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Severe congestive heart failure as the main symptom of eosinophilic granulomatosis and polyangiitis (Churg-Strauss syndrome)

Ciężka niewydolność krążenia jako zasadniczy objaw kwasochłonnego zapalenia naczyń (zespołu Churga-Strauss)

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Abstract

Patients with cardiovascular symptoms are mainly diagnosed in cardiological wards. However, sometimes the other reasons for acute coronary syndrome and heart failure are found. One of such reasons is hypereosinophilia which can be recognized if number of blood eosinophils exceeds 1500/mm^3. High eosinophilia is connected with production of cytotoxic eosinophilic proteins which can cause eosinophilic vasculitis or eosinophilic myocarditis. One of the better known hypereosinophilic syndromes is EGPA described by the pathomorphologists Churg and Strauss. The further research works allowed for the clinical characteristics of patients with EGPA. In the course of this disease the following three phases were recognized : prodromal-allergic, eosinophilic, vasculitic. The definitive diagnosis can be established only in the third phase, when vasculitis causes organ involvement. Besides symptoms of the respiratory tract (asthma, nasal polyps, eosinophilic lung infiltrations) also cardiovascular symptoms, gastrointestinal tract symptoms, as well as skin lesions and kidneys involvement can appear. The most dangerous for patients is involvement of the nervous and cardiovascular systems. We present a patient with asthma and eosinophilia in whom EGPA was diagnosed in the course of acute recurrent substernal chest pain, with subsequent signs of cardiac insufficiency.

Key words: eosinophilia, lung edema, eosinophilic myocarditis, EGPA

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Streszczenie

Chorzy z objawami ze strony układu krążenia są diagnozowani przede wszystkim w oddziałach kardiologii. Czasem jednak objawy o typie ostrego zespołu wieńcowego czy ostrej niewydolności serca są spowodowane innymi przyczynami. Jedną z nich jest hypereozynofilia tzn., stan gdy liczba eozynofilów przekracza 1500/mm^3. Zwiększona liczba eozynofilów oraz nadmierna produkcja przez nie cytotoksycznych białek mogą wywołać m.in. kwasochłonne zapalenie naczyń czy kwasochłonne zapalenie serca. Jednym z lepiej poznanych zespołów samoistnej hypereozynofilii jest EGPA (*eosinophilic granulomatosis with polyangiitis*) opisane przez

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Churga i Strauss i scharakteryzowane przez nich cechami patomorfologicznymi. Dalsze badania pozwoliły na określenie przebiegu klinicznego EGPA. Wyróżniono 3 następujące fazy: prodromalną związaną z objawami alergii, fazę eozynofilii obwodowej i tkankowej oraz fazę zapalenia naczyń. Rozpoznanie ostateczne można ustalić dopiero w fazie 3, gdy wystąpi zapalenie naczyń i wywoła objawy narządowe. Obok objawów ze strony układu oddechowego (astma, polipy nosa, nacieki kwasochłonne w płucach) mogą wystąpić objawy ze strony układu krążenia, pokarmowego, skóry, nerek. Najniebezpieczniejszymi są objawy ze strony układu nerwowego i układu krążenia. Opisujemy chorego z astmą i eozynofilią, u którego dopiero wystąpienie ostrego bólu dławicowego z objawami niewydolności serca doprowadziło do rozpoznania EGPA

Słowa kluczowe: eozynoflilia, obrzęk płuc, eozynofilowe zapalenie mięśnia serca, EGPA

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Introduction

Patients with substernal pain and signs of cardiac insufficiency are usually hospitalized in the cardiac intensive care unit. High levels of necrotic markers without occluded arteries at coronarography suggest other reasons for the acute coronary syndrome. One of those reasons can be eosinophilic coronary vasculitis and eosinophilic myocarditis in the course of eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss syndrome [1–3].

We present a patient with EGPA diagnosed after the appearance of heart symptoms.

Case report

A 55-year-old man, nonsmoker, with the history of nasal polyps , after polypectomy in 2012, with asthma and mild eosinophilia, was admitted in January 2014 to the IIIrd Department of Lung Diseases in the National Institute of Tuberculosis and Lung Diseases because of the massive lung lesions found in radiological examination.

Symptoms had begun on the 15 of December 2013 with abrupt onset of severe and reccurrent substernal chest pains, the longest lasting for 20 minutes, with acute dyspnea, severe cough and hemoptysis especially in the supine position and after exertion.

He was hospitalized with suspicion of heart infarct in the Clinic of Cardiology , then in the Clinic of Internal Diseases. WBC was from 16.53 $\times 10^9$/mm^3 to 20.16 $\times 10^9$/mm^3 and eosinophilia from 7.11 $\times 10^9$/mm^3 to 7.68 $\times 10^9$/mm^3, 43% to 38.1%, respectively. D-dimer, other biochemical parameters were within normal limits. In electrocardiogram (ECG) ST segment elevation in precordial leads was observed, with poor anteroseptal R-wave progression , and diffuse T-wave inversion (Fig. 1). High level of troponin up to 21.727 ng/ml (normal result < 0.1 ng/ml) and CK-MB up to 104.1 IU/l (normal limits 2–24 IU/l) suggested heart muscle necrosis.

A diagnosis of myocardial infarct was suspected. Echocardiography showed decreased contractility of the left ventricle (LV), LV ejection fraction (LVEF) was 35%, and very small amount

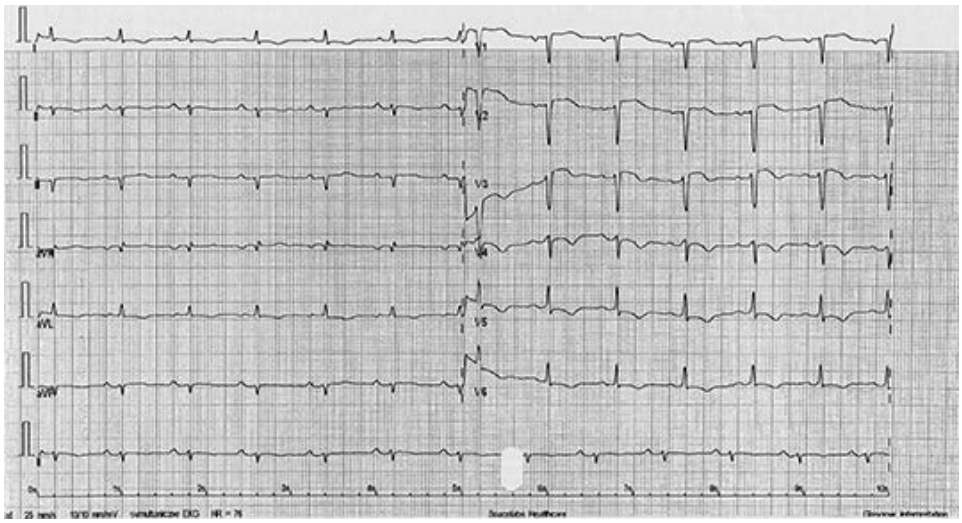

Figure 1. Electrocardiogram (ECG): ST segment elevation in precordial leads with poor anteroseptal R-wave progression, and T-wave inversion

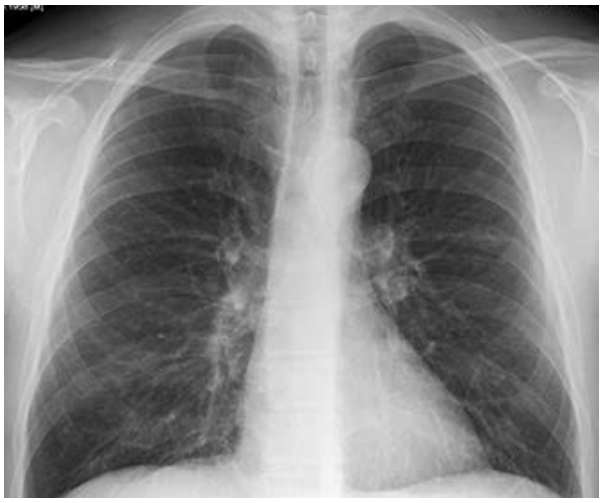

Figure 2. Initial chest X-ray — both lungs and heart are normal; slightly enlarged hila

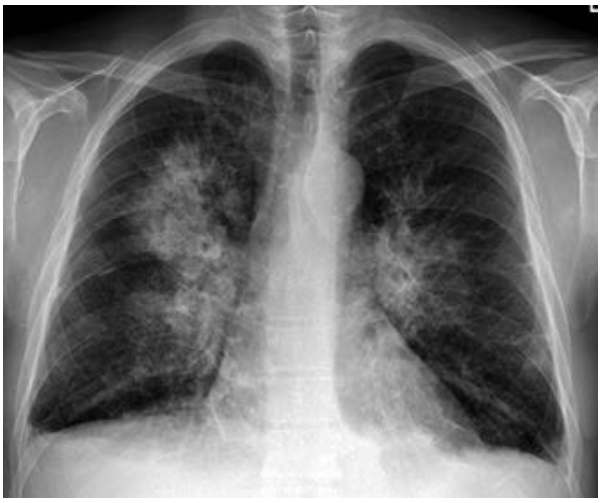

Figure 3. Chest X-ray after one year — big, perihilar foci of abnormal opacities, bilateral pleural effusion; heart is slightly enlarged

of fluid in pericardium was present. Coronarography revealed only segmental small discentric atheroslerosis up to 40–50% of the lumen in left anterior descending artery (LAD). Then heart infarct was excluded and acute coronary syndrome with suspicion of cardiomyopathy in the patient with asthma and nasal polyps was diagnosed. A few days later the patient's performance status worsened.

Chest-x ray and CT scans were done due to suspicion of interstitial lung disease, and revealed the presence of parenchymal consolidations and ground glass shadows. The patient was treated with several antibiotics because of suspicion of pneumonia, also with inhaled corticosteroids and bronchodilatators, furosemidum, nebivolol, and etamsylat. He still complained for shortness of breath, so in January 2014 he received hydrocortisone hemisuccinatum intravenously for a few days. After this therapy he felt better and was send to the National Institute of Tuberculosis and Lung Diseases for diagnosis and treatment of lung lesions.

Previous history: Two years earlier, in 2011, the diagnosis of asthma and nasal polyps was established. He was treated with inhaled bronchodilator and inhaled corticosteroid with clinical improvement. In January 2013 chest x-ray revealed slightly enlarged hilar lymph nodes (Fig. 2). On high resolution computed tomography of lungs (HRCT), delicate disseminated lesions in the middle and lower parts of lungs with slight enlargement of hilar lymph nodes were found. Radiologic appearance could be connected with sarcoidosis but histologic examination of the bronchial wall samples taken during bronchofiberoscopy did not confirm sarcoidosis, signs of chronic inflammation with some eosinophilis were seen. WBC was from 7.71 $\times$ 10^9/mm^3 to 7.88 $\times$ 10^9/mm^3, eosinophils from 0.99 to 1.2 $\times$ 10^9/mm^3, from 14.3% to 15.6%, respectively. In spirometry mild obstruction with significant increase of FEV_1 and FVC after salbutamol was observed. After discharge from the hospital he continued treatment with inhaled bronchodilator, inhaled and nasal corticosteroid. His GP advised him to start therapy with leukotriene receptor antagonist (montelukast) and patient had been treated with this drug for a few months.

In January 2014 the patient was admitted to the National Institute of Tuberculosis and Lung Disease. He was in a severe state, he had shortness of breath at rest, especially when lying in bed, and after slight exertion, with severe cough, hemoptysis, and substernal pain. Physical examinations were unremarkable. He had no symptoms of viral or bacterial infection. Blood examination tests revealed WBC 12.7 $\times$ 10^9/mm^3, with high eosinophilia 30.6%, 3.88 $\times$ 10^9/mm^3. IgE level was slightly elevated to 125.8 IU/ml (normal limits 0–100.0 IU/ml). ANCA (antineutrophil cytoplasmic antibodies) test was negative. CRP 77.9 mg/l (normal result < 10). Troponin level was 0.25 ng/ml. Pro-BNP was elevated to 4702 pg/ml (normal limits 0–125 pg/ml).

Arterialized blood gases revealed hypoxemia, PaO_2 was 55.6 mm Hg, $Sat.O_2$ 91.4%, $PaCO_2$ 35 mm Hg, pH 7.48, HCO_3 26 mmol/l. Initially he was treated with oxygen, nebivol and additionally with diuretics. Some short lasting relief of symptoms was observed. Neurologic examination did

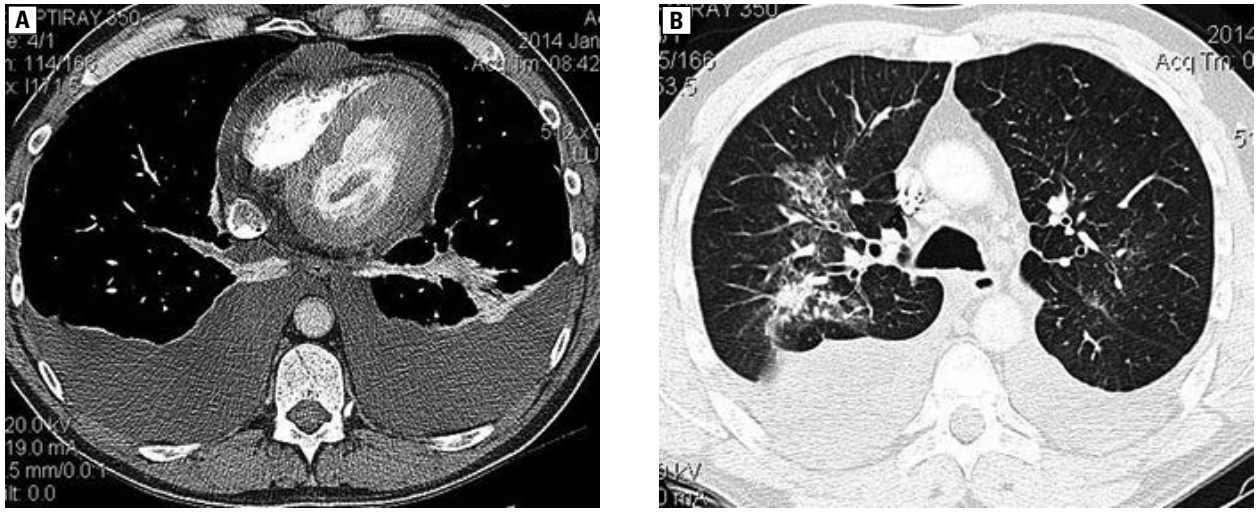

Figure 4. A — CT, mediastinal window: big amount of pleural fluid bilaterally; **B** — CT, lung window: bilateral, perihilar foci of ground-glass opacity and thickened interlobular septa

Figure 5. Cine images in four chamber view: end-systole (left), end-diastole (right). Impairment of systolic LV function. LVEF reduced to 36%. Small pericardial effusion

not reveal any pathologic signs. The result of the radiologist's consultation of the chest X-ray and CT scans done in the Cardiological Ward, was as follows: massive parenchymal lesions caused by lung edema in the course of the left ventricular heart insufficiency with bilateral pleural fluid (Figs 3, 4AB). In ECG ST segment depression, poor R wave progression in precordial leads, and diffuse T-wave inversion were observed.

Echocardiography revealed severe hypokinesis of the left ventricular wall, LVEF was very low, 29%, also small amount of pericardial effusion was seen.

Magnetic resonance of the heart (CMR) revealed signs of acute myocarditis, indicative of eosinophilic etiology. Prominent delayed contrast enhancement (DE) in endocardium of the left ventricle (LV) was observed, mostly prominent in the apical, and basal segments. Additionally, subepicardial, intramural as well as right ventricle (RV) involvement was present.

T2-weighted images revealed increased signal of LV myocardium as compared to the skeletal muscles, indicative of myocardial edema. Subendocardial perfusion defects were observed in the apical and basal segments of the left ventricle. LVEF was low, 36% (Figs 5–8).

The above mentioned cardiac disturbances in patient with asthma, nasal polyps, high eosinophilia > 1500/mm^3, were diagnosed as EGPA with eosinophilic myocarditis and cardiac failure.

Our patient started treatment with prednisone 1 mg/kg per day (60 mg) and cyclophosphamide 2 mg/kg per day (150 mg). Clinical improvement was observed very soon. Control examination of blood after 1 week of therapy

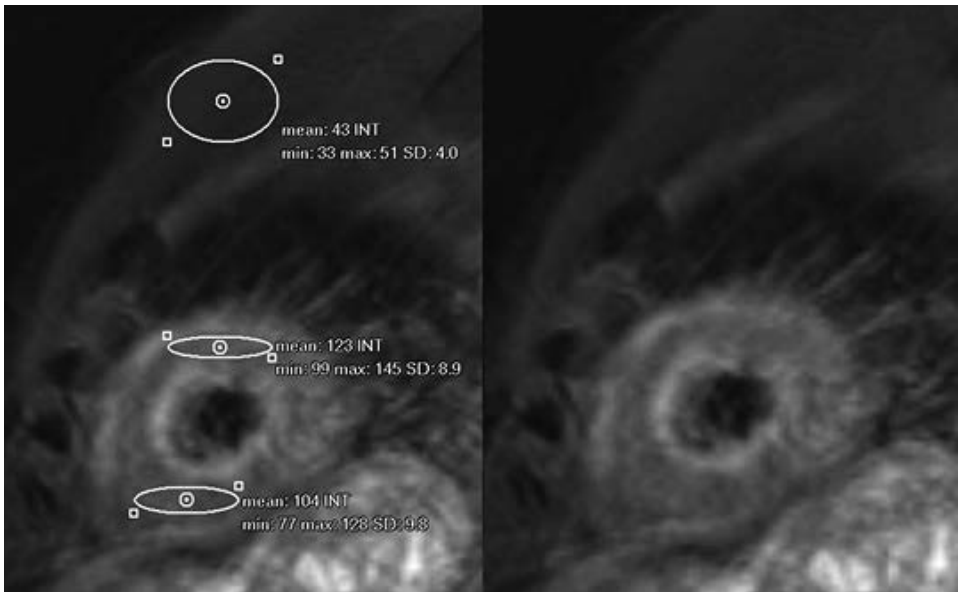

Figure 6. Increased T2 signal ratio between myocardium and sceletal muscles > 2 , suggestive of acute myocarditis

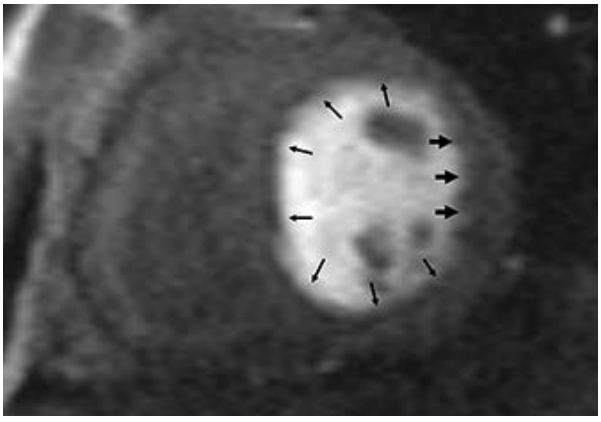

Figure 7. First-pass perfusion, short axis view at basal level. Subendocardial perfusion deficits (arrows) pronounced in the lateral segments (thick arrows)

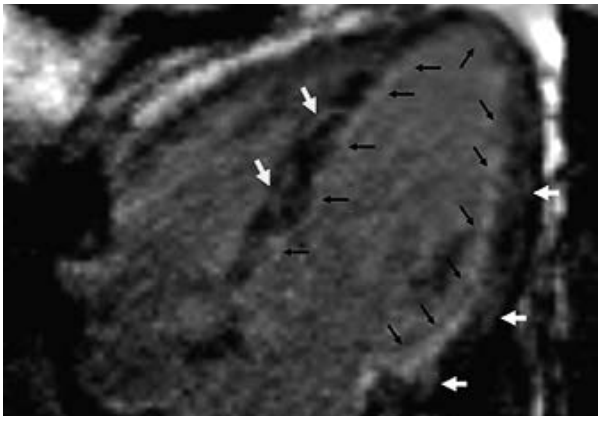

Figure 8. DE image in four chamber view shows typical for eosinophilic myocarditis enhancement pattern involving endocardium, epicardium and intramural myocardium. Black arrows: subendocardial DE, white arrows: epicardial and intramural DE, grey arrows: intramural and RV subendocardial DE in the interventricular septum

revealed no eosinophilia and normalization of troponin level. One month later patient was in a good condition with better tolerance of exertion. At echocardiography partial remission was observed, EF increased to 41%. Chest x-ray revealed regression of the previous lesions (Fig. 9). Patient continued immunosuppressive treatment, and he was allowed to return to work.

Disscusion

EGPA is a rare disease, very difficult to diagnose. The clinical course of EGPA is characterized by the three phases such as: 1. allergic inflammation of the upper airways with polyps, asthma, often corticosteroid-dependent 2. blood and tissue eosinophilia without vasculitis 3. organ involvement caused by eosinophilic and necrotizing vasculitis [4]. In some patients the above mentioned phases can appear simultaneously. Rarely the upper airways allergy is not evident until the development of vasculitis [5–7]. In our patient allergic inflammation of the upper airways with nasal polyps, and asthma have been diagnosed at the same time two years before the heart involvement. Mild blood eosinophilia and eosinophils in histologic examination from bronchial wall were found 1 year before the EGPA diagnosis.

Although, those phases of EGPA are known, the diagnosis of this disease can be established

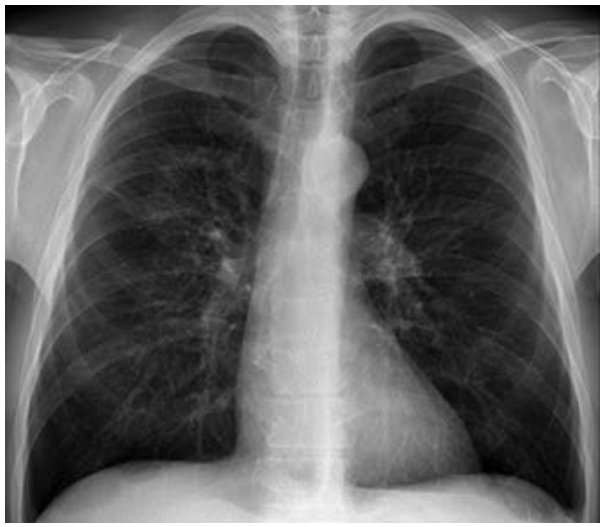

Figure 9. Follow-up chest X-ray after treatment is normal

only in the third phase when the organ involvement appears. In the case with high eosinophilia and suspicion of myocardial or coronary arteries involvement, histologic confirmation of EGPA is often impossible to achieve. In those cases diagnosis have to be established based on the following criteria defined by Guillevin et al. from the French Vasculitis Group: asthma, eosinophilia > 1500/mm^3 or > 10% of WBC, clinical manifestation consistent with systemic vasculitis, with or without histologic evidence [1, 5]. Our patient had nasal polyps, asthma, high blood eosinophilia, and eosinophilic myocarditis (EM) with congestive heart failure, so according to the above diagnostic criteria described by members of the French Vasculitis Group we established the diagnosis of EGPA.

In the pathogenesis of EGPA a major role play eosinophils. Activated tissue eosinophils release toxic granule proteins such as eosinophil basic protein (EBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EP), eosinophil – derived neurotoxin (EDN), which can damage surrounding tissue. Especially ECP and EBP are known as the tissue-damaging protein. Activity of these two cytotoxic proteins is very dangerous for heart and neurologic system [2, 8, 9].The number of eosinophils increases rapidly in the 2nd and 3rd phase of disease.

There are three following stages of heart damage caused by eosinophilic proteins: 1. acute myocardial necrosis, characterized by eosinophil damage of endocardium and infiltration of myocardium mainly with eosinophils, in histologic examination myocardial necrosis with eosinophil microabsceses is seen, 2. thrombotic stage, characterized by formation of thrombi along the endocardium, fibrosis of endocardium, myocardium, and chordae tendinae, leading to endomyocardial fibrosis complicated by restrictive cardiomyopathy, and 3.valve dysfunctions [2, 5, 8, 10, 11].

Cardiac involvement in EGPA can be observed in about 27–60% of patients.

Cardiac manifestations can vary from mild symptoms to the life-threatening entities [3, 9, 12]. According to the reports of Guillevin et al. cardiac involvement in EGPA can even range from 16.6% of patients, when assessed by electrocardiography, to 92.3% of patients, when assessed by the postmortem examination [1]. Cardiac insufficiency was estimated as 34% of patients with EGPA, and was connected with increased mortality rate. Among patients with heart failure/cardiomyopathy caused by EGPA the mortality rate was estimated as up to 50% [1, 6, 11].

In EGPA patients cardiac involvement may be demonstrated clinically as: acute pericarditis, pericardial eosinophilic effusion, myocarditis, endocarditis, endomyocarditis, myocardial ischemia, arrhythmia, conductance disturbances, coronary vasculitis, valvular heart dysfunction, sudden cardiac death. Complications of the above mentioned cardiac disease in EGPA can be as follows: contrictive pericarditis , acute left ventricular dysfunction , cardiomyopathy, congestive heart failure, myocardial fibrosis, intracavitary thrombus, cardiac tamponade [3, 6, 10, 13–16].

Acute and constrictive pericarditis (8–35%), eosinophilic myocarditis (13–25%), heart failure (17%), signs of myocardial ischemia, coronary vasculitis, and arrhythmia were found in the majority of patients with heart involvement in EGPA [10, 15]. Neuman et al. published results of the analysis of 49 patients with EGPA, of those 22 patients (45%) had cardiac disease, and in 13 of those — endomyocarditis was the major presentation proved by CMR or histologic examination of the endomyocardial biopsy [2, 14].

The patient presented in this report had no preexistent heart disease. During hospitalization in the cardiology ward high troponin (21.727 ng/ml) and CK-MB levels (104 ng/ml) were found indicating cardiac necrotic lesions, and electrocardiogram showed signs of heart ischemia. At this time also high blood eosinophilia was present but in the beginning it was not considered as an important finding. At echocardiography, diffuse hypokinesis with LVEF decreased to 35% was observed. Heart stroke was suspected initially but coronarography revealed only small dyscentric atherosclerosis in LAD, so the diagnosis was changed to the suspicion of cardiomyopathy.

The appearance of the new massive pulmonary lesions was recognized by cardiologists as pneumonia. The accurate radiological estimation of pulmonary lesions as lung edema, in connection with asthma, and eosinophilia suggested EGPA. The presented patient had severe eosinophilic myocarditis with heart failure, at echocardiography acute left ventricular dysfunction with hypokinesis, and LVEF reduced to 29% was shown. In this phase of disease high blood eosinophilia was also found.

Cardiac involvement in our patient with clinical suspicion of eosinophilic myocarditis was proved by cardiovascular magnetic resonance imaging (CMR) [17, 18]. CMR might serve as a noninvasive method for diagnosis of myocarditis. Delayed contrast enhancement, especially in apical and middle segments of LV is connected with active myocarditis in EGPA [18]. Our patient had similar pattern of lesions and radiologist conclusion was that examination indicated EM probably in EGPA. Moosig et al. reported that use of CMR increases the frequency of detecting heart involvement in the course of EGPA[19]. It is useful method in differentiating EGPA myocarditis from other causes of myocardial diseases [17].

Even in patients with EGPA in remission, heart lesions in CMR can be found. Dennert et al. demonstrated, that in 62% of a group of 32 patients with EGPA remission, CMR revealed cardiac involvement, such as wall motion disturbances then focal fibrosis, and in some patients obliterated RV, reduced LV function, and valvular disease. In the majority of those patients the subclinical heart disease was observed. Only 26% of examined patients (8 patients) complained of cardiac symptoms such as dyspnea, palpitations, and chest pain [6]. It is concluded that the decision to intesify treatment of patients with EGPA in remission with subclinical cardiac involvement is uncertain [6, 18].

Some authors pointed out that repeated unspecific immunologic stimulation such as vaccination, desensitization or quick discontinuation of systemic corticosteroid therapy in patients with unstable asthma could result in systemic vasculitis [1]. Our patient has been treated for a few months with leukotriene receptor antagonist (LRA). Wechsler et al. reported that in patients with uncontrolled moderate or severe asthma treated with systemic or even with high doses of inhaled corticosteroids and LRA, tapering the corticosteroids doses can be connected with unmasking of the underlying systemic vasculitis. However according to research works there is no evidence that LRA can directly cause vasculitic syndrome [20, 21].

Sable-Fourtassou et al. from the French Vasculitis Group analyzed the published patients with EGPA receiving LRA and found out that in the majority of them cardiomyopathy was diagnosed [22].

ANCA test in our patient with EGPA and congestive heart failure was negative. Two phenotypes of EGPA according to presence of ANCA are recognized , with clinical and pathogenetic differences. In about 40% of EGPA patients, ANCAs were found in examination of blood, and in the majority of cases these antibodies were myeloperoxidase (MPO)-specific ANCA. ANCA-positive EGPA is characterized by higher percentage of involvement of kidney, skin, peripheral nerves. On the contrary to that, most patients with ANCA-negative EGPA have higher involvement of lungs and heart [1, 2, 5, 11, 17, 22]. Patients treated with antileukotriene drugs are usually ANCA-negative as our patient [20, 22]. More relapses, but better overall prognosis were described in ANCA- positive EGPA [1, 2, 5, 11, 17, 22].

Patient with cardiac failure in the course of EGPA requires immediate immunosuppressive treatment with corticosteroid and cyclophosphamide, which can reduce the mortality rate and can improve myocardial function [1, 17, 19].

The prognosis in treated patients is good, relapses were rarely observed. According to Guillevin et al. 10-year survival was achieved in above 80% to 90% of patients [1]. However in some patients with heart involvement in the course of EGPA the prognosis was worse. Guillevin et al. reported that in the group of 96 patients, 8 of them did not respond to immunosuppressive treatment and died. During the follow-up 32 patients died, among those — 5 patients because of the progressive cardiac insufficiency, 4 — because of sudden death, probably due to heart insufficiency, the others died mainly because of the uncontrolled vasculitis [1]. Comarmond et al. after analysis of the clinical characteristics and follow-up of 383 patients with EGPA concluded that cardiomyopathy is the main independent risk factor for death [17]. Our patient received treatment comprised of prednisone 1 mg/kg per day and of cyclophosphamide 2 mg/kg per day orally. He responded very well to the immunosupressive therapy. After a few days eosinophilia disappeared and very soon clinical and the heart function improvement was observed.

Conclusions

Patient with asthma, high eosinophilia and acute coronary syndrome without other causes should be suspected of the EGPA diagnosis. However, in this case always cardiological examinations, and especially coronarography are necessary to exclude heart disease. Nowadays cardiovascular magnetic resonance imaging might serve as a noninvasive method for the quick diagnosis of heart involvement. Among patients with heart involvement caused by EGPA the mortality rate was estimated as up to 50%. Early immunosuppressive treatment of patient with life-threating heart disease in EGPA can allow for the restoration of heart function and reduction of the mortality rate.

Conflict of interest

The authors declare no conflict of interest.

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