Dear Editor,

Eosinophilic otitis media (EOM) is a recently recognized intratable middle ear disease in Japan and has been focused on in Western country.1 EOM is characterized by the strong infiltration of eosinophils in highly viscous ear effusion (eosinophilic mucin) and in the middle ear mucosa.2,3 Unlike conventional chronic otitis media, EOM is generally resistant to all pharmacological therapies except for systemic steroid treatment. Surgical techniques are often warranted to improve the drainage pathway so as to remove obstructive eosinophilic mucin. Patients with EOM have a high risk of conductive hearing loss in the early stage, and half of all patients develop an increased bone-conduction threshold, leading to deafness in 6% of cases.2,4

The high levels of toxic eosinophil granule proteins observed in the eosinophilic mucin are suggested to be pathogenic and to cause epithelial damage.5 Eosinophil degranulation is mediated by several mechanisms, namely exocytosis, piecemeal degranulation, and cytolysis. Cytolysis is a well recognized pathology in diverse eosinophil-associated diseases, including EOM,6 and was suggested to represent a full activation of eosinophils,7 although its precise mechanism is not understood. A recent finding showed that extracellular trap cell death (ETosis), a novel form of cell death, mediates eosinophil cytolytic degranulation.5 Eosinophil ETosis (EETosis) is characterized by its striking final morphology: the release of intact granules and web-like chromatin structures (DNA traps/extracellular traps: ETs) through the breakdown of nuclear and plasma membranes. It does not feature apoptotic signatures such as phosphatidylserine exposure on the cell surface and DNA fragmentation. We have previously reported the presence of eosinophil ETs (EETs) in the middle ear secretions obtained from a few EOM patients.7 To clarify whether the presence of cytolysis and ETs is common in EOM, we conducted a case series study.

All patients met the diagnostic criteria of Iino et al.2 and were seen by experienced ENT doctors at Yamagata City Hospital Saiseikai, Yamagata University Faculty of Medicine, and Tohoku Medical and Pharmaceutical University between February 2010 and August 2017. Informed consent was obtained under protocols approved by the Institutional Review Board. Clinical features of the patients with EOM are summarized in Table 1. The patients were 4 men and 4 women who ranged in age from 25 to 72 years. Audiometry was performed by audiologists using a pure-tone audiometer (AA-76, Rion, Tokyo, Japan). All patients had comorbid chronic rhinosinusitis with nasal polyps and asthma. Seven of them had allergic rhinitis. Five showed eosinophilia (mean 11.6%, range 1.2%–32.9%) and elevated serum IgE levels (mean 604.6 IU/ml, range 104–1348 IU/ml). All patients had hearing impairment; three had sensorineural hearing loss and the others had conductive hearing loss. All patients had perforated tympanic membranes with eosinophilic mucin and granulation in the middle ear cavity without bacterial infections.

We microscopically evaluated eosinophil morphology in middle ear effusions. Eosinophilic mucin and granulation in the middle ear cavity undergo cytolysis to release their toxic granules.

ETosis that mediates lytic degranulation is an activation-induced programmed cell death. IL-5, a well known eosinophil survival-promoting cytokine, paradoxically induces EETosis in conjunction with platelet activating factor in low-serum/albumin culture conditions.6 Indeed, higher concentrations of IL-5 have been detected in the middle ear effusions of EOM patients.9 Other
stimuli, including immobilized immunoglobulins, calcium ionophores, fungi, and phorbol myristate acetate, also induce EETosis.\(^6,10\)  Difficult-to-remove, highly viscous eosinophilic mucin might be associated with disease severity.\(^4,7\) The mechanisms that regulate cytolysis/EETosis and DNA traps in EOM patients are worth further exploring, and their control might be important for developing future therapies.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Asthma</th>
<th>Allergic rhinitis</th>
<th>CRSwNP</th>
<th>Blood Eo (%)</th>
<th>Serum IgE (IU/mL)</th>
<th>Perforation</th>
<th>Hearing loss</th>
<th>Hearing levels (dB)</th>
<th>Viscous mucin</th>
<th>Eo</th>
<th>Cytolytic Eo</th>
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</table>

CRSwNP, chronic rhinosinusitis with nasal polyposis; Eo, eosinophils; IgE, immunoglobulin E; md, mixed hearing loss; cd, conductive hearing loss; sn, sensorineural healing loss; ETs, extracellular DNA traps. Hearing level (dB): Air conduction hearing level (dB).

**Table 1**

Clinical and pathological characteristics of EOM patients.

**Fig. 1.** Eosinophilic otitis media affecting a 25-year-old man (case 1) referred to our department because of antibiotic-resistant right middle ear effusion. (A) Otoendoscopic image of perforation of tympanic membrane associated with granulation and highly viscous discharge on admission. (B) CT scan shows soft tissue density mass in the meso-tympanic cavity. (C) Audiogram shows right conductive hearing loss of 25–45 dB across air–bone gap. (D) Section of highly viscous effusion was stained with anti-human nuclear histone H1 monoclonal antibody (green) and DNA stain (Hoechst 33342; blue) and analyzed under a Carl Zeiss LSM510 laser scanning confocal microscope. Images show web-like formation of histone, DNA, and both merged. The middle ear effusion and granulation declined rapidly after treatment with 30 mg/day oral prednisolone.

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Conflict of interest

The authors have no conflict of interest to declare.

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