

A CASE REPORT OF EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

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Abstract.

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome or allergic granulomatous angiitis, is defined as a systemic vasculitis identified by the presence of allergic rhinitis and/or asthma, correlated with the presence of marked eosinophilia in the peripheral blood, eosinophilic infiltration of various organs with extensive areas of necrosis, eosinophilic, giant cell vasculitis of vessels of small and medium caliber, as well as perivascular and interstitial necrotizing granulomas. The frequency is 10 - 14 cases per million in the adult population. The average time interval from the onset of the disease to establishing the diagnosis is 49.7 (± 6.1) months. Knowledge of the diagnostic criteria and features of the course of EGPA is necessary for early diagnosis and timely initiation of protocolic treatment. This article presents a clinical case of atypical EGPA without existing asthma and with atypical immunological changes.

Key words. Glucocorticoids, eosinophilic granulomatosis with polyangiitis, cyclophosphamide.

Introduction.

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare disease attributed to asthma, blood eosinophilia and tissue eosinophilic infiltration, and necrotizing vasculitis of small-to-medium-size vessel [1]. Despite the fact that EGPA develops mainly in people with allergic manifestations, this disease can also be present in the absence of an atopic history. Hereby, this article describes a clinical case of the development of EGPA in a 60-year-old female patient without a history of allergy. There is presence of isolated similar cases in the literature, but not much examples [2,3]. The chronology of the clinical and laboratory manifestations of EGPA of the patient is described, as well as induction therapy and dynamics of the disease are given. She was eventually diagnosed with EGPA. Our case report highlights the features of EGPA and the process of diagnosing this potentially life-threatening type of vasculitis, despite its low frequency.

Case presentation.

60-year-old female patient, on February 5, 2023, was admitted to the neurological department of the Kyiv City Clinical Hospital in a moderate state with complaints on the incapability to walk and even stand (she wasn't able to feel her feet), pain and swelling of the left ankle joint, severe general weakness, weight loss of 5 kg in the last 3 months. She was examined by a neurologist with suspicion of Guillain-Barré syndrome with lower paraparesis and was hospitalized.

Anamnesis morbi:

Severe burning pains in the legs appeared 6 days ago, which slightly decreased with the use of NSAIDs, after 3 days the

patient felt weakness in both legs, there was a loss of sensitivity in the feet and the outer surface of the right thigh, the left ankle joint began to swell and hurt, appeared subfebrile temperature, a palpable rash appeared on the left shin (Figures 1 and 2). More than 5 years earlier she was diagnosed with chronic rhinosinusitis, odontogenic sinusitis. In December 2022 and January 2023, she was hospitalized and underwent treatment in the pulmonology department with the diagnosis of chronic bronchitis. On October 13, 2022, was performed an operative treatment of mediastinal neoplasm (cyst). Atopic anamnesis was non-prominent.



Figure 1. A palpable rash on the left shin.



Figure 2. A palpable rash on the left shin.

On February 06, 2023, was performed Chest X-ray that showed signs of initial infiltrative/post-inflammatory changes in the basal parts of the right lung. Complete blood count was fulfilled (February 06, 2023): Leukocytes - $22.68 \cdot 10^9/l$, neutrophils - 52.0%, eosinophils - 31.2%, erythrocytes - $4.25 \cdot 10^{12}/l$, hemoglobin - 129.0 g/l, platelets - $275.0 \cdot 10^9/l$. Rheumatologist consulted the patient, EGPA was suspected, further examination was determined and prescribed methylprednisolone per os at a dose of 48 mg per day. On February 08, 2023, there were lessening of the pain in the legs and positive changes in Complete blood count: Leukocytes - $20.23 \cdot 10^9/l$, eosinophils - 17.8%. There were changes in urinalysis: Protein - 0.08 g/l, RBC - 45-50 HPF, WBC - 10-15 HPF, superficial squamous epithelium in significant amount, daily proteinuria - 1.24 g/24h. Blood biochemistry showed next: CRP - 50.84 mg/l, RF - 40 IU/ml, ASLO - 85 U/ml, Glucose - 4.3 mmol/l, ALT - 39.5 U/l, AST - 46.8 U/l, Total protein - 63.8 g/l, creatinine - 91.1 $\mu\text{mol/l}$, urea - 5.44 mmol/l, uric acid - 158.6 $\mu\text{mol/l}$. Coagulation profile – normal.

On February 09, 2023 the results of more specific tests were obtained for the diagnosis of EGPA and differential diagnosis of other pathological processes accompanied by eosinophilia: Ig E - 2.44 U/ml, anti-CCP - 8.02 IU/ml, ANA, IgG - 0.2, Procalcitonin - 0.19ng/mL, Toxocara antibodies, Ig G - 0.55, Antineutrophil cytoplasmic IgG antibodies to myeloperoxidase (anti-MPO, MPO - ANCA) - >134 (>5 is positive).

Chest CT was accomplished (January 4, 2023) and nodular formations, infiltrative changes were not detected. The walls of the bronchi were thickened, a few peribronchial thickenings of 2-4 mm were visualized, mainly in the lower lobes. Bronchoscopy (January 10, 2023) was performed and a direct biopsy of the middle lobar bronchus of the right lung was taken for differential diagnostics between infiltrative changes and cancer. Fragments of the bronchus wall were presented. Mucosa - peeling in areas, focally with pronounced hyperplasia of epithelial cells. In the submucous base growths of connective tissue fibers and diffuse focal non-specific inflammatory cell infiltration in places with pronounced eosinophilia.

Esophagogastroduodenoscopy (February 14, 2023) showed erosive gastropathy and cicatricial deformation of the duodenal bulb. Test for *H. pylori* - negative. On biopsy: chronic subatrophic erosive (pyloric part) gastritis with mild activity of the inflammatory process. The stage of atrophy according to the OLGa system was 1, the degree of inflammation was 2. The expression of intestinal metaplasia according to the OLGIM system was 1.

Stimulation electroneuromyography (February 28, 2023) demonstrated signs of axonal sensorimotor polyneuropathy of the lower extremities (no M-response from the foot muscles is registered; markedly reduced amplitude of the M-response from the muscles of the legs, more on the left).

On February 11, 2023, the patient's condition worsened abruptly after the patient decided to have the dosage of methylprednisolone decreased to 32 mg per day: pronounced shortness of breath appeared, no improvement was observed after administration of dexamethasone and inhalation treatment with corticosteroids, respiratory rate increased to 30 per 1

min, saturation (SpO₂) decreased to 92 and the patient was transferred to the intensive care unit. After the use of antibiotic therapy and prednisolone at a dose of 120 mg IV twice a day, the patient's condition normalized, and a day later the patient was transferred to the therapeutic department, where she continued taking methylprednisolone per os at a dose of 48 mg per day.

Considering positive antineutrophil cytoplasmic IgG antibodies to myeloperoxidase (anti-MPO, MPO - ANCA) on February 9, 2023: more than 134 and p- ANCA - 1:<10 (N - 1:<10), c-ANCA - 1:400 (N - 1:<10) on February 15, 2023, the classification criteria of EGPA ACR/EULAR 2022 were applied:

Obstructive disease of the respiratory tract (+3) nasal polyposis (+3), multiple mononeuritis or motor neuropathy (+1) laboratory and pathological criteria: the maximum number of eosinophils $\geq 1 \cdot 10^9/l$ (+5) extravascular, mainly eosinophilic inflammatory biopsy (+2) positive cytoplasmic ANCA (c-ANCA) or antibodies to proteinase-3 (anti-PR3) (-3) hematuria was absent in our case.

At the time of diagnosis, the patient scored 11 points, while the diagnosis of EGPA can be established if the total number of points is ≥ 6 .

Diagnosis was established: Eosinophilic granulomatosis with polyangiitis, positive for c-ANCA, MPO-ANCA, chronic course with severe exacerbation (acute respiratory failure February 11, 2023), involvement of the respiratory tract (recurrent infiltration of the middle lobar bronchus and basal sections of the right lung, chronic purulent bronchitis in exacerbation phase (bronchoscopy from December 19, 2022 and January 4, 2023), condition after the removal of neoplasm of the posterior mediastinum (true cyst) November 13, 2022, organs of upper respiratory tract (chronic allergic rhinitis, sinusitis), nervous system (peripheral polyneuropathy with pronounced motor and vegetative-sensory disorders with predominant damage to the lower limbs, impaired gait function and signs of sensitive ataxia), kidneys (nephrotic syndrome), joints (polyarthritis of the ankle joints, functional insufficiency II), skin (purpura), general trophic syndrome (fever, weight loss), hematological syndrome (hypereosinophilia, leukocytosis), eosinophilia according to biopsy results on January 10, 2023, BVAS-30, VDI-5.

Before the induction therapy several laboratory tests were performed to determine the possibility of prescribing the cytostatic therapy: procalcitonin - 0.26 ng/mL, quantiferon test - negative, HBsAg - negative, Anti-HCV antibodies (qualitative) – negative. On March 1, 2023 specific treatment was started: Methylprednisolone 1000 mg IV - 3 days, Methylprednisolone 48 mg per os + cyclophosphamide 500 mg IV once every 2 weeks. Sulfamethoxazole/trimethoprim in a dose of 400/80 mg per day.

At a medical examination on February 23, 2023 were shown next laboratory dynamic: in complete blood count - Leukocytes - $13.5 \cdot 10^9/l$, eosinophils - 12.0%, ESR - 31 mm/h; urea - 13.28 mmol/l, creatinine - 94.6 $\mu\text{mol/l}$, CRP - 38.5mg/l, Urinalysis: protein - (negat.), RBC - 0-1-2 HPF, WBC - 10-12 HPF, hyalinecasts – 1-2HPF.

After 3 months on April 14, 2023, we assessed the patient's condition: pain and swelling of the left ankle joint practically did not bother, severe general weakness and rash disappeared,

the sensitivity of the limb somewhat improved, gain function has been slightly restored. In complete blood count - Leukocytes – $10.6 \times 10^9/l$, eosinophils -1.0%, ESR-4mm/h; in biochemistry - CRP - negative, creatinine, ALT, AST – normal; MPO - ANCA <3.5 (negative), PR3-ANCA <2.0 (negative). In urinalysis: protein - (negat.), RBC - 0-1-2 HPF, WBC - 5-7 HPF, hyaline casts - 0-1 HPF; daily proteinuria - 0.121 g/24h.

Starting April 27, 2023, decreasing the dose of Methylprednisolone was initiated by 1 mg every 7 days.

The patient's condition after 6 months: temperature does not increase, there are no shortness of breath, the general condition has significantly improved (there is no weakness, night sweats, sleep has normalized), gait function has been partially restored, there is no swelling and pain in the extremities, there are no skin rashes. BVAS-4, VDI-2. Complete blood count: Leukocytes – $10.7 \times 10^9/l$, eosinophils -1.0%, ESR-7 mm/h; CRP - negative, creatinine, ALT, AST - normal.

Urinalysis: protein - (negative), RBC - 0-1-2 HPF, WBC – 8-10 HPF, squamous and transitional epithelium; daily proteinuria – 0

Discussion.

Initially, EGPA was described by Churg and Strauss in 1951 [4], but the current definition was established by the Chapel Hill Consensus Conference on vasculitis nomenclature in 2012 and is based on the main changes, related to pathologic such as 'eosinophil-rich and granulomatous inflammation' and 'necrotizing small-vessel vasculitis' among patients with asthma and eosinophilia [5].

EGPA is classified as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and could be present in approximately half of the patients [6-9]. The abnormal immunologic activity is characterized by the increase of Th1 and Th2 lymphocyte function, heightened eosinophil recruitment and decreased eosinophil apoptosis [10,11]. EGPA pathogenesis nowadays is still not well-known HLA-DRB1*04 and *07, HLA-DRB4 and IL10.2 haplotype of the IL-10 promoter gene are the most explored genetic determinants [11]. Two main clinic-pathologic subgroups can be identified according to their ANCA status, to be specific an ANCA-positive one, with vasculitis, and an ANCA-negative, with leading eosinophil organ inclusion [10]. The disease typically appearing in patients with foregoing asthma and could strike at multiple organs and manifest in the involvement of lungs, kidneys, heart, peripheral nervous system etc. [12].

EGPA frequently progresses into three sequential phases, that may overlap: 1) the allergic phase or prodromal, marked by the development of asthma, allergic rhinitis, and sinusitis, 2) the eosinophilic phase, marked by the eosinophilic organ infiltrations (lungs, heart, gastrointestinal system, etc.), and the vasculitic phase, identified by purpura, peripheral neuropathy, and different constitutional symptoms [10].

Enzymes that are stored in the cytoplasmic granules of eosinophils have a variable cytotoxic effect, which leads to certain manifestations of organ damage, especially this is reflected in cardiac involvement [13]. The leading role in this belongs to the eosinophilic cationic protein (ECP) which alter the membrane sodium permeability of cardiomyocytes and therefore inhibit mitochondrial respiration. ECP induce the release of fibrogenic

cytokines transforming growth factor β (TGF- β), IL-1 α , and IL-1 β as well which leads to the fibrogenesis [14,15].

The involvement of the heart, such as myocarditis, endomyocardial fibrosis, coronary artery vasculitis, valvular disorders, pericarditis, and heart failure at the end, are the leading causes of death of patients with EGPA. The presence of the different neurological abnormalities such as mononeuritis multiplex is a very common occurrence leading to the sensory disturbances and weakness, and not so very common but nevertheless severe central nervous system involvements such as hemiparesis, seizures, and coma. Renal manifestations aren't very common, but are life-threatening and include pauci-immune, focal segmental necrotizing glomerulonephritis with crescent formation and eosinophilic or granulomatous inflammation. The presence of severe organ disorders require immunosuppressive treatment with the aggressive approach, using such medications, as cyclophosphamide. Asthma, severe and corticosteroid-dependent, often manifests in the adulthood. Non-destructive sinusitis and transient patchy pulmonary infiltrates are common as well. Approximately half of patients has skin involvement: nodules and papules (due to the extravascular granulomatous lesions with necrosis in the center), purpura or erythematous papules (associated with leukocytoclastic vasculitis). Among musculoskeletal enrolment are myalgias, arthralgias, and arthritis. The presence of eosinophilic gastroenteritis or mesenteric ischemia are the gastrointestinal manifestations [1, 5, 16]. Conducting a biopsy of the involved areas allows us to confirm the suspected clinical diagnosis. In ANCA-positive patients vasculitis on the biopsy is more frequently than in ANCA-negative, but the frequency of eosinophilic infiltrates as well as granulomas are equal in both groups. Unfortunately, it is not always possible to conduct this diagnostic procedure [12,16].

Treatment typically includes prolong use of glucocorticoids and immunosuppressants, such as cyclophosphamide or rituximab in the remission induction regimen, but azathioprine and methotrexate could be the therapeutic alternatives and maintenance therapy [11,17,18], although a new interleukin-5 monoclonal inhibitor such as Mepolizumab, in December 2017 was approved by the FDA for use in medical practice, is helpful in management of this disease [1,19].

Conclusion.

Eosinophilic granulomatosis with polyangiitis is a condition, strongly associated with obstructive diseases of the respiratory tract and eosinophilia. Our case shows that the complete picture regarding the pathogenesis of EGPA is still missing. Therefore, in the absence of classic atopic and pulmonary symptoms, one should still remember this pathology and try to diagnose it using the classification criteria of EGPA ACR/EULAR 2022.

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РЕЗЮМЕ

СЛУЧАЙ €ОЗИНОФИЛЬНОГО ГРАНУЛЕМАТОЗА С ПОЛИАНГИИТОМ

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Эозинофильный гранулематоз с полиангиитом (ЭГПА), ранее известный как синдром Чарга-Стросса или аллергический гранулематозный ангиит, определяется как системный васкулит, идентифицированный наличием аллергического ринита и/или астмы, коррелирующий с наличием выраженной эозинофильной инфильтрации разных органов с обширными участками некроза, эозинофильным, гигантоклеточным васкулитом сосудов мелкого и среднего калибра, а также периваскулярными и интерстициальными некротизирующими гранулемами. Частота составляет 10 – 14 случаев на миллион взрослого населения. Средний временной период от начала заболевания до установления диагноза составляет 49,7 ($\pm 6,1$) месяцев. Знание его диагностических критериев и особенностей необходимо для ранней диагностики и своевременного начала протокола лечения. В данной статье представлен клинический случай атипичного ЭГПА без бронхиальной астмы и с нетипичными иммунологическими изменениями.

Ключевые слова: глюкокортикоиды, эозинофильный гранулематоз с полиангиитом, циклофосфамид.

აგრძელება

პოლიანგიიტით თანდართული ეოზინოფილური გრანულომატოზის შემთხვევა

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ანოტაცია

პოლიანგიიტით თანდართული ეოზინოფილური გრანულომატოზი, ადრე ცნობილი როგორც ჩარგ-სტროსის სინდრომი, განისაზღვრება როგორც სისტემური ვასკულიტი, რომელიც იდენტიფიცირდება ალერგიული რინიტით და/ან ასთმის არსებობით, რაც კორელირდება სხვადასხვა ორგანოების გამოხატული ეოზინოფილური ინფილტრაციისა და ვრცელი ნეკროზული უბნების არსებობით, ეოზინოფილური, მწვრილი და საშუალო სისხლძარღვების გიგანტუჯრედოვანი ვასკულიტით, აგრეთვე პერივასკულარული და ინტერსტიციალური მანეკროტიზირებელი გრანულომებით. სიხშირე შეადგენს 10 – 14 შემთხვევას ერთ მილიონ ზრდასრულ მოსახლეზე. დაავადების დაწყებიდან დიაგნოზის დადგენამდე საშუალო დროის მონაკვეთი შეადგენს 49,7 ($\pm 6,1$) თვეს. მისი სადიაგნოსტიკო კრიტერიუმისა და თავისებურობების ცოდნა საჭიროა ადრეული დიაგნოსტიკის და მკურნალობის პროტოკოლის დროულ დასაწყისად. ამ სტატიაში წარმოდგენილია ატიპიური პოლიანგიიტით თანდართული ეოზინოფილური გრანულომატოზის კლინიკური შემთხვევა ბრონქიალური ასთმის გარეშე და არატიპიური იმუნოლოგიური ცვლილებებით.

საკვანძო სიტყვები: პოლიანგიიტით თანდართული ეოზინოფილური გრანულომატოზი, ციკლოფოსფამიდი, გლუკოკორტიკოიდები