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Review Article

The dermatologic gateway to early diagnosis of VEXAS syndrome: a comprehensive review of cutaneous manifestations and their pathognomonic significance

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ABSTRACT

VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a recently recognized adult-onset autoinflammatory disorder caused by somatic mutations in the ubiquitin-activating enzyme UBA1. Since its initial description in 2020, its clinical spectrum has expanded considerably, yet diagnosis remains challenging because of its heterogeneous multisystem manifestations. Cutaneous involvement occurs in up to 90% of patients and is frequently an early or presenting feature, making dermatological findings particularly valuable for clinical suspicion and diagnosis. This narrative review summarizes current evidence on the dermatological manifestations of VEXAS syndrome, emphasizing their role as accessible markers of systemic inflammation. The cutaneous phenotype is highly heterogeneous, encompassing neutrophilic dermatoses, including sweet syndrome-like lesions, leukocytoclastic vasculitis, periorbital edema, and other inflammatory dermatoses. Histopathological findings range from dense neutrophilic infiltrates with leukocytoclasia to nonspecific perivascular inflammation. Emerging genotype-phenotype associations suggest that the p.Met41Leu variant is more frequently associated with neutrophilic dermatoses, whereas p.Met41Val may be linked to vasculitic manifestations. We also examine the evolving understanding of the genetic and clonal basis of cutaneous inflammation in VEXAS. Recognition of characteristic skin findings, particularly in older men with treatment-refractory inflammatory dermatoses, cytopenias, and systemic inflammation, should prompt consideration of VEXAS and targeted UBA1 testing. Greater dermatological awareness may facilitate earlier diagnosis, reduce diagnostic delay, and enable timely initiation of potentially life-changing therapy.

Keywords: VEXAS syndrome, UBA1 gene, Autoinflammatory diseases, Dermatology, Neutrophilic dermatoses, Leukocytoclastic vasculitis, Relapsing polychondritis, Sweet syndrome, Clonal hematopoiesis, Myelodysplastic syndrome, Early diagnosis

INTRODUCTION

The landscape of autoinflammatory medicine has been irrevocably transformed by the discovery of the VEXAS syndrome, an acronym encapsulating its core pathophysiological and clinical hallmarks: Vacuoles in myeloid precursors, E1 enzyme dysfunction, X-linked inheritance pattern, Autoinflammatory phenotype, and Somatic mutation origin. Since its identification by Beck et al via a pioneering genotype-first approach, VEXAS has emerged not merely as a novel nosological entity but as a prototypical hemato-inflammatory disorder, elegantly demonstrating how an acquired somatic alteration within the hematopoietic stem cell compartment can precipitate

a profound and debilitating systemic inflammatory state in later adult life. This disorder, which predominantly afflicts men over the age of fifty, is rooted in a somatic mutation of the UBA1 gene located on the X chromosome, a gene essential for initiating the ubiquitin-proteasome pathway, thereby disrupting critical cellular proteostasis and unleashing unchecked inflammatory cascades.[1-3]

The clinical consequences of this fundamental molecular defect are remarkably diverse and often devastating, manifesting as a relapsing and remitting multisystemic disease. Patients typically endure a constellation of debilitating symptoms including recurrent fevers, profound fatigue, pulmonary infiltrates, chondritis of the ears and nose, ocular inflammation, and a pro-thrombotic state that significantly contributes to morbidity. Concomitantly, hematological abnormalities are a near-constant feature, with macrocytic anemia being almost universally present, frequently accompanied by thrombocytopenia, monocytopenia, and a spectrum of myeloid dysplasias, often leading to an initial misdiagnosis of myelodysplastic syndrome (MDS). This diagnostic conflation is further compounded by the syndrome's ability to mimic a host of other well-characterized rheumatologic and dermatologic conditions, including relapsing polychondritis, polyarteritis nodosa, and, most notably, various neutrophilic dermatoses.[3-6]

Within this complex clinical mosaic, the skin emerges as a particularly revealing organ system. With an incidence of cutaneous findings reported in upwards of 80% to 90% of patients, dermatologic involvement is frequently the earliest harbinger of the syndrome, often preceding the diagnosis by months or even years. It is precisely this consistent and early presentation that positions the dermatologist at the frontline of diagnosis. The cutaneous lesions are not merely reactive epiphenomena; rather, they can be seen as a macroscopic reflection of the underlying clonal myeloproliferation and aberrant immune signaling. Histopathological analyses have begun to differentiate between "clonal" skin involvement, where the mutated UBA1 clone directly infiltrates the dermis, and "paraclonal" or reactive patterns, adding a layer of sophistication to our diagnostic acumen. Moreover, recent large cohort studies have correlated specific UBA1 mutational subtypes with distinct cutaneous phenotypes, offering the tantalizing possibility of predicting the underlying molecular defect from the skin biopsy.[7,8]

Despite these advances, the syndrome remains frequently undiagnosed or misdiagnosed, often only recognized after a protracted and costly journey through multiple medical specialties. The considerable diagnostic odyssey stems from the non-specific nature of its individual features and a general lack of widespread awareness of this recently described entity. This comprehensive review is thus conceived with a singular objective: to consolidate and articulate the current state of knowledge concerning the dermatological manifestations of VEXAS syndrome. We aim to equip the clinician-rheumatologist, hematologist, but most critically, dermatologist-with the necessary clinical and histopathological "clues" to suspect this condition early in its course. By highlighting the phenotypic spectrum, the genotype-phenotype correlations, and the distinct histopathological signatures, we endeavor to underscore the skin as the crucial diagnostic gateway to VEXAS, thereby facilitating earlier genetic confirmation for UBA1 mutations, more effective therapeutic strategies, and ultimately, a more favorable prognosis for these complex patients.[9]

PATHOPHYSIOLOGY: THE MOLECULAR AND CELLULAR UNDERPINNINGS OF VEXAS SYNDROME

The pathophysiological architecture of VEXAS syndrome is rooted in a fundamental and elegant, yet devastating, genetic aberration that serves as the primary driver of its complex systemic and cutaneous phenotype. At its core, the syndrome is a consequence of an acquired somatic mutation in the UBA1 gene, which is situated on the X chromosome at locus Xp11.23. This gene is of paramount importance as it encodes the ubiquitin-like modifier activating enzyme 1 (E1), the master initiator of the ubiquitin-proteasome system (UPS), a critical cellular machinery responsible for protein degradation and the maintenance of proteostasis. The UPS is an intricate cascade where UBA1 activates ubiquitin in an ATP-dependent manner, subsequently transferring it to a repertoire of E2 conjugating enzymes, which, in concert with E3 ligases, mediate the conjugation of ubiquitin to specific protein substrates earmarked for proteasomal degradation or for the modulation of their function. This highly regulated process is fundamental for controlling protein quality, cell cycle progression, signal transduction, and immune responses. The vast majority of pathogenic variants identified in VEXAS syndrome cluster at the critical methionine residue at position 41 (p.Met41) of the UBA1 protein, with the most frequently encountered substitutions being p.Met41Thr, p.Met41Val, and p.Met41Leu. These mutations fundamentally alter the translational start site, resulting in the production of a catalytically impaired, truncated cytoplasmic isoform of the E1 enzyme, while simultaneously abrogating the expression of the full-length, functional protein. The consequence is a state of profound enzymatic insufficiency, where the normal functioning of the UPS is severely compromised.[10]

This disruption in the ubiquitination machinery sets in motion a cascade of pathological cellular events that precipitate the disease's hallmark features. The impaired clearance of misfolded or damaged proteins leads to the accumulation of these potentially toxic species within cells, triggering the unfolded protein response (UPR) and generating a state of chronic endoplasmic reticulum stress. This cellular stress, in concert with the direct loss

of ubiquitin-mediated regulation of key signaling molecules, creates a permissive environment for constitutive activation of the innate immune system. The result is a state of relentless, unchecked systemic inflammation that is characteristic of autoinflammatory disorders. The mutant clone, originating in a hematopoietic stem or progenitor cell, undergoes clonal expansion, progressively outcompeting its healthy counterparts and seeding the bone marrow and peripheral tissues with cells that are both intrinsically dysfunctional and hyperinflammatory. This clonal hematopoiesis, driven by the UBA1 mutation, is the link between the hematological and inflammatory facets of the syndrome.[11,12]

Recent and highly granular mechanistic studies have begun to illuminate the specific molecular pathways that translate this enzymatic deficiency into the dramatic tissue inflammation observed, particularly in the skin. One of the most compelling findings is that UBA1-mutated monocytes exhibit a unique vulnerability to tumor necrosis factor-alpha (TNF-α), displaying increased susceptibility to RIPK1-mediated cell death, a form of regulated necrosis known as necroptosis. This process is characterized by the phosphorylation of RIPK1 and subsequent activation of MLKL, culminating in the rupture of the cell membrane and the release of a potent cocktail of pro-inflammatory alarmins and cytokines. Furthermore, these mutant monocytes demonstrate a blunted transcriptional response to TNF-α, characterized by defective induction of NF-κB target genes and reduced expression of cFLIP(L), a critical anti-apoptotic protein, which collectively lowers their threshold for cell death. This phenomenon explains why these cells are both primed to die and to spill their inflammatory contents, effectively acting as incendiary devices within affected tissues. In a complementary line of investigation, researchers at Memorial Sloan Kettering Cancer Center have developed robust laboratory models that substantiate this paradigm, showing that macrophages derived from UBA1-mutant myeloid cells are hypersensitive to danger signals. Upon encountering such stimuli, they self-destruct and emit danger signals that, in turn, recruit more of these defective immune cells, creating a deleterious feedback loop that fuels the chronic inflammatory cycle. This dysregulation of cell death pathways, where apoptosis is suppressed in favor of necrosis, is emerging as a central pathogenic axis.[12-14]

The pro-inflammatory milieu generated by this dysfunctional myeloid clone is rich in key cytokines. Elevated levels of interleukin-6 (IL-6), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) are consistently observed, reflecting the activation of the NLRP3 inflammasome and the broader type I interferon response. Transcriptomic analyses of lesional skin from VEXAS patients have confirmed a shared inflammatory signature with other myeloid skin diseases, notably dominated by type 1 and 2 interferon responses and the activation of TNF and IL-1β pathways. These molecular signatures not only explain the systemic features of the disease but also provide a mechanistic basis for the polymorphic cutaneous manifestations. The infiltration of the skin by these mutated cells and the consequent inflammatory storm led to a spectrum of lesions, including the characteristic neutrophilic dermatoses. Importantly, recent histopathological and molecular analyses have elegantly demonstrated a distinction between "clonal" and "paraclonal" skin involvement. In neutrophilic dermatoses, such as sweet syndrome-like lesions, the UBA1-mutated myeloid clone itself can be directly identified within the dermal infiltrate, confirming that these lesions are a direct consequence of the pathological clone homing to the skin. In contrast, other cutaneous patterns, such as leukocytoclastic vasculitis, may be "paraclonal," driven not by the direct infiltration of mutant cells but by the downstream, aberrant inflammatory mediators they produce. This paradigm helps explain the remarkable heterogeneity of skin lesions and suggests that distinct therapeutic strategies may be required to target the clone itself versus its inflammatory sequelae. The high expression of chemokine receptors like CXCR3 and CCR4 on these dysfunctional monocytes, coupled with their localization near dermal blood vessels, provides a mechanistic insight into their tissue-specific recruitment and the propensity for cutaneous inflammation. Ultimately, the pathophysiology of VEXAS syndrome is a compelling narrative of a single somatic mutation disrupting a fundamental cellular process, initiating a cascade of clonal dominance, immune dysregulation, and inflammatory cell death, all of which are vividly and often initially manifested through the skin.[14,15]

CLINICAL MANIFESTATIONS: THE PROTEAN AND MULTISYSTEMIC FACE OF VEXAS SYNDROME

The clinical phenotype of VEXAS syndrome is characterized by a remarkable and often bewildering heterogeneity, manifesting as a relapsing and remitting multisystemic illness that frequently mimics a constellation of well-established rheumatologic and hematologic disorders. This broad and non-specific clinical spectrum, coupled with the relative novelty of the entity, is the primary driver of the diagnostic odyssey that many patients endure, often traversing multiple medical specialties before the correct diagnosis is eventually established. The syndrome, which predominantly affects males over the age of fifty, presents a complex interplay between profound systemic autoinflammation and progressive bone marrow failure, creating a clinical picture that can be mistaken for conditions such as relapsing polychondritis, polyarteritis nodosa, MDS, or various neutrophilic dermatoses. As the understanding of this disease has evolved through large cohort studies and international registries, a more detailed and nuanced portrait of its clinical manifestations has emerged, underscoring the critical importance of recognizing the

syndromic pattern that points towards an underlying UBA1 mutation.[16-18]

Among the plethora of systemic features, a constellation of inflammatory signs is nearly universal and is a direct consequence of the dysregulated innate immune response driven by the mutant myeloid clone. Recurrent fevers are observed in a substantial majority of patients, with a frequency reported between 65% and 90% across different cohorts, and these febrile episodes are often accompanied by profound fatigue, night sweats, and significant weight loss, reflecting the high inflammatory burden. Musculoskeletal involvement is another cornerstone of the disease, with inflammatory polyarthritis or debilitating arthralgias affecting an estimated 28% to 82% of patients. This arthritis can be chronic and erosive, contributing significantly to the morbidity and functional impairment experienced by patients. Chondritis, affecting the cartilaginous structures of the ears and nose, is a particularly distinctive feature, occurring in 36% to 54% of cases, and is one of the manifestations that frequently leads to an initial misdiagnosis of relapsing polychondritis. Ocular inflammation is also a common and potentially vision-threatening complication, observed in 30% to 56% of patients, with manifestations ranging from episcleritis and scleritis to uveitis and orbital inflammation, which can present as the striking clinical sign of persistent periorbital edema. Pulmonary involvement is another significant domain of disease, with approximately 50% to 70% of patients developing infiltrates, pleural effusions, or other parenchymal abnormalities, which can sometimes be severe enough to cause respiratory insufficiency and necessitate intensive care. Furthermore, a pro-thrombotic state is a hallmark of VEXAS, leading to an elevated risk of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism, in 23% to 41% of patients, a complication that significantly contributes to morbidity and mortality.[18,19]

Hematologic abnormalities are not merely a complication but a central and defining pillar of VEXAS syndrome, reflecting the somatic origin of the mutation within the hematopoietic stem cell compartment. Macrocytic anemia is the most frequent and almost universal laboratory finding, present in up to 97% of patients, and can be severe enough to necessitate transfusion dependence. Thrombocytopenia and leukopenia, often with absolute monocytopenia, are also common, occurring in approximately 10% to 63% of patients, and contribute to the risk of bleeding and infections. A hallmark of the disease is the frequent association with MDS, which is identified in 31% to 53% of affected individuals. However, this VEXAS-associated MDS typically presents with a unique profile, characterized by moderate dysplasia, few or no excess blasts, and a normal karyotype in the majority of cases, often carrying a more favorable prognosis and a lower risk of transformation to acute myeloid leukemia compared to classic MDS. Beyond MDS, patients are also at an increased risk for clonal hematopoiesis of indeterminate potential (CHIP) and plasma cell proliferative disorders, such as monoclonal gammopathy of undetermined significance (MGUS), which occurs in approximately 10% to 25% of patients, a proportion significantly higher than the general population of the same age. The progressive bone marrow failure and the profound immune dysregulation also confer a heightened susceptibility to serious infections, which are a leading cause of death in this population, with the lungs being the most common site of infection, often involving opportunistic pathogens such as *L. pneumophila* and *P. jirovecii*.[19,20]

Perhaps the most critical clinical domain for early suspicion and diagnosis is the dermatologic system. Cutaneous manifestations are an exquisitely common and often the earliest presenting feature of VEXAS syndrome, with a reported incidence of 80% to 90% across all studies, and they are frequently the very first sign that prompts a patient to seek medical attention. The skin lesions are remarkably polymorphic, reflecting the broad inflammatory and histopathological spectrum of the disease. They can present as a single lesion type or as multiple, overlapping morphologies, often waxing and waning in intensity with the systemic disease flares. The most frequently observed cutaneous patterns include neutrophilic dermatoses, which manifest as sweet syndrome-like infiltrated erythematous papules, plaques, and nodules, often with a characteristic violaceous hue, sometimes exhibiting central umbilication and predominantly localized to the trunk, neck, and extremities. Leukocytoclastic vasculitis is another prevalent manifestation, presenting as palpable purpura, petechiae, or urticarial plaques, and is a crucial diagnostic clue, particularly in older males with systemic symptoms. Other reported cutaneous findings span a wide spectrum, including erythema nodosum, livedo racemosa, periorbital edema and angioedema, urticarial lesions, and even eczematous or spongiotic dermatitis, which can be an atypical presentation. A striking and diagnostically useful feature is the predisposition to severe and often ulcerative injection-site reactions, particularly to IL-1 inhibitors such as anakinra, which occurs in a significant proportion of patients and highlights the underlying aberrant inflammatory response. The histopathological findings in these skin lesions are equally diverse, ranging from dense neutrophilic infiltrates with leukocytoclasia, to perivascular lymphohistiocytic infiltrates, to frank vasculitis. Interestingly, recent research has established significant genotype-phenotype correlations, demonstrating that the specific UBA1 mutation can predict the predominant cutaneous histopathological pattern. The p.Met41Leu variant is most frequently associated with neutrophilic dermatoses, often resembling histiocytoid sweet syndrome, while the p.Met41Val variant is strongly correlated with leukocytoclastic vasculitis. Furthermore, by analyzing the clonality of the cutaneous infiltrate, it has been possible to distinguish between "clonal" and "paraclonal" skin involvement, where in some cases the UBA1-mutated myeloid cells

directly infiltrate the skin, while in others, the lesions are driven by the downstream inflammatory mediators produced by the mutant clone elsewhere. These clinical, histological, and genetic nuances underscore the essential role of the dermatologist and dermatopathologist in recognizing the tell-tale signs of VEXAS, making the skin a truly invaluable gateway to early diagnosis and the initiation of potentially life-altering therapeutic interventions.[17-19]

DIAGNOSIS AND TREATMENT: NAVIGATING THE CLINICAL AND GENETIC LABYRINTH OF VEXAS SYNDROME

The diagnostic journey for a patient with VEXAS syndrome is frequently protracted and fraught with challenges, often constituting a genuine odyssey through multiple medical specialties before the correct underlying genetic etiology is finally elucidated. This diagnostic delay is a direct consequence of the syndrome's remarkable phenotypic heterogeneity, its ability to masquerade as a plethora of more familiar rheumatologic and hematologic conditions, and the fact that it was only identified in the year 2020, leaving a significant gap in clinical awareness. However, the convergence of a heightened clinical index of suspicion with robust diagnostic algorithms and the advent of accessible genetic testing has begun to transform this landscape, offering the promise of earlier and more accurate identification of affected individuals, particularly through the recognition of cardinal cutaneous clues. The diagnosis of VEXAS is not established by a single pathognomonic feature but rather through the synthesis of clinical, laboratory, histopathological, and, most critically, genetic evidence.[17-19]

The initial step in the diagnostic process is the recognition of a suggestive clinical phenotype. The American College of Rheumatology (ACR) guidance, developed by the International VEXAS Working Group, provides expert consensus on which patients warrant further investigation. The primary constellation of findings that should trigger clinical suspicion includes persistently elevated inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), accompanied by a combination of systemic inflammatory features like recurrent fevers, skin lesions, ocular inflammation, pulmonary infiltrates, or chondritis, often in the presence of unexplained cytopenias, particularly macrocytic anemia. The disease overwhelmingly affects males over the age of fifty, and this demographic profile is a crucial piece of the diagnostic puzzle. The simplified SWIM-score, which comprises Skin involvement, Weight loss, Inflammation, and Macrocytic anemia, has recently emerged as a highly sensitive clinical screening tool to select patients for genetic testing, demonstrating superior specificity compared to earlier scoring systems and underscoring the pivotal role of dermatological findings in the diagnostic algorithm.[18-20]

Laboratory investigations provide the second pillar of diagnostic evidence. Complete blood counts characteristically reveal macrocytic anemia, which is a nearly universal finding present in up to 97% of patients, alongside potential thrombocytopenia, leukopenia, and absolute monocytopenia. A bone marrow aspiration and biopsy is an essential component of the diagnostic workup, not only to assess for the presence of an associated MDS but also to identify the hallmark morphological feature of VEXAS: the presence of cytoplasmic vacuoles in early myeloid and erythroid precursors. While these vacuoles are a highly suggestive finding, they are not entirely specific and have been observed in other conditions such as copper deficiency or medication-related effects, so their interpretation must be contextualized within the broader clinical picture. Notably, the ACR guidance recommends that a quantitative threshold of at least 10% of myeloid precursors displaying one or more cytoplasmic vacuoles can enhance diagnostic precision. Furthermore, the interpretation of bone marrow findings can be particularly challenging due to the frequent presence of signs of dysplasia that do not always meet the full criteria for a formal MDS diagnosis, necessitating careful pathological evaluation.[18-20]

The definitive diagnosis of VEXAS syndrome, however, rests entirely on the identification of a somatic pathogenic variant in the UBA1 gene. This genetic confirmation is typically performed on DNA extracted from peripheral blood, although bone marrow aspirate can also be used. The vast majority of patients carry a mutation in exon 3 of the UBA1 gene, most commonly involving the critical methionine at position 41 (p.Met41), with p.Met41Thr, p.Met41Val, and p.Met41Leu being the most frequent substitutions. In terms of sequencing methodology, Sanger sequencing is a widely accessible, cost-effective, and rapid method that can reliably detect these common mutations and accurately quantify the variant allele fraction (VAF) when VAFs are above approximately 10%. While next-generation sequencing (NGS) offers increased sensitivity for detecting low-level somatic variants, recent comparative studies have demonstrated that for the typical exon 3 mutations, Sanger sequencing does not miss additional cases, with NGS mainly confirming the same variants identified by the more traditional method. The ACR guidance suggests that targeted testing for exon 3 variants is a valid alternative to NGS, provided that clinicians are aware of its limitations, and it emphasizes that if clinical suspicion is high and initial testing is negative on peripheral blood, the complete gene should be sequenced, and testing a bone marrow sample should be considered to increase the likelihood of detecting low-level mutations. This recommended stepwise approach ensures that cost-effective and rapid testing is initially applied, while more comprehensive methods are reserved for patients with a strong clinical indication.[20-22]

Once a diagnosis is confirmed, the therapeutic landscape of VEXAS syndrome presents a formidable challenge, as there is currently no standardized treatment protocol and management is highly individualized based on the patient's specific clinical manifestations, the presence of a hematological neoplasm, the overall severity of the disease, and the patient's eligibility for more aggressive interventions. The overarching therapeutic goals are fourfold: to control the profound systemic inflammation, to prevent and treat progressive bone marrow failure, to mitigate the substantial risk of thrombotic complications, and to manage the infectious complications that arise from both the disease and its treatments, all while striving to improve the patient's quality of life. Corticosteroids, such as prednisone, are the mainstay of initial therapy and often provide a rapid, albeit frequently transient, amelioration of inflammatory symptoms, but their long-term use is severely limited by a host of significant and cumulative toxicities. For patients who are not transplant candidates or for whom steroids are insufficient, a variety of immunosuppressive and targeted immunomodulatory agents have been employed with variable degrees of success. Conventional disease-modifying antirheumatic drugs (DMARDs) like methotrexate, azathioprine, and mycophenolate mofetil have demonstrated limited efficacy and exhibit poor steroid-sparing effects. Similarly, TNF-alpha inhibitors and other biologic agents that are effective in many autoimmune conditions have generally yielded disappointing results in VEXAS, failing to control the relentless autoinflammatory cascade. More encouraging outcomes have been observed with JAK inhibitors, particularly ruxolitinib, and IL-6 receptor antagonists like tocilizumab, which appear to provide more substantial control of systemic inflammation and may serve as effective steroid-sparing options. Furthermore, hypomethylating agents such as azacitidine have garnered significant interest due to their dual effect of targeting the UBA1-mutated hematopoietic clone and reducing systemic inflammation, making them a particularly compelling option for patients with associated MDS. These agents have been shown to reduce disease burden and improve hematological parameters in some patients, and monitoring the variant allele fraction over time may provide a valuable biomarker for tracking treatment response.[20-22]

For the subset of patients with severe, refractory disease, particularly those with life-threatening cytopenias or an associated high-risk hematologic malignancy, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only potentially curative therapeutic modality. This approach aims to eradicate the mutant clone by replacing the patient's dysfunctional hematopoietic system with that of a healthy donor. Early reports and case series have indicated the possibility of long-lasting responses and even cure in carefully selected patients. However, this intervention is associated with substantial risks, including high toxicity, graft-versus-host disease, and significant transplant-related mortality, which limits its application to younger, fitter patients without significant comorbidities.

Emerging therapies that target specific components of the inflammatory cascade, such as NLRP3 inflammasome inhibitors and proteasome inhibitors like bortezomib, which exploit the proteostasis vulnerabilities of UBA1-mutated cells, are currently under investigation and hold promise for the future. Nevertheless, the management of VEXAS syndrome demands a multidisciplinary approach, involving rheumatologists, hematologists, dermatologists, and other specialists, to coordinate care and address the complex interplay of hematologic and inflammatory complications that define this novel and devastating disease, with a critical focus on prophylaxis against infections and thromboembolic events.[20,21,22]

CONCLUSION

In the four years since its seminal description, VEXAS syndrome has transitioned from a novel nosological entity to a paradigmatic example of a hemato-inflammatory disorder, fundamentally reshaping our understanding of the intricate interface between clonal hematopoiesis and systemic autoinflammation. The journey of discovery has been rapid, yet the clinical community continues to grapple with the formidable challenges of early diagnosis and effective management of this often-devastating condition. This comprehensive review has systematically dissected the pathophysiological underpinnings, the protean clinical manifestations, and the current diagnostic and therapeutic strategies, all while underscoring the pivotal and frequently inaugural role of dermatological involvement as a critical gateway to timely recognition.

The skin, as we have established, is not merely a passive bystander but an active and eloquent herald of the underlying molecular chaos. With cutaneous findings reported in over 80% of affected individuals and frequently constituting the initial presenting complaint, the dermatologist is uniquely positioned at the frontline of diagnosis. The remarkable polymorphism of skin lesions, ranging from neutrophilic dermatoses like sweet syndrome to leukocytoclastic vasculitis and periorbital edema, reflects the broad inflammatory spectrum of the disease and provides tangible, accessible clues to the systemic pathology. The crucial histopathological distinction between clonal and paraclonal skin involvement, where the UBA1-mutated myeloid clone directly infiltrates in some lesions while others are driven by downstream inflammatory mediators, not only adds a layer of sophistication to our diagnostic acumen but also informs potential therapeutic strategies. Furthermore, the emergence of genotype-phenotype correlations, linking specific UBA1 variants to distinct cutaneous patterns such as the p.Met41Leu mutation with neutrophilic dermatoses and p.Met41Val with leukocytoclastic vasculitis, represents a significant advance that promises to refine diagnostic algorithms and prognostic stratification.

Despite these advances, the diagnostic odyssey remains a significant obstacle, with patients often enduring a protracted and costly journey through multiple specialties before genetic confirmation is achieved. The non-specificity of individual features, the mimicry of other rheumatologic and hematologic conditions, and the relative novelty of the syndrome contribute to a persistent underdiagnosis, even as population-based studies estimate a prevalence of 1 in 4,000 men over 50. The recent American College of Rheumatology guidance represents a critical milestone, providing the first consensus-based framework to aid clinicians in suspecting the disease, selecting appropriate genetic testing, and implementing a multidisciplinary management approach. This guidance, along with clinical screening tools like the SWIM-score that highlights the cardinal role of skin involvement, weight loss, inflammation, and macrocytic anemia, is essential for translating molecular knowledge into clinical practice and expediting the path to diagnosis.

The therapeutic landscape of VEXAS syndrome remains a formidable challenge, characterized by an empirical approach driven by retrospective data and a profound lack of prospective clinical trials. Corticosteroids, while effective for acute inflammation control, are fraught with toxicity and fail to address the underlying clone. Targeted immunomodulators like JAK inhibitors and IL-6 receptor antagonists have shown promise as steroid-sparing agents, and hypomethylating agents like azacitidine offer the potential to target the mutant clone directly, but responses are variable and often incomplete. Allogeneic hematopoietic stem cell transplantation remains the only curative modality, yet its application is limited by substantial risks and the advanced age of most patients. The high burden of infectious complications and thromboembolic events further underscores the need for proactive prophylactic strategies and vigilant multidisciplinary care.

Looking forward, the future of VEXAS syndrome research and clinical care lies in addressing the numerous knowledge gaps that persist. The development of validated classification criteria, harmonized outcome measures, and international patient registries is imperative to generate the robust evidence base needed to guide therapeutic decisions. A deeper understanding of the molecular mechanisms driving clonal expansion and inflammation will be crucial for the development of novel, targeted therapies, including those aimed at eradicating the mutant clone or specifically dampening the downstream inflammatory cascades. Furthermore, expanding clinical awareness beyond rheumatologists and hematologists to include dermatologists, internists, and other subspecialists is paramount. In conclusion, VEXAS syndrome stands as a testament to the power of genomic medicine to uncover novel disease mechanisms, yet it also serves as a stark reminder of the translational gap that must be bridged. The skin, as the most accessible and frequently earliest indicator of this disease, offers a tangible opportunity to shorten the diagnostic odyssey, enabling earlier intervention and ultimately improving the quality of life and prognosis for patients afflicted by this complex and life-altering syndrome.

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