



## Case Report

# Intractable Otitis Media Presenting as Falsely Positive for Proteinase 3-ANCA: A Case Report

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Cite this article as: Okada M, Ogawa H, Suemori K, Takagi D, Teraoka M, Yamada H, et al. Intractable Otitis Media Presenting as Falsely Positive for Proteinase 3-ANCA: A Case Report. J Int Adv Otol 2018; 14(2): 337-40.

Herein, we report a case of otitis media caused by methicillin-resistant *Staphylococcus aureus* (MRSA), presenting as falsely positive for proteinase 3 (PR3)-antineutrophil cytoplasmic antibodies (ANCA). A 47-year-old woman was referred to our hospital with a complaint of left otorrhea. An otorrhea culture yielded MRSA, and the patient was treated using tympanoplasty. Postoperative administration of teicoplanin led to drug-induced neutropenia and was discontinued 4 days after the operation. One month after the operation, the patient's otorrhea recurred, and it was accompanied by hearing impairment. The otorrhea culture yielded MRSA again, while serum was positive for PR3-ANCA (6.8 U/mL). As MRSA was detected in the patient's otorrhea sample, she was treated with linezolid. Her symptoms then improved immediately. Although the PR3-ANCA positivity remained, the patient's otorrhea and hearing impairment had not recurred for 3 years when this report was submitted. Therefore, we conclude that this is a case of false PR3-ANCA positivity.

**KEYWORDS:** Methicillin-resistant *Staphylococcus aureus*, granulomatosis with polyangiitis, Wegener granulomatosis, teicoplanin, linezolid

## INTRODUCTION

Antineutrophil cytoplasmic antibodies (ANCA) to myeloperoxidase (MPO) and proteinase 3 (PR3) are associated with primary vasculitis affecting small- to medium-sized vessels. Systemic vasculitis involving these antibodies is known as ANCA-associated vasculitis (AAV) <sup>[1]</sup>. The initial signs of AAV are otologic symptoms, such as otitis media, hearing loss, vertigo, and facial palsy. Nonetheless, the AAV diagnosis is often challenging when symptoms are localized to the ear <sup>[2]</sup>. For this reason, the study group of the Japan Otological Society recently proposed a new diagnosis: otitis media with AAV (OMAAV) <sup>[3]</sup>. OMAAV is classified if the following three criteria (A, B, C) are fulfilled: (A) a disease onset with initial sign/symptoms due to intractable otitis media with effusion or granulation, which was resistant to antibiotics and insertion of tympanic ventilation tubes; (B) at least one of the following three findings: (1) positivity for the serum MPO- or PR3-ANCA; (2) histopathology consistent with AAV, which is necrotizing vasculitis predominantly affecting small vessels with or without the granulomatous extravascular inflammation; and (3) at least one accompanying sign/symptom of the AAV-related involvement other than the ear (eye, nose, pharynx/larynx, lung, kidney, facial palsy, hypertrophic pachymeningitis, and others); and (C) exclusion of the other types of intractable otitis media, such as bacterial otitis media, cholesterol granuloma, cholesteatoma, malignant osteomyelitis, tuberculosis, neoplasm, and eosinophilic otitis media, as well as exclusion of other autoimmune diseases and vasculitis diseases other than AAV, such as Cogan's syndrome and polyarteritis nodosa, among others. According to these criteria, OMAAV should only be diagnosed when the patient is positive for ANCAs or vasculitis, of which the latter is revealed during a pathological examination <sup>[3]</sup>. However, vasculitis is rarely diagnosed after the pathological examination of a head and neck lesion. Thus, positivity for ANCAs is an important finding in the diagnosis of OMAAV.

While false positivity for ANCAs occurs in ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus, infections, tuberculosis, and malignant tumor <sup>[4-6]</sup>, few cases of false positivity for ANCAs have been reported in otological diseases <sup>[7]</sup>. Herein, we report a case of otitis media caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and presenting as falsely positive for PR3-ANCA.

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**Submitted:** 25.10.2017 • **Accepted:** 03.04.2018 • **Available Online Date:** 01.08.2018

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**CASE PRESENTATION**

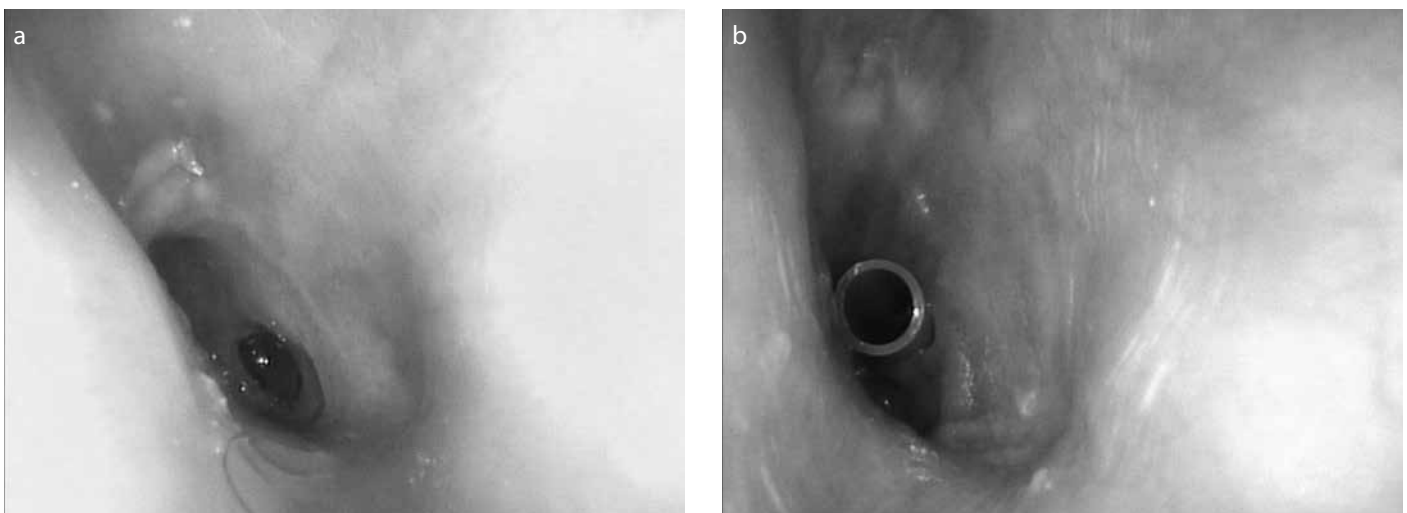
A 47-year-old woman with a history of hypertension was referred to our hospital with a complaint of left otorrhea that had persisted for 5 years. An otoscopic examination revealed that the tympanic membrane of her left ear was perforated (Figure 1a). A sample of the otorrhea was cultured, yielding MRSA. An audiogram showed mixed hearing loss in the woman's left ear (Figure 2a), and computed tomography (CT) revealed that the tympanic cavity was slightly clouded (Figure 3a).

Based on the diagnosis of chronic otitis media with MRSA, we performed a left tympanoplasty, with post-operative administration of teicoplanin (teicoplanin F; Fuji Pharma, Tokyo, Japan). Four days after the operation, the patient's temperature increased, and she developed a urinary tract infection. A blood test revealed a white blood cell (WBC) count of 1600/ $\mu$ L, with a differential neutrophil count of 640/ $\mu$ L, as well as elevated C-reactive protein (CRP) levels 4.6 mg/dL (normal range 0.00-0.20 mg/dL). The woman was diagnosed with drug-induced neutropenia caused by teicoplanin, and her antibiotics were discontinued. Her fever then subsided, and her WBC and neutrophil counts were normalized for several days. However, the left otorrhea recurred 1 month

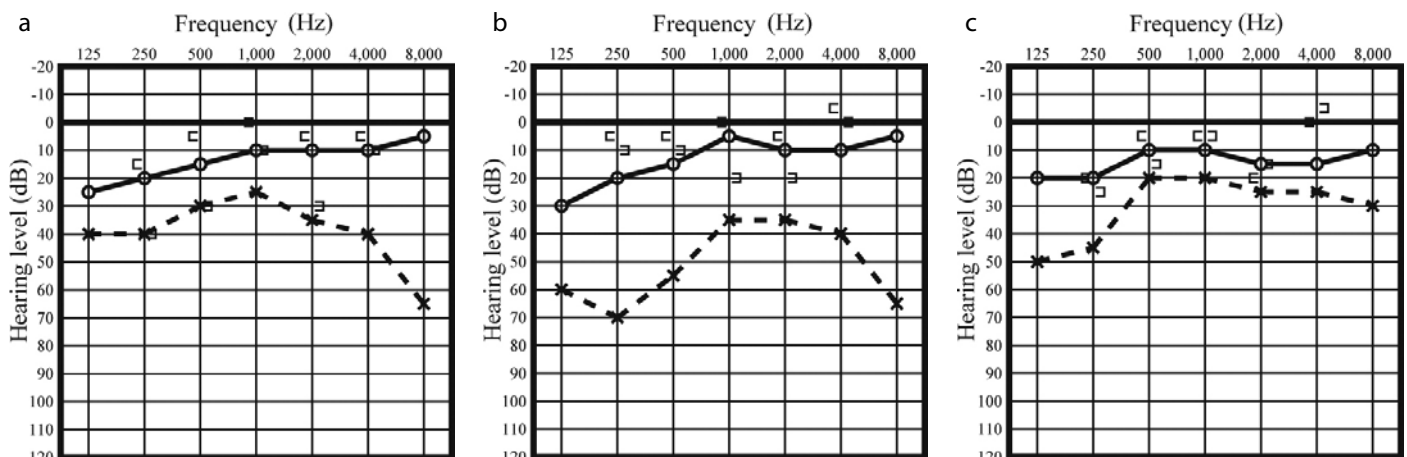
after the operation. Again, hearing impairment was observed (Figure 2b), and CT revealed that the tympanic cavity was slightly clouded (Figure 3b). A tympanic ventilation tube was inserted, and the ear was irrigated. However, these treatments were ineffective (Figure 1b). MRSA was once again detected in her otorrhea, while her serum PR3-ANCA levels-tested using the chemiluminescence enzyme immunoassay (CLEIA)-had increased to 6.8 U/mL (normal: <3.5 U/mL). No disorders were detected in any other organs (kidneys, lungs, eye, etc.). A pathological examination of the patient's middle ear granulation revealed non-specific inflammation. As MRSA was detected in a sample of her left otorrhea, she was administered linezolid (Zyvox; Pfizer, New York, USA) for 2 weeks, even though she was positive for PR3-ANCA. Following this treatment, the patient's otorrhea and hearing loss quickly improved (Figure 2c). After the treatment, her PR3-ANCA levels remained mildly elevated (6.5 U/mL), although her otitis media had not recurred for 3 years after the article was submitted. Therefore, we concluded that the patient was falsely positive for PR3-ANCA.

**DISCUSSION**

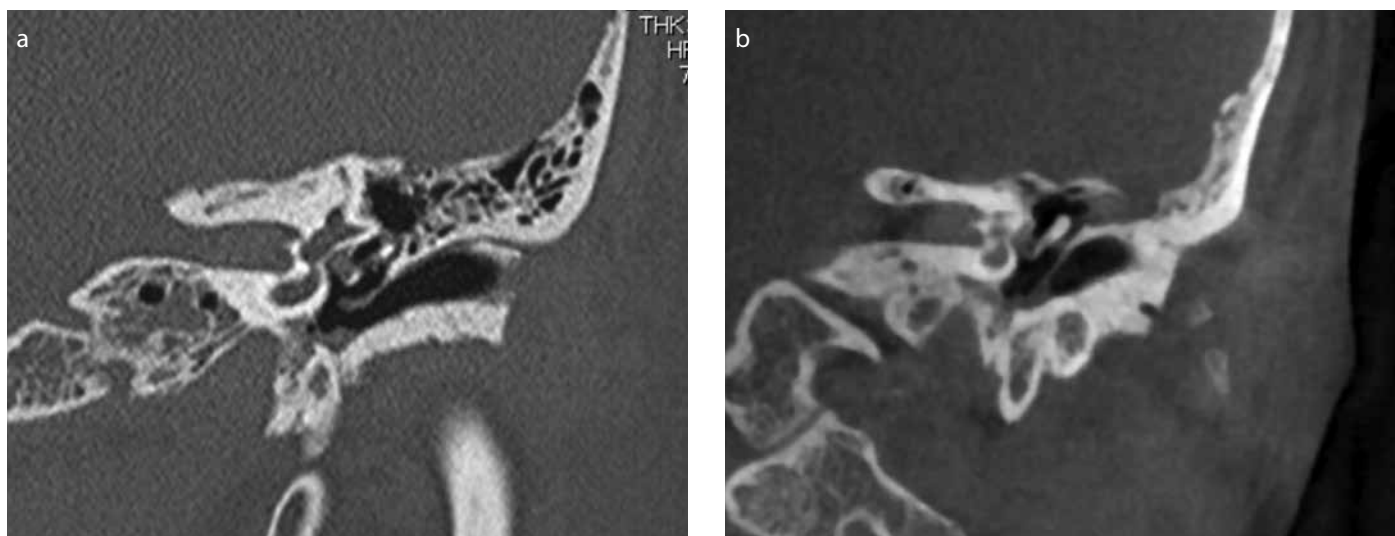
The typical clinical features of OMAAV, recently proposed by the Japan Otolological Society, are the following: (1) intractable otitis media with



**Figure 1, a, b.** (a) Left tympanic membrane (TM) before surgery. The TM is thickened and perforated. Otorrhea is observed. (b) Left TM after insertion of tympanic tube. The TM is still thickened.



**Figure 2, a-c.** (a) Pure tone audiometry (PTA) before surgery. (b) PTA performed when left otorrhea recurred 1 month after surgery. Hearing impairment is observed in the left ear. (c) PTA after linezolid therapy. Hearing level is improved.



**Figure 3, a, b.** (a) CT scan before surgery. The tympanic cavity is slightly clouded. (b) CT scan performed when left otorrhea recurred 1 month after surgery. The tympanic membrane is thickened, and the tympanic cavity is slightly clouded. No improvement is observed. A mastoidectomy was performed.

effusion or granulation that does not respond to antibiotics or insertion of a tympanic ventilation tube; (2) gradual hearing loss (in most cases) due to effusion and granulation in the middle ear, followed by sudden, progressive hearing loss within 2 months; (3) the MPO- or PR3-ANCA positivity (in most cases); (4) facial palsy and hypertrophic pachymeningitis (occasionally) [3]. According to the OMAAV diagnostic criteria, other disease, including intractable bacterial otitis media, must be excluded before OMAAV can be diagnosed [3]. In the present case, the otitis media was intractable, and the patient was positive for PR3-ANCA. However, MRSA was detected in her otorrhea, and neutropenia caused by teicoplanin was presumed to be one of the reasons for her intractable otitis media. In addition, linezolid administration improved her clinical symptoms immediately, and the disease did not recur, even though neither glucocorticoids nor immunosuppressants were used. Therefore, we concluded that the patient was falsely positive for PR3-ANCA.

False positivity for ANCA can occur in various diseases, such as other autoimmune diseases (ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus); infections (bacterial, fungal, tuberculosis); and malignant tumor [4-6]. In this regard, higher ANCA titers and the involvement of multiple affected organ systems may help to discriminate between AAV and other diseases in ANCA-positive patients [5]. In the cases of a low ANCA titer in which symptoms are localized to the ear, as in the present report, the possibility of false ANCA positivity should be considered.

The mechanism of false ANCA positivity is unknown. Some patients with PR3-ANCA-associated vasculitis have antibodies that react with a protein produced from PR3-antisense RNA. The amino acid sequence of this protein is partially homologous with a protein found in many microbes and viruses, including *Staphylococcus aureus*. Therefore, it has been speculated that such bacterial organisms mimic the peptide sequences of granule components and that this leads to the PR3-ANCA production [8]. It follows that the false ANCA positivity in the present case may have been related to a chronic MRSA infection.

Yamauchi et al. [7] reported a case of tuberculous otitis media presenting false PR3-ANCA positivity. Such intractable tuberculous

otitis media does share some clinical features with MRSA infection with false ANCA positivity, as well as with OMAAV. It follows that this disease might be misdiagnosed as OMAAV, and various diseases that can yield false ANCA positivity must be excluded when diagnosing OMAAV. Conversely, Azuma et al. [9] reported a case of otitis media with MPO-ANCA being positive in which the otorrhea culture showed MRSA infection. In that case, the administration of an anti-MRSA drug was ineffective, while immunosuppressant therapy did improve the otic symptoms. The authors concluded that the otitis media was a symptom of vasculitis. In future similar cases, tentative use of antibiotics might be useful in diagnosis.

In addition, the ANCA detection method should be considered carefully. A variety of different methods have been developed to detect ANCA, such as the enzyme-linked immunosorbent assay (ELISA), capture ELISA, anchor ELISA, and CLEIA. In particular, CLEIA, which has high sensitivity and specificity, has yielded a larger number of false-positive results than ELISA [10]. In the present study, we tested ANCA using CLEIA. Therefore, it may be that this detection method influenced the results of the PR3-ANCA detection.

In Japan, the number of patients diagnosed with AAV has increased two- to threefold over the past 10 years. The number of patients with OMAAV is expected to increase accordingly. Thus, in cases of intractable otitis media, clinicians should consider the possibility of OMAAV. However, they should also exclude other diseases, even in cases of the ANCA positivity, which were mentioned as diagnostic criteria for OMAAV.

**Informed Consent:** Written informed consent was obtained from patient who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - M.O.; Design - M.O., K.S.; Supervision - N.H.; Resources - M.O., K.S.; Materials - M.O., K.S., D.T., M.T., H.Y.; Data Collection and/or Processing M.O., D.T., M.T., H.Y.; Analysis and/or Interpretation - M.O., M.T., H.Y.; Literature Search - M.O., H.O.; Writing Manuscript - M.O., H.O.; Critical Review - N.H.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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