CLINICAL OBSERVATIONS

VEXAS syndrome: on the threshold of changing perceptions of known diseases

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This article presents the first case of VEXAS syndrome identified in the Russian Federation as well as characteristics of currently known clinical manifestations and treatment approaches. The clinical observation described is an impressive example of how the identification of a new pathogenic mutation can change the understanding of the classification, diagnosis and treatment of previously known immunoinflammatory diseases. Thus, in refractory forms of relapsing polychondritis, neutrophilic dermatosis, atypical forms of vasculitis, inflammatory joint diseases or undifferentiated systemic inflammatory syndrome, especially when associated with macrocytic anemia and myelodysplastic syndrome, VEXAS syndrome should be suspected and genetic testing should be performed to exclude the autoinflammatory nature of the existing condition.

Keywords: *VEXAS syndrome; macrocytic anemia; vasculitis; relapsing polychondritis; neutrophilic dermatosis; vacuolization of bone marrow cells; myelodysplastic syndrome.*

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Improvements in genetic research led to the description in 2020 of a new monogenic disease, which is characterized by a wide range of systemic immunoinflammatory and hematological manifestations and is called "VEXAS syndrome" (V – vacuoles, E – ubiquitin-activating protein E1, X – linkage to the X chromosome, A – autoinflammation, S – somatic mutation) [1]. The new disease was identified through whole exome sequencing of 2,560 patients, of whom 1,500 had fever of unknown origin and 1,083 had an undetermined diagnosis. In this study, pathogenic variants in the ubiquitin-activating protein (*UBA1*) gene were detected in 25 elderly men who had cytopenias and multisystem inflammatory manifestations. These variants were present in bone marrow hematopoietic progenitor cells and circulating myeloid cells [1].

Most monogenic autoinflammatory diseases (AIDs) arise from inherited germline mutations and are transmitted from generation to generation according to the Mendelian pattern of inheritance. VEXAS syndrome belongs to a new category of AIDs in which the pathogenic variant is somatic and acquired later in life. Somatic variants are not inherited, affect any cells of the body except germ cells, and lead to the formation of a cell clone (tissue or organ area) with a genotype that differs from that of healthy cells (somatic mosaicism). Often such somatic mosaicism can only be identified by next generation sequencing [2]. Penetrance of the disease associated with known pathogenic mutations in the *UBA1* gene appears to be approximately 100%. Moreover, unlike most known monogenic AIDs, VEXAS syndrome occurs exclusively in adults, mainly in men over 50 years of age (95%), although rare cases of the disease have been described in women with unequal lyonization of the X chromosome [3–5]. The prevalence of the syndrome is estimated to be 1:14,000 in the general population, 1:4000 among men over 50 years of age, and 1:26,000 among women over 50 years of age [6].

The *UBA1* protein is presented in cells in two isoforms: *UBA1a*, located in the nucleus, and *UBA1b*, located in the cytoplasm. [7]. In VEXAS syndrome, a somatic missense variant occurs in the *UBA1* gene, located on the X chromosome, which in most cases leads to the replacement of methionine at position 41 with valine, threonine or leucine, resulting in deficiency of *UBA1b* in the cytoplasm of hematopoietic progenitor cells, which is necessary for the activation of ubiquitin. As a result, the disease causes a disruption of the ubiquitination process and, as a consequence, reduced protein degradation and uncontrolled activation of the innate immune system with hyperproduction of interleukin (IL) 1, IL6, IL8, tumor necrosis factor (TNF) α and interferon γ [1, 3, 8]. Other rarer pathogenic and likely pathogenic variants in this gene have also been described [9].

This article presents the first case of VEXAS syndrome identified in the Russian Federation as well as characteristics of cur-

rently known clinical manifestations and treatment approaches. Informed consent was obtained from the patient for the publication of his data.

Case report

***Patient L.**, a 50-year-old man, applied to the V.A. Nasonova Research Institute of Rheumatology in March 2023 with complaints of recurrent febrile fever, painful swelling of the ears, joints and eyes. The patient fell ill in October 2021 – 2 weeks after acute respiratory infection he noted an increase in body temperature to febrile values, pain and swelling in the ankle joints, antibacterial therapy was carried out without a significant effect.*

In November 2021, an episode of bilateral conjunctivitis developed, the patient used eye drops with tobramycin and dexamethasone with a positive effect. Also, since the fall of 2021, blood tests have indicated mild anemia (Hb – 104–112 g/l [normal ranges 130–160 g/l]). In June 2022, febrile fever and pain in large joints reappeared, and the patient first noted painful swelling of the right auricle. A decrease in Hb level to 94 g/l, platelet count to 100 • 109/l, and an increase in ESR to 65 mm/h were recorded. The patient was consulted by an otorhinolaryngologist – an infectious disease was suspected. Therapy with antibacterial and antifungal drugs was ineffective, and therefore intravenous infusion of glucocorticoids (GC) was performed with a positive effect. However, in July 2022, there was a recurrence of febrile fever, swelling of the auricle and joints, blood tests showed persistent signs of systemic inflammatory reaction with increase in ESR to 140 mm/h, CRP to 27 mg/l (normal range 0–5 mg/l), ferritin to 627 μg/l (normal range 20–300 μg/l), while rheumatoid factor, antinuclear factor, antibodies to double-stranded DNA and antineutrophil cytoplasmic antibodies (ANCA) remained within normal ranges. Cancer screening (gastroscopy, colonoscopy, chest X-ray, ultrasound of the internal organs and prostate gland, prostate-specific antigen), blood culture and auricle scraping did not reveal any pathology.

The patient was consulted by a rheumatologist, a diagnosis of post-COVID syndrome was made. Since that time, the patient constantly took GC at a dose of 10 mg/day, a positive effect was noted – there were no relapses of fever and swelling/redness of the ears, eyes, a decrease in ESR, CRP and ferritin levels was noted, but when trying to cancel therapy, the symptoms and increase in acute phase markers returned. In the fall of 2022, in order to reduce the dose of GC, hydroxychloroquine was added to therapy at a daily dose of 200 mg, which the patient took for 2 months without a positive effect. In August 2022, a blood test revealed: macrocytic anemia up to 85 g/l, thrombocytopenia – $141 \cdot 10^9$/l, leukocytes – $9.1 \cdot 10^9$/l, ESR – 50 mm/h. Therapy with vitamin B_{12}, folic acid and iron supplements did not produce results, macrocytic anemia persisted.

The patient was examined at the National Medical Research Center for Hematology. Noteworthy was the presence of two-lineage cytopenia (macrocytic anemia and thrombocytopenia) in the absence of signs of vitamins B and iron deficiency. Cytomorphological examination of the bone marrow was carried out repeatedly: the number of blast cells was within 2.0% without a tendency to increase, narrowing of the erythroid lineage to 3.2–6.4% (normal range – 14.6–26.6%), expansion of the granulocytic lineage up to 80.2–85.2% (normal range – 52.8–68.8%), signs of dyserythropoiesis in 50% of cells, dysgranulocytopoiesis in 10–29% of cells, dysmegakaryocytopoiesis in 10–29% of cells, in single cells (<10%) of erythroid and granulocytic lineage – vacuolization of the cytoplasm. The histomorphological examination data were difficult to interpret. Karyotyping of bone marrow cells revealed a normal male karyotype; no hidden abnormalities of the 5th and 7th chromosomes were detected by FISH. Direct Coombs test, polymerase chain reaction and detection of antibodies to parvovirus B19 were negative. Biochemical parameters, including creatinine, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, γ-glutamyl transpeptidase, were within normal ranges. No paraprotein was detected by blood protein electrophoresis and immunofixation. The erythropoietin concentration was elevated to 271 mU/ml (normal range 4.3–29 mU/ml).

Since February 2023, GC therapy was discontinued, which resulted in painful redness and swelling of the left ear, redness of the left eye, an increase in ESR to 130 mm/h, and macrocytic anemia to 82 g/l. A differential diagnosis was made between myelodysplastic syndrome (MDS) with multilineage dysplasia and connective tissue diseases. Considering the lack of progression of MDS into variants with excess blasts, a possible combination with an autoimmune disease and stable hemogram values, the patient was referred for consultation to the V.A. Nasonova Research Institute of Rheumatology.

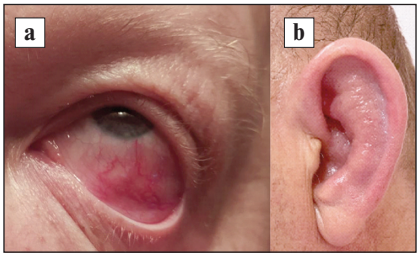

Fig. 1. *Redness of the conjunctiva of the left eye (a), redness and swelling of the left auricle (b) in patient L.*

When examining the patient in March 2023, painful redness and swelling of left eye and left ear were noted (Fig. 1), no other pathological abnormalities were identified. VEXAS syndrome was suspected and genetic testing was recommended; during this period, GC intake was resumed at a dose of 10 mg/day with a positive result – conjunctivitis and chondritis ceased. However, anemia persisted, which became the reason for several transfusions of erythrocyte-containing components of donor blood in a hematology hospital. In addition, in July and August 2023, the patient also experienced thrombocytopenia up to $76 \cdot 10^9$/L without hemorrhagic syndrome.

According to whole-exome sequencing, a pathogenic variant of the nucleotide sequence was identified in the 3rd exon of the UBA1 gene (chrX:47058451T>C, NM_003334.4: c.122T>C), leading to the replacement of amino acid p. (Met41Thr). The variant was detected in 83% of reads, which indicates that the patient has a somatic variant in the majority of circulating nucleated cells. When reviewing the myelogram, signs of vacuolization were detected in single bone marrow cells (Fig. 2).

In September 2023, the patient was hospitalized at the clinic of the V.A. Nasonova Research Institute of Rheumatology. Examination revealed no fever, arthritis, chondritis, or conjunctivitis. Blood tests revealed: Hb – 97 g/l, macrocytosis (mean corpuscular volume – MCV – 100 fL, normal range 80–97 fL), leukocytes – $5.1 \cdot 10^9$/l, thrombocytes – $63 \cdot 10^9$/l, ESR – 46 mm/h (normal range – 2–20 mm/h), CRP – 5.8 mg/l (normal range – 0–5 mg/l), serum iron – 40.1 μmol /l (normal range – 6.6–29 μmol/l), ferritin –737 μg/l (normal range – 20–300 μg/l).

Computed tomography (CT) of the chest revealed bilateral minimal interstitial ground-glass opacities in the subpleural lower lobes, residual right-sided pleuritis and a mild enlargement of the right bifurcational lymph node (Fig. 3). According to pulmonary functional tests, no ventilation disorders were detected, a mild decrease in the

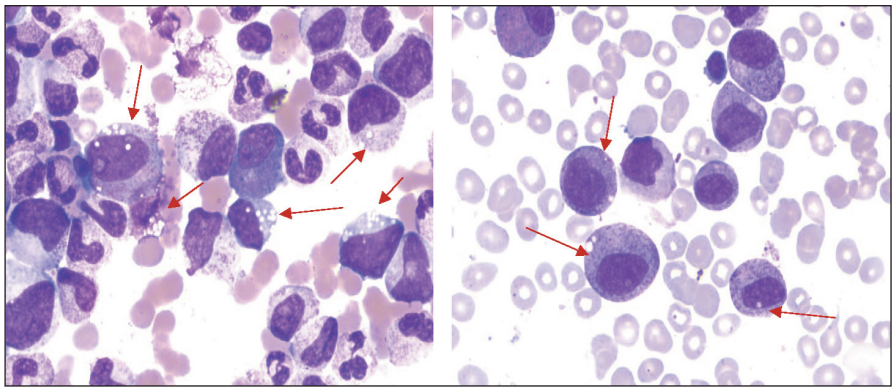

Fig. 2. *Myelogram of patient L. Few cells of granulocytic and erythroid lineages of hematopoiesis have signs of vacuolization (5–7%; arrows). Pappenheim staining, ×1000*

amined at the National Medical Research Center for Hematology. 9 months after the initial consultation, macrocytic anemia remained (Hb – 85 g/l, erythrocytes – $2.4 \cdot 10^{12}$/l, MCV – 104.1 fl) with dependence on transfusions of erythrocyte-containing components of donor blood, thrombocytopenia ($71 \cdot 10^{9}$/l) without hemorrhagic syndrome, leukocytes – $7.6 \cdot 10^{9}$/l with a shift to myelocytes (4%) and lymphopenia (12%). Cytomorphological examination of the bone marrow demonstrated the same picture: blast cells – 1.2%, narrowing of the erythroid lineage to 8.4%, expansion of the granulocytic lineage to 83.6%, the presence of dysmyelopoiesis in three lineages of hematopoiesis in >10% of cells and vac-

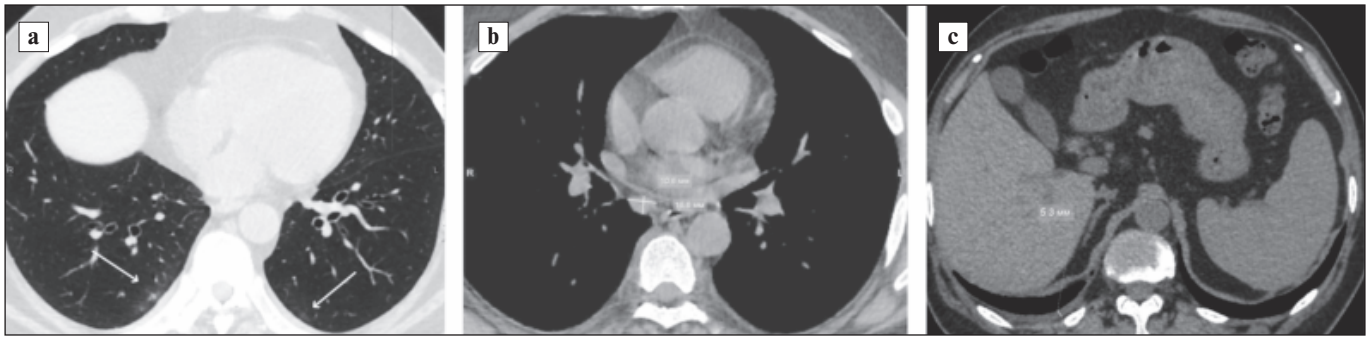

Fig. 3. *Chest CT scan of patient L.: a – minimal interstitial changes of a ground-glass opacity type in the subpleural parts of the lower lobes of both lungs (arrows); b – enlargement of the intrathoracic lymph node of the bifurcation group on the right (up to 16.6 × 10.6 mm); c – residual right-sided pleurisy (up to 5.3 mm)*

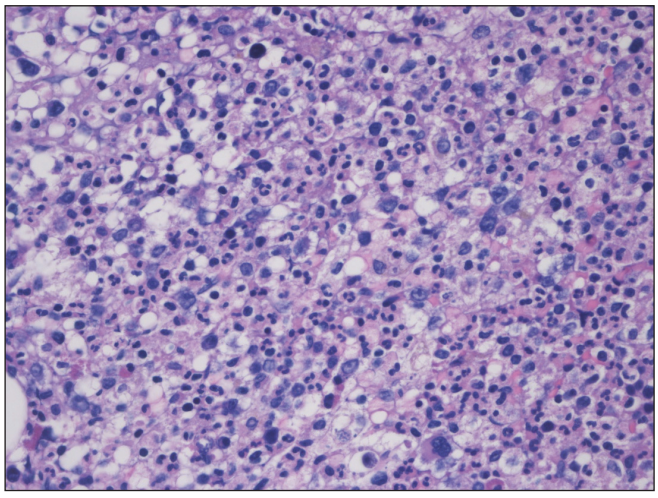

Fig. 4. *Trephine biopsy of the bone marrow of patient L. The bone marrow shows increased cellularity due to the expansion of the granulocyte lineage with the expansion of the intermediate pool. The erythroid lineage is reduced. Among the megakaryocytes, small cells with hyperchromic monolobular nuclei predominate – signs of dysmegakaryocytopoiesis are pronounced. Hematoxylin and eosin staining, ×400*

diffusion capacity of the lungs was recorded (74.3%). A diagnosis of VEXAS syndrome was made and, given the presence of combined autoimmune and hematological manifestations, the patient was re-ex-

uolization of the cytoplasm in 7–9% of cells of erythroid and granulocytic lineages of hematopoiesis.

A pathomorphological study of bone marrow trephine biopsy revealed characteristic MDS changes, with an increase in bone marrow cellularity, expansion of the granulocyte lineage, narrowing of the erythroid lineage of hematopoiesis and an increase of megakaryocytes with signs of dysplasia (Fig. 4). Karyotyping again revealed a normal male karyotype. Based on the examination, a diagnosis of MDS with multilineage dysplasia was established, a low-risk group according to the IPSS-R prognostic scale, VEXAS syndrome. Specific therapy with azacitidine was started at a dose of 75 mg/m2 subcutaneously, on days 1–7 of a 28-day cycle, with evaluation of the effect after the 2nd course. A search for an HLA-matched donor to perform allogeneic hematopoietic stem cell transplantation (allo-HSCT) was also started.

Discussion. The clinical spectrum of VEXAS syndrome is extremely heterogeneous – the autoinflammatory process can involve almost all organs and tissues, imitating various immunoinflammatory diseases (Fig. 5).

Like most other AIDs, VEXAS syndrome is characterized by nonspecific constitutional symptoms such as recurrent fever, fatigue and weight loss, as well as increased acute phase markers (ESR, CRP, IL6, ferritin) [3, 8].

One of the most common clinical manifestations of VEXAS syndrome are skin lesions, which occur in the majority of patients (83.6% according to the largest cohort) [3]. The most common are neutrophilic dermatosis (often in the form of Sweet's syndrome), leukocytoclastic vasculitis and septal panniculitis, less often – ur-

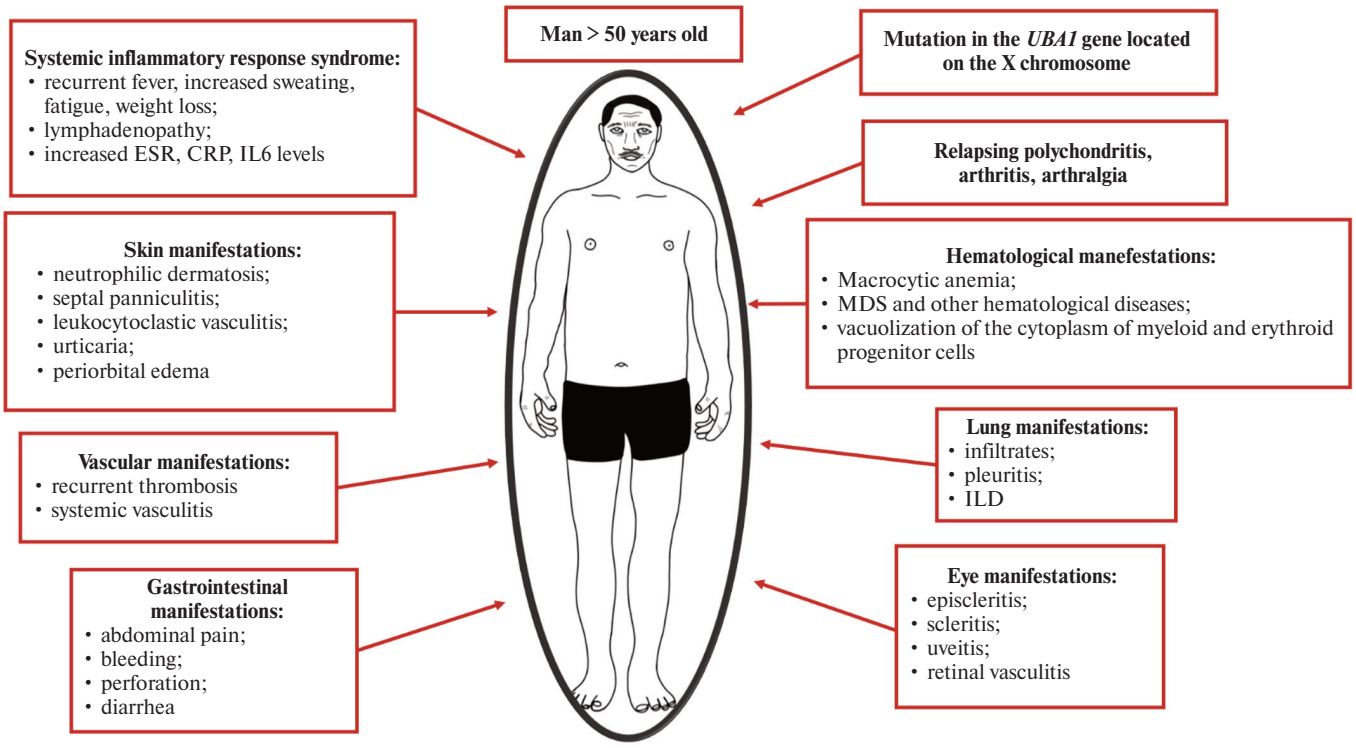

Fig. 5. *Portrait of a patient with VEXAS syndrome. ИЗЛ (ILD) – interstitial lung disease; РП (RP) – relapsing polychondritis; ЖКТ (GT) – gastrointestinal tract*

ticaria and periorbital edema [10]. Interestingly, skin lesions in VEXAS-associated neutrophilic dermatosis are caused by direct damage of the skin by *UBA1*-mutant neutrophils, while other variants of skin manifestations appear to have a nonspecific origin due to hyperactivation of the immune system [11, 12]. In a study by C. Gurnari et al. [13], which evaluated 19 patients with a previously established diagnosis of Sweet's syndrome associated with hematological diseases, 3 patients were diagnosed with VEXAS syndrome based on the detection of a mutation in the *UBA1* gene and bone marrow vacuolization.

Lung involvement is observed in approximately half of patients, most often in the form of infiltrates and pleuritis, as well as interstitial lung disease with ground glass opacities, consolidation or reticular changes [3, 14, 15]. Cases of obliterating bronchiolitis, alveolitis, pulmonary hemorrhage, vasculitis, bronchiectasis have also been described [16].

Articular manifestations are present in 28–58% of patients and more often occur as nonspecific arthralgia [3, 8]. However, cases of the onset of the disease with severe rheumatoid factor-positive erosive polyarthritis, refractory to therapy with methotrexate and TNF-α inhibitors [17], as well as with HLA-B27-associated spondyloarthritis that occurred in a 57-year-old man, followed by a positive effect of therapy with an IL17 inhibitor [18], have been described.

Vasculitis occurs in 8–64% of patients [3, 19, 20]. It is interesting that a wide variety of vasculitides have been described in VEXAS syndrome patients – cutaneous vasculitis, polyarteritis nodosa, aortitis, central nervous system vasculitis, giant cell arteritis, Behзet's disease, cryoglobulinemic vasculitis, ANCA-associated vasculitis [1, 15, 21, 22]. In an Italian retrospective study of 147 patients admitted with suspected vasculitis, VEXAS syndrome was identified in 3 patients [23]. Thus, as with DADA2 [24] and SAVI [25] syndromes, previously known forms of primary vasculitides may in fact be of secondary origin and be a component of VEXAS syndrome.

Relapsing polychondritis (RP) develops in 36–64% of patients; the cartilages of the ears and nose are most often affected; on the contrary, damage to the tracheal cartilages is almost never observed [1, 3, 8]. In most cases, RP in patients with VEXAS syndrome is indistinguishable from idiopathic. This was the reason for studying the frequency of *UBA1* gene mutations in patients with idiopathic RP: the mutation was identified in 7.6% of patients in a prospective cohort with idiopathic RP [26]. Interestingly, the prognosis and severity of the disease with VEXAS-RP is significantly worse than with idiopathic. Thus, in the study mentioned above, the mortality rate of patients with a mutation in the UBA1 gene was 27% versus 2% in patients without this mutation [26]. In another study, patients with VEXAS-RP were significantly more likely to have fever, skin, lung, heart, and eye involvement, as well as an older age at onset and higher CRP levels. [27]. Signs associated with VEXAS syndrome in patients with RP were also identified: age over 45 years, fever, ear chondritis, cutaneous vasculitis, deep vein thrombosis, pulmonary infiltrates [26]. The authors also suggested that all patients with RP should be screened for VEXAS syndrome if they have the following characteristics: male gender, macrocytosis with MCV >100 fL, decreased platelet count $<200 \cdot 10^9$/l. The sensitivity of this algorithm in the study was 100%, and the specificity was 96%.

Up to 40% of VEXAS syndrome patients may have ocular involvement such as uveitis, scleritis, episcleritis and retinal vasculitis [3, 27, 28]. Eye damage in VEXAS syndrome can be associated with the *HLA-B51/B27* genes [29], however, in our case *HLA* gene

typing was not performed. Also, patients with VEXAS syndrome can have gastrointestinal tract damage with abdominal pain, bleeding, perforation and diarrhea, enlargement of peripheral and internal lymph nodes [3], cardiac damage with myocarditis, pericarditis and vasculitis of the coronary arteries [30], nervous system damage with chronic inflammatory demyelinating polyneuropathy [31].

Thrombosis is observed in approximately a third of patients [3, 8], and venous thrombosis is significantly more common than arterial [32, 33]. There is evidence of increased serum levels of coagulation factors VIII and IX, as well as lupus anticoagulant and antiphospholipid antibodies [34], however, these abnormalities are not detected in every patient with thrombosis. Thus, thrombosis in VEXAS syndrome appears to develop due to endothelial dysfunction during chronic systemic inflammation [35].

Hematological manifestations of VEXAS syndrome allow to suspect the disease and often determine treatment tactics. A typical hematological abnormality is macrocytic anemia with normal levels of vitamin B_{12} and folic acid, which is detected in most patients [36] and in a third of cases leads to dependence on blood transfusions [8]. Lymphopenia occurs in 80% of patients, neutropenia and thrombocytopenia occur in half of patients and are possibly associated with MDS [2, 37, 38], which occurs in 25–63% of patients [1, 3, 19, 36, 39]. MDS in VEXAS syndrome is associated with additional mutations in myeloid genes, which are also observed in clonal hematopoiesis (*DNMT3A, TET2, ASXL1*) [40–42]. It was shown that it is the *UBA1* mutation that is primary and precedes the secondary myeloid mutation, leading to clonal hematopoiesis [42]. Most often, MDS is represented by variants with ring sideroblasts or multilineage dysplasia, usually low or very low risk [8]. When comparing VEXAS patients with and without MDS, the former were more likely to have recurrent fever, gastrointestinal, lung and joint damage, a reduced platelet count and a higher requirement for GC [36]. Also, in VEXAS syndrome, cases of acute myeloid leukemia, multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), hemophagocytic lymphohistiocytosis, chronic myelomonocytic leukemia, primary myelofibrosis and Kikuchi–Fujimoto disease have been described [1, 13, 36, 43–45]. The contribution of the *UBA1* gene mutation to the formation of such diverse hematological manifestations remains unclear [21].

Vacuolization of the cytoplasm of granulocytic and erythroid hematopoietic cells is considered a typical cytological sign for VEXAS syndrome, but does not occur in all patients [9, 20, 39, 46–48]. Vacuoles can also be found in eosinophils, monocytes, megakaryocytes and plasma cells, but are absent in mature lymphocytes and fibroblasts, which may be due to the location of the *UBA1* mutation [49]. At the same time, vacuolization of myelopoiesis cells is not specific only to VEXAS syndrome, but is also a cytomorphological sign of MDS and occurs with copper deficiency, toxicity of zinc, alcohol and antibiotics [46, 50]. However, the amount of this vacuolization is also important – the presence of >1 vacuole in 10% of neutrophil precursors indicates a diagnosis of VEXAS syndrome with a sensitivity and specificity of 100% [51]. In another study examining the bone marrow of 16 VEXAS syndrome patients, vacuolization was found in all cases, as was macrocytic anemia, with MDS identified in 6 patients, and another 4 had plasma cell dyscrasias, including multiple myeloma (n=2) and MGUS (n=2) [36]. Taking these data into account, the presence of cytoplasmic vacuolization in <10% of myeloid and erythroid cells according to cytomorphological studies of the bone marrow in our patient is interesting and should be interpreted with caution.

It must be emphasized that VEXAS syndrome has obvious genetic and phenotypic parallelism – the spectrum and severity of clinical manifestations, as well as the prognosis of the disease, directly depend on the type of pathogenic variant in the *UBA1* gene. For example, it was shown that inflammatory eye damage is significantly more common in patients with the p. Met41Thr variant, which is also consistent with our observation, whereas Sweet's syndrome is more common with variant p. Met41Leu, and undifferentiated inflammatory syndrome is more common with p. Met41Val (but ear chondritis is less common) [3, 8]. The mortality rate for this disease is 15–50% [1, 3, 8, 19, 20, 36], but it is also associated with the genotype – in the presence of the p. Met41Val variant, the concentration of *UBA1*b is significantly lower, and the disease is more severe and has a significantly worse prognosis than with the p. Met41Leu and p. Met41Thr variants [8]. Thus, according to a recent study, independent predictors of increased mortality in VEXAS syndrome are dependence on transfusions of blood components and the p. Met41Val variant, while the p. Met41Leu variant and ear chondritis are factors for a more favorable prognosis [3, 8]. Thus, the residual concentration of *UBA1b* in the cytoplasm, the value of which depends on the specific genotype, is of fundamental importance for the pathogenesis of VEXAS syndrome. It is also important to note that in the largest published study of 116 VEXAS syndrome patients, the presence of MDS was not associated with increased mortality, in contrast to gastrointestinal, pulmonary damage and mediastinal lymphadenopathy [3]. Thus, our patient had clear factors of unfavorable prognosis, such as dependence on transfusions of blood components, pulmonary damage and mediastinal lymphadenopathy, which requires an intensive therapeutic approach, although there is a prognostically more favorable mutation (p. Met41Thr).

Recommendations for the treatment of VEXAS syndrome have not yet been developed. Currently, its therapy includes three main components: elimination of the pathological clone of *UBA1*-mutant cells, systemic anti-inflammatory therapy, supportive therapy [7].

Elimination of the pathological clone of *UBA1*-mutant cells is possible using allo-HSCT, which so far remains the only method of biological cure, but, given the high frequency of post-transplantation complications, cannot be used in all cases [43, 52–56]. The effectiveness of this procedure has been demonstrated in case reports or small case series, and results from larger prospective studies are currently awaited (NCT05027945). Also, in order to eliminate the pathological clone of *UBA1*-mutant cells, it is possible to use the hypomethylating agent azacitidine, the effectiveness of which in VEXAS-MDS was assessed in three small retrospective studies [19, 57, 58] and one open prospective phase II study [59], according to which 46–75% of patients achieved complete or partial clinical response of both MDS and immunoinflammatory manifestations, including a decrease in the need for GC. However, such therapy was accompanied by the development or worsening of cytopenias and a high incidence of infections. At the same time, in the study by M.H.G.P. Raaijmaikers et al. [58], which assessed the effectiveness of azacitidine in 3 patients with VEXAS-MDS, therapy led to almost complete elimination of pathological clones with both *UBA1* mutation and *DNMT3A* mutation in 2 patients, but was ineffective in 1 patient with a *TET2* mutation. Larger randomized trials are needed to reliably assess the effectiveness of hypomethylating therapy and its place in the treatment of VEXAS syndrome.

Anti-inflammatory therapy is based on the use of GC in medium and high doses, which most often allows one to achieve a positive clinical and laboratory response, however, in most cases, when the dose is reduced to <15–20 mg/day, an exacerbation of the disease occurs, this contributes to the formation of steroid dependence and adverse reactions associated with cardiometabolic and infectious complications [1, 3, 34, 60]. In our case, there was no relapse of fever, chondritis and arthritis, or an increase in acute phase markers during therapy with prednisolone 10 mg/day, but progressive anemia with dependence on regular transfusions and thrombocytopenia persisted, at the same time a relapse of clinical symptoms occurred when trying to reduce the dose of GC. Azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, cyclosporine A, tacrolimus, hydroxychloroquine, dapsone, colchicine, intravenous immunoglobulin, inhibitors of IL6, IL1, IL17, IL12/23, TNFα, Janus kinase, abatacept, rituximab have been used in small retrospective studies to reduce the dose of GC, however, this therapy in most cases was characterized by complete or partial ineffectiveness, frequent relapses and intolerance [9, 12, 20, 51, 61–63]. At the same time, there has been no direct comparison of the effectiveness of the drugs; larger, long-term studies are needed to form an evidence base. Positive results were obtained with the use of the Janus kinase inhibitor ruxolitinib, the effectiveness of which was assessed in a multicenter retrospective study that included 30 patients with VEXAS syndrome receiving various Janus kinase inhibitors [64]. Ruxolitinib therapy after 6 months led to a complete clinical response in 87% of cases versus 11% when using other drugs in this group, but the short observation period, small sample size and retrospective design of the study do not allow definitive conclusions to be drawn—longer prospective studies in larger cohorts are required. In addition, therapy with ruxolitinib did not lead to the elimination of the pathological clone of *UBA1*-mutant cells, which means that the drug can only be considered as an additional anti-inflammatory agent in complex therapy of the disease. Thus, there is insufficient data to determine the preferred steroid-sparing drug and the question of optimal treatment of systemic inflammation in VEXAS syndrome remains open, the choice of treatment method in each specific case should be based on a comprehensive assessment, taking into account the prevailing clinical manifestations, the patient's age and concomitant pathology.

Maintenance therapy in patients with cytopenias includes transfusions of donor blood components, administration of colony-stimulating factors and drugs that stimulate erythropoiesis, as well as prevention of bacterial and fungal infections in cases of severe neutropenia [7]. For recurrent thrombosis, thromboprophylaxis is carried out, during which relapses are often observed, which probably indicates the need for adequate control of systemic inflammation to reduce the risk of thrombosis. For patients receiving GC ≥15 mg/day, trimethoprim/sulfamethoxazole is prescribed to prevent Pneumocystis jirovecii infection and vaccination is given to prevent other infections [7].

In summary, allo-HSCT is currently considered the first-choice treatment strategy of VEXAS syndrome, both with and without MDS. However, older age and the high frequency of comorbidities in VEXAS syndrome patients significantly limit the use of this method, and therefore it is necessary to develop an algorithm for selecting patients for allo-HSCT. If the patient has immunoinflammatory manifestations, it seems reasonable to use bridge-therapy before the transplantation procedure, the most suitable drugs for which are probably GCs, ruxolitinib, IL6 or IL1 inhibitors, which have a rapid clinical effect [62, 64]. If allo-HSCT is not possible, other treatment methods should be considered: when combined with MDS – combination of GC and azacitidine, in the absence of MDS – GC, ruxolitinib, IL6/IL1 inhibitors or other immunosuppressants [3, 7]. Also, given the different prognosis for different genotypes of VEXAS syndrome and MDS, the choice of treatment tactics may be influenced by the molecular status of the patient [3, 8].

In conclusion, VEXAS syndrome is a hematological and immunoinflammatory monogenic disease characterized by a wide range of clinical manifestations. For its correct diagnosis and determination of optimal treatment tactics, established interdisciplinary interaction between a rheumatologist, hematologist, geneticist and physicians of other specialties is necessary. The clinical observation described is an impressive example of how the identification of a new pathogenic mutation can change the understanding of the classification, diagnosis and treatment of previously known immunoinflammatory diseases. Thus, in refractory forms of relapsing polychondritis, neutrophilic dermatosis, atypical forms of vasculitis, inflammatory joint diseases or undifferentiated systemic inflammatory syndrome, especially when associated with macrocytic anemia and myelodysplastic syndrome, VEXAS syndrome should be suspected and genetic testing should be performed to exclude the autoinflammatory nature of the existing condition.

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