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Vasculitis associated with VEXAS syndrome: A literature review

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Vasculitis is an inflammatory disorder of the blood vessels that causes damage to a wide variety of organs through tissue ischemia. Vasculitis is classified according to the size (large, medium, or small) of the blood vessels. In 2020, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, a novel autoinflammatory syndrome, was described. Somatic mutations in methionine-41 of UBA1, the major E1 enzyme that initiates ubiquitylation, are attributed to this disorder. This new disease entity connects seemingly unrelated conditions: inflammatory syndromes (relapsing chondritis, Sweet's syndrome, or neutrophilic dermatosis) and hematologic disorders (myelodysplastic syndrome or multiple myeloma). Notably, such patients sometimes develop vasculitis, such as giant cell arteritis and polyarteritis nodosa, and fulfill the corresponding classification criteria for vasculitis. Thus, vasculitis can be an initial manifestation of VEXAS syndrome. In this research topic exploring the link between autoinflammatory diseases and vasculitis, we first provide an overview of the disease mechanisms and clinical phenotypes of VEXAS syndrome. Then, a literature review using the PubMed database was performed to delineate the clinical characteristics of vasculitis associated with VEXAS syndrome. Finally, the therapeutic options and unmet needs of VEXAS syndrome are discussed.

KEYWORDS

autoinflammatory disease, giant cell arteritis, leukocytoclastic vasculitis, vasculitis, VEXAS syndrome

Introduction

In 1997, gain-of-function mutations in *MEFV* were reported to cause familial Mediterranean fever (FMF) (1). Based on this discovery, the concept of autoinflammation was proposed to delineate a group of disorders characterized by recurrent episodes of fever and systemic inflammation (2). Since then, advances in genomic techniques have identified multiple monogenic disorders and their corresponding signaling pathways (3–5). Accordingly, the disease concept of autoinflammation has shifted from monogenic disorders to complex multifactorial conditions (6).

Autoimmunity and autoinflammation were considered distinct disease entities, but it has become clear that they form a spectrum of diseases, with monogenic autoinflammatory diseases and autoimmune diseases characterized by multiple autoantibodies representing the two ends (7, 8). Systemic lupus erythematosus is a representative autoimmune disease that depends on acquired immunity, whereas FMF

and tumor necrosis factor (TNF) receptor-associated periodic syndromes are the best described autoinflammatory diseases in which innate immunity considerably contributes to pathogenesis (9, 10). Most rheumatic and musculoskeletal diseases show a mixed pattern of autoinflammation and autoimmunity.

In 2020, a novel autoinflammatory syndrome [vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic (VEXAS) syndrome] was reported (11). Hereafter, we refer to this paper as “the initial report”. This new disease is attributable to somatic mutations in methionine-41 of UBA1, the major E1 enzyme that initiates ubiquitylation. Surprisingly, this syndrome connects seemingly unrelated conditions, such as inflammatory syndromes (relapsing chondritis, Sweet’s disease, or neutrophilic dermatosis) and hematologic disorders (myelodysplastic syndrome or multiple myeloma). Each organ manifestation often fulfills the corresponding diagnostic or classification criteria. Thus, this syndrome is considered to exhibit a mixed pattern of autoinflammation and autoimmunity.

In addition, patients with VEXAS syndrome sometimes develop vasculitis such as giant cell arteritis (GCA) and polyarteritis nodosa (PAN) (11). However, as case reports and series of VEXAS syndrome have been accumulated, various types of coexisting vasculitis have been reported, including leukocytoclastic vasculitis (LCV), immunoglobulin A (IgA) vasculitis, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (12–14). Moreover, this disease was considered to be found only in males, since *UBA1* lies on the X chromosome. However, several female cases of inherited or acquired monosomy of the X chromosome have been reported (15–18). Thus, the clinical picture of VEXAS syndrome is heterogeneous and continuously expanding.

In this review, we provide an overview of the disease mechanisms and clinical phenotypes of VEXAS syndrome. We focused on the clinical characteristics of vasculitis associated with VEXAS syndrome through a literature review using the PubMed database. Finally, we discuss the therapeutic options and unmet needs of this syndrome.

How do somatic mutations in UBA1 cause VEXAS syndrome?

Ubiquitylation is a multi-step post-translational modification that triggers proteasomal degradation (19). In this process, ubiquitin covalently binds to the substrate sequentially. Ubiquitylation is essential for multiple cellular processes such as cell cycle progression, DNA damage response, and immune signaling pathways (20, 21). Thus, dysregulation of the ubiquitin-proteasome system results in many disease states, such as infantile neurodegeneration, susceptibility to infection, lymphoproliferative disorders, and malignancy (21–23). Several

autoinflammatory diseases have also been linked to alterations in the ubiquitylation system (24).

Ubiquitylation is initiated by the attachment of a single ubiquitin molecule to a target protein through a three-step enzymatic cascade that includes ubiquitin-activating (E1), ubiquitin-conjugating (E2), and ubiquitin-ligating (E3) enzymes (25). The concerted action of E1, E2, and E3 enzymes, as well as deubiquitylases, generates specific ubiquitylation patterns, which trigger the recognition and degradation of substrates by the proteasome. Ubiquitin-like modifier-activating enzyme 1 (UBA1), the major E1 enzyme, has two isoforms: UBA1a and UBA1b (26). UBA1a is the long isoform starting from codon 1 (Met1) of UBA1 and is localized in the nucleus, whereas UBA1b is the short isoform starting from codon 41 (Met41) and is localized in the cytoplasm without a nuclear localization signal.

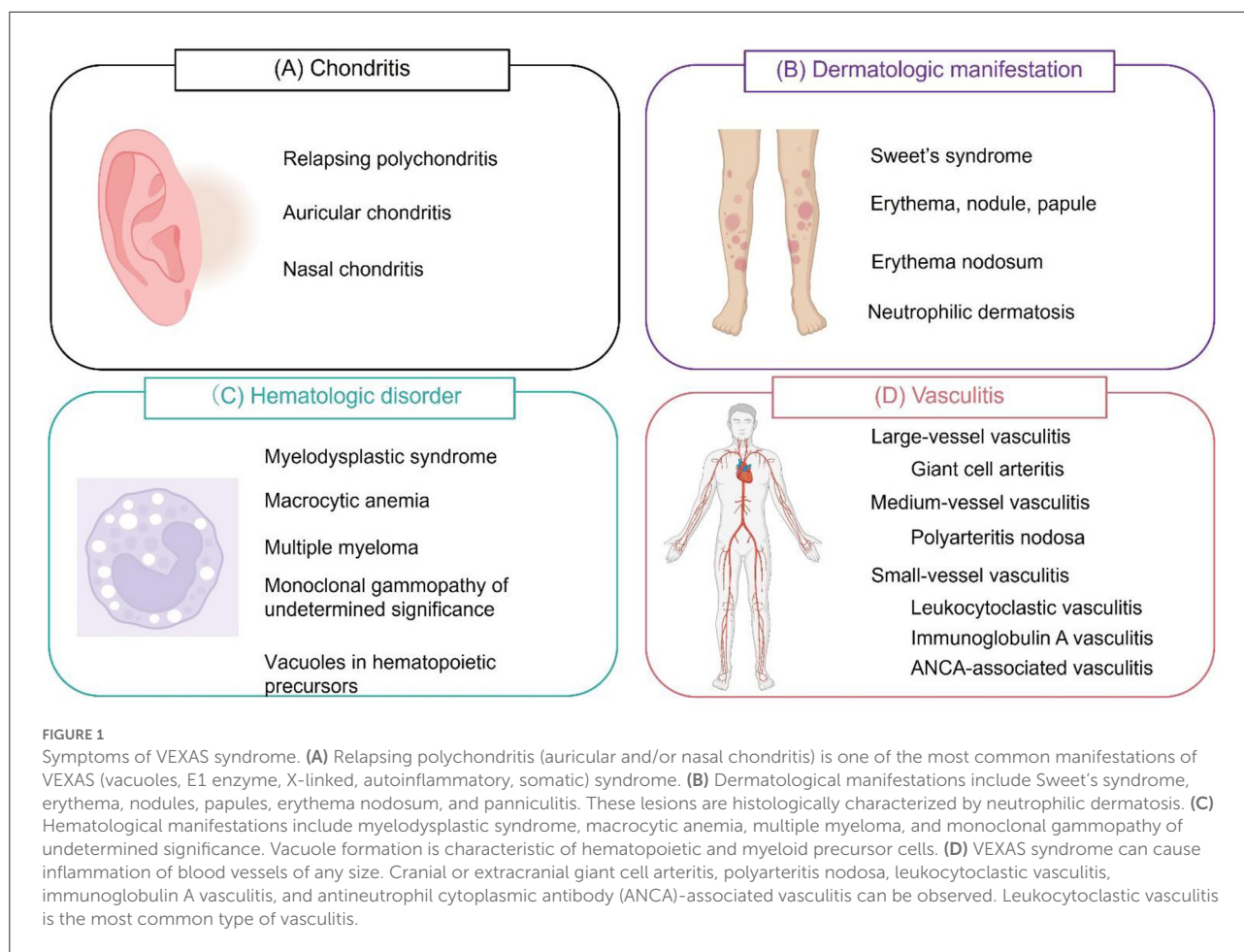
Individuals with VEXAS syndrome acquire missense mutations at or around the start codon for UBA1b (Met41), which abrogates the expression of UBA1b. More than half of myeloid and erythroid precursor cells harbor such loss-of-function mutations (11). Therefore, somatic mutations found in VEXAS syndrome lead to a reduction in cytoplasmic UBA1 function, and the resultant decreased ubiquitylation activates the unfolded protein response and type I interferon production (21). Indeed, transcriptome analysis of the peripheral blood from patients with VEXAS syndrome showed highly activated inflammatory signatures in multiple pathways, including TNF, interleukin-6 (IL-6), interferon- γ , and IL-8 (11). Neutrophils may also participate in exacerbating the inflammatory response by enhancing neutrophil extracellular trap (NET) formation (27).

Clinical phenotypes of VEXAS syndrome

Chondritis

In the initial report, 25 patients were diagnosed with VEXAS syndrome based on the confirmation of somatic mutations in codon 41 of *UBA1* (p.Met41Val, p.Met41Thr, or p.Met41Leu) (11). The median age at disease onset was 64 years, and all patients were male. Auricular and/or nasal chondritis was one of the most common organ manifestations (Figure 1), with 15 (60%) patients meeting the classification criteria for relapsing polychondritis (RP). According to other cohort studies, the incidence of chondritis was 36–50% (28–30).

The frequency of *UBA1* mutations in patients with RP has varied greatly in previous reports, ranging from 7.6% (7/92 patients) to 72.7% (8/11 patients) (17, 31). The reason for this difference remains unclear but could be due to racial differences. RP patients with *UBA1* mutations (VEXAS-RP) had significantly higher mortality rates than those without, necessitating the early identification of VEXAS-RP (31). A decision tree algorithm



based on male sex, mean corpuscular volume >100 fl, and platelet count $<200 \times 10^3/\mu\text{l}$ may help differentiate VEXAS-RP from RP (31).

non-neutrophilic dermatosis, suggesting a distinction between “clonal” (neutrophilic dermatosis) and “paraclonal” (LCV and panniculitis) cutaneous involvements (37).

Skin manifestations

Skin manifestations are also common in VEXAS syndrome, including Sweet's syndrome, erythema, nodules, papules, erythema nodosum, and panniculitis (14, 29, 32–36). The histological hallmark of skin lesions is neutrophilic dermatosis, which is often accompanied by LCV. The most commonly affected sites are the neck and trunk, but they also appear in the extremities (37). According to a literature review, approximately 90% (126/141) of published cases of VEXAS syndrome had cutaneous signs (14).

Zakine et al. performed molecular analyses of skin tissue samples and demonstrated that dermal infiltrates are derived from pathological myeloid clones with *UBA1* mutations (34). However, Lacombe et al. identified *UBA1* mutations only in neutrophilic dermatosis, but not in

Hematologic disorder

Hematologic disorders are also prevalent in VEXAS syndrome, including myelodysplastic syndrome (MDS), macrocytic anemia, multiple myeloma, and monoclonal gammopathy of undetermined significance (38). The name “V”EXAS syndrome stems from “vacuoles” in myeloid and erythroid cells, but not in T lymphocytes, B lymphocytes, or fibroblasts (11). Of note, myeloid and erythroid vacuolization is not specific to VEXAS syndrome, but has been described in other disorders, including copper deficiency (39), acute myeloid leukemia (40), Menkes disease (41), and transcobalamin II deficiency (42).

Thrombotic manifestations occur in approximately 40% of patients with VEXAS syndrome (43). The reported incidence of venous thromboembolism (36.4%) is much higher than that

of arterial thrombosis (1.6%) (44). Crosstalk between aberrantly activated immune cells, platelets, and endothelial cells may result in the dysregulation of hemostasis and endothelial dysfunction.

Other clinical manifestations

Lung involvement, such as pulmonary infiltration, organizing pneumonia, and pleural effusion, can be found in approximately 50–70% of patients with VEXAS syndrome (11, 29, 30). Other symptoms include recurrent fever, arthritis, lymphadenopathy, and ocular manifestations. A wide array of clinical manifestations necessitate generalists, primary care providers, and rheumatologists to familiarize themselves with this syndrome (45).

Vasculitis associated with VEXAS syndrome

Large vessel vasculitis

In the initial report, 1 of 25 patients (4%) was diagnosed with GCA based on temporal artery biopsy. A 77-year-old male with a *UBA1* mutation (p.Met41Val) presented with fever, pulmonary infiltrates, deep vein thrombosis, and MDS. Despite treatment with glucocorticoids, the patient died at 78 years old (11). As of June 25, 2022, 102 papers regarding VEXAS syndrome have been published in the PubMed database when the search term “VEXAS” was applied, and all papers were carefully reviewed. Table 1 summarizes the vasculitides associated with VEXAS syndrome. To the best of our knowledge, another case was diagnosed as extra-cranial GCA (46). This patient was a male in his sixties presenting with fever, pulmonary infiltrates, ear and nose chondritis, macrocytic anemia, and thrombocytopenia with a *UBA1* mutation (p.Met41Thr). 18F-fluorodeoxyglucose positron emission tomography showed increased uptake in the aortic wall of the ascending aorta and aortic arch. The patient showed resistance to glucocorticoids and multiple biological disease-modifying antirheumatic drugs (bDMARDs) such as tocilizumab, anakinra, and infliximab, and died 8 years later (Table 1). Since only two cases of VEXAS-GCA have been reported, sufficient examination to discriminate GCA and VEXAS-GCA could not be conducted. The differential diagnoses of large vessel vasculitis are diverse (53), and these cases illustrate that VEXAS syndrome could be a potential mimicker of large vessel vasculitis (54).

The incidence of GCA in reported cases with VEXAS syndrome seems rare. The question is how often *UBA1* mutations are found in patients with GCA. To address this, Poulter et al. sequenced *UBA1* in 612 male samples obtained from the UK GCA Consortium. No samples showed *UBA1* mutations, whereas the mutation was identified in seven out of 1,055 samples from the cytopenic cohorts (55). 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.

Medium vessel vasculitis

In the initial report, 3 (12%) patients with VEXAS syndrome fulfilled the classification criteria for PAN (58), which is a medium-sized vessel vasculitis (59). Our literature review found nine cases of medium vessel vasculitis (Table 1) (11, 35, 47–50). 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 anemia 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. Notably, two of the three survivors successfully underwent allogeneic hematopoietic stem cell transplantation (49).

Small vessel vasculitis

The most common vasculitis is small-vessel vasculitis, particularly LCV. The reason stems from the fact that skin manifestations, which are observed in 80–90% of patients, often reveal the histopathology of LCV (14, 37, 60). LCV is histologically characterized by angiocentric segmental inflammation, fibrinoid necrosis, and neutrophilic infiltration around the blood vessel walls (14, 61). In the initial report, LCV was histologically confirmed in seven of 25 patients (28%) with VEXAS syndrome and in seven of 22 patients (31.8%) with dermatologic manifestations. Although the demographics of patients who developed LCV was unclear in the initial report, an additional nine cases of LCV were identified in our literature review (Table 1) (12, 30, 37, 51, 52). The average age at disease onset was 68.3 years (ranging from 55 to 87 years) and all were male. Clinical features of these patients seem not different from patients without LCV.

Furthermore, it has become clear that VEXAS syndrome can be associated with small vessel vasculitides other than LCV, such as IgA vasculitis (13) and AAV (microscopic polyangiitis and granulomatosis with polyangiitis) (12, 35). It remains unclear whether the complications of these diseases are coincidental or causative; however, aberrant neutrophil activation with excessive NETs formation is a common feature of both VEXAS syndrome and AAV (27, 62). In AAV, ANCA activates neutrophils to produce reactive oxygen species and extrude chromosomal DNA in the form of NETs. The neutrophil activation highly depends on the priming by TNF, lipopolysaccharide, or complement factor 5a (C5a) (62). The efficacy and safety of C5 receptor

TABLE 1 Vasculitis associated with VEXAS syndrome identified by our literature review.

	Case	Age at onset	Sex	Vasculitis	UBA1 mutation	Chondritis	Skin	MDS	Macrocytic anemia	Pulmonary infiltrates	Use of GCs	Use of b/tsDMARDs	Prognosis	References
Large vessel vasculitis	1	77	M	GCA	p.Met41Val	-	-	+	+	+	+	-	deceased	(11)
	2	60 s	M	GCA	p.Met41Thr	+	-	-	+	+	+	TCZ, ANK, IFX	deceased	(46)
Medium vessel vasculitis	1	56	M	PAN	p.Met41Val	-	+	+	+	+	+	IFX, ANK	deceased	(11)
	2	55	M	PAN	p.Met41Val	+	+	+	+	+	+	ANK, CAN, ADA, IFX	deceased	(11)
	3	80	M	PAN	p.Met41Thr	-	+	+	+	+	+	-	deceased	(11)
	4	80	M	MVV	+	-	+	-	+	+	+	-	deceased	(35)
	5	50	M	PAN	p.Met41Thr	-	+	-	+	pulmonary nodule	+	IFX, RTX	deceased	(47)
	6	74	M	PAN	p.Met41Val	-	+	-	+	pulmonary infarction	+	RTX, TCZ	Survived	(48)
	7	43	M	PAN	p.Met41Val	-	+	-	+	-	+	ANK, CAN	Survived	(49)
Small vessel vasculitis	8	63	M	PAN	p.Met41Leu	+	+	-	+	-	+	ANK, CAN, TCZ	Survived	(49)
	9	55	M	MVV	p.Met41Val	-	+	-	+	-	NA	NA	deceased	(50)
	1	72	M	LCV	Not tested	-	+	+	+	+	+	-	NA	(12)
	2	55	M	LCV	p.Met41Val	-	+	+	+	+	+	TCZ, CAN, ETN	NA	(51)
	3	68	M	LCV	p.Met41Thr	-	+	+	+	+	+	TCZ, ADA, CAN	waiting HSCT	(52)
	4	72	M	LCV	p.Met41Thr	NA	NA	NA	NA	NA	NA	NA	NA	(37)
	5	63	M	LCV	p.Met41Leu	NA	NA	NA	NA	NA	NA	NA	NA	(37)
	6	87	M	LCV	p.Met41Val	NA	NA	NA	NA	NA	NA	NA	NA	(37)
	7	55	M	LCV	p.Met41Val	+	+	+	+	+	+	ANK, RTX	Survived	(30)
	8	69	M	LCV	p.Met41Thr	+	+	+	+	-	+	ANK, TCZ	Survived	(30)
	9	74	M	LCV	p.Met41Thr	+	+	-	+	-	+	-	Survived	(30)
	10	76	M	IgAV	p.Met41Thr	+	+	+	+	+	+	TCZ	Survived	(13)
11	72	M	MPA	p.Met41Val	-	-	+	+	+	+	RTX	Survived	(12)	
12	71	M	GPA	+	-	+	-	anemia	-	+	IFX, RTX, TCZ	Survived	(35)	

ANK, anakinra; bDMARDs, biological disease-modifying antirheumatic drugs; CAN, canakinumab; ETN, etanercept; GC, glucocorticoid; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; HSCT, hematopoietic stem cell transplantation; IFX, infliximab; IgAV, IgA vasculitis; LCV, leukocytoclastic vasculitis; MDS, myelodysplastic syndrome; MPA, microscopic polyangiitis; MVV, medium vessel vasculitis; NA, not available; PAN, polyarteritis nodosa; RTX, rituximab; TCZ, tocilizumab; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

blockade by avacopan has been demonstrated in patients with AAV (63), but has not yet been tested in VEXAS syndrome.

Current therapeutic approach for VEXAS syndrome

Immunosuppressive agents and DMARDs

Considering the inflammatory aspect, immunosuppressive therapies are a sensible treatment option for this syndrome. Glucocorticoids, cyclophosphamide, conventional synthetic DMARDs (methotrexate, mycophenolate mofetil, azathioprine), and bDMARDs [including anti-IL-1 (anakinra, canakinumab), anti-TNF (infliximab and adalimumab), anti-IL-6 (tocilizumab), anti-CD20 (rituximab), anti-IL-17 (secukinumab), anti-IL-12/IL-23 (ustekinumab) therapies, and abatacept] have been administered to patients with VEXAS syndrome (11, 47, 64–66). In addition, janus kinase (JAK) inhibitors, such as ruxolitinib, tofacitinib, and baricitinib, have been introduced to some patients to block intracellular cytokine signalings (67–70). Given that multiple cytokines are involved in the disease mechanism of VEXAS syndrome, use of JAK inhibitors seems better therapeutic strategy rather than single cytokine blockade. However, these therapies work great for some patients and not for others, yielding varying results. Biomarkers that distinguish patients who are responsive to these therapies and those who are not should be established.

Hypomethylating agents (azacytidine)

Since abnormal DNA methylation patterns drive the disease mechanisms of MDS, standard therapies for MDS include hypomethylating agents such as azacytidine (71). Considering the high prevalence of MDS in VEXAS syndrome, azacytidine could be a good candidate for this syndrome (67). Indeed, there have been a case report of successful treatment with azacytidine (72). However, in the French registry, 11 patients with VEXAS syndrome and MDS were treated with azacytidine, and the clinical response was achieved only in five patients (73), suggesting that this agent does not necessarily guarantee sufficient therapeutic effect and long-term prognosis.

Allogeneic hematopoietic stem cell transplantation

If above-mentioned therapies fail, allogeneic hematopoietic stem cell transplantation (ASCT) may be the last treatment option for VEXAS syndrome. Although the incidence of treatment-related mortality remains high, given that irreversible somatic mutations have already been introduced in myeloid

precursor cells in VEXAS syndrome, rejuvenation of the immune system by ASCT may be an ideal treatment. In fact, a series of cases showing the successful treatment courses with ASCT has been accumulated (49, 74).

Unmet needs in VEXAS syndrome

Diagnosis

VEXAS syndrome was discovered using an innovative genotype-driven approach. Currently, the diagnosis of this syndrome depends solely on the presence of *UBA1* mutations confirmed by Sanger sequencing, the gold standard for genetic sequencing (75). However, Sanger sequencing method is time-consuming and has several limitations such as the missed recognition of variations (76). Therefore, it remains unclear whether this is sufficient. Use of next-generation sequencing (NGS), including whole-genome sequencing and whole-exome sequencing, may favorably serve in the faster and more accurate diagnosis.

In addition, classification criteria for the syndrome should be established to conduct clinical studies. In addition to genetic sequencing, a point-based system that weighs each clinical manifestation may be required.

Treatment

As described, VEXAS syndrome shows resistance to multiple therapeutic agents, resulting in high mortality rates. Early identification of this syndrome by NGS and classification criteria may alter the treatment course. Furthermore, if the precise mechanism by which somatic mutations in *UBA1* occur in middle-aged or elderly males is elucidated, a more disease-specific therapeutic approach for this syndrome, and even prevention of this mutation, could be possible.

In conclusion, VEXAS syndrome has led to the recognition that somatic mutations may be a more frequent cause of human disease than previously recognized (77). Further studies are required to provide appropriate diagnosis and treatment.

Author contributions

MK and RW conducted a literature review and generated Figure and Table. RW drafted the manuscript. MH finalized the manuscript. All authors contributed to the article and approved the submitted version.

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