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Case Report

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Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea

Corresponding author:
Doo-Ho Lim, MD, PhD
Department of Internal Medicine,
Ulsan University Hospital,
University of Ulsan College of Medicine
877 Bangeojinsunhwan-doro,
Dong-gu, Ulsan,
South Korea 44033
Tel; +82-52-250-8970
Fax: +82-52-250-7048
E-mail: dlaengh@hanmail.net
ORCID ID: 0000-0002-8012-7364

ABSTRACT

Pneumocystis jirovecii pneumonia (PCP) is an opportunistic pulmonary infection in immunosuppressed hosts such as human immunodeficiency virus–positive or organ transplant patients. An increasing number of PCP cases have been reported among patients with rheumatoid arthritis (RA) treated with disease-modifying anti-rheumatic drugs. While PCP with diffuse alveolar hemorrhage (DAH) has been mostly documented in human immunodeficiency virus–positive patients, it has been rarely reported in patients with RA. Herein, we report a case of PCP with DAH in a female patient with RA who was treated with infliximab. We confirmed PCP and DAH by bronchoalveolar lavage, and the patient was successfully treated with trimethoprim-sulfamethoxazole. PCP should be considered in the differential diagnosis of DAH in RA patients receiving infliximab.

KEYWORDS: *Pneumocystis jirovecii* pneumonia, diffuse alveolar hemorrhage, rheumatoid arthritis, disease-modifying anti-rheumatic drugs

INTRODUCTION

Pneumocystis jirovecii pneumonia (PCP), which was initially discovered in human immunodeficiency virus (HIV)–positive patients in the 1980s, is an opportunistic pulmonary infection caused by *Pneumocystis jirovecii* in immunosuppressed patients.[1] PCP cases were also reported to increase in rheumatoid arthritis (RA) patients who were treated with disease-modifying anti-rheumatic drugs (DMARDs), including biologic agents, and resulted in high mortality rates.[2] However, it is difficult to diagnose PCP, because often, the condition has not only non-specific symptoms such as cough and fever but also non-specific findings on radiographic examination.[1,3]

Diffuse alveolar hemorrhage (DAH) is a distinct syndrome of pulmonary hemorrhage due to disruption of the alveolar-capillary basement membrane.[4] In general, pulmonary infections are rarely associated with DAH, and infectious etiologies such as infection with cytomegalovirus, adenovirus, and *Mycoplasma* and *Legionella* species; influenza; invasive aspergillosis; leptospirosis; and malaria have been reported.[5] While PCP-associated DAH has been mostly documented in HIV-positive patients,[6] it has been rarely reported in patients with RA.

Herein, we report a case of PCP complicated by DAH in an RA patient receiving infliximab, who was stabilized with antibiotics.

CASE REPORT

A 75-year-old woman was admitted to our hospital with a 2-week history of general weakness. She was diagnosed with RA 10 years ago, and disease remission was maintained with infliximab treatment for 2.5 years (200 mg intravenously per 2 months), methotrexate (10 mg per weeks), and acetaminophen (650 mg per day). She also had a history of osteoporosis and hypertension. For the former, she received denosumab (60 mg subcutaneous injection per 6 months), calcium carbonate (1250 mg per day), and cholecalciferol (1000 international unit per day), and for the latter, she received amlodipine 5 mg daily and

losartan 50 mg daily. The patient denied any smoking history and was a social drinker.

On admission, her blood pressure, heart rate, body temperature, respiratory rate, and oxygen saturation on room air were 135/85 mmHg, 93 beats/min, 38.1°C, 20 breaths/min, and 91 %, respectively. She complained of mild respiratory symptoms such as dry cough and sore throat; however, sputum production was scanty. Physical examination revealed clear lung sounds and no pharyngeal injection. The patient was awake and alert, and the rest of her examinations, including cardiac and abdominal examinations, were normal. Initial laboratory tests showed a mildly elevated white blood cell count (10,740/mm^3; polysegmented neutrophils: 59.7 %, lymphocytes, 30.3 %) but a normal hemoglobin level (12.4 g/dL) and platelet count (362,000/mm^3). The results of the coagulation profile, liver function, and serum creatinine tests were within the normal range; however, erythrocyte sedimentation rate (73 mm/h) and C-reactive protein level (3.71 mg/dL) were elevated. An arterial blood gas test on room air showed a pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), and oxygen saturation of 7.440, 36.2 mmHg, 58.1 mmHg, and 92 %, respectively. A chest X-ray showed diffuse mildly increased interstitial opacities in both lungs (Fig 1), while chest computed tomography (CT) showed multiple ill-defined ground-glass opacities in both lungs (Fig 2). Blood culture and tests for *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Mycobacterium tuberculosis*, and influenza were negative. Initially, the patient was started on ceftriaxone (2000 mg per day intravenously) and azithromycin (500 mg per day intravenously) for community-acquired pneumonia. Of the RA medications, methotrexate and infliximab were discontinued. Despite using the above antibiotics for 3 days, clinical symptoms such as fever, dyspnea, and elevated C-reactive protein level did not improve.

On day 4 of admission, fiberoptic bronchoscopy was performed, and it revealed airway erythema in the left and right bronchial trees. Bronchoalveolar lavage (BAL) performed in the lower left lobe showed progressive bloody returns consistent with DAH (Fig 3). Examination of the BAL fluid revealed 190 cells/mm^3 white blood cells and 17,000 cells/mm^3 red blood cells. Hemosiderin-laden macrophages were found in the BAL fluid (Fig 4). BAL cultures and galactomannan test and the molecular diagnostic test for tuberculosis were negative, while polymerase chain reaction for *Pneumocystis jirovecii*-specific DNA was positive. The results of additional autoimmune workup, including tests for antinuclear antibody, cytoplasmic and perinuclear antineutrophilic cytoplasmic autoantibodies, and glomerular basement membrane antibody, were negative. Based on the clinical, bronchoscopic, and laboratory findings, a diagnosis of PCP complicated by DAH was established.

Therefore, treatment with trimethoprim-sulfamethoxazole (TMP-SMX) (15 mg TMP/kg/day intravenously divided q 6 h) was started. Methylprednisolone (8 mg per day) was administered due to inflammatory exacerbation of RA accompanied by PCP. Her symptoms and laboratory data gradually improved with a 3-week course of TMP-SMX treatment. At follow-up 2 weeks after discharge, she was free of symptoms, and methotrexate and infliximab were restarted.

DISCUSSION

Over the past decades, the management of RA has changed markedly through the early use of methotrexate and introduction of biological DMARDs. With the increased use of such anti-rheumatic drugs, RA patients are at increased risk of PCP.[2] However, DAH related to PCP has been rarely reported in patients with RA; it has been described mostly in HIV-positive patients.[6] To our knowledge, this is the first report of PCP complicated by DAH in an RA patient receiving infliximab.

The incidence of PCP in RA patients treated with tumor necrosis factor inhibitors (TNFis) varies among countries, with the rate being 0.4 % in Japan,[7] 0.02 % in the United Kingdom,[2] and 0.01 % in the United States.[8] The possible explanations for the difference include a possibly more severe influence of TNFis on host defenses among Asian patients owing to ethnic differences and a higher prevalence of *Pneumocystis jirovecii* colonization in Japanese patients. Meanwhile, there were several pieces of evidence suggesting that TNF plays a critical role in host defenses against a *Pneumocystis* infection. First, *Pneumocystis murina* has been shown to directly enhance the secretion of TNF from murine alveolar macrophages by activation of Toll-like receptors. Second, *Pneumocystis*-induced TNF stimulated the production of reactive nitrogen substances, which are important mediators for killing microorganisms. Finally, adenoviral gene transfer of the mouse IgG/p55 TNF receptor in immunocompetent mice delayed the clearance of *Pneumocystis jirovecii* after intratracheal inoculation.[9]

DAH is a distinct syndrome of pulmonary hemorrhage that could complicate many clinical conditions and might be life-threatening, requiring prompt treatment.[10] It may have various manifestations such as acute or subacute cough, hemoptysis, diffuse radiographic pulmonary infiltrates, and hypoxemic respiratory distress. Hemoptysis, the major sign of DAH, may develop suddenly or over a period of days to weeks. However, as in the case of our patient, this sign is initially absent in up to 30 % of patients, in whom establishing a diagnosis could be difficult. Therefore, a high degree of suspicion is necessary for the early recognition and diagnosis of DAH.[5]

The diagnosis of DAH required bronchoscopy with BAL, revealing progressively bloody returns, and additionally hemosiderin-laden macrophages could be found in the BAL. BAL cultures also need to be evaluated for potential infectious causes.[11] Routine laboratory studies and serologic analyses for connective tissue diseases and systemic vasculitis are essential as part of the initial workup in patients diagnosed with DAH. In rare cases, a surgical biopsy might be necessary if the history and laboratory examinations are not adequate to establish a diagnosis of DAH.[12] In our case, DAH was diagnosed based on both progressively increased red coloration and hemosiderin-laden macrophages in BAL along with extensive ill-defined ground-glass opacities in both lungs on chest CT. Chest radiography is usually performed to further support the diagnosis of DAH. Radiological findings of DAH might include areas of widespread ground-glass opacities or consolidation in the acute phase. In the subacute phase, chest CT might show fine, diffuse, nodular densities, and in the later stage, there might be evidence of interlobular septal thickening due to intralymphatic accumulation of hemosiderin.[13] However, early- stage DAH is difficult to diagnose because chest X-ray and CT findings are non-specific and required differentiation from other lung diseases.

The etiology of DAH could be categorized into infectious and non-infectious causes. Usually, pulmonary infections are rarely reported in association with DAH; however, they should be considered in the diagnostic evaluation, due to the obvious therapeutic implications.[10] In immunocompromised patients, the main causes of DAH are infection with cytomegalovirus, adenovirus, and *Mycoplasma, Legionella*, and *Strongyloides* species; and invasive aspergillosis. On the other hand, in immunocompetent patients, the infectious diseases that frequently cause DAH are influenza A (H1N1), dengue, leptospirosis, malaria, and *Staphylococcus aureus* infection.[5] Very few reports have described an association between PCP and DAH,[14] and that too only in HIV-positive patients.[6,15] In our patient, DAH was related to PCP, suggesting that PCP might be considered as one of the possible causes of DAH in RA patients.

Treatment of DAH involves supportive respiratory care and control of any underlying systemic disease. In patients with pulmonary capillaritis, a combination of systemic glucocorticoids and immunosuppressive therapy should be considered. For patients with infection-related DAH, treating the underlying infection is essential,[4] In our case, as soon as positivity of *Pneumocystis jirovecii*-specific DNA was confirmed, TMP-SMX was administered. With a 3-week course of TMP-SMX treatment, her symptoms and laboratory data improved without any complications.

CONCLUSION

PCP complicated by DAH is rare in RA patients receiving immunosuppressive drugs but could be lethal. Both PCP and DAH might be difficult to diagnose in the early stage because the symptoms and radiologic findings of both are initially non-specific and require differentiation from those of other lung diseases. Therefore, when an RA patient with respiratory symptoms does not respond to the initial treatment, we suggest early bronchoscopic examination with BAL, as this will enable the diagnosis of DAH as well as associated infections.

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Author contributions: SK: data collection, writing and original draft. SWC: supervision, writing, review and editing. DHL: supervision, writing, review and editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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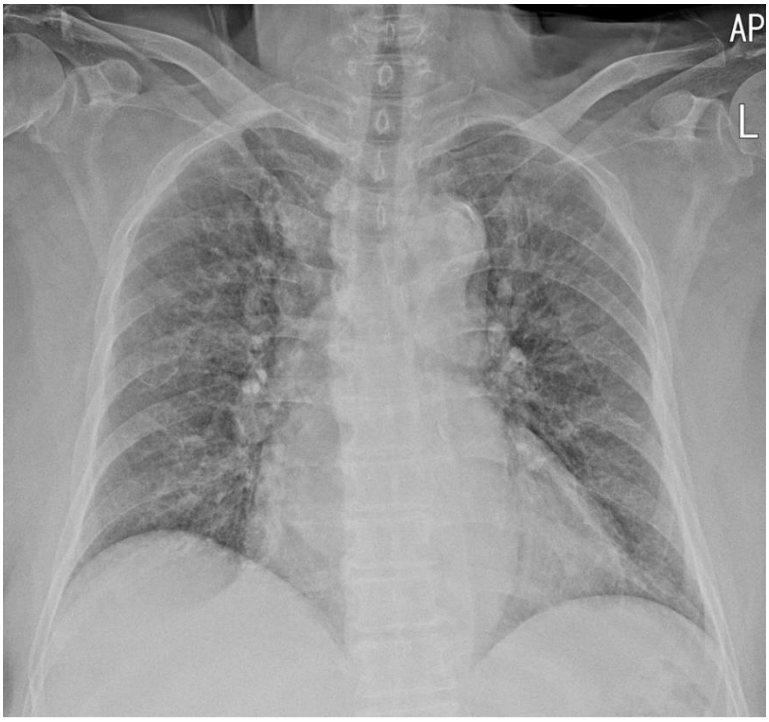

Figure 1: Chest X-ray obtained at admission. Diffuse mildly increased interstitial opacities in both lungs.

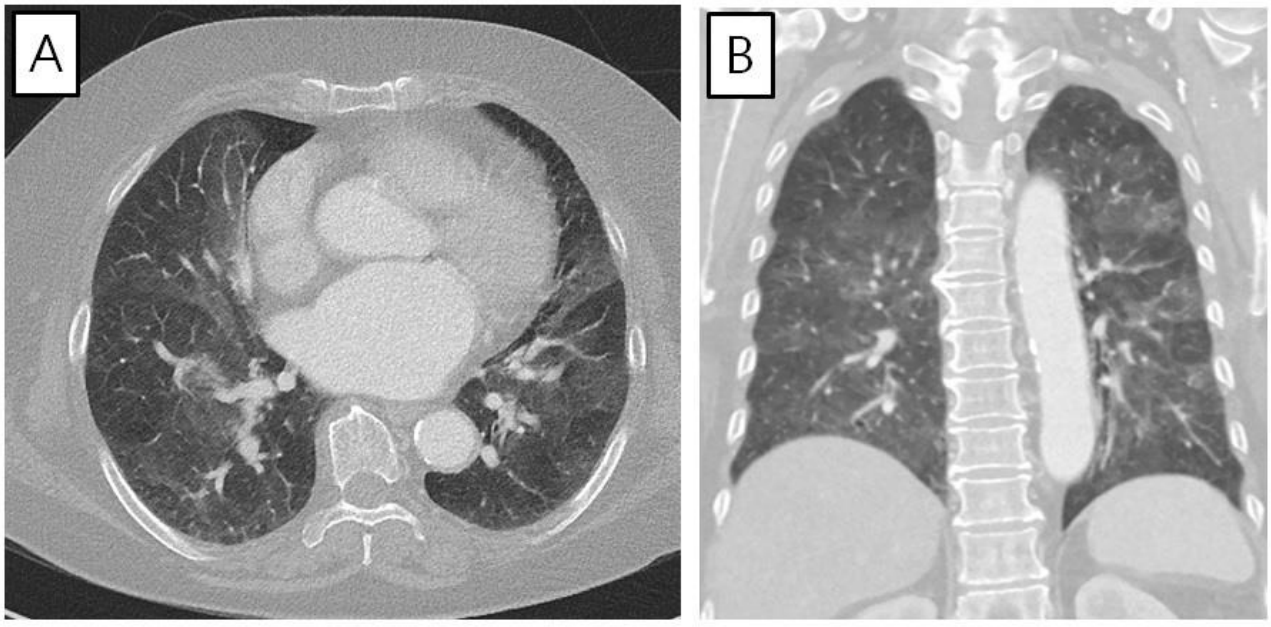

Figure 2: Computed tomography of the chest showing multiple ill-defined ground-glass opacities in both lungs. (A: axial plane, B: coronal plane)

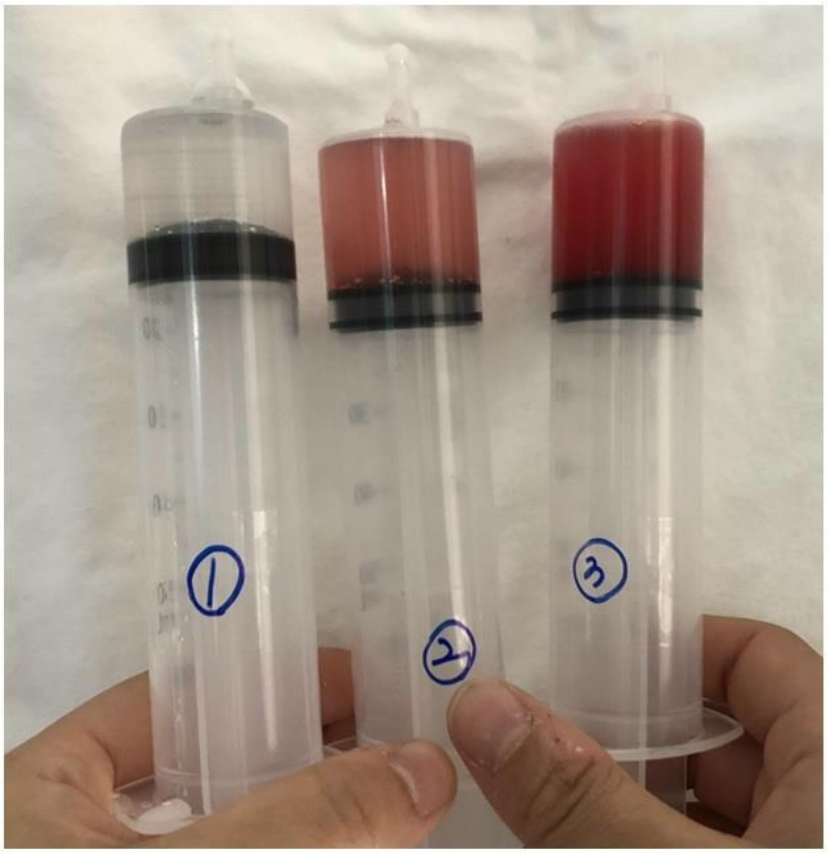

Figure 3: Examination of serially collected bronchoalveolar lavage fluid samples revealed progressively bloody returns, suggesting alveolar hemorrhage.

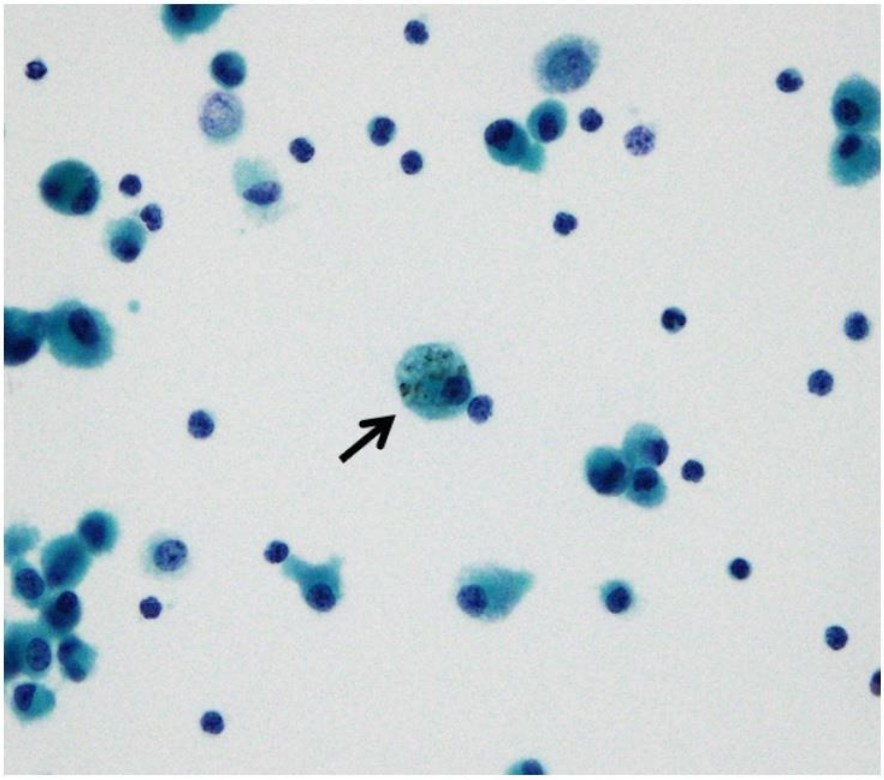

Figure 4: Hemosiderin-laden macrophages seen on bronchoalveolar lavage smears (Papanicolaou staining, ×400).