

# Immunosuppressive therapy ameliorates refractory vasospastic angina, severe pulmonary hypertension, and bronchiolitis in a patient with eosinophilic granulomatosis with polyangiitis: a case report

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Received 21 December 2017; accepted 27 March 2018; online publish-ahead-of-print 25 April 2018

## Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by tissue and blood eosinophilia, vasculitis of small to medium-sized vessels, and allergy symptoms, and can cause various manifestations, including heart, lung, gastrointestinal, skin, and peripheral nerve disorders.

## Case presentation

A 34-year-old woman with a history of asthma, nasal polyp, and sinusitis presented with ventricular fibrillation after severe chest pain. Emergent coronary angiography showed no coronary stenosis. After admission, she suffered from hypoxaemia and recurrent chest pain with ST-segment changes, suggesting vasospastic angina (VSA). Chest computed tomography (CT) showed centrilobular nodular shadows, suggesting bronchiolitis. Since she had hyper-eosinophilia, we administered oral prednisolone, which resulted in improvements of hypereosinophilia, hypoxaemia, and recurrent chest pains in 3 days. Right heart catheterization showed severe pulmonary hypertension (PH) with a mean pulmonary artery pressure (mPAP) of 48 mmHg and pulmonary vascular resistance (PVR) of 12 Wood units (WU). Ergonovine provocation test induced severe diffuse spasm of the left coronary artery including the left main trunk. Based on asthma, sinusitis, hypereosinophilia, and chest CT findings, the diagnosis of EGPA associated with VSA and PH was made. Thereafter, we started intravenous cyclophosphamide (IV-CY) pulse therapy in addition to prednisolone and pulmonary vasodilators. Six months after IV-CY therapy, mPAP and PVR decreased to 34 mmHg and 5.1 WU, respectively. Moreover, repeated ergonovine provocation test was negative without coronary spasm or electrocardiogram (ECG) changes.

## Discussion

This case indicates that EGPA can cause severe PH, refractory VSA, and bronchiolitis, which could be markedly improved by treating underlying conditions with immunosuppressive therapy.

## Keywords

Vasospastic angina • Ventricular fibrillation • Pulmonary hypertension • Eosinophilic granulomatosis with polyangiitis • Immunosuppressive therapy • Case report

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## Learning points

- Eosinophilic granulomatosis with polyangiitis (EGPA) can cause various life-threatening cardiac diseases including vasospastic angina and pulmonary hypertension, and is not ruled out by anti-neutrophil cytoplasmic antibody negativity in the patients with heart involvement of hypereosinophilia.
- Immunosuppressive therapy is needed for cardiac involvement in EGPA.

## Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg–Strauss syndrome, is characterized by anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, tissue and blood eosinophilia, vasculitis of small to medium-sized vessels, and allergy symptoms, such as asthma and allergic rhinitis.<sup>1</sup> Eosinophilic granulomatosis with polyangiitis can cause various organ manifestations including lung, heart, gastrointestinal, skin, and peripheral nerve disorders,<sup>2</sup> which makes patients more complicated. Among these, cardiovascular involvement is thought to be of most importance.<sup>1,2</sup> In 1951, Churg and Strauss<sup>3</sup> reported that cardiac involvement was observed in 64% of autopsied cases. Since cardiac symptoms were associated with higher 5-year mortality in the patients with EGPA, the five factor score (FFS) has been developed to assess the prognosis of ANCA-associated vasculitis.<sup>4</sup> Indeed, patients with EGPA can present with coronary vasculitis, myocarditis, pericarditis, and arrhythmias.<sup>5</sup>

We here report the first case of EGPA complicated by refractory vasospastic angina (VSA), severe pulmonary hypertension (PH), and serious hypoxaemia caused by hypereosinophilic obliterative bronchiolitis (HOB), which were all markedly improved in response to immunosuppressive therapy.

## Timeline

## Case presentation

A 34-year-old woman with a smoking history but no family history of cardiovascular disease presented with severe chest pain and developed ventricular fibrillation (VF). She had a history of asthma, nasal polyp, and sinusitis. After cardiopulmonary resuscitation, she was transported to a general hospital. Her consciousness and vital signs were normal. Her cardiac enzyme levels were elevated; creatine kinase MB level of 7.1 ng/mL (normal range <5.0 ng/mL) and a troponin I level of 0.23 ng/mL (normal range <0.028 ng/mL). Electrocardiogram (ECG) showed right ventricular hypertrophy (RVH) without ischaemic abnormality. Echocardiography revealed preserved left ventricular function, right ventricular (RV) dilatation, tricuspid regurgitation with peak gradient of 61 mmHg, and RV fractional area change (FAC) of 16.5%. Acute coronary syndrome, pulmonary embolism (PE), and aortic dissection which were emergency diseases had to be ruled out because of her severe chest pain and RV overload. Emergent contrast-enhanced computed tomography (CT) revealed no PE or aortic dissection. Urgent catheterization showed no coronary stenosis and mean pulmonary artery pressure (mPAP) of 66 mmHg, indicating severe PH. After admission, she suffered from recurrent chest pains, even under treatment with multiple vasodilator drugs, such as benidipine, nicorandil, and nitrates. During the chest pain episodes, ECG showed ST-segment elevation (I, aVL), large T-wave (V3–V6), and ST-segment depression (II, III, and aVF), which were highly suggestive of VSA attacks. She also developed severe hypoxaemia with SpO<sub>2</sub> of 92% despite O<sub>2</sub> administration at 10 L/min by reservoir mask, for which 2-weeks of inhaled corticosteroid therapy was ineffective. She was transferred to our hospital for further treatment of PH, suspected VSA, and severe hypoxaemia.

On admission, she had no fever, infection symptoms, skin eruptions, lymphadenopathy, splenomegaly, or abnormal neurological findings. Her lung sounds were normal, but she had an accentuated second heart sound. Her troponin T level was elevated (0.244 ng/mL, normal range <0.1 ng/mL). She had sputum eosinophilia, and a differential blood count showed hypereosinophilia of  $2.0 \times 10^9/L$  (normal range  $<0.9 \times 10^9/L$ ), accounting for 17% of total leukocytes (normal

Day	Events
1	The patient presented with severe chest pain and developed ventricular fibrillation, severe hypoxaemia, and hypereosinophilia. Mean pulmonary artery pressure was 66 mmHg.
2	The patient suffered from recurrent chest pains.
7	The patient was transferred to our hospital. Pulmonary vascular resistance was 12 Wood units (WU).
17	We administered oral prednisolone for treatment of hypereosinophilia.
20	Hypereosinophilia, severe hypoxaemia, and recurrent chest pains resolved.
38	Pulmonary vascular resistance was 11.5 WU. We started oral pulmonary vasodilators. Ergonovine provocation test induced severe diffuse coronary spasm of the left coronary artery.
46	We started intravenous cyclophosphamide pulse therapy.
73	Pulmonary vascular resistance was 5.7 WU, indicating the improvement of pulmonary hypertension.
87	The patient was discharged.
87 + 6 months	Ergonovine provocation test induced no coronary artery spasm.

range <10%). Serum electrolytes and blood glucose levels were normal. Anti-neutrophil cytoplasmic antibody test and specific IgE testing for aspergillus were negative twice. Neither interstitial deletion of chromosome 4q12 nor peripheral blood blast cells was noted. Stool ova or parasites were also negative. Chest CT showed centrilobular nodular shadows, and  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET) showed diffuse abnormal accumulation in the lungs (Figure 1A). In right heart catheterization (RHC), mPAP, and pulmonary vascular resistance (PVR) were 48 mmHg and 12 Wood units (WU), respectively.

For treatment of severe hypoxaemia associated with eosinophilia, we administered oral prednisolone (50 mg/day). Thereafter, her hypereosinophilia, severe hypoxaemia, and recurrent chest pains promptly resolved after initiation of prednisolone. Moreover, echocardiography showed decreased RV dilatation and RVFAC improved to 26%. Three weeks later, ECG signs of RVH disappeared, and we repeated RHC, which showed that her PH was not improved enough (mPAP 37 mmHg). Furthermore, ergonovine provocation test induced severe diffuse coronary spasm of the left coronary artery involving the left main trunk (Figure 2A and 2B), associated with ST-segment depression in leads V1 and V2. Endomyocardial biopsy showed no eosinophilic infiltration. Cardiac magnetic resonance imaging revealed no late gadolinium enhancement. We finally diagnosed that she had EGPA based on her asthma, sinusitis, hypereosinophilia, and chest CT findings.<sup>6</sup> Vasospastic angina and PH were thought to be cardiovascular complications of EGPA (FFS of 1). Thus, we intensified immunosuppressive therapy for EGPA with intravenous cyclophosphamide (IV-CY) pulse therapy (500 mg each month) in addition to prednisolone and oral pulmonary vasodilators.

Six months after discharge, she had no cardiopulmonary symptoms, indicating FFS of 0. The abnormal accumulation of FDG-PET in the lungs had disappeared (Figure 1B). Repeated RHC showed that mPAP and PVR were decreased to 34 mmHg and 5.1 WU, respectively. Her troponin T level was normalized (0.007 ng/mL). Neither coronary artery spasm nor ECG changes were induced by ergonovine provocation test (Figure 2C and 2D).

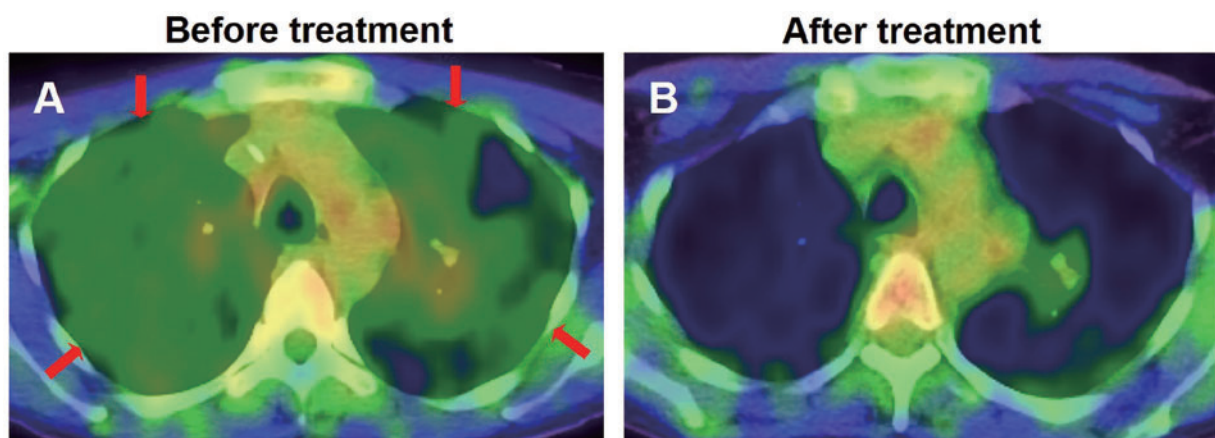
## Discussion

This patient presented with a diverse constellation of symptoms, including chest pain followed by cardiopulmonary arrest due to VF caused by refractory VSA, severe PH, and hypoxaemia. This made her diagnosis very challenging. However, we assumed that there was the same underlying disease for her diseases because each symptom is life-threatening and rarely occurs simultaneously. In this case, the diagnosis of EGPA was finally made based on her medical history, hypereosinophilia, and chest CT findings.<sup>6</sup> We believe that EGPA can explain her complex life-threatening cardiopulmonary conditions.

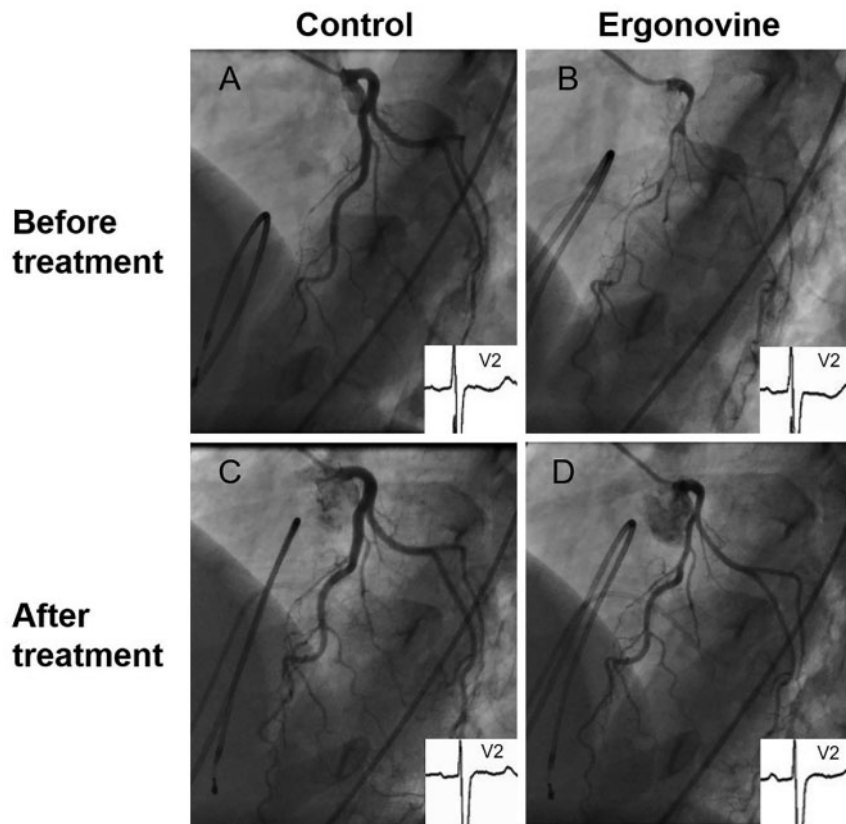
Interestingly, her ANCA test was negative. The previous study suggested that ANCA-negative EGPA is associated with a higher frequency of heart and lung involvement than ANCA-positive phenotype,<sup>7</sup> which was also the case in our patient. This finding suggests that cardiologists may treat patients with ANCA-negative EGPA more frequently than ANCA-positive phenotype and thus should recognize that EGPA is not ruled out by negative ANCA alone.

Previous cases with EGPA complicated by VSA showed that coronary spasm was resistant to vasodilators but was highly responsive to immunosuppressive therapy, as in our case.<sup>8–10</sup> We observed disappearance of coronary artery spasm in the second ergonovine provocation test after the IV-CY therapy. Although the exact mechanism of this improvement is unclear, it is conceivable that local eosinophilic inflammation in the coronary arterial wall could induce coronary artery spasm. Importantly, the immunosuppressive therapy with IV-CY was effective for her refractory VSA, probably by suppressing EGPA-related coronary vasculitis.

Inflammation of the pulmonary artery is one of the important stimuli to cause PH.<sup>11</sup> In schistosomiasis, eosinophilic inflammation, induced by the immune response to parasite eggs, is a primary factor for the development of PH.<sup>12</sup> Moreover, it also has been reported that eosinophilic inflammation could cause pulmonary vascular remodelling in mice.<sup>13</sup> In our case, eosinophilic inflammation may have contributed to the development of pulmonary vascular



**Figure 1**  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography in the lungs.  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography images before (A) and after (B) immunosuppressive therapy, showing marked improvement in response to the therapy (red arrows).



**Figure 2** Ergonovine provocation test of coronary artery spasm. Coronary angiograms during ergonovine provocation test before (A, B) and after (C, D) immunosuppressive therapy, showing marked improvement of coronary vasospastic activity in response to the therapy (see [Supplementary material](#) online).

remodelling. Her severe PH was markedly improved in response to additional IV-CY pulse therapy on the top of pulmonary vasodilators and prednisolone. It is conceivable that severe pulmonary artery remodelling might have already occurred before her presentation and that additional IV-CY pulse therapy was necessary in order to improve her PH.

In our case, it was possible that EGPA and HOB co-existed. Hypereosinophilic obliterative bronchiolitis is a new characterized syndrome by eosinophilia, ineffectiveness of inhaled corticosteroid therapy, and CT features of bronchiolitis, as shown in our case.<sup>14</sup> Computed tomography features of EGPA, such as centrilobular nodules and bronchial wall thickening, are found in patients with HOB.<sup>14</sup> Moreover, a case of HOB was reported to be diagnosed with lung-limited EGPA based on the pathological features of EGPA.<sup>14</sup> Increasing recognition of HOB may increase the chance to identify HOB in patients with EGPA.

## Conclusion

To the best of our knowledge, this is the first case of EGPA presented with VF complicated by refractory VSA, severe PH, and HOB, all of which were markedly improved by the immunosuppressive therapy.

Eosinophilic granulomatosis with polyangiitis can cause various life-threatening diseases concomitantly. Thus, accurate diagnosis and prompt immunosuppressive therapy are needed for this complicated disorder.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

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