CASE REPORT

ANCA-negative eosinophilic granulomatosis with polyangitis (EGPA) manifesting as a large intracardiac thrombus and glomerulonephritis with angionecrosis

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SUMMARY

A 59-year-old woman with a history of bronchial asthma presented with a prolonged fever and eosinophilia. There was transient proteinuria and troponin level was elevated. Antineutrophil cytoplasmic antibody was negative and she did not fulfil criteria for eosinophilic granulomatosis with polyangitis (EGPA).

Echocardiography showed a large apical mass in the left ventricle, but there was no systolic dysfunction, local asynergy or ventricular remodelling. On MRI, apical mass was compatible with a thrombus and endocardial region was diffusely damaged. Loeffler endocarditis-like cardiac manifestation led to meticulous examination, which found no aetiology for eosinophilia. Finally, renal biopsy revealed eosinophil infiltration and glomerular angionecrosis, confirming as EGPA. This case highlights the isolated large cardiac thrombus as a rare presenting sign for EGPA and underscores current complicated strategy to diagnose EGPA. Of note, this clinical challenge was mostly caused by inchoate comprehension of hypereosinophilia-related disorders.

BACKGROUND

Eosinophilic granulomatosis with polyangitis (EGPA) and hypereosinophilic syndrome (HES) are known to induce hypereosinophilia and organ injuries. Diagnosis of EGPA is usually straightforward when the patient has antineutrophil cytoplasmic antibody (ANCA) or shows typical clinical features as defined by American College of Rheumatology.¹ However, in cases with negative ANCA or atypical clinical characteristics, diagnosis of EGPA is often indeterminate without histological proof. Consequently, diagnosis of HES is also indeterminate because exclusion of other possible disorders is a prerequisite for HES.²

We experienced a rare case with ANCA-negative EGPA who presented with a large intracardiac thrombus without cardiac dysfunction or remodelling, which was typical cardiac form of HES.

CASE PRESENTATION

A 59-year-old woman presented with a 4-week history of prolonged fever. She had a 25-year history of bronchial asthma and took 10 mg of montelukast and 320 µg of budesonide daily, but did not have any documented allergies, additions or premorbidities. On examination, she was febrile (37.5°C), blood pressure was 117/74 mm Hg and

pulse was 94 bpm. She had no tachypnoea or hypoxia. Paranasal sinus, cardiac, chest, abdominal, skin and neurological examination were normal.

INVESTIGATIONS

Chest radiograph was normal, whereas electrocardiogram showed T-wave inversion in the lateral and inferior leads. White cell count was 12 000/µL with an eosinophilia of 3600/µL (norm, <450/µL). Haemoglobin was 13.7 g/dL, and platelet count was 141×10⁹/L. C reactive protein was raised at 3.2 mg/dL (norm, <0.3 mg/dL), and troponin-I was 1.88 µg/L (norm, <0.04 µg/L). Creatinine was 70.8 µmol/L. Urinalysis was positive for blood and protein, and 24-hour urine protein was 0.4 g (norm, <0.15 g). Echocardiography showed preserved left ventricular ejection fraction of 67%, with a large soft isoechoic structure suggestive of left ventricular mural thrombus (figure 1). T2-weighted cardiac MRI demonstrated diffuse endocardial enhancement and a large apical thrombus (figure 2A). Endocardium also showed late gadolinium enhancement (figure 2B). Chest CT only revealed mild pericardial effusion with clear lung fields. She had negative antinuclear antibody, anti-double-strand DNA antibodies, MPO-ANCA and PR3-ANCA. Peripheral nerve conduction study was normal.

DIFFERENTIAL DIAGNOSIS

Paucity of findings suggestive of EGPA made us suspect cardiac involvement of HES in a thrombotic stage. Examinations to identify the cause of hypereosinophilia were subsequently performed. However, she took no potentially hazardous agent, including herbal compounds and nutritional supplements. She had negative test for stool blood and parasites, anti-aspergillus antibodies, interferon-γ assay for tuberculosis, hepatitis and HIV serology, and *FIP1L1/PDGFRA* fusion gene. Abdomen–pelvis CT showed no splenomegaly, lymphadenopathy or abnormal mass. Neither of her peripheral blood smear nor bone marrow showed dysplastic eosinophils or blasts. In renal biopsy, there were 10 glomeruli, of which one showed angionecrosis, another crescent formation. The biopsy also revealed subcapsular infiltration of eosinophils (figure 3). Accordingly, she was diagnosed as EGPA according to Lanham criteria.³

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Figure 1 A transthoracic echocardiogram showing a large intracardiac mass. (A) Apical four-chamber view. (B) Apical two-chamber view.

TREATMENT

Treatment with oral glucocorticoid 40 mg daily (1 mg/kg body weight) was initiated and intravenous cyclophosphamide 500 mg daily was added twice. In accordance with guidelines, the patient was anticoagulated with oral warfarin.⁴ In response to the therapy, her eosinophil count rapidly fell to the normal value and the intramural thrombus began to shrink. After 1-month therapy, oral glucocorticoid was tapered to 30 mg. She was discharged and continued the therapy as an outpatient.

OUTCOME AND FOLLOW-UP

Eight months later, she was still free of relapse with normal eosinophil count, whereas shrunk thrombus became organised to be left in the ventricle (figure 4).

DISCUSSION

EGPA is a rare systemic vasculitis characterised as the presence of blood and tissue eosinophilia, bronchial asthma or other allergic condition, and multiorgan involvement either through vasculitis or through eosinophil infiltration. Lung, peripheral

neuron, skin and kidney are often involved. ANCA often accompanies with this disease and supposed to have a pathophysiological role, although its prevalence was around 40%.

In patients with EGPA, a large thrombus was mostly associated with cardiac dysfunction and ventricular remodelling.^{5–10} The presence of a large thrombus without ventricular remodelling is rare, but the present case showed that an intramural thrombus alone can be indicative of EGPA. In addition, subendocardial inflammation and fibrosis as indicated by MRI was consistent with a thrombotic to fibrotic stage of HES.¹¹ These clinical findings apparently lead to misdirected initial diagnosis as HES.

Furthermore, clear discrimination between EGPA and HES is inherently difficult. It was due to the continuing confusions regarding the taxonomy of EGPA and HES, and the surrogate use of the classification criteria instead of diagnostic one. Consequently, patients with indecisive diagnosis of EGPA could also be diagnosed as HES by original definition, or even unclassified by the most updated consensus statement involving multidisciplinary experts.² Another problem was that only positive

Figure 2 Cardiac MRI in long-axis planes. (A) A T2-weighted image showing diffuse enhancement in the subendocardial region of left ventricle and a large thrombus as a non-enhanced apical mass (*). (B) A contrast-enhanced image showing late gadolinium enhancement in the same subendocardial region as T2-weighted image.

Figure 3 Light microscopic images of the kidney showing subcapsular infiltration of eosinophils (white arrow), glomerular crescent formation (black arrow) and angionecrosis (arrowhead).

ANCA was helpful. This ANCA-negative case did not fulfil American College of Rheumatology classification criteria for EGPA, and accordingly required meticulous work-up not only for determining EGPA but also for omitting other causes of hypereosinophilia. In the end, invasive biopsy of the kidney was needed to confirm EGPA.¹² To reorder this complicated diagnostic process, the worldwide study to establish diagnostic and classification criteria for vasculitis is now under way.¹³

This case also indicates still unknown disease mechanisms regarding EGPA, because ANCA-mediated disease pathophysiology was not applicable to the patient. Preclinical researches showed causality between ANCA and necrotizing vasculitis, and clinical studies have demonstrated significant differences in susceptible organs and mode of injury between ANCA-positive and ANCA-negative patients with EGPA: vasculitic injury such as glomerulonephritis was predominant in positive ANCA, whereas eosinophilic injury such as myocarditis was frequent in negative ANCA. Renal involvement was particularly characteristic to positive ANCA, where 75% of any renal disease and

100% of histologically proven necrotizing glomerulonephritis had positive ANCA.^{14–16} A nationwide survey in Japan, as well as multicentre observational studies across countries, consistently reported significantly higher prevalence of renal disease and lower prevalence of cardiac disease in ANCA-positive patients (OR, 95% CI—renal: 1.8, 1.3 to 2.5; cardiac: 0.6, 0.3 to 1.0).^{17–18} This case was accompanied by glomerulonephritis with angionecrosis and crescent formation, which rarely appears in ANCA-negative EGPA patients.

In the present case, contribution of montelukast to the onset of EGPA is unclear. There is a possible causal relationship between EGPA and leukotriene receptor antagonists (LRA), including montelukast.¹⁹ However, the causal association remains to be elucidated. Glucocorticoid-tapering effect conferred by LRA might mediate the apparent causality by unblinding the vasculitic component of EGPA.²⁰ Further prospective studies are needed to address this issue; however, currently, its use is considered non-hazardous.^{12–16}

This case highlights the isolated large cardiac thrombus as a rare presenting sign for EGPA and underscores current complicated strategy to diagnose EGPA caused by inchoate comprehension of hypereosinophilia-related disorders.

Learning points

- ▶ Cardiac manifestation of eosinophilic granulomatosis with polyangitis (EGPA) can mimic as thrombotic to fibrotic stage of hypereosinophilic syndrome (HES).
- ▶ A large cardiac thrombus without cardiac dysfunction or ventricular remodelling is rare in EGPA.
- ▶ Discrimination between antineutrophil cytoplasmic antibody (ANCA)-negative EGPA and HES is often difficult because of the continuing confusions regarding the taxonomy of EGPA and HES.
- ▶ ANCA-negative EGPA can present with histologically proven glomerulonephritis that was known to be highly specific to positive ANCA.

Figure 4 A transthoracic echocardiogram showing a regressed cardiac mass. (A) Apical four-chamber view. (B) Apical two-chamber view.

Competing interests None declared.

Patient consent Obtained.

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