

Promise of Jak Inhibition in the Management of VEXAS, Case Report with Review of the Literature

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Abstract: VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a recently described adult autoinflammatory disease associated with somatic mutations in the gene encoding ubiquitin-activating enzyme 1 (UBA1) in hematopoietic progenitor cells. Loss of function mutation of UBA1 results in a broad range of inflammatory and hematological conditions. To date, there are no established targeted therapies for VEXAS syndrome, especially in patients who are refractory to conventional immunosuppressive treatments. We report the case of a 75-year-old Hispanic gentleman with hypertension, dyslipidemia, and type 2 diabetes mellitus who presented with a 2-year history of intermittent fever, weight loss, recurrent sore throat, recurrent soft tissue swelling (mimicking cellulitis), oligoarthritis, erythema nodosum, and venous thrombosis. Laboratory workup showed elevated inflammatory markers, macrocytic anemia, and leukopenia. Patient received several rounds of antibiotics and corticosteroids for presumed cellulitis and throat infections, with limited improvement. He subsequently underwent bone marrow biopsy, which showed characteristic vacuolization of myeloid precursors. Genetic testing revealed a missense mutation in UBA1, Exon 3 c.121A>G, pMet41Val. He was diagnosed with VEXAS syndrome. He was started on corticosteroids and Tocilizumab (anti-IL-6 receptor antibody). He had severe leukopenia with Tocilizumab and was switched to Ruxolitinib (Jak inhibitor). He had a significant clinical response to Ruxolitinib and was able to be tapered off prednisone. Our case report and review of the literature report Jak inhibition as a possible target for the management of inflammatory symptoms of VEXAS.

Keywords: VEXAS, autoinflammation, UBA1, genetic testing, Jak inhibition

Introduction

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is an adult-onset autoinflammatory disease first reported by Beck et al in 2020. It is associated with acquired errors of immunity caused exclusively by somatic mutations in the ubiquitin-activating enzyme 1 (UBA1) gene in hematopoietic progenitor cells.¹ This gene is located on the X chromosome and encodes for the ubiquitin-activating enzyme 1, which is required to initiate a cellular ubiquitylation cascade that facilitates protein degradation and adequate regulation of inflammatory pathways. Missense mutations of UBA1 gene result in dysregulated ubiquitylation and hyperactivation of innate immune cells, leading to overexpression of inflammatory cytokines including interferon-gamma (IFN γ), interleukin (IL)-6 and tumor necrosis factor-alpha (TNF- α).² This X-linked genetic disorder is primarily observed in men with onset around middle age or later. There are reports of such syndrome in women with inherited or acquired monosomy of the X chromosome. It is characterized by combined features of hematological disease and autoinflammation involving the skin, joints, cartilage, lungs, and blood vessels.¹ Current literature lacks standardized therapeutic guidelines given the rarity and complexity of VEXAS syndrome. Treatment with corticosteroids and conventional immunosuppressants is often inadequate. While the use of JAK inhibitors remains investigational, they represent a promising therapeutic option by targeting key cytokine pathways implicated in VEXAS pathogenesis.³

Case Presentation

A 75-year-old Hispanic gentleman with controlled essential hypertension, dyslipidemia, and type 2 diabetes mellitus presented with a 2-year history of intermittent drenching night sweats, high-grade fever 39.5–40.5 Celsius, and unintentional weight loss of 20 pounds over 3 months. This was associated with recurrent sharp pain in the right lower jaw, diffuse right facial redness and swelling, enlarged submandibular lymphadenopathy, left ankle arthritis, and paresthesia involving bilateral lower extremities. He did not have cough, hemoptysis, sore throat, dysphagia, dental cavities, or oral ulcers. CT head and neck with contrast showed an edematous appearance of the soft palate with effacement and mild leftward displacement of the oropharyngeal airway with scattered multicompartment edema mostly within the lower submandibular region, right anterior neck, and right oropharyngeal and carotid spaces concerning for angioedema with possible retropharyngeal infection (**Figure 1a**). Flexible fiberoptic laryngoscopy was unremarkable. Laboratory work showed ESR elevated to 77 mm/hr (reference range: 0–20 mm/hr), CRP of 71.2 mg/L (reference range: <0.3 mg/dL), with normal white cell counts. Further testing was negative for HIV, coccidioidomycosis, and active tuberculosis. He was treated empirically with a short course of oral corticosteroids and broad-spectrum antibiotics with gradual improvement of his symptoms.

Three months later, he developed erythema nodosum-like tender, red, swollen nodules in bilateral lower legs. At that time, he did not have oral/genital ulcers, redness or swelling of the eyes, diarrhea, or recent infection. Laboratory workup was negative for ANA, ANCA, RF, anti-CCP antibodies, and fecal calprotectin and showed normal levels of ACE. CT chest was negative for lymphadenopathy or cavitary lesions. Colonoscopy was done to rule out colon cancer or inflammatory bowel disease and was unremarkable. He was empirically started on colchicine 0.6 mg orally daily with gradual resolution of the nodules.

Shortly after this episode, he had two more episodes of left facial and neck swelling associated with low-grade fever. He also had an unprovoked left upper extremity DVT. CT scan of soft tissues of the neck without contrast showed extensive soft tissue enlargement and thickening of the retropharyngeal and prevertebral tissues. Repeated laryngoscopy was negative. PET/CT was negative for FDG avid lesion. Laboratory workup showed leukopenia of 3.1 k/mm³ (reference range: 4–11 k/mm³) with an absolute neutrophil count (ANC) of 1340/uL (reference range: 1600–9300/uL), macrocytic anemia with Hgb of 10.5 g/dL (reference range: 13–18 g/dL), low iron at 24 mcg/dL (reference range 35–150 mcg/dL), low iron saturation at 9% (reference range: 20–50%), with normal ferritin levels. Serum protein electrophoresis showed high alpha-2 globulin at 1.3 g/dL (reference range: 0.6–1.0 g/dL), elevated kappa light chain at 31.7 mg/L (reference range: 3.3–19.4 mg/L), and elevated lambda chain at 31.2 mg/L (reference range: 5.7–26.3 mg/L) with normal kappa/lambda ratio. Immunoglobulin and immunofixation were normal, as well as vitamin B12, Folate, C1 esterase, and C1q inhibitor functional assay. Bone marrow biopsy showed mildly hypercellular marrow (50%) with trilineage hematopoiesis and vacuolization of myeloid precursors (**Figure 1b**). No dysplasia in erythroid or megakaryocytic cells, reticulin fibrosis or increased blasts were seen. GMS and AFB stains were negative for fungal and acid-fast organisms.

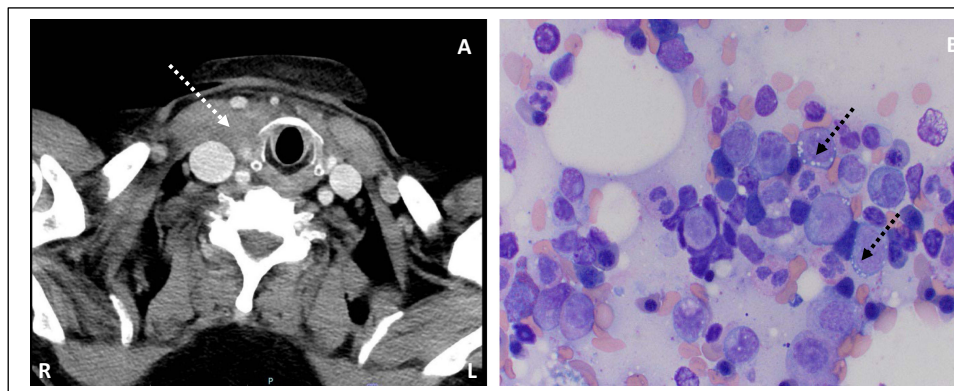


Figure 1 (A) Scattered multi-compartment edema, mostly within the right side, involving subcutaneous tissue of the anterior neck, right parapharyngeal, and carotid with mild enlargement of the right strap muscle compared to the left spaces (white arrow). (B) Bone marrow aspirate showing frequent vacuoles within the cytoplasm of myeloid precursor cells (black arrow).

Cytogenetic analysis showed no evidence of an acquired clonal abnormality. Serum ceruloplasmin, copper, and zinc were unremarkable.

Given his recurrent fever, night sweats, unintentional weight loss, skin rashes, bone marrow biopsy results, and leukopenia, there was a concern for possible myelodysplastic syndrome (MDS). Genetic testing for MDS was done and showed a missense mutation in UBA1, Exon 3 has c.121A>G, pMet41Val. This mutation has been reported to be associated with VEXAS syndrome. The diagnosis of VEXAS syndrome was made, and the patient was started on prednisone 60 mg orally daily for 4 weeks, followed by a slow taper of prednisone down to 10 mg orally daily over 3 months. He had improvement with high doses of prednisone, with a recurrence of fever and skin rashes on lower dosages. He then started on Tocilizumab 162 mg subcutaneously every 2 weeks (anti-IL-6 receptor antibody). At 6 weeks follow-up, he had improvement in fevers, skin rash, and night sweats. At that visit, he also had leukopenia of 1.9 k/mm³ (reference range: 4–11 k/mm³) and ANC of 300/ul (reference range: 1600–9300/uL), which recovered to >1000/ul after temporarily holding Tocilizumab. Treatment with Tocilizumab was resumed at 162 mg every 4 weeks instead of every 2 weeks, however, the patient had flare-up with increasing the dosing interval of Tocilizumab. Tocilizumab was discontinued, and the patient was started on Ruxolitinib 10 mg orally twice daily. At the 6-month follow-up, he was off prednisone and doing well with no flare-ups.

Discussion

Clinical Features

Prevalence of VEXAS syndrome is 1 in 13591.⁴ VEXAS is associated with a mutation in the UBA1 gene located in the X chromosome and is only reported in males. This syndrome is characterized by progressive bone marrow failure and myeloid-driven inflammation that has overlapping hematological and rheumatological clinical features. It usually presents with recurrent unexplained fevers that occur in 74% of patients associated with poor appetite and weight loss. These constitutional symptoms are usually accompanied by relapsing multisystemic inflammatory symptoms and elevated acute phase reactants. The most common manifestations are the cutaneous manifestations that occur in approximately 88% of patients and could be the primary manifestation of VEXAS syndrome, including non-vasculitic lesions such as neutrophilic dermatoses, erythema nodosum, erythematous papules, periorbital edema, and injection site reactions or vasculitic lesions such as leukocytoclastic vasculitis.⁵

Relapsing polychondritis is found in more than 50% of the patients before the confirmed diagnosis of VEXAS syndrome. About 50% of patients can have lung involvement with various manifestations, including pleural effusions and pulmonary infiltrates, including neutrophilic alveolitis, pleural inflammation, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, and bronchiolitis obliterans. Musculoskeletal manifestations occur in 36% of patients, including myalgia, arthralgia, and arthritis. Furthermore, patients may present with systemic vasculitis affecting blood vessels of any size, including giant cell arteritis, polyarteritis nodosa. ANCA-associated vasculitis, have also been reported in rare cases.⁶

Hematological manifestations are present in almost all patients. Presentations include progressive cytopenia, macrocytic anemia, myelodysplastic syndrome and, less commonly, deep venous thrombosis (38%), and lymphadenopathy (34%). Cytoplasmic vacuoles in myeloid and erythroid precursors are the key findings in bone marrow biopsy of patients with VEXAS syndrome. However, they are not pathognomonic for VEXAS syndrome, and other conditions should be excluded, such as myelodysplastic syndrome, alcohol intoxication, copper and zinc deficiency.⁷ Our patient presented with unexplained constitutional symptoms along with cutaneous, musculoskeletal and hematological manifestations raising clinical suspicion for VEXAS syndrome. However, definitive diagnosis requires identification of a pathogenic UBA1 mutation via targeted next-generation sequencing (panel sequencing).

Genotypes of VEXAS and Genotype-Phenotype Correlation

VEXAS syndrome is associated with somatic mutations involving the start codon for UBA1b isoform that initiates translation at Met41 (p.Met41) in hematopoietic progenitor cells. Mutations include c.122T>C pMet41Thr (present in 47–50% of patients), c.121A>G pMet41Val (present in 24–31% of patients), c.121A>C pMet41Leu (present in 19–20%

of patients). Other rare mutations include splice motif mutation, c.118-1G>C pMet41, c.167C>T pSer56Phe, c.118-2A>G, c.122T>G pMet41Thr, c.118-2A>C.^{8,9} Much remains to be known regarding the genotype-phenotype correlation. Hematologic, skin, and pulmonary involvement is seen in most patients. Our patient was found to have c.121A>G, pMet41Val variant, which has been associated with severe macrocytic anemia and corticosteroid dependence.¹⁰ Patients with c.122T>C pMet41Thr have a dominance of ocular symptoms. Patients with c.121A>C pMet41Leu present with gastrointestinal involvement, pulmonary infiltrates, and mediastinal adenopathy and have better survival than patients with the other mutations.^{10,11}

The cause of death is related to the disease itself, as well as toxicities from glucocorticoids and immunosuppressive medications used for management. In published reports, a Dutch cohort had 50% mortality at a median follow-up of 4 years, a French cohort had a 15.5% mortality at 3 years and an NIH cohort had a mortality of 25% with a median survival of 10 years.^{10,12,13}

Pathophysiology

VEXAS syndrome is caused by somatic mutations in UBA1 gene in the hematopoietic stem and progenitor cells. There is lineage bias in that UBA1 myeloid progenitors have increased cell cycling and differentiation, whereas UBA1 lymphoid progenitors undergo apoptosis. This results in increased myeloid cells and decreased lymphoid cells. There is dysregulated protein degradation, as the protein ubiquitination and proteasome pathways are dysregulated without compensatory autophagy, resulting in increased stress response leading to upregulation of inflammatory pathways involving IFN γ , TNF- α and IL-6 in mutated myeloid clones. This pathway is further augmented by increased cell-cell interaction between hematopoietic stem cells and myeloid cells in the context of inflammatory cytokines such as IFN γ and TNF- α . Pathophysiology is driven by mutated clones that promote inflammation via the upregulation of IFN γ , TNF- α and IL-6.^{1,2,9}

Treatment

Treatment is challenging due to multiorgan involvement, heterogeneity of presentation, association with hematological malignancies, and infections associated with management options. There is limited data on successful treatment options, with no guidelines or standardized treatment algorithms. Current treatment is based on a limited number of case reports and case series. High-dose glucocorticoids (GC) (20–40 mg orally daily) are the most effective treatment, with relapse on lower dosages and increased incidence of side effects associated with the chronic use of high-dose GC.^{14,15} Conventional DMARDs such as methotrexate, tacrolimus, cyclosporine, mycophenolate, cyclophosphamide, and azathioprine have been used with modest or no efficacy.^{16–19} Hydroxychloroquine, dapsone, colchicine, lenalidomide, bortezomib, abatacept, and Intravenous Immunoglobulin have all been tried without any clinical improvement.^{3,9,19}

Biologic therapy with IL-1 antagonists (Anakinra and Canakinumab) and TNF- α targeted therapies has limited efficacy.^{3,16,20} Other biologics, such as Rituximab, Secukinumab, and Ustekinumab, had no therapeutic efficacy.^{16,20} IL-6 targeted therapy with tocilizumab has shown some improvement in skin, hematological manifestations, and reduction in dependence on prednisone. However, such responses are transient and may be associated with increased side effects such as gastrointestinal perforation.^{3,15,16,20–22} In our patient, IL-6 targeted therapy with tocilizumab caused severe leukopenia of 1.9 k/mm³ and ANC of 300/ul, resulting in discontinuation of therapy.

To date, Jak inhibitors Ruxolitinib, Tofacitinib, Baricitinib, and Upadacitinib have shown some clinical efficacy in the management with a reduction in skin involvement, improvement in anemia, and reduction in glucocorticoid dosing (Table 1). In one report, 50% of patients at 1 month, 57% of patients at 3 months, and 82% of patients at 6 months had a good clinical response with Jak inhibitors. Bacterial and viral infections and increased thrombotic events are a concern with Jak Inhibitors.^{3,10,15,19} We initiated our patient on Ruxolitinib 10 mg orally twice daily, resulting in improved clearance of skin rash, anemia, fatigue, and fevers, as well as a significant reduction in prednisone dosage. At 6 months follow-up, our patient is off prednisone and continues on Ruxolitinib 10 mg orally twice daily with significant improvement and without any flare-ups.

Jak pathways are utilized by various inflammatory cytokines to signal into cells and mediate downstream effects (Figure 2). Jak inhibitors are approved for a number of autoimmune inflammatory conditions (Table 2). UBA1 mutation causes the production of a number of inflammatory cytokines such as IFN γ , TNF- α , and IL-6. It is thus plausible that Jak

Table 1 Review of Literature of VEXAS Syndrome Receiving Jak Inhibition (JAKi)

Study Type	Number of Patients	Median Age (yr)	Genetic Mutation (n)	Previous Immuno-Suppressive Treatment	JAKi (n) - Dose (If Available)	Clinical Outcome
Retrospective study						
Hadjadj 2024 ²³	110	71	p.Met41Val-(33%) p.Met41Thr-(29%) p.Met41Leu-(20%) Others- (15%)	MTX, MMF, AZA, CYC	Ruxolitinib (68)-10-40 mg/day Tofacitinib (7) Baricitinib (2) Upadacitinib (1)	At 12 months, clinical remission, CRP $\leq$ 10 mg/L and $\leq$ 10 mg/day of prednisone equivalent) was noted in 20% of patients treated with JAKi
Moura 2023 ²⁴	45	68	p.Met41 Val-(10) p.Met41Thr-(24) p.Met41Leu-(4) Splice-(7)	TCZ, TNFi, ANA, MTX, AZA, HCQ	Ruxolitinib (1)-10-40 mg/day Tofacitinib (2) Baricitinib (2) Upadacitinib (2)	All seven patients treated with JAK inhibitors appeared to respond well with symptom control (cough or dyspnea) and resolution of imaging abnormalities.
Heiblig 2022 ²⁵	30	67	p.Met41Val p.Met41Thr p.Met41Leu c.118-1G>C (splice) c.118-2T>C (splice)	TCZ, ANA, TNFi, MTX, HCQ	Ruxolitinib (12)-10-20 mg/day Tofacitinib (11) Baricitinib (4) Upadacitinib (3)	After 6 months, higher clinical response in patients treated with Ruxolitinib (87%) vs other JAKi (11%) with a higher biological response (>50% reduction of CRP) in patients treated with Ruxolitinib
Georgin-Lavialle 2022 ¹²	116	67	p.Met41Val p.Met41Thr p.Met41Leu	Unavailable	JAKi (15)-No class specified	Unavailable
Bourbon 2021 ²⁶	11	66	p.Met41Val-(3) p.Met41Thr-(5) p.Met41Leu-(1) Splice motif-(2)	MTX, MMF, AZA, TCZ, TNFi	Ruxolitinib (2) Tofacitinib (1)	A dramatic regression of skin lesions after starting Ruxolitinib without an increase in corticosteroids in 1 patient.
Case Series						
Salehi 2023 ²⁷	3	71	p.Met41Val-(2) p.Met41Thr-(1)	MMF, MTX, AZA, TCZ	Tofacitinib (3)-5 mg BID	1 patient- ameliorated disease symptoms, resolved cytopenia, and inflammatory markers. 1 patient- blood transfusion-dependent with no major flares requires hospitalization 1 patient-no clinical response

(Continued)

Table 1 (Continued).

Study Type	Number of Patients	Median Age (yr)	Genetic Mutation (n)	Previous Immuno-Suppressive Treatment	JAKi (n) - Dose (If Available)	Clinical Outcome
Islam 2022 ²⁸	3	68	p.Met41Thr	TCZ, TNFi	Baricitinib (1)	Remained on prednisone 15–25 mg/day and transfusion-dependent
Al-Hakim 2022 ²⁹	4	59	p.Met41Val-(1) p.Met41Thr-(1)	TCZ, AZA, ANA, MMF	Baricitinib (2)	No response and transfusion-dependent
Muratore 2022 ³⁰	3	67	p.Met41Thr-(3)	AZA, MTX	Upadacitinib (1)- 15 mg/day	Disease remission
Koster 2021 ³¹	9	74	p.Met41Val-(1) p.Met41Thr-(7) p.Met 41Leu-(1)	RTX, MMF, TNFi, TCZ, MTX, ANA, CYC	Tofacitinib (1)	Unavailable
Case Report						
Beecher 2024 ³²	1	68	p.Met41Val	MMF	Tofacitinib (1)-5 mg BID	Significant improvement with quiescence of orbital and systemic symptoms
Burgei 2024 ³³	1	40s	p.Met41Val	RTX	Ruxolitinib (1)	Resolution of symptoms and lymphadenopathy, but anemia persisted and remained transfusion-dependent
Bindoli 2023 ³⁴	1	65	p.Met41Leu	None	Filgotinib (1)	After two months, clinical conditions generally ameliorated with no fever, chondritis, dyspnea, or asthenia
Stiburkova 2023 ³⁵	1	59	p.Gly477Ala	MTX, TNFi	Tofacitinib (1)	Partially alleviation of inflammatory symptoms
Kao 2022 ³⁶	1	56	p.Met41Thr	RTX	Ruxolitinib (1)- 15 mg po BID	Fevers, respiratory symptoms, and edema resolved after starting Ruxolitinib. However, it was complicated by severe sepsis and death.
Magnol 2021 ³⁷	1	59	p.Met41Thr	MTX, ZAZ, CYC, TNFi, TCZ, ANA	Baricitinib (1)	Failed to prevent the recurrences of inflammatory disorders or to decrease the dose of prednisone.
Lötscher 2021 ³⁸	1	68	p.Met41Thr	MTX, TCZ, TNFi, CyA Canakinumab	Tofacitinib (1)- 20 mg/day	No clinical benefit during the 3 months applied

Notes: The data presented in the table were obtained through a PubMed search and retrieval of references from pertinent articles utilizing the search term “VEXAS” and “JAK Inhibitors”. This table exclusively incorporates articles featuring and detailing newly reported articles of VEXAS syndrome. Inclusion criteria were limited to articles published in English from the inception of records to January 22, 2025, and restricted to human studies.

Abbreviations: ANA, Anakinra; AZA, Azathioprine; CyA, Cyclosporin A; CYC, cyclophosphamide; HCQ, Hydroxychloroquine; MTX, Methotrexate; MMF, Mycophenolate Mofetil; RTX: TCZ, Tocilizumab, TNFi, Tumor necrosis factor inhibitors.

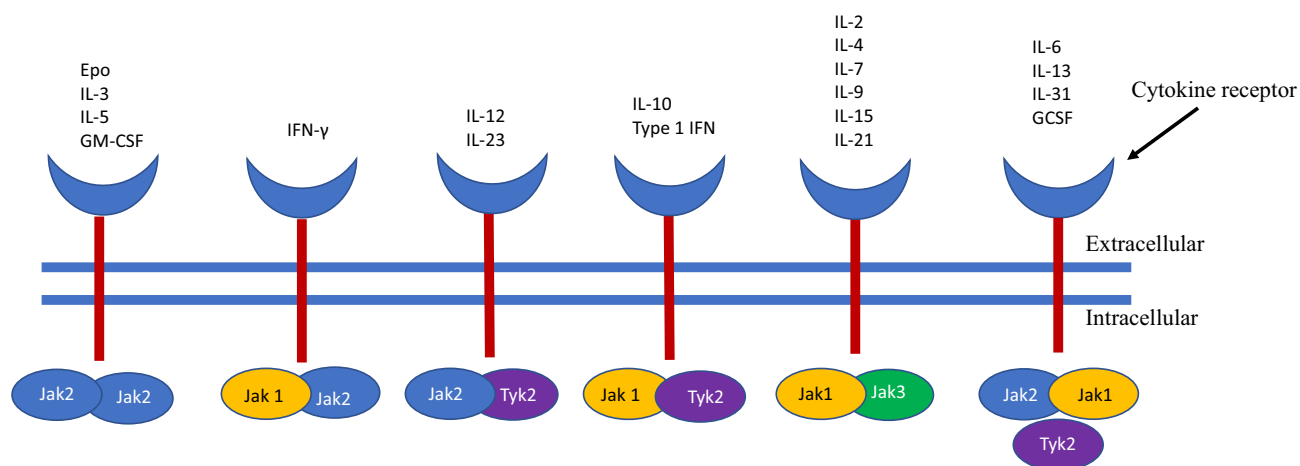


Figure 2 Cytokine receptors and their Jak-Stat signaling pathway.

inhibitors, which block various inflammatory cytokine pathways would be more efficacious than targeted therapies for individual cytokines such as IL-6, TNF- α or IL-1. Furthermore, it is plausible that IFN γ may be playing a significant role in VEXAS mediated inflammation, thus Jak inhibition works better than IL-6, TNF- α or IL-1 targeted therapies.

Although both Baricitinib and Ruxolitinib both selectively inhibit JAK1 and JAK2, Ruxolitinib has a lower IC₅₀ than Baricitinib for JAK2 and thus is a more potent suppressor than Baricitinib. Additionally, hematopoietic cells signal via JAK2 homodimers, and since Ruxolitinib is a stronger inhibitor than Baricitinib, it is more effective in suppressing inflammation originating in hematopoietic cells in VEXAS.^{39,40} Consequently, retrospective studies have shown that Ruxolitinib is associated with higher response rates with steroid-sparing effects, whereas Baricitinib showed no or limited benefit.^{14,23,25}

About one-third of patients with other myeloid disorders, such as MDS and chronic myelomonocytic leukemia, can have inflammatory and autoimmune disorders as well. Jak inhibitors such as Upadacitinib and Ruxolitinib have also been shown to induce a therapeutic response in such patients.⁴¹ Some patients with VEXAS also have concurrent

Table 2 Targets of Individual Jak Inhibitors and Approved Indications

	Jak1	Jak2	Jak3	Indications
Tofacitinib	X	X	X	Psoriatic Arthritis Rheumatoid Arthritis Ulcerative Colitis
Baricitinib	X	X		Rheumatoid Arthritis Atopic Dermatitis SARS-COV-2
Ruxolitinib	X	X		Myelofibrosis Polycythemia Vera Atopic Dermatitis
Filgotinib	X	X		No approved indications
Upadacitinib	X			Psoriatic Arthritis Rheumatoid Arthritis Ulcerative Colitis
Pacritinib		X		Myelofibrosis

myelodysplastic syndrome. In these patients, management with azacytidine and decitabine is associated with a reduction in inflammatory symptoms, normalization of bone marrow abnormalities, and reduction of mutated clones.^{3,14,16,42} Jak inhibitor Pacritinib is used to treat myelofibrosis. Clinical trial is underway to study efficacy of Pacritinib in VEXAS (Clinical trial NCT 06538181). Stem cell transplant has shown some promise, and clinical trials on stem cell transplant are underway (Clinical Trial NCT 05027945). It is possible that certain treatments will be specific for individual phenotype or specific UBA1 mutation genotypes.²⁶

Conclusion

Early recognition and diagnosis of VEXAS syndrome is challenging, and it should be considered as a differential diagnosis in older patients with unexplained recurrent/relapsing fever, systemic inflammation, and abnormal hematologic findings. Genetic screening is the gold standard diagnostic test and should be done to all patients with suspicious clinical and laboratory findings.

Much remains to be known regarding the management of VEXAS syndrome. The current report supports the use of Jak inhibitors. Ongoing clinical trial on Pacritinib will shed more light in the future on the role of Jak inhibitor in this condition.

Abbreviations

ACE, Angiotensin-converting enzyme; AFB, Acid-Fast Bacilli; ANA, Antinuclear antibody; ANC, Absolute neutrophil count; ANCA, Anti-neutrophil cytoplasmic antibody; Anti-CCP, Anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; CT, Computed tomography; DMARDs, Disease-modifying antirheumatic drug; DVT, Deep Vein Thrombosis; ESR, Erythrocyte Sedimentation Rate; FDG, Fludeoxyglucose; GC, Glucocorticoids; GMS, Gomori methenamine silver stain; HIV, Human immunodeficiency virus; IFN γ , Interferon-gamma; IL, Interleukin; JAK, Janus kinase; MDS, Myelodysplastic syndrome; PET, Positron emission tomography; RF, Rheumatoid factor; TNF- α , Tumor necrosis factor-alpha; UBA1, Ubiquitin-activating enzyme 1; VEXAS, Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

Ethical Approval

Institutional approval was not required for the publications of the patient's case details.

Patient Consent

Signed informed consent was obtained from the patient regarding the use of patient information for the purposes of writing a case report publication.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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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. Wu Z, Gao S, Gao Q, et al. Early activation of inflammatory pathways in UBA1-mutated hematopoietic stem and progenitor cells in VEXAS. *Cell Rep Med*. 2023;4(8):101160. doi:10.1016/j.xcrm.2023.101160
3. Al-Hakim A, Savić S. An update on VEXAS syndrome. *Expert Rev Clin Immunol*. 2023;19(2):203–215. doi:10.1080/1744666X.2023.2157262
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. Zhang Y, Dong X, Wang H. VEXAS Syndrome-Review. *Glob Med Genet*. 2023;10(3):133–143. doi:10.1055/s-0043-1770958
6. Itagane M, Teruya H, Kato T, et al. Clinical images: VEXAS syndrome presenting as treatment-refractory polyarteritis nodosa. *Arthritis Rheumatol*. 2022;74(11):1863–1864. doi:10.1002/art.42257
7. 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
8. Kouranloo K, Dey M, Almutawa J, et al. Clinical characteristics, disease trajectories and management of vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome: a systematic review. *Rheumatol Int*. 2024;44(7):1219–1232. doi:10.1007/s00296-023-05513-0
9. 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
10. Heiblig M, Ferrada MA, Koster MT, et al. Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study. *Blood*. 2022;140(8):927–931. *Blood*. 2023;141(13):1647.
11. Nicholson LT, Madigan LM. Working towards a better understanding of VEXAS syndrome. *Br J Dermatol*. 2022;186(3):392–393. doi:10.1111/bjd.20949
12. 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
13. 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
14. Boyadzhieva Z, Ruffer N, Kötter I, et al. How to treat VEXAS syndrome: a systematic review on effectiveness and safety of current treatment strategies. *Rheumatology*. 2023;62(11):3518–3525. doi:10.1093/rheumatology/kead240
15. Koster MJ, Samec MJ, Warrington KJ. VEXAS syndrome—A review of pathophysiology, presentation, and prognosis. *JCR: J Clin Rheumatol*. 2023;29(6):298–306.
16. Hernández-Rodríguez J, Mensa-Vilaró A, Aróstegui JI. Paradigm shift in monogenic autoinflammatory diseases and systemic vasculitis: the VEXAS syndrome. *Med Clin*. 2022;159(10):489–496. doi:10.1016/j.medcli.2022.06.018
17. Watanabe R, Kiji M, Hashimoto M. Vasculitis associated with VEXAS syndrome: a literature review. *Front Med*. 2022;9:983939. doi:10.3389/fmed.2022.983939
18. Martín-Nares E, Vargas-Serafin 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
19. Heiblig M, Patel BA, Groarke EM, et al. Toward a pathophysiology inspired treatment of VEXAS syndrome. *Semin Hematol*. 2021;58(4):239–246. doi:10.1053/j.seminhematol.2021.09.001
20. Staels F, Betrains A, Woei-A-Jin FS, et al. Case Report: VEXAS syndrome: from mild symptoms to life-threatening macrophage activation syndrome. *Front Immunol*. 2021;12.
21. Goyal A, Narayanan D, Wong W, et al. Tocilizumab for treatment of cutaneous and systemic manifestations of vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome without myelodysplastic syndrome. *JAAD Case Rep*. 2022;23:15–19. doi:10.1016/j.jdcr.2022.02.022
22. Kirino Y, Takase-Minegishi K, Tsuchida N, et al. Tocilizumab in VEXAS relapsing polychondritis: a single-center pilot study in Japan. *Ann Rheum Dis*. 2021;80(11):1501–1502. doi:10.1136/annrheumdis-2021-220876
23. Hadjadj J, Nguyen Y, Mouloudj D, et al. Efficacy and safety of targeted therapies in VEXAS syndrome: retrospective study from the FRENVEV. *Ann Rheum Dis*. 2024;83(10):1358–1367. doi:10.1136/ard-2024-225640
24. Casal Moura M, Baqir M, Tandon YK, et al. Pulmonary manifestations in VEXAS syndrome. *Respir Med*. 2023;213:107245. doi:10.1016/j.rmed.2023.107245
25. Heiblig M, Ferrada MA, Koster MT, et al. Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study. *Blood*. 2022;140(8):927–931. doi:10.1182/blood.2022016642
26. Bourbon E, Heiblig M, Gerfaud Valentin M, et al. Therapeutic options in VEXAS syndrome: insights from a retrospective series. *Blood*. 2021;137(26):3682–3684. doi:10.1182/blood.2020010177
27. Salehi T, Callisto A, Beecher MB, et al. Tofacitinib as a biologic response modifier in VEXAS syndrome: a case series. *Int J Rheum Dis*. 2023;26(11):2340–2343. doi:10.1111/1756-185X.14785
28. Islam S, Cullen T, Sumpton D, et al. VEXAS syndrome: lessons learnt from an early Australian case series. *Intern Med J*. 2022;52(4):658–662. doi:10.1111/imj.15742
29. Al-Hakim A, Poulter JA, Mahmoud D, et al. Allogeneic haematopoietic stem cell transplantation for VEXAS syndrome: UK experience. *Br J Haematol*. 2022;199(5):777–781. doi:10.1111/bjh.18488
30. 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
31. 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
32. Beecher MB, Tong JY, Halliday LA, et al. Recurrent orbital inflammation associated with VEXAS syndrome. *Orbit*. 2024;43(3):350–353. doi:10.1080/01676830.2022.2126501
33. Burgei J, Alsheimer KM, Lantry J, et al. Mediastinal lymphadenopathy due to VEXAS syndrome. *BMJ Case Rep*. 2024;17(8):e261179. doi:10.1136/ber-2024-261179
34. Bindoli S, Baggio C, Doria A, et al. JAK inhibitors for the treatment of VEXAS syndrome. *Exp Biol Med*. 2023;248(5):394–398. doi:10.1177/15353702231165030

35. Stiburkova B, Pavelcova K, Belickova M, et al. Novel Somatic UBA1 variant in a patient with VEXAS syndrome. *Arthritis Rheumatol.* **2023**;75(7):1285–1290. doi:10.1002/art.42471
36. Kao RL, Jacobsen AA, Billington CJ, et al. A case of VEXAS syndrome associated with EBV-associated hemophagocytic lymphohistiocytosis. *Blood Cells Mol Dis.* **2022**;93:102636. doi:10.1016/j.bcmd.2021.102636
37. Magnol M, Couvaras L, Degboé Y, et al. VEXAS syndrome in a patient with previous spondyloarthritis with a favourable response to intravenous immunoglobulin and anti-IL17 therapy. *Rheumatology.* **2021**;60(9):e314–e315. doi:10.1093/rheumatology/keab211
38. 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.* **2021**;12:800149. doi:10.3389/fimmu.2021.800149
39. Choi J, Cooper ML, Staser K, et al. Baricitinib-induced blockade of interferon gamma receptor and interleukin-6 receptor for the prevention and treatment of graft-versus-host disease. *Leukemia.* **2018**;32(11):2483–2494. doi:10.1038/s41375-018-0123-z
40. Bonelli M, Kerschbaumer A, Kastrati K, et al. Selectivity, efficacy and safety of JAKinibs: new evidence for a still evolving story. *Ann Rheum Dis.* **2024**;83(2):139–160. doi:10.1136/ard-2023-223850
41. Mishra R, Calabrese C, Jain AG, et al. Association between myeloid disorders and adult onset-inflammatory syndromes, successful treatment with JAK-inhibitors: case series and literature review. *Leuk Res.* **2024**;146:107584. doi:10.1016/j.leukres.2024.107584
42. Raaijmakers M, Hermans M, Aalbers A, et al. Azacytidine treatment for VEXAS syndrome. *Hemasphere.* **2021**;5(12):e661. doi:10.1097/HS9.0000000000000661

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