INTERNAL MEDICINE

□ CASE REPORT □

Diffuse Alveolar Hemorrhage following Itraconazole Injection

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Abstract

Diffuse alveolar hemorrhage (DAH) syndrome is potentially fatal. We encountered a nearly fatal case of DAH possibly due to intravenous itraconazole (ITCZ). A 53-year-old man with chronic pulmonary aspergillosis underwent pneumonectomy of the left lung 15 days prior to the onset of DAH, which was confirmed by bronchoalveloar lavage. The battery of diagnostic evaluations performed revealed no other positive etiological factor, leading to the diagnosis of DAH possibly induced by intravenous ITCZ with a positive drug lymphocyte stimulation test. The patient did not respond to pulse methylprednisolone therapy, but responded dramatically to direct hemoperfusion using a polymyxin B-immobilized fiber column (PMX) therapy.

Key words: diffuse alveolar hemorrhage, intravenous itraconazole, PMX

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Introduction

Diffuse alveolar hemorrhage (DAH) syndrome is caused by bleeding into the alveolar spaces due to disruption of the alveolar-capillary basement membrane. A variety of diseases and drugs are associated with this syndrome (1, 2). Infection, systemic vasculitides (Behçet's syndrome, Henoch-Schoenlein purpura and Wegener's granulomatosis), connective tissue diseases (Goodpasture's syndrome and systemic lupus erythematosis) and drugs (amiodarone and penicillamine) are well-known causes of DAH syndrome. DAH syndrome is potentially fatal, although its cause might not always be clear, even when hemorrhage is severe. Intravenous itraconazole (ITCZ), an azole antifungal, has been widely used worldwide for deep-seated mycosis, including chronic pulmonary aspergillosis (3). Very few adverse reactions in terms of DAH have been reported in the manufacture's data (data not published).

We report here a rare and potentially fatal case of DAH that occurred in a patient with chronic pulmonary aspergillosis who had only one lung, the DAH being possibly induced by ITCZ injection.

Case Report

A 53-year-old man patient, previously diagnosed with chronic pulmonary aspergillosis (CPA), admitted to Nagasaki University Hospital with complaints of hemosputum, cough and slight dyspnea for 3 months. He had left lower lobectomy due to bronchiectasis 11 years previously and two episodes of pneumothorax 5 years previously. The diagnosis of CPA was made 1 year previously on the basis of the typical aspergilloma-like shadow in his residual left lung and a positive *Aspergillus* antibody titer. He had received oral voriconazole and intravenous micafungin for two and four weeks after the diagnosis of CPA due to consistent hemosputum, however both treatments were discontinued due

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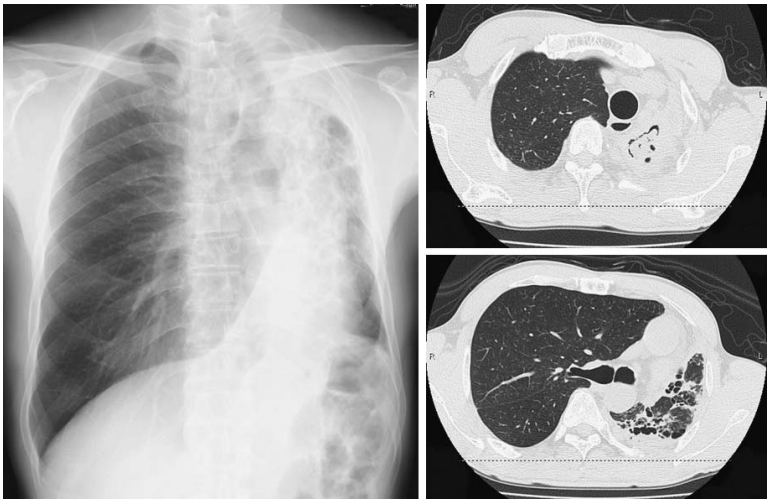

Figure 1. Chest X-ray films on admission demonstrated pericavity infiltrative shadows with cavitation, indicating possible aspergilloma of the left upper lung field, with no significant abnormality of the right lung.

to liver dysfunction and poor compliance, respectively. Although hemosputum was continued intermittently, he did not visit the hospital until this admission.

On admission, vital signs of the patient were as follows: body temperature, 36.7℃; heart rate, 82 beats/minute with a regular rhythm; SpO_2, 98% (on room air); and blood pressure, 85/56 mmHg. Physical examination revealed emaciation and diminished respiratory sounds in the left lower lung field with fine rales in the left upper field. No respiratory sounds were heard in the right lung field. No signs of systemic lymphadenopathy, hepatosplenomegaly, or pre-tibial edema were seen. Laboratory findings on admission were: white blood cell (WBC) count, 8.6×10^3/μL with a shift to the left (neutrophils: 73%); C-reactive proteins (CRP), 0.84 mg/dL; erythrocyte sedimentation rate, 14.5 mm/h; β-D-glucan, 185 pg/mL; and *Aspergillus* galactomannan antigen, negative. Sputum microbiology test revealed no bacteria including mycobacterium but it was positive for *Aspergillus fumigatus*. Chest X-ray films revealed infiltrative shadows with cavitation, suggestive of an aspergilloma of the left upper lung field with no abnormal findings in the right lung (Fig. 1). An oral solution of ITCZ (200 mg/day), carbazochrome sodium sulfonate hydrate and tranexamic acid were administered for 25 days after admission and bronchial arteriography (BAG) was performed on day 20. BAG revealed hypervascularization and broncho-pulmonary shunt in the left bronchial artery and minor extravasation of contrast media in left internal thoracic artery. Though following selective bronchial artery embolization (BAE) with gelfoam particles to both of left bronchial and internal thoracic artery was attempted, complete embolization was not achieved. Since hemosputum did not diminish with this treatment, the fatal risk of severe hemoptysis leading to suffocation still remained. Pulmonary function tests revealed that left lung function was only 5% of total lung function and unilateral pulmonary artery occlusion testing also revealed that there was no pressure increase in the right pulmonary artery. Hence, pneumonectomy of the residual left lung was performed on day 33. The several fungus balls within the cavities were recognized in the resected lung and the propagation of Y-shaped branching filamentous fungi was observed in the pathology. The immediate postoperative period was uncomplicated and the patient gradually recovered from surgery. Oral solution of ITCZ (200 mg/day) was initiated postoperatively for prophylaxis of secondary *Aspergillus* infection and switched to intravenous ITCZ (200 mg/day) on day 6 after the operation in order to ensure the ITCZ concentration in serum. On the 10th postoperative day, however, he once again experienced hemosputum and severe dyspnea occurred on postoperative day 15. Laboratory findings on postoperative day 15 were as follows: red blood cell count, 405×10^4/μL; hemoglobin, 12.3 g/dL; WBC count, 16.4×10^3/μL with a shift to the left (neutrophils: 92%); platelet count, 35.1×10^4/μL; CRP, 16.8 mg/dL. The international normalized ratio of prothrombin time and activated partial thromboplastin time were 57% and 39.7 sec, respectively. The results of arterial blood gas analysis with the inhalation of 6 L/min oxygen with face mask were as follows: pH, 7.458; PaO_2, 62 mmHg; $PaCO_2$, 41.2 mmHg and HCO_3^-, 28.8 mmol/L. Chest X-ray films revealed diffuse ground-glass opacities in the entire right lung together with pleural effusion (Fig. 2).

Bronchofiberscopy was immediately performed and no apparent bleeding was seen in the airway, trachea and at the site of the resected bronchus. Bronchoalveloar lavage (BAL) analysis, however, indicated that the fluid recovered from right middle lobe was bloody in appearance. A total of 48 mL out of 100 mL fluid was recovered in BAL fluid and cell count analysis indicated alveolar macrophages 8.3%, neutrophils 81.2%, lymphocytes 10.5% and no eosinophils. No microorganisms were isolated by routine microbiology tests including fungus and mycobacterium. KL-6 value was 212 U/mL (normal range: <500). Twelve-lead electrocardiography revealed sinus rhythm and left ventricular high volt-

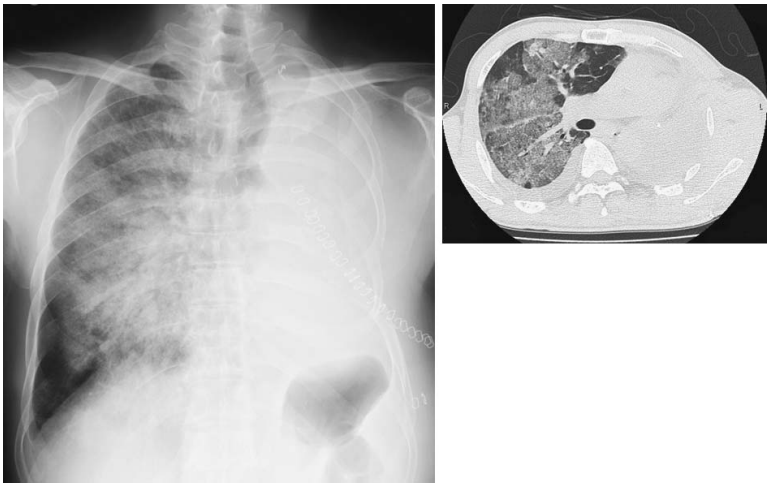

Figure 2. **Chest X-ray films 15 days after the left pneumonectomy. Diffuse ground-glass opacity of the right lung and pleural effusion are seen.**

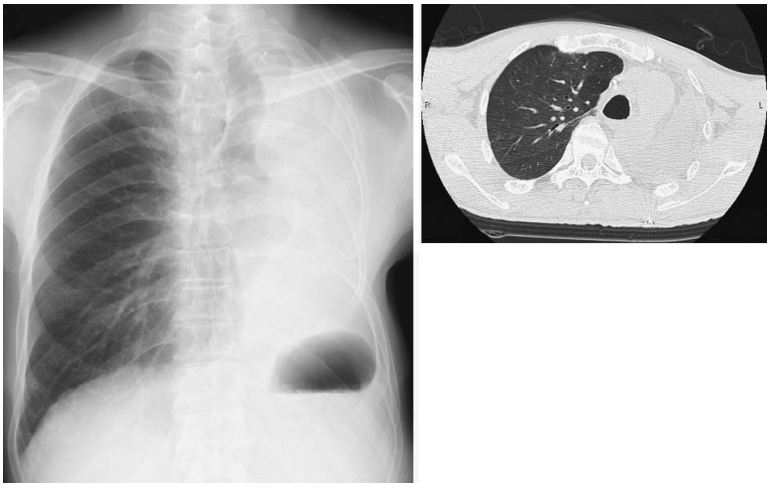

Figure 3. **Chest X-ray films 22 days after the left pneumonectomy. Only slight diffuse ground-glass opacity still remained over the right lung.**

age (RV5+SV1=4.31 mV). Echocardiography revealed normal cardiac function with an ejection fraction of 71.2%, indicating he had no (left-sided) heart failure. Antibody tests for collagen diseases, such as proteinase 3-antineutrophil cytoplasmic antibodies (PR3-ANCA), myeloperoxidase (MPO)-ANCA, anti-glomerular basement membrane (GBM) antibodies and anti-nuclear antibodies were all negative. No hematuria or proteinuria was observed. Alveolar hemorrhage due to unknown causes was suspected and the patient was immediately transferred to the intensive care unit and intubated. The PaO_2/FiO_2 ratio was 142.4 mmHg with the patient on the respirator. Intravenous pulse steroid therapy with 1,000 mg/day of methylprednisolone for 3 days, together with intravenous sivelestat, sulbactum ampicillin and ciprofloxacin, was initiated. Despite the intensive treatment, however, the PaO_2/FiO_2 ratio did not improve. Direct hemoperfusion using a polymyxin B-immobilized fiber column (PMX) therapy was started 3 days after intubation. The perfusion was carried out at a rate of 100 mL/min for 24 hours continuously and the PaO_2/FiO_2 ratio started to improve during the perfusion. By day 5 after intubation, the patient had recovered sufficiently that mechanical ventilation was discontinued and CT scan images were almost clear (Fig. 3). The patient became symptom-free and was discharged from the hospital 44 days after surgery. No recurrence of symptoms was observed after discharge. Retrospective examination with a drug lymphocyte stimulation test (DLST) was performed with both intravenous and oral forms of ITCZ, loxoprofen sodium hydrate and lafutidine. The stimulation index (SI) was positive in only the intravenous formula of ITCZ (SI; 267%, normal range: <180%). In this patient, the intravenous form of ITCZ was initiated 6 days after surgery and discontinued on the day of intubation. Hence, the intravenous form of ITCZ was assumed to be the possible cause of this nearly fatal case of DAH.

Discussion

The consistent hemosputum before the pneumonectomy of the current case was caused by chronic *Aspergillus* infection

based on the pathological findings of the resected lung and the result of culture examination. Complete remission of chronic pulmonary aspergillosis is difficult to achieve. Hence, in our patient, due to the ineffectiveness of almost one month of antifungal treatment together with BAE, pneumonectomy was performed.

DAH occurred 15 days after surgery with the patient complaining of hemosputum 4 days after the start of administration of intravenous ITCZ. Hemosputum and BAL fluid analysis indicated alveolar hemorrhage in this patient, although there was no means of acquiring pathological evidence from the affected right lung due to the risk of pneumothorax. Extensive investigation to identify the cause of DAH revealed no positive clues, so that by a process of elimination, intravenous ITCZ, which was initiated just 4 days before the onset of symptoms, was assumed to be the cause of DAH in this patient. Congestive heart failure associated with ITCZ (4) was believed to be the pathology behind the respiratory failure, although no strong evidence of cardiogenic heart failure, arrhythmia or other drug usage which may cause cardiovascular side effects with co-use of ITCZ were recognized.

Although there is no definite tool for evaluating the relationship between immunological status and drugs, DLST is one of the tools to hypothesize the causative agent in clinical cases (5, 6). There are several reports indicating its usefulness in some drug-induced diseases (7-10), though its clinical utility has not been established. In the present case, retrospective DLST evaluation indicated a high SI titer with intravenous ITCZ, but not with the oral solution ITCZ. This supported the assumption that the causative agent for the almost fatal DAH in our patient was the injectable form of ITCZ. Since the oral solution of ITCZ tested negative with DLST, supplemental agents, but not ITCZ in the injectable preparation of the drug might be responsible for this side effect. No challenge tests to this agent were performed in our patient due to the severe risk of fatal pneumonitis.

Although glucocorticoids are the mainstay of therapy for DAH syndrome, additional immunosuppressive therapy (with cyclophosphamide or azathioprine) should also be considered in severe cases. Since our attempt of 3 consecutive days of pulse methylprednisolone therapy (1,000 mg/day) was not effective, we performed PMX therapy. Surprisingly, the patient showed a dramatic response right after the initiation of PMX treatment. Although plasma exchange is an established treatment of DAH associated with Goodpasture's syndrome (11), PMX therapy is not an established treatment for DAH syndrome. However, our previous case report showed its effectiveness in the treatment of severe Lemierre's syndrome with ARDS (12) and other recent studies have also proved that PMX treatment improves the PaO_2/FiO_2 ratio (13) and suppresses the function of activated monocytes in the peripheral blood of ARDS patients (14). Further accumulation of clinical data is warranted for the evaluation of PMX treatment.

In conclusion, we encountered a rare case of DAH possibly induced by the intravenous ITCZ and successfully treated with PMX treatment. Further investigations to reveal the mechanism of DAH syndrome due to drugs and to establish newer treatment strategies are required.

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