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Review

VEXAS Syndrome: an Updated Literature Review

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Abstract

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a newly described autoinflammatory disease with various manifestations mimicking myelodysplastic syndrome, vasculitis, and neutrophilic dermatosis, affecting males over 50 years old. The etiology is an acquired error of innate immunity due to a somatic mutation in the ubiquitylation-controlling gene UBA1, resulting in an aberrant inflammatory process. Although there is no specific therapy for VEXAS syndrome, many agents including cyclophosphamide, anti-IL-6, and Janus kinase (JAK) inhibitors have been tried, with varying results so far. Hereby, a literature review is presented, summarizing the current knowledge regarding the pathogenesis, clinical manifestations, and treatment options for VEXAS syndrome.

Keywords: Autoinflammation, literature review, myelodysplastic syndrome, UBA1 mutation, VEXAS syndrome

Introduction

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a novel, adult-onset, autoinflammatory disease that manifests with both inflammatory and hematologic symptoms.[1] The pathophysiology of VEXAS syndrome arises from a somatic mutation in the X-linked *UBA1* gene which normally codes for the ubiquitin-activating E1 enzyme in the precursor cells of the myeloid lineage. The clinical spectrum of the disease keeps expanding as the number of newly diagnosed cases increases. At present, the identification of this syndrome relies exclusively on the verification of pathogenic UBA1 mutations and its diagnosis should be considered in patients exhibiting treatment-resistant inflammatory disease accompanied by progressive hematologic abnormalities.

Methods

We performed a research on the medical databases Medline and Scopus using the following keywords: "VEXAS," "UBA1 mutation," "vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome," filtering papers from December 2020 until May 2024. This research yielded results in the form of case reports, case series, cohorts, and reviews.

Literature Review

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome is an adult-onset, male-predominant, newly described autoinflammatory condition with overlapping rheumatologic and hematologic features that is also cited as "highly inflammatory clonal cytopenia,"[2] which occurs because of an acquired mutation of the *UBA1* gene (located on chromosome X) that disrupts the physiological cellular ubiquitylation mechanisms, resulting in a variety of clinical manifestations. The disease penetrance linked to the, as far, identified pathogenic mutations in UBA1 seems to approach 100%, regardless of the variant allele fraction in the mutated cells.[3]

Ubiquitylation, a multi-step post-translational modification, initiates mostly protein degradation by the proteasome and plays an important regulatory role in cases of misfolded protein accumulation or excessive protein production, e.g., inflammatory conditions, but also mediates signaling, gene regulation, endocytosis, autophagy, and DNA repair.[4] Therefore, ubiquitin-proteasome system disruptions result in many disease states, such as infantile neurodegeneration, e.g., X-linked spinal muscular atrophy, infection susceptibility, malignancy, lymphoproliferative disorders, and autoinflammation.[5]

The ubiquitylation machinery consists of 3 different groups of enzymes (E1, E2, E3). Although there are multiple E2 and E3 enzymes, E1 enzyme group is mainly encoded by the *UBA1* gene and is essential for initiating cellular ubiquitylation.

The unfolded protein response (UPR) is a series of intracellular stress pathways that is stimulated when the protein processing capacity of the endoplasmic reticulum is saturated, leading to activation of innate

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immune responses, including NF-κB pathways and interferon (IFN) type I responses.[6] Triggering of the UPR is thought to be responsible for the inflammatory syndrome that characterizes the patients with VEXAS syndrome.[1,3]

In their breakthrough, "genome-first" approach, Beck et al,[1] grouped almost 2.500 patients with undiagnosed systemic inflammation and/or fever of unknown origin and screened their genome in their effort to discover any common genetic cause between them and identified initially 3 men, and other 22 who were added afterwards, each with a heterozygous somatic UBA1 variant (also known as mosaic or postzygotic), due to inactivating mutations at the same methionine-41 (p.Met41) codon, exceeding 71% variant allele frequency (a substitute indicator for the percentage of DNA molecules in the initial specimen harboring the variant). Mosaicism was confirmed by analyzing hematopoietic cell populations (from peripheral blood and isolated from bone marrow) and fibroblasts and interestingly the latter did not carry any variants, while hematopoietic stem cells, multipotent progenitors, lymphoid progenitors, and myeloid lineage cells were mutated with mature lymphocytes being wild-type. Additionally, the participants displayed reduced peripheral lymphocyte counts, indicating that the mutant cells either did not proliferate or were eliminated, leading to an increased proportion of the wild-type genotype and resulting to genetically heterogeneous cells carrying either hemizygous wild-type or mutated UBA1.

Epidemiology

According to the "Geisinger cohort",[7] pathogenic UBA1 mutations prevalence was estimated as 1 in 14.000 from the entire cohort, 1 in 4.269 for males over 50 years old, 1 in 26.000 for females over 50 years old and 1 in 8.000 combined for both sexes in individuals aged over 50 years old, suggesting a prevalence similar to Behçet's disease (around 1 in 10.000) and MDS (around 1 in 14.000). While the majority of VEXAS syndrome cases are diagnosed in men, it can also manifest in women (11 cases), with inherited or acquired monosomy of the X chromosome (4 in total, 1 with Turner syndrome) or without.[7-12]

Main Points

- Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a disease fusing hematological dyscrasias with systemic inflammatory manifestations.
- A male patient over 50 years old with unexplained constitutional symptoms, thrombosis, skin, and lung manifestations, accompanied by myelodysplasia and cytopenias, is worth checking for VEXAS-causing UBA1 mutations.
- Although there is no standard therapy, anti-interleukin-6 agents, hypomethylating agents, and allogeneic bone marrow transplantation seem to bear positive results.

Clinical Manifestations

With onset in middle age or later, VEXAS syndrome manifests with constitutional symptoms and multisystemic inflammation affecting multiple organs like the skin, the cartilages, the lungs, the eyes, and the hematopoietic system. As a result, these patients are probable to be misdiagnosed as having relapsing polychondritis (RP), vasculitis, neutrophilic dermatoses, or myelodysplastic syndrome (Table 1).

Constitutional - Among the various studies, common ground is that constitutional symptoms such as recurrent fever, fatigue and weight loss affect >90% of the patients and occur early in the course of the disease, while lymphadenopathy reaches 58.3%.[1,2,13,14]

Skin - Skin manifestations are the next most common presentation after fever, as they are present in >83% of the patients and include Sweet's syndrome (16.7%-46%), leukocytoclastic vasculitis (LCV) (26%-41.6%), erythematous papules/plaques (21.6%-66.6%), purpura, nodules, erythema nodosum (12.5%-41.6%), panniculitis, livedo reticularis, and more rarely urticaria.[13-16] According to Zakine, cutaneous manifestations were the initial presentation of 63% of patients and the distinctive histological feature of the skin lesions is neutrophilic dermatosis with dermal infiltrates stemming from pathological myeloid clones with UBA1 mutations, frequently accompanied by LCV (angiocentric segmental inflammatory infiltrations, commonly composed of neutrophils and fibrinoid necrosis).[17] Nevertheless, Lacombe detected UBA1 mutations exclusively in neutrophilic dermatosis, but not in non-neutrophilic dermatosis, proposing a differentiation between "clonal" (neutrophilic dermatosis) and "paraclonal" (LCV and panniculitis) skin manifestations.[18]

Hematopoietic system - Macrocytic anemia is the most common feature reaching up to 96%, followed by thrombocytopenia, lymphopenia (neutropenia is rare), myelodysplasia, multiple myeloma, plasma cell dyscrasia, and MGUS.[1,19] Poulter, the first to study the frequency of UBA1 mutations in patients with undiagnosed cytopenia, gathered almost 1000 cases and found that two thirds of cytopenic patients had a UBA1 mutation, suggesting that screening for UBA1 mutations in individuals with undiagnosed cytopenia should be contemplated, especially in those with concurrent inflammatory or autoimmune conditions.[8]

Respiratory system - Respiratory symptoms can be observed in roughly 50%-70% of individuals.[1,13,14] Kouranloo performed a systematic review regarding the pulmonary manifestations, according to which, the manifestation most commonly reported was pulmonary infiltrates (43.1%), succeeded by pleural effusion (7.4%) and idiopathic interstitial pneumonia (3.3%).[20] Additional pulmonary manifestations that have been described include bronchiolitis obliterans, pulmonary vasculitis, bronchiectasis, alveolar hemorrhage, bronchial stenosis, and alveolitis. According to the French registry, individuals with UBA1 p.Met41Thr or p.Met41Val mutations exhibited a higher prevalence of lung infiltrates compared to those with p.Met41Leu mutations.[13] In addition to skin lesions and hematologic manifestations, these represent the most commonly described features of VEXAS and constitute a primary cause of mortality in affected individuals.

Cartilage - A cardinal symptom of VEXAS syndrome is cartilaginous damage varying from 32% to 64%, in the form of nasal / auricular / airway chondritis or costochondritis.[1,2,13]

Thrombosis - As a highly inflammatory disorder, another characteristic manifestation is the increased tendency to thrombotic events, mostly venous, in the form of deep vein thrombosis (DVT), pulmonary embolism, and superficial thrombophlebitis and rarely of arterial nature on the form of cardiovascular incidences.[14,19] The large French cohort estimated the occurrence of venous thrombosis to be 34.7%, a percentage lower than that of Beck's original publication (44%).[1,13] Another study documented that 43% of VEXAS patients manifest recurrent thrombotic events, all in the initial stages of the illness, 33% of them while receiving sufficient oral anticoagulation.[21] Data from the Spanish cohort confirmed the same percentage of 43% for venous thromboembolism and 4% for arterial thrombosis.[16] Khitri and Ferrara both compared VEXAS-RP patients to non-VEXAS-RP patients and regarding the aspect of thrombotic events, the first study revealed similar frequency of 20%-25% between the 2 groups, while the other marked

Table 1. Clinical Manifestations of Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic Syndrome

	Georgin-Lavialle[13] (N = 116) %	Ferrada[2] (N = 83) %	van der Made[14] (N = 12) %	Mascaro[16] (N = 30) %	Bourbon[15] (N = 11) %	Beck[1] (N = 25) %
Constistutional						
Noninfectious fever	64.7	83	90.9	66.7	91	92
Weight loss	54.5	–	50	–	55	–
Fatigue	–	–	41.6	–	55	–
Cutaneous	83.6	82	83.3	90	100	88
Neutrophilic dermatosis (Sweet syndrome)	39.7	22	16.7	–	46	32
Cutaneous vasculitis	26	–	41.6	–	55	–
Erythematous papules	21.6	–	33.3	66.6	–	–
Erythema nodosum	12.5	–	41.6	–	–	–
Urticaria	8.6	–	–	–	–	–
Panniculitis	–	–	–	30	–	–
Pulmonary	49.1	–	66.7	66.7	–	–
Pulmonary infiltrates	40.5	57	25	–	46	72
Pleural effusion	9.5	13	–	–	–	–
Ocular	40.5	24	25	56.7	46	–
Uveitis	9.5	–	16.7	16.7	27	–
Scleritis	8.6	–	8.3	–	–	–
Episcleritis	12.1	–	–	–	9	–
Periorbital edema	8.6	30	8.3	26.7	9	–
Orbital mass	3.4	–	–	–	–	–
Venous thrombosis	35.3	–	–	–	–	–
DVT	–	41	–	–	46	–
Venous thromboembolism	–	13	–	40	–	44
Arterial thrombosis	–	–	16.6	13.3	9	–
Relapsing polychondritis	36	52	–	–	–	–
Chondritis	36.2	–	41.6	53.3	46	64
Ear	32	54	33.3	–	46	–
Nasal	15.5	36	16.7	–	9	–
Airway chondritis	–	2	–	–	–	–
Arthralgia	28.4	–	8.3	–	100	–
Arthritis	–	58	25	53.3	27	–
Lymph node enlargement	34.5	–	58.3	–	46	–
Splenomegalia	13.8	–	–	–	27	–
Hepatomegalia	7.8	–	—	–	18	–
Peripheral nervous	14.7	–	16.7	–	–	–
Hematological	50	–	–	–	–	–
MDS	50	31	33.3	–	55	24
MGUS	9.6	–	—	–	9	20
Macrocytic anemia	–	97	66.6	72.4	64	96
Thrombocytopenia	–	48	16.6	48.2	18	–

(*Continued*)

Table 1. Clinical Manifestations of Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic Syndrome (*Continued*)

	Georgin-Lavialle[13] (N = 116) %	Ferrada[2] (N = 83) %	van der Made[14] (N = 12) %	Mascaro[16] (N = 30) %	Bourbon[15] (N = 11) %	Beck[1] (N = 25) %
Anemia	–	–	–	83.3	100	–
Leukopenia	–	–	25	33	45	–
Gastrointestinal tract	14	–	25	–	–	–
Abdominal pain	8.6	–	–	–	9	–
Diarrhea	6.9	–	–	–	–	–
Gastrointestinal bleeding	0.9	–	–	–	–	–
Digestive perforation	0.9	–	16.7	–	–	–
Heart	11.2	–	–	–	–	–
Pericarditis	4.3	–	–	–	–	–
Myocarditis	2.6	–	8.3	–	–	–
Arterial involvement	10.3	–	–	–	–	–
Aortitis	1.7	–	–	–	–	–
Aneurysms	3.4	–	–	–	–	–
Kidney	9.5	–	16.7	–	9	–
Genital	–	–	–	–	–	–
Orchitis	–	12	8.3	–	27	–
Epididymitis	–	–	25	–	9	–

DVT, deep vein thrombosis; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance.

a tremendous difference of 62% over 5% among the groups.[12,22]

Laboratory studies concerning the thrombotic occurrences in VEXAS patients exhibited lupus anticoagulant (LA) positivity while anticardiolipin antibodies and b2-glycoprotein antibodies were mostly negative. Some patients have shown elevated level of factors VIII and IX.[1,21]

Vasculitis - The relationship between VEXAS syndrome and vasculitis has been examined as well. Most of the cases are associated with medium-size vessel vasculitis, some of them fulfilling the criteria for the diagnosis of PAN.[1,5,10,15] However, the most common diagnosis preceding or accompanying that of VEXAS is small vessel vasculitis, mostly as LCV,[1,5,18] followed by reports of ANCA-associated vasculitis and immunoglobulin A (IgA) vasculitis.[23-25] It has been speculated that VEXAS can be even misdiagnosed as giant-cell arteritis (GCA), based on case reports,[1,26] a hypothesis that is only rarely valid, as Poulter screened the genome of 612 males diagnosed with GCA and found no UBA1 mutations among them.[8]

Musculoskeletal system - Joint inflammation was also a commonly reported feature. Data from cohorts in France, Spain and UK/USA state that arthritis is found in 28.4%, 53% and 58% respectively.[2,13,16] Interestingly, in a retrospective cohort of 11 male patients with VEXAS, arthritis/ arthralgia was noticed in all patients (100%), while in a Dutch case series arthritis alone was 33%.[14,15] There are also 2 reported cases of refractory and erosive arthritis mimicking rheumatoid arthritis.[27,28] Lastly, there is 1 case report of a VEXAS patient with coexisting HLA-B27 positive spondyloarthritis and MDS.[29]

Eyes - Ocular inflammation includes both orbital and extraorbital involvement, affecting up to nearly half of VEXAS patients at some point during the course of their disease, especially in conjunction with RP.[13,16,30] The most common manifestations are uveitis, (epi)scleritis, conjunctivitis, and periorbital edema, while most recent studies add orbital myositis, dacryoadenitis, and blepharitis to the ever-increasing list.[30,31] Though data is varying, periorbital edema seems to be the most common ocular symptom, presented in up to 30%,[2] while episcleritis is almost always linked to coexistent RP.[30]

Other systems - Manifestations from other systems are reported as well but in lower recurrence, including myo-pericarditis, kidney involvement (glomerulonephritis and interstitial nephritis), gastrointestinal system occurrences (abdominal pain, diarrhea and intestinal perforation maybe linked to treatment with tocilizumab), peripheral neuropathy in the form of sensory neuropathy and multiple mononeuropathy and orchitis.[2,12-16,22,32] VEXAS has also been associated with other systematic systemic inflammatory conditions like the macrophage-activation system (a form of hemophagocytic lymphohistiocytosis), especially following infections (bacterial or viral), underlining the complex interplay between immune homeostasis disruption, immunosuppression, and excessive inflammation.[16,33,34] Recently, more clinical features were added to the syndrome's spectrum, for example necrotizing myositis and myofasciitis.[31]

Pathogenesis

The UBA1 gene is located on the long (q) arm of the X chromosome, specifically at position 28.1 and as a result it is no wonder why VEXAS syndrome is predominantly affecting males. Although there is an increasing number on female cases diagnosed with VEXAS syndrome (with or without X chromosome monosomy), the current opinion is that the presence of a second X chromosome in women allele serves as protection against the adverse effects of the mutated UBA1 allele. It is noteworthy that

Table 2. Clinical Manifestations Correlated with UBA1 Mutations

	Val		Thr		Leu	
	Georgin-Lavialle[13] (N = 116)	Ferrada[2] (N = 83)	Georgin-Lavialle[13] (N = 116)	Ferrada[2] (N = 83)	Georgin-Lavialle[13] (N = 116)	Ferrada[2] (N = 83)
	%	%	%	%	%	%
Fever	82.4	94	70.6	78	19	87
Skin	82.9	83	84.6	80	81	87
Pulmonary	68.6	55	50	54	9.5	67
Arthralgia/Arthritis	28.6	55	19.2	60	42.9	53
Chondritis	14.3	–	40.4	–	52.4	–
Ear chondritis	–	22	–	66	–	53
Nose chondritis	–	16	–	42	–	33
Ocular	28.6	5	46.2	36	38.1	6
Venous thrombosis	37.1	33	38.5	38	28.6	60
MDS	68.6	44	42.3	26	33.3	33

Leu, leucine, MDS, myelodysplastic syndrome; Thr, threonine, Val, valine.

germline mutations in UBA1 cause a rare neuromuscular disease, X-linked infantile spinal muscular atrophy.

Two isoforms of UBA1 have been identified as products of translation of the same mRNA molecule, initiated at 2 alternate sites: UBA1a is the nuclear isoform (with p.Met1 as the initiation site) and UBA1b is the cytoplasmic isoform (with p.Met41 as the initiation site).[35] Disruption of the initiation of transcription at p.Met41 due to mutations, has as a result the defective expression of UBA1b which, in turn, moves the initiation site at p.Met67, producing an alternative isoform, UBA1c, which lacks catalytic capacity. Most of the pathogenic mutations causing VEXAS syndrome provoke a shift of the transcriptional activity from p.Met41 to p.Met67 and the production of UBA1c.[3] However, other type of mutations that do not cause the production of UBA1c have been identified, as an example, mutations that produce a catalytically impaired UBA1b (and UBA1a) in a temperature-dependent manner (p.Ser56Phe mutation) or by abnormal thioester formation (p.Gly477Ala).[6,36] More specifically, most of cases (>90%) show substitutions of methionine-41 in exon 3 of UBA1 gene with threonine (most often), valine and leucine (least often),[1,2,13,16] while the rest are cases of mutations outside of exon 3, in the splice acceptor site preceding it yielding the same result regarding the transcriptional procedure, in exon 14 or elsewhere, marked as UBA1non-p.Met41 mutations (Figure 1).[31,37,38] Hence, it may be speculated that the variety of symptoms belonging to different phenotypes of VEXAS syndrome are ruled by the differences in the genetic background, defined by the range of causative mutations.

Results from the French registry come in line with this speculation as the research team tried to correlate UBA1 mutations with clinical phenotypes (Table 2).[13] The most commonly encountered mutations were p.Met41Thr (c.122T>C) and p.Met41Val (c.121A>G) and those patients presented more frequently with fever, lung involvement, anemia, MDS, and higher C-reactive protein (CRP) levels. On the contrary, patients with p.Met41Leu (c.121A>C) mutation presented with a less aggressive phenotype and a more favorable prognosis. Accordingly, in the study conducted by Ferrada et al,[2] the most common mutation was that of threonine variant, followed by the valine variant and lastly by the leucine one.[2] More specifically, patients with the threonine mutation presented more frequently with ear chondritis and ocular inflammation while patients with the leucine variant with venous thrombosis and slightly more pulmonary infiltrates. Patients exhibiting the mutation with substitution by valine presented slightly more often with fever and MDS and with significantly less with ear/ nose chondritis.

It is noted that VEXAS syndrome is the result of somatic mutations occurring in the UBA1 gene, leading to mosaicism where there is both a functionally altered UBA1c and a normal UBA1b with residual enzymatic activity.[1,39] Interestingly, Ferrada et al[2] tried to correlate the manifestations of the disease with the residual activity of UBA1b. Although the universal start codon codes for methionine, in cases of mutation by substitution, only 3 of the 9 possible alternatives (those coding for threonine, valine of leucine) can start the translatory process even in a small degree, resulting in the production of a certain amount of UBA1b. Therefore, one can pose the question of whether a minimum UBA1b production required in order for a cell to survive and for the disease to manifest, as a level of UBA1b below a certain threshold could halt the expansion of the clone bearing the mutation, or conversely, if it is the presence of UBA1c that causes the difference in the clinical manifestations.

In the original work by Beck et al[1] it is shown that causative mutations are harbored only in cells stemming from myeloid and erythroid progenitors, while lymphocytes present the wild-type allele. Consecutively, this states the fact that either the causative somatic mutations happen only in the multipotent progenitors of the hematopoietic lineage or that such mutations are incompatible with survival for the lymphoid cells. Furthermore, fibroblasts from the same patients were tested negative for UBA1 mutations, supporting this way the hypothesis of UBA1 mosaicism being myeloid-restricted. Strikingly though, the Spanish cohort of VEXAS showed UBA1 variants in some of the participants' nails, that are of ectodermal provenance, resulting in the dispute of the aforementioned theory.[16]

Of note, there are reports of patients exhibiting VEXAS-like constellation of symptoms without bearing any UBA1 mutation.[6] It is therefore speculated that mutations affecting other steps of the ubiquitylation process might result in the same disease.

Even since the first description of VEXAS syndrome, the analysis of the inflammatory profile has been of interest. The main cytokines

Table 3. Treatment Options in Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic Syndrome

Category	Medication	Mechanism of action
Glucocorticoids[1,13,16]		Multiple mechanisms: 1) Inhibition of the synthesis of almost all known inflammatory cytokines by regulating gene expression 2) Lymphocyte proliferation suppression 3) Leukocyte migration inhibition
Hypomethylating agents	Azacytidine[1,15,46,49] Decitabine[16]	DNA methyltransferase inhibition, leading to hypomethylation, allowing expression of silenced onco-suppressor genes
Anti-interleukin agents		
anti-IL-1[1,14]	Anakinra	IL-1 receptor antagonist
	Canacinumab	anti-IL-1β monoclonal antibody
anti-IL-6[1,14,40,52]	Tocilizumab	anti-IL-6 receptor monoclonal antibody
anti-IL-17	Secukinumab[29]	anti-IL-17A monoclonal antibody
JAK inhibitors[53]	Ruxolitinib[15]	JAK1/2 inhibitor
	Baricitinib	JAK1/2 inhibitor
	Upadacitinib	JAK1 inhibitor
Calcineurin inhibitors	Cyclosporine[15]	T-cell activation blockade by calcineurin inhibition
Allogeneic bone marrow transplant	HSCT[10,24,50,51]	eradication and replacement of host's immune system
anti-CD20[16]	Rituximab	B-cell depletion via 3 mechanisms: antibody-dependent cellular-cytotoxicity complement-dependent cellular-cytotoxicity direct cell death
IVIG[29]		Multiple mechanisms: Saturation of FcRn. Saturation of Fc receptors on cells of the reticuloendothelial system. Blockade of Fas ligand-mediated apoptosis by anti-Fas antibodies in the IVIG Supply of anti-idiotypic antibodies that bind either to circulating autoantibodies, resulting in increased clearance, or to BCR, leading to downregulation of antibody production. Solubilization and clearance of immune complex deposits and/or inhibition of the binding of active complement components such as C4b and MAC to target tissues.

BCR, B-cell receptor; DHFR, dihydrofolate reductase; Fas, first apoptosis signal; FcRn, neonatal fragment crystallizable (Fc) receptor; HSCT, Hematopoietic stem cell transplantation; IMPDH, Inosine monophosphate dehydrogenase; IVIG, intravenous immunoglobulin G; MAC, membrane attack complex; MP-acid, mycophenolic acid.

mediating the inflammatory cascade in the syndrome are interferon-γ (IFN-γ), tumor necrosis factor-alpha (TNF-α), inteleukin-6 (IL-6) and inteleukin-8 affecting the interplay between cells of innate and acquired immunity.[1,40] Another inflammatory mechanism participating in the pathogenesis of VEXAS is enhanced neutrophil extracellular traps formation (NETosis).[1,41]

Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic syndrome and Relapsing Polychondritis

Due to their clinical similarities, before the discovery of VEXAS syndrome, many cases were diagnosed as RP and inversely, many miscellaneous manifestations were attributed to RP without strong pathogenic explanation, as the co-occurrence of MDS. According to current data, 7.6% of the patients diagnosed as RP have in reality VEXAS syndrome.[22]

Khitri et al[12] divided 98 RP patients in 2 groups (RP and VEXAS-RP, according to if they had UBA1 mutations) and found that the VEXAS-RP group consisted predominantly of males (the 2 VEXAS women included had acquired X-monosomy) who displayed higher prevalence of fever, ear chondritis, skin manifestations including neutrophilic dermatosis and cutaneous vasculitis, pulmonary infiltrates and periorbital edema as well as newly described symptoms like uveitis, (epi)scleritis and myopericarditis. Additionally, the same group of patients had higher values of inflammatory markers (ESP, CRP) accompanied by thrombocytopenia and anemia with macrocytosis and lower values of absolute lymphocyte and monocyte count and/or MDS, comparing to their RP group equivalents. It is noteworthy that they also had a significant prevalence of positive rheumatoid factor and LA. Rates for peripheral arthritis, large airway chondritis, costochondritis, and venous thrombosis were similar among the groups. Patients with RP had higher prevalence of nose chondritis. In terms of prognosis, VEXAS-RP patients have a less favorable disease outcome, regardless of the co-existence of MDS.

Similar general findings were recorded by Ferrada et al,[22] in a prospective observational cohort of 92 RP patients, where 7 of them were further diagnosed to have VEXAS syndrome. The only exceptions were in the domains of venous thrombosis, for which the VEXAS group had higher prevalence and of airway chondritis, for which the highest prevalence was in

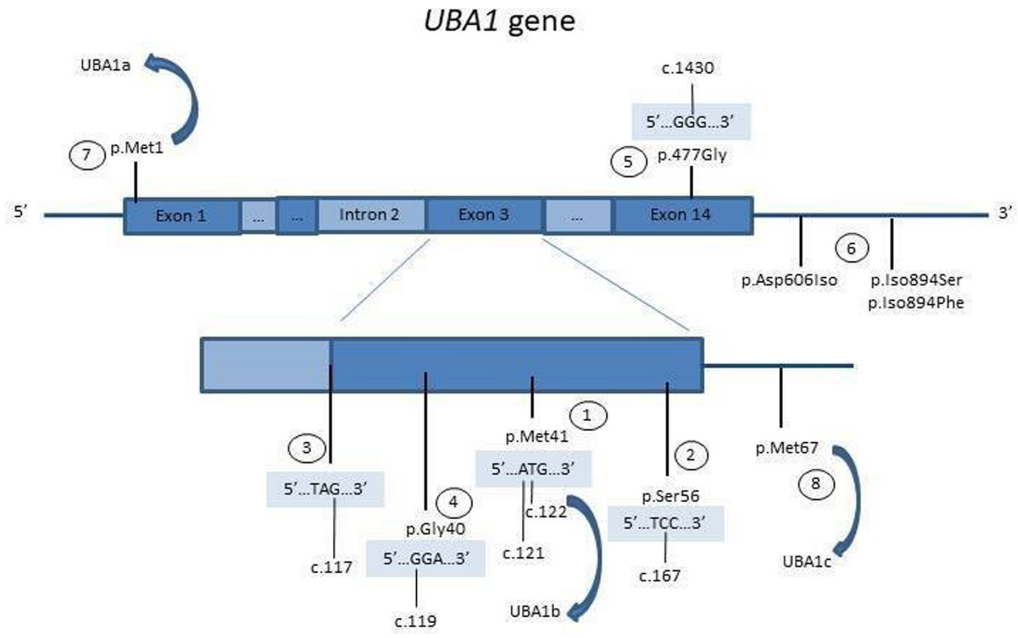

Figure 1. UBA1 gene mutations leading to vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome. Dark blue: exons, light blue: introns. 1) p.Met41 is the initiation site for the production of UBA1b. Point mutations in the coding position 121 or 122 (c.121A>G → p.Met41Val, c.121A>C → p.Met41Leu, c.121A>T → p.Met41Leu, c.122T>C → p.Met41Thr) lead to defective expression of UBA1b, as the initiation of transcription is moved to p.Met67. 2) Point mutation in the coding position c.167 (p.Ser56Phe) produces UBA1a and UBA1b with temperature-dependent enzymatic activity. 3) Mutations in the splice acceptor site move the transcription initiation to p.Met67. 4) Point mutation in the coding position c.119 (p.Gly477Ala) produces an impaired UBA1b, due to abnormal thioester formation. 5) Point mutation in exon 14 has been shown to lead to the onset of VEXAS syndrome despite being a UBA1non-p.Met41 mutation. 6) Other UBA1non-p.Met41 mutations, leading to VEXAS syndrome phenotype. 7) p.Met1 is the initiation site for the production of UBA1a. 8) p.Met67, the alternative initiation site, in cases of p.Met41 mutations.

the RP group. Further on, the team developed an algorithm with the scope to help identify those RP patients that have VEXAS syndrome. According to their proposal, a male patient with MCV>100fL and platelet count <200K/uL can be diagnosed with VEXAS syndrome with 100% sensitivity and 96% specificity.

Vacuoles in bone marrow

A characteristic finding in the bone marrow of patients with VEXAS syndrome is the presence of vacuoles in myeloid and erythroid precursor cells. Despite its prevalence, it does not constitute a pathognomonic finding for the syndrome, as it can be found in lymphoid malignancies and more infrequently in abnormalities of myeloid origin, as well as in various other conditions such as copper deficiency (congenital or acquired), transcobalamin II deficiency, alcoholism, zinc toxicity or even in autoimmune diseases (rheumatoid arthritis or ulcerative colitis) and MDS.[32,42] Characteristically in a study reported by Obiorah, vacuolization in early erythroid and myeloid lineage precursors in the bone marrow of 16 patients diagnosed with VEXAS syndrome reached 100% but was not present in mature lymphocytes.[21]

In line with the findings of the original study by Beck, case series and/or retrospective studies have shown that the prevalence of vacuolization reaches exceeds 90%[41] but their absence should not exclude the diagnosis.[1,14] Conversely, only a low percentage of patients exhibiting vacuolization were found to have a UBA1 mutation (0.08%).[42] When the clinical suspicion is high, clinicians should perform a genetic testing on selected patients and according to Lacombe, one can diagnose VEXAS syndrome with 100% sensitivity and specificity in a patients exhibiting ≥10% of neutrophil precursors with >1 vacuole.[41]

Vacuoles in the myeloid/erythroid precursor cells are not the only pathologic finding in bone marrow aspiration in patients with VEXAS; high myeloid/erythroid ratio, hypercellularity, and decreased B-cell precursors can also be found.[21]

Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic Syndrome and Myelodysplastic Syndrome

A link between autoimmune diseases and MDS development has long been established, with MDS patients exhibiting both clinical and laboratory signs of systemic autoimmunity, such as fever, vasculitis, arthritis and positive autoantibodies in 10%-30% of cases.[43] Interestingly, VEXAS syndrome manifests itself in a similar way, thus bridging myelodysplasia and autoimmune phenomena, although it is not clear if the expansion of the UBA1 mutation-bearing clones is the cause or the causative. The occurrence of VEXAS in patients with a diagnosed myeloid malignancy has previously been documented by Zhao, who screened males with MDS/ chronic myelomonocytic leukemia for UBA1 mutations using Sanger sequencing, revealing mutations in 12% of them.[44]

Data extracted from studies on VEXAS patients confirm that the co-occurrence of VEXAS and MDS has a frequency ranging from 24% to 55%, many cases of which are transfusion-dependent.[3,15] According to French data, VEXAS-MDS cases presented more frequently with fever, pulmonary infiltrates, and manifestations from the gastrointestinal system.[13]

Currently, there seem to be 2 theories aiming to explain this co-occurrence between MDS and general autoimmunity, with the most supported one stating that the emerging clone has an intrinsic survival advantage and it alters the bone marrow environment resulting in the creation of conditions that favor its expansion in detriment of the normal hematopoietic cells. The alternative thought supposes that it is the highly inflammatory milieu that gives birth to dysplastic clones.[45]

It's worth mentioning that UBA1 variants may coexist with other somatic mutations, such as

in DNMT3A (9.2%-22% of cases) and TET2 (5%-11% of cases) genes, which are well established MDS-causing mutations.[8,13,46]

Thrombosis in Vacuoles, E1 Enzyme, X-Linked, Autoinflammatory, Somatic Syndrome

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome is characterized by both venous and arterial thromboembolism. With parentages varying from 35% to 46% for DVT and/or venous thromboembolism and almost 16% for arterial thrombosis (manifested as transient ischaemic attack, ischaemic stroke, and myocardial infarction).[13-15,21] According to current knowledge, VEXAS syndrome has a high risk for thrombosis as many other inflammatory conditions do, due to various reasons affecting the activation of the coagulation cascade, the direct or indirect effect of inflammatory cytokines on the endothelium and on the platelets and the presence of antiphospholipid antibodies.[21]

Oo et al[39] tried to unravel the etiopathogenesis by detailing successive events leading to thrombosis. Intracellular accumulation of proteins that are inadequately degraded due to disruption of the normal ubiquitylation process as a result of UBA1 mutations, lead to UPR and consequently to an inflammatory cascade mediated by tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8) and interferon-γ (IFN- γ). Henceforth, tissue factor expression is upregulated and platelets and endothelial cells are activated resulting in influx and activation of neutrophils and monocytes. Augmented NETosis is also noted which further consolidates the prothrombotic milieu. In a parallel manner, some VEXAS patients have shown increased levels of antiphospholipid antibodies, as well as a positive LA test.

Treatment

To date, there is no specific treatment for VEXAS syndrome while the 2 main therapeutic regimens aim to either eliminate the UBA1-mutated clone or to limit the inflammatory torrent. High-dose corticosteroids constitute a cornerstone for the management of the various manifestations of the disease across the literature, whereas other options extend from Janus kinase (JAK) inhibitors, hypomethylating agents, and anti-interleukin biologic agents to bone marrow transplantation (Table 3).[1,13,16]

Hypomethylating agents – Azacytidine is a drug used for high-risk MDS and has proved efficacy also for those cases of MDS associated with autoimmune diseases.[47,48] As a result, it has been mainly used in cases of VEXAS coexisting with MDS. According to data from the French registry, 45% of patients with VEXAS and MDS were benefited, whereas in another case series, despite azacytidine having the longest survival time (21.9 months) compared to other medications, no specific amelioration in cytopenia or general MDS symptoms was noted.[15,49] In this case, though, it is underlined that most patients received only a small amount of cycles, which could explain the inefficacity, given that the usual time to response of hypomethylating agents in MDS is 4-6 months.[48] In cases where along with a UBA1 mutation there is also a mutation in DNMT3A (loss-of-function, resulting in MDS), the use of azacytidine was proved substantially effective, effacing the pathogenic clone.[1,46] In the Spanish cohort, 1 patient was treated with decitabine and showed amelioration in both the inflammatory and hematological manifestations of the disease.[16]

Allogeneic bone marrow transplant – A case series of retrospectively identified VEXAS patients who underwent allogeneic bone marrow transplantation gave hopeful results since most of them were in complete remission 2 and even 37 months after.[10] Another case series showed similar beneficial results of remission.[24] Hematopoietic stem cell transplantation (HSCT), however, does not come without complications, some of them being detrimental and lethal, as is liability to infections and graft-versus-host disease, which proved this method to be dangerous enough in a UK case series.[50] As a result, a prospective study was conducted seeking to define indications for allogeneic HSCT, balancing safety and danger, concluding that those would be refractory inflammation, co-existent MDS, and transfusion-dependent cytopenias, since most of the participants exhibited elimination of the vacuoles in their bone marrow aspiration and extinction of the UBA1-mutated clone from cells in the peripheral blood.[51]

Anti-Interleukin agents

IL-1: anakinra and canacinumab have been used with unsatisfactory results as only a minority had a good response while most of the patients on anti-IL-1 treatment discontinued because of reactions on the injection site.[1,14]

IL-6: a significant amount of data gathers around the use of anti-IL-6 agents and especially tocilizumab, not only from single case reports but also from larger case series, indicating its efficacy in cutaneous, constitutional, and hematologic manifestations.[1,40,52] It seems that VEXAS patients with RP respond better to this agent and according to a 1-year longitudinal observational study in Japan where tocilizumab was administered in dosage modified according to disease activity (subcutaneously 162 mg every week or intravenously 8 mg/kg every 2-4 weeks) with concomitant corticoid administration, patients were able to taper glucocorticoids albeit not achieving total discontinuation.[52] The writers suggested that tocilizumab can be a considerable option for patients with low International Prognostic Scoring System MDS score or for those with a prevailing inflammatory phenotype without MDS. However, data from the Dutch case series suggest that in VEXAS patients (where intestinal involvement is probable), tocilizumab might augment the risk for intestinal perforation, a recognized and fatal complication concerning the treatment with this agent.[14]

JAK inhibitors - ruxolitinib is a selective JAK1/2 inhibitor indicated in the treatment of myelofibrosis, polycythemia vera not responding to hydroxyurea and steroid-refractory acute graft-versus-host disease. In a multicenter international retrospective analysis of genetically proven VEXAS patients, half of whom had also MDS, different JAK inhibitors were used (mostly ruxolitinib and baricitinib and some cases with upadacitinib).[53] Overall, 50% of the patients had a good clinical response within the first month of treatment with a JAK inhibitor while the ruxolitinib subgroup manifested higher response rates, irrespective of the association with MDS. However, all blood transfusion-dependent MDS/VEXAS patients achieved transfusion independency within the first month. Regarding the survival of the treatments, almost one third of patients discontinued any JAK inhibitor other than ruxolitinib, within 6 months, and among those who did not, during the follow-up period (median time 6.9 months), the majority of patients initially on ruxolitinib (75%) were still receiving it versus only 28% of the other groups. Interestingly, the patients on ruxolitinib group managed to achieve a bigger steroid reduction by month 6, comparing to the other groups. The most common adverse effects attributed to JAK inhibitor treatment were infections (36.7%) and thromboembolic events (20%). Nonetheless, according to the study by Bourbon, all 3 patients that received ruxolitinib showed excellent results regarding the cutaneous manifestations but the duration of the treatment varied from 1.8 to 4.5 and 6.9 months respectively, suggesting a lower survival time for the drug, with no benefit on the peripheral cytopenia.[15]

"Time to next treatment" was a term conceived by Bourbon in his retrospective study of 11 male patients with VEXAS, referring to the time elapsed under a certain treatment until a new steroid-sparing agent was added. In this manner, the writers tried to compare the efficacy of different agents and the results showed that the longest median duration was linked to azacytidine (21.9 months), followed by cyclosporine (12.7 months) and tocilizumab (8 months), while the lowest was linked to adalimumab (3.4 months).[15]

A variety of other treatments has been tested, without therapeutic result whatsoever. As an example, in the Spanish cohort classical synthetic Disease-Modifying Antirheumatic Drugs (DMARDs) like methotrexate, mycophenolate mofetil, and azathioprine were mostly insufficient, as were anti-IL-6 and anti-TNF agents.[16] Interestingly though, anti-CD20 treatment provided a partial response in 75% of the patients while JAK inhibitors offered complete response in 20%. In 1 case study, a patient with HLA-positive axial spondyloarthritis, VEXAS syndrome and MDS was successfully treated with intravenous immunoglobulin G (IVIG) and secukinumab after failure of other agents like methotrexate, azathioprine, JAK inhibitors, infliximab, tocilizumab, anakinra, and ustekinumab.[29]

Prognosis

VEXAS syndrome appears to be a disease with high mortality. In their original publication, Beck et al[1] stated that 40% of the participants passed away either from causes associated with the disease itself (ex. progressive anemia, respiratory failure) or from complications from the administered treatment. Similarly, results from the case series published by Bourbon, showed 63% of 5-year survival rate, whereas in another study, 56% of patients died due to causes attributed to VEXAS syndrome.[15,21]

Data from the French cohort[13] confirm that survival rates were consistent between VEXAS-MDS and VEXAS cases without MDS, both exhibiting a 5-year survival probability of 83% and 76.3%, respectively. However, higher mortality (5-year mortality probability of 37.3%) was noted in patients exhibiting higher inflammatory burden and an association with hematologic dyscrasias (cluster 2). Data from the same cohort seem to differentiate the mortality risk among the UBA1 variants. Specifically, among the 3 variations (p.Met41Leu, p.Met41Val, p.Met41Thr), the p.Met41Leu mutation was associated with a more favorable prognosis. On the contrary, in another study, the Val variant was linked with a higher mortality risk.[2]

Conclusion

As a fusion between autoinflammatory and myelodysplastic conditions, VEXAS syndrome manifests with polysystemic symptoms, many of which can be alarming. Diagnosis is made using genetic testing of UBA1 gene mutations, however, high clinical suspicion should be raised in patients with persistent inflammatory syndrome and myelodysplasia. Corticosteroids in combination with targeted agents like tocilizumab seem to have promising results. Despite its recent discovery, literature regarding VEXAS syndrome is rapidly expanding and as more patients are being diagnosed, more case series and cohorts are being studied, with the hope of better profiling the disease and of finding more efficient treatment options.

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