Antineutrophil Cytoplasmic Antibody-associated Vasculitis Superimposed on Infection-related Glomerulonephritis Secondary to Pulmonary *Mycobacterium avium* Complex Infection

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Abstract

A 73-year-old woman was diagnosed with pulmonary *Mycobacterium avium* complex (MAC) infection and received no treatment. Disease progression was evident one year later with the development of myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA) titers and systemic symptoms of a fever, polyarthritis, purpura, and rapidly progressive glomerulonephritis. Her symptoms did not improve with antibi-otic treatment. A renal biopsy revealed crescentic glomerulonephritis with immunodeposition. According to these findings, she was diagnosed with ANCA-associated vasculitis (AAV) superimposed on infection-related glomerulonephritis (IRGN). Although there was a risk of aggravating an underlying infection, the combination therapy of corticosteroid and antibiotics improved AAV, IRGN, and even the lung radiological findings. To the best of our knowledge, this is the first case of AAV and IRGN secondary to pulmonary MAC infection.

Key words: myeloperoxidase-antineutrophil cytoplasmic antibody, antineutrophil cytoplasmic antibody-associated vasculitis, infection-related glomerulonephritis, *Mycobacterium avium* complex


Introduction

An increase in the occurrence of nontuberculous mycobacteria (NTM) has been reported in North America, with annual increases of 2.6-8.5% (1, 2). Similarly, a steady increase in the mortality and estimated prevalence of NTM has been reported in Japan (3). Pulmonary *Mycobacterium avium* complex (MAC) infection is considered to be the cause for most instances of NTM. This infection can cause progressive lung disease, leading to respiratory failure and even death in patients with no history of lung disease or immunodeficiency. Adverse medication reactions, insufficient antibacterial activity, and frequent relapses often preclude successful therapy. Patients are occasionally not treated and instead are just conservatively observed for any possible progression when their symptoms are minimal or when they are elderly.

Bacterial infections can induce immune complex-mediated glomerulonephritis, which is referred to as infection-related glomerulonephritis (IRGN) or postinfectious glomerulonephritis. There are only a few reports of IRGN caused by NTM (4-7). Immune complexes against bacterial antigens are suspected to be contributing factors in IRGN development. On the other hand, there are several reports of the coexistence of systemic vasculitis and chronic supplicative lung disease, including patients with cystic fibrosis, bronchiectasis, and rarely mycobacterium infection (8, 9). We herein re-
report the first case of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and IRGN that appeared to have developed secondary to pulmonary MAC infection. This case suggests the possibility of a common pathophysiology underlying AAV and IRGN.

**Case Report**

A 73-year-old woman was diagnosed with pulmonary MAC infection in June 2013. She had no subjective symptoms at that time and received no treatment. There was no deterioration in her chest radiological findings until March 2014. In May 2014, she was admitted to our hospital with a two-week history of a productive cough and a fever of approximately 38.0°C. The patient had been unsuccessfully treated using the antibiotics ceftriaxone and clarithromycin (CAM) by her local medical doctor, and a rash was present on both forearms.

On admission, a physical examination showed a body temperature of 37.2°C, a regular pulse rate of 89 beats/min, a respiratory rate of 22 breaths/min, SpO₂ of 98%, and blood pressure of 142/67 mmHg. Livedo reticularis was present in her extremities. A computed tomography (CT) scan showed partial progression of consolidation in both lungs as compared with two months previously (Fig. 1). Laboratory test results were as follows: white blood cell count, 8,800/μL; neutrophils, 7,050/μL (80.1%); lymphocytes, 1,060/μL (12.0%); eosinophils, 440/μL (5.0%); red blood cell count, 391 million/μL; hemoglobin, 10.9 g/dL; total protein, 6.4 g/dL; albumin, 2.6 g/dL; blood urea nitrogen (BUN), 13 mg/dL; creatinine (Cre), 0.82 mg/dL; and C-reactive protein (CRP), 9.59 mg/dL. Enzyme-linked immunosorbent assay titers of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) were positive at 7.9 U/mL (normal < 3.5 U/mL). Because the titers of MPO-ANCA were relatively low and the kidney function did not appear to have deteriorated, we presumed that she had not developed vasculitis. Gram staining and a bacterial culture of her sputum were both negative, and Ziehl-Neelsen staining was negative for acid-fast bacilli. Polymerase chain reaction (PCR) amplification to detect *M. tuberculosis*, *M. avium*, and *M. intracellularare* was negative.

The patient was diagnosed with community-acquired pneumonia, and she started treatment with a tazobactam/piperacillin and azithromycin antibacterial regimen; however, her symptoms did not improve. A sputum culture performed two weeks after admission was positive for *M. avium*, and thus, it was considered that her symptoms were caused by MAC disease. Antimycobacterial treatment for MAC [CAM, 800 mg/day; rifampicin (RFP), 300 mg/day; and ethambutol, 500 mg/day] was initiated but was stopped after two days due to nausea and vomiting. A lower dose treatment (CAM, 200 mg/day, followed by RFP, 150 mg/day) was resumed along with antiemetic agents, however, she was unable to

Figure 1. (A, B) A computed tomography (CT) scan performed at admission showed patchy distribution of centrilobular nodules, bronchiectasis, and increased consolidation compared with two months previously. (C, D) A CT scan performed two weeks after the initiation of prednisolone therapy showed a marked improvement in bilateral consolidation.
orally take the antibiotics due to nausea and vomiting. Although her lung radiological findings and productive cough improved slightly after three weeks of hospitalization, the patient developed new symptoms, including purpura of the extremities, nausea, and arthralgia. Laboratory tests performed two weeks after admission revealed that the serum Cre and BUN levels were elevated to 1.54 mg/dL and 27 mg/dL, respectively. A urinalysis showed proteinuria (1.23 g/24 hours), hematuria [20-30 red blood cells/high-power fields (HPF)], and granular casts (1/10 HPF) in the urinary sediment. The serum immunoglobulin (Ig) E level was elevated to 249 IU/L, but IgG, IgM, and IgA levels were all within the normal ranges. The serum complement levels were also within the normal range, C3=122.5 mg/dL, C4= 33.5 mg/dL, and CH50=55.6 U/mL. Immunologic test results were negative for antinuclear antibody, cryoglobulin, anti-streptolysin O antibody, and proteinase-3 antineutrophil cytoplastic antibody (PR-3ANCA), whereas MPO-ANCA titers were elevated to 14.2 U/mL.

According to these findings, AAV with rapidly progressive glomerulonephritis (RPGN) was highly suspected and a renal biopsy was performed. On light microscopy, six glomeruli were observed, two of which showed global sclerosis, whereas the remaining four all showed cellular crescents and focal fibrinoid necrosis of the glomerular tuft with wrinkled and collapsed capillaries and disruption of Bowman’s capsule. Segmental endocapillary proliferation was also noted in the glomerulus (Fig. 2). Tubulitis, interstitial inflammation, and peritubular capillaritis were observed; however, findings of vasculitis were not detected in the arteries and arterioles. Immunofluorescent staining was positive for IgG, IgM, C3, kappa light chains, and lambda light chains in the mesangium and along the capillary walls (Fig. 3). Electron microscopy (EM) revealed mesangial and subendothelial electron-dense deposits as well as hump-shaped subepithelial deposits (Fig. 4). These histologic findings suggested IRGN accompanied by MPO-ANCA related, severe, necrotizing crescentic glomerulonephritis.

To evaluate the involvement of lung disease in the pathologic condition, bronchoscopy was performed. There was no sputum in the trachea, and her bronchoalveolar lavage specimen was smear- and culture-negative for Mycobacterium, but did show an increase in lymphocytes. A transbronchial lung biopsy of the consolidation showed nonspecific inflammation associated with alveolar and bronchiolo macrophages and lymphocytes. No alveolar capillaritis or granulomas were observed.

The symptoms of a fever and productive cough present
before admission may have been caused by MAC. However, purpura, nausea, arthralgia, and RPGN, which presented after the admission, could be clinical manifestations of AAV and IRGN. The necessity of antibiotic treatment was clear because IRGN and AAV were presumed to have developed secondary to infection. The patient could not tolerate antibiotics due to her poor general condition possibly as a result of AAV. We therefore started treatment with prednisolone, 1 mg/kg/day. Although her AAV disease classification of the European Vasculitis Study Group was “Generalized,” the addition of cyclophosphamide was suspended due to a potential deterioration of the pulmonary infection (10). Her fever improved immediately, and nausea, purpura, and arthralgia also gradually improved. Thereafter, antimycobacterial treatment was successfully resumed at full dose without nausea (Fig. 5). The CRP and MPO-ANCA titers decreased and prednisolone treatment was tapered. Her renal function did not fully recover, although the aggravation stopped. A CT scan performed two weeks after starting prednisolone treatment showed a marked improvement in bilateral consolidation (Fig. 1). Repeated sputum smears for acid-fast staining and mycobacterial cultures were negative during the 12-month follow-up.

Discussion

Our patient initially had a pulmonary MAC infection, which was followed by the appearance of RPGN and systemic symptoms, such as a fever, purpura, and arthralgia. We initially presumed that she had developed AAV, however, a renal biopsy revealed the coexistence of IRGN. Although RPGN was thought to be caused by AAV and IRGN, it was difficult to determine whether her fever and CRP elevation were caused by MAC infection or AAV. These symptoms

Figure 3. Immunofluorescent staining revealed granular deposits of IgG, IgM, C3, kappa light chains, and lambda light chains along the capillary walls and in the mesangial region, original magnification 400×.

Figure 4. Electron microscopy showing electron-dense deposits in the mesangium area and hump-shaped subepithelial deposits (arrow). Bar=5 μm.
improved immediately after the introduction of corticosteroid therapy, and a bronchoalveolar lavage specimen obtained to monitor for disease progression was smear- and culture-negative for *Mycobacterium*. These findings suggested that the main causes of her symptoms were AAV and IRGN.

A previous study reported an association of chronic airway infection with AAV (8, 9). Particularly, a significant number of articles reported the cases of PR-3ANCA and Wegener's granulomatosis in relation to staphylococcal infection (11). Although further investigation is still required, certain infections are considered to induce autoimmune responses through antigenic mimicry and enhanced immunogenicity of host antigens as a result of activation of the innate immune system (8, 12-14).

Regarding mycobacterium, it is well established in the literature that ANCA seropositivity can be elevated in patients with *M. tuberculosis* infection (15). These patients occasionally develop vasculitis, such as that in Takayasu's arteritis, cutaneous leukocytoclastic vasculitis, and AAV (11). In contrast, we found only three published case reports pertaining to comorbid AAV with MAC infection, although an increase in the occurrence of MAC has been reported (16-18). As a result, potential differences in etiology between *M. tuberculosis* and MAC infections should be considered.

Previously, predominant cases of IRGN were observed in children following streptococcal upper respiratory tract or skin infections. However, a significant percentage of recent cases were adults, particularly elderly or immunocompromised individuals. Non-streptococcal infections have become frequent precipitants in adults, whereas cases caused by NTM were rarely reported (19).

Although the diagnostic criteria of IRGN are not established, Nasr et al. reported at least 3 of the following 5 criteria were required for inclusion in their case series: 1) clinical or laboratory evidence of infection either preceding or occurring at the onset of glomerulonephritis; 2) depressed serum complement; 3) endocapillary proliferative and exudative glomerulonephritis; 4) C3-dominant or co-dominant glomerular immunofluorescent staining; and 5) hump-shaped subepithelial deposits on EM (20, 21). The present case satisfied 4/5 of these criteria, with the exception of the depressed serum complement.

The precise mechanisms underlying IRGN have not been fully elucidated. Roles for *in situ* immune complex formation by antibodies directed against stationary cationic bacterial antigens or directed toward intrinsic glomerular antigens via “molecular mimicry” have been proposed. Other theories support glomerular *in situ* localization of circulating cationic bacterial antigens that are capable of activating complement through lectin or alternative pathways, independent of Ig (19).

IRGN is characterized by endocapillary proliferative glomerulonephritis with immune complex deposits and rarely with necrotizing crescentic glomerulonephritis, which is commonly caused by AAV. Nasr et al. reported that crescentic and necrotizing glomerulonephritis with ≥50% cres-
cents were observed only in 4.7% of adult cases of IRGN (20), and 5 of 66 elderly patients with IRGN had ANCA seropositivity. Among the five ANCA seropositive patients, two patients showed diffuse crescentic and focal endocapillary proliferative glomerulonephritis with C3-dominant immunofluorescent staining and hump-shaped subepithelial deposits on EM on the biopsy (21). These features are similar to the pathological findings from the present case. There appears to be some degree of common etiology between IRGN and AAV caused by infection, with possible overlap in the disease features. In the present case, a renal biopsy showed necrotizing crescentic glomerulonephritis and peritubular capillaritis. Furthermore, there were symptoms of systemic vasculitis such as polyarthritides, purpura, and a possible fever. We determined that AAV development was superimposed on preexisting IRGN.

To the best of our knowledge, there are only four case reports of IRGN secondary to NTM, among which there was only one case with MAC (4-7). Wen et al. reported a case of IRGN with crescentic glomerulonephritis secondary to pulmonary MAC; however, ANCA seropositivity was not stated and the patient responded to antibiotic treatment. Thus, our paper is the first reported case of AAV and IRGN secondary to pulmonary MAC infection.

A chest CT scan, which was obtained two weeks after the administration of corticosteroids and antimycobacterial treatment, showed a marked improvement of the consolidation in both lungs. Although the radiological findings were typical of MAC infection, we have never experienced such a rapid and dramatic improvement with antibiotic treatment alone. Among Mycobacterium, the efficacy of systemic corticosteroids is well documented for several conditions, such as tuberculous meningitis and pericarditis (22). The precise mechanisms by which corticosteroids elicit a benefit are not clear, but may be related to regulation of excessive immune responses. With regard to MAC (from the same Mycobacterium), there is very little evidence to support the effect of corticosteroid therapy. Hamada et al. reported a case of pulmonary MAC accompanied by organizing pneumonia that improved with corticosteroids (23). In the present case, although the lung radiological and pathological findings were not typical of organizing pneumonia, there may have been excessive inflammation that responded to corticosteroid therapy.

In summary, we herein described the first known case of AAV and IRGN secondary to pulmonary MAC infection. Although there was a risk of aggravating an underlying infection, the combination therapy of corticosteroid and antibiotics improved AAV, IRGN, and even the lung radiological findings.

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

References


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