A.S. Asekritova, E.A. Emelyanova, A.P. Dalbaraeva

CLINICAL CASE OF EOSINOPHILIC GRANULOMATOSIS WITH POLYANGITIS: DIAGNOSTIC DIFFICULTIES AND CLINICAL MANIFESTATIONS

DOI 10.25789/YMJ.2020.72.30

The article presents a clinical case of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), which was diagnosed for the first time in a 27-year-old man with bronchial asthma, eosinophilia, and gastrointestinal tract involvement. A retrospective analysis of the disease demonstrates the difficulties in diagnosing this disease. In this clinical case, the diagnosis was made 1.5-2 years after the onset of the first manifestations of the disease, in the second period of the development of the disease, based on the symptoms of the disease that were identified in the patient: bronchial asthma, rhinosinusopathy, pulmonary infiltrates, hypereosinophilia, despite the absence of biological markers of vasculitis. This syndrome is infrequently in clinical practice; however, doctors of various specialties should be aware of identifying this syndrome in their patients.

Keywords: Churg-Strauss syndrome, eosinophilic granulomatosis with polyangiitis, EGPA, Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis, bronchial asthma.

Introduction. Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Chard-Strauss syndrome) was first described by J. Churg and L. Strauss in 1951. They presented a triad of histopathological features: necrotizing vasculitis, eosinophilic inflammation and extravascular granulomas at autopsy in 13 patients who had similar clinical manifestations: severe bronchial asthma, fever, eosinophilia, heart and renal failure, and peripheral neuropathy [1,2,6].

Currently, the disease is a form of vasculitis associated with antibodies against neutrophilic cytoplasm (ANCA), which is characterized by eosinophilic granulomatous inflammation and small and medium-sized vasculitis associated with asthma and eosinophilia [3-5].

Depending on the geographic regions and the criteria used, the annual incidence and prevalence of EGPA is 0.9-2.4 and 10.7-17.8% per million population, respectively. Men and women get sick equally often. The average age of the onset of the disease is 38–49 years [1,2,4,6].

The pathogenesis of EGPA is still not fully understood, and there is no standard therapy, which is based on the results of clinical studies [3-7]. Patients with EGPA usually see general practitioners and physicians with clinical symptoms of one or more internal organ involvement. Damage to many organs and systems for a long time can proceed under the guise of other nosologies, which presents significant difficulties in diagnosing a true disease [1,2,6].

The rare occurrence of this pathology, the variety of symptoms with the involvement of many organs and systems emphasizes the relevance of studies that are not only scientific, but, above all, of practical interest.

Material and research methods. A retrospective analysis was made of the medical history of a patient (male, 27 years old) who was treated at the Yakutsk Republican Clinical Hospital in 2019, where a full examination was carried out according to all standards and clinical guidelines.

Case description and discussion. The patient was admitted to the gastroenterology department at the end of February 2019. Complaints at admission: constant, aching pain in the epigastrium and along the colon; diarrhea up to 10-15 times a day, without pathological impurities; periodic nausea and vomiting; episodes of dizziness; frequent headaches; pain in the left maxillary sinus and discharge from the nose of a purulent character with a fetid odor, mainly from the left nasal passage; aching pains in the lumbar parts and knee joints; general weakness; decrease in body weight by 8 kg over the past six months.

Medical history: In the fall of 2017, the patient received ambulatory treatment for an unproductive cough at the place of residence. His condition was regarded as an exacerbation of chronic bronchitis. Despite the treatment, the disease progressed, episodes of shortness of breath, attacks of suffocation, cough with difficult to separate viscous sputum began to disturb for the first time. In the future, treatment was prescribed Symbicort 80 mcg / 4.5 mcg / dose, 1 breath 2 times a day. There was some improvement in the condition, which was manifested by a decrease in the frequency of asthma attacks and a decrease in the cough syndrome. Pain appeared in the epigastrium, which arose regardless of food intake, bloating, since the spring of 2018. In this regard, with an increase in the intensity of abdominal pain, the appearance of loose stools up to 3-4 times a day, an increase in general weakness and a decrease in body weight, the patient was referred in July 2018 for examination at the Republican Hospital № 2. The patient was diagnosed based on laboratory and instrumental studies: Ulcerative colitis with lesions of the rectosigmoid part, bronchial asthma, allergic genesis, partially controlled and recommended treatment at the place of residence: Mesakol 400 mg / day, Symbicort 80 mcg / 4.5 mcg / dose, 2 breaths 2 times a day. The patient was discharged with improvement. Despite constant medication, the patient's condition worsened since the beginning of 2019. Among the background of constant abdominal pain, the frequency of diarrhea increased up to 8-10 times a day, pain in the left maxillary sinus appeared for the first time, as well as purulent discharge from the left nasal passage, episodes of dizziness, headaches, knee pain and daily bouts of unproductive cough.

ASEKRITOVA Aleksandra Stepanovna – Candidate of Sciences in Medicine, Associate Professor of the Department of Internal Diseases and General Medical Practice (Family Medicine) of M.K. Ammosov Medical Institute of the North-Eastern Federal University. 677000, Yakutsk, st. Belinsky, 58. e-mail: aleksaykt@mail.ru, **EMELYANOVA Elvira Andreevna** – Candidate of Sciences in Medicine, Associate Professor of the Department of Hospital Therapy, Occupational Diseases and Clinical Pharmacology, Medical Institute of M.K. Ammosov North-Eastern Federal University. 677000, Yakutsk, st. Belinsky, 58. e-mail: elviraemelyanova03@mail.ru**, DALBARAEVA Alena Petrovna** – Resident of the Department of Internal Medicine and General Medical Practice (Family Medicine), Medical Institute of M.K. Ammosov North-Eastern Federal University. 677000, Yakutsk, st. Belinsky, 58. e-mail: alyona_petrovna@mail.ru

Life history*:* The patient grew and developed according to his age. He did not work. He smoked, 1 pack of cigarettes a day, smoking experience more than 5 years, he drank alcohol in moderation. Heredity is not burdened.

The patient's condition is grave upon admission. His consciousness is complete. BMI 18.4 kg / m² (underweight). The skin is pale, clean. Respiration rate 17 / min. The lungs have normal boundaries. In the lungs: percussion sound is dulled below 10 ribs from the posterior axillary to the paravertebral line on both sides; in the same place, weakened vesicular respiration, vesicular respiration over the rest of the lung surface, no wheezing. Heart sounds are sonorous, the rhythm is correct, heart rate is 70 per minute. BP 70/50 mm Hg. Art. The tongue is moist, coated with a grayish-white bloom. The abdomen is soft, moderately distended, painful in the iliac parts, along the colon. The liver and spleen are of normal size. Beating symptom is positive on the left. Diarrhea was up to 10-15 times a day, without pathological impurities. Urination is free, painless.

The following deviations were found in the analyzes dated 02/28/19: eosinophilia 28.6%, accelerated erythrocyte sedimentation rate 62.0 mm / h, low hemoglobin 112 g / l, high fibrinogen 10.626 g / l. The fecal occult blood test was negative; coprogram: digested plant fiber was moderate; there was little neutral fat; the consistency was mushy; the color was light brown.

Superficial erosive proctitis is on rectoscopy from 02/28/19.

Therapy with sulfasalazine, ciprofloxacin and metronidazole, parenteral administration of electrolytes and glucose was started.

Considering the patient's complaints, anamnesis data (bronchial asthma, lesions of the large intestine), hypereosinophilia, accelerated erythrocyte sedimentation rate and changes in the coagulogram, the diagnostic search was continued in the hospital.

In the biochemical blood test from 03.03.19, there is an increase in C-reactive protein (9.54 mg / l) and immunoglobulins (IgM - 4.1 mg / ml; IgE - 741.7 IU / ml).

Esophagogastroduodenoscopy from 03/04/19 - superficial gastritis. Duodeno-gastric reflux.

Echocardiography from 03/04/19 - the cavities of the heart are not dilated, the ejection fraction is 48%. The global contractility of the left ventricle is slightly reduced. Diffuse hypokinesia of the left ventricle. The effect of spontaneous contrasting left ventricle. Regurgitation on the mitral valve is stage 0-1, on the pulmonary trunk there is stage 1, on the tricuspid valve there is stage 1.

X-ray of the paranasal sinus from 03/05/19 - symptoms of bilateral maxillary sinusitis.

Computed tomography (CT) of the chest organs with contrast from 03/06/19: pulmonary embolism (PE) in both lungs. There are multiple focuses on both sides. Lymph nodes are enlarged in the mediastinum and roots of the lungs. Bilateral pleural effusion.

CT scan of the abdominal cavity with contrast from 03/06/19: there are signs of a defect in the filling of the contrast agent in the preparation of the lumen of both renal veins - thromboembolism. There is a hypodenseous zone in the left kidney, differentiating between infarction and nephritis.

Ultrasound examination of leg veins dated 03/06/19 - a developing non-occlusive thrombosis of the superficial vein of the thigh is on the right.

Considering the clinical manifestations of the disease (bronchial asthma, sinusitis, pulmonary infiltrates, hypereosinophilia, gastroenteritis, high CRP and IgE levels, accelerated ESR, changes in the coagulogram), the concilium was convened on 03/06/19 to clarify the diagnosis and decide on the patient's treatment tactics. Diagnosis: Eosinophilic granulomatosis with polyangiitis (Chard-Strauss syndrome). Complications: thromboembolism of the pulmonary arteries in both lungs, non-occlusive thrombosis of the superficial vein of the thigh on the right, reactive pleurisy, secondary enteropathy, erosive proctitis. The transfer was recommended to the rheumatology department on 03/07/19. In the department, basic therapy was prescribed with prednisolone at the rate of 1 mg / kg / day, symptomatic therapy was continued, which is aimed at correcting the manifestations of the activity of the systemic vascular immune inflammatory process.

The patient's examination continued to verify the diagnosis and assess the effectiveness of the basic therapy.

In the analyzes dated 03/11/19, there is a violation of hemostasis (D-dimer 8618.9 ng / ml; fibrinogen 7.804 g / l; thrombin time 20.7 sec). In immunoblotting, antinuclear, antimitochondrial, antineutrophilic cytoplasmic antibodies and antibodies to cyclic citrullinated peptide were not detected; class G antibodies to double-stranded DNA, IgG antibodies to myeloperoxidase, and antibodies to nucleosomes are normal.

CT scan of the paranasal sinuses dated 03/14/19: signs of pathological contents are present in the right maxillary sinus, the mucous membrane is thickened in the frontal sinus, the sinuses of the main bone and ethmoid cells. These disorders were confirmed by MRI of the brain. Also, for the first time, pathological foci were found in the bones of the skull on the right. Signs of right-sided sinusitis and multiple round-shaped defects with clear uneven contours, ranging in size from 9.3 * 15 mm to 10 * 13 mm in the bones of the skull on the right were detected on X-ray CT of the skull bones 03/23/19

Trepanobiopsy from the iliac crest was performed: signs of plasma cell myeloma were not detected in the punctate. The histological picture and immunophenotype of the hypocellular bone marrow with diffuse infiltration of plasma cells without signs of monoclonality were regarded by the Hematologist as reactive changes.

In laboratory tests, changes were revealed that were carried out after 1 month against the background of basic therapy, in the general blood test: the level of leukocytes was normalized to 9.03x109 / l, hemoglobin was 130 / l, eosinophil was 0.6%, while maintaining an accelerated ESR of 23 mm / hour; in the biochemical blood test there is a tendency to an increase in the level of total protein and albumin, the level of CRP normalized to 3.7 mg / l, the rheumatoid factor values were high 16.3 IU / ml, total cholesterol was high 10.7 mmol / l, ALT was 90, 8 units / l. The coagulogram showed the normalization of indicators, with the exception of the level of fibrinogen (5.180 g / l) and D-dimer (4555.6 ng / ml).

The patient was discharged from the rheumatology department in April 2019 with positive dynamics, the level of eosinophils returned to normal, the inflammatory process regressed, the CT picture of the chest organs improved (infiltration in the lungs was partial regression), clinical symptoms and general well-being improved significantly. The patient was recommended to continue treatment at the place of residence. In the future, he is scheduled for a consultation at the Clinic of Rheumatology, Nephrology and Occupational Pathology named after N. Tareeva.

The difficulty of diagnosis and the characteristic staging of the Chardzha-Strauss syndrome are demonstrated in this clinical case.

According to the literature, three stages are distinguished in the development of the disease: at the initial stage, the disease debuts with bronchial asthma, allergic rhinitis. The severity of the

course of bronchial asthma increases gradually, and resistance to therapy often appears [1,5]. Hypereosinophilic syndrome with various clinical manifestations (Leffler's syndrome, eosinophilic pneumonia, eosinophilic gastroenteritis, etc.) is noted in the second stage and at this stage the maximum number of diagnostic errors is allowed. Clinical signs of systemic vasculitis (fever, systemic inflammatory reaction syndrome, nephritis, cutaneous manifestations, etc.) manifest themselves at the third stage. The severity of bronchial asthma may regress [1,4,6].

In clinical practice, the diagnosis of systemic vasculitis is always difficult and long-term to establish. For several months (sometimes years), the patient can be observed by many specialists, as the presented clinical case demonstrates.

In this case, the diagnosis was made at the second stage of the development of the disease, 1.5-2 years after the appearance of the first clinical manifestations, based on the classification criteria of the disease identified in the patient: bronchial asthma, rhinosinusopathy, pulmonary infiltrates and hypereosinophilia, despite the absence of biological vasculitis markers.

In the diagnosis of EGPA, like other vasculitis, an increase in the level of antineutrophilic cytoplasmic antibodies, the action of which is directed against various cytoplasmic antigens - myeloperoxidase, elastase, protease, is of great importance [1,3-7]. ANCA-positive patients (70 to 75%) have antibodies to myeloperoxidase with perinuclear staining (pANCA) and more often kidneys (especially necrotizing glomerulonephritis), the central nervous system, peripheral polyneuropathy, purpura and other skin manifestations are affected [3,7].

In ANCA-negative variant, the process begins with the lungs (pulmonary infiltrates, pleurisy) and the heart (myocarditis, pericarditis, cardiomyopathy, heart rhythm disturbances, etc.). According to the literature, the absence of ANCA does not exclude the diagnosis, since autoantibodies are found in 50-70% of cases with a single study [3,6,7].

This patient has ANCA-negative EGPA type, the disease began with the lungs (bronchial asthma, sinusitis, pulmonary infiltrates, pleurisy) and the gastrointestinal tract (gastroenterocolitis), hypereosinophilia, with a predominance of the clinic of eosinophilic infiltration into organs and tissues, as well as the absence of ANCA in blood.

The variety of clinical and immunological forms of the disease necessitates a differential diagnostic search to exclude a wide range of diseases and pathological conditions.

Broncho-obstructive syndrome, first of all, requires a differential diagnosis between bronchial asthma and chronic obstructive pulmonary disease, as well as allergic bronchopulmonary aspergillosis and chronic eosinophilic pneumonia. In contrast to these conditions, bronchial asthma with EGPA from the moment of onset becomes difficult for therapy, is characterized by the development of pulmonary infiltrates with the involvement of other organs and systems.

The revealed erosive-ulcerative ulceration in the mucous membrane of the rectosigmoid colon was initially regarded as manifestations of ulcerative colitis. At the same time, a timely biopsy of the intestinal mucosa is important in establishing the true cause of destructive changes in the intestinal wall, revealing granulomatous vascular inflammation and eosinophilic tissue infiltration in the biopsy specimen.

Treatment tactics depend on the clinical course of the disease. In this case, the patient was prescribed prednisolone at a dose of 1 mg / kg / day as a basic therapy. This tactic is indicated for patients with a good prognosis, without systemic manifestations of the disease, within 1 month or until the signs of process activity are reduced (up to 1 year) [1,4].

At the same time, high levels of D-dimer and fibrinogen in the blood plasma revealed in our patient, accompanied by systemic thrombosis (PE, thrombosis of the renal veins, forming non-occlusive thrombosis of the superficial vein of the thigh), local impaired contractility of the left ventricle, a decrease in ejection fraction up to 48%, are poor prognostic factors of EGPA, when the most effective pulse therapy with methylprednisolone (1g intravenously for 3 days), followed by 40-60 mg of prednisolone, for a long time [1,3,4].

Conclusion. In the diagnosis of EGPA (Chardzha-Strauss syndrome), a detailed examination of the patient with a targeted search for pathognomonic symptoms of damage to organs and systems is of decisive importance. From the moment of the onset of the disease, the patient was observed by various specialists (pulmonologists, gastroenterologists, therapists), for a long time he was treated for bronchial asthma and ulcerative colitis without positive dynamics. Given the presence of several competing diagnoses, a comprehensive laboratory and instrumental examination was carried out, which made it possible to make a diagnosis.

The presence of this rare disease should be suspected in patients with bronchial asthma with the appearance of infiltrates in the lungs, against the background of high eosinophilia and accelerated ESR in the peripheral blood. Timely diagnosis and adequate therapy can prevent irreversible organ damage and significantly improve the prognosis of the course of the disease.

References

1. Клинический случай синдрома Чарджа-Стросс: трудности диагностики, терапевтическая тактика. Т.В. Адашева, О.И. Нестеренко, В.С. Задионченко и др. Архив внутренней медицины. 2016;5:63-69. [Clinical case Churg-Strauss syndrome: difficulties in the diagnosis, therapeutic tactics. Adasheva TV, Nesterenko OI, Zadionchenko VS. The Russian Archives of Internal Medicine.2016;6(5):63-69. (In Russ.)] DOI:10.20514/2226-6704-2016-6-5-63-69

2. Похазникова, М.А., Мохика Эстепа М.О. Случай выявление синдрома Чарджа-Стросс в практике семейного врача. Российский семейный врач, 2012;2(16):42-44. [Pokhaznikova MA, Mohika Estepa MO. The case of diagnosis of Chgrg-Stragss syndrome in general practice. Russian Family Doctor. 2012;2(16):42-45. (In Russ.)]. DOI:10.17816/RFD2012242-45

3. Сложности в диагностике эозинофильного гранулематоза с полиангиитом (Синдром Черджа-Стросс). Н.В. Багишева, Д.И. Трухан, И.В. Викторова и др. Consilium medicum. 2018; 20(11):55-60. [Difficulties in the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Bagisheva NV, Truhan DI, Viktorova IV. Consilium medicum. 2018; 20(11):55-60] DOI: 10.26442/20751753.2018.11.180092

4. Федеральные клинические рекомендации по диагностике и лечению системных васкулитов. Ассоциация ревматологов России. [Federal guidelines for the diagnosis and treatment of systemic vasculitis. Association of Rheumatology Russia (In Russ.)]. http://rheumatolog.ru/experts/klinicheskie-rekomendacii

5. Classification criteria for the ANCA-associated vasculitides. Robson J, Grayson P, Ponte C et al. Rheumatology. 2019;2(58). Issue Supplement. DOI: 10.1093/rheumatology/kez058.050

6. Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. *Allergol Int.* 2019;68(4):430-436. DOI:10.1016/j.alit.2019.06.004

7. Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. Am J Med. 2003 Sep;115(4):284-90. DOI: 10.1016/s0002-9343(03)00359-0. PMID: 12967693.