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А.В. Ягода[1], П.В. Корой[1], Д.П. Харченко[2], Н.Н. Гладких[1], И.П. Попова[2]

[1] — ФГБОУ ВО «Ставропольский государственный медицинский университет» Минздрава России, Ставрополь, Россия
[2] — ГБУЗ СК «Ставропольская краевая клиническая больница», Ставрополь, Россия

КЛИНИЧЕСКИЙ СЛУЧАЙ VEXAS-НЕГАТИВНОГО РЕЦИДИВИРУЮЩЕГО ПОЛИХОНДРИТА, АССОЦИИРОВАННОГО С ЛИМФОИДНОЙ ОПУХОЛЬЮ

A.V. Yagoda[1], P.V. Koroy[1], D.P. Kharchenko[2], N.N. Gladkikh[1], I.P. Popova[2]

[1] — Stavropol State Medical University, Department of Hospital Therapy, Stavropol, Russia
[2] — Stavropol Regional Clinical Hospital, Stavropol, Russia

Clinical Case of VEXAS-Negative Recurrent Polychondritis Associated with Lymphoid Tumor

Резюме

Представлено наблюдение лимфоидной опухоли, скрывающейся под «маской» рецидивирующего полихондрита с высокой активностью воспалительного процесса и ограниченным ответом на лечение. Помимо поражения ушной раковины, заболевание сопровождалось неэрозивным недеформирующим артритом, теносиновитом ахиллова сухожилия с его разрывом, эписклеритом, хондритом носа, поражением кожи в виде нейтрофильного дерматоза Свита, дилатацией восходящего отдела аорты, субклиническими признаками поражения лёгких и перикарда, а также развитием макроцитарной анемии при нормальном содержании в крови витамина B12 и фолиевой кислоты, отсутствием лабораторных проявлений аутоиммунизации. Несмотря на то, что рецидивирующий полихондрит с подобными клинико-лабораторными признаками может быть частью фенотипа недавно описанного аутовоспалительного синдрома взрослых (VEXAS), определение его генетического маркера дало отрицательный результат.

Ключевые слова: *рецидивирующий полихондрит, синдром VEXAS, Свит-синдром, лимфома*

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Abstract

A clinical case of lymphoid tumor hiding under the «mask» of recurrent polychondritis with high activity of inflammatory process and limited response to treatment is presented. In addition to auricle damage, the disease was accompanied by non-erosive non-deforming arthritis, tenosynovitis of the Achilles tendon with its rupture, episcleritis, nasal chondritis, skin lesions in the form of Sweet neutrophilic dermatosis, ascending aorta dilation,

subclinical signs of lung and pericardial damage, and development of macrocytic anemia with normal blood levels of vitamin B12 and folic acid, absence of laboratory manifestations of autoimmunity. Despite the fact that recurrent polychondritis with similar clinical and laboratory signs may be part of the phenotype of recently described adult autoinflammatory syndrome (VEXAS), the determination of its genetic marker gave a negative result.

Key words: *recurrent polychondritis, VEXAS syndrome, Sweet syndrome, lymphoma*

Conflict of interests

Co-author of the article Yagoda A.V. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Yagoda A.V. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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Conformity with the principles of ethics

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AID — autoinflammatory disease, ANCA — anti-neutrophil cytoplasmic antibodies — AS-DNAse — serum DNase activity in ankylosing spondylitis, ACPA — antibodies against cyclic citrullinated peptide, EBV — Epstein-Barr virus, BT — biological therapy, MDS — myelodysplastic syndrome, MSCT — multi-spiral computed tomography, MRI — magnetic resonance imaging, PET — positron emission tomography, RP — relapsing polychondritis, RF — rheumatoid factor, SLE — systemic lupus erythematosus, CRP — C-reactive-protein, CLL — chronic lymphocytic leukemia, CIC — circulating immune complexes, ENMG — electroneuromyography, EchoCG — echocardiography, HHV — human herpesvirus, HLA — human leukocyte antigen, MCV — mean corpuscular volume, SM IgG — IgG-antibodies against the extracted nuclear antigen, UBA1 — ubiquitine-activating protein, VEXAS — a new monogenic disease — adult autoinflammatory syndrome (V — vacuoles, E — ubiquitine-activating protein E1, X — X-linked, A — autoinflammation, S — somatic mutation)

Relapsing polychondritis (RP) is a rare multisystemic inflammatory cartilaginous progressive disease of unknown etiology. All ethnic groups are affected. In specific countries the rate of RP is 4.5 cases per 1 million population, while the prevalence is 0.71 cases per 1 million population annually [1, 2]. The disease is not associated with gender and significantly not associated with age [3], is characterized by relapsing inflammation and cartilage destruction, in particular affecting auricles, nose, and the respiratory tract [4, 5]. Joints, eyes, the internal ear [6], heart valves and blood vessels, including the aorta [7, 8], may be affected.

Inflammatory auricular lesions (tenderness, swelling, induration, violaceous-erythematous discoloration/flaccid formless "cauliflower-like" ear) are observed almost in all patients, while nasal chondritis (cartilaginous septum lesions with the saddle-like nasal deformity), nasal congestion, rhinorrhea, epistaxis — in 82 % patients [9]. Various ocular symptoms caused by the inflammation of the fibrous ocular layer are detected in every second patient, including scleritis, episcleritis, non-granulomatous uveitis, conjunctivitis; proptosis with chemosis, periorbital edema, ophthalmoplegia [9, 10]. Classical arthropathy manifestations in RP patients include the symmetric non-erosive non-deforming arthritis, although they may vary from arthralgias to monoarthritis or polyarthritis with the involvement of large and small joints, parasternal joints. Every fourth patient has cardiovascular lesions in the form of aortitis — aortic root dilation/aneurysm, aortic regurgitation, myocardial infarction, arterial thrombosis (one of the most common causes of death in RP). Cutaneous lesions are detected in 30 % patients with RP, including cutaneous (and oral) ulcers, papules, purpura, nodules [6]. These were primarily presented with vasculitis, although neutrophilic dermatosis (Sweet syndrome), panniculitis without vasculitis, aseptic abscess, and non-specific changes were also described [7]. It should be noted that neutrophilic dermatosis was observed in RP almost exclusively in combination with the myelodysplastic syndrome [7]. Respiratory lesions are considered the most severe and prognostically significant — these include dysphonia, aphonia, voice hoarseness, respiratory failure symptoms resembling bronchopulmonary infections or asthma; laryngeal and tracheal lesions are often accompanied by tenderness of the thyroid cartilage and the anterior tracheal wall [6, 11].

RP is often associated with autoimmune and autoinflammatory diseases: SLE, rheumatoid arthritis, seronegative spondylitis, mixed connective tissue disorder, Sjogren disease; vasculitides (granulomatosis with polyangiitis, polyarteriitis nodosa, Takayasu aortoarteriitis), Behcet's diseases, Cogan syndrome are other common associations [12, 13].

Cases of RP association with other rheumatic and autoimmune diseases, myelodysplastic syndromes, rarely lymphomas have also been described [14–16]. For example, J. Dion et al. [7] examined 142 patients with RP, and 18 (13 %) of those had concomitant hematological malignancies, predominantly myelodysplastic syndrome,

which occurred only in older males that also had cutaneous lesions (commonly neutrophilic dermatosis), sometimes associated with vasculitis. 4 lymphoma cases and 2 myeloproliferative disorder cases were among more rare hematological diseases. It is commonly considered that myelodysplasia-associated RP should be considered a paraneoplastic syndrome [17], and its poor prognosis reflects the prognosis of the main myelodysplastic disorder [18]. Very rare cases of RP association were described with several solid tumors, including those of the colon and rectum, pancreas, bladder, bronchi, lungs, breast [9, 10].

Classification (major) RP criteria [19] include auricular lesions, nasal chondritis, laryngotracheal chondritis; minor criteria include ocular lesions (conjunctivitis, keratitis, episcleritis, uveitis), hearing loss, vestibular dysfunction, and seronegative arthritis. 2 major or 1 major and 2 minor criteria are sufficient to confirm the diagnosis. Considering clinical manifestations, disease evolution and prognosis, 3 specific phenotypes (clusters) have been defined: 1) hematological; 2) respiratory; 3) mild (with a good prognosis) [7].

The etiology and pathogenesis of RP are unknown. Associations between RP and several histocompatibility antigens (HLA-DRB1*16:02, DR4, etc.) have been established [20]. The trigger role of infectious agents in the emergence of autoimmune disorders has been confirmed by detecting a large amount of antibodies against collage II [21], IX, and XI along with the diffuse infiltration of affected cartilages with lymphocytes (CD4+, plasma cells) during the high activity period. Antinuclear, antineutrophil cytoplasmic antibodies, rheumatoid factor may also be detected in the blood of patients, thus confirming the immune-mediated RP character.

A new monogenic disease, described in 2020, VEXAS adult autoinflammatory syndrome (vacuoles; E1 enzyme; X-linked; autoinflammation; somatic mutation), has largely changed insights into the autoinflammatory diseases in general and possible mechanisms of RP in particular. The disease associated with the emergence of pathogenic variants in the ubiquitine-activating protein (UBA1) gene is characterized by a wide spectrum of systemic manifestations, including immunoinflammatory and hematological ones due to the presence of UBA1 in bone marrow precursor cells and circulating myeloid cells [22]. Unlike the majority of autoinflammatory diseases (AIDs) emerging due to hereditary mutations and inherited in successive generations, VEXAS syndrome is acquired in an older age and is somatic (non-inherited). The penetrance (gene realization in signs) associated with the UBA1 gene mutations is very high. With that, VEXAS syndrome emerges exclusively in adults (more often males) after 50 years of age with the prevalence of 1:4000. The pathological gene variant promotes methionine substitution to valine, threonine, or leucin. The resulting cytoplasmic UBA1 failure in hematopoietic cells leads to the decreased ubiquitine activation and, thus, to uncontrollable activation of the congenital immunity system, excessive production of pro-inflammatory cytokines, TNF-α, interferon-γ.

It is interesting to note that relapsing polychondritis may be a part of the VEXAS phenotype — this variant (VEXAS-RP) has some specific features, i.e. fever, auricular and nasal chondritis, cutaneous lesions, pulmonary infiltrates, and venous thrombosis; it is characterized by frequent relapses and steroid dependence, which are not typical for idiopathic RP [23, 24].

In a recently published (first Russian) clinical case study of the VEXAS syndrome [25], a male patient presented with febrile fever, tender swelling and hyperemia of auricles, joint and ocular lesions, two-lineage cytopenia (macrocytic anemia and thrombocytopenia), high CRP, ESR, and ferritin levels, although with the absence of rheumatoid and antinuclear factors, anti-double-stranded DNA antibodies and anti-neutrophil cytoplasmic antibodies (ANCA), but with the significant positive corticosteroid effects. The bone marrow biopsy revealed alterations typical for the myelodysplastic syndrome, with enhanced bone marrow cellularity, expanded granulocytic lineage, narrowed erythroid lineage, and elevated megakaryocyte counts with signs of dysplasia. Based on the whole-exome sequencing, a pathogenic variant of the nucleotide sequence was detected in exon 3 of the UBA1 gene with methionine substituted to threonine in 83 % reads — this defined the somatic variant in the majority of circulating nucleated cells.

The clinical RP variant analyzed by us included many signs typical for RP, Sweet syndrome, and VEXAS syndrome, thus providing specific diagnostic difficulties in the various disease stages.

Below we present a proper case study

The male patient S., 53 years old, visited the rheumatologist in early 2021 complaining of periodic fever (37.3–37.6 °C), body aches, myalgias (especially in calf muscles), fleeting migratory arthralgias (sometimes in right sternocostal joints), headache, as well as malaise, fatigability, diaphoresis, weight loss, ocular hyperemia, periodic pain and swelling of Achilles tendons.

Almost 10 years ago he first develop episodic pain in small hand and foot joints, ankles and wrists. In 2020 he was treated for chronic relapsing episcleritis of both eyes.

Since March 2021, he starting having almost constant pain in feet (plantar surface, Achilles tendons), wrist joints, sacroiliac joints, ocular hyperemia, headache, subfebrile fever; pain, swelling, and hyperemia of the right auricle also emerged. He lost 4 kg of body weight. In childhood the patient was sick with rubella and

mumps. At the moment of examination, his concomitant diseases included urolithiasis (multiple urinary stones in the pyelocalyceal system of both kidneys), degenerative disc disease, open-angle glaucoma of both eyes. The patient was not infected with COVID-19, although he was vaccinated in December 2020 and January 2021 (1.5–2 months before the expansion of the symptom spectrum and worsening severity).

Physical examination: the patient was of adequate nutrition (BMI=25); scleral vascular injection, thickened nasal septum were noted. The skin of the right auricle was congestively hyperemic, hot to the touch, tender on palpation. The left ankle joint was enlarged, with limited motions and mild tenderness on palpation. Entesopathy, achillodynia, talalgia were confirmed. Functional insufficiency: Grade 0-1. Varicose subcutaneous veins were detected in both lower extremities (legs) without signs of inflammation and trophic disorders. Locations of cartilaginous rib attachments to the sternum were tender on the right side (Tietze syndrome).

Blood counts demonstrated elevated C-reactive protein (CRP) levels to 147 mg/L (reference range: < 5 mg/L), as well as ESR (80 mm/h) and CIC levels (289 U, reference range: 0–120 U). Levels of ACPA, ANCA (IgG), anti-Sm (IgG), antibodies against native and double-stranded DNA, antinuclear antibodies, rheumatoid factor, AS-DNAase were within normal limits; HLA-B51 and B27 antigens were negative. MRI confirmed osteoarthritis of both hip joints (Grade 1), moderate sacroileal osteoarthritis. PET/CT scan demonstrated a focus of label hyperfixation in the T3 vertebra. The patient was counseled by the hematologist, TB specialist. Relapsing polychondritis was diagnosed, and in May 2021 the treatment was started (methylprednisolone + sulfasalazine; eye drops (Tobradex)). His well-being improved mildly: myalgias in calf muscles, body aches, diaphoresis, hyperthermia (high febrile fever) persisted, as well as elevated CRP and ESR levels.

In summer 2021 and in early 2022 the patient was examined twice in the Chief Clinical Hospital of the Russian Ministry of Internal Affairs.

During the first hospitalization, the blood count detected anemia and macrocytosis (Hb 106 g/L, MCV 102 fL) with normal folate and vitamin B_{12} levels, hyperthrombocytosis (498×10^9/L), elevated serum potassium and ferritin levels, high CRP — 85.1 mg/L (reference range: < 3 mg/L), normal rheumatoid factor (RF) levels. Transthoracic echocardiography (EchoCG) revealed a mild dilation of the ascending aorta (~3.8 cm). The bone scan demonstrated symmetric lesions of acromioclavicular and intertibial joints, lesions of the right elbow, left wrist, and metacarpophalangeal joints of the left hand, lesions of small hand joints (with a trend to symmetry). Ultrasound (US) examination detected lymph nodes in axillary regions bilaterally (sized from 2.4×0.8 to 3.0×0.86 cm) and in inguinal regions (max. 2.4×0.6 cm). Electroneuromyography (ENMG) revealed signs of moderately impaired conduction along the sensory fibers of the peroneal nerve in the left lower extremity (axonal sensory neuropathy). Besides the open-angle glaucoma, chronic episcleritis was diagnosed in both eyes. Methylprednisiolone was administered (pulse-therapy with subsequent oral dosing (20 mg/day)) along with the disease-modifying therapy (methotrexate 20 mg once weekly), which was complicated by the relapsing herpes infection; a small area of cutaneous hyperemia (without itching) appeared in the right shoulder region. Accounting for the verified RP diagnosis, outpatient treatment inefficacy, and high clinical & laboratory activity, biological therapy (BT) with tocilizumab (560 mg IV once monthly) was initiated; 3 plasmapheresis sessions were also arranged. As a result of treatment, myalgias and arthralgias, auricular hyperemia and swelling disappeared, while ocular symptoms diminished. CRP levels decreased from 85.1 to 16.8 mg/L, ESR normalized, while hemoglobin levels rose. It was recommended to continue treatment with oral methylprednisolone (20 mg/day) and methotrexate (20 mg once weekly intramuscularly).

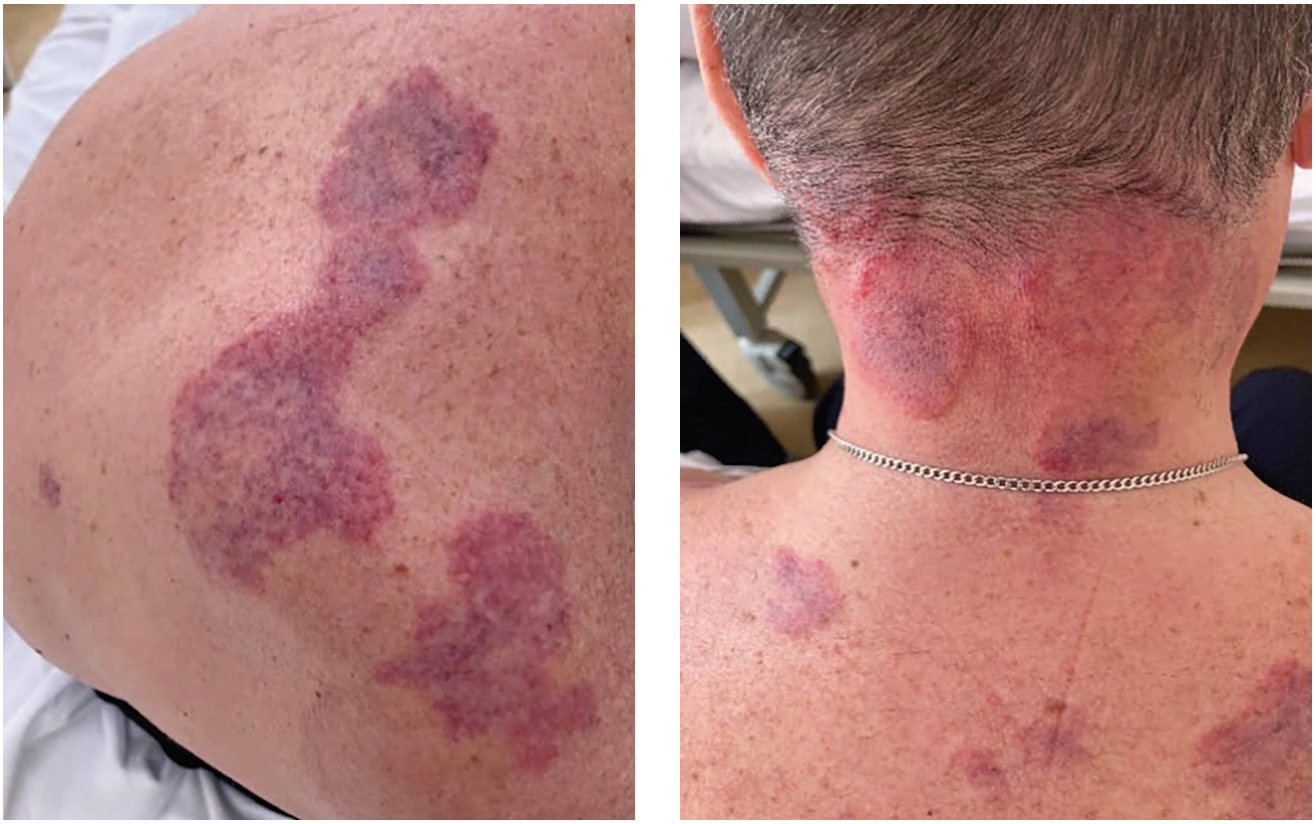
In December 2021 (before the second hospitalization to the Hospital of the Ministry of Internal Affairs), the following alterations were detected in the complete blood count: anemia (RBCs 3.75×10^{12}/L, Hb 106 g/L, Ht 34.6 %), moderate leukopenia (3.8×10^9/L), relative granulocytopenia (45.8 %) and lymphocytosis (43 %). MCV = 99.8 fL.

The second hospitalization confirmed the significantly decreased activity of the main disease — no anemia, CRP level normalization (0.334–0.185 mg/L), diminished (even eliminated) neurological and ophthalmological signs. The patient was administered tocilizumab (480 mg), oral methylprednisolone (4 mg) was preserved, and mofetil mycophenolate (50 mg twice daily) was administered for long-term therapy.

Final diagnosis: Relapsing polychondritis, Activity 3 (perichondritis of the right auricle; chronic episcleritis of both eyes; myalgias of the leg muscles; peripheral non-erosive arthritis of the left ankle joint, foot joints; axonal sensory neuropathy of the peroneal nerve in the left lower extremity; peripheral lymphadenopathy; subfebrile fever; mild anemia; thrombocytosis).

Results of laboratory tests in early 2022 (after the treatment with tocilizumab, methylprednisolone, and mofetil mycophenolate): MCV = 100.6, normal CRP level (3.3 mg/L), elevated antinuclear factor, 1:320 (reference range: < 1:160). Chondroperichondritis of the quadrangular cartilage of the nasal septum was first diagnosed by Professor V.P. Karpov.

In mid-April 2022, a rash in the form of edematous and erythematous papules, plaques emerged on the skin of the upper torso, neck, scalp (see Fig.). A biopsy was



Drawing. *Patient S. Sweet neutrophilic dermatosis*

arranged; the microscopy demonstrated cutaneous areas with focal epidermal atrophy and focal moderate hyperkeratosis. Significant dermal edema and fiber separation: severe inflammatory infiltration with segmented neutrophils is detected between collagen fibers. Histological signs correspond to the neutrophilic (Sweet) dermatosis (Professor S.Z. Chukov).

Paraaortic lymphadenopathy was detected with MSCT in April 2022. EchoCG demonstrated myocardial hypertrophy in the basal part of the interventricular septum, initial pulmonary hypertension, marginal induration of the right semilunar aortic valve leaflet, aortic dilation at the level of Valsalva sinuses and the ascending part, thickened visceral pericardial layer due to fibrin accumulation. Pulse-therapy with corticosteroids was administered (with no effect). Apixaban 5 mg was started, then (in June 2022) abatacept (750 mg once every 2 weeks) was administered for 3 months (also without significant effect).

Pain, swelling, subcutaneous hematoma emerged in the region of the right Achilles tendon with US signs of complete intra-trunk rupture of central tendon fibers with the distal end retraction, effusion in the tendinous vaginal cavity (tenosynovitis of the Achilles tendon).

The skin biopsy specimen was reviewed (on June 9, 2022). The changes detected did not contradict the diagnosis of neutrophilic (Sweet) dermatosis. However, one should not exclude exudative erythema multiforme. Due to new rash on the skin of upper and lower extremities, the patient was consulted by the dermatologist: accounting for arthralgia and malaise that accompanied the rash, paraneoplastic origin cannot be excluded.

In June 2022, the genetic testing for the VEXAS syndrome was arranged in the Scientific Research Institute of Rheumatology. The exome sequencing did not reveal pathogenic, probably pathogenic variants, as well as variants of undetermined clinical significance were not detected in the UBA1 genome.

PET-CT in August 2022 (V. A. Almazov NMRC). Signs of active lymphoproliferative disease affecting the cervical, intrathoracic, axillary, intraabdominal and extraperitoneal, pelvic, inguinal lymph nodes; foci of pulmonary tissue induration in S2 and S10 of the right lung could correspond to the main disease manifestations. Inguinal lymph node histology: normal nodular structure lost; a detected tumor was represented by lymphoid cells, sized a little larger than small lymphocytes. The tumor structure and immunophenotype most likely corresponded to chronic lymphocytic leukemia / small lymphocytic lymphoma.

Main diagnosis: Small lymphocytic lymphoma/CLL, Grade IVB, affecting cervical, axillary, intraabdominal, intrapelvic, inguinal lymph nodes, and the right lung.

Complication: Grade 1 anemia.

Concomitant diagnosis: Relapsing polychondritis affecting ears (auricular perichondritis), eyes (episcleritis),

musculoskeletal system (arthritis, arthralgias, tenosynovitis), skin (neutrophilic (Sweet) dermatosis/exudative erythema multiforme), ascending aorta (dilation), lungs (induration foci), asociated with a lymphoproliferative disease, high activity.

The increased perichondritis activity led to the increase in methylprednisolone dose to 32 mg/day with moderate positive effects. Specific immunotherapy (rituximab), target therapy (venetoclax ramp-up), maintenance immunosuppressive therapy (methylprednisolone), and preventive antiviral therapy (acyclovir) was administered.

Subsequently the disease progressed. The small lymphocytic lymphoma/CLL transformed into diffuse large B-cell lymphoma CD5+, non-GCB variant, bulky, IIB (Ann Arbor), with the refractory-relapsing course. Hypoplastic variant of the myelodysplastic syndrome also developed. Despite the treatment with corticosteroids, venetoclax, rituximab, glofitamab, 5-azacitidine (for MDS correction), blood component transfusions, polychemotherapy, and an attempt to inject donor (haplocompatible) T-lymphocytes, several complications (including thrombosis, steroid-induced myopathy, protein-energy deficiency) developed, and the patient died in August 2024.

Discussion

Rheumatic manifestations of malignancies and malignancies in patients with rheumatic diseases form one of the most interesting issues of internal diseases. Such associations are caused by simultaneous oncogenic and rheumatogenic potentials of various virus groups (hepatitis B, C, EBV, cytomegalovirus, HHV-8, etc.), chemical (including drug-induced) factors and autoantigens (oncoproteins, tumor suppressor, proliferative antigens) as triggers of antibody production with the activation of autoimmune mechanisms in patients with neoplasms (especially hematological ones). With that, the tumor either precedes the rheumatic disease (true paraneoplasia) or develops as a secondary pathology (RD as a risk factor of malignancies) [26].

The patient S. had a clear time association between the disease manifestation and vaccination against the SARS-CoV-2 virus, although several articular and even ocular symptoms were present earlier (within several years).

The diagnosis of RP was established in the patient very quickly, considering the presence of a single major (right auricular lesion) and two minor signs — episcleritis and non-erosive, non-deforming arthritis (affecting the hand and foot joints, sacroiliac and sternocostal joints), which were later joined by nasal chondritis, tenosynovitis of the Achilles tendon (with the intra-trunk fiber rupture); aortitis (aortic root dilation) was confirmed as well. The latter two lesions are not included into the diagnostic criteria, but their presence (including tenosynovitis first confirmed in RP) is a good addendum to the diagnosis, while aortitis is another evidence of the disease "visceralization". The patient S. had a rare (3 %) variant of cardiac lesions in the form of pericarditis (fibrin accumulation on the visceral layer) and peripheral neuropathy (detected less than in 4 % RP cases) [7]. Foci of the pulmonary tissue induration were also detected.

At the initial disease stage, no specific diagnostic doubts were present, although significant systemic signs observed in RP combined with the high activity and limited response to the treatment with methylprednisolone and methotrexate raised some questions. It is important to note (including the differential diagnosis) that the patient S. did not have laboratory signs of autoimmune pathologies that could be associated with RP (ANCA, ACPA, rheumatoid factor, anti-DNA, anti-Sm (IgG), antinuclear antibodies, etc.) — these sometimes allow to put relapsing polychondritis into the group of autoinflammatory diseases (often genetically determined), although the two-fold elevation in CIC levels (289 U; reference range: 0–120 U) and a single mild elevation in the antinuclear factor titer (1:320) could not lead to a unanimous decision.

The emergence of cutaneous lesions in the form of neutrophilic (Sweet) dermatosis became a turning point in the diagnostic search; this pathology is an inflammatory non-infectious cutaneous reaction with predominant dermal neutrophilic infiltrate, which often develops in response to the tumor, drug, immune diseases, sarcoidosis, Behcet's disease, etc. Based on the existing data, Sweet syndrome associated with malignancies (most often hematological, predominantly myeloid ones) forms a significant portion (85 %) of cases [27, 28]. Cutaneous manifestations (Sweet syndrome, etc.) is one of the most common signs emerging in 90 % cases of the VEXAS syndrome [29].

Meanwhile, simultaneous MSCT detected paraaortic lymphadenopathy in the patient, although 8 months before (almost 5 months after the RP manifestation) axillary and inguinal nodes sized up to 3.0x0.86 cm were detected in the patient S. during the US study in one of the inpatient departments.

One should discuss macrocytic anemia in the patient with normal folate and vitamin B_{12} levels in blood. It should be noted that this hematological phenomenon was detected in the majority of patients with the VEXAS syndrome [30], leading to the required repeated blood transfusions in every third case [31]. Macrocytic anemia was periodically accompanied by leukopenia (neutropenia) in the patient S. — almost a two-lineage cytopenia, which was possibly a precursor of myelodysplastic syndrome. The latter one is reported on average in half of patients with the VEXAS syndrome [30, 32], and it

developed during the final disease stage during the cytostatic therapy. Accounting for these data, the genetic testing for the VEXAS syndrome was arranged in June 2022, but its result was negative.

Conclusion

When comparing clinical and laboratory data of the patient S. with the VEXAS-negative paraneoplastic RP and results obtained by M.-Y. Khitri et al. [33] in the population of 55 patients with VEXAS-RP, we confirmed the presence of the following clinical signs in both cases: hyperthermia, lesions of the skin, eyes, heart (aorta), lungs; association with MDS, low treatment efficacy, poor prognosis. Thus, firstly, the combination of highly active RP with a wide spectrum of clinical manifestations, including Sweet syndrome, may be characterized by a severe progressive polychondritis course regardless of VEXAS presence; secondly, VEXAS-negative RP cases demonstrating a high activity, a wide spectrum of clinical manifestations (including visceral ones) in the absence of laboratory autoimmune signs should be considered a prognostically poor (possibly, hematological) variant.

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Ягода А.В.: разработка дизайна публикации, написание статьи, обзор публикаций по теме исследования

Корой П.В.: анализ данных, написание статьи, обзор публикаций по теме статьи

Харченко Д.П.: ведение пациента, сбор анамнеза, коррекция рукописи, обзор публикаций по теме статьи

Гладких Н.Н.: анализ данных, написание статьи, обзор публикаций по теме статьи

Попова И.П.: ведение пациента, обзор публикаций по теме статьи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

Yagoda A.V.: publication design, article writing, review of research publications, case management

Koroy P.V.: data analysis, article writing, review of publications on the topic of the article

Kharchenko D.P.: case management, history taking, manuscript correction, review of publications on the topic of the article

Gladkikh N.N.: data analysis, article writing, review of publications on the topic of the article

Popova I.P.: case management, review of publications on the topic of the article

Список литературы/References:

1. Mathew S.D., Battafarano D.F., Morris M.J. Relapsing polychondritis in the Department of Defense population and review of the literature. Semin. Arthritis Rheum. 2012;42(1):70-83. doi: 10.1016/j.semarthrit.2011.12.007
2. Hazra N., Dregan A., Charlton J. et al. Incidence and mortality of relapsing polychondritis in the UK: a population-based cohort study. Rheumatology (Oxford). 2015;54(12):2181-2187. doi: 10.1093/rheumatology/kev240
3. Mathian A., Miyara M., Cohen-Aubart F. Relapsing polychondritis: a 2016 update on clinical features, diagnostic tools, treatment and biological drug use. Best. Pract. Res. Clin. Rheumatol. 2016;30(2):316-333. doi: 10.1016/j.berh.2016.08/001
4. Денисов Л.Н, Виноградова И.Б., Бахтина Л.А. Рецидивирующий полихондрит: обзор литературы и описание клинического случая. Современная ревматология. 2023;17(1):83-88. doi: 10.14412/1996-7012-2023-1-83-88
Denisov L.N., Vinogradova I.B., Bakhtina L.A. Recurrent polychondritis: a review of the literature and a clinical case description. Modern Rheumatology Journal. 2023;17(1):83-88 [In Russian]. doi: 10.14412/1996-7012-2023-1-83-88
5. Shimizu J., Yamano Y., Yudoh K., Suzuki N. Organ involvement pattern suggests subgroups within relapsing polychondritis: comment on the article by Dion et al. Arthritis Rheumatol. 2018;70(1):148-149. doi: 10.1002/art.40330.
6. Puechal X., Terrier B., Mouthon L. et al. Relapsing polychondritis. Joint Bone Spine. 2014;81(2):118-124. doi: 10.1016/j.jbspin.2014.01.001
7. Dion J., Costedoat-Chalumeau N., Sène D. et al. Relapsing polychondritis can be characterized by three different clinical phenotypes: analysis of a recent series of 142 patients. Arthritis Rheumatol. 2016;68(12):2992-3001. doi: 10.1002/art.39790
8. Ягода А.В., Гладких Н.Н. Эндокард и клапаны сердца при системных ревматических болезнях. Ставрополь. 2021; 384 с.
Yagoda A.V., Gladkikh N.N. Endocardium and heart valves in systemic rheumatic diseases. Stavropol. 2021; 384 p. [In Russian].
9. Buckner J.H., Wu J.J., Reife R.A. et al. Autoreactivity against matrilin-1 in a patient with relapsing polychondritis. Arthritis Rheum. 2000;43(4):939-943. doi: 10.1002/1529-0131(200004)43:4<939::AID-ANR28>3.0.CO;2-Z
10. Cynthia M. Magro, Molly Dyrsen. Angiocentric lesions of the head and neck. Head Neck Pathol. 2008;2(2):116-130. doi: 10.1007/s12105-008-0049-2
11. Suyama Y., Ishimoto S.-I., Hagiwara K. Clinical images: arytenoid chondritis. Arthritis Rheumatol. 2017;69(6):1193. doi: 10.1002/art.40088
12. McAdam L.P., O'Hanlan M.A., Bluestone R., Pearson C.M. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine (Baltimore). 1976;55(3):193-215. PMID:775252
13. Черняк В.И., Савельев А.И., Погромов А.П. и др. Рецидивирующий полихондрит. Клиническая медицина. 2014;86(11):22-28.
Chernyak V.I., Savel'ev A.I., Pogromov A.P. et al. Relapsing holychondritis. Clinical Medicine (Russian Journal). 2014;86(11):22-28 [In Russian].
14. Hebbar M., Brouillard M., Wattel E. et al. Association of myelodysplastic syndrome and relapsing polychondritis: further evidence. Leukemia. 1995;9(4):731-733. PMID: 7723411
15. Yanagi T., Matsumura T., Kamekura R. et al. Relapsing polychondritis and malignant lymphoma: is polychondritis paraneoplastic? Arch. Dermatol. 2007;143(1):89-90. doi: 10.1001/archderm.143.1.89
16. Horváth A., Páll N., Molnár K. et al. A nationwide study of the epidemiology of relapsing polychondritis. Clin. Epidemiol. 2016;8:211-230. doi: 10.2147/CLEP.S91439
17. Cohen P.R. Paraneoplastic relapsing polychondritis. Arch. Dermatol. 2007;143(7):949-950. doi: 10.1001/archderm.143.7.949

18. Mekinian A., Grignano E., Braun T. et al. Systemic inflammatory and autoimmune manifestations associated with myelodysplastic syndromes and chronic myelomonocytic leukaemia: a French multicentre retrospective study. Rheumatology (Oxford). 2016;55(2):291-300. doi: 10.1093/rheumatology/kev294
19. Michet C.J., McKenna C.H., Luthra H.S., O'Fallon W.M. Relapsing polychondritis. Survival and predictive role of early disease manifestations. Ann. Intern. Med. 1986;104(1):74-78. doi: 10.7326/0003-4819-104-1-74
20. Terao C., Yoshifuji H., YamanoY. et al. Genotyping of relapsing polychondritis identified novel susceptibility HLA alleles and distinct genetic characteristics from other rheumatic diseases. Rheumatology (Oxford). 2016;55(9):1686-1692. doi: 10.1093/rheumatology/kew233
21. Foidart J.M., Abe S., Martin G.R. et al. Antibodies to type II collagen in relapsing polyhondritis. N. Engl. J. Med. 1978;229(22):1203-1207. doi: 10.1056/NEJM197811302992202
22. Beck D.B., Ferrada M.A., Sikora K.A. et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. N. Engl. J. Med. 2020;383(27):2628-2638. doi: 10.1056/NEJMoa2026834
23. Ferrada M.A., Sikora K.A., Luo Y. et al. Somatic mutations in UBA1 define a distinct subset of relapsing polychondritis patients with VEXAS. Arthritis Rheumatol. 2021;73(10):1886-1895. doi: 10.1002/art.41743
24. Tsuchida N., Kunishita Y., Uchiyama Y. et al. Pathogenic UBA1 variants associated with VEXAS syndrome in Japanese patients with relapsing polychondritis. Ann. Rheum. Dis. 2021;80(8):1057-1061. doi: 10.1136/annrheumdis-2021-220089
25. Чальцев Б.Д., Торгашина А.В., Лила А.М. и др. Синдром VEXAS: на рубеже смены представлений об известных заболеваниях. Современная ревматология. 2023;17(6):92-101. doi: 10.14412/1996-702-2023-6-92-101
Chaltsev B.D., Torgashina A.V., Lila A.M. et al. VEXAS syndrome: on the threshold of changing perceptions of known diseases. Modern Rheumatology Journal. 2023;17(6):92-101 [In Russian]. doi: 10.14412/1996-702-2023-6-92-101
26. Гусева Н.Г. Проблема ассоциации ревматологических и онкологических заболеваний (патогенетические и клинические аспекты). Научно-практическая ревматология. 2004;42(4):60-67.
Guseva N.G. Problem of rheumatic and oncological diseases association (pathogenetic and clinical aspects). Rheumatology Science and Practice. 2004;42(4):60-67 [In Russian].
27. Marcoval J., Martin-Callizo C., Valenti-Medina F. et al. Sweet syndrome: long-term follow-up of 138 patients. Clin. Exp. Dermatol. 2016;41(7):741-746. doi: 10.1111/ced.12899
28. Gurnari C., Mannion P., Pandit I. et al. UBA1 screening in Sweet syndrome with hematological neoplasms reveals a novel association between VEXAS and chronic myelomonocytic leukemia. Hemasphere. 2022;6(10):e775. doi: 10.1097/HS9.0000000000000775
29. Sterling D., Duncan M.E., Philippidou M. et al. VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) for the dermatologist. J. Am. Acad. Dermatol. 2023;89(6):1209-1214. doi: 10.1016/j.jaad.2022.01.042
30. Obiorah I.E., Patel B.A., Groarke E.M., et al. Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. Blood Adv. 2021;5(16):3203-3215. doi: 10.1182/bloodadvances.2021004976
31. Ferrada M.A., Savic S., Cardona D.O. et al. Translation of cytoplastic UBA1 contributes to VEXAS syndrome pathogenesis. Blood. 2022;140(13):1496-1506. doi: 10.1182/blood.2022016985
32. Temple M., Kosmider O. VEXAS syndrome: a novelty in MDS landscape. Diagnostics (Basel). 2022;12(7):1590. doi: 10.3390/diagnostics12071590
33. Khitri M.-Y., Guedon A.F., Georgin-Lavialle S. et al. Comparison between idiopathic and VEXAS-relapsing polychondritis: analysis of a French case series of 95 patients. RMD Open. 2022; 8:e002255. doi: 10.1136/rmdopen-2022-002255

Информация об авторах

Ягода Александр Валентинович — д.м.н., профессор, заслуженный деятель науки РФ, заведующий кафедрой госпитальной терапии ФГБОУ ВО СтГМУ Минздрава России, Ставрополь, e-mail: alexander.yagoda@gmail.com, ORCID ID: https://orcid.org/0000-0002-5727-1640
Корой Павел Владимирович — д.м.н., профессор, профессор кафедры госпитальной терапии ФГБОУ ВО СтГМУ Минздрава России, Ставрополь, ORCID ID: https://orcid.org/0000-0001-6392-8461
Харченко Дина Петровна — заведующая ревматологическим отделением ГБУЗ СК СККБ, Ставрополь
Гладких Наталья Николаевна — д.м.н., профессор, профессор кафедры госпитальной терапии ФГБОУ ВО СтГМУ Минздрава России, Ставрополь, ORCID ID: https://orcid.org/0000-0003-4510-3604
Попова Инна Петровна — врач терапевтического отделения ГБУЗ СК СККБ, Ставрополь

Information about the authors

Alexander V. Yagoda — Doctor of Medical Sciences, Professor, Head of the Department of Hospital Therapy, Stavropol State Medical University, Stavropol, e-mail: alexander.yagoda@gmail.com, ORCID ID: https://orcid.org/0000-0002-5727-1640
Pavel V. Koroy — MD, PhD, Professor, Professor of Department of Hospital Therapy, Stavropol State Medical University, Stavropol, ORCID ID: https://orcid.org/0000-0001-6392-8461
Dina P. Kharchenko — Head of the Rheumatology Department of Stavropol Regional Clinical Hospital, Stavropol
Natalia N. Gladkikh — MD, PhD, Professor, Professor of Department of Hospital Therapy, Stavropol State Medical University, Stavropol, ORCID ID: https://orcid.org/0000-0003-4510-3604
Inna P. Popova — Doctor of the Therapeutic Department of Stavropol Regional Clinical Hospital, Stavropol

Автор, ответственный за переписку / Corresponding author