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CASE REPORT

# Eosinophilic myocarditis as a first presentation of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

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## SUMMARY

We present the case of a 28-year-old man who presented with chest pain and elevated cardiac biomarkers, with no evidence of acute ischaemia. He had a pronounced eosinophilia, abnormal echocardiographic, cardiac MRI and CT findings. He underwent transbronchial biopsy of carinal lymph nodes and of lung parenchyma. Endomyocardial biopsy yielded an eosinophilic infiltrate. He was treated with high dose glucocorticoids and made a rapid recovery. Testing for FIP1L1-PDGFRA and other BCR-ABL1 mutations was negative. Ultimately, he was diagnosed with eosinophilic granulomatosis with polyangiitis, also known as Churg-Strauss syndrome.

## BACKGROUND

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome, is a rare vasculitis affecting small-sized/medium-sized vessels and multiple organs. Symptomatic cardiac involvement occurs in 27% to 47% of cases[1] and can range from palpitations and chest pain to fulminant heart failure and death. The mortality associated with EGPA myocarditis is estimated to be 50%.[2] Three distinct phases of the disease are described including prodromal, eosinophilic and vasculitic stages.

This case highlights the difficulties facing clinicians in making this diagnosis and reviews the diagnostic modalities available in cases of suspected eosinophilic myocarditis. Awareness of this disease entity and early diagnosis can reduce mortality and preserve cardiac function.

## CASE PRESENTATION

A 28-year-old man presented to the accident and emergency department with a 1-day history of severe central chest pain. He had no history of cardiac disease or cardiovascular risk factors. He worked as a geologist. He had been admitted to another hospital 2 months previously with a respiratory tract infection and received antibiotics and steroid therapy. He had a history of asthma since childhood. He noted unintentional weight loss of 6.5 kg, admitted to poor recent health and drenching night sweats. Interestingly, his occupation as a geologist involved him working at depths of up to 30 m below ground, and he could have potentially been exposed to unusual sources of infection as a result.

## INVESTIGATIONS

ECG showed non-specific ST segment changes and a sinus tachycardia, without repolarisation abnormality. Chest X-ray was normal.

Laboratory investigations revealed a white cell count of $13.6\times10^9$/L (4–11), eosinophils $3.4\times10^9$/L (0.04–0.4), C reactive protein of 72 and high sensitivity troponin I of 9031 ng/L (0–34 ng). Lactate dehydrogenase (LDH) was elevated at 422 U/L (125–243 U/L). Antistreptolysin O titre was at the upper limit of normal at 200 IU/mL (0–200 IU/mL). His renal and liver function tests were normal.

Echocardiography was performed and revealed a thickened left ventricular free wall and septum. There was global hypokinesia with an ejection fraction of 25%.

He was initially admitted to the coronary care unit for telemetry and started on colchicine 500 $\mu$g three times per day.

## DIFFERENTIAL DIAGNOSIS

Our working diagnosis was of a perimyocarditis of unknown origin. Given the presentation, we outlined three broad avenues of investigation which we would follow, namely infectious, autoimmune and malignant aetiologies.

CT of thorax, abdomen and pelvis was performed due to the concerning symptoms of night sweats, weight loss and elevated LDH. It revealed pathologically enlarged lymph nodes at the level of the carina and ground glass changes in the lung parenchyma at the right apex and at the lung bases bilaterally. Bronchoscopy and transbronchial biopsy of his pericarinal nodes and lung parenchyma plus bronchoalveolar lavage were performed.

On the third day of admission, our patient reported a new symptom of severe back pain, with radiation to both arms. We considered the possibility of infectious discitis as a diagnosis and ordered MRI spine to assess further. The scan did not show any evidence of spinal disease, but did incidentally reveal 13 cm splenomegaly.

An extensive infectious screen was performed and included testing for HIV, influenza, cytomegalovirus, Epstein-Barr virus, *Mycobacterium tuberculosis*, *Coxiella burnetii*, *Borrelia burgdorferi*, leptospirosis, antistreptolysin O titre, *Legionella*, brucellosis and an atypical pneumonia screen. Serological testing was positive for mycoplasma only,

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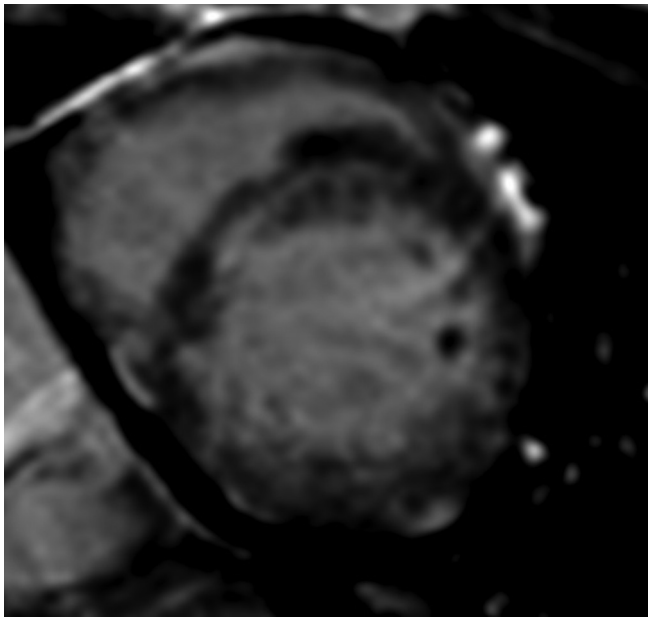

**Figure 1** Delayed enhancement imaging using gadolinium, showing abnormal patchy enhancement in the septal region in keeping with myocarditis.

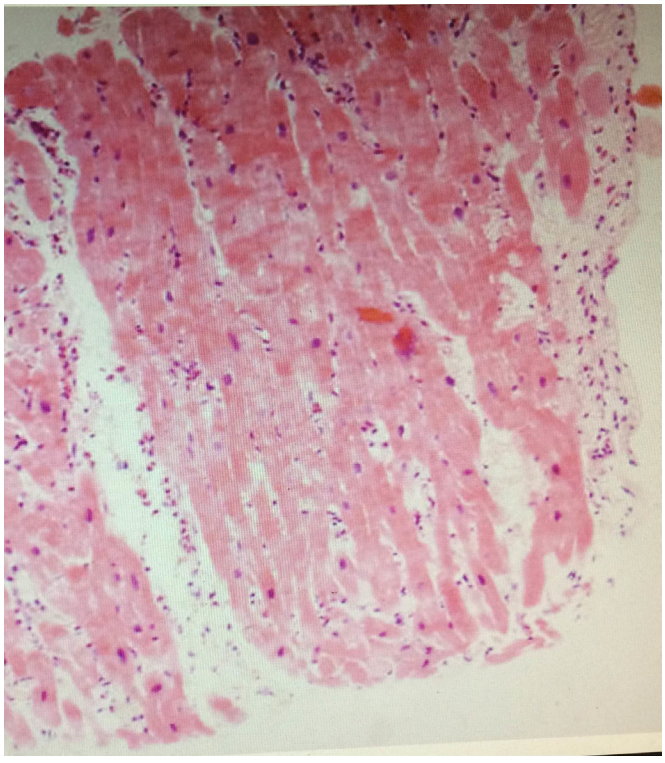

**Figure 2** Myocardial biopsy with visible eosinophilic infiltration of the myocardium.

the significance of which was unclear. Vasculitic screen was negative for all autoantibodies tested, including antineutrophil cytoplasmic antibodies (ANCAs), antimyeloperoxidase antibody and antiproteinase 3 antibody.

On hospital day 4, a pronounced eosinophilia of $6.75\times10^9$/L (0–0.4) was noted. IgE was also elevated at 332 kU/L (0–81 kU/L).

Given the pronounced eosinophilia, negative autoimmune and infectious screens, we considered a diagnosis of primary hypereosinophilic syndrome (HES). We performed a bone marrow biopsy testing for FIP1L1-PDGFRA and rare BCR-ABL1 variants associated with myeloproliferative disorders and also obtained a cardiac MRI.

Cardiac MRI showed a modest amount of oedema of the ventricular wall on T2-weighted imaging. However, on delayed enhancement imaging using gadolinium, there was patchy, mainly midwall and predominantly septal enhancement consistent with myocarditis (figure 1). We proceeded to endomyocardial biopsy to obtain a tissue sample prior to initiating glucocorticoid treatment for hypereosinophilia. This sample revealed substantial infiltration of eosinophils into the myocardium, confirming the diagnosis of eosinophilic myocarditis (figure 2). No granulomas were identified in the sample; however, focal myocyte damage and necrosis were present. This was supported by the finding of non-granulomatous eosinophilic infiltration of the bone marrow and the previously biopsied carinal nodes and lung parenchyma.

## TREATMENT

We commenced 1 mg/kg of methylprednisolone intravenous for 3 days, which resulted in a dramatic clinical and biochemical recovery in our patient. After 1 day, he reported resolution of his chest pain, his persistent tachycardia resolved and night sweats stopped. Biochemically, there was a marked reduction in his eosinophil count which dropped from $5.96\times10^9$/L on the day of methylprednisolone administration to $0.1\times10^9$/L 3 days later. A repeat echo performed 5 days after steroid therapy showed significant reduction in ventricular thickness and an improved ejection fraction, measured at 40%.

He was started on the tyrosine kinase inhibitor imatinib with a presumptive diagnosis of hypereosinophilia secondary to chronic myelogenous leukaemia (CML). This initial diagnosis was based on the symptom profile, splenomegaly, lymphadenopathy, histological findings and the absence of evidence of another pathological process. Treatment was started before the results of all investigations were available, as this agent has been shown to be very effective in reversing the clinical course of HES.[3] Unfortunately, imatinib did not result in normalisation of his blood count or improvement in his clinical condition, and the patient was recommenced on steroid therapy. His laboratory investigations for haematological mutations associated with primary hypereosinophilia, FIP1L1-PDGFRA and rare BCR-ABL1 variants, and lymphocyte flow cytometry were negative making a diagnosis of HES or chronic eosinophilic leukaemia very unlikely.[1]

Based on the absence of FIP1L1-PDGFRA and rare BCR-ABL1 variants and the history of asthma coupled with the clinical picture, we considered the diagnosis was in fact ANCA negative EGPA with multiorgan involvement. He is currently maintained on corticosteroids, with a potential for steroid sparing agents cyclophosphamide and rituximab in the future.

## OUTCOME AND FOLLOW-UP

Our patient has had a very good clinical response to corticosteroids and has returned to work. A recent cardiac MRI has shown an ejection fraction of 43%, 6 months after his original presentation.

## DISCUSSION

Eosinophilic myocarditis was first described by Löffler in 1936 when he reported two cases of fibrosing cardiomyopathy in patients with hypereosinophilia.[4] It is a rare disease with a prevalence of 0.1% in a cohort of patients biopsied for suspected myocarditis.[4 5] The 5-year mortality associated with eosinophilic myocarditis is 50%.[6]

Eosinophils contain high concentrations of hydrolases and cationic and basic proteins. The most important of these substances are major basic protein and eosinophil cationic protein. Release of these substances during degranulation causes cell death and fibrosis in the context of organ invasion.[4 6]

Three stages of eosinophilic heart disease have been described. The first stage is due to infiltration of eosinophils into the myocardium with degranulation and local destruction of myocytes. The second stage is characterised by hypercoagulability and the formation of thrombi in the coronary vasculature and in the ventricles. The final stage is represented by the formation of fibrous scar tissue,[4] which typically results in permanent cardiac dysfunction.

The differential diagnosis for eosinophilic myocarditis is very broad including viral and parasitic infections, atopic drug reactions, essential (idiopathic) hypereosinophilia syndrome, myeloproliferative disorders, acute and CML and the vasculitides including EGPA.[7]

EGPA is a rare autoimmune vasculitis affecting small-sized and medium-sized vessels. It is most commonly associated with asthma, sinusitis and peripheral blood eosinophilia. While the lungs are most commonly involved, the renal, gastrointestinal, neurological and cardiovascular systems are also frequently affected,[8 9] with cardiac involvement being the most important predictor of mortality.[10] It is classified as an ANCA-associated vasculitis, although ANCA is only detected in approximately 40% of cases.[11] ANCA positivity is associated with higher levels of involvement of the kidneys, skin and peripheral nerves. Whereas ANCA negativity is associated with higher rates of pulmonary and cardiovascular involvement.[1 2]

EGPA represents a challenging diagnosis as it may present in a protean fashion. The disease is traditionally associated with severe asthma, but can also present with varying degrees of renal, gastrointestinal, neurological, dermatological or cardiac diseases. The American College of Rheumatology has constructed a classification system for EGPA. It has a sensitivity of 85% and a specificity of 99.7% for EGPA in appropriate clinical settings if four or more of the following criteria are fulfilled.[11 12]

1. Asthma
2. Peripheral blood eosinophilia >10% on differential leucocyte count
3. Mononeuropathy or polyneuropathy
4. Migratory pulmonary infiltrates
5. Paranasal sinus abnormality
6. Extravascular eosinophilic infiltration of tissues on biopsy.

Our patient met four criteria confirming a diagnosis of EGPA.

The recent consensus task force recommendations by Groh *et al*[9] suggest serological testing for toxocariasis, HIV, specific IgE and IgG for *Aspergillus* spp, search for *Aspergillus* spp in sputum and/or bronchoalveolar lavage fluid, vitamin B12 levels, tryptase, peripheral blood film and chest CT scan, plus other investigations as clinically indicated as the basic initial work-up for suspected EGPA.[9] Our work-up contained the majority of the suggested investigations, but could have been improved on by the addition of toxocariasis serology and serum tryptase levels. One should consider testing for strongyloides in endemic areas and in patients with a risk of soil exposure, as glucocorticoid treatment in these patients can result in hyperinfestation syndromes even decades after infection.[9 13] Some authors also argue that cardiac MRI should be performed in patients with confirmed EGPA, as studies have shown evidence of myocardial involvement and fibrosis in patients without any clinical evidence of cardiovascular compromise.[10]

Eosinophilic myocarditis of any aetiology requires prompt treatment in order to prevent scarring of the myocardium and fibrotic change. This presents a therapeutic dilemma to the physician, as while treating the myocarditis with high dose glucocorticoids may improve the patient clinically in the short term, it will almost certainly delay confirmation of the underlying diagnosis in the longer term. In this case, we performed endomyocardial biopsy to confirm the diagnosis. Delayed enhancement imaging using gadolinium can provide strong corroborative evidence before biopsy is performed. Cardiac MRI is also very useful in the case of negative endomyocardial biopsy where clinical suspicion remains high.

Steroid sparing agents which are useful in the induction and maintenance of remission in EGPA are cyclophosphamide and rituximab, especially in patients with ANCA positivity or refractory disease.[9] Additionally, recent research has shown that mepolizumab, an anti-interleukin 5 monoclonal antibody, is also effective in the maintenance of remission in EGPA and represents a promising development in the treatment of EGPA.[14]

### Learning points

- Eosinophilic myocarditis secondary to eosinophilic granulomatosis with polyangiitis (EGPA) is a rare disease that may present with symptoms ranging from palpitations to heart failure and arrhythmia.
- EGPA with myocardial involvement should be considered in patients with chest pain and peripheral eosinophilia, particularly if there is a history of asthma or peripheral neuropathy.
- EGPA may be antineutrophil cytoplasmic antibody (ANCA) negative in 60% of cases.
- In patients with EGPA, myocardial involvement is more likely if they are ANCA negative.
- Early intervention with immunosuppressive therapy can reduce permanent cardiac dysfunction.
- Cardiac MRI is a useful non-invasive modality in patients where a diagnosis of eosinophilic myocarditis is suspected.

**Contributors** RB is the main author. DM performed literature review and helped to collate all laboratory results and so on for this paper. COD provided guidance and advice on how to construct the discussion and edited multiple drafts of the paper. CV edited multiple drafts of the paper and provided guidance and teaching to all the authors.

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**Patient consent** Obtained.

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## REFERENCES


1 Qiao L, Gao D. A case report and literature review of Churg-Strauss syndrome presenting with myocarditis. *Medicine* 2016;95:e5080.
2 Załęska J, Wiatr E, Zych J, *et al*. Severe congestive heart failure as the main symptom of eosinophilic granulomatosis and polyangiitis (Churg-Strauss syndrome). *Pneumonol Alergol Pol* 2014;82:582–9.
3 Pardanani A, Reeder T, Porrata LF, *et al*. Imatinib therapy for hypereosinophilic syndrome and other eosinophilic disorders. *Blood* 2003;101:3391–7.
4 Kuchynka P, Palecek T, Masek M, *et al*. Current Diagnostic and Therapeutic Aspects of Eosinophilic Myocarditis. *Biomed Res Int* 2016;2016:1–6.
5 Maisch B, Pankuweit S. Current treatment options in (peri)myocarditis and inflammatory cardiomyopathy. *Herz* 2012;37:644–56.
6 Li H, Dai Z, Wang B, *et al*. A case report of eosinophilic myocarditis and a review of the relevant literature. *BMC Cardiovasc Disord* 2015;15:15:15.
7 Goldberg L, Mekel J, Chita G. Acute myocarditis in a patient with eosinophilia and pulmonary infiltrates. *Cardiovasc J S Afr* 2002;13:29–34.
8 Setoguchi M, Okishige K, Sugiyama K, *et al*. Sudden cardiac death associated with Churg-Strauss syndrome. *Circ J* 2009;73:2355–9.
9 Groh M, Pagnoux C, Baldini C, *et al*. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med* 2015;26:545–53.
10 Cereda AF, Pedrotti P, De Capitani L, *et al*. Comprehensive evaluation of cardiac involvement in eosinophilic granulomatosis with polyangiitis (EGPA) with cardiac magnetic resonance. *Eur J Intern Med* 2017;39:51–6.
11 Levine AB, Kalliolias G, Heaney M, *et al*. Churg-strauss syndrome with eosinophilic myocarditis: a clinical pathology conference held by the division of rheumatology at hospital for special surgery. *Hss J* 2012;8:313–9.
12 Sharpley FA. Missing the beat: arrhythmia as a presenting feature of eosinophilic granulomatosis with polyangiitis. *BMJ Case Rep* 2014;2014:bcr2013203413.
13 Schär F, Trostdorf U, Giardina F, *et al*. Strongyloides stercoralis: Global Distribution and Risk Factors. *PLoS Negl Trop Dis* 2013;7:e2288.
14 Wechsler ME, Akuthota P, Jayne D, *et al*. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med* 2017;376:1921–32.