, and c119G>C, p.Gly40Ala which actually increased UBA1b production compared to wild type, thus concurrently bringing the UBA1b production to around the level of the p.Met41Val mutation and causing disease[23].

The same case series demonstrated that distinct genetic variations were linked to a specific clinical manifestation of the disease. Patients with the variations were more likely to have inflammatory eye illness, whereas those with the Val variant were less likely to acquire ear chondritis. Patients with the Leu variant were more likely to be diagnosed with Sweet's syndrome. To determine how these mutations cause different symptoms and if UBA1b production or other pathways are involved, more research is required.

Additional mutations have been found, and they are peculiar in that neither they appear to influence UBA1b initiation nor to result in UBA1c expression. According to two examples of the Ser56Phe, which is also present in UBA1 exon 3, UBA1's enzymatic activity is decreased due to a temperature-dependent decrease in ubiquitination[15].

Collins *et al.* also recently discovered six additional somatic mutations in UBA1 (p.His55Tyr, p.Gly477Ala, p.Ala478Ser, p.Asp506Gly, p.Asp506Asn, and p.Ser621Cys), all of which result in VEXAS syndrome but none of which produce UBA1c. Instead, they contributed to both UBA1a and UBA1b's decreased catalytic function and may be further split based on how they influenced catalysis[24].

PATHOGNOMIC MECHANISM

The UBA1 gene's somatic mutation is thought to be the etiopathogenic mechanism producing VEXAS syndrome. The UBA1 gene is located at Xp11.23 on chromosome X. The observed mutations are of four different sorts. The position 41 methionine residues are replaced by threonine in the most prevalent mutation (approximately 45 percent). The mutation that alters a single nucleotide (121 adenosine > guanosine) and causes the replacement of a valine residue for a methionine residue at position 41 of the enzyme polypeptide chain is less frequent (around 30%). Adenosine is replaced with cytosine in around 18% of individuals with VEXAS syndrome, causing methionine to be converted to leucine residues in the same location[25].

The UBA1 gene codes one of the enzyme isoforms of ubiquitin-like modifier activating enzyme 1. This isoform is called nuclear in the contrast to isoform 2 detected in the cytoplasm and known as the cytoplasmic isoform. Ubiquitins are small regulatory proteins, with a molecular mass of 8.6 kDa. UBA1 is responsible for activation of ubiquitin 1. The proteins bind to other proteins in a process called ubiquitination. Ubiquitination is important for metabolic processing of the proteins. It can mark proteins for degradation via the proteasome, alter their cellular location, affect their activity, and modify protein interactions. Loss of

ubiquitination has been suggested as a mechanism of so-called endothelial reticulum stress and can be associated with activation of the unfolded protein response. The suggested pathomechanism is a systemic phenomenon and it explains a variety of clinical symptoms and signs[26].

There are still many unanswered questions on how the clinical features of the VEXAS syndrome developed. It is unclear how the patients' cytopenias and recurrent inflammation proceed. It is theorised that a variety of diverse symptoms of the syndrome are brought on by inflammation and manifest in people who are predisposed to particular types of inflammatory responses. In several research, cytokines such interferon-, interleukin-8, and interferon-inducible protein 10 were shown to be overproduced. The mechanism behind these events and their contribution to the emergence of the syndrome's clinical signs are yet unclear[26].

CLINICAL FEATURES

VEXAS is a serious, developing illness with rheumatologic and hematologic-like clinical characteristics. Clinical diagnoses such as Sweet syndrome, recurrent polychondritis, polyarteritis nodosa, and giant cell arteritis are frequently assigned as a result of systemic inflammation affecting the

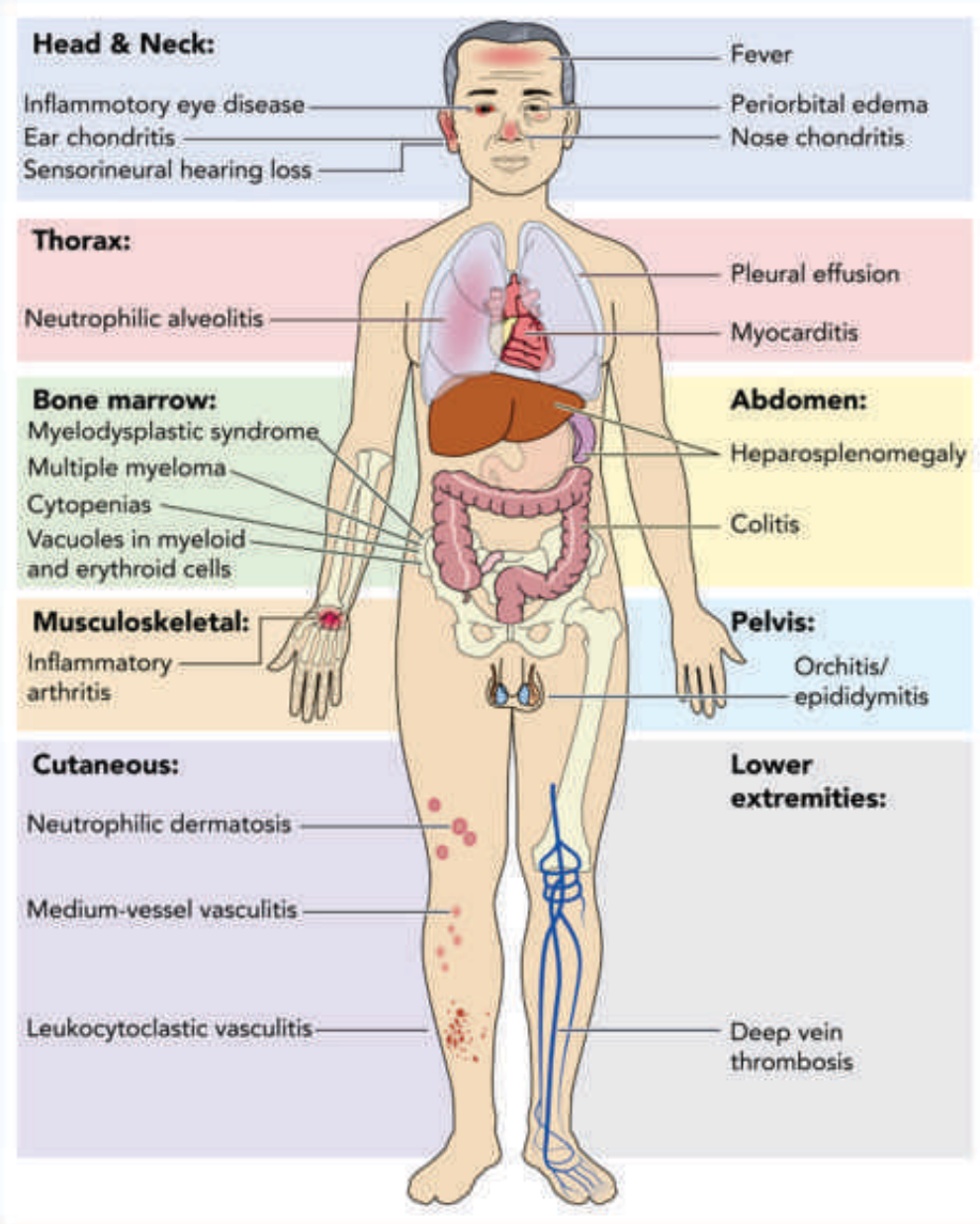

Figure 1: VEXAS Syndrome – Clinical Features[14]
(Professional illustration by Patrick Lane, ScEYEnce Studios)

skin, lungs, blood vessels, and cartilage. A variety of hematopoietic issues, such as macrocytic anaemia, thrombocytopenia, thromboembolic illness, and progressive bone marrow loss that can advance to hematologic malignancy, affect individuals with VEXAS as well (Figure 1)[14].

Broadly the syndrome manifests constitutionally such as Fever, Arthritis, Malaise, Easy fatiguability. With passing time myriad of systemic involvement throws the immune system in overdrive and disease generates diffuse systemic involvement.

Dermatological Involvement

More than four out of every five individuals with VEXAS syndrome report having skin involvement, which is highly prevalent. The variety of cutaneous symptoms is enormous. The patients have erythema nodosum, neutrophilic dermatitis, and erythematosus papules, which are the most typical symptoms of vasculitis. Urticaria, nodules that resemble the Sweet syndrome, periorbital oedema, and injection-site responses are cutaneous involvements that occur less commonly. Rarely are eczematous rash, purpuric macules, and stiff, painful infiltrates seen in the patients[27].

Heterogeneity of the skin involvement suggests various mechanisms responsible for its development. Pathological evaluation of a skin biopsy revealed leukocytoclastic vasculitis affecting small (and in some cases, medium) vessels. Cellular infiltrates were observed and consisted of various kinds of cells (mixed cell type) but infiltrates containing a single-cell composition were also found. These infiltrates were built up with lymphocytes, eosinophils or neutrophils[28,29].

A skin biopsy may reveal leukocytoclastic vasculitis in small to medium-sized vessels or mixed infiltrations of lymphocytes, neutrophils, and eosinophils; in other instances, a single-cell infiltrate may be seen. Less commonly, lymphocytic vasculitis and monocytic or histiocytoid dermal infiltrates might be seen in VEXAS patients, according to cutaneous pathology. A VEXAS patient has also reported skin nodules with lymphocytic infiltration but no signs of neutrophils, eosinophils, or vasculitis[30].

Additional histologic symptoms include panniculitis or cholesterol emboli in the medium vascular artery[1,31.32]. Numerous infiltrating cells exhibited characteristics of Sweet syndrome-like "histiocytoid" myeloid progenitor cells, including CD68 positivity and myeloperoxidase positivity[27]. It has been shown using paired sequencing research that the cutaneous infiltrates in VEXAS syndrome originate from the same diseased myeloid clone with UBA1 mutation that is seen in the bone marrow[33].

Pulmonary Involvement

About half of all patients have lung involvement, and the most prevalent disease symptoms are pulmonary infiltrates and pleural effusions. Patients with VEXAS have also been reported to develop vasculitis, bronchiolitis obliterans, and pulmonary fibrosis[1].

Renal and Gastrointestinal Tract Involvement

Only 13.8 percent of individuals had gastrointestinal problems, which is a rare occurrence. Abdominal discomfort (8.6% of cases), diarrhoea (6.9%), ulcerative lesions with gastrointestinal bleeding (0.9%), and digestive perforation or blockage are the next most frequent symptoms (0.9 %)[29]. There have been reports of the jejunum becoming perforated while on tocilizumab, an anti-IL-6 medication[20].

In 9.5% of the cases, kidney involvement has been noted[29]. It manifests as proteinuria, dysmorphic erythrocyturia, and progressive renal disease leading to kidney insufficiency. It has been reported that a kidney biopsy showed Endothelitis, medium-sized vascular vasculitis, and an interstitial infiltration of myeloperoxidase and CD68 positive myeloid cells[20].

Ocular and Nervous System

Up to 40.5 percent of cases involve the eyes, most commonly due to episcleritis (12.1%), uveitis (9.5%), scleritis (8.6%), orbital mass (3.4%), and blepharitis. There may be periorbital and orbital irritation[35].

Cardiac Manifestations

About 11% of individuals will have heart involvement, which may manifest as myocarditis, pericarditis, or even progress to cardiomyopathy[29].

It is necessary to rule out arterial involvement (10.3%), aortitis (1.7%), aneurysms (3.4%), and vasculitis with anti-neutrophil cytoplasmic antibodies (ANCA) negative. Approximately one-third of the patients suffer episodes of venous and arterial thrombosis, with 60% of these episodes happening within the first two years following the beginning of symptoms[29]. Between 10 to 56% of patients are said to be at risk for venous thromboembolism (VTE)[36]. Nine VEXAS patients with VTE were identified by Obiorah *et al.*, two of whom had high factor VIII levels, which are linked to an increased risk of venous thrombosis through accelerated thrombin production, and one patient had a high factor IX serum level[10]. Arterial thrombosis, in contrast to VTE, seems to occur less often (10% of cases recorded)[36].

All of these causes of VTE should prompt all VEXAS patients to think about receiving an anti-thrombotic prophylactic, especially those who also have other high-risk causes of prothrombosis, such immobilisation or recent surgery. Future research will focus on the more effective prophylaxis[29], which must take into account that these patients have a higher risk of bleeding, which is at least partially explained by

thrombocytopenia and the use of non-steroidal anti-inflammatory medicines (NSAIDs) to treat illness[36]. Some authors have also advised considering VEXAS syndrome in all males with spontaneous VTE accompanied with systemic inflammatory symptoms and macrocytic anaemia or thrombocytopenia based on the prevalence of venous thrombosis[37].

Rheumatological Manifestations

Myalgia, arthralgia, and mono-, oligo-, or poly-arthritis are frequently observed. It's interesting to note that chondritis of the ears, nose, and other cartilages may occur in up to 50% of patients[29].

According to the retrospective investigation by Ferrada *et al.*, p.Met41 mutations were found in the UBA1 gene in 7 out of 92 (7.6%) individuals who were diagnosed with RP using globally recognised criteria. Notably, neither chondritis of the airways nor costochondritis was found in any of the VEXAS-associated RP (VEXAS-RP) patients. Those with VEXAS-RP had a greater mortality rate than patients without UBA1 mutations (27 % vs. 2 %). Similar to VEXAS-RP patients, increased acute phase reactants and hematologic abnormalities were common. An algorithm was developed based on these results in order to separate patients with VEXAS-RP from those who do not.

The algorithm tree is composed by male sex at the first node, by mean corpuscular volume > 100 fL at the second node and platelet count < 200 k/μL at the third node. All patients fulfilling the three nodes were correctly identified with VEXAS-RP and three patients with RP were incorrectly classified as VEXAS-RP. Therefore, the algorithm showed 100% sensitivity and a 96% specificity[38]. Later, a retrospective study comparing 95 VEXAS-RP patients with 40 patients suffering from idiopathic RP confirmed that the male sex, older age, and the presence of fever, skin manifestations, ocular involvement, pulmonary infiltration, heart inflammatory affections, were more frequent in VEXAS patients[39].

Patients with VEXAS have been reported to have extensive and severe myofascitis, which is characterised by perimysial, epimysial, and fascial macrophagic CD68 positive inflammation with significant necrotizing myopathy at histology. Non-red-rimmed intramuscular vacuoles were prominent and noteworthy[40].

Lymphatic and Nervous System

About 35% of patients experience lymphadenopathy, which is most prevalent in the hilar and mediastinal lymph nodes but can also occur in the cervical, axillary, abdominal, and inguinal regions. In 13.8 percent of the patients, the spleen is said to be enlarged[29].

Meningitis, headaches, minor or severe cerebrovascular accidents, peripheral nervous system involvement with sensory neuropathy (5.2 percent) and multiple mononeuropathy (2.6 %), and peripheral nerve system involvement in general are seen[29]. In addition to axonal loss, a case of chronic inflammatory demyelinating polyradiculoneuropathy has also been documented; a nerve biopsy revealed demyelination with thin myelin sheaths and concentric growth of Schwann cells[41].

SYSTEMIC ASSOCIATIONS

Haematological Associations

More than half of individuals with an MDS also have haematological involvement. The MDS subtypes include forms with multilineage dysplasia and ring sideroblasts. Patients with VEXAS-MDS syndrome exhibit non-infectious recurring fevers, gastrointestinal tract involvement, pulmonary infiltrates, and arthralgia more frequently than people with VEXAS syndrome alone. Due to their reduced platelet counts, these individuals need glucocorticoid therapy more often. A monoclonal gammopathy of uncertain significance occurs in a small proportion of MDS patients (MGUS)[10,29].

A 67-year-old man with a 10-year history of essential thrombocythemia linked to a CALR mutation and skin infiltration of non-blastic tumour cells, sometimes known as "myelodysplasia cutis," linked to a UBA1 mutation was described by Hage-Sleiman et al. When the UBA1 gene mutation was discovered, both the CALR clone and the essential thrombocythemia phenotype vanished. This led the scientists to hypothesise that UBA1 mutations may offer a potent selection advantage sufficient to outcompete clones with CALR alterations. Further observations are needed to support the authors' theory since the finding might either be coincidental or caused by the usage of hydroxyurea and thalidomide[42].

Because VEXAS has both an inflammatory and a haematological component, any patient exhibiting cytopenias and systemic inflammatory symptoms should be given consideration for genetic testing. A typical symptom of the condition is macrocytic anaemia, which was seen in 96 percent (24/25) of the first cohort to be reported [Citation1]. Later, a retrospective examination of 18 patients revealed that cytopenias were common, with macrocytic anaemia (100%), lymphopenia (80%), thrombocytopenia (50%) and monocytopenia (50%) being the most common (50%)[10].

The syndrome's frequent correlation with haematological anomalies that result in malignant diseases is a serious clinical issue[43]. Myelodysplastic syndrome is present in around half of the patients. It is in line with past theories linking autoimmune diseases and myelodysplastic syndrome[44]. More in-depth research showed that myelodysplastic syndrome in VEXAS patients differs from the "classical" type of myelodysplasia in certain ways. Men over the age of 70 make up a large portion of the population where myelodysplastic syndrome

predominates, and it is caused by clonal changes in the hemopoietic stem cells that lead to ineffective haematopoiesis. Acute myeloid leukaemia develops from the condition in roughly 30% of cases. It is thought that hematopoietic cell clonal growth alters the marrow microenvironment, causing cytopenias. Myelodysplastic syndrome has been associated with many acquired genetic changes.

SPECTRUM OF VASCULITIS IN VEXAS SYNDROME

Vasculitis is a typical VEXAS syndrome symptom. Leukocytoclastic vasculitis, a kind of small-vessel vasculitis, is the most prevalent. Eighty to ninety percent of individuals with the disease who had skin biopsies examined histopathologically for this kind of vasculitis. Neutrophils and fibrinoid necrosis were frequently seen in the angiocentric segmental inflammatory infiltrations that the majority of them exhibited. Other types of vasculitis, such as IgA vasculitis and ANCA-associated vasculitis, were also identified in VEXAS patients in addition to leukocytoclastic vasculitis (granulomatosis with polyangiitis or microscopic polyangiitis). It is unclear if these ailments represent an unrelated sickness or have any connection to the syndrome's development[45].

PAN is a medium-vessel vasculitis with several clinical symptoms, such as cardiovascular damage, hypertension, renal failure, and skin abnormalities. Nine individuals with medium vessel vasculitis were identified by a literature analysis of vasculitis in VEXAS; seven of them met the criteria for PAN. LCV, which often presents as palpable purpura and is frequently identified on skin biopsies, is really the vasculitis that is reported most frequently in VEXAS. With two cases of giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) previously documented, large vessel vasculitis also occurs in VEXAS[46].

Furthermore, there have been two reported cases of ANCA-associated vasculitis in patients later diagnosed with VEXAS [Citation[41] and Citation[42]][47,48].

Large Vessel Vasculitis

Based on a temporal artery biopsy, 1 out of 25 patients (4%), according to the first report, had GCA. A 77-year-old guy with MDS, pulmonary infiltrates, deep vein thrombosis, and a UBA1 mutation (p.Met41Val) presented with these symptoms. Despite receiving glucocorticoid therapy, the patient passed away at the age of 78[1].

Only two cases of VEXAS-GCA have been documented, hence insufficient testing could be done to distinguish between GCA and VEXAS - GCA. Large vessel vasculitis has a wide range of differential diagnoses, and these instances show that VEXAS syndrome may be a possible mimic of large vascular vasculitis[49].

GCA appears to be uncommon among VEXAS syndrome instances that have been recorded. How frequently are UBA1 mutations discovered in GCA patients is the question. Poulter et al. sequenced UBA1 in 612 male samples taken from the UK GCA Consortium in order to address this. No samples had UBA1 mutations, whereas seven out of 1,055 samples from the cytopenic cohorts had the mutation[50].

The authors concluded that VEXAS syndrome is rarely misdiagnosed as GCA in the UK. However, as the incidence of GCA varies greatly by race, perhaps due to HLA differences[56,57], race-specific UBA1 mutations in patients with GCA need to be assessed[51].

Medium Vessel Vasculitis

Three (12%) of the patients with VEXAS syndrome in the first report met the criteria for the categorization of PAN52, a medium-sized vessel vasculitis. The average age at disease onset was 61.8 years (ranging from 43 to 80 years) and all were male. Seven of the nine patients fulfilled the classification criteria for PAN. Macrocytic anaemia and skin lesions were observed in all cases, while chondritis was found in only two of the nine cases. Despite the use of high-dose glucocorticoids and multiple bDMARDs, such as infliximab, anakinra, and rituximab, six of the nine patients died during the treatment course[46].

Small Vessel Vasculitis

Small-vessel vasculitis, especially LCV, is the most typical kind of vasculitis. The cause is that cutaneous symptoms, which are seen in 80–90% of patients, frequently show the histology of LCV[27,52]. Angiocentric segmental inflammation, fibrinoid necrosis, and neutrophil infiltration surrounding the blood vessel walls are histological features of LCV[27,53]. Seven out of 25 patients (28%) with VEXAS syndrome and seven out of 22 patients (31.8%) with dermatologic signs had LCV histologically verified in the initial report. Additional nine cases of LCV were found in our literature analysis (Table 1), despite the initial report's lack of clarity on the demographics of patients who had LCV[1,46].

AAV (microscopic polyangiitis and granulomatosis with polyangiitis) and IgA vasculitis[54], two other small vessel vasculitis that are not LCV, have also been shown to be related with VEXAS syndrome[48,55]. However, abnormal neutrophil activation with increased NETs creation is a common hallmark of both VEXAS syndrome and AAV, although the cause of the problems of both illnesses is yet unknown[56].

Thrombosis

About 40% of VEXAS syndrome patients experience thrombotic symptoms[36]. When compared to arterial thrombosis (1.6%), venous thromboembolism (36.4%) is known to occur substantially more often[57]. Haemostasis may be dysregulated

and endothelial dysfunction may occur from interactions between abnormally activated immune cells, platelets, and endothelial cells.

Uncertainty surrounds the underlying pathophysiology of thrombosis in VEXAS. A well-known phenomenon, thrombosis occurs when there is persistent inflammation and is likely to result from a variety of dysregulated pathways, such as improper fibrin formation (which attaches thrombi to the vessel walls) or decreased production and increased consumption of the natural anticoagulant protein C[36,58]. Despite the small sample size, there is some indication that certain patients with VEXAS have enhanced factor VIII activity, which is positively correlated with elevated CRP[10]. Obiorah *et al.* found a significant incidence of solitary or chronic lupus anticoagulant (LA) positive in their examination of 16 individuals, with rates of 69 percent (11/16) and 44 percent (7/16), respectively[10]. A thrombotic event occurred in five of the patients who had chronic LA positivity, and two of the five patients who had LA negativity also experienced one, demonstrating that the condition is characterised by numerous prothrombotic pathways.

Another factor to take into account is the increased rate of vasculitis associated with VEXAS and how this contributes to thrombus development. As a well-known side effect of vasculitic diseases, thrombosis is most likely to result from endothelial disruption in an inflammatory milieu, with neutrophil extracellular traps (NETs) being a crucial player. In order to bind external pathogens, neutrophils release their DNA as a network of fibres known as a NET. They are crucial for host defence, but when they are out of balance, they can cause thrombosis by acting as a web-like scaffold for platelets and coagulation factors and impairing endothelial function[36,59].

SEROLOGY AND LABORATORY

Almost all patients also have normal levels of folic acid and vitamin B12, and macrocytic anaemia. Thrombocytopenia and lower lymphocyte and monocyte numbers are also seen[60]. Blood smears demonstrate Pseudo-Pelger-Hut abnormality, granulocytic anaplasmosis, and increased erythrocyte volume. Bone marrow smears demonstrate hypercellular bone marrow, a steadily rising myeloid: erythroid ratio (which can indicate disease progression), and the distinctive cytoplasmic vacuolation of myeloid and erythroid progenitor cells[6]. When macrocytic anaemia is discovered in inflammatory disorders, doctors should take the potential of VEXAS syndrome into consideration because the anaemia of inflammation typically manifests as microcytic hypochromic anaemia[10,22].

The analysis of the peripheral blood from patients with VEXAS syndrome showed highly activated inflammatory signatures in multiple pathways, including tumour necrosis factor (TNF), interleukin-6 (IL-6), and interferon-γ. Inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, were significantly elevated in all patients. An elevated antinuclear antigen, rheumatoid factor, and antiphospholipid antibodies were also observed in patients with VEXAS[1,61].

It was demonstrated that the altered myeloid progenitor cells, which were primarily granular and erythroid precursor cells, included vacuoles. The vacuoles are just a general indicator of cellular damage and are not pathognomonic for VEXAS syndrome[62,63]. According to Templé and Kosmider, the presence of vacuoles in more than 10% of cells in a patient with a clinical profile like VEXAS syndrome is a sign that additional genetic research on UBA1 gene mutations is necessary[4].

MANAGEMENT PROSPECTS

In patients with VEXAS, there is no suggested therapy approach that is standardised. The majority of the information is gathered from observation of brief case series or single case reports. The medicine aims to eliminate the UBA1-mutated population of hematopoietic cells and reduce systemic inflammation in general. Additionally, organ symptoms should be treated symptomatically. As a result, treating patients with VEXAS calls for a multidisciplinary strategy and a team of specialists, including rheumatologists and hemologist.

The majority of observations and retrospective studies point to the temporary efficacy of high corticosteroid dosages. The need to reduce the medication's dose is typically linked to flare-ups or steroid-side effects after inflammatory symptoms have been somewhat controlled. Glucocorticoid is to be replaced with glucocorticoid-sparing medication after first being helpful in the disease management[2,26].

Immunomodulation

Retrospective multicenter research by Heiblig et al.64 on 30 VEXAS patients showed that ruxolitinib outperformed other medications in this class. A Janus kinase inhibitor with preference for JAK1 and JAK2 subtypes is roxolitinib. It is licenced for the treatment of polycythaemia vera, corticosteroid-refractory acute graft-versus-host disease, and intermediate or high-risk myelofibrosis. Results are inconsistent when the other Janus kinase inhibitors are used[4].

The use of Janus kinases (JAK) inhibitors in VEXAS syndrome has shown inconsistent outcomes, ranging from full control of inflammatory symptoms to lack of response. According to reports, the JAK1 and JAK2 inhibitor ruxolitinib is more successful than other JAK inhibitors, producing a clinical and laboratory response in 50% of patients after one month and in more than 80% of patients after three months. On the other hand, individuals receiving tofacitinib, baricitinib, and upadacitinib showed a noticeably lower percentage of clinical and biological response[62].

It's critical to emphasise how differently VEXAS patients respond to anti-inflammatory drugs. It's likely that there are several subtypes of the condition, in which case the therapeutic approach should be modified based on the subtype of the

disease or kind of mutation. In the case of VEXAS syndrome, there is a substantial inter-individual variation in therapy efficacy. Glucocorticoids, conventional disease-modifying antirheumatic medications (cDMARDs), biotechnological compounds that target IL-1 and IL-6, and Janus kinase (JAK) inhibitors are some of the therapies that have been tried thus far. Future gene-editing medicines and allogenic hematopoietic stem cell transplantation (HSCT) may be worthwhile treatments to look into[2].

Kunishita Y *et al.*[66] studied the effects of Tocilizumab as a agent of choice in a specific setting of VEXAS Syndrome with relapsing polychondritis. This year long observational study from Japan concluded that in the absence of significant hematologic abnormalities in VEXAS syndrome patients with an inflammatory-dominant phenotype, TCZ and low-to-moderate glucocorticoid combination therapy may be a viable alternative as a bridge therapy until new VEXAS syndrome therapies are discovered.

Haematopoietic Stem Cell: A Future Approach

The hematopoietic and immune systems can be rebuilt by hematopoietic stem cell transplantation (HSCT), which can remove defective bone marrow hematopoietic tissue through pre-treatment and then implant healthy hematopoietic stem cells. Due to inadequate glucocorticoid and immunosuppressive drug efficacy, severe inflammatory symptoms, or uncontrollable hematologic disease, six patients with VEXAS syndrome underwent allo-HSCT. Three of these patients experienced complete remission, two survived during short-term follow-up, and one patient passed away from infectious complications after HSCT. Another research described a patient who had autologous stem cell transplantation to treat MDS and clear cells containing the UBA1 mutation; this finding raises the possibility that HSCT might be utilised to treat VEXAS syndrome[12,65].

The Karnofsky Performance Scale score and Hematopoietic Cell Transplantation-Comorbidity Index are two of the available assessment tools that can be used to screen suitable patients and evaluate their condition. After that, doctors must choose the type of transplantation, the best preparative regimens, the precise timing of transplantation based on the patient's condition, and protocols to handle complications like GVHD. If at all feasible, long-term follow-up is advised to assess the effectiveness. However, early consideration of transplantation is advised since VEXAS-related problems may restrict the development and effectiveness of transplantation. There is now a formal clinical trial being conducted to assess the effectiveness of allogeneic stem cell transplantation in VEXAS patients[12,64,65,66].

CONCLUSION

Not only is VEXAS syndrome a novel clinical condition. It is a model condition for a new class of rheumatic illnesses called systemic-inflammatory disorders. Somatic mutations in the blood cells that are linked to multi-organ involvement and bone marrow pathology are what cause systemic inflammatory disorders. Proliferation (lymphoproliferation, myeloproliferation, or myelodysplasia) or myelodysplasia are linked to abnormalities of the bone marrow, which may develop into cancer.

The idea of "hematoinflammatory disorders" supports the significance of somatic mutations that are restricted to a subset of non-germline cells and suggests a connection between inflammatory, or "autoinflammatory," diseases and abnormalities of the bone marrow. It has been proposed that Erdheim-Chester illness, a rare type of histiocytosis brought on by mutations in a proto-oncogene, belongs to the new class of diseases.

Every patient with an unexplained systemic inflammatory illness should have the VEXAS syndrome seriously investigated, especially if it is accompanied by peripheral cytopenia, an elevated mean corpuscular volume, or other hematologic abnormalities. When adult patients experience recurring fevers, neutrophilic dermatosis, RP, and other autoinflammatory symptoms, the condition should be taken into consideration as a potential diagnosis. In this respect, multidisciplinary cooperation is necessary for the diagnosis and management of a clinical entity that may be very difficult to treat.

FUTURE PROSPECTS AND FURTHER READING

Our method for identifying, classifying, and treating inflammatory illnesses has undergone a major shift as a result of the discovery of the VEXAS syndrome. Since MDS is usually accompanied by inflammatory problems, the earlier description of late-onset NLRP3-associated autoinflammatory syndrome suggested that acquired, leukocyte-restricted, somatic mutations may play a role in the aetiology of a broader spectrum of inflammatory illnesses[69,70].

VEXAS might serve as the model for a brand-new category of "hematoinflammatory disorders". Somatic mutations in hematopoietic cells, systemic inflammatory response, and the propensity to develop into overt myelodysplastic, myeloproliferative, or lymphoproliferative disease would be the characteristics of these illnesses. A fraction of Felty syndrome patients have acquired STAT3 mutations in their lymphocytes, which increase their risk of developing large granular lymphocyte leukaemia[71].

Early findings in VEXAS syndrome and associated disorders are defining the function somatic mutations play in complicated, adult-onset diseases[72] and providing a framework for haematologists and rheumatologists to work together in the clinic and the research laboratory.

Described first in 2021, the index article or the initial reports serves as a rich and solid foundation for our current understanding of VEXAS Syndrome. However the idea has

rapidly wavered from just a UBA1 mutation, but it is still the basis of the entire cascade[1].

A comprehensive and illustrative review was put forth by Zhang Yue *et al.*[12], where they have underlined the alarming aspects of the disease and the stupendously high mortality rate, for which a broader effort is required.

You can read the extensive report on VEXAS Syndrome, by Vitale A. *et al.*[2] for a detailed clinical atlas and excellent pictorial depiction of disease manifestation.

Al-hakim A *et al.*[6] has the most current update on the state of the disease paradigm. They have outlined the basic requirement of understanding the disease progression and the importance of Immunomodulation along with Stem cell approach as the best method right now to tackle the disease effectively.

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REFERENCES

1. Beck DB, Ferrada MA, Sikora KA, et al. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. N Engl J Med. 2020; 383(27):2628-2638. doi:10.1056/NEJMoa2026834
2. Vitale A, Caggiano V, Bimonte A, et al. VEXAS syndrome: a new paradigm for adult-onset monogenic autoinflammatory diseases. Intern Emerg Med. 2023; 18(3):711-722. doi:10.1007/s11739-023-03193-z
3. 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.Published 2022 Jul 11. doi:10.3389/fmed.2022.926500
4. Beck DB, Bodian DL, Shah V, et al. Estimated Prevalence and Clinical Manifestations of UBA1 Variants Associated With VEXAS Syndrome in a Clinical Population. JAMA. 2023; 329(4):318-324. doi:10.1001/jama.2022.24836
5. Onuora S. VEXAS syndrome more common than originally thought? Nat Rev Rheumatol. 2023; 19(4):193. doi:10.1038/s41584-023-00931-7
6. Al-Hakim A, Savic S. An update on VEXAS syndrome. Expert Rev Clin Immunol. 2023; 19(2):203-215. doi:10.1080/1744666X.2023.2157262
7. Beck DB, Bodian DL, Shah V, et al. Genomic ascertainment for UBA1 variants and VEXAS syndrome: a population-based study. medRxiv. 2022.
8. Ma X. Epidemiology of myelodysplastic syndromes. Am J Med. 2012; 125(7 Suppl):S2-S5. doi:10.1016/j.amjmed.2012.04.014
9. Neukirchen J, Schoonen WM, Strupp C, et al. Incidence and prevalence of myelodysplastic syndromes: data from the Düsseldorf MDS-registry. Leuk Res. 2011; 35(12):1591-1596. doi:10.1016/j.leukres.2011.06.001
10. Obiorah IE, Patel BA, Groarke EM, et al. Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. Blood Adv. 2021; 5(16):3203-3215. doi:10.1182/bloodadvances.2021004976
11. Patel N, Dulau-Florea A, Calvo KR. Characteristic bone marrow findings in patients with UBA1 somatic mutations and VEXAS syndrome. Semin Hematol. 2021; 58(4):204-211. doi:10.1053/j.seminhematol.2021.10.007
12. Zhang Y, Dong X, Wang H. VEXAS Syndrome-Review. Glob Med Genet. 2023; 10(3):133-143. Published 2023 Jul 10. doi:10.1055/s-0043-1770958
13. Oganesyan A, Jachiet V, Chasset F, et al. VEXAS syndrome: still expanding the clinical phenotype. Rheumatology (Oxford). 2021; 60(9):e321-e323. doi:10.1093/rheumatology/keab225
14. Grayson PC, Patel BA, Young NS. VEXAS syndrome. Blood. 2021; 137(26):3591-3594. doi:10.1182/blood.2021011455
15. Gurnari C, McLornan DP. Update on VEXAS and role of allogeneic bone marrow transplant: Considerations on behalf of the Chronic Malignancies Working Party of the EBMT. Bone Marrow Transplant. 2022; 57(11):1642-1648. doi:10.1038/s41409-022-01774-8
16. Barba T, Jamilloux Y, Durel CA, et al. VEXAS syndrome in a woman. Rheumatology (Oxford). 2021; 60(11):e402-e403. doi:10.1093/rheumatology/keab392
17. Stubbins RJ, McGinnis E, Johal B, et al. VEXAS syndrome in a female patient with constitutional 45,X (Turner syndrome). Haematologica. 2022; 107(4):1011-1013. Published 2022 Apr 1. doi:10.3324/haematol.2021.280238
18. Guerrero-Bermúdez CA, Cardona-Cardona AF, Ariza-Parra EJ, et al. Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome (VEXAS syndrome) with prominent supraglottic larynx involvement: a case-based review. Clin Rheumatol. 2022; 41(11):3565-3572. doi:10.1007/s10067-022-06338-1
19. Tsuchida N, Kunishita Y, Uchiyama Y, et al. Pathogenic UBA1 variants associated with VEXAS syndrome in Japanese patients with relapsing polychondritis. Ann Rheum Dis. 2021; 80(8):1057-1061. doi:10.1136/annrheumdis-2021-220089

20.Van der Made CI, Potjewijd J, Hoogstins A, et al. Adult-onset autoinflammation caused by somatic mutations in UBA1: A Dutch case series of patients with VEXAS. J Allergy Clin Immunol. 2022; 149(1):432-439.e4. doi:10.1016/j.jaci.2021.05.014

21.Callis J. The ubiquitination machinery of the ubiquitin system. Arabidopsis Book. 2014; 12:e0174. Published 2014 Oct 6. doi:10.1199/tab.0174

22.Patel BA, Ferrada MA, Grayson PC, Beck DB. VEXAS syndrome: An inflammatory and hematologic disease. Semin Hematol. 2021; 58(4):201-203. doi:10.1053/j.seminhematol.2021.10.005

23.Ferrada MA, Savic S, Cardona DO, et al. Translation of cytoplasmic UBA1 contributes to VEXAS syndrome pathogenesis. Blood. 2022; 140(13):1496-1506. doi:10.1182/blood.2022016985

24.Collins, Jason C., et al. "Novel Disease-Causing Mutations in UBA1 Reveal Disease Mechanisms in Bone Marrow Failure and Inflammation." Blood 140.Supplement 1 (2022): 2914-2915.

25.Templé M, Kosmider O. VEXAS Syndrome: A Novelty in MDS Landscape. Diagnostics (Basel). 2022; 12(7):1590. Published 2022 Jun 29. doi:10.3390/diagnostics12071590

26.Kucharz EJ. VEXAS syndrome: a newly discovered systemic rheumatic disorder. Reumatologia. 2023; 61(2):123-129. doi:10.5114/reum/163090

27.Sterling D, Duncan ME, Philippidou M, Salisbury JR, Kulasekararaj AG, Basu TN. VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) for the dermatologist [published online ahead of print, 2022 Feb 2]. J Am Acad Dermatol. 2022; S0190-9622(22)00181-5. doi:10.1016/j.jaad.2022.01.042

28.Zakine È, Papageorgiou L, Bourguiba R, 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(4):917-920. doi:10.1016/j.jaad.2022.10.052

29.Georgin-Lavialle S, Terrier B, Guedon AF, 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(3):564-574. doi:10.1111/bjd.20805

30.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 EurAcad Dermatol Venereol. 2022; 36(6):e435-e437. doi:10.1111/jdv.17924

31.Staels F, Betrains A, Woei-A-Jin FJSH, et al. Case Report: VEXAS Syndrome: From Mild Symptoms to Life-Threatening Macrophage Activation Syndrome [published correction appears in Front Immunol. 2021 Aug 10;12:748756]. Front Immunol. 2021; 12:678927. Published 2021 Apr 23. doi:10.3389/fimmu.2021.678927

32.Poulter JA, Collins JC, Cargo C, et al. Novel somatic mutations in UBA1 as a cause of VEXAS syndrome. Blood. 2021; 137(26):3676-3681. doi:10.1182/blood.2020010286

33.Zakine E, Schell B, Battistella M, et al. UBA1 Variations in Neutrophilic Dermatosis Skin Lesions of Patients With VEXAS Syndrome. JAMA Dermatol. 2021; 157(11):1349-1354. doi:10.1001/jamadermatol.2021.3344

34.Himmelmann A, Brücker R. The VEXAS Syndrome: Uncontrolled Inflammation and Macrocytic Anaemia in a 77-Year-Old Male Patient. Eur J Case Rep Intern Med. 2021; 8(4):002484. Published 2021 Apr 13. doi:10.12890/2021_002484

35.Martín-Nares E, Vargas-Serafín C, Delgado-de la Mora J, et al. Orbital and periorbital inflammation in VEXAS syndrome. Scand J Rheumatol. 2022; 51(4):338-341. doi:10.1080/03009742.2022.2045791

36.Groarke EM, Dulau-Florea AE, Kanthi Y. Thrombotic manifestations of VEXAS syndrome. Semin Hematol. 2021; 58(4):230-238. doi:10.1053/j.seminhematol.2021.10.006

37.Khider L, Templé M, Bally C, et al. Systematic search for the UBA1 mutation in men after a first episode of venous thromboembolism: A monocentric study. J ThrombHaemost. 2022; 20(11):2697-2699. doi:10.1111/jth.15858

38.Ferrada MA, Sikora KA, Luo Y, et al. Somatic Mutations in UBA1 Define a Distinct Subset of Relapsing Polychondritis Patients With VEXAS. Arthritis Rheumatol. 2021; 73(10):1886-1895. doi:10.1002/art.41743

39.Khitri MY, Guedon AF, Georgin-Lavialle S, et al. Comparison between idiopathic and VEXAS-relapsing polychondritis: analysis of a French case series of 95 patients. RMD Open. 2022; 8(2):e002255. doi:10.1136/rmdopen-2022-002255

40.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(12):e371-e373. doi:10.1093/rheumatology/keac356

41.Bert-Marcaz C, Briantais A, Faucher B, et al. Expanding the spectrum of VEXAS syndrome: association with acute-onset CIDP. J NeurolNeurosurg Psychiatry. 2022; 93(7):797-798. doi:10.1136/jnnp-2021-327949

42.Hage-Sleiman M, Lalevée S, Guermouche H, et al. Dominance of an UBA1 mutant clone over a CALR mutant clone: from essential thrombocytemia to VEXAS. Haematologica. 2021; 106(12):3245-3248. Published 2021 Dec 1. doi:10.3324/haematol.2021.279418]

43.Matsumoto H, Fujita Y, Fukatsu M, et al. Case Report: Coexistence of Multiple Myeloma and Auricular Chondritis in VEXAS Syndrome. Front Immunol. 2022; 13:897722. Published 2022 Jun 9. doi:10.3389/fimmu.2022.897722

44.Braun T, Fenaux P. Myelodysplastic Syndromes (MDS) and autoimmune disorders (AD): cause or consequence?. Best Pract Res Clin Haematol. 2013; 26(4):327-336. doi:10.1016/j.beha.2013.09.003

45.Lötscher F, Seitz L, Simeunovic H, et al. Case Report: Genetic Double Strike: VEXAS and TET2-Positive Myelodysplastic Syndrome in a Patient With Long-Standing Refractory Autoinflammatory Disease. Front Immunol. 2022; 12:800149. Published 2022 Jan 20. doi:10.3389/fimmu.2021.800149

46.Watanabe R, Kiji M, Hashimoto M. Vasculitis associated with VEXAS syndrome: a literature review. Front Med. 2022;9. DOI:10.3389/FMED.2022.983939

47.Koster MJ, Kourelis T, Reichard KK, et al. Clinical Heterogeneity of the VEXAS Syndrome: A Case Series. Mayo Clin Proc. 2021; 96(10):2653-2659. doi:10.1016/j.mayocp.2021.06.006

48.Muratore F, Marvisi C, Castrignanò P, et al. VEXAS Syndrome: A Case Series From a Single-Center Cohort of Italian Patients With Vasculitis. Arthritis Rheumatol. 2022; 74(4):665-670. doi:10.1002/art.41992

49.Ramon A, Greigert H, Ornetti P, Bonnotte B, Samson M. Mimickers of Large Vessel Giant Cell Arteritis. J Clin Med. 2022; 11(3):495. Published 2022 Jan 19. doi:10.3390/jcm11030495

50.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(5):947-951. doi:10.1007/s10875-022-01258-w

51.Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica. N Engl J Med. 2014; 371(17):1653. doi:10.1056/NEJMc1409206

52.Stubbins RJ, Cherniawsky H, Chen LYC, Nevill TJ. Innovations in genomics for undiagnosed diseases: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome. CMAJ. 2022; 194(14):E524-E527. doi:10.1503/cmaj.211770

53.Iglesias-Gamarra A, Restrepo JF, Matteson EL. Small-vessel vasculitis. Curr Rheumatol Rep. 2007; 9(4):304-311. doi:10.1007/s11926-007-0049-3

54.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(3):e69-e71. doi:10.1093/rheumatology/keab782

55.Afsahi V, Christensen RE, Alam M. VEXAS syndrome in dermatology. Arch Dermatol Res. 2023; 315(2):161-164. doi:10.1007/s00403-022-02340-4

56.Lacombe V, Prevost M, Bouvier A, et al. Vacuoles in neutrophil precursors in VEXAS syndrome: diagnostic performances and threshold. Br J Haematol. 2021; 195(2):286-289. doi:10.1111/bjh.17679

57.Oo TM, Koay JTJ, Lee SF, Lee SMS, Lim XR, Fan BE. Thrombosis in VEXAS syndrome. J Thromb Thrombolysis. 2022; 53(4):965-970. doi:10.1007/s11239-021-02608-y

58.Branchford BR, Carpenter SL. The Role of Inflammation in Venous Thromboembolism. Front Pediatr. 2018; 6:142. Published 2018 May 23. doi:10.3389/fped.2018.00142

59.Yu S, Liu J, Yan N. Endothelial dysfunction induced by extracellular neutrophil traps plays important role in the occurrence and treatment of extracellular neutrophil traps-related disease. International Journal of Molecular Sciences. 2022 May 17; 23(10):5626.

60.Sikora KA, Wells KV, Bolek EC, Jones AI, Grayson PC. Somatic mutations in rheumatological diseases: VEXAS syndrome and beyond. Rheumatology (Oxford). 2022; 61(8):3149-3160. doi:10.1093/rheumatology/keab868

61.Li P, Venkatachalam S, Ospina Cordona D, et al. A clinical, histopathological, and molecular study of two cases of VEXAS syndrome without a definitive myeloid neoplasm. Blood Adv. 2022; 6(2):405-409. doi:10.1182/bloodadvances.2021005243

62.Rabut A, Jasserand L, Richard C, et al. Quantitative Assessment of Vacuolization of Myeloid Precursors in VEXAS Syndrome. Hemasphere. 2023; 7(2):e828. Published 2023 Jan 25. doi:10.1097/HS9.0000000000000828

63.Chabrun F, Lacombe V, Dieu X, Geneviève F, Urbanski G. Accurate stratification between VEXAS syndrome and differential diagnoses by deep learning analysis of peripheral blood smears. Clin Chem Lab Med. 2023; 61(7):1275-1279. Published 2023 Feb 2. doi:10.1515/cclm-2022-1283

64.Heiblig M, Ferrada MA, Koster MJ, et al. Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study [published correction appears in Blood. 2023 Mar 30; 141(13):1647]. Blood. 2022; 140(8):927-931. doi:10.1182/blood.2022016642

65.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(3):998-1003. doi:10.1182/bloodadvances.2021004749

66.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(3):e12-e15. doi:10.1111/bjh.18424

67.National Cancer Institute (NCI) A Phase II Study of Allogeneic Hematopoietic Stem Cell Transplant for Subjects with VEXAS (Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic) Syndrome. clinicaltrials.gov; 2022. Accessed November 3, 2022

68.Kunishita Y, Kirino Y, Tsuchida N, 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. Published 2022 Jun 13. doi:10.3389/fimmu.2022.901063

69.Zhou Q, Aksentijevich I, Wood GM, et al. Brief Report: Cryopyrin-Associated Periodic Syndrome Caused by a Myeloid-Restricted Somatic NLRP3 Mutation. Arthritis Rheumatol. 2015; 67(9):2482-2486. doi:10.1002/art.39190

70.Mekinian A, Grignano E, Braun T, et al. Systemic inflammatory and autoimmune manifestations associated with myelodysplastic syndromes and chronic myelomonocytic leukaemia: a French multicentre retrospective study. Rheumatology (Oxford). 2016; 55(2):291-300. doi:10.1093/rheumatology/kev294

71.Savola P, Brück O, Olson T, et al. Somatic STAT3 mutations in Felty syndrome: an implication for a common pathogenesis with large granular lymphocyte leukaemia. Haematologica. 2018; 103(2):304-312. doi:10.3324/haematol.2017.175729

72.Haroche J, Charlotte F, Arnaud L, et al. High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood. 2012; 120(13):2700-2703. doi:10.1182/blood-2012-05-430140