CASE REPORTS

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Myocarditis as the first manifestation of eosinophilic granulomatosis with polyangiitis

Miokarditis kao prva manifestacija eozinofilne granulomatoze sa poliangiitisom

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Abstract

Introduction. Myocarditis is not a rare diagnosis, but its etiology often remains unknown as it requires extensive diagnostic work. Eosinophilic granulomatosis with polyangiitis (EGPA) or Churg-Strauss syndrome is a very rare systemic disease that is not easy to diagnose. Myocarditis in EGPA is uncommon and usually occurs in the late stages of the disease. **Case report.** A 22-year-old man was admitted with acute coronary syndrome. Using coronary angiography, the presence of stenoses on the epicardial coronary arteries was ruled out, and a working diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) was established. Then, we found inflammatory syndrome, eosinophilia, and a lot of systemic symptoms and signs. The diagnostic work included extensive laboratory tests, which ruled out infectious agents. Then, immunological tests, a computed tomography scan of the chest, cardiac magnetic resonance imaging (MRI) and a biopsy of the bone marrow, nasal mucosa, and skin were performed. We managed to establish the diagnosis of myopericarditis by cardiac MRI. The cause of myocarditis – EGPA, was found only after the histopathological finding of the skin biopsy, which enabled adequate immunosuppressive therapy. **Conclusion.** The accurate diagnosis was crucial for the correct, causal treatment of the patient, especially because he needed life-long immunosuppressive therapy. In order for such complex patients to receive adequate treatment, a multidisciplinary approach and perseverance in the diagnostic evaluation of the etiology of myocarditis are necessary.

Key words:
diagnosis; histological techniques; myocarditis; eosinophilia; churg-strauss syndrome.

Apstrakt

Uvod. Miokarditis nije retka dijagnoza, ali njegova etiologija često ostaje nepoznata, jer zahteva obiman dijagnostički rad. Eozinofilna granulomatoza sa poliangiitisom (EGPA) ili Churg-Strauss-ov sindrom je vrlo retka sistemska bolest, čiju dijagnozu nije lako postaviti. Miokarditis u EGPA nije čest i obično se javlja u kasnim stadijumima bolesti. **Prikaz bolesnika.** Muškarac, starosti 22 godine, primljen je pod kliničkom slikom akutnog koronarnog sindroma. Koronarnom angiografijom isključeno je prisustvo stenoza na epikardnim koronarnim arterijama i postavljena je radna dijagnoza infarkta miokarda bez opstrukcije koronarnih arterija (*myocardial infarction with non-obstructive coronary arteries* – MINOCA). Potom su utvrđeni inflamatorni sindrom, eozinofilija i mnogobrojni simptomi i znaci sistemske bolesti. Dijagnostički rad uključio je obimna laboratorijska ispitivanja, kojima su isključeni infektivni agensi kao uzročnici. Zatim su urađena imunološka ispitivanja, kompjuterizovana tomografija grudnog koša, magnetna rezonanca (MR) srca i biopsija koštane srži, nosne sluznice i kože. Postavljena je dijagnoza mioperikarditisa, koja je potvrđena pomoću MR srca. Uzrok miokarditis – EGPA, je utvrđen tek nakon patohistološkog nalaza biopsije kože, što je omogućilo adekvatnu imunosupresivnu terapiju. **Zaključak.** Precizna dijagnoza bila je presudna za ispravno – kauzalno lečenje bolesnika, posebno zbog toga što mu je potrebna doživotna imunosupresivna terapija. Kako bi ovako kompleksni bolesnici dobili adekvatnu terapiju, neophodan je multidisciplinarni pristup i istrajnost u dijagnostici etiologije miokarditisa.

Ključne reči:
dijagnoza; histološke tehnike; miokarditis; eozinofilija; angiitis, granulomatozni.

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Introduction

Myocarditis is a common diagnosis, but its etiology often remains unknown. Eosinophilic granulomatosis with polyangiitis (EGPA) or Churg-Strauss syndrome is a very rare disease, a sporadic vasculitis described in 1951 [1]. It involves small and medium arteries and veins and is defined as eosinophil-rich and granulomatous inflammation involving the respiratory tract, combined with necrotizing vasculitis of small and medium vessels associated with asthma and eosinophilia [2]. The diagnosis is based on the presence of four or more criteria according to the American College of Rheumatology (ACR): asthma, eosinophilia > 10% in peripheral blood, paranasal sinusitis, transient pulmonary infiltrates, histological evidence of vasculitis with extravascular eosinophils and mononeuritis multiplex or polyneuropathy. When four or more criteria are present, the sensitivity for the diagnosis is 85%, and the specificity is 99.7% [3].

Myocarditis in EGPA is not common and usually occurs in the late stages of the disease [4].

We presented a young man with unusual myocarditis caused by a very rare systemic disease. The diagnosis required extensive multidisciplinary work, enabling adequate treatment and a good outcome.

Case report

A 22-year-old man was presented to the local hospital with a four-day history of intermittent chest pain in the form of tightness. On the day of admission, the pain lasted for one hour continuously. The electrocardiographic (ECG) finding showed QS in V1–V3 and negative T wave in V4–V6. The level of troponin (Tn) was 4,273.8 ng/L, 215 times above the upper limit (< 19.8 ng/L). It was interpreted as an acute coronary syndrome (ACS), and coronary angiography was performed. However, no narrowing of the coronary arteries was found. The working diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) was established. Complete laboratory tests were performed after the admission to the hospital, and their results showed some abnormalities: sedimentation rate 115 [normal values (NV) < 20], C-reactive protein (CRP) 89 mg/L [reference range (RR) 0.0–5.0), leukocytes (Le) 20.7 × 10^9/L (RR 4.0–9.0), eosinophils (Eo) 49.3% (RR 0.0–6.0), aspartate aminotransferase 51 U/L (RR 10–31), lactate dehydrogenase 1,020 U/L (RR 220–450), brain natriuretic peptide (BNP) 555.1 pg/mL (NV < 100). The rest of the evaluated parameters were within normal limits. Echocardiography showed no regional wall motion abnormalities, a left ventricle (LV) ejection fraction (EF) of 47%, and pericardial effusion 4–8 mm behind the posterior wall. A working diagnosis of perimyocarditis of unknown cause was made. Due to the pronounced inflammatory syndrome and high eosinophilia, an infectious disease specialist was consulted. The infectiologist prescribed the antiparasitic drug albendazole and asked for testing for trichinella and cysticercosis. A detailed history revealed that the patient runs a dog kennel, and his father is a hunter, so they often eat game meat. He had been treating asthma for a year and a half prior to admission.

In the following days, the patient became febrile in the late afternoon, reaching a temperature of 38.2 °C, followed by the appearance of vesicles on the skin of both hands and the left foot. The dermatologist characterizes the skin changes as dyshidrotic papules and hemorrhagic vesicles and prescribes an ointment containing an antibiotic, antifungal and corticosteroid, and antihistamine tablets. After the appearance of skin changes, he gives information about intermittent temperatures, weakness, and muscle pain for the past month. As there was no improvement (high value of Tn, associated with weakness and feverishness), and for further diagnostic work (cause of myocarditis, other diseases), the patient was referred from the local hospital to the University Clinical Center, more precisely, the Cardiology Clinic.

On admission, the patient was hemodynamically stable (blood pressure 130/90 mmHg, heart rate 95/min, and oxygen saturation 96%). The ECG was the same as described nine days earlier (Figure 1).

Changes according to the type of vasculitis were present on the palms and soles. On a heart ultrasound, we found the following: LV contractility at the lower normal limit (EF 50%), LV dimensions were normal (53/33 mm), walls were hypertrophic (septum and posterior wall 12 mm), the left atrium was enlarged (volume 78 mL), ratio of velocity E and A waves of mitral in-flow (E/A) was 2.07, and minimal separation of the pericardial sheets was found. In the laboratory tests, TnI was 1.113 ng/mL (upper limit

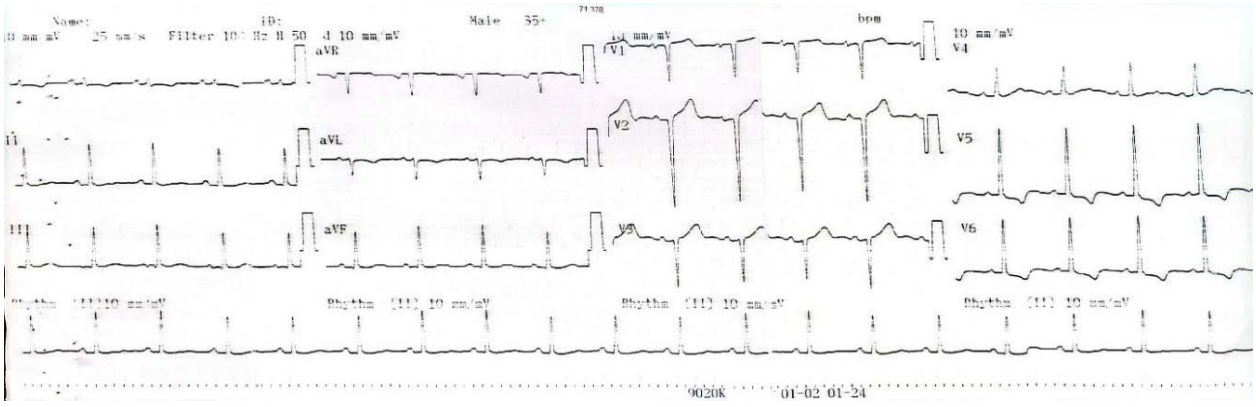

Fig. 1 – Electrocardiographic finding on admission: QS in V1–V3 and negative T wave in D1, aVL, V4–V6.

0.04 ng/mL) – 28 times above the upper limit, BNP 634.6 pg/mL, CRP 65.2 mg/L, Le 23.3 × 10^9/L (RR 4.0–9.0), Eo 53.4%. A multidisciplinary team consisting of an infectious disease specialist, a hematologist, an immunologist, and a pulmonologist was consulted. A chest computed tomography scan revealed mediastinal and hilar lymphadenomegaly (Figure 2).

A cardiac magnetic resonance imaging (MRI) was performed, and the diagnosis of myopericarditis was confirmed (Figures 3 and 4). Ten minutes after the

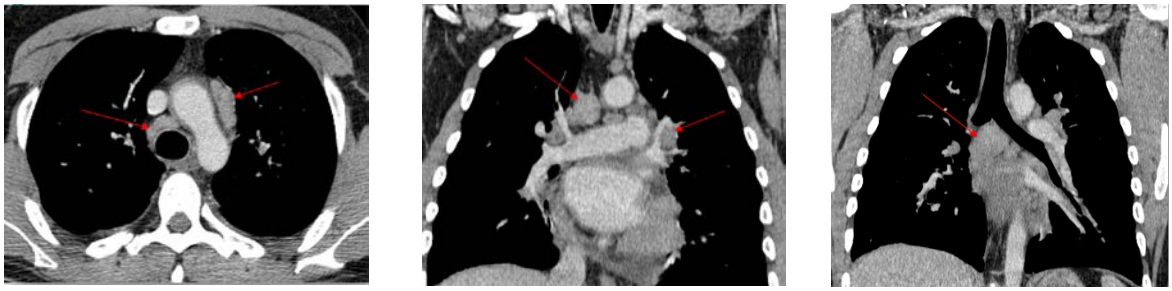

Fig. 2 – Computed tomography scan of the chest: enlarged lymph nodes in mediastinum (red arrows).

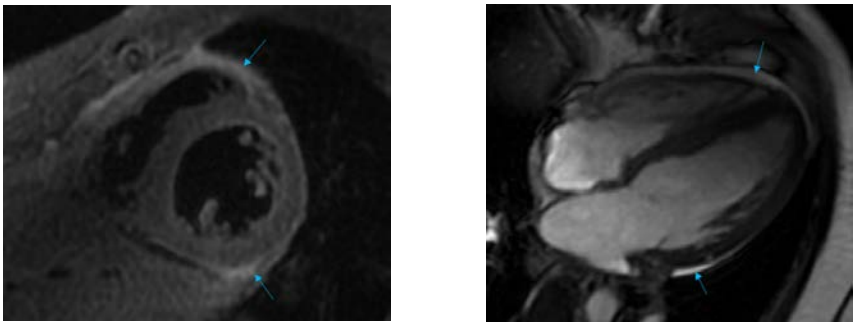

Fig. 3 - Cardiac magnetic resonance imaging, T2-weighted black blood triple inversion recovery sequence, short-axis view: signal of the myocardium is normal, no signs of edema. Pericardial effusion - hypersignal area (arrows, left picture). Cine bright blood sequence, four-chamber view; pericardial effusion – hypersignal area (arrows, right picture).

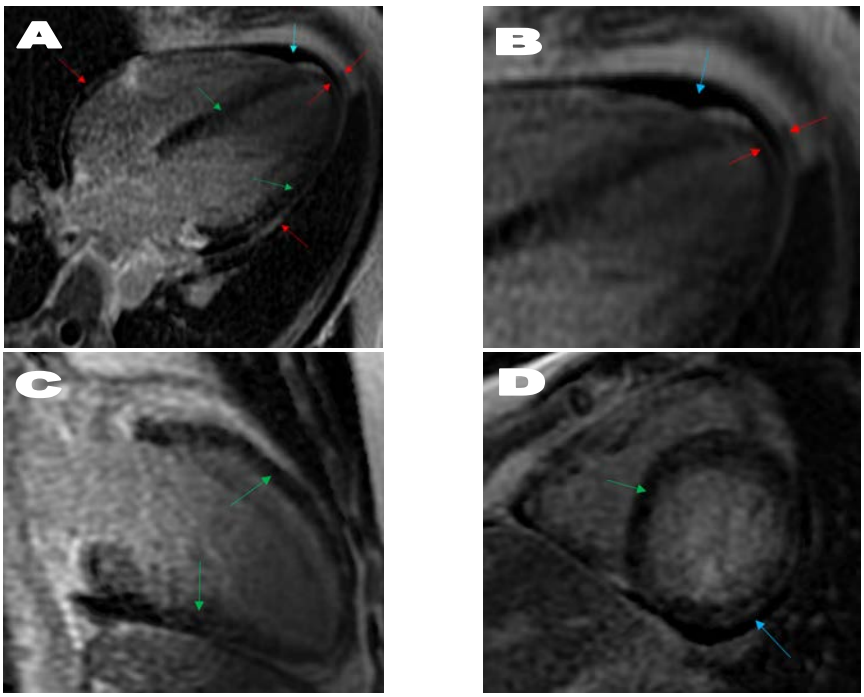

Fig. 4 – Cardiac magnetic resonance imaging, phase-sensitive inversion recovery (PSIR), four-chamber view (A, B), two-chamber view (C), short-axis view (D); to perform this sequence we choose inversion time to achieve appropriate nulling of the normal myocardium to accentuate late gadolinium enhance (LGE). Normal myocardium must be dark. In this case, that was not possible and we can conclude that LGE is diffuse heterogeneous transmural (green arrows). Pericardial effusion is hyposignal on PSIR (blue arrows). LGE of thickened pericardium is hypersignal (red arrows).

application of contrast, diffuse heterogeneous late gadolinium enhancement (LGE) of myocardium was found, which is the less common staining pattern in eosinophilic myocarditis. More common is subendocardial LGE, but cardiac MRI was performed more than three weeks after the symptoms began. A small pericardial effusion and signs of focal pericarditis can also be seen.

We have ruled out infection with parasites, protozoa, bacteria, viruses, and fungi with microbiological and immunological tests. Only Aspergillus immunoglobulin (Ig) M and IgG antibodies were positive. Additional immunological analyzes were performed: IgG 22.8 g/L (RR 7–16), IgE 818 IU/mL (NV < 100), IgA and IgM normal, complement (C) 3 2.09 g/L (RR 0.9–1.8), C4 0.476 g/L (RR 0.100–0.400); antinuclear antibodies (ANA), anti double stranded (ds) DNA antibodies, Sjögren's syndrome antibodies [anti-Ro (SS-A) and anti-La (SS-B)] and anti-Smith (Sm) antibodies within normal limits; cytoplasmic antineutrophil cytoplasmic antibody (ANCA) and perinuclear ANCA negative.

In addition, the patient gave information that he had frequent infections of the upper respiratory tract and that he had rhinosinusitis four months ago. At that time, an endocranium MRI was performed, confirming the existence of chronic pansinusitis.

The first working diagnosis was ACS; the second was MINOCA, then perimyocarditis and heart failure, and then parasitosis or some other infectious agent causing hypereosinophilia with myocardial involvement. The hematologist suspected T lymphoma of the mediastinum and asked for a biopsy of the mediastinal lymph glands. The pulmonologist suspected Churg-Strauss syndrome and indicated further investigation in that direction, but only after ruling out malignant diseases. Therefore, we referred the patient to the Institute for Pulmonary Diseases, where a biopsy of the bone marrow and nasal mucosa was performed. No pathological substrate was found, except for increased Eo with hypolobulation of the nucleus and cell enlargement in bone marrow histopathological (HP) findings. An electromioneurography was performed, which does not meet the electrodiagnostic criteria for polyneuropathy. We have noticed changes – papules on his right hand, and hence, an excisional skin biopsy was performed from that site (Figures 5 and 6). The HP finding indicated EGPA, formerly known as Churg-Strauss syndrome: necrotic vasculitis with eosinophilic granulomas present in the dermis (Figure 7).

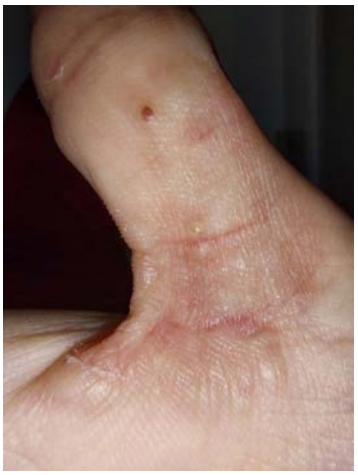

Fig. 5 – Papules on the right thumb.

Fig. 6 – The thumb after biopsy.

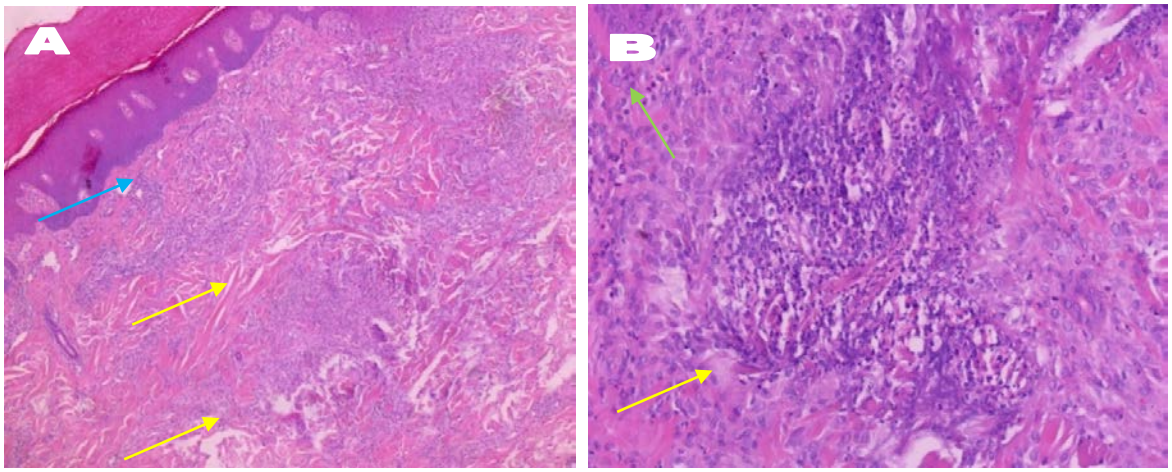

Fig. 7 – Histopathological finding of the dermis, hematoxylin-eosin staining: A) Necrotic vasculitis with eosinophilic granulomas (yellow arrows) in the dermis: Inside the dermis small blood vessels are affected by vasculitis (blue arrow) and granulomatous formations around necrotic foci (blue arrow) with lymphocytic and numerous eosinophilic infiltrate (green arrow) (×50); B) Eosinophilic granuloma (yellow arrows), lymphocytic and eosinophilic infiltrate (green arrow) (×200).

The patient's diagnosis of EPGA was confirmed by HP examination, and treatment with prednisone 1 mg/kg of body weight was started. Very quickly, there was an improvement. The disappearance of skin changes was noticed, new ones did not appear, CRP decreased to the RR, Le and Eo fell, and BNP decreased. The prednisone dose was gradually reduced until it was at the maintenance dose of 20 mg a day, which he receives to this day, six months after the onset of the disease. The patient feels good, and the disease is under control. EF was slightly improved (55%).

Discussion

Considering that our patient had pronounced eosinophilia and inflammatory syndrome dominated within laboratory tests, we considered the differential diagnosis of eosinophilia with myocardial involvement. We started from the most common and most likely causes, considering the patient's age, lifestyle, and habits. The cause of eosinophilia can be hypersensitivity to antibiotics, neurological drugs, vaccines, tuberculostatic agents, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, diuretics, digoxin, and others. However, the patient was not taking any medication, except for an asthma spray, nor had he recently received any vaccines. He had not been vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection. A common cause of eosinophilia could also be various infections: viral (for instance, human immunodeficiency virus – HIV), parasitic (*Toxocara canis*, Ascaris), protozoal (*Toxoplasma gondii*). However, we have ruled out all infectious agents. Following were autoimmune diseases (EGPA, giant cellular arteritis, sarcoidosis, allergic bronchopulmonary aspergillosis, polyarteritis nodosa), among which we found the cause of myocarditis. Nevertheless, it was necessary to exclude malignant diseases (lymphomas – Hodgkin, T and B cell, acute leukemias), primary hypereosinophilic syndrome, and chronic eosinophilic leukemia, which was the reason for performing a bone marrow biopsy. We did not consider primary immunodeficiency diseases (Hyper IgE syndrome, Omenn syndrome) because we previously came to the diagnosis of EGPA. In some cases, eosinophilia with myocardial involvement remains idiopathic/undefined [5].

Our patient had asthma, eosinophilia, and paranasal sinusitis. There were no transient pulmonary infiltrates or neurological criteria, so we had to look for HP confirmation of the disease, according to the recommendations of ACR [3]. We got it after a skin biopsy, which is a simpler and less invasive method compared to an endomyocardial biopsy (EMB), especially because there is no high-volume center with highly experienced staff for EMB in our country.

Myocardial contractility was satisfactory, and high BNP dominantly resulted from diastolic heart failure. Namely, myocardial involvement and damage in EGPA occur due to direct tissue eosinophilic infiltration and the release of cytotoxic proteins, which are directly involved in remodeling, fibrogenesis, cardiotoxicity, and fibrous degeneration [6]. Eo also have direct procoagulant activity, leading to a prothrombotic microenvironment. When Eo are > 20% in the peripheral blood, they infiltrate the myocardium [6]. They can lead to restrictive or dilated cardiomyopathy, which is precisely one of the reasons for the poor long-term prognosis of these patients [4, 6–8]. In our patient, Eo were over 50% in the peripheral blood.

According to the criteria of the European Respiratory Society (ERS) task force, which consist of asthma, eosinophilia, and at least two of the additional features of EGPA [9, 10], we could reach a diagnosis even without biopsy and HP findings, based on the presence of asthma, eosinophilia, paranasal sinusitis, and purpura. Compared with the criteria of ACR, new features in the ERS document are cardiomyopathy, glomerulonephritis, alveolar hemorrhage, palpable purpura, and ANCA-positivity [9, 10]. However, additional diagnostics were necessary to rule out malignancy in our case.

ACR and the European Alliance of Associations for Rheumatology published new criteria and their weights for patients with a diagnosis of vasculitis of small or medium vessels [11]. According to these criteria, Eo $\geq 1 \times 10^9$/L are scored with 5 points, obstructive airway disease and nasal polyps are scored with 3 points each, extravascular eosinophilic-predominant inflammation on biopsy – 2 points, and mononeuritis multiplex or motor neuropathy, not due to radiculopathy – 1 point. On the other hand, the presence of ANCA positive result and hematuria reduced the score by 3 points and 1 point, respectively. If the score is ≥ 6, vasculitis could be classified as EGPA with 85% sensitivity and 99% specificity, and these criteria are validated for use in research [11]. In our case, the score was 10, so the diagnosis of EGPA could be established.

The diagnosis was made, and the therapy started 51 days from the first day of hospitalization in the local hospital and 17 months from the onset of asthma. However, asthma and chronic sinus disease are only the prodromal phases of the disease. It is realistically possible to make a diagnosis in the second – eosinophilic phase, when eosinophilia occurs in the peripheral blood, followed by tissue infiltration of Eo with or without the formation of granuloma (upper and lower respiratory, gastrointestinal, renal tract, myocardium) [4]. The third stage is vascular, when systemic necrotizing vasculitis of small blood vessels occurs, especially in peripheral nerves, kidneys, and skin [4]. From the beginning of the disease to the diagnosis, it takes 8 to 49.7 months on average [12, 13]. Eosinophilic myocarditis of any etiology requires immediate treatment with glucocorticoids to prevent myocardial fibrosis. On the other hand, although this therapy leads to rapid clinical improvement, it will delay the establishment of the underlying diagnosis for an extended period [14]. Furthermore, glucocorticoid therapy is contraindicated until infection and malignancy have been ruled out [15], which we have done.

Our patient was ANCA-negative, which is consistent with literature data that cardiac and neuropathic manifestations are more common in ANCA-negative patients [16]. The two main clinical subgroups of patients with EGPA are ANCA positive, in which small vessel vasculitis predomi-

nates, and ANCA negative, in which organ damage is predominantly caused by eosinophilic tissue infiltration [7]. Cardiac involvement is present in 27–47% of patients, depending on whether it is observed only clinically or in patients undergoing systemic heart MRI, where changes are found in 47% of patients [4, 6]. The most common manifestations of myocardial involvement are heart failure, cardiomyopathy, myocarditis, pericarditis, acute myocardial infarction, and coronary vasculitis. Myocardial involvement is an independent predictor of mortality and morbidity in EGPA [6, 17]. Myocardial involvement is associated with many Eo in the blood and the absence of ANCA [4]. It is estimated that the mortality of patients with myocarditis caused by EGPA in the first few months from the onset of the disease is about 50% [18, 19].

How rare myocarditis is associated with EGPA is shown by the fact that a search of PubMed found only 116 results, which include these two keywords, most of which are reports of individual cases.

In patients with EGPA and myocardial involvement, monitoring Tn and creatine kinase-myocardial band (CK-MB), ECG, and heart ultrasound are necessary. In recent years, MRI of the heart has gained increasing importance [20]. In our case, cardiac MRI showed an unusual LGE distribution of eosinophilic myocarditis. We have one of two Lake Louise Criteria, myocardial enhancement without edema [21]. That could be an unusual form of eosinophilic myopericarditis in resolution. Coronary angiography excludes coronary artery disease. An endomyocardial biopsy can confirm the diagnosis in a center with great experience. Additional diagnostics aim to identify other causes of hypereosinophilic syndrome, which may involve the myocardium [20].

The treatment of these patients includes glucocorticoid therapy in the acute phase of the disease and as maintenance therapy. Initially, 1 mg/kg of weight of prednisone is given. The maintenance dose is the minimum effective dose. In severe forms, pulse glucocorticoid therapy for 1–3 days is indicated. Remission is achieved in > 85% of patients. If there is no response or a relapse occurs, immunosuppressants (cyclophosphamide, azathioprine, methotrexate) are added [12]. Biological therapy (rituximab), which targets IL-5, is also used [10].

Conclusion

We presented a patient with an unusual clinical presentation of myocarditis associated with numerous systemic manifestations, with dominant eosinophilia. The positive HP findings enabled us to diagnose EGPA and start adequate glucocorticoid treatment. This therapy could not have been prescribed earlier until we ruled out infection and malignancy. If it had been given, it would have masked a finding crucial for the correct diagnosis of EGPA, which requires lifelong treatment. This case showed the need for multidisciplinary work and perseverance in the diagnostic evaluation of the etiology of myocarditis for the treatment to be adequate.

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