Hypersensitivity Eosinophilic Myocarditis in a Patient Receiving Multiple Drug Therapy: Challenges in Diagnosis and Defining the Aetiology

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Abstract Eosinophilic myocarditis (EM) is a rare and potentially fatal disease if left untreated. Because the disease can have a delayed presentation and can appear even after 2 years, its underlying causes often remain unknown. We report the case of a 63-year-old man with an atypical clinical presentation of hypersensitive EM and significant coronary artery disease, which was confirmed through coronary angiography. The patient was treated with hydrochlorothiazide (12.5 mg once daily for 2 years) and budesonide/formoterol (160/4.5 µg once daily for 2 years). Amoxicillin/clavulanic acid (1000/200 mg three times daily for 2 days) and azithromycin (500 mg once daily for 2 days) were used to treat pneumonia, while ibuprofen (600 mg three times daily for 2 days) was used to treat pericarditis. Extremely high levels of eosinophils led to clinical suspicion of non-acute coronary syndrome as the cause of chest pain and myocardial necrosis. In addition, early pulse doses of methylprednisolone (500 mg intravenously once daily) were administered. Complete clinical recovery and a fast decrease in eosinophils and troponin levels were observed after a few hours on the same day. No signs of recurrent myocarditis were noticed after 3 days of administering the same pulse doses of methylprednisolone, which was then replaced by oral methylprednisolone administered for the next 2 months (step-down regimen, starting from 64 mg/day). Despite causality assessment being difficult, prompt therapy must be given as soon as possible to prevent fatal outcomes. Delayed corticosteroid treatment, which is necessary regardless of the underlying cause, can result in heart failure and death.

Key Points

- Due to an atypical clinical presentation, hypersensitivity eosinophilic myocarditis is rarely clinically recognised and the cause of the disease frequently remains unknown.
- Prompt diagnosis of hypersensitivity eosinophilic myocarditis and appropriate treatment with pulse doses of corticosteroids are crucial, because it can lead to a fatal outcome if left untreated.

Introduction

Eosinophilic myocarditis (EM) is a rare and potentially fatal disease if left untreated. It is rarely recognised clinically and is often first discovered during a post-mortem examination [1]. There are numerous drugs that have been involved in causing the hypersensitivity form of EM (antibiotics, anticonvulsants and diuretics) but the cause of the disease often remains unknown. The hypersensitivity form may develop early during use of the causative drug or may have a delayed presentation after as long as 2 years. According to Gell and Coombs [2], drug hypersensitivity
reactions with eosinophilic inflammation and T helper cell type 2 (T\(_h2\)) immune response (clinically maculopapular eruptions and a reaction to drugs with eosinophilia and systemic symptoms) present as a type IV reaction, which is a delayed type of hypersensitivity reaction; EM is considered to be a delayed hypersensitivity reaction [2–4].

Signs and symptoms of hypersensitivity (skin rash, fever, eosinophilia and malaise) and non-specific cardiac findings (electrocardiographic changes, tachycardia or elevated cardiac enzymes) suggest hypersensitivity myocarditis [3].

In this case report we present an atypical clinical presentation of hypersensitivity eosinophilic myocarditis, presenting mostly as a respiratory infection with flu-like symptoms with an abnormally high eosinophil count. Coronary angiography revealed significant pathomorphological changes.

**Case Report**

A 63-year-old man presented to the emergency department with a history of flu-like symptoms, fever and malaise followed by respiratory-dependent chest pain. The patient had a 2-year history of arterial hypertension and chronic bronchitis, which was treated with hydrochlorothiazide (12.5 mg once daily for 2 years) and budesonide/for-moterol (160/4.5 μg once daily for 2 years). There had been no prior animal exposure. Physical examination revealed reduced breathing sounds; there were no signs of heart failure. Laboratory tests revealed leukocytosis (leukocyte count of 16.3 \(\times\) 10\(^9\)/L) with a slightly elevated eosinophil count of 1.1 \(\times\) 10\(^9\)/L (reference range 0.8 \(\times\) 10\(^9\)/L), troponin of 1.7 μg/L (reference range <0.4 μg/L) and C-reactive protein of 32 mg/L (reference range <5.0 mg/L). Electrocardiography showed clockwise rotation without changes in the ST/T segment. Echocardiography revealed normal systolic function of the non-dilated left ventricle, a diastolic dysfunction of the first degree, and a slightly diffused and thickened myocardium with minimal pericardial effusion of up to 4 mm behind the posterior wall of the left ventricle. The possibility of initial right pneumonia was described on the chest radiography, without auscultatory findings confirming the diagnosis. Arterial blood gas analysis determined an adequate respiratory function with normal pH and gas levels. Despite the uncertainty of the diagnosis of pneumonia, empiric therapy including amoxicillin/clavulanic acid (1000/200 mg three times daily) and azithromycin (500 mg once daily) was administered. Ibuprofen (600 mg three times daily) was also administered due to the pericardial effusion. After 5 days of hospitalisation, the patient’s symptoms did not improve. Moreover, the patient was feeling even sicker, had chills, intensive muscular pain and a cough. His new laboratory tests revealed a leukocyte count of 19.2 \(\times\) 10\(^9\)/L and an eosinophil count of 11.2 \(\times\) 10\(^9\)/L (Fig. 1). Troponin levels rose to 4 μg/L. Echocardiography showed no difference as compared with the patient’s first check-up. Pulse doses of corticosteroids (methylprednisolone 500 mg intravenously) were administered and all other therapy was discontinued. The patient felt relief 7 h later. A fall in the absolute leukocyte and eosinophil counts was observed (leukocytes 9 \(\times\) 10\(^9\)/L; eosinophils 1.32 \(\times\) 10\(^9\)/L). No heart rhythm disturbance or heart failure symptoms were noted. Therapy with pulse doses of methylprednisolone (500 mg intravenously for each dose) was continued for up to 3 days, after which it was changed to oral methylprednisolone therapy (initially methylprednisolone 64 mg, which was decreased every week for 2 months). Coronary angiography showed two-vessel disease with significant stenosis of the circumflex and right coronary artery. In the same procedure, percutaneous coronary intervention was performed with the implantation of one stent in the circumflex artery (Fig. 2). Endomyocardial biopsy was also performed, which showed no inflammation. Ramipril was initiated as a new antihypertensive therapy and dual

**Fig. 1** Leukocyte and absolute eosinophil count chart
antiplatelet therapy with acetylsalicylic acid and clopido-
grel was prolonged.

A second percutaneous coronary intervention was per-
formed 3 weeks later with the implantation of one stent in
the right coronary artery (Fig. 3). The clinical status
showed no abnormalities. The echocardiography per-
formed showed regular systolic function of both ventricles
and that the wall thickness was of the same size as in the
first check-up, but without pericardial effusion. The patient
was asymptomatic and a complete blood count was normal
with normal levels of leukocytes and eosinophils.

Discussion

EM has high morbidity and mortality rates and early
administration of systemic corticosteroids is necessary
regardless of the underlying causes because delayed treat-
ment may result in fatal outcomes [4].

The diagnostic criteria proposed by the Japanese Cir-
culation Society Task Force can be very useful in the early
recognition of EM. Their criteria include three subgroups:
required clinical condition (blood eosinophilia >0.5 x 10^9/
L, cardiac symptoms, elevated cardiac enzymes, ECG
changes and abnormal echocardiography in the setting of
unremarkable coronary angiography); useful information
(previous allergy manifestations and flu-like symptoms);
and endomyocardial biopsy findings [5]. According to
these guidelines, our patient fulfilled enough criteria
required for strong suspicion of EM. There were no ECG
changes, but as proposed in these guidelines, electrocar-
diographic changes do not have to be present in 50 % of
patients. Respiratory-dependent chest pain with flu-like
symptoms and laboratory findings suggested inflammation
as a general mechanism of the disease. Echocardiography
findings of a thickened wall and pericardial effusion were
in favour of myopericarditis. According to the literature,
a few case reports of EM have been described with an
absolute eosinophil count of 3.5 x 10^9/L, but our patient
had much higher levels (11.2 x 10^9/L) [6]. Endomyocar-
dial biopsy revealed no myocardial inflammation, but it
was performed on the third day after a pulse dosage of
intravenous corticosteroids when the symptoms had com-
pletely disappeared. Also, it should be noted that EM is

Fig. 2 Significant coronary
stenosis of the circumflex artery
before percutaneous coronary
intervention (a) and successful
recanalisation after
percutaneous coronary
intervention (b)

Fig. 3 Significant coronary
stenosis of the right coronary
artery before percutaneous coronary
intervention (a) and successful recanalisation after
percutaneous coronary intervention (b)
usually a localised inflammatory disease, so bioptic material is not needed to prove the diagnosis as the sample does not have to be taken from inflamed tissue.

There are different types of EM. One of the most common causes described is a hypersensitivity to various drugs, usually antibiotics, anticonvulsants and diuretics. It is possible, but uncommon, that the appearance of drug-induced EM can be delayed for up to 2 years [3, 4]. The fact that drugs that cause one type of idiosyncratic drug reaction with allergic features often cause other types of similar idiosyncratic reactions only causes more doubt regarding the possible aetiology. A high incidence of such idiosyncratic drug reactions is not known to appear with hydrochlorothiazide and there are only a few case reports describing the potential cause of hydrochlorothiazide-induced EM in the literature, which highlights the difficulty of establishing a causal relationship [4, 6]. No connections between budesonide/formoterol and EM were found. In a clinical sense, it is unlikely that antibiotics could have caused EM in this case as the symptoms characterising EM were present before these agents were administrated. Therefore, because the causality assessment is difficult, it is unclear if this myocarditis was drug induced or if it may be idiopathic as well.

It is more obvious that coronary artery disease was a co-finding in this case, because the symptoms of acute coronary syndrome cannot be resolved using corticosteroids, and troponin levels would not decrease on the second day after the therapy was initiated. Trends in leukocyte and absolute eosinophil count support this hypothesis.

Conclusion

It should be emphasised that proper initial diagnosis of EM and early treatment with pulse doses of intravenous corticosteroid therapy should not be delayed, because untreated myocarditis could result in heart failure and death [7, 8].

Compliance with Ethical Standards

Written informed consent was obtained from the patient for publication of this case report.

Conflict of interest Gulin Dario, Sikic Jozica, Cerkez Habek Jasna, Jerkovic Gulin Sandra and Galic Edvard declare that there are no conflicts of interest concerning the content of this case report.

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