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A Review on VEXAS Syndrome

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ABSTRACT
VEXAS syndrome refers to a new adult-onset autoinflammatory disease, which results from acquired mutations in the UBA1 gene and leads to dysregulation of innate immunity and abnormal hematopoiesis. The disease is mainly seen in elderly men and manifests itself through systemic inflammation, recurrent fever, cutaneous manifestations, relapsing polychondritis, lung involvement, vasculitis, and hematological abnormalities including macrocytic anemia and myelodysplastic syndrome. Due to the heterogenous nature of symptoms of the disease as well as due to overlaps with some other autoimmune and hematological conditions, diagnosis of the disease is typically delayed and thus requires confirmation of UBA1 mutations via molecular methods. Currently, therapy for VEXAS syndrome includes corticosteroids, immunosuppressants, biological drugs, JAK inhibitors, hypomethylating drugs, and hematopoietic stem cell transplantation. The ongoing developments in the fields of molecular diagnostics, personalized treatment, targeted drug therapy, and gene editing can be viewed as promising means of treating VEXAS syndrome in the future.

Keywords: VEXAS syndrome, *UBA1* mutation, autoinflammatory disease, macrocytic anemia, myelodysplastic syndrome, Janus kinase inhibitors, hematopoietic stem cell transplantation, precision medicine.

I. INTRODUCTION

The VEXAS syndrome is a novel adult onset autoinflammatory disease that has attracted significant attention from 2020 onwards. This is because VEXAS is a groundbreaking development in the study of inflammatory diseases as the syndrome occurs due to acquired mutations in somatic cells of the UBA1 gene and not due to any inherited genetic defect. While most autoimmune diseases are linked with faulty adaptive immunity, the VEXAS syndrome is more linked with problems in innate immunity and the malfunctioning of bone marrow. The disease mainly affects older individuals with a predominance of males, who experience systemic inflammation, fever, skin lesions, lung involvement, cartilage inflammation, and hematologic manifestations. Due to such characteristics and variability in symptoms, the VEXAS syndrome is considered a significant condition for those suffering from inflammatory syndromes unresponsive to standard treatments.[1]

The word VEXAS is an abbreviation, which defines the main pathological, genetic, and clinical aspects of the syndrome. It was coined by scientists in 2020 when they discovered the condition and described its unique features. "V" denotes Vacuoles and means that there are characteristic cytoplasmic vacuoles that can be found in the myeloid and erythroid precursor cells of the bone marrow. "E" means E1 enzyme, ubiquitin-activating enzyme, which is coded by the gene UBA1. It is involved in the ubiquitin-proteasome system functioning and is responsible for the process of protein degradation and maintaining cellular homeostasis. Malfunctioning of this enzyme causes inflammation and disruption of hematopoiesis. The letter “X” implies the presence of the gene UBA1 at the X-linked locus on the X chromosome; hence the reason for predominance of the condition in men. “A” is for Autoinflammatory because the condition involves overactivity of the innate immune response leading to repetitive inflammation affecting various body organs. Lastly, “S” is for Somatic mutation because the underlying UBA1 mutation is acquired in adulthood within the hematopoietic stem cells as opposed to germline inheritance. This particular attribute makes VEXAS

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syndrome one of the earliest recognized autoinflammatory conditions in adults caused by acquired somatic mutations.[2]

The clinical manifestations of VEXAS syndrome are highly variable, which makes the disease very difficult to diagnose. The presentation may be dominated by constitutional symptoms such as prolonged fever, fatigue, weight loss, and malaise with inflammatory involvement of various organs. Neutrophilic dermatosis and vasculitis of the skin, arthritis, arthralgia, and relapsing polychondritis can all occur together with the syndrome. Hematological changes, especially macrocytic anemia, thrombocytopenia, and myelodysplasia, are regarded as defining features of the disease. Other manifestations that have been seen in many patients include pulmonary infiltration, venous thromboembolism, uveitis, and nephritis. Due to the fact that many of these clinical manifestations are similar to those seen in other conditions, patients usually go through many diagnostic procedures and end up being diagnosed with various other diseases before reaching a correct diagnosis[3]

The discovery of mutations in the UBA1 gene has significantly improved the understanding of the molecular basis of VEXAS syndrome. The UBA1 gene codes for the ubiquitin-activating enzyme E1, a key component of the ubiquitin-proteasome pathway, which controls protein degradation in the cell. Mutations in this enzyme lead to impaired protein processing, and thus the activation of inflammatory signaling pathways and the release of excessive amounts of pro-inflammatory cytokines. This leads to the development of chronic innate immune activation and altered hematopoiesis, which results in systemic inflammation and dysfunctional bone marrow. Improvements in genomics technologies have helped to identify affected individuals, and genetic testing has been proven to be a valuable diagnostic tool, especially when dealing with adult patients suffering from an unexplained inflammatory syndrome with cytopenia or bone marrow disorders.[4]

Although many advances have been made in relation to the development of knowledge about VEXAS syndrome, there are still many issues in connection with the diagnosis and treatment of this condition. At present, there is no single treatment strategy which could be universally recognized as a standard method for the treatment of this syndrome, and treatment strategies depend upon the severity of disease, organ involvement, and coexisting hematological diseases. Steroids remain the main treatment modality, but many patients become dependent on steroids, and even if their symptoms are relieved, they may recur. There were attempts to use immunosuppressants, biologics, Janus kinase inhibitors, hypomethylating agents, and allogenic stem cell transplantations in the treatment of this disease, but their efficacy is still under investigation.[5]

II. EPIDEMIOLOGY

VEXAS syndrome is regarded as a rare but probably under-diagnosed adult-onset autoinflammatory condition. In the past two years since the initial report, more than 500 genetically diagnosed cases of the disease have been identified around the world, yet the actual frequency is thought to be much higher, since many cases go undiagnosed or misdiagnosed as different inflammatory and hematological conditions. Based on population studies, the estimated frequency of VEXAS syndrome is about 1 in 4,000 men aged over 50 years and 1 in 26,000 women aged over 50 years. The disease usually develops among older patients, with the median age of diagnosis varying from 60 to 75 years, whereas cases younger than 40 years of age are very rare. The majority of reported patients (>90%) are males due to the X-linked inheritance of the UBA1 gene mutation; however, a few cases have been described among women with monosomy X or acquired X chromosome defects.

This syndrome is observed across North America, Europe, Asia, and Australia, implying its wide distribution worldwide with no particular race or ethnicity predisposition. Abnormalities of blood counts occur with a high degree of frequency, as macrocytic anemia is present in about 90-100% of patients, and myelodysplastic syndrome is seen in almost 30-50% of patients. Cutaneous symptoms are seen in 70-90% of patients, pulmonary symptoms in 40-60%, relapsing polychondritis in 40-60%, and venous thromboembolic manifestations in almost 30-40% of affected patients. Despite the improvements in diagnostic and therapeutic approaches for VEXAS syndrome, it still is linked with considerable mortality and morbidity, with 5-year survival rate of about 60-70% and overall mortality of 25-50% because of progressive hematologic disease, systemic inflammatory processes, infections, and thromboembolism.[6]

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ETIOLOGY OF VEXAS SYNDROME[7]

Etiological Factor	Description
Somatic mutation in *UBA1* gene	The primary cause of VEXAS syndrome is an acquired (somatic) mutation in the *UBA1* gene.
X-linked gene involvement	The *UBA1* gene is located on the X chromosome, which explains why the disease predominantly affects males.
Defective E1 ubiquitin-activating enzyme	Mutations impair the function of the E1 enzyme, disrupting the ubiquitin-proteasome pathway responsible for protein degradation.
Abnormal innate immune activation	Defective protein regulation leads to excessive activation of the innate immune system and chronic inflammation.
Clonal hematopoiesis	The mutation arises in hematopoietic stem cells, resulting in the expansion of abnormal blood cell clones.
Bone marrow dysfunction	Abnormal hematopoiesis causes characteristic cytoplasmic vacuoles, macrocytic anemia, and other cytopenias.
Pro-inflammatory cytokine overproduction	Increased production of cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and interferons contributes to systemic inflammation.
Non-hereditary origin	VEXAS syndrome is not inherited; the mutation develops during adulthood and is not passed to offspring.

III. PATHOGENESIS OF VEXAS SYNDROME

Acquisition of Somatic *UBA1* Gene Mutation

The process of developing VEXAS syndrome starts with a somatic mutation of the UBA1 gene that lies on the short arm of the X chromosome (Xp11.3). In contrast to genetic diseases inherited through genes, the mutation appears in an adult age and occurs in the hematopoietic stem cells of the bone marrow, therefore it cannot be inherited by descendants. The UBA1 gene synthesizes the ubiquitin-activating enzyme E1, which is the first enzyme of the ubiquitin-proteasome pathway. As the mutation appears in the multipotent hematopoietic stem cells, all the daughter cells, including neutrophils, monocytes, and other myeloid cells, inherit this mutated gene. The clone expansion becomes the basis of the disease and helps understand why inflammatory and hematologic symptoms arise simultaneously in patients.

Defective Ubiquitin-Activating Enzyme (E1) Function

Under normal physiologic circumstances, the initiation of the ubiquitination reaction occurs through the E1 enzyme that activates ubiquitin in an ATP-dependent fashion. Then, activated ubiquitin is further transferred to the E2 conjugating enzymes and E3 ligases, where ubiquitin is attached to damaged, misfolded, or unnecessary proteins that are targeted for degradation through the proteasome pathway. In patients suffering from the VEXAS syndrome, mutations in the UBA1 gene disrupt the function of the UBA1b isoform of the cytoplasmic form of the protein. This leads to malfunction of ubiquitination processes. The accumulation of aberrant proteins inside immune cells is the result, leading to cellular dysfunction and stress response induction.[8]

Cellular Stress and Activation of Inflammatory Pathways

The buildup of unprocessed proteins inside mutated myeloid cells leads to ER stress, oxidative stress, and the induction of the unfolded protein response. The aforementioned cellular stress processes activate various inflammatory pathways, such as the nuclear factor-kappa B (NF-κB) pathway and interferon-induced signaling. The activation of these pathways leads to a continuous production of genes coding for inflammatory agents. In contrast to regular inflammation, where there is strict regulation followed by inflammation cessation after removal of the initial agent, inflammation associated with VEXAS syndrome is a constant process due to the persistence of the genetic mutation in the hematopoietic cells.

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Dysregulation of the Innate Immune System

Mutations in the UBA1 gene predominantly affect the innate immune cells such as neutrophils, monocytes, macrophages, and dendritic cells. These cells get hyperactivated and start secreting inflammatory factors constantly, even in the absence of any kind of infection or injury. In contrast to classic autoimmune diseases wherein adaptive immunity and autoantibodies are responsible for the pathology, the pathology of VEXAS syndrome lies within the aberrant behavior of the innate immune response. Hyperactivated neutrophils and monocytes invade many organs, leading to inflammation of skin, cartilage, lungs, blood vessels, joints, and several other organs. Moreover, hyperactivation of these cells also causes damage to endothelial cells, thereby increasing the risk of thromboembolism.[9]

Excessive Cytokine Production

Innate immune cell hyperactivity results in excess pro-inflammatory cytokine generation, which includes interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), interferon-γ, and granulocyte colony stimulating factor (G-CSF). Cytokines enhance inflammation through positive feedback loops, resulting in self-perpetuating inflammation. Higher levels of these cytokines lead to systemic symptoms like fever, fatigue, weight loss, high C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and very high levels of ferritin. Continued secretion of these cytokines leads to an influx of inflammatory cells into the damaged tissue, worsening the condition.

Bone Marrow Dysfunction and Clonal Hematopoiesis

Due to the origin of the UBA1 mutation in hematopoietic stem cells, the functionality of bone marrow deteriorates over time. An abnormal stem cell clone grows over time, causing clonal hematopoiesis and poor maturation of progenitors of blood cells. The appearance of characteristic cytoplasmic vacuoles is observed in erythroid and myeloid cells' progenitors, which is one of the characteristic features of this disease. The consequence of ineffective hematopoiesis is macrocytic anemia, leukopenia, thrombocytopenia, or pancytopenia for many patients. Besides, the development of clonal evolution can cause hematologic diseases like myelodysplastic syndrome, chronic myelomonocytic leukemia, monoclonal gammopathy, or plasma cell dyscrasia.

Multisystem Organ Involvement

The combination of the inflammatory response within the body system and hematopoietic abnormalities causes involvement of different organs. The inflammation of the skin leads to neutrophilic dermatoses, cellulitis, and cutaneous vasculitis. The inflammation of cartilage leads to relapsing polychondritis of the ear, nose, and airway. Joint inflammation causes arthritis and arthralgias; while inflammation of the lungs causes interstitial lung disease, pulmonary infiltrates, pleural effusions, and hypoxemia. Small- and medium-size vessel vasculitis causes vascular damage and thromboembolism. The eyes, kidneys, GI tract, and neurologic involvement may occur based on organ involvement within the inflammatory process.[10]

Disease Progression and Clinical Outcomes

In absence of proper treatment, the chronic inflammation and worsening bone marrow dysfunction progress further. Patients rely heavily on high dose corticosteroids for symptomatic relief, whereas repeated relapses result in cumulative organ damage. The clonal proliferation leads to higher chances of development of advanced hematology diseases especially myelodysplastic syndromes. Severe infections due to immunosuppression, thrombosis, respiratory insufficiency, and bone marrow insufficiency account for the main factors causing morbidity and mortality. Treatment approaches at present include inflammation reduction, clonal proliferation suppression, and improvement in survival, despite that hematopoietic stem cell transplant is still the only cure for this condition.

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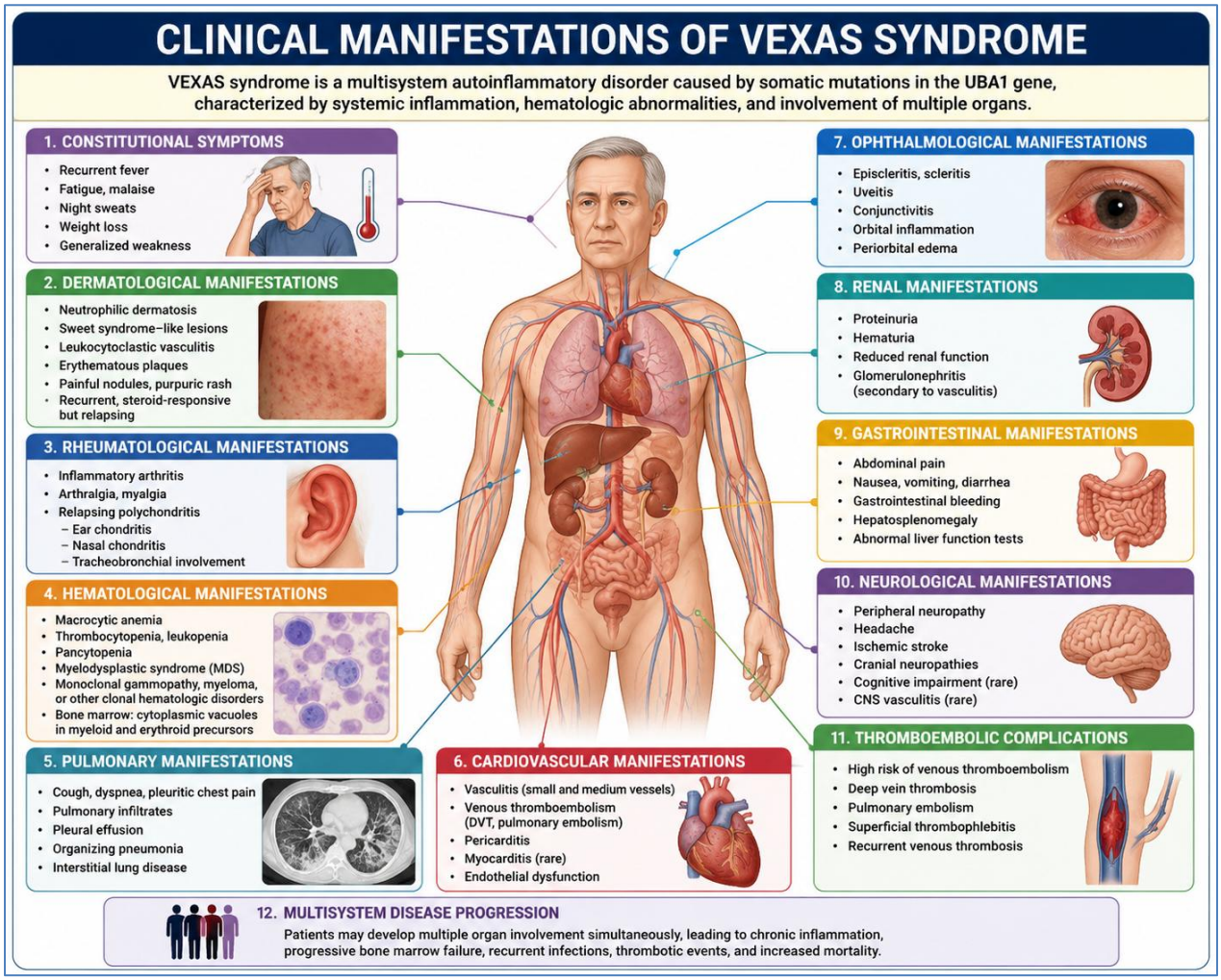
CLINICAL MANIFESTATIONS OF VEXAS SYNDROME[11]



IV. DIAGNOSIS OF VEXAS SYNDROME

1. Clinical Evaluation

The first line of diagnostics includes taking a complete medical history and doing a comprehensive physical exam. Symptoms that patients complain about include fever, tiredness, weight loss, arthritis pain, rashes, cartilage inflammation in the ears and nose, breathing problems, and general symptoms of illness. The physical examination can show red skin lesions, joint swelling, auricular cartilage inflammation, lung symptoms, swollen lymph nodes, or an enlarged spleen. Because these symptoms mimic other inflammatory conditions, a high degree of clinical suspicion is necessary, especially when there is unexplained inflammation with blood abnormalities.

2. Laboratory Investigations

Laboratory tests reveal signs of systemic inflammation and bone marrow abnormalities. These include the presence of macrocytic anemia, leukopenia, thrombocytopenia, or pancytopenia. Markedly elevated levels of inflammatory parameters, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum ferritin, are generally seen. Mildly elevated liver enzyme levels may occasionally be present in some patients. Serologic tests of autoimmunity like antinuclear antibody (ANA), rheumatoid factor (RF), and anti-neutrophil cytoplasmic antibody (ANCA) are usually negative or non-specific.[12]

3. Bone Marrow Examination

Bone marrow aspiration and biopsy form an integral part of assessing patients with suspected VEXAS syndrome. The presence of cytoplasmic vacuoles seen in erythroid and myeloid progenitor cells forms one of the distinguishing pathologic features seen in VEXAS syndrome, which is how the term "V" was derived from the name VEXAS. Bone marrow may

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show hypercellularity, dysplasia, ineffective hematopoiesis, and the presence of associated hematologic disorders like myelodysplastic syndrome. However, despite being indicative, cytoplasmic vacuoles are not pathognomonic and must be evaluated in conjunction with clinical and genetic features.

4. Genetic Testing

Genetic testing is considered the reference method for establishing the diagnosis of VEXAS syndrome. The molecular study performed by means of NGS, Sanger sequencing, or specific mutation analysis identifies somatic mutations in the UBA1 gene in peripheral blood or bone marrow samples. The mutations in UBA1 found more often are related to methionine in codon 41 (p.Met41), although other variants are known. Discovery of pathogenic mutation in the UBA1 gene in the proper context establishes the diagnosis and separates VEXAS syndrome from other inflammatory and hematologic disorders.

5. Imaging Studies

Imaging methods are used to evaluate the extent of organ involvement and severity of the disease. Chest high-resolution computed tomography (HRCT) may show pulmonary infiltrates, interstitial lung disease, pleural effusion, or organizing pneumonia. CT, MRI, PET-CT may identify inflammatory changes in blood vessels, cartilage, lymph nodes, or internal organs. Echocardiography is helpful for the detection of pericarditis.[13]

6. Differential Diagnosis

Due to similarities in clinical presentation to many other inflammatory diseases, differential diagnosis is important in VEXAS syndrome. These may include relapsing polychondritis, adult-onset Still's disease, Sweet's syndrome, ANCA-associated vasculitis, polyarteritis nodosa, Behçet's disease, giant cell arteritis, systemic lupus erythematosus, rheumatoid arthritis, IgG4-related disease, infections, and hematologic malignancy including myelodysplastic syndrome. A combination of severe systemic inflammation and macrocytic anemia with bone marrow vacuolation with an identified mutation in the UBA1 gene would lead to the diagnosis of VEXAS syndrome.

CURRENT TREATMENT STRATEGIES

Currently, there are no FDA-approved medications that can cure VEXAS syndrome. The goal of treatment in VEXAS syndrome includes controlling the systemic inflammation, preventing damage to organs, correcting hematological disorders, and improving the quality of life. Treatment is highly individual depending on the degree of the disease, organs involved, hematological disorder, and reaction to treatment. In view of the presence of inflammatory and hematological manifestations of VEXAS syndrome, it is recommended that the management include a team consisting of rheumatologists, hematologists, dermatologists, pulmonologists, and clinical pharmacists. Though corticosteroids form the basis of the treatment regimen, steroid dependency is common among most of the patients.[14]

1. Corticosteroids

Steroids are recommended as a primary choice for managing the inflammatory flare-ups caused by VEXAS syndrome. Treatment usually involves high doses of steroids, prednisolone or prednisone, based on the severity of the disease. The patient experiences quick relief from fever, skin problems, arthritis, lung problems, and other symptoms of inflammation in a few days. But remission is not common with this condition and the disease may relapse even during the steroid reduction process, leading to steroid dependency in most patients. Steroid use may cause problems like osteoporosis, diabetes mellitus, hypertension, obesity, cataracts, muscle weakness, and vulnerability to infections.

2. Conventional Immunosuppressive Drugs (DMARDs)

Traditional DMARDs are often employed as adjuvant treatments to decrease the dosage of corticosteroids, but their effectiveness is usually poor overall. Traditional DMARDs such as methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, and cyclosporine have been used in a subset of patients with variable effects. They may offer some relief from arthritis symptoms, skin lesions, and systemic inflammation; however, most patients continue to suffer from disease flare-ups. Thus, traditional immunosuppressants are mostly regarded as adjunct therapies, and in case of disease activity, they are replaced by more effective biological agents.[15]

3. Biologic Therapies

Anti-inflammatory cytokine biologics have proved to be significant therapeutic modalities in treating patients with VEXAS syndrome that is refractory. The anti-interleukin-6 biologics like tocilizumab have shown positive outcomes in treating fevers, elevated inflammation markers, arthritis, and steroid dependency in multiple patients. Anti-interleukin-1 drugs such as anakinra and canakinumab have also proven to be effective in some cases while being less useful in other patients. TNF-α inhibitors and

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rituximab have been used as treatment methods as well; however, their effectiveness varies from one case to another.

4. Janus Kinase (JAK) Inhibitors

Janus kinase inhibitors have emerged as one of the most effective treatment modalities in patients suffering from VEXAS syndrome since these drugs block various pathways of inflammatory cytokines at once. Ruxolitinib, baricitinib, and tofacitinib block intracellular JAK-STAT signaling pathways resulting in inhibition of inflammatory activity caused by cytokines. Various clinical trials have shown improvement in constitutional features, cutaneous lesions, pulmonary manifestations, inflammation markers, and need for corticosteroids mainly with ruxolitinib. However, close monitoring is needed since JAK inhibitors increase the risk of infections, herpes zoster, cytopenia, and thromboembolic events.[16]

5. Hypomethylating Agents

In VEXAS syndrome that is related to myelodysplastic syndrome (MDS), hypomethylating drugs like azacitidine and decitabine have yielded promising outcomes. Hypomethylating drugs work on the hematopoietic stem cell clones that are dysfunctional and may help in the management of hematological features along with inflammation. Various research studies have found reduction in need for transfusions, inflammation, and steroid use after treatment with azacitidine. However, there have been various responses among patients, and the problem of myelosuppression is not uncommon.

6. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Allogeneic hematopoietic stem cell transplant is currently seen as the only treatment that can possibly cure VEXAS syndrome because it removes the hematopoietic stem cell clone that is mutated and replaces it with healthy donor stem cells. There have been successful cases of hematopoietic stem cell transplants, where the inflammation symptoms were put into remission, and the hematologic defects were corrected. However, the procedure is not without its risks, which include graft-versus-host disease, opportunistic infections, mortality from the transplant, and toxicity to organs. This procedure is recommended only for selected candidates.[17]

7. Supportive Care

Supportive care forms an indispensable aspect of the management of the VEXAS syndrome. Blood transfusions could be necessary for severe anemia, and antimicrobial prophylaxis could be administered to patients undergoing long-term immunosuppressive therapy to lower the risk of infections from opportunistic pathogens. Anticoagulation treatment should be considered in patients with venous thromboembolism or those at a higher risk of thrombosis. Calcium, vitamin D, and bisphosphonate should be administered to protect bone health where the use of long-term corticosteroid drugs is necessitated. Immunizations to influenza, pneumococcal infection, and other possible infections should be conducted prior to initiation of intense immunosuppressive treatment.[18]

EMERGING THERAPIES

1. Advanced Janus Kinase (JAK) Inhibitors

JAK inhibitors continue to be among the most promising targeted drugs for the management of VEXAS syndrome. Selective JAK inhibitors have been developed in order to increase efficiency and minimize side effects arising from the suppression of immune system activity. This class of drugs suppresses several cytokine signal pathways, including those activated via interleukin-6, interferon, and granulocyte-macrophage colony stimulating factor signaling, leading to lessened systemic inflammation. Clinical trials are currently underway to find out the most effective JAK inhibitor, dosage, and safety aspects.

2. Novel Cytokine-Targeted Biological Therapies

The scientific literature has become progressively more interested in creating biological treatments for selective inhibition of inflammatory cytokines playing a role in the development of VEXAS. Alongside IL-1 inhibitors and IL-6 inhibitors, other innovative monoclonal antibodies against GM-CSF, interleukin 18, interferons, and other inflammatory mediators have also been introduced. These medications help decrease chronic inflammation without disturbing the physiological functions of the immune system. Personalization of biologics depending on an individual's cytokine profile can be an effective treatment approach.[19]

3. Precision Medicine and Genotype-Guided Therapy

Precision medicine is one of the approaches that involve the design of treatments according to a particular patient's UBA1 gene mutation and clinical phenotype, along with related hematological anomalies. The emergence of next-generation sequencing technology has made it possible to precisely classify various forms of the UBA1 gene and thus make accurate predictions of the disease severity and treatment effectiveness. In the future, treatment will involve combining genetic testing and

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inflammation biomarkers in order to achieve a personalized medicine approach.

4. Gene Editing and Gene Therapy

There is an opportunity to cure the underlying problem in VEXAS syndrome rather than manage the symptoms alone through gene therapy. There are experimental treatments using the CRISPR-Cas9 technology that attempt to correct the mutation of UBA1 found in the patient's hematopoietic stem cells. The treatment methods that can replace the faulty gene or selectively destroy the mutated clone of stem cells could result in remission. While these methods are still at the preclinical or early research phase, they present a good future option for VEXAS syndrome patients.[20]

5. Targeted Clonal Hematopoiesis Therapy

As VEXAS syndrome arises from mutations in hematopoietic stem cell clones, there has been an emerging interest in treatments aimed at eliminating or inhibiting these clones. There have been studies that suggest new drugs capable of targeting hematopoietic cells carrying mutations can delay the disease's progression as well as lower the likelihood of developing myelodysplastic syndromes and other types of blood cancers.

6. Cellular Therapies and Improved Stem Cell Transplantation

The improvements seen in the field of hematopoietic stem cell transplantation are increasing the efficacy and safety of the procedure which has curative potential in certain disorders. Reduced intensity conditioning protocols along with enhanced donor selection and supportive therapy have decreased the incidence of complications associated with the procedure. Furthermore, new cellular therapies such as engineered immune cells and modified stem cells are being tested to cure patients by eliminating the pathogenic clones without causing graft versus host disease. Despite being clinically unproven, these approaches may become a viable option for patients ineligible for transplantation.[21]

V. COMPLICATIONS OF VEXAS SYNDROME

1. Progressive Bone Marrow Failure

One of the most severe manifestations associated with VEXAS syndrome is bone marrow dysfunction. Constant clonal proliferation of hematopoietic stem cells carrying UBA1 mutation causes ineffective hematopoiesis, causing progressive macrocytic anemia, leukopenia, thrombocytopenia, or pancytopenia. As a result of impaired bone marrow function, patients might become reliant on blood transfusion and be more susceptible to bleeding and severe infections. Furthermore, some patients might develop myelodysplastic syndrome or other types of hematological malignancies.

2. Recurrent and Severe Infections

VEXAS syndrome itself, along with the long-term use of immunosuppressive drugs, such as corticosteroids and biological medications, make patients prone to infections. Patients are vulnerable to bacterial, viral, and fungal infections, such as pneumonia, urinary tract infections, skin infection, opportunistic fungal infections, and herpes zoster infection. Recurrent infections represent the reason for hospitalization and constitute a considerable share of disease-related mortality.[22]

3. Thromboembolic Events

The development of VEXAS syndrome is associated with a high risk of venous thromboembolism as a consequence of chronic systemic inflammation, dysfunction of the endothelium, and the activation of the coagulation system. These complications include deep vein thrombosis, pulmonary embolism, thrombophlebitis, and recurrent venous thrombosis. Thromboembolic conditions may be observed in spite of the ongoing treatment with immunosuppressive drugs and may represent a life-threatening condition.

4. Progressive Organ Damage

Due to persistent inflammation, there is a risk of progressive organ damage. Thus, pulmonary inflammation may progress and develop into interstitial lung disease, pulmonary fibrosis, or respiratory failure. In addition, recurrent relapsing polychondritis may cause the destruction of auricular, nasal, and tracheal cartilage leading to deformities and airway abnormalities. Moreover, vasculitis may damage blood vessels resulting in impaired organ perfusion, while skin inflammation may lead to ulcerations and scars.[23]

5. Treatment-Related Complications

The long-term use of corticosteroids can lead to problems like osteoporosis, diabetes, high blood pressure, cataract, glaucoma, muscle weakness, obesity, and suppression of the adrenal gland. The immunosuppressive drugs and biological treatments can cause liver toxicity, kidney toxicity, suppression of bone marrow function, infusion reactions, and increased chance of developing opportunistic infections. The janus kinase inhibitors are also linked to conditions such as cytopenia, infection with herpes zoster, and thromboembolism. It is crucial to conduct regular laboratory testing and

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adjust the doses appropriately to prevent treatment-related complications.

6. Increased Mortality

The mortality rate of patients suffering from the VEXAS syndrome is very high because of the development of progressive hematological disease, systemic inflammation, infections, respiratory problems, thromboembolism, and organ failure. Patients with associated myelodysplastic syndrome and advanced bone marrow failure tend to have a worse prognosis. Late diagnosis and poor disease control further worsen the chances of mortality.[24]

VI. FUTURE PERSPECTIVES ON VEXAS SYNDROME

Future perspectives of VEXAS syndrome investigations are aimed at enhancing early diagnosis, gaining an insight into disease pathogenesis, and introducing specific therapies directed to treating the fundamental cause of this disorder and not just its manifestations related to inflammation. The introduction of innovations in terms of next-generation sequencing and molecular diagnostics would help to detect mutations in the UBA1 gene and diagnose this disease prior to the development of irreversible tissue damage. The research concerning biomarkers of this condition and their use for prediction of its severity and response to therapy continues to be conducted. Individual approaches in medicine based on genetic data will be implemented in the future and will help to improve therapeutic results and decrease side effects of treatment.

Therapeutic developments in the future will be aimed at finding disease-modifying and possibly curative options. New treatments include selective JAK inhibitors, next generation biological drugs, and therapies that target certain inflammatory pathways that could improve disease control and result in fewer side effects. Molecular techniques like gene editing with CRISPR-Cas9 technology can help find ways to fix the genetic mutations or kill the abnormal stem cell clone that is responsible for disease progression. The improvement of the procedure of allogeneic hematopoietic stem cell transplantation will allow more patients to undergo curative treatment safely by optimizing preconditioning and donor selection. Further advances in clinical research may lead to a development of new treatment options that would positively affect patients' survival rates and quality of their lives.[25]

VII. CONCLUSION

VEXAS syndrome is a recently identified autoinflammatory disease with adult onset and has played a crucial role in developing the knowledge on the association between somatic mutations, immune deregulation, and hematological conditions. Being caused by somatic mutations of the UBA1 gene, VEXAS syndrome manifests itself in a wide variety of symptoms that include persistent systemic inflammation, fever, skin lesions, relapsing polychondritis, lung problems, vasculitis, and bone marrow problems. Heterogeneity of VEXAS syndrome symptoms often results in overlap of the syndrome with autoimmune, autoinflammatory, and hematological diseases, which complicates early diagnosis. Identification of somatic mutations in the UBA1 gene via molecular genetic testing became the hallmark of VEXAS syndrome diagnosis.

Despite the extensive advancements in the understanding of VEXAS syndrome pathogenesis and its characteristics, long-term treatment of this condition still proves difficult. Although there are several treatment options available to date such as corticosteroids, immunosuppressants, biological therapy, Janus kinase inhibitors, hypomethylating drugs, and allogenic hematopoietic stem cell transplantation, they yield various results but are not always efficient. Further research that will concentrate on precision medicine, molecular-targeted treatments, and genetic editing is expected to bring about a positive outcome. Early diagnosis, multidisciplinary care, and clinical research are all crucial in order to help the patients suffering from this syndrome to have a better quality of life.

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