

[CASE REPORT]

Propylthiouracil-induced Otitis Media with Antineutrophil Cytoplasmic Antibody-associated Vasculitis

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Abstract:

We herein report a case of otitis media with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (OMAAV) induced by propylthiouracil (PTU). A 30-year-old Japanese woman with Graves' disease, who was treated with PTU, reported with otitis media with sensorineural hearing loss bilaterally and trigeminal neuralgia on the left side, as well as elevated serum levels of myeloperoxidase-ANCA. Prior treatment with antibiotics was ineffective even after tympanostomy. However, clinical remission was immediately achieved after initiating prednisolone together with PTU withdrawal. These findings suggest that PTU therapy induces localized otological involvement as the concept of OMAAV.

Key words: ANCA-related vasculitis, OMAAV, propylthiouracil, MPO-ANCA

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Introduction

Antineutrophil cytoplasmic antibody (ANCA) plays an important role in the development of systemic vasculitis, which is characterized by small-sized necrotizing vasculitis. ANCA-associated vasculitis includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (1, 2). Symptoms of ear, nose, and throat (ENT) involvement are commonly observed in 10–90% of patients with MPA, GPA, and EGPA during their clinical course (3-5). Furthermore, the localized appearance of otological involvement, with symptoms such as otitis media and hearing loss, may present as the initial manifestation of antibody-associated vasculitis (AAV) (6, 7). Many patients experience only localized otological involvement and never meet the definite criteria of AAV (8). This raises concerns about disease progression because of delays in appropriate treatment. In contrast, the novel concept of otitis media with AAV (OMAAV) has been recently proposed for limited otitis media with progressive hearing loss that is attributed to AAV (7, 9, 10).

We herein report the case of a patient who developed

OMAAV during treatment with propylthiouracil (PTU), which is well-recognized as a secondary causative agent of AAV (11, 12).

Case Report

A 30-year-old Japanese woman with a 7-year history of receiving treatment for Graves' disease was admitted to our hospital because of bilateral sensorineural hearing loss (SNHL) and earache. She had had a previous episode of drug eruption due to thiamazole, but myeloperoxidase (MPO)- and proteinase 3 (PR3)-ANCA were negative at that time. PTU had been alternatively administered at a dose of 250 mg daily for 6 years, allowing for the maintenance of normal serum levels of free triiodothyronine (T3), free thyroxine (T4), and thyrotropin (TSH). She started oral treatment with an antibacterial agent a few days after the initial occurrence of bilateral hearing loss at a neighboring otolaryngology clinic. However, she subsequently developed a bilateral earache two weeks later and was diagnosed with otitis media resulting in SNHL. Although oral antibiotics had been consecutively administered for four weeks since her ear symptoms occurred, no improvement was achieved.

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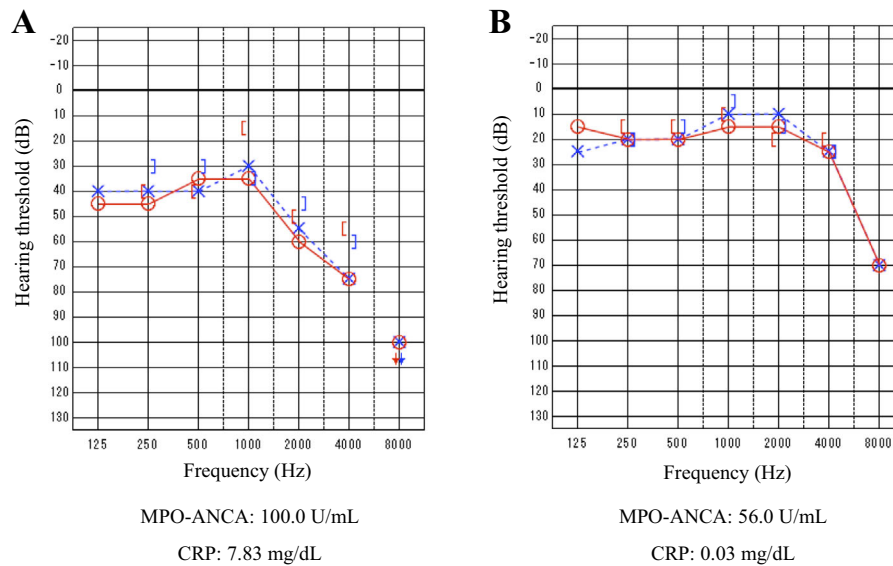


Figure 1. Pure-tone audiometry, serum levels of MPO-ANCA and CRP before (A) and three months after initiating prednisolone with cessation of propylthiouracil therapy (B). ○: air conduction (right), ×: air conduction (left), [: bone conduction (right),]: bone conduction (left). MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, CRP: C-reactive protein

At admission to our hospital, her body temperature was 36.8 °C, and her consciousness was clear. On a physical examination, signs of meningeal irritation were not observed, but painful paresthesia at the left mandibular division of the trigeminal nerve area and bilateral auditory impairment were present. However, no definitive findings indicating other physical disorders, such as ocular, cutaneous, cardiorespiratory, abdominal, articular, musculoskeletal, or extremity peripheral nerve involvement, were found. Laboratory examinations revealed normal findings for the renal and liver function. There were also no abnormal findings on urine tests. Increased counts of white blood cells ($9,340/\mu\text{L}$, normal: $3,040 - 8,720/\mu\text{L}$) and blood platelets ($41.1 \times 10^4/\mu\text{L}$, normal: $13.7 \times 10^4 - 37.8 \times 10^4/\mu\text{L}$) were shown, but the red blood cell counts and hemoglobin levels were within normal ranges. The eosinophil count was $140/\mu\text{L}$ (normal: $<500/\mu\text{L}$). The serum C-reactive protein (CRP) levels were elevated at 7.83 mg/dL (normal: <0.10 mg/dL). Serum levels of MPO- and PR3-ANCA, which were measured using an enzyme-linked immunosorbent assay, were 100.0 U/mL (normal: <3.4 U/mL) and less than 1.0 U/mL, respectively. Test results for anti-nuclear antibody, rheumatoid factor, and anti-citrullinated protein antibody were negative. Thyroid function tests revealed normal serum levels of free T3 (2.38 pg/mL, normal: 2.3 – 4.0 pg/mL), free T4 (1.17 ng/mL, normal: 1.0 – 2.0 ng/mL), TSH (3.0 $\mu\text{IU/mL}$, normal: 0.2 – 4.0 $\mu\text{IU/mL}$), TSH receptor antibody (0.50 IU/L, normal: <1.30 IU/L), anti-thyroid peroxidase antibody (5.0 IU/mL, normal: <5.2 IU/mL), and thyroglobulin antibody (13.4 IU/mL, normal: <40.6 IU/mL). A pure-tone audiogram showed bilateral SNHL involving high frequencies (Fig. 1A). An ear examination revealed redness of the eardrums and effusion in the tympanic cavities (Fig. 2A). Computed tomography (CT) of

the ear demonstrated soft tissue density in the middle ear and mastoid cavities (Fig. 3).

Tympanostomy was subsequently performed for a pathological and infection assessment. However, neither solid lesions, such as granuloma, nor pathogenic bacteria in the culture of effusion were detected in the middle ear cavity. A systemic survey, including whole-body CT; echocardiography; serological tests for syphilis, hepatitis B virus, hepatitis C virus, human-immunodeficiency virus, mumps virus, and cytomegalovirus; measurement of the procalcitonin and (1,3)- β -D-glucan levels; and mycobacterium tuberculosis-specific interferon- γ tests revealed no findings suggestive of malignancy, infection, pulmonary, or cardiac involvement. There were no findings of hypertrophic pachymeningitis (HP) in the magnetic resonance images of the brain.

Even after tympanostomy, as well as administering ceftriaxone sodium intravenously for one week, the symptoms of inflamed eardrums and impaired hearing persisted. Therefore, the patient was administered prednisolone (PSL) at a dose of 40 mg daily concomitantly with the cessation of PTU. Radioiodine (^{131}I) was administered as an alternative therapy for Graves' disease, which allowed for the maintenance of a normal thyroid function. Relief from trigeminal neuralgia and earache was immediately obtained, and the disturbance of her hearing also gradually recovered. The serum levels of CRP were within the normal range at two weeks after initiating PSL administration, and decreased MPO-ANCA levels were also revealed (Fig. 1B). A pure-tone audiogram performed 3 months later, when the PSL dose had been reduced to 20 mg daily, showed substantial improvement in the bilateral hearing (Fig. 1B). The findings of the eardrums were also apparently normal without effusion in the middle ear (Fig. 2B).

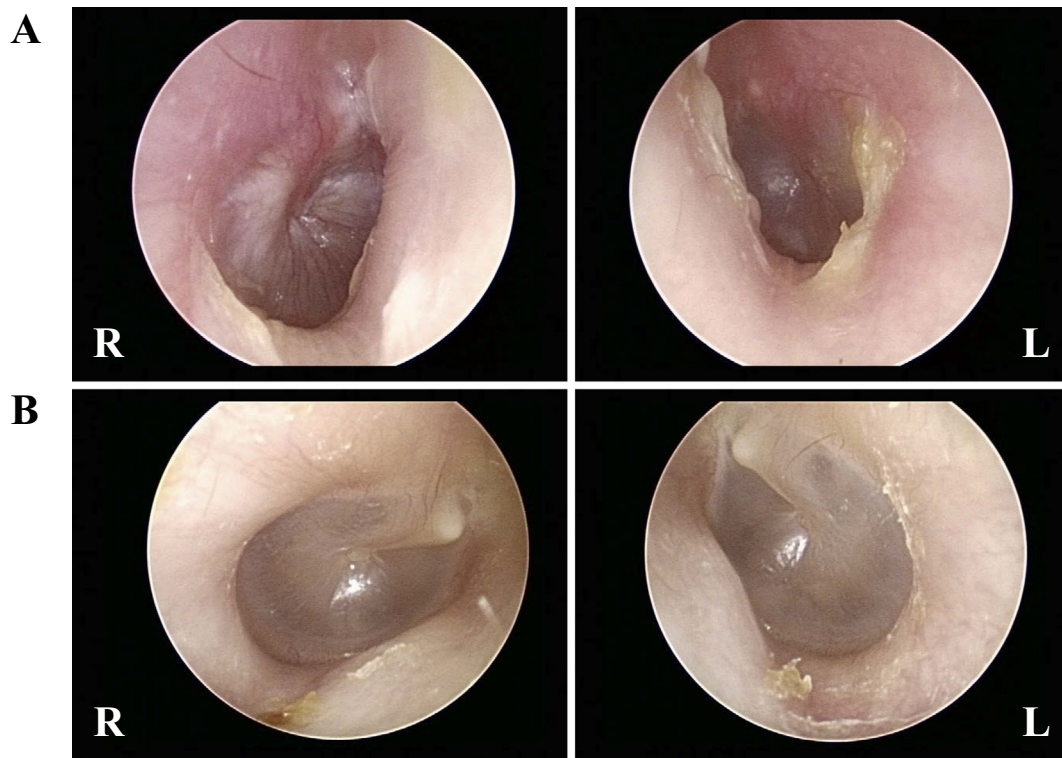


Figure 2. Otoscopy findings of the ear before (A) and three months after initiating prednisolone with propylthiouracil withdrawal (B). The findings of the eardrum revealing redness with effusion in the middle ear (A) and those that were normal (B) are displayed.

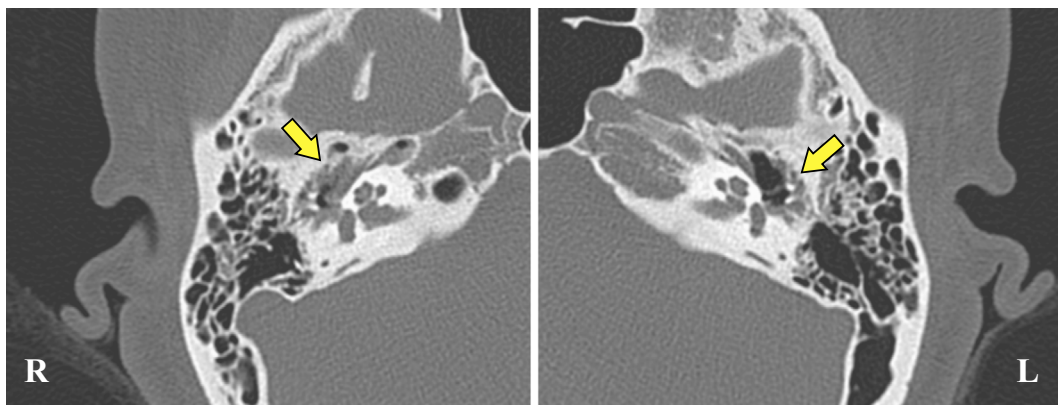


Figure 3. Computed tomography of the ear. Soft tissue density (arrow) surrounding the ossicles is observed, suggesting effusion due to inflammatory reaction.

Discussion

The present case demonstrated the following essential features meeting the criteria of OMAAV (7, 9, 10): 1) otitis media that was refractory to antibiotics even after tympanostomy, 2) a sudden onset and progression of SNHL, 3) positivity of serum MPO-ANCA, and 4) no other causes of illness identified. Limited manifestation of otitis media is sometimes found in the initial phase of AAV; however, it is difficult to make a definitive diagnosis of AAV unless the specific histopathological findings and/or other organic involvements are concomitantly detected (6-8, 13). This pa-

tient had a relatively short duration of otitis media compared with the duration suggested by the consensus algorithm proposed by the European Medical Agency (Watts' criteria) (14). Otitis media should be fundamentally demonstrated for more than three months for the definitive diagnosis of GPA; therefore, it was consequently impossible to meet the criteria for AAV. However, no significant differences have been noted in the clinical characteristics of patients with intractable otitis media among GPA, MPA, and EGPA, suggesting that the definite classification of these three categories of AAV is hardly applicable in cases of intractable localized otitis media associated with AAV (9). Accordingly, the concept of OMAAV can be applied in the

present case.

To our knowledge, three cases of MPO-ANCA-related SNHL induced by PTU have been reported (15-17); however, the concept of OMAAV associated with the administration of PTU has been hardly recognized so far. Regarding other drug-induced AAVs, hydralazine was found to be associated with ENT involvement (18), and one case report described atorvastatin-induced hearing loss and tinnitus (19). However, whether or not these inducible drugs affect the development of OMAAV is unclear. According to previous clinical studies, PTU-induced MPO-ANCA does not always induce symptomatic vasculitis, and mild involvements, such as arthralgia, myalgia, and cutaneous lesions, are common characteristics of PTU-induced AAV (11, 12, 20-22). Furthermore, a comparative study demonstrated that ear manifestations appear less frequently in patients with PTU-induced AAV than in those with primary AAV (22). However, the present case suggested that PTU could also induce OMAAV. Furthermore, trigeminal neuropathy was also shown in this patient. Only one other case of trigeminal neuropathy related to OMAAV has been reported (23), with HP and facial nerve palsy being more common complications and recognized as prognostic factors in OMAAV (7, 9). In patients with GPA, cranial nerve involvements are commonly complicated, and trigeminal neuropathy can also be found (24). However, cranial nerve manifestations are significantly less frequent in PTU-induced AAV than in primary AAV (22); furthermore, it has never been shown that trigeminal neuropathy is specific to PTU-induced AAV. Therefore, the appearance of trigeminal neuropathy may be a possible complication in OMAAV.

PTU therapy strongly induces MPO-ANCA production, despite the reduced frequency of PR3-ANCA (21, 22). The prevalence of MPO-ANCA positivity has been reported to be between 4.1% and 64% in patients with Graves' disease who receive PTU (20, 21). Regarding the pathogenic background of MPO-ANCA production, PTU was found to drive neutrophil extracellular trap formation, including MPO exposure *in vitro* (25); therefore, PTU contributes to the priming process of the AAV cascade. However, it has been shown that the epitopes corresponding to MPO related to PTU are different from those related to the primary AAV, suggesting that the pathogenic mechanism differs between patients with PTU-induced AAV and those with primary AAV (26).

Clinical remission was immediately achieved in the present case by initiating PSL along with ceasing PTU administration. In general, combination immunosuppressive therapy is initially required to achieve clinical remission as the common therapeutic strategy in AAV (27). Even in patients with OMAAV, co-administering immunosuppressants is recommended because of many cases being refractory to corticosteroid single therapy (7, 9). However, the clinical manifestations in PTU-induced AAV were found to be less serious than in primary AAV, as PTU withdrawal with or without corticosteroid single administration can lead to clinical

remission in a majority of patients (20, 22). Accordingly, the pathological mechanism in the present case may be related to PTU-induced AAV.

Of note, however: this is a single case report describing a limited and short clinical course. Therefore, longer observations of the clinical process will be required to determine the definitive prognosis of PTU-induced OMAAV.

This case suggested that patients with Graves' disease who are treated with PTU may develop localized auditory impairment resembling OMAAV. Prompt discontinuation of PTU therapy as well as corticosteroid administration should be performed in order to prevent irreversible hearing loss. However, more clinical experiences should be accumulated in order to establish an effective therapeutic strategy and ensure a favorable long-term prognosis.

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

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