Propylthiouracil-induced otitis media with anti-neutrophil cytoplasmic antibody-associated vasculitis: a case report and review of the literature

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Abstract. Propylthiouracil (PTU)-induced otitis media with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (OMAAV) is an extremely rare adverse event associated with anti-thyroid drugs and is not well recognized. A 42-year-old woman with Graves’ disease undergoing PTU therapy for 8 years visited our hospital because of earache and congested feeling in her left ear. Blood tests, a computed tomography scan and pure tone audiometry revealed otitis media and moderate mixed hearing impairment. Antibiotics, ear drops with antibiotics and painkillers were administered. However, her earache and hearing loss gradually got worse and symptoms of facial nerve palsy appeared. At several weeks after initiation of the treatment, a high serum level of myeloperoxidase (MPO)-ANCA, 75.6 U/mL, was revealed. After excluding other causes, she was diagnosed with OMAAV. PTU was suspected as the cause of her OMAAV and was immediately discontinued, and prednisolone was started. Hearing impairment in her left ear gradually got better and showed substantial improvement. Facial nerve palsy disappeared. Although PTU-induced OMAAV is an extremely rare disease, it is important to recognize the disease, as delayed treatment can lead to irreversible hearing loss, hypertrophic pachymeningitis, and subarachnoid hemorrhage. When patients taking anti-thyroid drugs, especially PTU, are diagnosed with refractory otitis media or hearing loss, it is possible that OMAAV might be the cause and thus serum ANCA levels should be evaluated.

Key words: Propylthiouracil, Anti-neutrophil cytoplasmic antibody, Vasculitis, Otitis media, Hearing loss

Previously, cases of refractory otitis media or progressive hearing loss with neutrophil cytoplasmic antibody (ANCA) that could not be diagnosed by conventional diagnostic criteria for ANCA-associated vasculitis (AAV) had been reported [1-5]. In recent years, a disease concept referred to this as otitis media with ANCA-associated vasculitis (OMAAV) was proposed [6]. The diagnostic criteria [7] were based on subsequent nationwide surveys, which enabled early diagnosis and treatment, followed by the practice guide proposed by Japan otological society [8, 9].

In Japan, anti-thyroid drugs (ATD) such as methimazole (MMI) and propylthiouracil (PTU) have been used as the first-line therapy for Graves’ disease (GD). However, ATD often cause adverse events [10-13]. AAV is a rare adverse event of ATD, mostly due to the use of PTU, with the frequency estimated to be 0.53–0.79/10,000 cases [14]. Of the cases with ATD-induced AAV, OMAAV is extremely rare with only occasional case reports. Because delayed treatment can lead to irreversible hearing loss and a fatal condition along with the disease progression, it is important to recognize this disease early.

Here, we report a case of PTU-induced OMAAV and a review of the literature to lead a better understanding of this disease.

Case Presentation

A 33-year-old woman was diagnosed with GD and 30 mg per day of MMI was started at a local clinic. After starting the treatment with MMI, rashes appeared and MMI was switched to PTU. She continued the treatment with PTU for 8 years without adverse events. One day at
the age of 42, she noticed a very slight pain in her left ear. Four days later, she began to have a congested feeling in her left ear, and she consulted a local general otolaryngologist. These symptoms were just observed and progressively worsened within a few days. Then, she visited St. Marianna University Hospital (DAY 1). At the time of the first examination, she had a severe earache and could not hear well. The patient’s past medical history included uterine fibroids, appendicitis and hay fever. She was not taking any medications other than PTU. Results of blood test were as follows: white blood cells (WBC) 5,300/μL (with 65.1% neutrophils, 27.9% lymphocytes, 5.4% monocytes, 1.1% eosinophils, 0.5% basophils), red blood cells 406 × 10⁶/μL, hemoglobin 13.1 g/dL, hematocrit 38.5%, platelets 29.4 × 10⁹/μL, C reactive protein (CRP) 0.54 mg/dL, free T₃ 2.89 pg/mL, free T₄ 0.97 ng/dL, TSH 2.53 μU/mL, TSH receptor antibody 1.8 IU/L (reference range, <2.0 IU/L), normal liver and renal functions. Urinalysis showed no abnormal findings. Computed tomography scan (Fig. 1) showed that the left middle ear and the mastoid cells were filled with soft tissue, with inflammation suspected. It was considered that inflammation started in the middle ear and spread to the mastoid cells. Pure tone audiometry showed a moderate mixed hearing loss in the left ear; the elevated air and bone conduction thresholds and their gap were noted (DAY 1; pure tone average: right 10 dB and left 41.3 dB) (Fig. 2). Although antibacterial ear drops (ofloxacin), antibiotics (clarithromycin) and painkillers (acetaminophen) were initiated, these were not effective and her earache and hearing loss in the left ear gradually worsened. At 8 days after her first visit, we changed the antibiotics to amoxicillin and the painkiller to loxoprofen and then ear drops with dexamethasone were started. However, there was no effect (DAY 15; pure tone average: right 17.5 dB and left 68.8 dB) (Fig. 3A). At 21 days after her first visit, a symptom of facial nerve palsy first appeared. Significant hearing impairment of her left ear occurred and resulted in a severe hearing loss (DAY 22; pure tone average: right 15 dB and left 73.8 dB) (Fig. 3B). There was no mass or bone destruction in her ears (Fig. 1) and the bacterial culture was negative. Based on these findings, the following were excluded as the causes of otitis media: cholesteatoma, cholesterol granuloma, eosinophilic otitis media, tuberculosis, malignant otitis externa, skull-base osteomyelitis and neoplasms. The cause of her otitis media that was resistant to antibiotics, resulted in refractory hearing loss and complication with facial nerve palsy, was suspected to be due to AA V. Subsequently, a high serum level of myeloperoxidase (MPO)-ANCA, 75.6 U/mL (reference range, <3.5 U/mL), was revealed (Table 1). As a result, she was found to meet the diagnostic criteria for OMAA V (Supplementary Table 1) as follows: A-1, A-2, B-2, B-4b, and C. Finally, she was diagnosed with OMAA V, and PTU was highly suspected as the cause of her OMAA V. After the diagnosis of OMAA V, PTU was immediately discontinued and 60 mg per day of prednisolone (PSL) was started (DAY 23). In addition, a middle ear ventilation tube was inserted. After these treatments, the hearing impairment in her left ear gradually improved (DAY 30 to 36; pure tone average: right 7.5 to 12.5 dB and left 55 to 35 dB) (Fig. 3C, 3D) and

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Fig. 1 Computed tomography of the patient’s ear. The left middle ear (white arrow) and mastoid cells (black arrow) were filled with soft tissue. There was no mass or bone destruction in her ears.

Fig. 2 Pure tone audiometry at the time of the patient’s first visit to St. Marianna University Hospital (DAY 1). The vertical axis represents hearing acuity and the horizontal axis indicates the frequency. Results indicate mixed hearing loss of the left ear, while the hearing in the right ear was normal (right 10 dB; left 41.3 dB). ○, air conduction in the right ear; ▲, bone conduction in the right ear; ×, air conduction in the left ear.
facial nerve palsy disappeared. PSL was reduced on dosage and then discontinued on DAY 38, with no further hearing impairment. The hearing impairment in her left ear improved enough not to disrupt her daily routines (DAY 71; pure tone average: right 6.3 dB and left 23.8 dB) (Fig. 3E). Approximately eight months later, her hearing acuity was maintained (DAY 253; pure tone average: right 6.3 dB and left 26.3 dB) (Fig. 3F). The serum level of the MPO-ANCA was gradually decreased (Table 1). Other than facial nerve palsy, she did not develop any severe complications, such as hypertrophic pachymeningitis.

Unfortunately, her thyroid hormone levels gradually became high, then, she was referred to Ito hospital, a specialized hospital for thyroid disease. She was subsequently administered radioactive iodine ($^{131}$I) for her GD as definitive therapy.

**Fig. 3**  Pure tone audiometry results show hearing loss and subsequent recovery in the patient’s left ear. DAY 1 indicates her first visit to St. Marianna University Hospital, with DAY 15 (A), DAY 22 (B), DAY 30 (C), DAY 36 (D), DAY 71 (E) and DAY 253 (F) showing the changes at her subsequent visits. At 125 Hz in her left ear on DAY 15 and DAY 22, hearing could not be measured because of scale-out. Hearing in her right ear was normal throughout the follow-up. ↓, scale-out.

**Table 1**  Change of serum anti-neutrophil cytoplasmic antibody level

|                | At diagnosis* | 1 month | 6 months | 12 months | 18 months |
|----------------|---------------|---------|----------|-----------|-----------|
| MPO-ANCA (U/mL)| 75.6          | 65.9    | 53.9     | 42.9      | 41.7      |
| PR3-ANCA (U/mL)| <1            | —       | —        | <1        | —         |

*, serum level of anti-neutrophil cytoplasmic antibody at diagnosis of otitis media with anti-neutrophil cytoplasmic antibody-associated vasculitis; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3 anti-neutrophil cytoplasmic antibody.
Discussion

We report a case of PTU-induced OMAAV. Our current case met the diagnostic criteria for OMAAV [7]: 1) otitis media that is refractory to antibiotics, 2) progression of the bone conduction threshold, 3) positivity for serum MPO-ANCA, 4) complication of facial nerve palsy and 5) ruling out other differential diseases (corresponding to A-1, A-2, B-2, B-4b, and C in Supplementary Table 1, respectively). Based on these findings and the diagnostic criteria, she was definitively diagnosed as OMAAV.

This case was considered as atypical for AAV because serum CRP level and WBC count were not high. However, elevation of CRP level and WBC count are not essential for diagnosis of AAV including OMAAV [7, 8] and normal CRP level and WBC count cannot rule out AAV [15]. In this case, other disorders with similar clinical features were excluded and facial nerve palsy developed. Among refractory otitis media, facial nerve palsy is characteristic of OMAAV, which appears in about 30% of OMAAV and is a poor prognostic factor for hearing acuity and survival [9]. The diagnosis of OMAAV in this case is considered reasonable.

Due to the complication of facial paralysis, it was considered our current case was a severe one of OMAAV. Otitis media itself is one of the common diseases, and it is difficult to assume OMAAV, which presents as an adverse event of ATD and requires immediate diagnosis and treatment. The ANCA-positive rate among the patients under the treatment with PTU has been reported to be approximately 4.1–64% [16-20]. The incidence of AAV is extremely higher among patients under the treatment with PTU as compared to MMI [14]. Of the 92 cases with ATD-induced AAV reported between 1979 and 2007, only one case who was taking PTU developed otitis media [14]. Thus, it is presumed that ATD-induced OMAAV is an extremely rare condition. If AAV involves multiple organs, then it is possible that otitis media might not be reported and thus, could be underestimated.

In 1992, a report clarified the link between ANCA and ear symptoms [1]. In conjunction with the spread of ANCA measurements during the late 1990s, there has been a significant increase in the number of OMAAV reports [21]. As a result, ANCA-associated hearing losses caused by ATD have been reported (Table 2) both before [2-5] and after [22-24] the OMAAV diagnostic criteria [7] were established. The mean age of these patients was 39 years old (range, 23–68 years old) and the mean duration of ATD use before OMAAV was 5 years (range, 0.15–30 years). 7 out of the reported 8 patients were taking PTU. The relationship between the antibody titer and severity has not been definitively established due to the fact OMAAV is a rare condition. In addition, we also found no clear tendency about their relationship in the present review (Table 2).

In the ATD-induced OMAAV cases shown in Table 2, 2 out of the 8 cases (25%) were unilateral. Similar frequency to this, 78 out of 297 cases (26%) were found to be a unilateral lesion in the OMAAV nationwide surveys that were conducted from December 2013 to January 2014 [9]. Although the mechanism of unilateral lesion is unknown, it has been presumed that these lesions do not necessarily occur on both sides, in contrast to that seen for polyneuropathy, arthritis, and non-fixed pulmonary infiltrates with AAV [25]. Therefore, it should be noted that OMAAV can develop as a unilateral lesion.

There have been no reports or guidelines regarding treatments that can be used for localized AAV of upper respiratory tract, so far. The European League Against Rheumatism (EULAR)/European Dialysis and Transplant Association (ERA-EDTA) have recommended methotrexate (MTX) or mycophenolate mofetil with glucocorticoid as treatment for non-organ threatening AAV, and cyclophosphamide (CY) or rituximab with glucocorticoid for organ or life-threatening AAV [26]. In Japan, PSL and CY are recommended for newly developed AAV [27]. Based on the national surveys and previous reports and the fact that OMAAV is sometimes resistant to treatment, PSL and immunosuppressive drugs such as MTX, CY or azathioprine have been recommended for OMAAV in Japan [9, 28].

As shown in Table 2, in the cases with ATD-induced OMAAV that have been reported so far, improvement has been noted after discontinuation of ATD in conjunction with the subsequent administration of steroids and/or immunosuppressants. Although the degree of the hearing impairment was varied, the improvement was noted in all these cases and no refractory cases were observed. As more than half of the PTU-induced AAV cases showed improvement due to only discontinuation of PTU [29], this suggests that ATD-induced OMAAV might be also improved due to only discontinuation of ATD. However, for ATD-induced OMAAV with refractory hearing loss and severe complication of facial nerve palsy and hypertrophic pachymeningitis, the use of PSL and/or immunosuppressants should be considered. Regarding an optimal treatment strategy for drug-induced OMAAV, it will be necessary to evaluate more cases and undertake further studies in the future.

Facial nerve palsy and hypertrophic pachymeningitis are considered as complications of OMAAV and as poor prognostic factors for hearing acuity and survival [9, 28]. Hypertrophic pachymeningitis is a pathological condition in which the dura is thickened as a result of inflammation of otitis media resulting in chronic inflammation.
of the dura and is a serious complication of OMAAV leading to death if treatment is delayed [9, 28]. A nationwide survey, which included OMAAV other than pharmaceutical-caused OMAAV, reported finding that delayed treatment in some cases led to severe hearing impairment and a fatal progression associated with hypertrophic pachymeningitis. In fact, in three of the cases that died of subarachnoid hemorrhage, it was assumed that hypertrophic pachymeningitis was associated with the cause of the symptoms and death [28]. As summarized in Table 2, no complications such as hypertrophic pachymeningitis or a fatal clinical course have been reported in the cases of ATD-induced OMAAV, so far. However, if OMAAV is overlooked and the treatment is delayed, the changes could become irreversible and potentially be fatal. The time taken for these irreversible situations to occur is currently unknown and it may differ among the cases. Whether or not there is a concrete period for preventing irreversible situations is a subject for a future study. Thus, at the present time, it is very important to make a diagnosis prior to the occurrence of these severe complications.

In general, AAV includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). OMAAV presents alone or as a partial symptom of these AAV [9, 28]. All but one of the ATD-induced OMAAV cases summarized in Table 2 were OMAAV single-onset cases. The association between OMAAV and ATD may be overlooked in single-onset cases.

## Conclusion

Although PTU-induced OMAAV is an extremely rare disease, it is important to consider the possibility of OMAAV when patients taking ATD, especially PTU, present with refractory otitis media as delayed treatment can lead to an irreversible hearing loss and a fatal condition.

## Disclosure

None of the authors have any potential conflicts of interest associated with this present report.

**Table 2** Reported cases of MPO-ANCA-associated sensorineural hearing loss caused by anti-thyroid drugs

| Authors/Year       | Age/Sex | History of ATD use | Symptom                                  | MPO-ANCA (U/mL) | PR3-ANCA (U/mL) | Treatment of OMAAV | Treatment of GD after OMAAV |
|--------------------|---------|--------------------|------------------------------------------|-----------------|-----------------|--------------------|------------------------|
| Maguchi/2001 [2]   | 36/F    | use of MMI for 5 years and use of PTU for 6 years | bilateral sensorineural hearing loss, tinnitus, vertigo | 74              | —               | mPSL 1,000 mg, PSL 60 mg, withdrawal of PTU | —                      |
| Thamprajamchit/2004 [3] | 23/F    | use of PTU for 3 years | bilateral sensorineural hearing loss, tinnitus, polyarthralgia, papules, cough | 20.2            | —               | PSL 60 mg, azathioprine 50 mg, withdrawal of PTU | surgery*               |
| Sano/2004 [4]      | 36/M    | use of PTU for 4 months | bilateral sensorineural hearing loss | 146             | negative        | mPSL 1,000 mg, withdrawal of PTU | surgery                |
| Raja/2010 [5]      | 68/M    | use of CBZ for 7 weeks | bilateral sensorineural hearing loss, tinnitus, vertigo | negative        | negative        | PSL 40 mg, withdrawal of CBZ | potassium iodide* surgery |
| Nishimura/2018 [22] | 42/M    | use of PTU for 3 years | bilateral sensorineural hearing loss, tinnitus, vertigo | positive        | positive        | intratympanic steroid injection, withdrawal of PTL | —                      |
| Suwa/2018 [23]     | 63/F    | use of PTU for 30 years | unilateral mixed hearing loss | positive        | —               | PSL 35 mg, rituximab 600 mg, tapering of PTU | —*                    |
| Tanaka/2018 [24]   | 30/F    | use of PTU for 7 years | bilateral sensorineural hearing loss, earache, trigeminal neuralgia | 100             | negative        | PSL 40 mg, withdrawal of PTU | radioactive iodine       |
| Present case       | 42/F    | use of PTU for 8 years | unilateral mixed hearing loss, earache, facial nerve palsy | 75.6            | negative        | PSL 60 mg, intratympanic steroid injection, withdrawal of PTU | potassium iodide, radioactive iodine |

*These cases used ATD for a short time and stopped immediately; ATD, anti-thyroid drug; MMI, methimazole; PTU, propylthiouracil; CBZ, carbimazole; mPSL, methylprednisolone; PSL, prednisolone; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3 anti-neutrophil cytoplasmic antibody; OMAAV, otitis media with anti-neutrophil cytoplasmic antibody-associated vasculitis; GD, Graves’ disease.
**Supplementary Table 1** Diagnostic criteria for OMAAV [7]

A. At least one of the following clinical courses:

1. Intractable otitis media with effusion or granulation, which is resistant to antibiotics and insertion of tympanostomy tube.
2. Progressive deterioration of bone conduction hearing levels.

B. At least one of the following features:

1. Already diagnosed as AAV (GPA, MPA, EGPA) based on the involvement of other organs.
2. Positivity for serum MPO- or PR3-ANCA.
3. Histopathology consistent with AAV, i.e., necrotizing granuloma with infiltration of giant cells, necrotizing vasculitis predominantly affecting small vessels with or without granulomatous extravascular inflammation.
4. At least one of the following accompanying signs/symptoms of AAV-related involvement:
   a. upper airway involvement other than ear, scleritis, lung, and kidney involvement
   b. facial palsy
   c. hypertrophic pachymeningitis
   d. multiple single neuritis
   e. improvement in symptoms/signs with administration of 0.5 to 1.0 mg/kg PSL (although recurrence occurs on discontinuation of treatment).

C. Differential diagnosis (the followings are excluded):

1. cholesteatoma
2. cholesterol granuloma
3. cosinophilic OM
4. tuberculosis
5. malignant otitis exterma, skull-base osteomyelitis
6. neoplasms (malignancy, inflammatory myofibroblastic tumor, etc.)
7. OM or inner ear inflammation caused by autoimmune diseases and vasculitis other than AAV.

A diagnosis of OMAAV can be made when the above three criteria (A, B, C) are fulfilled.

OMAAV, otitis media with anti-neutrophil cytoplasmic antibody-associated vasculitis; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; GPA, granulomatousis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatousis with polyangiitis; MPO, myeloperoxidase; PR3-ANCA, proteinase 3 anti-neutrophil cytoplasmic antibody; PSL, prednisolone; OM, otitis media.

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