Pathogenesis and Diagnosis of Otitis Media with ANCA-Associated Vasculitis

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ABSTRACT
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is histologically characterized by systemic necrotizing vasculitis and is clinically classified into two phases, systemic or localized. Recently, otological symptoms such as otitis media and hearing loss, not previously often associated with AAV, have been reported in AAV cases. In these cases we propose a diagnosis of otitis media with AAV (OMAAV). The ANCA titer is important for the diagnosis of OMAAV, and in most cases rapid progressive hearing loss is observed as localized AAV. Peripheral facial nerve palsy or hypertrophic pachymeningitis are coupled with 25% of cases and 18% of cases respectively. Proteinase 3-ANCA (PR3-ANCA) positive otitis media causes granulomatous formation or middle ear effusion in the middle ear, on the other hand myeloperoxidase-ANCA (MPO-ANCA) positive otitis media predominantly presents as otitis media with effusion. The early diagnosed case and the sensorineural hearing loss not progressed deaf could be recovered by the immunosuppressive therapy. Delayed diagnosis of AAV occasionally leads to progression to the irreversible phase; therefore, diagnosis at the early-localized stage is important for treating AAV. In this review, we discuss the current understanding of this newly proposed concept of OMAAV.

KEY WORDS
ANCA, antineutrophil cytoplasmic antibody, myeloperoxidase, otitis media, vasculitis

ABBREVIATIONS
ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; GPA, granulomatosis with polyangitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis polyangiitis; OMAAV, otitis media with ANCA-associated vasculitis; MPO-ANCA, myeloperoxidase ANCA; PR3-ANCA, proteinase 3 ANCA; OMG, otitis media with granulation; OME, otitis media with effusion; EOM, eosinophilic otitis media; ELISA, enzyme-linked immunosorbent assay.

INTRODUCTION
Antineutrophil cytoplasmic antibody (ANCA) has been recognized as the antibody against neutrophil and monocyte lysosomal enzymes, in particular myeloperoxidase (MPO) and proteinase 3 (PR3).¹,² ANCA is considered as a pathogen releasing lytic enzymes that cause vascular inflammation involving reactive oxygen species and lead to systemic vasculitis.³ ANCA-associated vasculitis (AAV) is histologically characterized by systemic necrotizing vasculitis and remains a significant cause of fatal disease despite progress in immunosuppressive therapy. AAV is classified into categories based on histological features and vessel size, from largest to smallest.⁴ In small vessels, AAV comprises granulomatosis with polyangiitis (GPA; formerly Wegener’s granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis polyangiitis (EGPA; formerly Churg-Strauss syndrome).⁵⁻⁷ GPA is defined as a necrotizing
granulomatous in the nose, ear, upper respiratory organ and lung. MPA is defined as a necrotizing vasculitis of small vessels and includes a renal subcategory known as idiopathic necrotizing crescentic glomerulonephritis. EGPA is defined as an eosinophilic inflammation including severe bronchial asthma, chronic rhinosinusitis/nasal polyps and eosinophilic bronchitis/pneumonia, and eosinophilia.6

Systemic AAV presents otologic symptoms in 19-61% of cases during its clinical course, whereas, less common localized AAV presents only otologic symptoms such as otitis media and hearing loss, aural fullness, tinnitus and vertigo, initially.8,10 Delayed diagnosis of AAV occasionally leads to progression to the irreversible phase; therefore, diagnosis at the early-localized stage is important for treating AAV.

In cases of etiology unknown intractable otitis media in which known diseases, such as a bacterial otitis media, cholesterol granuloma, malignant osteomyelitis, tuberculosis, neoplasm and eosinophilic otitis media (EOM), have been ruled out, the symptoms often indicate otitis media with AAV (OMAAV). In this review article, we summarize the current understanding of the clinical course and diagnosis of this newly proposed concept of OMAAV.

**DIAGNOSTIC INFORMATION REGARDING SYSTEMIC AND LOCALIZED AAV**

Two sets of diagnostic information are available with regard to GPA: 1) the American College of Rheumatology (1990) classified a typical case of GPA and provided the basic and clinical research relating to such a case; 2) the Chapel Hill Consensus Conference defined the concept of vasculitits.4,7 The classification for GPA proposed by the American College of Rheumatology, which did not include MPA or ANCA, includes four criteria: 1) nasal or oral inflammation with oral ulcers or purulent or bloody nasal discharge; 2) abnormal chest radiograph showing the presence of nodules, fixed infiltrates, or cavities; 3) microhematuria or red blood cell casts in urine sediment; 4) histologic changes showing granulomatous inflammation within the wall of an artery or perivascular area in biopsy samples.7 In 2012, the Chapel Hill Consensus Conference proposed the revised nomenclature of vasculitits.6

The histopathological identification of necrotizing vasculitis is the key to diagnosis of AAV.4,6 However, in many cases there are difficulties obtaining suitable specimens for histopathologic study because of the anatomical location and limitations regarding sample size. A biopsy from a middle ear specimen showed a lower positive rate compared to the other specimen taken from nose or lung.11-13 Therefore, clinical symptoms and an elevation of proteinase 3 ANCA (PR3-ANCA) and/or myeloperoxidase ANCA (MPO-ANCA) titers are important factors in the diagnosis of AAV.6

The sensitivity of the titers of PR3- and MPO-ANCA is different in GPA, MPA and EGPA. For GPA, PR3-ANCA has 66% sensitivity and MPO-ANCA has 24% sensitivity; for MPA, PR3-ANCA has 26% sensitivity and MPO-ANCA has 50-80% sensitivity;4,3,14,15; and for EGPA, PR3-ANCA has 2.3% sensitivity and MPO-ANCA has 30-40% sensitivity.16,18 MPO-ANCA-positive EGPA showed similar clinical features to MPA with kidney dysfunction, peripheral neuropathy, alveolar hemorrhage and purpura, whereas PR3-ANCA-positive EGPA showed granulomatous formation with peripheral neuropathy, similar to GPA.18

The main target organs involved in GPA are the ear, nose, throat, upper respiratory tract (85-95%), glomerulonephritis of the kidneys (40-70%) and the lungs (40-60%).19 AAV commonly manifests as a rapidly progressive glomerular nephritis with necrotizing glomerular tufts, alveolar hemorrhage or interstitial pneumonia, and therefore the patient is often diagnosed with a systemic condition. However, some cases of AAV show only localized disease in the ear and/or nose. Nasal symptoms such as rhinorrhea, nasal granulation, nasal crusts, epistaxis and septum perforation are common initial signs.7 One-third of GPA cases present with otitis media during the clinical course of AAV.11,20

Localized GPA is considered to be a short-term disease stage that occurs early on in the clinical course of the disease and limited expression to the upper or lower respiratory tract.6,21 Most patients present to the clinician at the systemic stage of the disease already showing lung or kidney dysfunction, but it may take time to reach a final diagnosis of AAV if the signs had not been detected at the localized stage.22 Long-term follow-up of localized GPA has indicated that 10% of patients develop systemic disease and 46% relapse despite immunosuppressive therapy.21

Hearing loss has been reported in the clinical course of AAV, but only recently as an early-stage symptom.10,11,23-33 Table 1 shows the 41 OMAAV cases reported in the English literature that presented at an early phase or were initially diagnosed by otologic symptoms. Of these 41 cases, 12 were male and 29 were female, with ages ranging from 20 to 77 years, and 20 were PR3-ANCA positive and 21 were MPO-ANCA positive. In addition to these cases, the OMAAV working group in Japan reported 90 cases, including 8 cases reported previously,33 that were preliminarily analyzed for the clinical features of OMAAV.34 A total of 123 cases (35 male and 88 female, with ages ranging from 20 to 85 years) showed the clinical features of OMAAV.10,11,23-34 The diagnosis of GPA can be difficult and in most cases can only be provided by histological examination. Of the 123 cases, 16% were GPA positive by histological examination, without any systemic symptoms, and 87% were ANCA positive. Of the ANCA-positive cases, 33% were PR3 positive and 53% were MPO positive, only
Table 1  Otitis media with ANCA-associated vasculitis presented at an early stage or initially diagnosed by otological symptoms, as reported in the English literature

<table>
<thead>
<tr>
<th>Authors, Published year</th>
<th>Number of Cases (Gender)</th>
<th>Age</th>
<th>PR3-ANCA</th>
<th>MPO-ANCA</th>
<th>Hearing Loss</th>
<th>Ear Symptom</th>
<th>Facial Palsy</th>
<th>Therapy</th>
<th>Hearing Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maguchi S et al. 2001</td>
<td>1 (Male)</td>
<td>36</td>
<td>Negative</td>
<td>Positive</td>
<td>Mixed</td>
<td>Tinnitus</td>
<td>None</td>
<td>mPSL</td>
<td>Recovered</td>
</tr>
<tr>
<td>Takagi D et al. 2002</td>
<td>7 (Male 3, Female 4)</td>
<td>20-71</td>
<td>7 Positive</td>
<td>Negative</td>
<td>6 Mixed</td>
<td>1 SNHL</td>
<td>7 COM</td>
<td>PSL + CPA</td>
<td>3 Recovered 2 No change, 2 Dead (complication)</td>
</tr>
<tr>
<td>Takagi D et al. 2004</td>
<td>6 (Male: 1, Female: 5)</td>
<td>36-82</td>
<td>Negative</td>
<td>6 Positive</td>
<td>5 Mixed</td>
<td>1 SNHL</td>
<td>5 OME</td>
<td>PSL</td>
<td>Complete recovered to No change</td>
</tr>
<tr>
<td>Ferri E et al. 2007</td>
<td>1 (Female)</td>
<td>59</td>
<td>Positive</td>
<td>Negative</td>
<td>Conductive</td>
<td>OME</td>
<td>Yes</td>
<td>PSL + CPA</td>
<td>Recovered</td>
</tr>
<tr>
<td>Sugimoto T et al. 2007</td>
<td>1 (Female)</td>
<td>77</td>
<td>Negative</td>
<td>Positive</td>
<td>SNHL</td>
<td>None</td>
<td>None</td>
<td>PSL</td>
<td>Recovered</td>
</tr>
<tr>
<td>Tsuzuki K et al. 2009</td>
<td>2 (Female)</td>
<td>44-50</td>
<td>Negative</td>
<td>2 Positive</td>
<td>Mixed</td>
<td>Tinnitus</td>
<td>Yes</td>
<td>Steroid pulse</td>
<td>Recovered</td>
</tr>
<tr>
<td>Yamamoto T et al. 2011</td>
<td>1 (Female)</td>
<td>69</td>
<td>Negative</td>
<td>Positive</td>
<td>Mixed</td>
<td>OME</td>
<td>None</td>
<td>mPSL</td>
<td>Dead (SAH)</td>
</tr>
<tr>
<td>Okura T et al. 2011</td>
<td>1 (Female)</td>
<td>70</td>
<td>Negative</td>
<td>Positive</td>
<td>Mixed</td>
<td>None</td>
<td>None</td>
<td>PSL</td>
<td>Recovered to No change</td>
</tr>
<tr>
<td>Lim EJ et al. 2011</td>
<td>1 (Female)</td>
<td>54</td>
<td>Negative</td>
<td>Positive</td>
<td>SNHL</td>
<td>NR</td>
<td>None</td>
<td>PSL + CPA</td>
<td>Recovered</td>
</tr>
<tr>
<td>Wierzbicka M et al. 2011</td>
<td>7 (Male 3, Female 4)</td>
<td>32-46</td>
<td>7 Positive</td>
<td>Negative</td>
<td>NR</td>
<td>OM</td>
<td>2 cases</td>
<td>PSL + CPA</td>
<td>3 Recovered, 2 Progress, 2 Dead</td>
</tr>
<tr>
<td>Yamazaki H et al. 2012</td>
<td>3 (Male 1, Female 2)</td>
<td>55-67</td>
<td>1 Positive</td>
<td>2 Positive</td>
<td>Mixed</td>
<td>Thick TM, Serous otorrhea</td>
<td>None</td>
<td>PSL + CPA</td>
<td>Recovered</td>
</tr>
<tr>
<td>Sriskanarajah V et al. 2012</td>
<td>2 (Male 1, Female 1)</td>
<td>36-62</td>
<td>2 Positive</td>
<td>Negative</td>
<td>Mixed</td>
<td>Intractable OM</td>
<td>None</td>
<td>PSL + MTX</td>
<td>Recovered</td>
</tr>
<tr>
<td>Yoshida N et al. 2014</td>
<td>8 (Male 2, Female 6)</td>
<td>54-73</td>
<td>2 Positive</td>
<td>6 Positive</td>
<td>SNHL</td>
<td>OME intractable OM</td>
<td>5 cases</td>
<td>PSL + CPA</td>
<td>Recovered to No change</td>
</tr>
</tbody>
</table>

SNHL, sensorineural hearing loss; COM, chronic otitis media; OME, otitis media with effusion; OM, otitis media; TM, tympanic membrane; NR, not recorded; mPSL, methylprednisolone; PSL, prednisolone; CPA, cyclophosphamide; MTX, methotrexate; SAH, subarachnoid hemorrhage.

1% were both PR3 and MPO positive and 13% were both PR3 and MPO negative. This result is similar to previously published reports that the sensitivity of ANCA varies in relation to disease progression, with only 60% of cases being ANCA positive in localized GPA compared with 97% in systemic GPA. This ANCA positivity also shows regional differences. MPO-ANCA positivity is predominant in Asian countries, whereas PR3-ANCA positivity is predominant in northern Europe, suggesting the influence of some environmental factors such as silica, microbes or concomitant diseases, on the etiology of AAV disease. Indeed, MPA and MPO-ANCA was more common in Japan and GPA and PR3-ANCA is more common in the UK. Recently it became clear that PR3-ANCA positive patients and MPO-ANCA positive patients had a different genetic background.

**THE CLINICAL FEATURES OF OMAAV**

Figure 1 shows a case of OMAAV initially diagnosed by the otologic symptoms. In this typical case, a 69-year-old man was treated for right-sided, mild hearing loss with otorrhea for 6 months. One month later, right-sided peripheral facial incomplete nerve paralysis occurred with progressive hearing loss. The ear, nose and throat investigation revealed right middle ear effusion, with a right mean air conduction level of 85.0 dB and an air-bone gap of 35 dB, and a left mean air conduction level of 26.7 dB with an air-bone gap of 10.35 dB. Histologically, no obvious necrotizing vasculitis was observed in the mucosa of the middle ear. MRI with gadolinium enhancement did not demon-
The major clinical symptoms resulting in a visit to the primary ear, nose and throat clinic in the 123 cases discussed previously were hearing loss (75%), otalgia (12%), otorhoea (9%), aural fullness (6%), peripheral facial palsy (5%), headache (3%), tinnitus (2%) and nasal discharge. During treatment at the ear, nose and throat clinic, almost all patients were treated for intractable otitis media with effusion (OME) or chronic otitis media, or sensorineural hearing loss. It took 3 months on average, and 8 years at most, to reach a final diagnosis of OMAAV. The symptoms for referral to the territory medical center and the reason for suspecting OMAAV were: otitis media 99%, hearing loss 99%, tinnitus 33%, otorhoea 30%, otalgia 30%, headache 20%, nasal symptoms 24%, hypertrophic pachymeningitis 9% and facial palsy 19%. The majority of cases (94%) showed sudden progressive hearing loss and secretion or granulation in the tympanic cavity (93%). A positive ANCA titer leads relatively easily to a diagnosis of AAV; however, a negative ANCA result can take time to reach a final diagnosis and begin immunosuppressive therapy.34

The typical symptoms and clinical findings of OMAAV are: 1) otitis media following sudden progressive hearing loss; 2) intractable otitis media not effected by antibiotics and tympanic tube insertion; 3) mostly PR3- and/or MPO-ANCA positive; 4) occasionally clinical complications such as facial palsy or hypertrophic pachymeningitis; 5) tympanic membrane showing a dull appearance similar to OME and vessel dilatation of tympanic membrane ‘OME type’, otitis media with granulation ‘OMG type’, or normal appearance only with sensorineural hearing loss; 6) effectiveness of corticosteroid and immunosuppressive therapy using cyclophosphamide or methotrexate.10,11,20,23-34

In most cases of gradual hearing loss due to effusion and granulation in the middle ear, treated as an intractable otitis media, sudden progressive hearing loss over less than 2 months followed.10,11,20,23-34 Antibiotics were not effective against the ear infection, and often bacterial examination of the otorhoea was negative, with only normal bacterial flora being detected in the middle ear. The trigger leading to sud-
den hearing loss in intractable otitis media is not clear. Several case reports have shown that ear condition progressed after myringotomy or mastoidectomy. As the activation of neutrophils is necessary for generating ANCA, invasive surgical procedures or infection have the possibility of accelerating inflammation. After starting immunosuppressive therapy, ANCA titers rapidly returned to the normal range and hearing levels improved in 67% of ears. Those with complete loss of hearing could not recover. After treatment, speech discrimination scores improved by 85-100% in hearing-recovered cases. A retrocochlear disease resulted in poor speech discrimination scores. Good speech discrimination after treatment might indicate that the hearing loss of OMAAV was not due to retrocochlear deafness but instead due to cochlear dysfunction.

Some of the clinical features differ between PR3-ANCA positive and MPO-ANCA positive cases. PR3-ANCA-positive cases showed ‘OMG-type’ a little bit predominantly and ‘OME type’ symptoms, whereas MPO-ANCA-positive cases showed predominantly ‘OME type’ symptoms. These otological features were similar with the systemic AAV previously reported that granulomas were predominantly seen in patients with PR3-ANCA positive and rarely in patients with MPO-ANCA positive, but in a postmortem study, some MPO-ANCA showed granulomatous formation.

In 25% of reported cases of OMAAV, reversible facial palsy is a symptom. In over 10% of patients, hemi/bilateral facial palsy occurred after hearing loss. It remains unclear whether the facial palsy occurred via an intracranial route, the fallopian canal or the extra temporal region. Dehiscence of the facial canal has been reported previously and is not that rare. It is possible that granulation might spread to the facial canal, leading to destruction of the bony canal of the horizontal portion of the facial nerve, as in the case of complete deafness by GPA reported previously.

Hypertrophic pachymeningitis is another cranial symptom observed in some MPO-ANCA-positive patients. Otalgia was observed in 30% of patients; however, some patients complained of severe headache. Even in cases where the ear drum does not appear reddish or inflamed, if patients complain of a severe headache, hypertrophic pachymeningitis should be considered. It has been proposed that MPO-ANCA-positive hypertrophic pachymeningitis should be categorized as a central nervous system-limited form of AAV. MPO-ANCA positivity 47% (17/36) was more frequent compared with PR3-ANCA positivity 11% (4/36) in cases of immune-mediated hypertrophic pachymeningitis among Japanese patients. These cases of MPO-ANCA-positive hypertrophic pachymeningitis showed some characteristic clinical features: 1) predominance of elderly female patients; 2) 82% diagnosed with GPA; 3) mostly limited to the dura mater, upper airways, developing headaches, chronic sinusitis, otitis media and mastoiditis.

**THE CONCEPT OF OMAAV**

ANCA positivity is one of the important serological findings used for the diagnosis of OMAAV, particularly because of the difficulties in obtaining specimens for pathohistology. ANCA titer is examined by an enzyme-linked immunosorbent assay (ELISA); however, this test does not always give a positive result depending on the course of the disease or the medication used, such as a corticosteroid for hearing loss. OMAAV that was initially diagnosed by otological symptoms showed acute hearing loss in over 90% of cases. Idiopathic sudden sensorineural hearing loss is usually caused by a viral infection, membrane brakes in the cochlea or by reduction or occlusion of the microcirculation of the cochlear artery. Corticosteroid is generally medicated for the idiopathic acute sensorineural hearing loss. This medication of corticosteroid is also temporarily effective for hearing loss resulting from OMAAV, but also reduced the ANCA titer. However, this steroid effect is usually short-lived and the hearing impairment and other systemic or cranial nerve palsies, especially facial palsy, typically relapse.

A range of serological assays are used for the detection of ANCA, these include an indirect immunofluorescence assay, an ELISA and chemiluminescence enzyme immunoassay, and a new generation of serological assays such as a capture ELISA or an anchor ELISA. The sensitivity differs among these methods, and a negative ANCA result obtained by one method may give a positive result after reexamination using another immunoassay.

There are some ANCA-negative cases in which the clinical features of otitis media are identical to those of ANCA-positive OMAAV cases. Treatment of these ANCA-negative intractable otitis media cases is particularly challenging. Corticosteroid is temporarily effective; however, the negative ANCA result generally discourages clinicians from the use of further immunosuppressive therapies because of their side effects. Indeed, one of our cases of intractable otitis media showed sensorineural hearing loss following peripheral facial palsy, hypertrophic pachymeningitis, bulba palsy, and abducens nerve palsy, without ANCA titer elevation or positive pathological findings of AAV. This patient later died from a subarachnoid hemorrhage resulting from dissection of the basilar artery despite receiving intensive immunosuppressive therapy.

This proposed concept of OMAAV is shown in Figure 2. This novel concept encompasses cases of ANCA-positive otitis media, otitis media diagnosed as GPA, MPA or EGPA, or ANCA-negative cases. OMAAV encompasses all patterns of hearing loss.
such as a conductive hearing loss, sensorineural hearing loss and mixed hearing loss. PR3-ANCA positive hearing loss showed ‘OMG-type’ and ‘OME-type’ disease in the middle ear, whereas MPO-ANCA showed predominantly ‘OME-type’ disease. Facial nerve palsy was observed in 22% of PR3-positive cases and 25% of MPO-positive cases, and hypertrophic pachymeningitis was observed in 14% of PR3-positive cases and 18% of MPO-positive cases. 10,11,20,23-34

**MECHANISM OF HEARING LOSS IN OMAAV**

Conductive hearing loss, sensorineural hearing loss and mixed hearing loss are all observed in OMAAV at different clinical phases. Conductive hearing loss is caused by granulation and effusion in the middle ear. Obstruction in the Eustachian tube, or vasculitis in the middle ear mucosa, can lead to effusion in the middle ear. 51 Conductive hearing loss is recovered by immunosuppressive therapy in most cases. In contrast, sensorineural or mixed hearing loss is caused by inflammation in the inner ear leading to inner ear dysfunction. Among MPO-ANCA-positive cases, 51% showed mixed hearing loss and 36% showed sensorineural hearing loss. Among PR3-ANCA-positive cases, 60% showed mixed hearing loss, 38% showed sensorineural hearing loss and 2% showed conductive hearing loss. 10,11,20,23-34

OMAAV showed reversible hearing loss in cases where it had not progressed to complete deafness. 24,33,34 The reversible nature of this hearing loss with the onset of immunosuppressive therapy indicates that the hair cells remain intact at the pre-treatment stage. The inner ear maintains a specific ionic balance via an ion pumping mechanism which ensures a high level of K+ ions in the endolymph and creates a 140-180 mV driving force by stria vascularis for positively charged K+ ions to flow through the stereocilia. 52 Hair cells are morphologically coupled to fibrocytes and supporting cells by gap junctions and K+ ions recirculate from the endolymph to the stria vascularis through hair cells and supporting cells. Fibrocytes play an important role in ion transport and the activation of fibrocytes causes pericyte and capillary function and fibrovascular coupling, which is important for recycling K+ ions from hair cells. 53,54

The proposed mechanism for reversible sensorineural hearing loss involves homeostatic function, such as the stria vascularis or spiral ligament. Significant hearing recovery after idiopathic sudden sensorineural deafness is mainly observed 1-2 months after onset. However, AAV patients exhibited considerable reversibility in hearing levels after immunosuppressive therapy, even after several months of hearing loss. Inner ear infections, such as early bacterial labyrinthitis, elevated the high threshold because of the chemotactic factors that infiltrated into the round and oval window, the region responsible for high frequency detection in the cochlea. The recovery of high frequency loss after labyrinthitis is usually difficult. However, the air and bone hearing thresholds at 4000 Hz and 8000 Hz were recovered after immunosuppressive therapy.

Figure 3 shows the proposed mechanism behind hearing loss. AAV effects two sites: the middle ear in which granulation or secretion occurs leading to con-
Otitis Media with ANCA Vasculitis

Fig. 3 Possible mechanism of hearing loss in OMAAV. Left scheme shows the anatomy of the cochlea. Right scheme shows the possible mechanism of hearing loss. RW, round window; OW, oval window.

ductive hearing loss, and the inner ear which is the area related to sensorineural hearing loss. Conductive hearing loss caused by secretion and granulation in the middle ear is usually recovered by immunosuppressive therapy in the early ‘reversible’ stage of disease. As AAV is progresses, granulation in the middle ear spreads into the inner ear through the round and oval windows. AAV can also effect the inner ear, most likely the stria vascularis and capillaries. The early ‘reversible’ state of sensorineural hearing loss might be caused by a reduction in K⁺ ions in the endolymph due to dysfunction of the stria vascularis where the microcirculation networks are well developed in the cochlea. This sustained microvasculitis might lead to dysfunction of fibrovascular coupling following permanent ‘irreversible’ damage of hair cells. The temporal bone histopathology of cases of complete deafness caused by GPA showed that tympanic granulation and inflammatory substances also invade the inner ear through the round window, the stria vascularis was slightly atrophic and spiral ganglion cells were well preserved.⁴⁵

TREATMENT

The stage-dependent use of immunosuppressive drugs, such as a cyclophosphamide or methotrexate, has been questioned because of possible clinical complications.⁵⁵ Following studies that showed that glucocorticoid treatment alone could not achieve complete remission, combination therapy using glucocorticoids and cyclophosphamide was tested and shown to be effective.³³,⁵⁶,⁵⁷

The European League Against Rheumatism recommended that AAV should be categorized according to different levels of severity to assist treatment decisions; a combination of cyclophosphamide and prednisolone should be used for remission and induction in patients with AAV and renal or other organ threatening disease, whereas a combination of methotrexate and prednisolone should be used for remission and induction in patients with AAV with non-organ threatening or non-life threatening disease.⁴⁶,⁵⁸ Prednisolone (0.8-1 mg/kg/day) is tapered slowly (20% reduced every month) and then maintained (5-10 mg/day) while monitoring the ANCA titer, C-reactive protein levels and clinical conditions. Cyclophosphamide was administered for 2 years. The tapering of immunosuppressive therapy is important to control AAV. ANCA titers were usually decreased by immunosuppressive therapy. In long-term follow-up studies of localized GPA, it has been reported that 10% of patients develop a systemic disease and 46% relapse despite therapy.²¹ The persistence of high ANCA titers after the induction of remission has been associated with a strongly increased risk of relapse.⁵⁹ The changes in ANCA titer levels in GPA were not associated with a shorter remission time and increases were not associated with relapse.⁶⁰ Although ANCA titers do not strongly reflect disease activity, some cases experienced a gradual increase in MPO-ANCA titer 3 years after remission without any changes in hearing or general symptoms.³³ Close follow-up would be essential for the early detection of relapse evidenced by not only the general health of the pa-
tient but also more specifically by hearing changes and ear condition.

The sudden onset of progressive sensorineural hearing loss was evident in most cases and is one of the major ontological symptoms indicative of AAV. Hearing loss was partially recovered by treatment with corticosteroid alone. However, corticosteroid alone could not achieve complete remission in many cases, and relapsed cases after this therapy were progressed to severe systemic phase and resistant to immunosuppressive therapy and therefore difficult to control. Initial immunosuppression therapy that includes corticosteroid, cyclophosphamide or methotrexate is therefore essential for achieving long-term remission for OMAAV.

If OMAAV is suspected but the ANCA titer is negative, histology of the mastoid granulation taken by mastoidectomy or nasal mucosa is recommended. In a previous report, a biopsy from a middle ear specimen showed a lower positive rate. However, if the ANCA titer is negative and ANCA-positive otitis media and other possibilities causing intractable otitis media can be excluded, clinicians have the therapeutic option to start immunosuppressive therapy with prednisolone and cyclophosphamide so as not to waste time seeking histological evidence for AAV and trying to match disease criteria for GPA.

**RELATIONSHIP BETWEEN EGPA AND OMAAV**

EGPA is a form of AAV, characterized by eosinophil infiltration into the mucosa. EGPA is an eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting the small to medium vessels, that is associated with asthma and eosinophilia.

The American College of Rheumatology or Lanham criteria for EGPA specify an MPO-ANCA titer of 30-40%. The most common symptoms of EGPA are bronchial asthma, eosinophilia (over 10% of peripheral white blood cells), single neuritis and chronic rhinosinusitis, especially infiltrated with eosinophils. Otitis media in EGPA patients is different from other AAV diseases such as GPA and MPA because eosinophilic infiltration is observed compared with neutrophilic infiltration in GPA. EGPA patients exhibited mucous and glue secretion in the tympanic cavity similar to EOM. The criteria for EOM were proposed in 2011. The major criterion was OME or chronic otitis media with eosinophil-dominant effusion, the minor criteria were: 1) highly viscous middle ear effusion; 2) resistance to conventional treatment for otitis media; 3) association with bronchial asthma; and 4) association with nasal polyposis. Definitive cases are positive for the major criterion plus two or more of the minor criteria. The EOM criteria exclude EGPA and hypereosinophilic syndrome. EOM does not show necrotizing vasculitis in the middle ear mucosa. Clinical features relating to eosinophil infiltration, middle ear effusion and mucosal changes are similar in both EOM and localized EGPA. The middle ear mucosa of EOM contains IgE positive cells, and IgE, RANTES and eotaxin derived from eosinophils were detected in the middle ear effusion. The severity of EOM correlated with the total IgE concentration in the middle ear effusion, and antigen-specific IgE of fungus (i.e., *Aspergillus* and *Candida*) were detected in the middle ear effusion not in serum. Therefore, EOM is an allergic-type disease not related to vasculitis. The clinical features of EOM resemble localized EGPA. During treatment for EOM, some patients presented numbness in the leg or skin eruptions characteristic of EGPA. It is therefore necessary to pay close attention to the mononeuritis, polyneuritis or skin purpura-specific nature of EGPA during diagnosis.

**CONCLUSION**

AAV diagnosed by the otological symptoms of otitis media or hearing loss has been reported recently more than previous reports. In cases of intractable otitis media, previously unknown etiologies and resistance to conventional therapies have been reported. OMAAV might be one of the strong candidates to explain these discrepancies. Localized AAV can lead to systemic AAV, which has a high rate of fatal disease despite immunosuppressive therapy. A possibility of OMAAV should be considered when encountering intractable otitis media and progressive hearing loss. Immunosuppressive therapy should be started as soon as an elevated ANCA titer is detected or matched with the clinical features of OMAAV, even in the absence of typical histological findings. Thus, establishment of the diagnostic criteria of OMAAV obtained from further analysis for many more intractable otitis media cases should be followed by the development of its therapeutic strategies.

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