CASE REPORT

Missing the beat: arrhythmia as a presenting feature of eosinophilic granulomatosis with polyangiitis

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SUMMARY

Palpitations are a common presenting symptom in patients attending the emergency department; however, eosinophilic infiltration of the myocardium is rarely the cause. This case describes a 77-year-old woman who presents with sudden onset palpitations and is later diagnosed with eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome). Cardiac involvement does occur in 50% of cases but heart failure, myocarditis, pericarditis, constrictive pericarditis and myocardial infarction are much more commonly recognised complications. Arrhythmia is less well described. In this report, we propose eosinophilic inflammation as the precipitant for an aberrant conduction pathway.

BACKGROUND

Eosinophilic granulomatosis with polyangiitis is a rare, diffuse vasculitis that has multisystem manifestations. As a result, all manner of pulmonary, cardiac, renal and neurological clinical presentations have been described. The American College of Rheumatology in 1990 defined the classification criteria for the condition; however, acute presentations of eosinophilic granulomatosis often do not conform to classical descriptions. This unusual case is atypical because of the patient's presentation. The case stresses the importance of a prompt diagnosis and treatment, which is vital if significant morbidity is to be avoided.

CASE PRESENTATION

A 77-year-old woman presented to accident and emergency with sudden onset palpitations. There was no associated chest pain or syncope. There was no history of cardiac symptoms or disease prior to this episode and no other relevant factors were elicited on presentation. On examination, she was alert but clammy and pale, with an irregularly, irregular pulse with a rate of 220 bpm. Atrial fibrillation was confirmed by an urgent ECG (figure 1). Her blood pressure was 90 systolic and so the patient was cardioverted with oral amiodarone while further history was obtained.

One month prior to this episode her general practitioner had referred her to a respiratory physician for a cough lasting 8 weeks, which had failed to resolve despite two courses of antibiotics. She reported being troubled by a cough productive of greyish sputum, nasal blockage and the occasional morning wheeze. There were no systemic features. A sputum culture was negative and radioallergen sorbent testing to aeroallergens and aspergillus was

only positive to house dust mite. The respiratory physician suspected bronchial hyper-responsiveness and started her on regular inhaled fluticasone and salbutamol. He requested a high-resolution CT scan to further clarify her airways disease.

Other than this, she had been fit and well, with no other medical history. She did not suffer from hay fever or eczema. There were no rashes and her drug history comprised only of her recently started inhalers. She had no known drug allergies and there was no relevant travel history. There was no family history of respiratory disease, and she did not smoke nor drink alcohol. She lived alone and kept no pets.

INVESTIGATIONS

Initial bloods were normal; however, on day 4 she became feverish and bloods revealed a raised C reactive protein (CRP), white cell count and d-dimer. A chest X-ray demonstrated no focal consolidation (figure 2) and urinalysis was negative; a blood gas demonstrated normal oxygenation, but a raised lactate. Intravenous amoxicillin was started and her inflammatory markers improved.

An echocardiogram demonstrated no evidence of structural heart disease and good overall systolic function. Verapamil and warfarin were started for her atrial fibrillation and a CT-pulmonary angiogram was planned given the raised d-dimer.

On day 13 the patient developed paraesthesia in her left arm. An ECG demonstrated sinus rhythm and normal complexes; however, troponin was significantly elevated at 2877 ng/L. Acute coronary syndrome treatment was started and the antibiotics switched owing to persistent fever. Warfarin was stopped pending an angiogram.

On further assessment of the patient's chest pain it was noted that she had a significant peripheral eosinophilia at $6.9 \times 10^9/L$ (54%). At about this time the patient also had an episode of epistaxis. She was promptly seen by the ear, nose and throat (ENT) team who cauterised the nose but reported no inflammation. A respiratory opinion was then sought and the patient transferred to a specialist centre for further investigation and management.

DIFFERENTIAL DIAGNOSIS

Eosinophilic granulomatosis with polyangiitis was suggested given a very high peripheral blood eosinophil count in the setting of recently diagnosed bronchial-hyper-responsiveness, cardiac abnormality and upper airways inflammation. However, the antineutrophil cytoplasmic antibody, myeloperoxidase and antiproteinase-3 antibodies

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Figure 1 Admission ECG.

were all negative and there was no variability in peak flow measurements. The differential diagnosis of a blood eosinophilia is wide. Infections, particularly parasitic and helminth infections, atopic conditions, drug hypersensitivity, neoplastic and primary haematological disorders can all cause elevated eosinophil levels.

Stool microscopy and culture were negative for ova, cysts and parasites, and a CT of her chest, abdomen and pelvis reported only a non-specific small area of ground glass opacification at the right apex.

An atypical presentation of an autoantibody negative eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome) was deemed most likely. The patient went on to have a cardiac MRI (cMRI) scan looking for signs of

cardiac involvement. The scan reported normal left and right ventricle volumes and ejection fractions but myocardial inflammation of the inferoseptal wall, consistent with myocarditis (figure 3).

TREATMENT

Pulsed, high-dose methylprednisolone was started for 3 days and followed by high-dose prednisolone with proton-pump inhibitor cover and bone protection (a dual-energy X-ray absorptiometry scan confirmed osteoporosis). The eosinophil count prior to steroid therapy was $9.8 \times 10^9/L$, CRP was 90 mg/L, erythrocyte sedimentation rate (ESR) 35 mm. After a single dose of 1 g of methylprednisolone, the eosinophil count had fallen to $0.0 \times 10^9/L$. Troponin levels fell back to normal, as did CRP and ESR. Subsequent ECGs initially demonstrated bigeminy but sinus rhythm was restored after 10 days of immunosuppression,

Figure 2 Chest X-ray on admission.

Figure 3 Cardiac MRI: myocardial inflammation and late gadolinium enhancement in the inferoseptal wall in keeping with myocarditis.

confirmed by a 24 h Holter monitor. A myocardial perfusion scan demonstrated no inducible ischaemia underlying her symptoms and the antiplatelet therapy initiated following the elevated troponin was discontinued. In view of the risk of thromboembolic episodes in the event of further rhythm disturbance, warfarin was started. Furthermore, for cardioprotective purposes, a small dose of cardioselective β -blocker, which did not affect the patient's respiratory status, was initiated. She was subsequently pulsed with cyclophosphamide.

OUTCOME AND FOLLOW-UP

The patient was discharged with follow-up planned with both the asthma and cardiology physicians. She will attend regularly for review of clinical status, inflammatory markers and eosinophil count and for a repeat cMRI scan in 8 weeks time.

DISCUSSION

Eosinophilic granulomatosis with polyangiitis is a rare small and medium-sized arteries vessel vasculitis characterised by fever and eosinophilia in the setting of asthma in 97% of patients.^{1 2} Traditionally, the association is with severe asthmatics; however, this patient had milder airways involvement. Eosinophilic infiltration can affect the heart (85%), skin (70%), peripheral nervous system (66%), central nervous system (60%), kidneys (40%), gastrointestinal tract (40%) and musculoskeletal system (20%)³ and given the possible constellation of symptoms and signs a diagnosis is often difficult to reach.

The American College of Rheumatology (ACR) was constructed as a classification tool. A patient can be said to have eosinophilic granulomatosis with polyangiitis if at least four of the following six criteria are met:

1. Asthma
2. Eosinophilia greater than 10%
3. Migratory pulmonary infiltrates
4. Paranasal sinus abnormality
5. Mononeuropathy/polyneuropathy
6. Extravascular eosinophilic infiltration of tissues on biopsy

The patient in this case report met only two of the above criteria: spirometry demonstrating obstructive airflow limitation with reversibility and eosinophilia greater than 10%. There were no migratory pulmonary infiltrates on serial imaging, an ENT review reported no paranasal abnormalities and the patient reported no neuropathic pain. A tissue sample would have required a cardiac biopsy which was deemed too high risk. It must be noted that this case might be an exception. The ACR criteria have a specificity of 99.7% and a sensitivity of 85% for the condition.

An arguably better aid to diagnosis has been the division of eosinophilic granulomatosis with polyangiitis into three phases: a prodromal phase where allergic rhinitis, asthma, weight loss and flu-like symptoms predominate; an eosinophilic infiltrative phase and finally the vasculitic phase. The patient described here clearly transits through phases over a matter of weeks; however, others take decades for this progression.

Cardiac involvement in allergic granulomatosis is relatively well described and is considered to be a poor prognostic feature.⁴ However, arrhythmia as a presenting feature is relatively rare.⁵ Indeed, the incidence of cardiac involvement in allergic granulomatosis was estimated at only 17% alone when using ECG and so cMRI remains the imaging modality of choice.⁶ Rothenberg proposes eosinophilic infiltration and

release of cytotoxic inflammatory mediators as the cause for myocyte destruction and the subsequent generation of arrhythmias.⁷ Others suggest more permanent replacement of the myocardium with granulomas and scar tissue.⁸ The cMRI in this case described myocarditis suggesting that inflammation alone may have been responsible for causing focal myocyte inflammation and aberrant electrical pathways within the heart. This proposition is consistent with the restoration of normal electrical conduction after the initiation of high-dose steroids.

This case highlights the importance of a prompt diagnosis and initiation of high-dose immunosuppressive therapy so as to avoid more permanent myocardial scarring, fatal arrhythmias and sudden cardiac death. Earlier assessment of the peripheral eosinophil count may have expedited the diagnosis and management, as few conditions cause an eosinophil count of greater than $1 \times 10^9/L$.

Learning points

- Eosinophilic granulomatosis with polyangiitis is a diffuse vasculitis where no one presentation is diagnostic.
- Arrhythmia may be an initial presenting feature of the syndrome as this case report highlights.
- The perinuclear antinuclear cytoplasmic antibody may not always be positive.
- Rapid correction of eosinophilia, leucocytosis and sedimentation rate occur with early initiation of high-dose steroids.
- Early initiation of immunosuppressants can prevent permanent end-organ damage and help improve patient prognosis.⁹

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