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Case report

A patient with sudden hearing loss induced by propylthiouracil

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ABSTRACT

A 39-year-old man with type 1 diabetes, who had a 4-year history of Graves' disease being treated with propylthiouracil (PTU), had developed sudden hearing loss. However, he showed no other clinical manifestations. Intratympanic administration with dexamethasone had failed, and his hearing had deteriorated. Magnetic resonance imaging showed the contrast effect on T1-weighted image in both cochleae, and the serum immunological analysis showed the high titers for anti-neutrophil cytoplasmic antibodies (ANCA). Therefore, his sudden hearing loss was presumed to be initial presentation of ANCA-associated vasculitis owing to PTU. His hearing was rapidly restored by a PTU withdrawal while no use of immunosuppressive agents, and he confirmed his hearing improvement in ordinary conversation. The patient's clinical course suggests that bilateral sensorineural hearing loss that occurs during treating hyperthyroidism could be initial presentation of ANCA-associated vasculitis, and discontinuing anti-thyroid drugs should be considered before treating with glucocorticoids.

1. Introduction

Antineutrophil cytoplasmic antibody (ANCA) plays an important role in the development of systemic vasculitis, which is characterized by small-sized necrotizing vasculitis. Anti-thyroid drugs (ATD) such as methimazole (MMI) and thiouracil derivative such as propylthiouracil often cause adverse events [1, 2, 3, 4]. ANCA-associated vasculitis is a rare adverse event of ATD, mostly due to the use of propylthiouracil, with the frequency estimated to be 0.53–0.79/10,000 cases [3]. Of the cases with ANCA-associated vasculitis owing to ATD, progressive hearing loss or otitis media is extremely rare with only occasional case reports. Moreover, sudden hearing loss as an initial manifestation of the ATD-associated vasculitis has not been reported. 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 with sudden hearing loss associated with the seropositivity for ANCA, being induced by PTU.

2. Method and results

Case report of sudden hearing loss induced by propylthiouracil

A 35-year-old Japanese man with type 1 diabetes mellitus (T1DM) was diagnosed as having Graves' disease on the basis of hyperthyroidism with undetectable serum TSH levels and high titers of antibodies against the TSH-receptor. He immediately began taking thiamazole 30mg daily. A few weeks later, thiamazole was discontinued due to skin eruption and neutrophil count reduction. He began receiving propylthiouracil (PTU) 300mg daily. The daily dosage of PTU was then increased to 600mg. Approximately 2 years later, when he was 37 years old, he complained of bilateral hearing loss and tinnitus, and was diagnosed with sudden sensorineural hearing loss by an otolaryngologist (Figure 1A). Although he received dexamethasone administration into the tympanic cavity, his hearing was not restored. He ultimately required a hearing aid. After dexamethasone discontinuation, he experienced fluctuation of his hearing.

Two years later, when the patient was 39 years old, he presented to the department of otolaryngology of our hospital due to rapid deterioration of his hearing. Audiograms showed that his hearing apparently worsened as compared with that at the diagnosis (Figure 1B). An ear examination revealed no redness of the eardrums and no effusion in the tympanic cavities. Computed tomography showed no alteration of inner ear bone structure (Figure 2, A and B). As previously observed, his

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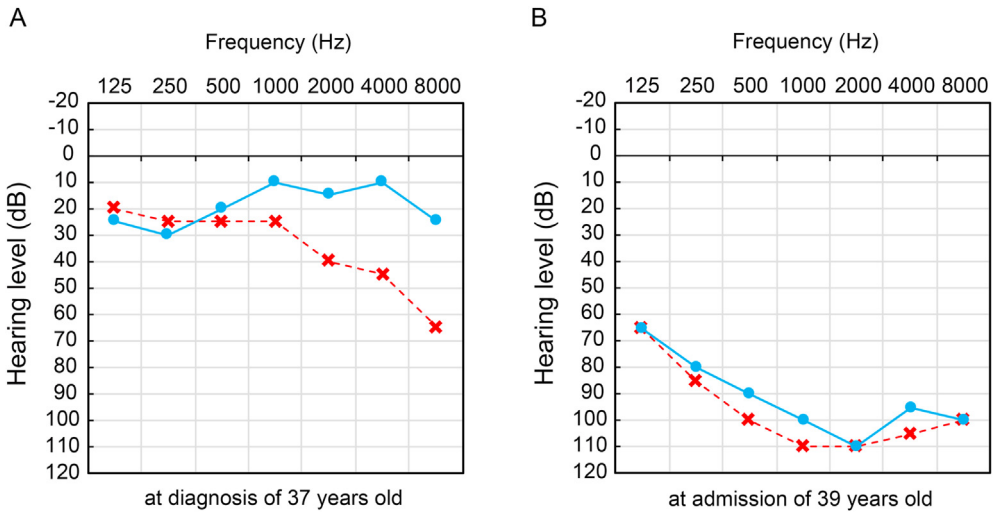

Figure 1. Progression of hearing impairment. The patients' hearing levels were assessed by pure-tone audiometry at the diagnosis of 37 years old ages (A) and the admission of 39 years old (B). blue circle: air conduction (right), red cross: air conduction (left).

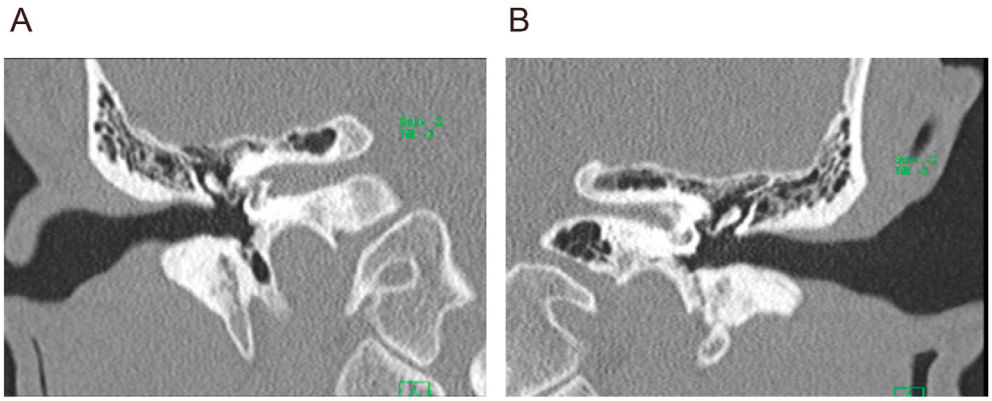

Figure 2. Computated tomography of inner ear. (A) right inner ear, (B) left inner ear.

hearing was not affected by 1·5 mg dexamethasone intermittent intratympanic administrations into each ear. After the initiation of steroid administration, despite multiple basal and bolus injections of insulin analogs with dose adjustments based on blood sugar levels, his glycaemia apparently worsened along with frequent fasting hypoglycemia. Then, he was referred to our department for investigation of potential systemic diseases underlying his steroid-refractory hearing loss. Whereas leucocytes, erythrocytes, inflammatory markers, complement factors and each subclass of immunoglobulin were all within normal limits (Table 1), he showed seropositivity for anti-neutrophil cytoplasmic antibodies (ANCA). The levels of ANCA against the proteinase 3 (PR3) and myeloperoxidase (MPO), being measured by chemiluminescent enzyme immunoassay, elevated to 31·2 U/ml and 159 U/ml, respectively, with both reference ranges of less than 3.5 U/mL (Table 1). At the same time, high titers of antibodies against cyclic citrullinated peptide (CCP) and glutamic acid decarboxylase (GAD) were also detected. However, this patient showed no other organ involvement related to either small vessel vasculitis or rheumatoid arthritis. He showed intact renal function with no evidence of proteinuria and urine occult blood (Tables 1 and 2), and computed tomography showed no paranasal sinuses and pulmonary involvements (Figure 3, A and B). However, nuclear magnetic resonance images revealed the contrast effect on T1-weighted images in both cochleae (Figure 4, A and B), although the structure of cochleae appeared to be maintained in T2-weighted images (Figure 4, C and D). Based on these findings, we deemed his bilateral sensorineural hearing loss to have been caused by local small vessel vasculitis associated with ANCA. At that

Table 1. Blood and serological tests prior to the PTU withdrawal.

COMPONENT	REFERENCE RANGE	RESULT
Creatinine	57–95 μmol/L	68
Blood urea nitrogen	2.9–7.1 mmol/L	5.7
eGFR	N.A./ml/min/1.73m^2	88.3
Erythrocyte sedimentation	N.A./mm	5
CRP	0.00–0.14 mg/L	0.01
White blood cell count	3.3 to 8.6 X 10^9/L	4440
Neutrophils	41–64 %	53.4
Lymphocyte	30–46 %	35.2
Monocytes	4–10 %	7.3
Eosinophils	1.0–5.0 %	2.9
Basophils	0.0–2.0 %	1.2
Red blood cell count	435 to 555 X 10^{10}/L	449
Hemoglobin	12.5–17.0 g/dL	14.1
Platelets	120 to 400 X 10^9/L	23.4
IgG	861–1747 mg/dL	1084.6
IgM	93–393 mg/dL	275.1
IgA	33–183 mg/dL	164.9
PR3-ANCA[a]	0.0–3.5 U/mL	31.2
MPO-ANCA[b]	0.0–3.5 U/mL	159
Anti-nuclear antibody	N.A.	undetectable

(*continued on next page*)

Table 1 (*continued*)

COMPONENT	REFERENCE RANGE	RESULT
CH50[c]	30.0–60.0 U/mL	53.2
C3	73–138 mg/dL	70.2
C4	11–31.0 mg/dL	13.9
Anti-CCP[d] antibody	0–4.4 mg/dL	17.3
Anti-GAD[e] antibody	0–4.9 U/mL	697.8
C-peptide immunoreactive	0.17–0.66 nmol/L	undetectable

[a] PR3-ANCA, proteinase 3-anti-neutrophil cytoplasmic antibody
[b] MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody
[c] CH50, total complement hemolytic activity
[d] CCP, cyclic citrullinated peptide
[e] GAD, glutamic acid decarboxylase

involvements of other organs. The levels of PR3-ANCA and MPO-ANCA had decreased to 9.8 U/ml and 118·2 U/ml, respectively, at 24 weeks after the withdrawal (Figure 6). His glycemic control was stable with a hemoglobin A1c of 6·7%.

Written informed consent for this report was obtained from the patient.

3. Discussion

Sudden hearing loss is a rare initial presentation of ANCA-associated vasculitis, and it sole does not meet the diagnosis criteria. This raises concerns about disease progression because of delays in appropriate treatment. Indeed, our patient presented no other clinical features associated with otitis media that could be manifested with ANCA-associated vasculitis. This led to a delayed diagnosis for ATD-associated vasculitis, which may have caused a limited restoration of his hearing by a PTU withdrawal.

Table 2. Urinalysis prior to the PTU withdrawal.

COMPONENT	REFERENCE RANGE	RESULT
Urinalysis		
Color	N.A.	Pale yellow
Clarity	N.A.	Clear
pH	N.A.	5.5
Specific gravity	N.A.	1.050
Glucose	Negative	4+
Blood	Negative to 1+	Negative
Protein	Negative	Negative
Nitrite	Negative	Negative
Urine microscopy		
White blood cells	0 to 5 per high-power filed	1.0
Red blood cells	0 to 4 per high-power field	0.20
Urinary casts	N.A. per low-power field	1.19

time, although increases in titers of antibodies against the TSH-receptor were still evident, his thyroid function remained normal with 600mg daily administration of PTU. We thus discontinued PTU. Approximately 2 weeks after the withdrawal of PTU, his hearing began to improve and, despite discontinuing dexamethasone administration, no fluctuations were noted. At 4 weeks after the PTU withdrawal, the audiogram showed bilateral hearing restoration at frequencies of 250Hz, 1000Hz and 4000Hz (Figure 5). He confirmed his hearing improvement in ordinary conversation. Two months after the withdrawal of PTU, a subtotal thyroidectomy was performed, after which his thyroid function was maintained with levothyroxine replacement. When seen at 24 weeks after the PTU withdrawal, our patient's hearing was still improving without immunosuppressive agent administration (Figure 5), and he presented no

Our patient's clinical course strongly suggests a pathological role of PTU in bilateral sensorineural hearing loss. Inner ear blood flow impairment from PTU-induced ANCA-associated vasculitis presumably caused cochlear dysfunction in our patient. There is increasing evidence that anti-thyroid drugs (ATD) cause ANCA-associated vasculitis. Among such drugs, thiouracil derivatives are reportedly associated with a higher prevalence of ANCA positivity and clinical vasculitis [3, 4]. PTU-mediated actions involving neutrophils might provide pathological mechanisms underlying the induction of ANCA: alterations in the

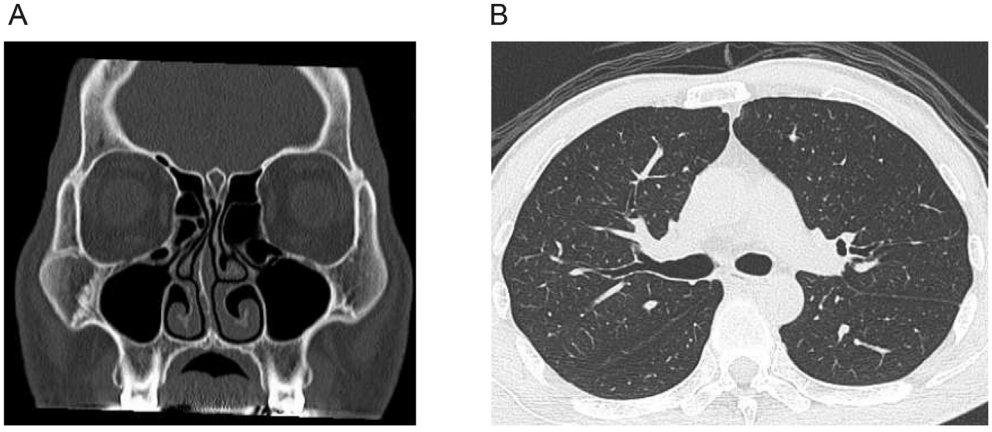

Figure 3. Computed tomography of paranasal sinuses (A) and lung (B).

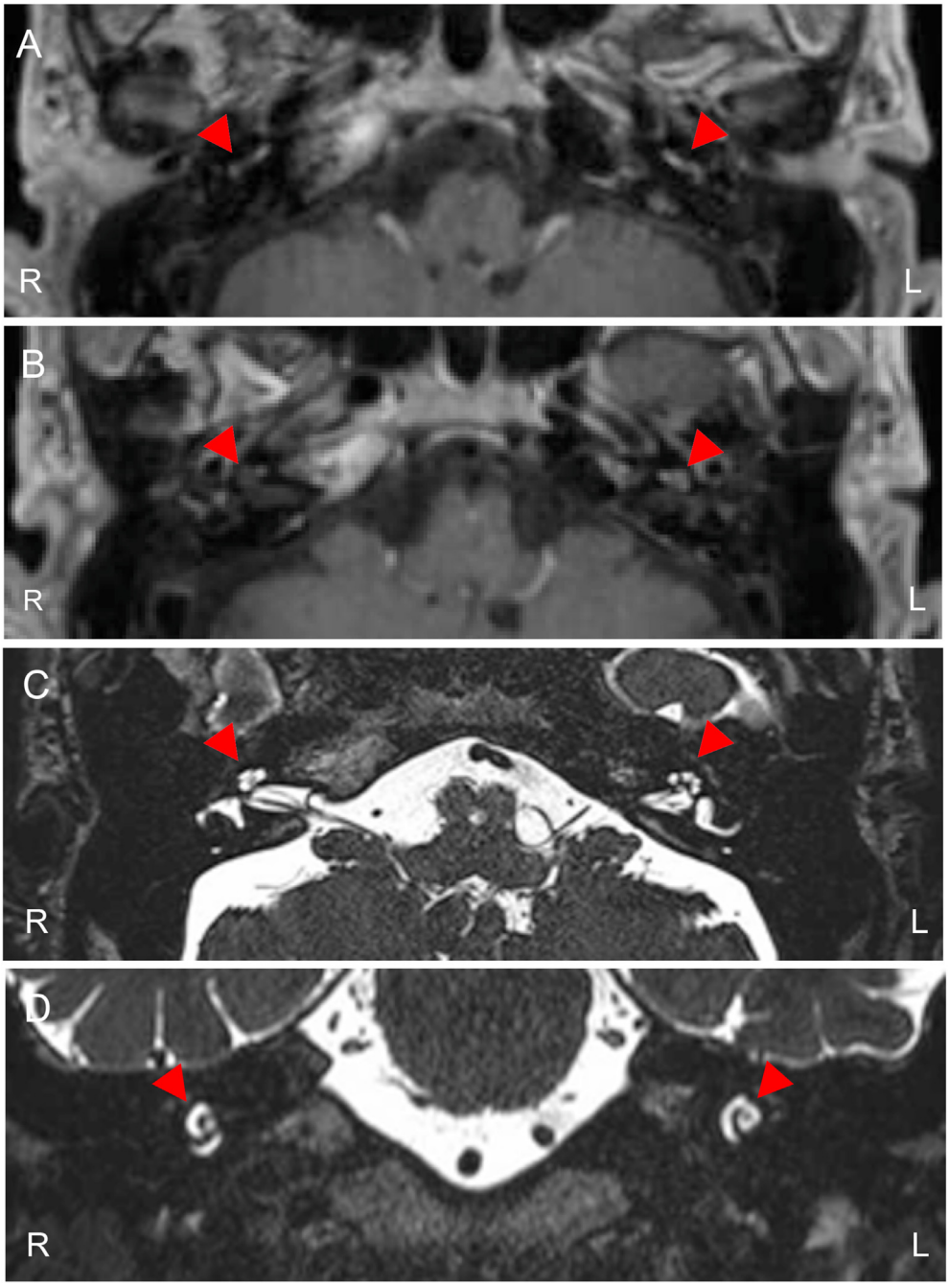

Figure 4. MRI demonstrated the contrast effects in bilateral cochleae. (A) and (B): Horizontal sections of gadolinium enhanced T1-weighted image of cochleae, (C): Horizontal section of T2-weighted image of cochleae. (D): Coronal section of T2-weighted image of cochleae. Arrowheads indicate cochleae.

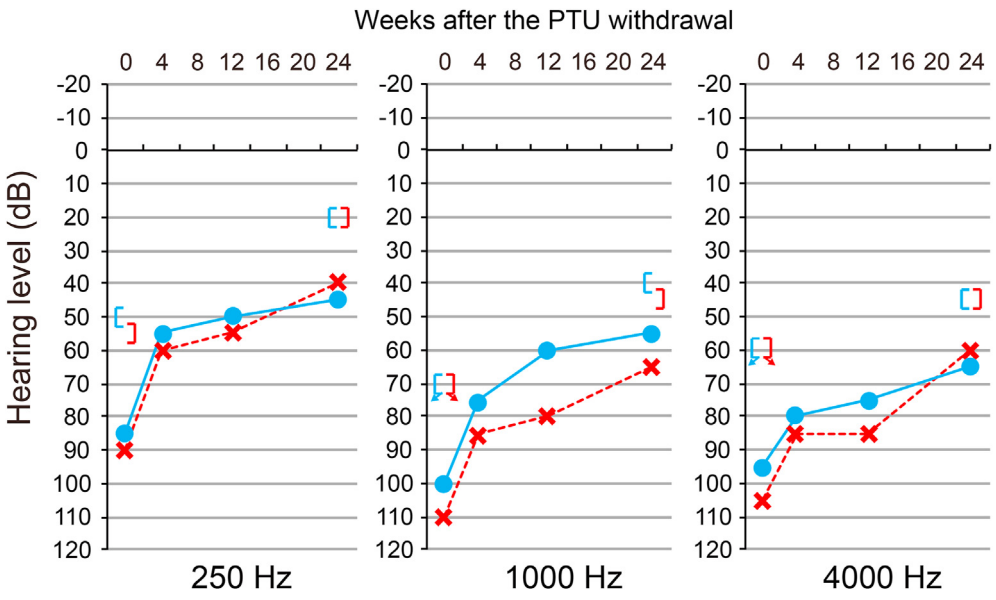

Figure 5. Change in hearing levels after a PTU withdrawal. Change in hearing levels at 250 Hz, 1000 Hz and 4000 Hz, being assessed by pure-tone audiometry. blue circle: air conduction (right), red cross: air conduction (left), [: bone conduction (right),]: bone conduction (left)

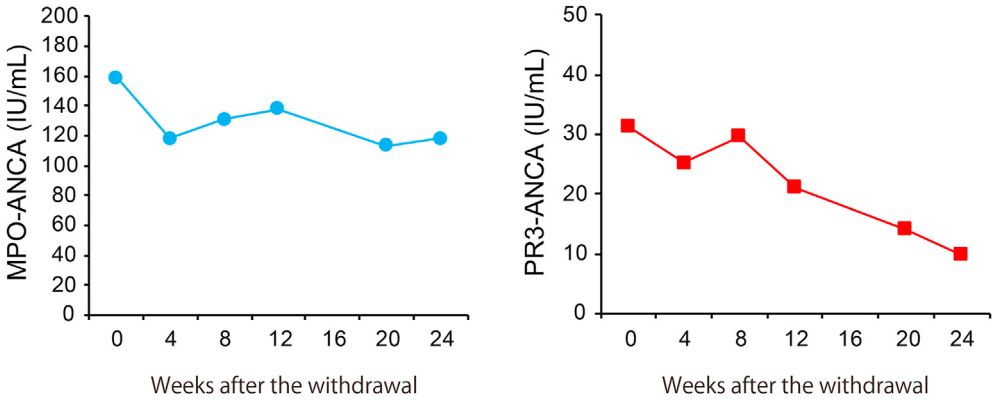

Figure 6. Change in ANCA levels after the PTU withdrawal. MPO-ANCA and PR3-ANCA was measured at indicated time points. blue circle: MPO-ANCA (left), red square: PR3-ANCA (right).

configuration of granules containing myeloperoxidase [5], direct binding to myeloperoxidase [6] and oxidization of PTU itself by myeloperoxidase [7]. To the best of our knowledge, our report is the first to show sudden hearing loss to be reversed in a patient with Graves' disease solely by the withdrawal of PTU. Due to the presence of T1DM, systemic steroid administration was not an option in our present case. Indeed, even intermittent local dexamethasone administration made it difficult to manage our patient's glycaemia. Because our case showed no involvement of other organs including the kidneys, lungs, airway, skin, joints and nervous system, we decided not to use other immunosuppressive agents. However, the PTU withdrawal was followed by rapid hearing improvement and a favorable clinical outcome. Although the incidence of sudden hearing loss in ATD-induced ANCA-associated vasculitis is low [3], in cases with sudden hearing loss that occurs during treating hyperthyroidism, it is prudent to test ANCA with a view to treating the vasculitis, avoiding unnecessary immunosuppressive therapy.

4. Conclusion

We report a case with bilateral sensorineural hearing loss induced by PTU. When sudden hearing loss occurs in patients with Graves' disease, discontinuing ATD should be considered even with no other manifestations being presented.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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