INTERNAL MEDICINE

□ CASE REPORT □

Diffuse Alveolar Hemorrhage in a Patient with Ankylosing Spondylitis

Shintaro Hara, Noriho Sakamoto, Yuji Ishimatsu, Tomoyuki Kakugawa, Midori Shimada and Shigeru Kohno

Abstract

Ankylosing spondylitis (AS) primarily affects the spine and axial skeleton. Various pulmonary manifestations have been reported; however, diffuse alveolar hemorrhage (DAH) has not been previously described in a patient with AS. A 49-year-old man with longstanding AS visited our hospital complaining of progressive dyspnea and hemoptysis. DAH was diagnosed based on the findings of chest computed tomography and bronchoscopy. No positive findings suggested any cause of DAH other than weakly positive results for perinuclear antineutrophil cytoplasmic antibodies on indirect immunofluorescence. Following the administration of steroid and plasmapheresis therapy, the patient's symptoms and chest radiographic findings improved. Further clinical case reports and investigations are needed to clarify whether DAH represents a possible pulmonary manifestation of AS.

Key words: pulmonary manifestations of ankylosing spondylitis, diffuse alveolar hemorrhage, antineutrophil cytoplasmic antibodies, plasmapheresis

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that primarily affects the axial skeleton and sacroiliac joints and certain extra-articular organs, including the cardiovascular and pulmonary systems. The pulmonary manifestations of AS include apical fibrosis, interstitial lung disease, chest wall restriction, ventilatory abnormalities, spontaneous pneumothorax and sleep apnea (1).

Diffuse alveolar hemorrhage (DAH) is a potentially fatal clinical syndrome that is often associated with systemic vasculitides, connective tissue diseases, infections and drugs (2). However, no reports have so far described DAH as a complication in a case of AS. This article represents the first report of DAH in a patient with AS.

Case Report

A 49-year-old man visited our hospital with a three-day history of progressive dyspnea and hemoptysis. No preceding common cold-like symptoms were observed. Twenty-four years prior to this admission, the patient had felt chronic pain and stiffness in the middle part of the spine and had been diagnosed with AS based on a combination of symptoms, radiography of the spine and detection of the HLA-B27 genotype. He had since been treated for AS with prednisolone at a dose of 5 mg/day and indomethacin at a dose of 50 mg/day. Although the patient's chronic dorsal and lumbar pain had improved, the ankylosis of the spine had gradually advanced, and he was unable to rest in a supine position due to contractures of the spine and hip joints. The treatment for AS described above had remained unchanged for the last 20 years. The patient also had a 30-year history of smoking one pack of cigarettes a day (Brinkman index =600).

On initial presentation, the patient's vital signs were as follows: body temperature, 37.5℃; heart rate, 130 beats/min with a regular rhythm; blood pressure, 112/74 mmHg; respiratory rate, 22 breaths/min; and peripheral oxygen saturation, 88% (on room air). A physical examination revealed areas of coarse crepitation in both lower lung fields. The pa-

Second Department of Internal Medicine, Nagasaki University School of Medicine, Japan
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Correspondence to Dr. Noriho Sakamoto, nsakamot@nagasaki-u.ac.jp

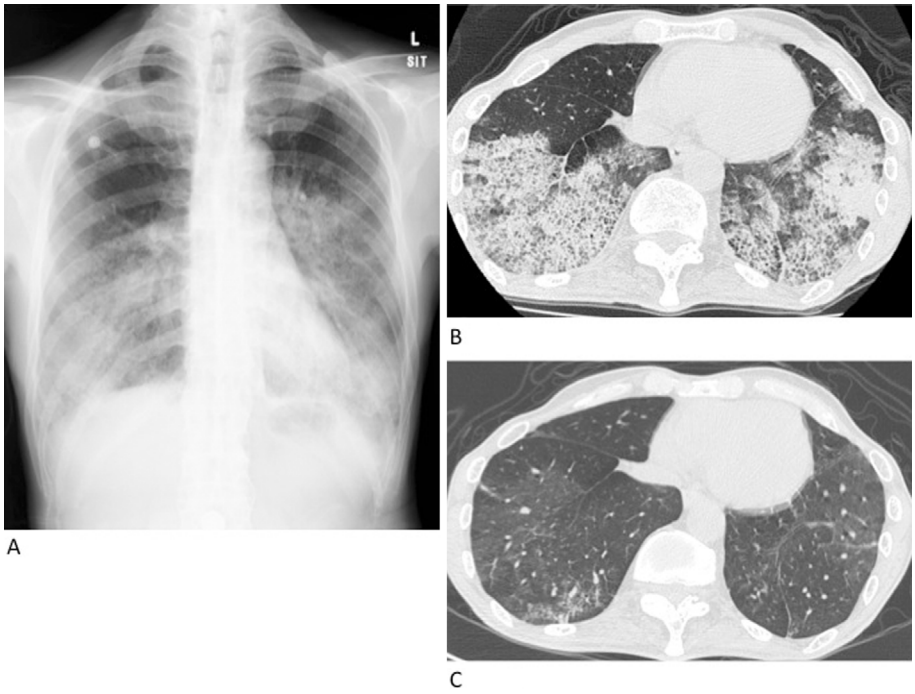

Figure 1. **A) Chest radiography performed on admission revealing infiltration in the lower lung fields. B) Chest computed tomography (CT) showing consolidation and fine reticular shadows superimposed on areas of ground-glass opacity in the bilateral lower lobes. C) After one month of therapy, the chest CT findings improved.**

tient's chest expansion was diminished to 1.5 cm, and the motion of the thoracic and lumbar spine was severely decreased. No signs of systemic lymphadenopathy, hepatosplenomegaly or pretibial edema were evident. The laboratory findings on admission were as follows: white blood cell count, 6.3×10^3/μL (neutrophils, 85%); hemoglobin, 11.6 g/dL; hematocrit, 34.4%; platelet count, 20.8×10^4/μL; C-reactive protein, 25.1 mg/dL; international normalized ratio of prothrombin time, 1.25; and activated partial thromboplastin time, 29.6 s. An arterial blood gas analysis with the inhalation of 3 L/min of oxygen through a nasal cannula showed the following results: pH, 7.422; PaO_2, 82.0 mmHg; $PaCO_2$, 43.6 mmHg; HCO3-, 27.9 mmol/L; and KL-6, 143 U/mL. Negative results were obtained from all serological and urinary studies for pathogens, including *Legionella* spp., *Streptococcus pneumoniae*, *Mycoplasma pneumonia*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, cytomegalovirus antigenemia and β-D glucan. Sputum, intratracheal aspirate, blood and urine cultures also yielded negative results. Antibody tests for connective tissue diseases and vasculitides, such as antinuclear, anti-SS-A, anti-SS-B, anti-ds-DNA, anti-RNP, anti-Sm, anti-Jo-1, anti-cardiolipin, anti-glomerular basement membrane, proteinase 3 (PR3)-antineutrophil cytoplasmic (ANCA) and myeloperoxidase (MPO)-ANCA antibodies, were all negative. Perinuclear-ANCA (P-ANCA) antibodies exhibited a weakly positive reaction on indirect immunofluorescence. No hematuria or proteinuria were observed. Echocardiography demonstrated no evidence of either heart failure or valvular disease. Chest radiography revealed infiltrative shadows in both lower lung fields (Fig. 1A). High-resolution computed tomography (HRCT) of the chest revealed consolidation and a fine reticular pattern superimposed on an area of ground-glass opacity (i.e., a "crazy-paving" appearance) in both lower lobes (Fig. 1B). No interstitial fibrosis, emphysematous changes, old tuberculosis or bronchiectasis were evident on HRCT. Respiratory function testing was not performed due to the patient's dyspnea.

Broad-spectrum antibiotics (meropenem: 3.0 g/day, ciprofloxacin: 600 mg/day) were started; however, a fever of over 38.0℃ and hemoptysis continued. The bronchoscopic findings observed on hospital day 3 revealed bleeding in the bronchi of both lower lobes. We abandoned any attempts to obtain bronchoalveolar lavage fluid or perform a transbronchial lung biopsy due to hypoxia. DAH was diagnosed based on the bronchoscopic and chest HRCT findings. Intravenous pulse steroid therapy was initiated with 1,000 mg/day of methylprednisolone for three days in association with plasmapheresis for two days resulting in improved oxygenation and chest radiography findings. The chest HRCT findings improved after one month of steroid therapy (Fig. 1C), and the dose of prednisolone was tapered to the original 5 mg/day used to treat AS within four months. No recurrence has occurred as of the time of writing. The clinical course of the patient is shown in Fig. 2. The P-ANCA antibodies observed on indirect immunofluorescence became negative after two weeks of treatment.

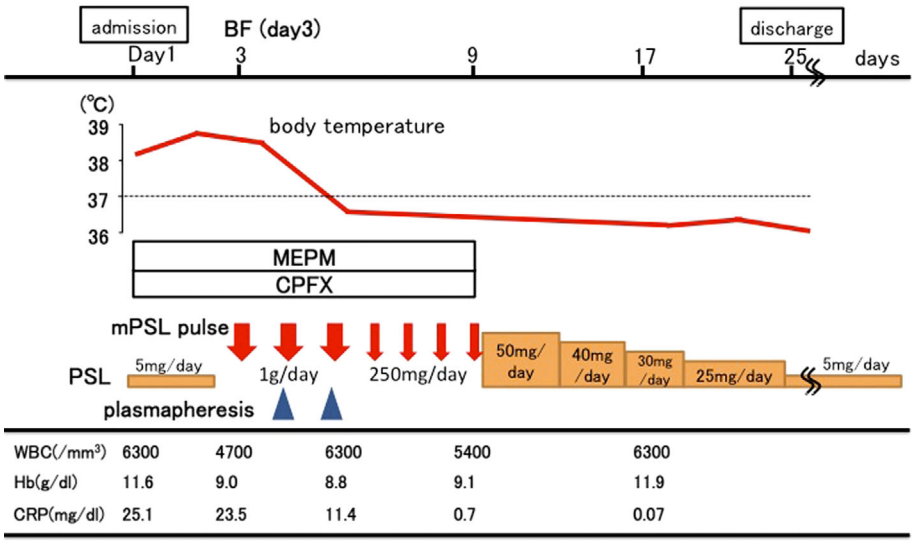

Figure 2. **Summary of the patient's clinical course and treatment. MEPM: meropenem, CPFX: ciprofloxacin, mPSL: methylprednisolone, PSL: prednisolone, WBC: white blood cell count, Hb: hemoglobin, CRP: C-reaction protein**

Discussion

The key issue in this case is whether the DAH represented a complication of AS or it occurred incidentally in a patient with AS. DAH is clinically characterized by hemoptysis, a decreasing level of hematocrit, hypoxemic respiratory failure and the presence of diffuse pulmonary infiltrates. Newsome et al. reviewed the causes of DAH and created an optional decision diagram for diagnosing DAH (2). AS is a chronic inflammatory rheumatic disease that affects certain extra-articular organs, including the cardiovascular and pulmonary systems. The pulmonary manifestations of AS include apical fibrosis, interstitial lung disease, chest wall restriction, ventilatory abnormalities, spontaneous pneumothorax and sleep apnea (1). No descriptions of DAH occurring as a complication in a patient with AS have been previously reported. In the current case, ankylosis of the spine had gradually persisted over 24 years of AS. The patient's thoracic deformity and diminished lower chest expansion were progressive due to a hump back. However, no acute exacerbations of AS or obvious cardiorespiratory manifestations were apparent at the time of admission. Extensive investigations performed to identify the cause of DAH revealed no positive clues, such as infectious diseases caused by unknown organisms, connective tissue diseases, systemic vasculitis or other drugs or toxins. The patient had taken long-term indomethacin regularly throughout the course of DAH. No reports have described DAH being caused by indomethacin or any other nonsteroidal anti-inflammatory drugs (NSAIDs), except for aspirin (3). Aspirin suppresses the production of prostaglandins and thromboxanes, the former resulting in analgesia and the latter resulting in an antiplatelet effect. The antiplatelet properties of aspirin, which are not shared by other NSAIDs, can induce DAH. Furthermore, in the present case, the dose of indomethacin remained unchanged for over 20 years and continued even after treatment of DAH. These facts suggest that indomethacin was not a likely cause of DAH in the present case. Cigarette smoking is recognized to be a causative agent or precipitant of specific diffuse lung diseases characterized by bronchiolar and interstitial lung inflammation, such as respiratory bronchiolitis interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP) (4). One report described a case of DAH in a young male smoker (5); however, no direct associations between smoking and DAH have been demonstrated. Although the present patient was a current smoker, neither an increase in the amount of smoking nor any changes in cigarette brands were reported. The patient's obstructive pulmonary function was unclear because pulmonary function testing was not performed. Through this process of elimination, AS was suggested as a potential cause of DAH in the present case. AS is a rare disease with a prevalence of 0.1-0.8% in Caucasians (6). DAH is also rare. Comparing the probability of two rare diseases occurring incidentally with the probability of the two diseases occurring in association, the latter is higher.

P-ANCA antibodies were identified in this case on indirect immunofluorescence; however, no MPO-ANCA antibodies were evident in an enzyme-linked immunosorbent assay. ANCA positivity in patients with AS has been reported by several researchers, with 0-28% of AS patients exhibiting ANCA positivity (7-10). In these reports, the ANCA-positive AS patients showed no symptoms of vasculitis or pulmonary manifestations. The ANCA patterns encountered in patients with AS primarily involve P-ANCA, which is considered to be a predictor of chronic and progressive inflammatory joint disease in AS patients (8-11). Locht et al. reported that target antigens (ANCAs) include MPO (2/43 cases) and other minor antigens, such as lactoferrin (3/43

cases) and alpha-antigen (2/43 cases) (8). Although the clinical significance remains unclear, antibodies to these minor antigens have also been reported in patients with systemic vasculitis (12). Interestingly, the results of indirect immunofluorescence for P-ANCA in the present case turned negative following the administration of multimodal therapy. ANCAs other than those to PR3/MPO may represent a factor that mediates DAH and AS.

Although glucocorticoids represent the mainstay of therapy for DAH, additional immunosuppressive therapy should also be considered in severe cases. Plasmapheresis is an established treatment for DAH caused by small-vessel vasculitis (13-15). ANCAs and some inflammatory cytokines sustain disease progression, and prompt removal of these molecules via plasmapheresis offers the best means of controlling pulmonary capillaritis and decreasing the potential for ongoing alveolar hemorrhage. The response to plasmapheresis observed in this case indicates the presence of deleterious effects from unknown autoantibodies or pathogens in the plasma.

In conclusion, we herein provided the first description of DAH in a patient with AS. Further clinical case reports and investigations are needed to answer the question of whether DAH is a pulmonary manifestation of AS.

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

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