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DIFFICULTIES IN THE EARLY DIAGNOSTICS OF EOSINOPHILIC GRANULOMATOUS POLYVASCULITIS (CHURG-STRAUSS SYNDROME) IN INTERNAL DISEASE CLINICS

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The clinical and immunological forms of systemic vasculitis are highly variable making it necessary to carry out differential diagnostics with account for a wide range of conditions, such as allergic, infectious, hematological, and oncological. This poses significant difficulties for physicians of different specialties.

The present paper provides case reports-based evidence of difficulties in the diagnostics of systemic vasculitis associated with anti-neutrophil cytoplasmic antibodies, in particular eosinophilic granulomatous polyvasculitis (Churg-Strauss syndrome), which is a rare disease. Carefully compiled anamnesis and the involvement of specialists in different disciplines, as well as retrospective analysis of laboratory and instrumental test results make it possible to verify diagnoses and prescribe adequate therapies.

The message of the paper is that the early diagnostics of eosinophilic granulomatous polyvasculitis can help to make therapy more effective and prognosis more favorable if they account for the international recommendations worked out in 2015 by leading experts from Europe, USA and Canada to provide a basis for choosing of personalized approaches to therapy.

***Keywords**: marine medicine, systemic vasculitis, Churg-Strauss syndrome, anti-neutrophil cytoplasmic antibodies*

Introduction

Eosinophilic granulomatous polyvasculitis (allergic granulomatous angiitiss, Chardz-Strauss syndrome) is an eosinophilic granulomatous inflammation involving the respiratory tract and necrotizing vasculitis, affecting small (fine) and medium-sized blood vessels, combined with bronchial asthma and eosinophilia [1, p. 187-192].

The first observation of the disease dates back to 1900 and belonged to William Osler, a Canadian doctor. However, clinical and pathological signs of the disease were described only in 1951 by Jacob Churg and Lotte Strauss, and from that time the disease is called their name, the Chard-Strauss syndrome (SPS) [2, p. 277-301]. In their study of 13 cases the disease manifested with severe bronchial asthma, fever, hypereosinophilia, cardiac and renal insufficiency, and polyneuropathy. Most patients had infiltrates in their lungs, sinusitis, hypertension, abdominal pain, bloody diarrhea, and skin lesions, in particular purpura and subcutaneous nodules. 11 patients died, which was not surprising, since by that time corticosteroids had not been used yet. The authors described a triad of histopathological features, including necrotizing vasculitis, eosinophilic tissue infiltration, and extravascular granulomas. Further study of pathophysiological mechanisms

of the disease made it possible to establish that the CSS, along with Wegener's granulomatosis and microscopic polyarteritis, refers to necrotizing vasculitis. In this case, the CSS is much less common.

The etiology of most of primary systemic vasculitis (SV) is unknown. Only some of their forms are associated with certain causal factors. Separate reports on the role of certain microorganisms as potential etiologic factors (influenza and parainfluenza viruses, measles, rubella and Epstein-Barr viruses, B19 parvovirus, cytomegalovirus, and tuberculosis mycobacteria) are occasional and not supported by a series of observations [3, p. 43-47].

Since recently, the international rheumatological community has been engaged in an active revision of the classification and obsolete nomenclature of SV [4, p. 1-11].

Efforts of the world's leading experts created a number of scientifically grounded recommendations on the management of patients with SV [5, p. 634-643; 6, p. 310-317; 7, p. 2306-2309], which is undoubtedly relevant for diseases associated with antineutrophil cytoplasmic antibodies (ANCA), which include eosinophilic granulomatosous polyvasculiyis (EGPV), formerly known as the Charge-Strauss syndrome.

EGPV, being the most rare disease from the ANCA-SV group (the prevalence of 7-13 cases per 1 million adults) [8, p. 214-223; 9, p. 92-99], is characterized by the heterogeneity of clinical and immunological forms and determines the need for differential diagnostic search, with the exception of a wide range of diseases, such as allergic, infectious, hematological, and oncological, which often presents significant difficulties for physicians of various specialties.

EGPV was previously considered as an asthmatic form of nodular polyarteritis and only in the last decade the syndrome was identified as a separate nosology. Men are more often ill at the age from 35 to 45 years [10, 720].

The main signs of the disease include angiitis and allergic manifestations. Eosinophilia of peripheral blood belongs to the number of essential signs of EGPV, with the number of eosinophils exceeding> 1.5□109/l (in relative values> 10%), the boundaries of the percentage of eosinophils range from 6 to 77%. In addition, eosinophils are detected in sputum and in infected tissues. In clinical pathology of the disease, particular attention is given to ANCA, which are considered biomarkers of vasculitis. This is a heterogeneous population of autoantibodies that react with various enzymes of the cytoplasm of neutrophils, primarily proteinase 3 and myeloperoxidase. It has been proved that the binding of ANCA with the corresponding targets of activated neutrophils and monocytes leads to their premature degranulation with liberation of lysosomal enzymes and the production of toxic oxygen radicals that cause destruction of the vessel wall. In addition, transendothelial migration of leukocytes from the vasculature is disturbed, which leads to development of an inflammatory granuloma that forms the basis of the morphological picture of granulomatous vasculitis [11, p. 21-27].

Two phenotypes of EGPV were identified: the ANCA-positive (40-60% of all cases), in which antibodies to myeloperoxidase with perinuclear staining (the so-called MRO-ANCA or PANZA) are more often determined, and the ANCA-negative. Each variant has its own clinical features.

As for the ANCA-positive variant, the presence of clinical signs of vasculitis is more frequent: the kidneys, the central nervous system, the peripheral nervous system (mono- or polyneuropathy), and the skin are often affected. The nature of the development is recurrent.

In the ANCA-negative EGPV, the rheumatic heart disease is more frequent and severe, which determines the worst prognosis (coronary artery disease, pericarditis, cardiac rhythm disturbance, and heart failure) and pulmonary infiltrates, while kidney damage is fewer. In the ANCA-negative variant IgE is more often detected. Cardiomyopathy is the main independent predictor of death in patients with EGPV, and younger age is another independent parameter of the unfavorable prognosis [12, p. 270-281].

In connection with the rare occurrence of EGPV and a diverse clinical picture, timely early diagnosis and treatment can affect the EGPV prognosis, while the shortcomings of existing diagnostic standards may be the cause of too late diagnosis and fatal outcome. To standardize modern approaches for managing patients with EGPV, the European Respiratory Society, together with the Foundation for the Development of Internal Medicine in Europe, established an ad hoc working group of 23 key experts who represented five countries of Europe, the USA and Canada. Using scientific achievements, clinical experience, modified Delphic method, systematic literature review, and GRADE evidence-based scoring system, the expert group developed 22 recommendations on standards for diagnosis and treatment of EGPV. These recommendations were published in 2015 [13, p. 129-137; 14, p. 545-553].

At the same time, the authors noted that a large number of proposed recommendations had a low degree of evidence or were based on expert opinion, and therefore should not be considered as final standards and should be the basis for choosing a personalized strategy for managing patients with EGPV.

In clinical practice, the diagnosis of EGPV is almost always difficult and long-term, and a patient can be observed before the verification of the diagnosis by many medical specialists for several months (sometimes years) [15, p. 86-92], as is seen from considered clinical cases.

We bring our own clinical observations, which testify to the difficulties of diagnostic search, which occur when establishing the diagnosis of EGPV.

1. Patient G., born in 1990 (27 years old), complained of asthma attacks, accompanied by a cough with hard-to-recover sputum, constant obstruction of nasal breathing, itching rashes in the lower third of the lower leg, appearing after an attack, loss of body weight (about 4 kg for 1 month), and subfebrile condition in the evening hours.

From his anamnesis, it is known that from the age of 6, he suffers from pollinosis and allergic rhinitis. At the age of 16 he was treated for community-acquired right-sided severe pneumonia.

Since the age of 22, the patient has been increasing in frequency and duration of allergic rhinitis and for the first time there have been attacks of suffocation, with eosinophilia up to 6% found in his blood.

Conducted in 2013 (when he was 23 years) radiographic examination of the paranasal sinuses (PNS) revealed bilateral sinusitis.

At the age of 24, the patient was diagnosed for the first time: bronchial asthma (BA), mixed form, medium-heavy course, sensitization to pollen allergens, seasonal pollinosis. In the clinical analysis of blood,

leukocytosis was 13×10^9 - 17×10^9/L, eosinophilia - up to 14%. At his X-ray examination of PNS, pansinusitis was detected. In the same year, a biochemical blood test showed an increase in ALT to 363 u/e (a norm of up to 50 u/e), and abdominal pain, diarrhea, and dyspepsia began to disturb him.

In 2015 (24 years), the patient developed a right-sided pneumothorax. In the computed tomography (CT) scan in S1 of the right lung, a 14×5 mm center of medium density was identified with a small seal of the type of frosted glass around. At his discharge, these changes were regarded as a condition after a community-acquired pneumonia in S1 of the right lung.

In the same year there was heartburn and pain in the epigastric region. When performing fiberoptic gastroduodenoscopy (eophagogastroduodenoscopy, EGD), a peptic ulcer of the duodenum with the diameter of up to 0.8 cm was found. In a clinical blood test, the leukocytosis was $13,8\times10^9$/L. According to X-ray data, large focal infiltration was revealed in all pulmonary fields against the background of intensified pulmonary pattern.

In 2017 (26 years), an intense pain syndrome behind the sternum developed with irradiation to the left hypochondrium, accompanied by nausea. His ECG fixed some signs of myocardial infarction (MI) in the region of the anterior wall of the left ventricle. An emergency coronary angiography was performed, stenting of the anterior interventricular artery (PMLA) was carried out and followed by nausea and vomiting with blood clots. Conducted in connection with this EGD revealed he presence of an ulcer of the body of the stomach complicated by bleeding.

A month later the patient developed a repeated MI, and stenting of the infarction of the associated artery was performed. In the postoperative period, shortness of breath as manifestations of bronchospasm, fever to febrile digits, and itching papular rash were observed. Against the background of 15 mg of prednisolone, all skin phenomena and bronchospasm were regressed, andthe temperature normalized. Later on, the dose of prednisolone was reduced to 10 mg/day, a replacement for methylprednisolone at a dose of 8 mg/day was made. When trying to further reduce the dose, skin rashes recurred.

The patient was sent to the Military Medical Academy. CM. Kirov for further examination in order to verify the possible autoimmune disease and determine the tactics of treatment. He entered the clinic of naval therapy in January 2017.

In the clinical analysis of blood, leukocytosis in dynamics from $11,1\times10^9$/L up to 15×10^9/L and eosinophilia up to 26% were fixed. In general urinalysis proteinuria was determined up to 0.3 g/L. CRP was increased to 20.5 mg/L (the norm <5 mg/L). In the analysis of sputum, eosinophils were found up to 10-12 in the field of vision. Helminthes were not revealed.

Immunological studies conducted in February 2017 revealed a stable increase in IgE level from 236 to 1119 IU/ml (the norm is 1-87 IU/ml), rheumatoid factor (RF) up to 158.9 IU/ml (the norm is up to 30 IU/ml). ANCA were not found.

Radiography of paranasal sinuses conducted in January 2017 revealed a thickening of the mucosa across all the walls of the right and left maxillary sinuses to 1.2 cm and 0.5 cm respectively, without any fluid. Thickening of nasal conchaes on the right with preservation of differentiation was detected.

With computer tomography of thoracic cavity organs (in January 2017), signs of bronchiolitis without pulmonary infiltrative changes were registered as multiple poorly outlined centrilobular foci, in subpleural sections of the upper lobes of both lungs.

The pulmonary function (PF) of the patient was characterized by a sharp violation of bronchial patency and a positive test with salbutamol.

When bodipletizmografii (in February 2017), a moderate decrease in the vital capacity and significant violations of airway patency, as well as a decrease in pulmonary gas exchange at rest were found (FEV_1 = 54%, FEV_1/FVC = 60%, PFER = 54%).

On the ECG there was focal cicatricial changes in the antero-marginal region with perifocal ischemia in the region of the septum and the anterior wall.

Echocardiography visualized cicatricial changes in the region of the apex of the left ventricle. Cardiac chambers, cardiac valves, aorta, the general contractile function of the myocardium, and the indices of diastolic filling were in the normal condition.

In January 2017, the CT coronary angiography was performed, the data of which are regarded as a condition after stenting of FIVA in the middle third and the first diagonal branch in the proximal third of October 13, 2016. Stents were found to be passable, there was no evidence of restenosis. CT-signs of atherosclerotic changes in the coronary arteries were not revealed. The contractile function of the left ventricle was not reduced.

During the EGD (in February 2017), multiple submucosal hemorrhages and duodenojegunal gastroesophagenal reflux were determined in the region of the body of the stomach.

Scintigraphy with labeled leukocytes revealed a moderate increase in the accumulation of leukocytes in the projection of the nasopharyngeal pharynx.

The patient had been consulted by a pulmonologist. The diagnosis was: bronchial asthma, mixed form (atopic, infectious-dependent), moderate severity, unstable remission, respiratory insufficiency 0-1.

In the advisory opinion of a neurologist a syndrome of vegetative dystonia and a polyneuritic syndrome were diagnosed.

Given the positive dynamics, an attempt was made to abolish oral glucocorticosteroids. However, 3 weeks after the withdrawal, an attack of suffocation developed and an erythematous rash appeared on the skin of the lower third of the lower leg and on the back surface of the hands, as well as the enanthem of the mucous palate.

So there had been an assumption of a systemic vasculitis with the involvement of the upper respiratory tract and lungs, skin syndrome, peripheral polyneuropathy, changes in the hemogram (leukocytosis, eosinophilia up to 26%), and an increase in acute phase parameters, IgE 1119 IU/ml, rheumatoid factor 159 IU/ml.

In this regard, the patient consulted by the rheumatologist who diagnosed: eosinophilic granulomatous polyvasculitis (Churg-Strauss syndrome), the ANCA-negative variant, the IgE-positive, chronic course, unfolded stage with the involvement of the upper respiratory tract infection (rhinitis, rhinosinusitis), lungs

infection (bronchial asthma syndrome), heart disease (polyangiitis: myocardial infarction from September 2016, stenting from September 2016, repeated myocardial infarction in October 2016, stenting in October 2016), mucous membranes damage (enanthema of the palate), gastrointestinal tract disease (hemorrhagic gastritis complicated by hemorrhage in October 2016), skin disease (urticaria rashes), and disease of the nervous system (polyneuropathy), activity 2.

Attention is drawn to the fact that the deterioration of the disease began in 2012: appeared and, during the next 3 years, asthma attacks became more severe, the symptoms of polyangiitis developed, with the involvement of the gastrointestinal tract. The myocardial infarction developed in 2016 significantly worsened the course and prognosis of the disease. The polyorganic nature of the lesion and the staged nature of the process made us think about systemic vasculitis in the patient.

For the final diagnosis of EGPV, a careful analysis of clinical manifestations, anamnestic data (from the age of 6), and conclusions of consultations of narrow specialists of five specialties (allergist, otolaryngologist, pulmonologist, gastroenterologist, and cardiologist) was required.

In February 2017, treatment of GCS by prednisolone (20 mg/day) and cytostatics (azathioprine 50 mg/day) was started. After six months of therapy, positive dynamics were noted: there have not been any seizures of bronchial asthma, cardialgia and gastralgia, the nasal congestion disappeared. The patient is observed by a rheumatologist.

2. Patient M., born in 1953 (64 years old) complained of a chest congestion, difficulty in breathing at night or before awakening, low-yield cough, permanent disability in nasal breathing, anosmia, rare pains in the chest pressing behind the breast bone irradiated to the right and left shoulder after walking 150-200 m lasted for several minutes and stopped when the load decreased, weight loss (8 kg in 3 years), hearing loss, and visual impairment.

In 1987 (at the age of 34), transmural myocardial infarction was diagnosed in him, but by the time of his discharge there were some signs of small-focal myocardial infarction in his ECG. At the same time he suffered neuritis of the auditory nerve to the right. In 1988 (in 35 years) he had bilateral cochlear neuritis of the auditory nerve with persistent hearing impairment, and bilateral sensorineural hearing loss. In 1998 (in 45 years) he had repeated Q-wave myocardial infarction in the area of the lower wall.

Since his 47 years of age (in 2000) he has suffering disturbance of nasal breathing, which was regarded as an allergic sinusitis, episodes of shortness of breath. Allergy to dust and to animal hair, as well as cold reaction was revealed. In the study, his IgE level was up to 200 IU/ml (the norm is 1-87 IU/ml), eosinophilia of his blood up to 25%, and for the first time in him bronchial asthma of mixed form (atopic and infectious-dependent) was diagnosed. Since 2006 (in his 53 years) he has persistently inhaling budesonide and formoterol.

In 2000, there were abnormalities of sensitivity in the right side of his face, body and limbs; deterioration of vision on the right eye (diagnosis of the ophthalmologist: corneal erosion, reduced visual acuity on OD). With MRI data for acute cerebrovascular event (ACE) was not obtained, however, glial formation with dimensions of 2.3-1.5-0.8 mm was detected in the projection of the corpus callosum and the posterior horn of

the left lateral ventricle. After 2 months with repeated MRI in the vascular regime, glial formation was not detected.

In 2013 (at the age of 58) community-acquired pneumonia was diagnosed in the lower lobe on the left with normal values leukocytes and Erythrocyte Sedimentation Rate, eosinophilia up to 12%, and an increase in the IgE level to 252 IU/ml. 3 years later community-acquired pneumonia was found in the upper lobe of the left lung. In the blood, eosinophilia was up to 25%, and IgE was up to 535 IU/ml.

At 63 years of age (2016), the complaints of numbness in the left foot appeared began. A MRI of the brain was performed, in which a segment of cystic-gliotic changes, 30 mm in diameter, was revealed paraventricularly in the right frontal lobe, as well as MR-picture of consequences of ACE in the basin of the right middle cerebral artery (RMCA), and dyscirculatory encephalopathy, as well as expansion of the subarachnoid space. When examined by a neurologist, a diagnosis was made: discirculatory encephalopathy of the 2^{nd} degree, external hydrocephalus, mild cognitive impairment, consequences of ischemic stroke in RMCA, left-sided atactic hemiparesis, and distal sensorimotor polyneuropathy of the lower extremities.

A retrospective analysis of laboratory indicators from 2010 indicates an increase in eosinophilia up to 25%, an increase in the IgE value to 535 IU/ml, an and an increase in the level of CRP, ESR.

Since the age of 57, cholesterol levels have been raised to 6.5 mmol/L, and statins have been prescribed for this purpose. In 64 years for the first time a study was performed for the presence of antibodies to the cytoplasm of neutrophils (ANCA), which were not found in the blood. On the ECG series, cicatricial changes in the area of the lower wall were recorded in the dynamics.

The study of respiratory function was characterized by moderately pronounced obstructive disorders and a positive test with bronchodilator (an increase in FEV_1 to 27%).

In 2007 (54 years), lung radiography revealed moderate peribronchial pneumofibrosis and emphysema; in 2012 (59 years) – large-scale hardy fibrosis of lung tissue, in which the roots were structural with reduction of the volume of the middle lobe on the right and compaction of the interlobar pleura; in 2014 (61 years) – hypoventilation in the ligulate segments of the upper lobe on the left. The main interlobar pleura on the left was underlined with a moderate diffuse enhancement of the vascular pattern in the basal zone and formation of pleura-diaphragmatic adhesion on the right.

With multislice computed tomography (MSCT) of the thorax in March 2017 (63 years) in S4 and S10 on the right and S8 on the left, linear pneumofibrosis, a 7 mm centrilobular bullet in S1 of the right lung was revealed.

An analysis of the X-ray archive of PNS from 2007 to 2016 shows that there was a thickening of the mucous membrane of the maxillary sinuses with signs of a drained fluid on the right, followed by an increase in the thickening of the mucosa on both sides.

At the MSCT of PNS in March 2017, a left-sided pas-sinusitis was identified.

In April 2017 (63 years), a biopsy of the mucosa of the middle nasal passage was performed from 2 sides, as a result of which focal polypoid outgrowths and edema, subepithelial diffuse leukocyte, and

lymphoplasmocytic infiltration were found in fragments of the mucous membrane, which corresponds to chronic polyposis sinusitis.

The otorhinolaryngologist in April 2017 suggested the systemic nature of the long-existing pancinusitis.

The diagnosis was made by a pulmonologist: BA (atopic, infectious-dependent), bronchial hyperreactivity, partially controlled, of moderate severity. Chronic respiratory failure of 0 degree. Allergic polypous rhinosinusopathy, IgE was mediated.

The medical jugement about EGPV was formed when combining the symptoms of the involvement of the upper respiratory tract and ENT organs (polyposive pansinusitis, sensorineural hearing loss), vision organs (corneal erosion), bronchi (BA), central nervous system (ACE in the RMCA basin, glial macrophage on the basal brain surface), and the symptoms of persistent eosinophilia. To confirm the diagnosis, the patient was consulted with a rheumatologist, as a result of which the following diagnosis was made: eosinophilic granulomatous polyvasculitis (Churg-Strauss syndrome), ANCA-negative variant, IgE-positive, chronic course, with pulmonary disease (BA) of the upper respiratory tract and ENT organs (rhinitis, rhinosinusitis, and sensorineural hearing loss), the organ of vision (corneal erosion, decreased visual acuity on OD), the heart (polyangiitis: IM 1984, 1998, postinfarction cardiosclerosis), central nervous system (ONMI from 2013), and peripheral nervous system (polyneuropathy), assets 2.

This diagnosis corresponds to the EGPV criteria currently accepted. The main manifestation is the syndrome of bronchial hyperreactivity, which precedes vasculitis in most cases. However, in the patient M. polyangiitis (MI) preceded allergic rhinitis, eosinophilia and asthma attacks. Simultaneously with the progression of asthma, ACE was diagnosed, which was the result of cerebral polyangiitis.

Thanks to carefully collected history, participation of specialists of different profiles, and a retrospective analysis of laboratory and instrumental data, it was possible to verify the diagnosis and prescribe adequate therapy.

After 3 months of treatment with GCS (prednisolone, 20 mg/day), the patient’s nasal breathing and sense of smell recovered for the first time in many years, his exercise tolerance improved, his anginal attacks ceased, numbness in his right foot decreased; it had been possible to significantly reduce the dose and the multiplicity of bronchodilators and inhalation steroids for him. As one could see from the CT of his PNS, there was a parietal thickening of the mucous membrane of the sinuses of his nose and the trellis labyrinth in the both sides. In the left maxillary sinus, a cystform mass of 12×17×17 mm had appeared and remained on the anterolateral wall. The nose cycle was saved. Significant positive dynamics compared with March 2017 was found.

Discussion

Thus, the described two clinical cases had a number of clinical symptoms similar in many respects, and they are referred to ANCA-negative phenotype of EGPV.

Both patients had typical manifestations of EGPV in the form of allergic rhinitis, asthma, and eosinophilic infiltrates in the lungs, which was accompanied by peripheral blood eosinophilia> 10%, increased IgE level.

Both patients at different ages (27 years and 34 years, respectively) suffered myocardial infarction. Despite the fact that the cardiovascular system disease is not included in the criteria for the diagnosis of EGPV, according to the literature data, this vascular region is affected in 28-60% of the cases [9]. The most significant in this regard are developing coronarities, which are manifested by acute coronary syndrome with both ST-segment elevation and without it. According to autopsy data, 50% of cases describe lesions of the coronary arteries, which had not been described during the lifetime [16, p. 35-42; 17, p. 7-10]. Moreover, the rheumatic heart disease (RHD) largely determines the further prognosis of this category of patients with EGPV.

Despite the similarities of the cases described, there are some differences in their clinical pictures. The patient G. has so-called classic course of the disease: a stormy debut at the age of 27, sinusitis, asthma, viral infections characterized by skin and mucous membrane lesions, gastrointestinal issues (digestive hemorrhage and erosive gastritis). Later, polyangiitis (myocardial infarction) and lesions of the peripheral nervous system (polyneuropathy) joined. Adequate therapy in this patient led to regression of a number of vasculitis symptoms, which has improved the quality of life.

Unlike the classical course of EGPV, patient M lacked a clear staging and sequence in the process development. This case is unusual by the onset of the disease with polyangiitis (MI), which developed 13 years before the onset of symptoms of asthma. The course of myocardial infarction also had its own peculiarities: transmural infarction on the background of heparin therapy was transformed into the small-focal (by activation of fibrinolytic properties of blood and immunosuppressive action of the drug and improvement of coronary blood flow). The level of cholesterol and its fractions at the time of the vascular accident did not go beyond the limits of normal values, and the increase in these parameters in the patient M. begins only in his 53 years, which does not confirm the atherosclerotic genesis of the infarction.

With the progression of asthma, the development of the central (glial formation of the base of the brain and ONMC) and the peripheral nervous system disease (polyneuropathy) occurred. In the classical course of EGPV, from the beginning to the unfolded picture, as a rule, 3-5 years pass, though in the patient M. this process took about 30 years.

Presented cases demonstrate a late diagnosis of EGPV. This problem is taken on the first place by the international group of experts in their recommendations. They emphasizes the complexity of management and the relative scarcity of the EGPV, which is practically unknown to a wide range of practicing doctors, which is, being the reason for a lack of such alertness for them, often leads to too late diagnosis, inadequate treatment and a deterioration in the prognosis. This opinion was justified in the results of the 20-year retrospective study of more than 100 patients with EGPV, according to which qualified management of patients was associated with a milder course of the disease and an increase in life expectancy [18, p. 1011-1017].

Besides, in modern clinical practice, patients with asthma get an inhaled glucocorticosteroids at too early stages of the disease. Perhaps, this tactic influences the staging, course and duration of the development of the complete symptomatology of EGPV.

The diagnosis of EGPV should be remembered when performing a differential diagnostics in the presence of: eosinophilia (>10% of the total number of leukocytes or 1.5×10^9// L), classical clinical

manifestations making up the diagnostic criteria of EGPV (bronchial asthma, neuropathy, migratory pulmonary infiltrates, and pathology of the maxillary sinuses), and of morphological signs (necrotizing vasculitis of predominantly small (fine) and medium-sized blood vessels, and/or eosinophilic infiltration, and/or granulomatous inflammation) [4, p. 1-11; 19, p. 1094-1100]**.**

Significant diagnostic difficulties can occur at an early stage, before the formation of a complete classical triad described by J. Lanham et al. [20, p. 65-81], especially in ANCA-negative patients. In the course of several years, three stages of EGPV are consistently unfolding: symptoms of bronchial asthma, allergic rhinosinusitis and manifestations of drug intolerance, with peripheral eosinophilia not always pronounced; attachment of episodes of eosinophilic infiltrates in the form of eosinophilic pneumonia or gastroenteritis often combined with peripheral eosinophilia above 10%; development of systemic necrotizing vasculitis. Before addition of systemic vasculitis, EGPV manifestations are similar to those with hypereosinophilic syndromes of various genesis. When manifesting EGPV, asthma is naturally present, nevertheless, in some cases it may develop later.

Respiratory tract disease diagnostics requires evaluation of the function of external respiration and use of high-resolution imaging techniques (CT significantly exceeds radiography).

The difficulties in the differential diagnosis of EGPV are primarily caused by eosinophilia, which can occur in a wide range of diseases. The range of diagnostic search is indicated in the published classification of pathologies associated with eosinophilia [21, p. 607-612]. A careful differential diagnosis of reactive eosinophilia, familial hypereosinophilia, eosinophilia of drug and infectious genesis (caused primarily by helminths and fungi) is necessary. It is necessary to exclude parasitic invasions (trichinosis, strongyloidosis, ankylostomosis, ascaridosis, toxocarosis, etc.), which are often accompanied by severe eosinophilia, ubiquitous and asymptomatic [22, p. 692-695].

The presence of ANCA in the blood serum of patients and the correlation of their level with severity of clinical manifestations led to the identification of a subgroup of systemic necrotizing vasculitis associated with the synthesis of ANCA, including the Churg-Strauss syndrome [23, p. 211-220]. The need for a detailed study of ANCA in the process of differential diagnostic search, given the importance of this study in determining the forecast, is beyond doubt.

In the absence of classical clinical manifestations, the diagnosis is based on the expressed indirect clinical data or morphological confirmation of vasculitis, which is not always possible. In patients with suspected EGPV, a biopsy is recommended. When choosing a biopsy site, the individual characteristics of the patient and the safety of obtaining a sample that can provide reliable information are taken into account [15, p. 86-92].

Conclusion

Thus, diagnosis of eosinophilic granulomatous polyvasculitis (Churg-Strauss syndrome) causes considerable difficulties, especially at the initial stages, while requiring the integration of histological evidence, clinical signs, medical history, laboratory data, and additional research methods.

To establish the diagnosis, according to the recommendations of the American Society of Rheumatology, there are 4 criteria and more of the following: asthma, eosinophilia>10%, peripheral mono- or polyneuropathy, migratory or transient pulmonary infiltrates, paranasal sinus pathology, and extraovascular eosinophilia (congestion of eosinophils in the extravascular space) [19, p. 1094-1100]. For the purposes of early diagnosis of EGPV, caution is necessary when pulmonary infiltrates occur in patients with asthma with allergic rhinitis or rhinosinusopathy in combination with peripheral blood hypereosinophilia. In the laboratory diagnosis of the disease, particular attention should be paid to ANCA, which are biomarkers of vasculitis.

The clinical observations of eosinophilic granulomatous polyvasculitis presented in the article indicate the need for early diagnosis, which will improve the effectiveness of the therapy and the overall prognosis for this disease.

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