



Case report

Refractory diffuse alveolar hemorrhage caused by eosinophilic granulomatosis with polyangiitis in the absence of elevated biomarkers treated successfully by rituximab and mepolizumab: A case report

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ABSTRACT

Here we report on a 61-year-old man with refractory eosinophilic granulomatosis with polyangiitis (EGPA) who presented with dyspnea. Despite treatment with glucocorticoids, intravenous cyclophosphamide, and plasma exchange, his symptoms worsened despite his eosinophil count and myeloperoxidase antineutrophil cytoplasmic antibody titer trending downwards. EGPA with diffuse alveolar hemorrhage was diagnosed on analysis of bronchoalveolar lavage fluid. The patient was treated with rituximab and methylprednisolone pulse therapy and a remission was achieved. He has been receiving mepolizumab since then and remains in remission. It should be recognized that refractory diffuse alveolar hemorrhage can occur in patients with EGPA without elevation of biomarkers if they are receiving systemic corticosteroids.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a multi-system disorder caused by vasculitis of the small and medium arteries. The pathogenesis of the EGPA is unknown. The disease is characterized by chronic rhinosinusitis, asthma, and eosinophilia, and can affect any organ system, including the lungs, skin, and nerves [1]. Diffuse alveolar hemorrhage (DAH) is a critical condition characterized by bleeding into the alveolar spaces of the lungs and is a rare complication of EGPA. Glucocorticoids are the mainstay of treatment for EGPA [2,3]. An immunosuppressive agent, typically cyclophosphamide, is used for more advanced or refractory cases. Recently, rituximab, an anti-CD20 monoclonal antibody targeted against B-cells, was reported to be an effective induction therapy for EGPA and can be considered in patients whose disease is refractory to cyclophosphamide [4]. Mepolizumab, an anti-IL-5 monoclonal antibody, is an option for maintenance therapy in patients with EGPA [5]. There has been a case report of effective use of mepolizumab in a patient with EGPA that manifested as refractory asthma, eosinophilia, neurologic impairment, and pulmonary infiltration [6]. (see Fig. 1)

The activity of EGPA is monitored by symptoms and laboratory investigations. The eosinophil count and myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) level can be biomarkers of the underlying disease process [7]. Administration of corticosteroids

decreases eosinophilic inflammation, which can decrease the eosinophil count and MPO-ANCA level even when disease activity is present [8].

Here, we report our experience of a patient with cyclophosphamide-resistant DAH caused by EGPA without elevation of biomarkers, such as eosinophils or MPO-ANCA, in whom induction therapy with rituximab followed by maintenance therapy with mepolizumab was successful.

2. Case report

A 61-year-old man was transferred to the emergency department at Kameda Medical Center complaining of dyspnea. Eighteen years previously, he had been diagnosed with asthma at another hospital. Fourteen years earlier he had developed fever, rash, pinprick sensation in both legs, and eosinophilia. Although a serum test for MPO-ANCA at that time was negative, EGPA was suspected on clinical grounds and he was treated with oral prednisone 60 mg/day. He showed an immediate response to treatment, so the oral prednisone was gradually tapered to 5 mg/day. Six years earlier, he had developed chronic wheezing and cough, and was referred to our clinic at Kameda Medical Center. At that time, his eosinophil count and MPO-ANCA titer were high. We diagnosed EGPA on the basis of his symptoms and increased the dose of oral prednisone. His eosinophil count and MPO-ANCA titer trended downward but his symptoms continued to worsen. He developed wheezing, cough, purpura on the extensor surfaces of the right arm and left elbow,

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Abbreviations list

BALF	bronchoalveolar lavage fluid
DAH	Diffuse alveolar hemorrhage
EGPA	eosinophilic granulomatosis with polyangiitis
MPO-ANCA	myeloperoxidase antineutrophil cytoplasmic antibody

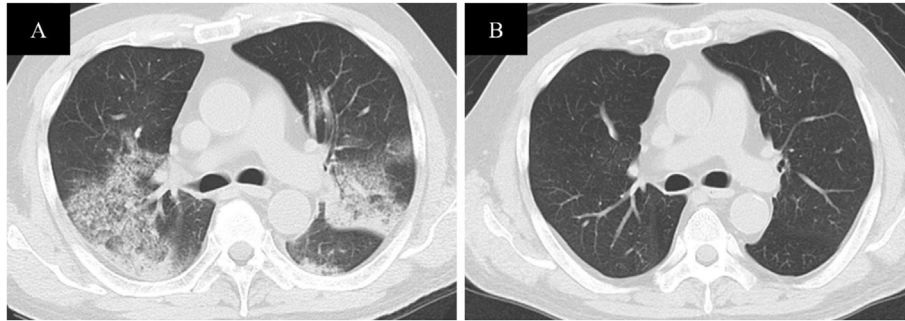


Fig. 1. (A) Computed tomography of the chest reveals bilateral consolidation. (B) Significant radiologic improvement was observed after rituximab induction therapy.

pinprick sensation in both arms and both legs, hearing impairment, and sinusitis. Magnetic resonance imaging of the brain revealed multiple cerebral infarcts. Intravenous glucocorticoid pulse therapy and intravenous cyclophosphamide were started. Despite frequent administration of both treatments, one year prior to the current admission he was diagnosed with DAH based on findings in bronchoalveolar lavage fluid (BALF). The DAH relapsed despite addition of plasma exchange to his treatment regimen. Before the present admission, the total dose of intravenous cyclophosphamide was 12.8 g and the total number of plasma exchanges was 7. The patient then developed dyspnea and was transferred to our hospital on the same day. He denied bloody sputum, palpitations, or chest pain. His medical history included diabetes mellitus, thalamic and left putamen hemorrhage, and right caudate infarction. He was taking oral prednisone at a dose of 55 mg/day, aspirin, and trimethoprim-sulfamethoxazole, and was administering subcutaneous insulin. He had smoked 1–2 packs of cigarettes daily for 30 years and had quit smoking 15 years earlier. He was employed as an office worker.

On physical examination, the patient was alert and oriented. He had a blood pressure of 123/78 mmHg, a pulse rate of 108 beats/minute, a respiratory rate of 25 per minute, an oxygen saturation of 99% on 10 L/minute of oxygen via a nasal cannula, and a temperature of 37.8 °C. On chest auscultation, fine crackles were detected in the lung fields bilaterally. Fissured hyperkeratotic lesions were observed on the palmar surfaces of all fingers on both hands. The pinprick sensation persisted in both legs, but no other neurologic abnormality was found. Laboratory findings revealed only mild inflammation. The peripheral white blood cell count was 40,000 cells/ μ L with 95% neutrophils. The blood eosinophil count was almost zero. A peripheral blood smear did not reveal any circulating blast cells. Serum MPO-ANCA levels had been negative in the previous two years. Tests for anti-nuclear antibody, proteinase 3-antineutrophil cytoplasmic antibody, and anti-glomerular basement membrane antibody were negative. The lactate dehydrogenase level was 330 U/L, the C-reactive protein level was 3.2 mg/dL, and tests for β -D glucan and galactomannan were negative. Urinalysis revealed no proteinuria or hematuria. High-resolution computed tomography showed alveolar consolidation spreading to both lower lobes. Bronchoalveolar lavage was performed using a high-flow nasal cannula; the fluid returned became progressively more bloody in appearance. Analysis of BALF revealed the following: total cells, 2,100,000; neutrophils, 90%; lymphocytes, 0%; eosinophils, 0%; and alveolar

macrophages, 10%. The results of the BALF analysis were the same as those noted on previous DAH tests. BALF cytology with Prussian blue demonstrated siderophages (hemosiderin-containing macrophages). A BALF culture showed group alpha and gamma streptococci phagocytosed by neutrophils. Cytology of the BALF did not reveal any malignant cells. There was no indication of involvement of the myocardium on an echocardiogram. Nerve conduction studies were performed twice, but did not show any abnormalities. A skin biopsy at the left elbow

showed leukocytoclastic vasculitis. A biopsy performed at the left inferior nasal concha revealed eosinophilic infiltration.

After hospitalization, based on the BALF analysis and Gram stain results, we suspected DAH caused by EGPA and complicated by gram-positive bacterial pneumonia. Rituximab 600 mg once weekly for four weeks was used as induction therapy for the refractory DAH. Following the steroid taper, we administered pulse treatments of methylprednisolone 1 g intravenously for three successive days. We also administered linezolid to cover gram-positive bacteria and tazobactam/piperacillin and azithromycin to cover a broad range of other bacteria. On hospital day 6, his oxygen saturation recovered to 95% without oxygen inhalation therapy. His radiologic findings improved gradually and he was discharged on hospital day 11. He achieved a remission, and mepolizumab 100 mg once a month was started for maintenance therapy. He has remained in remission ever since. We arrived at a final diagnosis of EGPA with DAH complicated by bacterial pneumonia caused by alpha and gamma streptococci.

3. Discussion

We have shown that EGPA can cause refractory DAH and that steroids can modify the clinical presentation of EGPA. The clinical course in this patient provides two important clinical learning points.

First, we need to recognize that refractory DAH can occur in patients with EGPA. Generally, DAH is recognized to be less common in EGPA than in microscopic polyangiitis and granulomatosis with polyangiitis [9]. There are no published case reports of refractory DAH caused by EGPA. We diagnosed DAH in our patient based on imaging studies, the results of bronchoscopy, and the behavior of the disease. The patient has been in remission since his treatment for refractory EGPA. We used rituximab for induction therapy because it works via a mechanism that is different from that of cyclophosphamide [10]. After achieving a remission, we used mepolizumab for maintenance therapy. The dose of mepolizumab used in our patient was not as high as that used in a previously reported case [5]. In our country, mepolizumab is only approved in the indication of severe asthma, so we needed to use it at a dose of 100 mg once per month. There have been no signs of recurrence since the patient was discharged from hospital.

Second, the clinical manifestations can change as a result of steroid use. Steroids have been reported to play a role in inducing apoptosis of eosinophils [8]. Biomarkers such as the blood eosinophil count, number

of eosinophils in BALF, and MPO-ANCA titers are unreliable in patients on high doses of steroids. In general, relapses are common in EGPA and are often accompanied by blood eosinophilia and increased ANCA titers [11]. However, in our patient, the blood eosinophil counts were normal before the most recent relapse, so it was difficult to interpret the disease activity. In this case, culture of BALF revealed alpha and gamma streptococci phagocytosed by neutrophils, and bacterial pneumonia was also suspected. Every time bronchioalveolar lavage had been performed in this patient, the BALF analysis showed that the DAH was neutrophil-dominant without bacterial infection. On presentation to our department, the BALF cultures again did not reveal any other bacteria or malignant cells. Interestingly, our BALF cytology and manual cell counting showed that the DAH was eosinophil-dominant, which suggests that automated cell counting in BALF could be inappropriate in this patient. Moreover, in retrospect, mepolizumab was useful for controlling the activity of the disease. These results indicate that this patient's DAH was caused by relapse of EGPA.

In conclusion, we have successfully used rituximab and mepolizumab to treat a patient with an atypical presentation of cyclophosphamide-refractory DAH caused by EGPA. We need to recognize that refractory DAH can occur in a patient with EGPA without elevation of biomarkers if they are receiving high-dose systemic corticosteroids.

Declarations of interest

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