Diffuse Alveolar Hemorrhage Developing Immediately after Immunosuppressive Treatments in a Patient with Granulomatosis with Polyangiitis who had Pulmonary Nodules

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Abstract:
A 65-year-old man was diagnosed with granulomatosis with polyangiitis (GPA) based on the detection of high MPO-ANCA, vasculitis and granulomas in a lung biopsy specimen and crescentic glomerulonephritis in a kidney biopsy specimen. Soon after the initiation of intravenous methylprednisolone pulse therapy (mPSL pulse) and intravenous cyclophosphamide pulse therapy (IVCY), the patient experienced cough and hemoptysis. Based on emerging anemia and bilateral diffuse lung consolidation on computed tomography, we judged that diffuse alveolar hemorrhage (DAH) was complicated by GPA. The patient's DAH improved following additional mPSL pulse and IVCY. Physicians should be aware of the possible occurrence of DAH, even when a patient’s symptoms improve after mPSL pulse and IVCY.

Key words: diffuse alveolar hemorrhage, granulomatosis with polyangiitis, intravenous pulse methylprednisolone, intravenous cyclophosphamide pulse therapy, ANCA associated vasculitis


Introduction
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a form of necrotizing vasculitis, with few or no immune deposits, that predominantly affects the small vessels associated with ANCA (1); however, its etiology remains unknown. Granulomatosis with polyangiitis (GPA) is a form of AAV that affects the airways, lungs, kidneys, skin, eyes and nervous system (2). Diffuse alveolar hemorrhage (DAH) is a lung manifestation that appears in 10% of GPA cases (3). DAH is a catastrophic clinical syndrome that causing hypoxemic respiratory failure and which is histopathologically characterized by pulmonary capillaritis and clinically characterized by diffuse radiographic pulmonary infiltration, hemoptysis, and anemia (4). In AAV, in particular, DAH is often associated with kidney disease (5). The poor prognosis of DAH associated with kidney disease, including AAV, which has a one-year survival rate of only 50%, has previously been reported (6). However, a study on DAH with small vessel vasculitis, which had a short follow-up period, revealed that treatment with plasma exchange can achieve a survival rate of 95% (7). We present a characteristic case of GPA that was complicated by DAH soon after the administration of methylprednisolone pulse therapy and cyclophosphamide pulse therapy.

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Case Report

A 65-year-old man was admitted to our hospital with a fever of one month in duration. The patient’s appetite declined and hyperemia of the bilateral conjunctiva and pitting edema in the bilateral legs appeared. His past medical history included angina pectoris, hypertension, and dyslipidemia, which were treated with aspirin, telmisartan, and pitavastatin. He had smoked 40 cigarettes a day for 45 years (from 20 to 64 years of age).

On physical examination, the patient’s body temperature was 38.0°C. His bilateral conjunctiva showed hyperemia. Auscultation of the chest showed no abnormal findings. Pitting edema were observed in the bilateral legs. There were no signs or symptoms suggesting involvement of the ears, nose, and throat (ENT). He had no skin eruptions. The laboratory data were as follows: white blood cell (WBC) count, 10,300/μL; hemoglobin, 11.3 g/dL; platelets, 407,000/μL; C-reactive protein (CRP), 8.29 mg/dL; serum creatinine (Cr), 1.79 mg/dL; antinuclear antibody, 40 IU/mL (normal range: <15 IU/mL); KL-6, 200 U/mL; and a high myeloperoxidase (MPO)-ANCA level of 81.7 enzyme-linked immunosorbent assay (ELISA) units (EU)/ml (normal range: <12 EU/ml). Proteinase 3 (PR3)-ANCA was negative. A urinalysis revealed microscopic hematuria (31-50 red blood cells/high-power field), proteinuria (0.32 g/g Cr) and erythrocyte casts. Chest computed tomography (CT) showed multiple pulmonary nodules in the bilateral lung fields and partial interstitial reticular markings in the lingular segment (Fig. 1A, B). Bronchoalveolar lavage demonstrated no erythrocytes suggesting DAH. Lung biopsy specimens showed vasculitis with vessel destruction (Fig. 2A) and noncaseating epithelioid granulomas (Fig. 2B). A kidney biopsy specimen demonstrated a glomerular crescent formation (Fig. 3A), histocyte infiltration, and the rupture of Bowman’s capsules (Fig. 3B).

Because there were high degrees of MPO-ANCA, vasculitis and noncaseating epithelioid granulomas in the lung biopsy specimens and due to the presence of crescentic glomerulonephritis in the kidney biopsy specimens, the patient was diagnosed with GPA based on the Chapel Hill Consensus Conference (CHCC) criteria (1) and the European Medicines Agency (EMA) algorithm (8). Treatment with oral prednisolone (PSL, 60 mg/day) followed by intravenous pulse methylprednisolone (mPSL pulse; 1,000 mg/day for 3 consecutive days) on day 10. The patient’s fever declined. His CRP level also declined (2.15 mg/dL on day 14); however, his creatinine levels showed no improvement. We added intravenous cyclophosphamide pulse therapy.

Figure 1. Multiple pulmonary nodules in the bilateral lung fields (red arrows) and partial interstitial reticular markings in the lingular segment (red circles).

Figure 2. (A) Vasculitis with vessel destruction (red arrows). (B) Noncaseating epithelioid granulomas (blue arrowheads) in the lung.
On day 15, the patient experienced cough and hemoptysis. Chest CT showed emerging diffuse consolidation in the bilateral lower lobes, suggesting DAH (Fig. 4A and B). The partial interstitial reticular markings in the lingular segment that had been seen in the previous CT scan changed to a larger ground glass opacity and consolidation, and diffuse consolidation also spread in an area in which no opacity had been observed on the previous chest CT scan. Multiple pulmonary nodules in the bilateral lung fields showed no changes in size in comparison to the previous CT scan (Fig. 4A and B, the same levels of nodules as Fig. 2A and B). The patient’s hemoglobin level suddenly declined (9.1 g/dL on day 15) and his CRP level became elevated (7.11 mg/dL on day 15). We judged that DAH was complicated by GPA, despite the improvement of his fever. We administered mPSL pulse therapy for 3 consecutive days twice (on days 15-17 and days 21-23) and performed plasma exchange six times (three times per week). Because his respiratory status gradually worsened despite the use of oxygen (by reservoir mask), we used non-invasive positive pressure ventilation. His respiratory status showed a brisk recovery, and he could be managed without intubation. We administered IVCY a second time two weeks after the first IVCY (Fig. 5). His chest CT findings improved within two months. Although his serum Cr level was kept, the red blood cell casts in the urine disappeared and his MPO-ANCA titer declined.

We administered a total of 9 courses of IVCY. One year later, he continues to receive PSL (3 mg/day) and has shown no signs of relapse.

Discussion

We presented the case of a patient with GPA associated with DAH following mPSL pulse and IVCY. DAH occurred soon after the initiation of mPSL pulse and IVCY, despite the improvement of the patient’s fever and laboratory data (including his CRP level).

The incidence of DAH in AAV is between 8% and 36%. Among AAV patients with DAH, 41% of patients are diagnosed with GPA (mainly in Western countries) (9). In Japan, it was reported that among 1,147 AAV patients, 177 had...
DAH (10). Only 2 of 13 (15%) AAV patients with DAH had GPA, because more patients are diagnosed with MPA than GPA in Japan (11).

In our patient, DAH emerged in a way that was not parallel to the other activities or results of AAV, including the patient’s fever and CRP levels. The patient’s GPA disease activity may have been high because his creatinine level did not improve. Our patient showed two factors (renal insufficiency and no ENT manifestations) from the revised five factor score (2009 FFS) that indicated a poor prognosis (12). However, treatment based on the five factor score is not applicable to GPA, in which immunosuppressants combined with corticosteroids are compulsory. Thus, we used IVCY after mPSL pulse. DAH occurred in our patient despite the administration of mPSL pulse and IVCY. To the best of our knowledge regarding DAH after mPSL pulse, there is one reported case of a patient with GPA and systemic lupus erythematosus complicated by DAH at one week after the initiation of mPSL pulse while the patient’s symptoms including fever, skin eruptions, renal function and otitis media were improving by PSL (50 mg/day) (13).

Our patient had pulmonary nodules and interstitial reticular markings and subsequent DAH. In Japan, among 600 AAV patients with pulmonary involvement, 50 patients had both DAH and interstitial lung disease, and 6 patients had both DAH and pulmonary granuloma; however, it is unclear when DAH and interstitial lung disease or pulmonary granuloma occur (10). The changes in the lung opacity on the patient’s chest CT scans was a valuable finding.

There is little information regarding risk factors for DAH in AAV. AAV patients with hypocomplementemia are reported to show a higher incidence of DAH in comparison to AAV patients without hypocomplementemia (14); however, our patient had no hypocomplementemia. DAH (not limited to AAV) is reported to be caused by antiplatelet (15) and anticoagulant medications (16). Our patient was treated with aspirin for angina pectoris. Thus, caution should be exercised with regard to the administration of antiplatelet or anticoagulant medications.

In conclusion, DAH may occur after the initiation of mPSL pulse and IVCY. Physicians should be aware of the possibility of DAH, even when a patient’s symptoms and inflammatory marker levels improve after mPSL pulse and IVCY. It is necessary to evaluate the risk factors for DAH in AAV patients.

The authors state that they have no Conflict of Interest (COI).

References

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