Case Report

Granulomatosis with polyangiitis diagnosed during the treatment of otitis media with prednisolone in a patient with anti-neutrophil cytoplasmic antibody-associated vasculitis: A case report

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ABSTRACT

A 78-year-old woman with severe auditory disturbance was referred to our hospital and was diagnosed with otitis media with anti-neutrophil cytoplasmic antibody-associated vasculitis (OMAAV). The auditory disturbance improved moderately with prednisolone 40 mg/day, but multiple pulmonary masses were detected on chest computed tomography six months later. Transbronchial lung biopsy revealed granulomatosis with polyangiitis (GPA). Administration of prednisolone 50 mg/day and cyclophosphamide 500 mg once every two weeks for 12 weeks improved the lung lesions, but no further improvement in the hearing ability was observed. Prednisolone monotherapy was not able to prevent progression of OMAAV to GPA.

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of small-vessel vasculitis that includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic GPA. Otological symptoms are often observed in the initial stages of AAV [1]. However, patients with early symptoms might not meet the standard diagnostic criteria for systemic AAV [2,3], and delayed diagnosis could result in permanent and profound hearing loss or flare-up of vasculitis. Therefore, the Japan Otological Society proposed a new category called otitis media with AAV (OMAAV) for allowing the early treatment of AAV [4]. However, therapies for AAV localized in the upper respiratory tract and OMAAV have not been standardized.

Herein, we report the case of a patient with OMAAV, in whom treatment with prednisolone (PSL) improved hearing loss, but did not prevent progression to GPA with lung involvement.

2. Case report

In the beginning of March 2021, a 78-year-old woman with history of bronchial asthma and diabetes was referred to our hospital with bilateral hearing loss for a week. She was a never smoker. Physical examination findings were as follows: body temperature, 37.0 °C; pulse rate, 78/min; respiratory rate, 20/min; and blood pressure, 132/85 mmHg. No skin lesions were observed, but peripheral lymphadenopathy was noted in the bilateral submandibular glands. Respiratory and cardiac sounds were clear. Otolaryngologi—

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Examination revealed right-sided otorrhea and purulent nasal discharge. However, otorrhoeal fluid culture yielded no bacterial growth. Audiometric tests showed a severe sensorineural hearing loss: the pure tone averages for the right and left ears were 100.0 dB and 91.3 dB, respectively. Computed tomography (CT) revealed bilateral otitis media, sinusitis, multiple nodular shadows in the lungs, bronchiectatic changes, infiltrates, and centrilobular branching opacities (Fig. 1A). However, there was no mass or bone destruction were noted in the ears and paranasal sinuses. The white blood cell count was \(8.3 \times 10^9/L\) with 80.0% neutrophils, 14.2% lymphocytes, 4.0% monocytes, 1.4% eosinophils, and 0.4% basophils. The C-reactive protein level was slightly elevated to 1.31 mg/dL, and the (1 → 3)-β-D glucan level was within the normal range. Results of liver and kidney function tests were normal, urinalysis showed no abnormal findings, and QuantiFERON-TB GOLD Plus was negative. Further, serum Proteinase-3 (PR3)-ANCA level was elevated to 19.5 U/mL (normal, < 3.5 U/mL), and myeloperoxidase (MPO)-ANCA was < 1.0 U/mL (Table 1). Biopsy of the submandibular gland

![CT images](image)

**Fig. 1.** (A-1, A-2, and A-3) Chest CT images at the first visit show pulmonary multiple nodular shadows, bronchiectatic changes, infiltrates, and centrilobular branching opacities. (B-1, B-2, and B-3) Six months after the first visit, chest CT at the emergency center visit shows multiple cavitary and noncavitary lung masses with peripheral and upper-lobe predominance in both lungs.

**CT,** computed tomography.

**Table 1**

| Laboratory data. | Hematology | Serology | Biochemistry | Urinalysis |
|------------------|------------|----------|--------------|------------|
|                  |            |          |              |            |
| WBC              | 8300       | CRP      | TP           | Sugar      |
| Neut             | 80         | IgG      | Alb          | Protein    |
| Eosin            | 1.4        | IgA      | AST          | Blood      |
| Mono             | 4          | IgM      | ALT          |            |
| Lymph            | 14.2       | C3       | LDH          |            |
| RBC              | 383 × 10^6 | C4       | ALP          |            |
| Hb               | 11.7       | CH50     | BUN          |            |
| Ht               | 36.2       | > 60     | Cr           |            |
| Plt              | 40.0 × 10^4| 19.5     | Na           |            |
|                  |            | < 1.0    | K            |            |
|                  |            | IU/mL    | CI           |            |
|                  |            | IU/mL    | BS           |            |
|                  |            | IU/mL    | HbA1c        |            |

**Abnormal values are underlined.**
revealed suppurative sialadenitis without granulation. Antibiotic therapy with intravenous ampicillin/sulbactam (6.0 g/day) was initiated, but the otitis media did not improve. Bronchoscopic examination with endobronchial ultrasonography with a guide sheath was performed on the left B2, and results of polymerase chain reaction tests on the bronchial lavage fluid were negative for *Mycobacterium avium-intracellulare* and *M. tuberculosis*. A bronchial lavage fluid smear was positive for acid-fast bacilli (1+; 1–9 acid-fast bacilli per 100 field), but culture revealed no bacterial growth in the mycobacterial growth indicator tube. Furthermore, histological examination of transbronchial biopsy specimens obtained from lung nodules revealed non-specific inflammation without granulomas. The patient was diagnosed with OMAAV based on bilateral severe sensorineural hearing loss, intractable otitis media, and elevated serum PR3-ANCA levels. Moreover, we considered non-tuberculous mycobacteria-associated pulmonary disease (NTM-PD); therefore, oral PSL 40 mg/day was initiated, and we did not administer immunosuppressants to avoid the exacerbation of NTM-PD. After bronchoscopic examination, minocycline 200 mg/day was administered for five months to treat the suppurative sialadenitis of the submandibular gland. The serum PR3-ANCA level decreased to within the normal range in April 2021 with PSL 35 mg/day and remained within the normal range thereafter. As the auditory capacity gradually improved, we tapered the PSL dosage to 20 mg/day. The hearing ability improved to 61.3 dB (right) and 57.5 dB (left) at the end of August 2021.

At the end of September, the patient presented with high fever for three days and visited our emergency center on foot. Chest CT showed multiple cavitary and noncavitary masses with peripheral and upper-lobe predominance in both lungs (Fig. 1B). The CRP and PR3-ANCA levels were significantly elevated to 22.39 mg/dL and 9.8 U/mL, respectively. A second bronchoscopic examination with endobronchial ultrasonography with a guide sheath was performed on the right B2. There was no evidence of bacterial infection, including in the results of polymerase chain reaction tests for *Mycobacterium avium-intracellulare* complex on the bronchial lavage fluid. Furthermore, histological examination of transbronchial biopsy specimens obtained from masses revealed micro abscesses and necrotizing granulomatous vasculitis, which were consistent with GPA (Fig. 2).

The patient was diagnosed with GPA based on the diagnostic criteria of the Japanese Ministry of Health Labour and Welfare [2]. Therefore, we increased to PSL 50 mg/day (1 mg/kg) with a dose reduction every 2 weeks and administered intravenous cyclophosphamide (CY) 500 mg once every two weeks for 12 weeks as a remission-induction therapy. NTM-PD did not progress, and no antimycobacterial therapy was administered. The patient's symptoms and CT findings rapidly improved, and the PR3-ANCA level promptly decreased to within the normal range. However, with regard to the auditory capacity, moderate hearing loss persisted without further improvement in hearing ability at the end of the remission-induction therapy (Fig. 3).

3. Discussion

GPA is a multisystem disease of unknown cause characterized by necrotizing granulomatous vasculitis that predominantly affects the upper and lower respiratory tract, lungs, and kidneys. The estimated prevalence of GPA in Japan is approximately 2 cases per 1 million populations with a male:female ratio of approximately 1:1 [5]. The prevalence of otological manifestations in GPA has been reported to be between 19% and 61% [6,7]. Initially, our case could not be definitively diagnosed as GPA according to the diagnostic criteria of the Japanese Ministry of Health Labour and Welfare. It is proposed that AAV-associated progressive intractable otitis media or hearing loss, which may not meet the standard diagnostic criteria of systemic AAV, is classified as OMAAV [4]. In our patient, a definitive diagnosis of OMAAV was made based on the bilateral worst hearing loss, elevated PR3-ANCA levels, and exclusion of other types of intractable otitis media.

Pulmonary involvement in GPA occurs in 25–80% of cases [8]. In pulmonary GPA, the most common abnormalities observed on radiographs and CT images are lung nodules and masses, that are often multiple and with cavitation. In addition, infiltrates, airspaces, and ground-glass opacities are frequent findings. This variety in clinical presentation makes the diagnosis of GPA challenging, and GPA can be difficult to distinguish from other diseases such as infection, sarcoidosis, or malignancy [9]. Furthermore, clinical and histologic similarities between AAV and NTM-PD have been reported [10,11]. At the first visit, chest CT images of our patient showed multiple nodules, bronchiectasis, infiltrates, and centrilobular branching opacities, and some parts of the image were suggestive of pulmonary mycobacterial infection. Thus, the patient's lung images suggested the concurrence of AAV and NTM-PD.

A sample of the bronchial lavage fluid was stained and the presence of mycobacteria was examined according to the procedures recommended by Centers for Disease Control and Prevention [12]. The results confirmed the presence of acid-fast bacilli in the smear of the bronchial lavage fluid from the first bronchoscopic examination. However, no mycobacterial growth was detected on culture.

![Fig. 2](image-url)  
**Fig. 2.** The lung biopsy specimen shows micro abscesses (▲), necrotizing vasculitis (▼), rupture of the internal elastic plate (△), and granuloma (○). Scale bar = 100 μm. (A, C: Hematoxylin and eosin staining, B: Elastica van Gieson staining).
This may be attributed to the death of the bacteria in the process of digestion and decontamination of the specimen [13]. Based on the findings on microbiological examination and lung imaging, we considered the patient to have NTM-PD. The treatment of patients with AAV and NTM-PD is controversial. Addy et al. reported successful dual treatment with immunosuppressive therapy for vasculitis and antimicrobial therapy for NTM-PD [14]. Generally, achieving a balance between controlling pulmonary infection and immunosuppression is difficult. Adequate immunosuppression therapy could lead a deterioration of NTM-PD. Treatment regimens against NTM are prolonged and toxic and the effectiveness is uncertain. Fortunately, in this case, no exacerbation of the lung infection was observed during the treatment of GPA with PSL and CY. This could be attributed to the fact that long-term use of minocycline may be effective for NTM-PD [5].

In a survey of 235 Japanese patients with OMAAV, 60%, 19%, and 16% of patients were MPO-ANCA-positive, PR3-ANCA-positive, and both ANCA-negative, respectively [4]. In this report, the PR3-ANCA-positive group showed the higher rates of involvement of the nose (64%) and lungs (51%) than the other groups throughout the clinical course. Corticosteroids (CS) alone were administered to 50% and 34% of MPO-ANCA-positive and PR3-ANCA-positive patients, respectively. Disease relapse after introduction of treatment presented as symptoms associated with various organs during the clinical course. Although the two-group comparison analysis failed to show significant differences, the relapse rate was lower in patients treated with CS plus an immunosuppressant than in patients treated with CS alone (36% versus 47%). The hearing improvement rate was significantly better in patients who received CS plus an immunosuppressant than in those who received CS alone (68% vs. 56%; p < 0.01). In our patient, comparison of the median air-conduction hearing levels pre- and post-treatment with PSL revealed an improvement of > 30 dB, indicating significant recovery, as described previously [15]. Moreover, when growing lung masses indicated a relapse, hearing levels did not worsen. Interestingly, the secondary treatment with CS plus immunosuppressant did not improve hearing levels further, indicating that CS therapy had led to remission.

Currently, therapies for OMAAV have not been standardized. The patient with OMAAV was treated with PSL alone due to suspected concomitant NTM-PD. The treatment improved the patient’s hearing loss, but could not prevent progression to GPA with lung involvement. OMAAV relapse is reported to be associated with an unfavorable and life-threatening clinical course [5]. Therefore, PSL combined with immunosuppression should be considered for OMAAV therapy even in patients receiving antimicrobial therapy.

**Declaration of competing interest**

The authors declare that they have no conflicts of interest.
