CASE REPORT

Rise and fall of the eosinophils in heart failure: a rare but important phenomenon seen with cardiomyopathy

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SUMMARY

A 65-year-old lady and a 69-year-old gentleman, both with a background history of adult-onset asthma, presented with clinical features of heart failure (HF). High-sensitivity cardiac troponin T and eosinophils were significantly raised, along with poor left ventricular (LV) systolic function on cardiac imaging. Endocardial and skin biopsy (in cases 1 and 2, respectively) showed eosinophilic infiltration. This in combination with the clinical features confirmed the diagnosis of eosinophilic myocarditis (EM) secondary to eosinophilic granulomatosis with polyangiitis in case 1. Both cases were managed with high-dose intravenous corticosteroids and conventional HF medication. Case 1 successfully responded clinically with improvement in LV systolic function. Case 2 required further immunosuppressive therapy (rituximab) and cardiac resynchronisation therapy, but eventually died of septic shock secondary to immunosuppressives. Our cases highlight the importance of early diagnosis and treatment of EM and ongoing monitoring of patients on immunosuppressive therapy.

BACKGROUND

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a multisystem disorder where vasculitis occurs in small-sized and medium-sized arteries and is characterised by raised blood eosinophils, asthma and chronic rhinosinusitis.¹ While heart failure (HF) is commonly caused by ischaemic heart disease, hypertension and valvular heart disease, we present a case series of an unusual cause of cardiomyopathy; eosinophilic myocarditis (EM) secondary to EGPA, highlighting the importance of early diagnosis and treatment, as well as discussing the complications of treatment of EM.

CASE PRESENTATION

Case 1

A 65-year-old lady presented to the acute medical team with several months' history of lethargy, malaise and progressive dyspnoea. She had a history of adult-onset asthma, allergic rhinitis and peripheral neuropathy. A previous skin rash was labelled as physical urticaria. There was no history of cardiovascular disease or a significant family history. The patient was on a salbutamol inhaler. Clinically, there were signs of biventricular failure.

Initial laboratory tests revealed a significantly raised eosinophilic count of $23 \times 10^9/L$ and an elevated high-sensitivity cardiac troponin T (hs-cTnT) level of 3153 ng/L. The rest of the full blood count, renal and liver function tests were normal. In addition, serum complement levels were normal, antineutrophil cytoplasmic antibodies (ANCA) were of indeterminate pattern and IgE, as well as rheumatoid factor, were elevated. Other investigations for a secondary cause of eosinophilia including stool examination and screening for HIV and trypanosomiasis were unremarkable. There was no history of recent foreign travel or of medications that could cause eosinophilic hypersensitivity. Her resting 12-lead ECG was normal, and the chest radiograph showed an increased cardiothoracic ratio of 0.54 with evidence of pulmonary venous congestion, but there were no pulmonary infiltrates.

A CT pulmonary angiogram was performed, as her D-Dimer was elevated, but revealed no pulmonary embolism, consolidation or cardiomegaly. However, tiny bilateral pleural effusions suggesting possible HF were observed. A bedside transthoracic echocardiogram (TTE) demonstrated a non-dilated left ventricle with poor systolic function (left ventricular ejection fraction (LVEF) <30%), with severe hypokinesis in all but the LV basal inferior segment. There was no significant valvulopathy or mural thrombi. Given her raised eosinophil count, history of asthma and poor LV systolic function, EM was strongly considered as the likely diagnosis, but at this stage, EGPA was not confirmed. In order to exclude acute coronary syndrome as a cause of the raised hs-cTnT and severe LV systolic dysfunction (LVSD), a coronary angiogram was performed, which showed normal coronary arteries. Cardiac MRI showed patchy mid-wall delayed enhancement in the septum and lateral wall (figure 1) in a distribution and pattern not typical of coronary artery disease along with a low LVEF of 28%, as well as pleural and pericardial effusions. On T2-weighted imaging, there was co-localisation of the increased T2 signal to the areas of delayed enhancement indicating myocardial oedema suggestive of myocarditis. An endomyocardial biopsy (figure 2) was next performed from the right ventricle and sent for histopathology which confirmed EM with no definite evidence of vasculitis, but the tissue sample had only a few blood vessels. Following a haematology assessment, a bone marrow aspirate and trephine

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Figure 1 Cardiac MRI showing patchy delayed enhancement not confined to specific coronary artery territories.

were performed which were consistent with reactive eosinophilia and did not show features of myeloproliferative syndrome; the genetic tests for BCR-ABL, Kit mutation, FGFR1, PDGFRA and B were all negative.

Putting asthma, neuropathy and EM together, it was felt that she was suffering from EGPA.

Case 2

A 69-year-old gentleman with a background of treated hypertension and adult-onset asthma presented initially to the acute medical team with several months' history of exertional dyspnoea, non-cardiac chest pain and rash on both the lower legs. The patient did not have a history of cardiovascular disease or any significant family history. His medication list included montelukast 10 mg once per day, Ventolin and Seretide inhalers, aspirin 75 mg once per day and simvastatin 40 mg once per day. The chest radiograph showed an increased cardiothoracic ratio of 0.6 with clear lung fields. The ECG showed sinus rhythm with complete left bundle branch block (LBBB) and left atrial enlargement. Initial laboratory tests

Figure 2 Endocardial biopsy showing clear extensive eosinophilic inflammation with destruction of the myocytes in keeping with eosinophilic myocarditis (100 µm).

Figure 3 Skin biopsy showing eosinophils within the dermis, more so superficially but also some towards the deeper end (50 µm).

showed a grossly elevated eosinophil count ($23 \times 10^9/L$) and an hs-cTnT level (5491 ng/mL) and abnormal renal function (estimated glomerular filtration rate 44 ml/min). Serum complement levels and ANCA were normal. TTE showed a dilated LV with a poor LV systolic function (LVEF 21%). Cardiac MRI confirmed a dilated LV with poor systolic function (LVEF 27%), moderate to severe mitral regurgitation and mildly impaired right ventricular systolic function. There was subendocardial delayed enhancement involving the mid-anteroseptal, mid-inferoseptal, apical septal, apical anterior and apical lateral LV segments. There were no features of myocarditis. The differential diagnosis was felt to be triple vessel coronary disease and eosinophilic endomyocardial fibrosis.

Coronary angiography performed subsequently revealed no significant coronary disease raising a strong suspicion of the diagnosis being EM. A myocardial biopsy was intended and proposed to the patient, but he was unkeen on the procedure. A chest CT found small bilateral peripheral pulmonary nodules or infiltrates ranging up to 5 mm in the right upper lobe which had radiological appearances of eosinophilic infiltrates, especially in the clinical setting of peripheral blood eosinophilia. A skin biopsy of the leg lesion was performed which showed eosinophilic dermatopathy (figure 3). The biopsy was next subjected to further immunohistochemistry in the form of direct immunofluorescence microscopy which revealed the presence of dermal vessels labelling with all immunoreactions (IgM, IgG, IgA and fibrinogen), features consistent with vasculitis (figure 4). Although, there was no direct histological diagnosis obtained from a myocardial biopsy, we felt that the combination of gross peripheral blood

Figure 4 Higher resolution of the skin biopsy showing eosinophils infiltrating into the wall of a capillary, consistent with vasculitis (250 µm).

eosinophilia, a vasculitis rash (with confirmation of eosinophilic dermatopathy on skin biopsy), a history of adult-onset asthma and a clinical picture of EM led to the conclusion that EGPA was the likely underlying diagnosis.

DIFFERENTIAL DIAGNOSIS

In both cases, given the dramatically high eosinophilic counts with poor LV systolic function in the absence of obstructive coronary artery disease, EM was strongly suspected. However, the underlying diagnosis of EGPA was derived mainly based on the clinical features of peripheral neuropathy, asthma, in combination with the endocardial biopsy (case 1) and skin biopsy (case 2), and patchy subendocardial delayed enhancement with gadolinium on cardiac MRI. In case 2, aspirin-exacerbated respiratory disease was a differential diagnosis; however, this was unlikely given the systemic involvement. Both hypereosinophilic syndrome and eosinophilic leukaemia were considered as important differentials, but the absence of pulmonary involvement and the reactive bone marrow (respectively) made these unlikely. Histology in case 1 supported EGPA as the diagnosis, whereas, in case 2, the skin biopsy result coupled with a grossly elevated troponin T in the absence of coronary artery disease on angiography was strongly suspicious of EM, although not confirmed by direct histological diagnosis.

TREATMENT

Both cases received initial treatment with high-dose intravenous systemic glucocorticoids, alongside conventional HF medication and loop diuretics. However, neither patient required inotropic or vasopressor support. Once clinical improvement was seen, along with dramatic reduction in blood eosinophilia levels ($23 \times 10^9 \rightarrow <1.0 \times 10^9$ in case 1 and $28 \times 10^9 \rightarrow 0.3 \times 10^9$ in case 2) in a few days, oral prednisone was commenced with glucocorticoid-sparing therapy azathioprine (AZA), which was successfully initiated for case 1 under the care of a rheumatologist. Case 2 developed steroid-induced delirium after which AZA was tried, but the patient remained in HF and rituximab was administered, again under rheumatology supervision. Owing to ongoing HF, in the presence of broad LBBB and poor LV systolic function, cardiac resynchronisation therapy (CRT) was performed.

OUTCOME AND FOLLOW-UP

A repeat cardiac MRI after 3 months of steroids, AZA and HF medications showed an improvement of LVEF from 28% to 42% in case 1, whereas case 2 experienced complications of steroid therapy, remained in significant HF and received CRT with a poor clinical response. The patient in case 2 died in the same year of the initial diagnosis due to the complication of septic shock in the setting of immunosuppressive therapy.

DISCUSSION

EM is relatively rare but a likely underdiagnosed type of myocarditis that can be easily suspected from peripheral blood eosinophilia. Its prevalence has been stated as 0.5% in an unselected series of autopsies and in 0.1% of cases among a patient cohort biopsied for suspected myocarditis.¹ Cardiac MRI and myocardial biopsy (or that of other involved organs; such as skin) are helpful in confirming the diagnosis of EM secondary to EGPA. Early diagnosis and treatment with steroids and immunosuppressants can prevent irreversible myocardial damage.

The exact pathogenesis of EGPA is unknown, and the clinical features typically occur in several phases²:

1. prodromal phase—characterised by atopic disease, such as asthma and allergic rhinitis
2. eosinophilic phase—this comprises peripheral blood eosinophilia with eosinophilic infiltration of multiple organs, particularly the lungs and gastrointestinal tract
3. vasculitis phase—systemic vasculitis occurs of the small and medium vessels frequently associated with both vascular and extravascular granulomatosis.

In terms of the diagnostic criteria for EGPA, the most commonly used is the American College of Rheumatology (ACR) and the Lanham criteria.^{3,4}

In patients with documented vasculitis, the ACR has recognised six criteria for the classification of EGPA. The occurrence of ≥ 4 of these criteria has a diagnostic accuracy of 99.7% specificity and 85% sensitivity for EGPA⁴:

- ▶ asthma (a history of wheezing or the finding of diffuse high pitched wheezes on expiration)
- ▶ $>10\%$ eosinophils on the differential leucocyte count
- ▶ mononeuropathy (including multiplex) or polyneuropathy
- ▶ migratory or transient pulmonary opacities detected radiographically
- ▶ paranasal sinus abnormality
- ▶ biopsy containing a blood vessel displaying the accumulation of eosinophils in extravascular areas.

Both of the cases presented satisfied the ACR and Lanham criteria for diagnosis of EGPA. Prompt identification of the cardiac manifestations is paramount, as this carries a worse prognosis in patients with EGPA.⁵ Cardiac manifestations of EGPA include pericarditis, coronary vasculitis, valvular heart disease and, the most common form, EM, which is defined by eosinophilic infiltration of the myocardium with destruction of myocytes. Damage to myocytes is the underlying reason for irreversible loss of myocardial function. Alternative presentations include dilated cardiomyopathy (as in case 2) or, often, myocardial hypertrophy due to eosinophilic infiltration.⁶ In both cases presented, cardiac hypertrophy was absent. With regard to guideline-recommended treatment and management for EM, no formal criteria exist. However, in EM, systemic glucocorticosteroid therapy is the mainstay of treatment (prednisolone 1 g/kg/day), alongside standard HF therapy.⁷ However, once remission is achieved, glucocorticoid therapy can be tapered with the addition of steroid-sparing immunosuppressive therapy, for example, AZA. Case 2 was refractory to high-dose glucocorticosteroid therapy and AZA, after which rituximab infusion was commenced. Several case series/reports have reported successful decrease in disease activity after rituximab infusion. In a retrospective observational study, 43 patients treated with a single rituximab infusion or more achieved 83% remission after 6 months.⁸ However, in case 2, no significant cardiac improvement was observed despite rituximab infusion and CRT, and the patient died due to the complication of immunosuppression. Therefore, close monitoring is required once immunosuppressive therapy has been commenced.

In the absence of a confirmatory myocardial biopsy and lack of response to immunosuppression, the diagnosis of EM could be challenged. In our patient, though, there was extensive patchy fibrosis of the left ventricle in the setting of a large troponin rise and eosinophilic infiltration of the skin (which indicates that his LVSD was most probably due to EM) making it likely that the lack of improvement in clinical markers and LVEF with immunosuppression was merely due to advanced myocardial disease which had gone beyond the stage of reversibility.

Learning points

- ▶ Eosinophilic myocarditis (EM) secondary to eosinophilic granulomatosis with polyangiitis (EGPA) should be suspected in a patient with heart failure (HF) and eosinophilia.
- ▶ In EGPA, identification of cardiac involvement is vital, as this carries a worsened prognosis.
- ▶ EM can be treated successfully with steroids, immunosuppressive and standard HF medication.
- ▶ Patients with EM require multidisciplinary, specialist care with close monitoring when started on immunosuppressive therapy.
- ▶ The objective of immunosuppression is resolution of the inflammatory response. In both cases discussed, there was a rapid resolution of the eosinophilia. Maintenance level of immunosuppression may be warranted to prevent recurrence of the eosinophilia, as case 2 indicates, but this needs to balance against the risk of infection.
- ▶ Immunosuppression can eliminate the eosinophilia, but not the underlying cause. It will reduce ongoing myocardial damage but will not promote myocyte recovery. Myocyte loss is irreversible, hence the importance of early diagnosis and intervention.
- ▶ Following the inflammatory stage, EM-related cardiomyopathy is likely to be refractory to immunosuppression, and alternative strategies need to be considered.
- ▶ There is considerable value in early endomyocardial biopsy in the setting of a new unexplained cardiomyopathy and peripheral blood eosinophilia. Consideration should also be given to a skin biopsy (if there is a skin rash) and a bone marrow biopsy and trephine.

Contributors DA conducted the literature review and provided significant contribution towards drafting the manuscript. DS provided analysis of the histology obtained and provided contribution towards the manuscript. VAD provided analysis and interpretation of the cardiac MRI images obtained and edited the manuscript. PB was responsible for the overall clinical care of the cases and provided significant contribution towards editing the case report.

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