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CASE REPORT

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Case report of eosinophilic granulomatosis with polyangitis presenting as acute myocarditis

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Abstract

This case presents a challenging diagnosis of EGPA presenting as eosinophilic myocarditis. It is a condition that can mimic many other diseases and where prompt diagnosis and early treatment is essential for recovery. The diagnosis was made after an endomyocardial biopsy (EMB) and showed the importance of EMB in the diagnostic work-up.

KEYWORDS

cardiac magnetic resonance imaging, cardiomyopathy, case report, EGPA, endomyocardial biopsy, eosinophilic myocarditis, eosinophils, myocarditis

Timeline	Description
2 days prior to admission	Patient had fever and general fatigue while on holiday.
Day 0	On the flight back home, he had progressive chest pain, dyspnea, and syncope.
Day 0–2 h after admission	At hospital admission, elevated inflammatory markers and positive troponins were observed. Electrocardiogram showed atrial fibrillation at 160 beats/min and new onset complete right bundle branch block (RBBB).
Day 0–12 h after admission	Transthoracic echocardiogram (TTE), computer tomography, and coronary angiogram were performed.
Day 2	Cardiac magnetic resonance (CMR) was performed.
Day 7	Endomyocardial biopsy showed eosinophilic myocarditis. Treatment with high-dose corticosteroids started.
Within 21 days from admission	The patient was diagnosed with eosinophilic granulomatosis with polyangitis (EGPA) and was treated by high-dose corticosteroids and intravenous cyclophosphamide.
2 months after discharge	Repeated TTE and CMR showed stationary results. The eosinophilic count was normal, and the patient was doing well. Treatment is planned to continue with methotrexate and prednisolone in tapering doses.

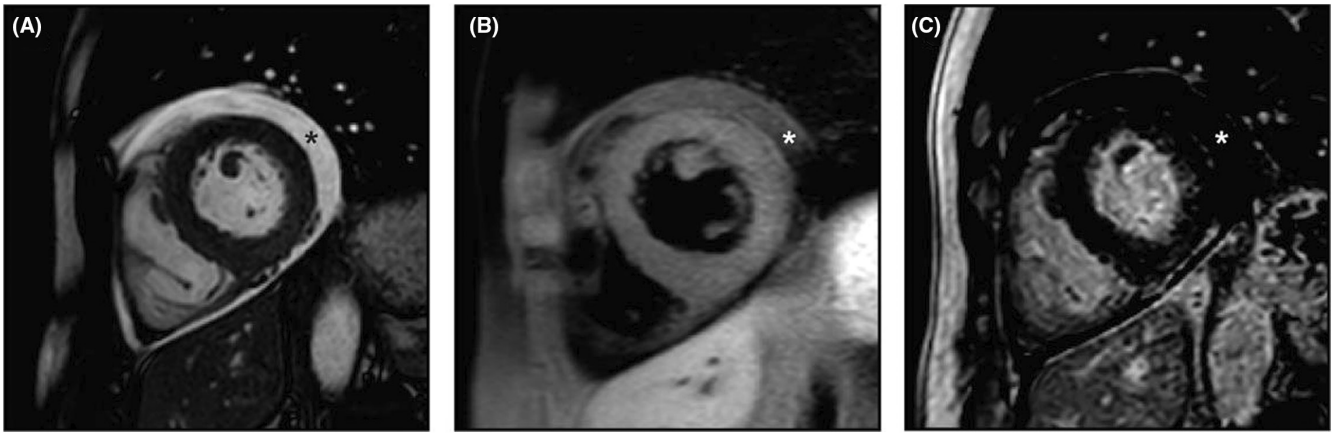

FIGURE 1 CMR. (A) Steady-state free precision sequence in short-axis projection. (B) T2-weighted image in short-axis projection with no clear signs of edema. (C) 2D phase-sensitive inversion recovery sequence in short-axis projection showing no clear signs of delayed enhancement. *indicate pericardial effusion.

1 | BACKGROUND

Eosinophilic myocarditis (EM) is a rare form of myocardial inflammation, characterized by eosinophilic infiltration, and often accompanied by hypereosinophilia.[1,2] The clinical presentation can range from paucisymptomatic to acute fulminant myocarditis (so called acute necrotizing EM) or chronic restrictive cardiomyopathy (Loeffler cardiomyopathy).[3] Clinical diagnosis is challenging, and EM is often first discovered at postmortem examination.

There are several underlying causes of EM and it has been reported in association with hypersensitivity reactions, immune-mediated disorders, such as eosinophilic granulomatosis with polyangitis (EGPA) (formerly Churg-Strauss syndrome), undefined complex hypereosinophilic syndrome (HES) or its myeloproliferative variant, infections and cancer, although the relative proportion of these associations remains incompletely understood.[1] Furthermore, in a relatively large number of cases, the underlying cause of EM remains unknown.[1]

However, if diagnosed early, it can be treated with anti-inflammatory therapy and patients can make a full recovery[1]

Studies have reported EM seen in 0.5% of unselected autopsy series, and in more than 20% of explanted hearts from heart transplant recipients.[4] Although only endomyocardial biopsy (EMB) allows for a definite diagnosis, it is often underused in the diagnostic work-up.[3]

2 | CASE PRESENTATION

A 63-year-old Caucasian male developed a fever while on holiday in Cyprus. On the flight back home, he had an episode of progressing chest pain, shortness of breath, heart palpitations, and finally syncope. In the ambulance from the airport, a standard 12 lead electrocardiogram (ECG) showed atrial fibrillation at 160 beats/min and new onset complete right bundle branch block (RBBB). At admission to the Cardiac Care Unit (CCU), the patient was dyspneic, had chest pain, and severe hypotension (systolic blood pressure 80 mmHg). No signs of overt fluid retention were observed.

The patient had a medical history of arterial hypertension, hyperlipidemia and spinal stenosis. He was on treatment with losartan, atorvastatin, omeprazole, and naproxen. He was a former smoker with a stable social situation. No relevant family history was reported.

Laboratory data showed a white blood cell count (WBC) of 19.1×10^9/l (3.5–8.8), hemoglobin (Hb) 126 g/L (134–170), Troponin-T (TnT) 400 ng/L (<14), c-reactive protein (CRP) 76 mg/L (<5), and N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) 6440 ng/L (<400).

Transthoracic echocardiogram (TTE) performed at the first day revealed mild left ventricular hypertrophy (LVH) but normal left ventricular ejection fraction (LVEF 50%–60%) and no valve abnormalities. There was a small amount of pericardial effusion without hemodynamic significance and an elevated central venous pressure of 10 mmHg. Global longitudinal strain was not performed.

Because of chest pain, the patient's medical history, gender, and age, the first suspicion upon admission was acute coronary syndrome but the coronary angiogram showed no significant stenosis. Computed tomography of the chest was negative for pulmonary embolism.

The atrial fibrillation converted spontaneously to sinus rhythm and over the next 2 days, the patient was hemodynamically stable but continued to have intermittent chest pain, fever (38°C), and elevated TnT (ranging from 400 to 650). He was not treated with antibiotics.

Since he presented with symptoms of infection, elevated TnT, and normal coronary arteries, myocarditis was

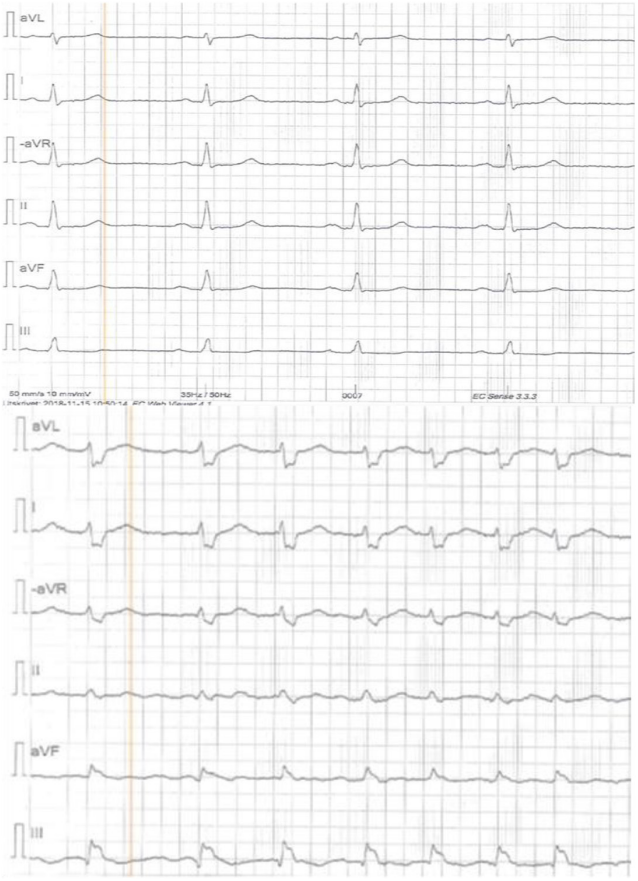

FIGURE 2 ECG (limb leads) in 2016 (above) and at admission (below). Showing RBBB, atrial fibrillation and lower QRS-amplitudes.

suspected. Cardiac magnetic resonance (CMR) performed at day two showed signs of mild LVH, normal LVEF (65%), and pericardial effusion, but neither clear evidence of edema nor delayed enhancement (Figure 1). However, tissue characteristics were difficult to assess due to the patient's pericardial effusion. Consequently, CMR imaging could not confirm the presence of myocarditis, a distinct cardiomyopathy or infiltrative disease.

Further investigation of inflammatory parameters showed elevated eosinophils at 1.3×10^9/l (0.04–0.4). The WBC had then fallen to 9.1×10^9/l and basophils, lymphocytes, neutrophils, and monocytes were in normal range. Erythrocyte sedimentation rate (ESR) was 60 mm/h (<20). Rheumatologic screening showed negative antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibody (ANCA). Serum- and urine-electrophoresis were normal.

The preliminary diagnosis at this point was cardiac amyloidosis based on the presentation with conduction disturbances, history of spinal stenosis and, after further questioning, also suspicion of neuropathic symptoms. Moreover, QRS-amplitudes on ECG had decreased markedly compared with a few years earlier despite the

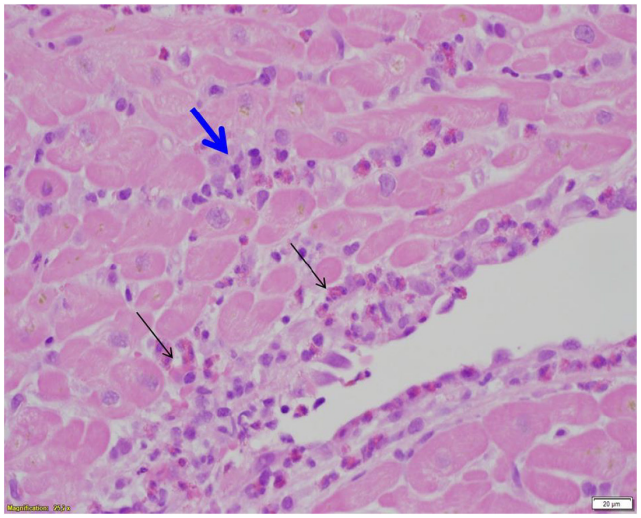

FIGURE 3 EMB showing inflammatory infiltrates of eosinophils (arrow)

findings of LVH on TTE and CMR (Figure 2). However, myocarditis was still a possibility as the CMR might have been false negative.

A bone scintigraphy was ordered and an endomyocardial biopsy (EMB). The result of the EMB came back showing eosinophilic myocarditis (Figure 3). The referral for scintigraphy was then retracted. New blood tests 6 days after admission revealed rising eosinophils (4.8×10^9/l) meanwhile the CRP and TnT had normalized. In consultation with rheumatologists, the patient was started on 60 mg Prednisolone daily and eosinophilic granulomatosis with polyangitis (EGPA, formerly Churg–Strauss syndrome) was suspected. The patient was then transferred to the rheumatology department for further work-up, including a bone marrow biopsy, which was normal. He was diagnosed with EGPA with the involvement of the heart and a mononeuritis of the left arm and hand with atrophy of the thenar and hypothenar musculature. However, there was no involvement of the lungs, sinuses, or kidneys and no history of asthma typical for EGPA. Nine days after starting Prednisolone, the eosinophils normalized (0.4×10^9/L). ESR was 4 mm/h, CRP <1 mg/L, TnT 7,5 ng/L, and NT-pro BNP 135 ng/L. At the rheumatology ward, the patient also started treatment with intravenous cyclophosphamide and later also rituximab in addition to prednisolone, according to the current treatment guidelines for EGPA.[5,6]

Two months later, TTE showed neither left ventricular hypertrophy nor pericardial effusion. This was confirmed by a CMR after 6 months with no signs of edema or certain delayed enhancement. The ECG was normalized with no RBBB and normal QRS-amplitudes and width. The eosinophilic count was normal, and the patient was doing well. He received a total of nine cycles of cyclophosphamide

and one with rituximab. Treatment is planned to continue with methotrexate and prednisolone in tapering doses.

3 | DISCUSSION AND CONCLUSIONS

Eosinophilic myocarditis (EM) is a broad term to describe inflammatory cardiomyopathies of various pathogeneses associated with eosinophilia. Eosinophils contain cytoplasmic granules that release cytotoxic proteins on activation from immunogenic stimuli, leading to free radical formation and subsequent apoptosis and necrosis.[7] Two manifestations are Löffler endocarditis and endomyocardial fibrosis. It can be associated with systemic eosinophilic syndromes such as EGPA or be drug or vaccine related. It can lead to an acute life-threatening inflammatory disease of the heart. Embolic complications are common and if the disease is left untreated the prognosis is poor. EM is probably under-diagnosed and often discovered on post-mortem examination.[1] Uncertainty remains regarding signs and symptoms at presentation, clinical course, and outcome.[8] The course of eosinophilic myocarditis is variable due to the heterogeneity of the disease. A systemic review by Brambatti et al.[1] found that the disorders most frequently associated with EM are hypersensitivity and EGPA, which accounted for 34, 1% and 12, 8% of cases, respectively. EGPA is a rare disease with a prevalence of 11–13 cases/million inhabitants, and a reported annual incidence from 0.5 to 6.8 new cases/million inhabitants.[6] It is characterized by small- and medium-sized-vessel vasculitis and often distinguishes itself from other small-vessel vasculitis by the presence of severe asthma and blood and tissue eosinophilia. However, our patient did not have asthma and ANCA was negative. It has been shown that these patients present more frequently with cardiomyopathies, in different reports the frequency of cardiac involvement in EGPA ranges from 15% to 56%.[6]

Hypereosinophilic syndrome (HES) is a differential diagnosis, and this was also considered in our patient as the syndrome may also present with neuropathy and cardiomyopathy. However, HES patients rarely exhibit mononeuritis simplex,[6] and the diagnosis of EGPA was established by the rheumatologists in consultation with hematologists.

In this case, a number of other diagnoses were considered before EM; pulmonary embolism (dyspnea, new onset RBBB, hypotension), acute coronary syndrome (elevated TnT, new onset RBBB), myocarditis (elevated CRP, fever, small pericardial effusion), and amyloidosis (history of spinal stenosis, LV hypertrophy, smaller R-waves than previously on ECG).

Parasitic infections were never considered in this case but should have been a part of the diagnostic work-up since they are an important cause of eosinophilia.

Since peripheral eosinophilia is absent in up to 25% of patients with EM, EMB plays a pivotal role in diagnosing EM.[1] It is also important to know that eosinophilia may be absent at admission and develop later.[1] In our case, the eosinophilic count was elevated at the time of the first blood test but rose further a few days later. According to a joint scientific statement from the American heart association/American college of cardiology and the European society of cardiology, performing EMB is reasonable in the setting of unexplained heart failure associated with dilated cardiomyopathy (DCM) of any duration that is associated with eosinophilia.[9] Our patient did not have echocardiographic findings consistent with DCM and the case shows that EBM may be beneficial also in cases with eosinophilia without DCM. In this case, the use of EMB was pivotal. Many other diagnoses were considered and ruled out before the final diagnosis was established by EMB. A correct diagnosis allowed for successful immune modulating treatment whereas undiagnosed the prognosis is very poor. Since EGPA is a recurrent disease monitoring remission and relapse is important;, however, this is difficult since there is currently no reliable biomarker to measure EGPA activity.[10] The total eosinophil count is considered the most valuable.[11] The definition of EGPA remission is the absence of clinical systemic manifestations and it is of importance that patients undergo lifelong monitoring and clinical evaluation.[10]

AUTHOR CONTRIBUTIONS

Marie Björkenstam was the principal author responsible for writing the case report. Emanuele Bobbio, Entela Bollano, Christian Polte, Niklas Bergh, and Fransesco Giallauria involved in co-writing and approval of final version of case report. Tomas Mellberg involved in contact with patient and co-writing and approval of final version of case report.

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None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent for publication of their clinical detail and/or clinical images was obtained from the patient.

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