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REVIEW ARTICLE

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VEXAS syndrome — long recognised, recently named

ABSTRACT

VEXAS syndrome was first described in 2020. It is a syndrome of autoimmune and haematological manifestations and is caused by a somatic mutation of the *UBA1* gene of bone marrow progenitor cells. This mutation results in abnormal protein ubiquitination and systemic inflammatory process. The main symptoms of the syndrome include recurrent fever, polychondritis, neutrophilic dermatosis, vasculitis, ophthalmic and haematological manifestations with myelodysplastic syndrome. The treatment of VEXAS syndrome has proven to be effective with high-dose corticosteroids, monoclonal antibodies directed against interleukin 1, interleukin 6, tyrosine kinase inhibitors — JAK inhibitors and allogeneic haematopoietic stem-cell transplantation. The prognosis is unfavourable, many patients do not improve after treatment and die.

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KEY WORDS: *UBA1* gene; myelodysplastic syndrome; VEXAS syndrome

INTRODUCTION

VEXAS syndrome (*Vacuoles, E1 ubiquitin activating enzyme, X chromosome, Autoinflammation, Somatic*) is a new, not fully understood disease entity at the borderline between rheumatology and haematology. This syndrome was first described in 2020 by Beck et al. [1]. The name of the disease is an acronym (Tab. 1). VEXAS syndrome occurs mainly in adult males and manifests as inflammation of the skin, joints, vessels, cartilages; visual and hearing impairment, haematological disorders. Studies show that VEXAS syndrome is most commonly diagnosed in patients with other autoimmune diseases — systemic lupus erythematosus (SLE), Sweet syndrome, relapsing chondritis, vasculitis or blood cancers [2].

AIM OF THE STUDY

The aim of this study is to present the aetiopathogenesis, clinical manifestations and treatment of VEXAS syndrome.

EPIDEMIOLOGY

Epidemiological data on VEXAS syndrome come from a small number of publications. Beck et al. described VEXAS syndrome in 25 men with a mean age of 64 years (45-80) [1]. Georgin-Lavalle et al. described the disease in 116 men with a mean age of 67 years (62.5-73) [3]. In a subsequent study, Beck et al. analysed a population of 163,000 patients; VEXAS syndrome was found in only nine men and two women. After statistical analysis, the incidence of VEXAS syndrome was 1/14,000 in the entire cohort, 1/4,000 in men aged over 50 and 1/26,000 in women aged over 50 years [4, 5]. Initially, VEXAS syndrome was thought to affect only men due to a gene mutation on the X chromosome. Over time, isolated cases of the disease have been reported in women, which were associated with the presence of monosomy of the X chromosome (Turner syndrome — 45,X) or somatic mosaicism [5]. Poulter et al. described the case of a woman suffering from VEXAS syndrome

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Table 1. Detailed development of the acronym VEXAS [2]

Letter of the acronym	Explanation in English	Meaning
V	***V****acuoles*	Cytoplasmic vacuoles found in bone marrow cells
E	***E****1 ubiquitin activating enzyme*	An enzyme encoded by the *UBA1* gene, a mutation of which results in the development of syndrome
X	***X*** *chromosome*	The *UBA1* gene is located on chromosome X
A	***A****utoinflammation*	The syndrome causes autoimmune inflammation of various organs
S	***S****omatic*	The mutation causing the syndrome is somatic, arises during life, is not inherited

who did not have any of the above-mentioned genetic disorders [6].

PATHOGENESIS

The proven pathogenetic factor for VEXAS syndrome is a somatic mutation of the *UBA1* gene, located on chromosome X (Xp11.23) [7]. The most common is a missense mutation affecting methionine at codon 41 (Met41), less frequently are mutations affecting codon 56 (milder clinical manifestation, only haematological) and splicing mutations [8]. The *UBA1* gene encodes isoform 1 of the enzyme that activates protein ubiquitination. Impairment of the ubiquitination process leads to a disruption of protein activation and degradation, and interactions between them. This, in turn, results in the formation and accumulation of misfolded, abnormal peptides, which generate endoplasmic reticulum-related cellular stress [8–10]. The dysfunction of the ubiquitin-proteasome system and its role in inducing immune responses is confirmed by increased phosphorylation of eukaryotic translation initiation factor 2α (eIF2-α) and X-box binding protein 1 (XBP 1) [11]. The *UBA1* mutation and the aforementioned molecular abnormalities are observed in haematopoietic cells of the myeloid and erythroid lineages of the bone marrow and in mature peripheral blood cells (neutrophils, monocytes). Mutant neutrophils and monocytes overexpressed tumour necrosis factor α (TNF-α), interleukin (IL) 1, 6 and 8, interferon gamma (IFN-γ) and interferon-induced protein 10 (IFIT-10) [7, 10]. In addition, increased production of neutrophil extracellular nets (NETosis) that also have pro-inflammatory potential was observed in patients with VEXAS syndrome [7]. All the disorders described explain the genesis of the varied clinical manifestations of VEXAS syndrome.

CLINICAL MANIFESTATIONS

The clinical picture of VEXAS syndrome is heterogeneous. Georgin-Lavialle et al. distinguished three basic disease phenotypes (Tab. 2) [3, 10].

A common clinical manifestation of VEXAS syndrome is recurrent fever, which is present in 65–91% of patients [1, 7, 12]. In addition, there are other general symptoms: weight loss, chronic fatigue, muscle pain and night sweats.

The organ manifestations of VEXAS syndrome include skin manifestations (85–100%), most commonly neutrophilic dermatitis, small- and medium-vessel vasculitis, erythema nodosum, urticaria, and periorbital oedema [13, 14]. Skin blisters, subcutaneous nodules and maculopapular rash were observed in individual patients. In skin biopsy, there are monocytic or polycytic cellular infiltrates composed

Table 2. VEXAS syndrome phenotypes according to Georgin-Lavialle et al. [3]

Disease phenotype	Characteristics
I — with mild to moderate severity of symptoms	Recurrent fever, weight loss, less frequent pulmonary involvement, lymphadenomegaly, lower risk of thrombotic complications, lower CRP and leukocytosis levels
II — related to MDS	Relapsing chondritis, frequent cardiac and gastrointestinal involvement, pulmonary infiltrates, frequent infections, haematological manifestations, thrombocytopenia
III — "inflammatory", in older patients	Frequent weight loss, vasculitis, less frequently relapsing chondritis, high CRP levels

MDS — myelodysplastic syndrome; CRP — C-reactive protein

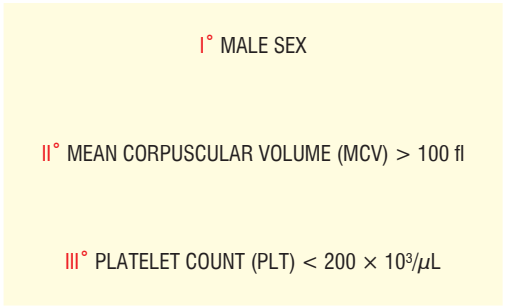

Figure 1. Diagnostic algorithm for chondritis in VEXAS syndrome according to Ferrad et al. [16]

of lymphocytes, neutrophils, eosinophils, or cells with the phenotype MPO(+) CD68(+) which are similar to bone marrow precursors. Cells in the dermal infiltrates were from altered myeloid clones with a *UBA1* mutation [15]. Cutaneous manifestations also result from inflammation of the subcutaneous tissue and cholesterol blockages of the arteries [7].

Another characteristic symptom is chondritis (46–100%) [13]. Auricular cartilages (100%) and nasal cartilages (92%) are most commonly involved, while costal cartilages and cartilages that are found in the lower respiratory tract are less frequently involved. Chondritis in the setting of VEXAS syndrome had a significantly higher mortality rate compared to chondritis not associated with this syndrome (27 *vs.* 2%) [13, 16, 17]. It can be speculated that VEXAS syndrome significantly worsens the prognosis of other diseases. Ferrada et al. proposed a diagnostic algorithm that helps distinguish chondritis in VEXAS syndrome from relapsing polychondritis without *UBA1* mutation [16] (Fig. 1).

The main rheumatological manifestations of VEXAS syndrome include arthritis (28-67%), myositis and fasciitis [9, 17]. Typically, medium and large joints are affected, and sometimes polyarthritis develops. Myositis can be the predominant symptom of VEXAS syndrome, sometimes manifesting after 10 years of the disease [18, 19]. It is likely to be the result of an inflammatory process rather than a targeted immune response directed against myocytes. The muscle biopsy revealed extensive macrophage infiltration with a CD68(+) phenotype and moderate necrosis; cytoplasmic vacuoles were present within the cells [18]. Some patients have symptoms of vasculitis (16–100%) [12]. In their review, Wanatabe et al. reported 23 cases of vasculitis patients diagnosed with VEXAS syndrome. These included two cases of giant-cell arteritis, nine cases of medium-vessel vasculitis, seven of which met the diagnostic criteria for polyarteritis nodosa, and 12 cases of small-vessel vasculitis, most commonly leukocytoclastic vasculitis (nine patients). Immunosuppressive treatment failure and premature death were observed in the majority of patients [20].

Haematological abnormalities are part of clinical picture of the disease. VEXAS syndrome with MDS manifests as fever, gastrointestinal, pulmonary and joint involvement. Laboratory tests revealed macrocytic anaemia with normal vitamin B12 and folic acid levels, thrombocytopenia (50%), lymphopenia (80%), neutropenia (13%). Immature granulocyte precursors and monocytes and neutrophils with cytoplasmic vacuoles were also observed in the peripheral blood. Myelodysplastic syndrome appeared approximately five years after the first symptoms of the disease. Development of multiple myeloma (MM) (20%), monoclonal gammopathy of undetermined significance (MGUS) (20%), chronic lymphocytic leukaemia (CLL) (20%) and isolated cases of macrophage activation syndrome (MAS) and haemophagocytic lymphohistiocytosis (HLH) were also observed in some patients with VEXAS syndrome. Obiorah et al. concluded that VEXAS syndrome manifests as rheumatological disease, while the increased mortality rate is due to haematological manifestations [7, 21].

Symptoms of VEXAS syndrome also include:

— ocular manifestations (67% of patients): episcleritis (12%), less commonly uveitis, scleritis, eyelid and orbital inflammation;
— cardiovascular manifestations (11.2% of patients): myocarditis, pericarditis, cardiomyopathies;
— pulmonary manifestations (49.1% of patients): pulmonary infiltrates, pleural effusion, interstitial pneumonia, and inflammatory alveolitis;
— gastroenterological manifestations (13.8%): abdominal pain, diarrhoea, ulcers, perforation, gastrointestinal obstruction;
— neurological manifestations (14.7%): headaches, meningitis, neuropathies;
— genitourinary manifestations (9.5%): nephritis with proteinuria and haematuria, renal failure, epididymitis, orchitis and prostatitis;
— lymphadenopathy (35%), hepatomegaly (7.8%), splenomegaly (13.8%) [3, 7, 9, 12].

Thrombotic complications were observed in 35–40% of patients: venous (36–56%) and arterial (1.6%) thrombotic complications. They were caused by elevated levels of factor VIII, factor IX and the presence of antiphospholipid and lupus anticoagulant antibodies, as well as endothelial dysfunction caused by the inflammatory process [7, 9, 22, 23].

DIAGNOSTICS

The diagnosis of VEXAS syndrome is made based on clinical presentation, laboratory, histopathological and genetic findings. According to Al-Hakim et al., the diagnosis of VEXAS syndrome is possible based on the characteristic clinical picture and mutation of the *UBA1* gene [5]. According to Vitale et al., the diagnosis of MDS and the presence of vacuoles in bone marrow cells (particularly observed in promyelocytes, myelocytes, erythroid progenitor cells and blasts) raises the suspicion of VEXAS syndrome [7]. However, it should be noted that cytoplasmic vacuoles are not pathognomonic of the syndrome and their absence does not exclude its diagnosis. They can occur in sepsis, alcohol poisoning, zinc and copper disorders, sideroblastic anaemia and bone marrow cancers [2, 8, 24]. In the histopathological examination of bone marrow, in addition to cytoplasmic vacuoles, increased cellularity, atypical megakaryocytes, haemophagocytosis, and percentage of blasts < 5% are characteristic. Lacombe et al. indicated that the finding of at least 10% of neutrophil precursors with at least 1 cytoplasmic vacuole in the bone marrow is strongly associated with the presence of mutations in the *UBA1* gene [25].

Laboratory tests aiding in the diagnostic evaluation of VEXAS syndrome are inflammatory index (elevated CRP, ESR levels), full blood count (macrocytic anaemia, thrombocytopenia, leukopenia — especially lymphopenia and monocytopenia), ferritin levels (moderately elevated levels, lower than in Still disease) [3 ,4, 7].

Imaging examinations, including computed tomography, ultrasonography, magnetic resonance imaging, angiography and positron emission tomography are helpful in the diagnostic evaluation of organ changes in this disease [7].

All authors agree that the best diagnostic method is to demonstrate mutations in the *UBA1* gene by Sanger sequencing [20].

TREATMENT

The treatment of VEXAS syndrome should follow a two-pronged approach: haematological disorders should be treated, including the eradication of haematopoietic cells with the UBA1 mutation, and inflammation and its consequences should be managed at the same time. Collaboration between the rheumatologist and haematologist is essential. To date, there is no standardised treatment for patients with VEXAS syndrome. The data on this subject come from single case observations. The main group of drugs are glucocorticosteroids (GCSs). These drugs are very effective in reducing the symptoms of inflammation; however, high doses are needed in most patients. Synthetic disease-modifying anti-rheumatic drugs (DMARDs), i.e. methotrexate, mycophenolate mofetil, azathioprine, were proven to be effective in some patients [6, 12, 20]. The best effects among biologics were observed with the use of IL-1 antagonists — anakinra, IL-6 antagonists — siltuximab and tocilizumab [5, 7, 26]. Some authors found that Janus kinase (JAK) inhibitors were effective, particularly ruxolitinib [27]. In individual patients, IL-17A antagonists proved to be useful — secukinumab in combination with immunoglobulins and abatacept [7,28]. DNA methyltransferase (DNMT) inhibitors such as azacitidine and decitabine are effective drugs, especially in patients with coexisting MDS and a mutation in the *DNMT3A* gene but without *TET2* mutation. In terms of the treatment of cytopenia, erythropoiesis-stimulating drugs and the thrombopoietin receptor agonist (TPO-RA) — eltrombopag — hold great promise. The drugs proved efficacy in the treatment of MDS, however, there are no studies on patients with VEXAS syndrome [5]. Allogeneic haematopoietic (bone marrow) stem cell transplantation (allo-HSCT) was used in patients who are refractory to drug treatment. Performance of allo-HSCT is particularly beneficial in the early stages of the disease for high-risk patients with a poor clinical response (p.Met-41Val variant of the *UBA1* mutation, blood transfusion dependency, clonal haematopoiesis) [5, 7]. It should be noted that VEXAS syndrome is marked by a variable response to anti-inflammatory treatment. It is possible that there are clinical and genetic subtypes of

this syndrome to which the therapeutic strategy should be adapted in the future.

PROGNOSIS

The prognosis in VEXAS syndrome is unfavourable. Approximately 50% of patients show resistance to treatment, and more than half of patients die (50-63%) [3,29]. Georgin-Lavialle et al. found that 5-year survival for patients with VEXAS syndrome and MDS was comparable to patients with VEXAS syndrome and without MDS (83% *vs.* 76%). The worst prognosis can be found in patients with type II disease phenotype, the best — in patients with type I disease phenotype. Poor prognosis factors include younger age of onset, p.M41Val variant of the *UBA1* mutation, blood transfusion dependency, gastrointestinal involvement, lung involvement and mediastinal lymphadenomegaly [3, 7, 29]. Auricular chondritis and other *UBA1* mutation variants are good prognostic factors [7].

CONCLUSIONS

VEXAS syndrome is a disease with rich rheumatological and haematological symptomatology and a poor prognosis. Data on VEXAS syndrome come from approximately 200 original, review and case reports. It is necessary to maintain a patient register and share experiences so that criteria for diagnosing the disease can be developed and treatment standards can be established.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and writing of the manuscript.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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