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A case of a patient with IgG4+ plasma cell infiltration, an IgG4-related disease, localized to the auditory ossicles

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ABSTRACT

Immunoglobulin G4+ (IgG4+)-related disease may lead to lesions in various systemic organs. Based on several cases of patients with suspected IgG4-related Mikulicz's disease, the definitive diagnosis of IgG4-related Mikulicz's disease has been established, depending on head and neck lesions (e.g., swelling of the salivary glands, enlargement of the lacrimal glands, and bilateral paranasal sinus shadow mainly of the maxillary sinus). In this study, we report a case with suspected IgG4-related disease based on findings of abnormal auditory ossicles obtained accidently by temporal bone computed tomography (CT). The patient was a 27-year-old woman. She was previously diagnosed with IgG4-related dacryoadenitis and rhinosinusitis, which did not lead to a definitive diagnosis. Her temporal bone CT during her visit to our hospital due to left aural fullness during the course showed a soft tissue density shadow around the left auditory ossicles. Thereafter, the presence of the shadow led to slow progression of decalcification, mainly of the left incus. The relationship between the symptoms and decalcification of the auditory ossicles during the course was unclear. Although steroid therapy was performed because of rapidly progressive, severe sensorineural hearing loss, her hearing did not recover. No central nervous system lesions were apparent in magnetic resonance imaging. The biopsy of the left auditory ossicles, obtained after her informed consent, showed jelly-like osteolytic changes in the left incus, and microscopic results showed infiltration of IgG4+ plasma cells in the tissue of the auditory ossicles. The direct relationship between her severe sensorineural hearing loss and the pathological findings of the auditory ossicles is unclear. However, to our knowledge, this is the first case report of suspected IgG4-related disease that had pathological changes, mainly of the auditory ossicles.

1. Introduction

Immunoglobulin G4+ (IgG4+)-related disease was first reported in Japan. It was first reported by Hamano et al., in 2001 that high serum IgG4 levels in autoimmune pancreatitis can be used for the differential diagnosis of pancreatic cancer [1]. According to their later report [2], increased IgG4+ plasma cells were found in the lesions of patients. These reports lead to the recent establishment of a new disease concept of IgG4-related disease. The disease may lead to lesions in various systemic organs. In some cases, clinical findings of head and neck in the otolaryngology area (e.g., swelling of the salivary glands, enlargement of the lacrimal glands, and paranasal sinus shadow) lead to suspected IgG4-related disease, resulting in the ultimate diagnosis. The prevalence of IgG4-related disease is not so high in the entire otolaryngology area. However, IgG4-related disease should be considered during daily practice.

Here, we report a case of a patient with a rare disease course from our hospital. She visited our department with the chief complaint of aural fullness. Temporal bone CT for screening accidently revealed a unilateral, soft-tissue density shadow around the auditory ossicles. Thereafter, the legions led to slow decalcification of the auditory ossicles. She had severe, acute-onset ipsilateral and unilateral sensorineural hearing loss during the follow-up period. Laboratory findings showed infiltration of IgG4+ plasma cells in the auditory ossicles. She had a history of decalcification, mainly of the auditory ossicles, without otologic signs (e.g., a wide enlargement of middle ear mucosa, mastoid air cells shadow, and abnormal tympanic membrane findings). To our knowledge, this is the first reported case of IgG4+ plasma cell infiltration in the tissue of the auditory ossicles.

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2. Case report

The patient was a 27-year-old woman, with the chief complaint of left aural fullness. Her medical history included examinations for bronchial asthma (adult onset) and seasonal allergic rhinitis. She also had a history of diagnosis of a persistent shadow in the bilateral maxillary sinus and enlargement of the lacrimal glands in another hospital 4 years before the first visit to our department. At that time, she was diagnosed with possible IgG4-related dacryoadenitis. The subsequent lacrimal gland biopsy revealed epithelioid granulomas. Infiltration of CD138+ cells inside the granulomas was also found. The results of immunostaining (IgG4/IgG >50%) suggested the presence of IgG4-related dacryoadenitis. Thereafter, her visits to our department were discontinued because she did not want additional examinations or treatment.

She visited our department with a chief complaint of left aural fullness. The examination showed no abnormal tympanic membrane findings. However, pure tone audiometry revealed reduced air conduction thresholds at high-frequency for the left ear. The audiometry did not show significantly reduced bone conduction thresholds (Fig. 1-a). At that time, the examination did not indicate left tinnitus. Therefore, the pathological significance of the results of audiometry was unclear. However, temporal bone CT for screening for hearing loss showed a light soft-tissue density shadow around the left auditory ossicles (incus). Imaging diagnosis showed early-stage middle ear cholesteatoma and granuloma in the tympanic cavity after she was suspected to have otitis media (Fig. 2-a). In addition, the diagnosis showed the presence of a partial shadow in the tympanic cavity. The growth of mastoid air cells was normal, and no shadow was observed in the same site.

After discussion with the patient, regular observation of the inner ear, audiometry, and temporal bone CT were performed, and conservative follow-up was planned. However, she revisited our department with the chief complaint of worsening of hearing loss of the left ear 3 weeks after the first visit. At that time, increased high-frequency thresholds of the left ear were observed (Fig. 1-b). After 2-week oral steroid (prednisolone [PSL]) therapy with gradual increase in the dose (starting at 60 mg), the symptoms improved. However, 3 months later, she revisited our department because of acute and severe left tinnitus and the worsening of hearing loss. Her hearing loss of the left ear with scaled-out levels. Therefore, 1-week intravenous steroid (PSL) therapy with gradual increase in the dose starting at 60 mg was reintroduced. However, she did not respond to the therapy (Fig. 1-c).

Gadolinium-enhanced magnetic resonance imaging (MRI) for additional examination of sensorineural hearing loss showed contrast T1-weighted images of nodules with a diameter of 5 mm in the site of the left auditory ossicles (Fig. 3). Gadolinium-enhanced MRI did not reveal morphologic anomalies of the central nervous system (e.g., lesions of the inner ear, hypertrophic pachymeningitis) that could explain the acute sensorineural hearing loss of the left ear. MRI also did not show any shadow inside the mastoid air cells.

Temporal bone CT immediately before the onset of hearing loss of the left ear with scaled-out levels (during the follow-up) showed the loss of shadow around the left incus and the decalcification of the left incus (Fig. 2-b).

Blood tests for the diagnosis of rapidly progressive sensorineural hearing loss of the left ear was performed considering the possibility of IgG4-related disease, anti-neutrophil cytoplasmic antibody (ANCA) -associated vasculitis, etc. Blood test did not show a significant increase in IgG4, IgG, p (perinuclear) -ANCA, and c (cytoplasmic) -ANCA levels. In addition, mumps virus-specific antibody titers showed patterns of patients with infection or vaccination. Syphilis and HIV infection were not observed.

Subsequent regular temporal bone CT performed every three to six months revealed slow decalcification of the left incus (Fig. 2-c, Fig. 2-d).

Persistent slow-progressing decalcification was observed mainly in the left incus. However, this was not an organic cause of acute-onset severe sensorineural hearing loss of the left ear. Therefore, conservative treatment was continued. Because she had had a history of diagnosis of IgG4-related dacryoadenitis in another hospital, systemic diagnosis was performed in the Division of Rheumatology, Department of Medicine, Showa University School of Medicine for the re-screening of IgG4-related disease, ANCA-associated vasculitis, and other collagen diseases. Blood test did not indicate any of these conditions. However, the blood test showed increased angiotensin converting enzyme (ACE). Systemic contrast CT revealed abnormal nephrographic patterns. Therefore, renal tuberculosis and papillary necrosis were also tested for using differentiation assay. However, she tested negative for the QuantiFERON-TB (QFT) test. In addition, the results of gallium scintigraphy were normal. These results did not strongly suggest the presence of renal tuberculosis or sarcoidosis or show the presence of other systemic lymphadenopathy, neoplastic changes, or organ failure.

Thereafter, only follow-up was performed for a period of time because the patient did not want additional examination. However, after she provided informed consent to tentative biopsy of auditory ossicles for the above-mentioned progressive decalcification of the auditory ossicles, she underwent transcanal endoscopic ear surgery (TEES) for the biopsy of the left auditory ossicles under general anesthesia at approximately 2 years after the first visit to our department.

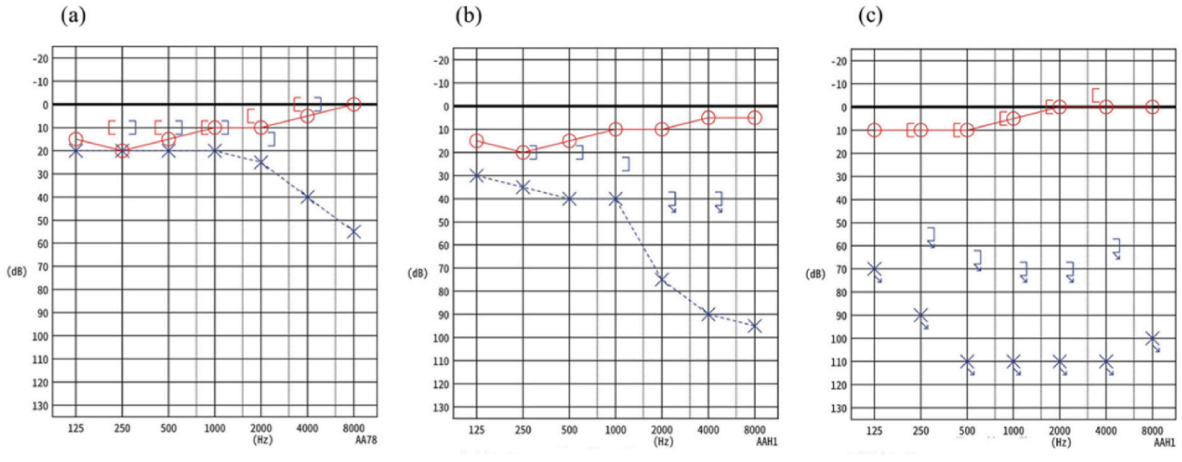

Fig. 1. 1-a: Increased air conduction high-frequency thresholds of the left ear was observed at the first visit.
1-b: The patient visited our department with the chief complaint of the worsening of left aural fullness 3 weeks after the first visit to our department. Sensorineural hearing loss (mainly of high-frequency sounds) of the left ear was observed. 1-c: The patient with hearing loss of the left ear with scaled-out levels did not respond to steroid therapy 3 months after the first visit to our department. Thereafter, her hearing remained unchanged.

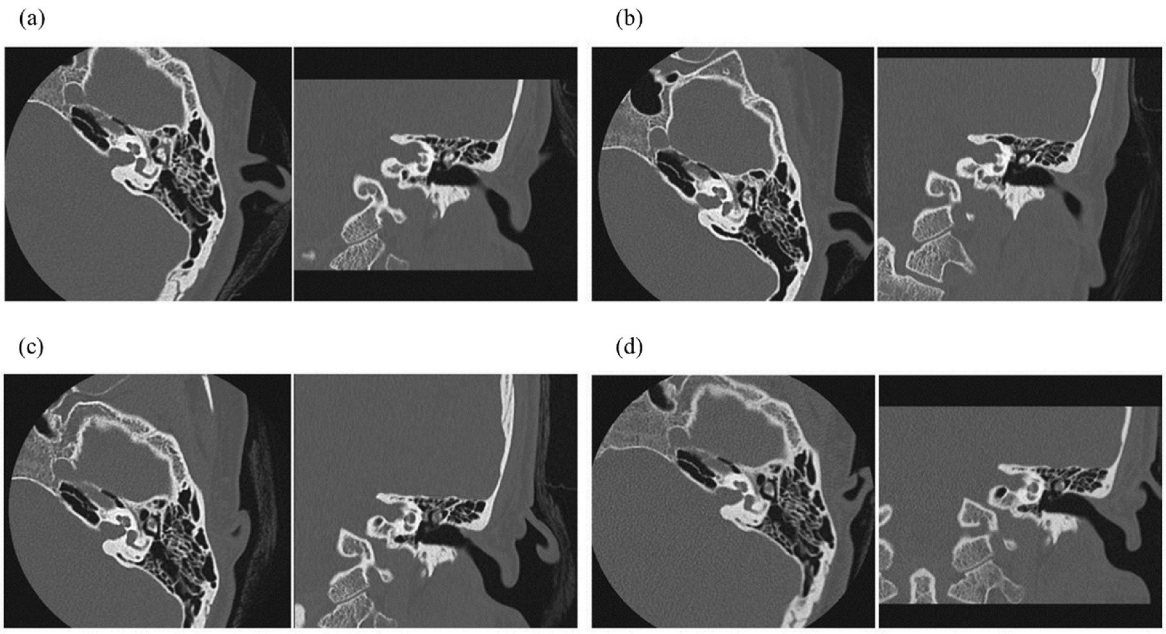

Fig. 2. 2-a: The patient was suspected of early-stage cholesteatoma and middle ear granulation because of a soft-tissue density shadow around the MI-joint at the first visit.
2-b (3 months later), 2-c (11 months later), and 2-d (20 months later): Loss of a shadow around the auditory ossicles was observed at the first visit. However, slow-progressing decalcification, mainly in the incus, was observed.

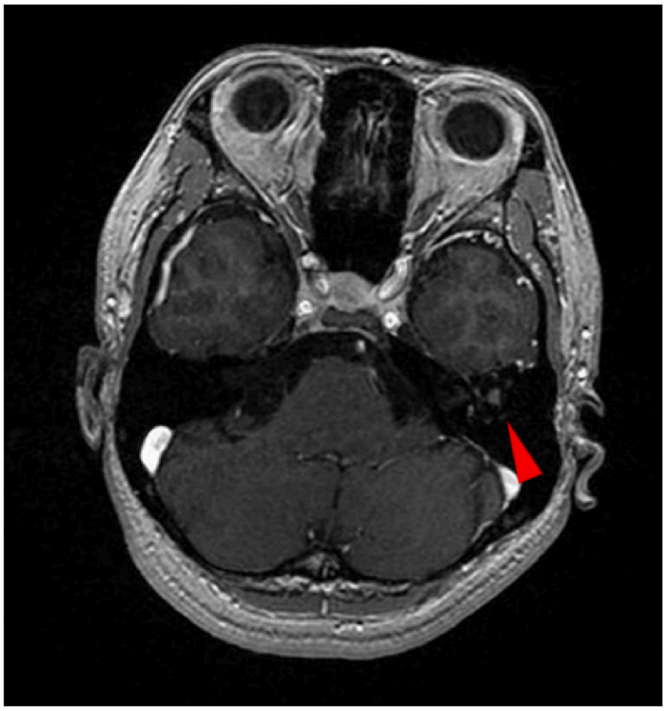

Fig. 3. Magnetic resonance imaging (MRI) of severe acute sensorineural hearing loss of the left ear 3 months after the first visit to our department.
Gadolinium-enhanced MRI and T1-weighted images showed nodules with a diameter of 5 mm in the site of the left auditory ossicles (red arrowhead). No anomalous inner ear symptoms were observed. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Macroscopic findings showed jelly-like osteolysis of the left incus (Fig. 4-a). Intraoperative findings showed the loss of the range of motion of the malleus-incus (MI) joint. In other words, the differential diagnosis suggested a possible, although not evident, presence of malignant tumors. Thus, partial removal of the malleus head was also performed. Because she had preoperative severe steroid-refractory sensorineural hearing loss of the left ear, the reconstruction of sound conducting pathways was not performed after the biopsy of auditory ossicles. Pathological findings showed the absence of malignant tumors. Hematoxylin and eosin staining revealed a significant infiltration of plasma cells in the tissue surrounding the incus (Fig. 4-b, Fig. 4-c). Therefore, according to the immunohistopathological findings, clinical significance of the symptoms was unclear. Infiltration of IgG4+ plasma cells was observed in the biopsied tissue from the auditory ossicles (Fig. 4-d, Fig. 4-e). Because of heterogeneous infiltration of IgG4+ plasma cells, accurate evaluation was impossible. However, the number of IgG4+ plasma cells in the aggregation site of the cells was reportedly >30 per high power field (HPF) in the biopsies (IgG4/IgG = approximately 40%), suggesting the presence of IgG4-related disease. As shown in CT imaging, intraoperative findings showed no pathological swelling of middle ear mucous membrane. In addition, the biopsied middle ear mucosa did not show infiltration of IgG4+ plasma cells. The proposed tentative simultaneous biopsy of the maxillary sinus mucosa during surgical biopsy of auditory ossicles was not performed because the patient did not provide informed consent to it. Fortunately, neither hearing impairment of the right ear (unaffected side) nor new-onset multiple organ failure has been observed. She did not respond to steroid therapy in the acute phase for preceding rapidly progressive sensorineural hearing loss of the left ear. The pros and cons of future reintroduction of steroids are currently being explored.

3. Discussion

Elevated serum IgG4 levels, infiltration of IgG4+ plasma cells in one or multiple organs, localized enlargement due to fibrosis, and, in some cases, tumor nodes or hypertrophic lesions, are characteristic of IgG4-related disease. Historically speaking, dacryoadenitis and sialoadenitis, known today as Mikulicz's disease, were first reported by a surgeon, Johann von Mikulicz-Radeki, in Europe in 1892. The difference between Mikulicz's disease and Sjögren syndrome that involves the enlargement

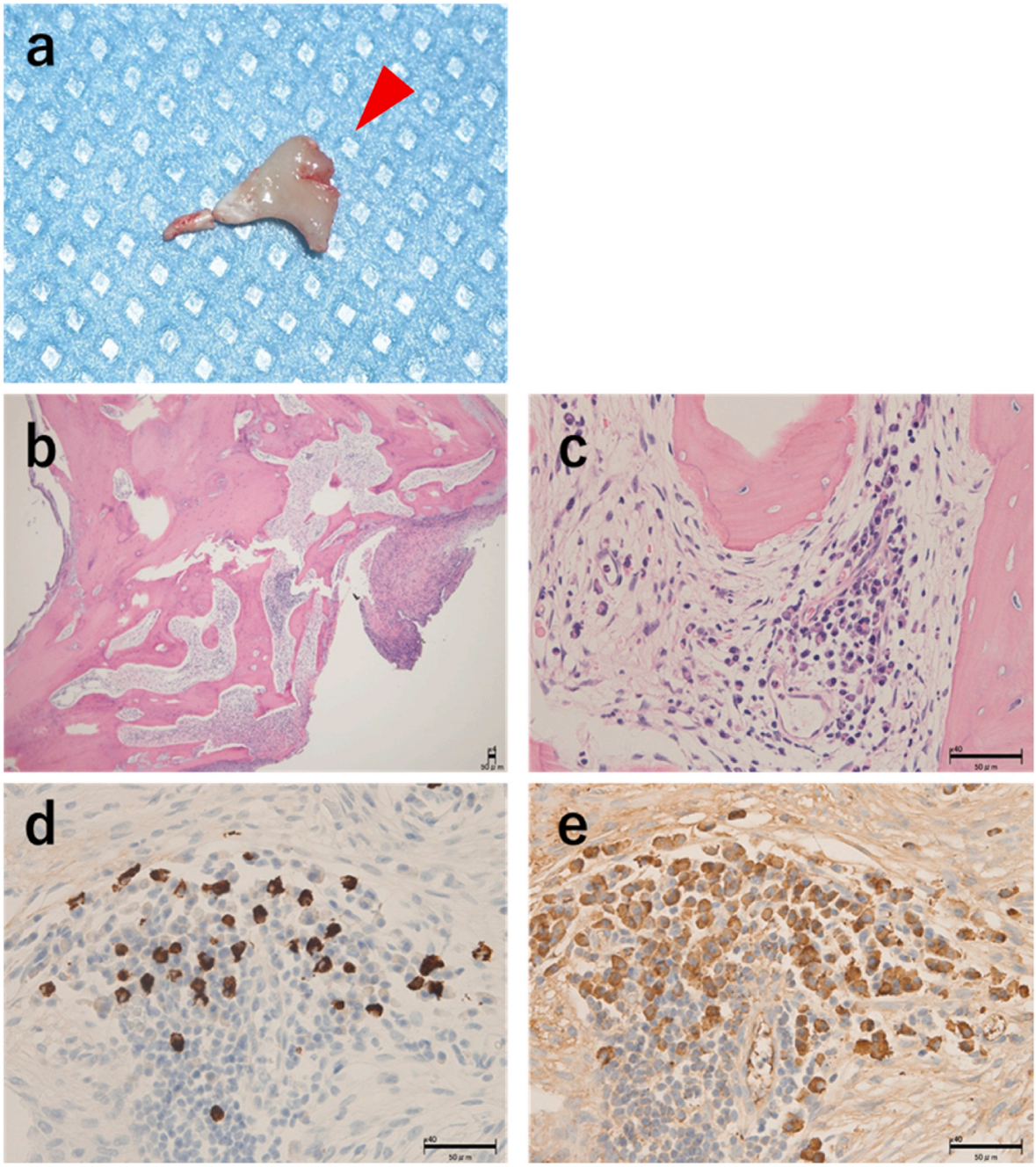

Fig. 4. 4-a: The biopsy sample of the auditory ossicles. Macroscopic identification of the jelly-like osteolytic changes, mainly of the incus, was performed (red arrowhead).
4-b: Jelly-like osteolytic changes, mainly of the incus, was visually observed (red arrowhead). 4-c: A high-power view of the hematoxylin-eosin (HE)-stained incus. 4-d: Thirty-five IgG4+ plasma cells per HPF in biopsies were observed in the biopsies. 4-e: Approximately 100 IgG + plasma cells per HPF were observed in the biopsies. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of salivary glands had long been a topic of discussion. Pathologists, Morgan and Castleman in the United States compared Mikulicz's disease and Sjögren syndrome and concluded that the two diseases were histopathologically identical. Therefore, Mikulicz's disease was considered a subtype of Sjögren syndrome. However, Hamano et al. [1] reported the relationship between autoimmune pancreatitis and IgG4 in 2001. Thereafter, Yamamoto et al. in Japan suggested that Mikulicz's disease and Sjögren syndrome are two different diseases because elevated serum IgG4 levels and IgG4+ plasma cell infiltration of lacrimal and salivary gland tissue were observed in Mikulicz's disease but not in Sjögren syndrome [3]. Thereafter, IgG4 has been associated with several systemic diseases (e.g., Küttner's tumor, sclerosing cholangitis, retroperitoneal fibrosis, periarteritis, hypertrophic pachymeningitis, interstitial pneumonia, and interstitial nephritis). Therefore, it was proposed to comprehensively call these various IgG4-related organ lesions as "IgG4-related disease." After such process, Umehara et al. in Japan reported proposed comprehensive diagnostic criteria for IgG4-related disease (Table 1) [4]. Furthermore, in the case of probable or possible diagnosis based on comprehensive diagnostic criteria, in some cases, definitive diagnosis is possible by the combination of diagnostic criteria for each organ (autoimmune pancreatitis, IgG4-related sclerosing cholangitis, IgG4-related Mikulicz's disease, and IgG-related renal disease).

Table 1
Diagnostic criteria for IgG4-related disease comprehensive (quoted from Reference 4).

1. Diffuse or focal enlargement, tumor, nodes, or hypertrophic lesions clinically characteristic in one or multiple organs
2. Hematologically high serum IgG4 levels (≥135 mg/dL)
3. The following two histopathological criteria:
① Significant infiltration and fibrosis of lymphocytes and plasma cells
② IgG4+ plasma cell infiltration: IgG4/IgG + cell ratio of ≥40% and >10 IgG4+ plasma cells per high powered field (HPF) in biopsies
***Those who meet 1, 2, and 3: Definite diagnosis group**
***Those who meet 1 and 3: Probable diagnosis group**
***Those who meet 1 and 2: Possible diagnosis group**
Diagnosis is possible based on diagnostic criteria for each organ even when definitive diagnosis based on clinical criteria is not possible.
In the case of probable or possible diagnosis based on comprehensive diagnostic criteria, the criteria are used in combination with diagnostic criteria for organ-specific IgG4-related disease. The following has been published to date: "IgG4-related dacryoadenitis and sialoadenitis (IgG4-related Mikulicz's disease) the diagnostic criteria," "Diagnostic criteria for autoimmune pancreatitis," "Diagnostic criteria for IgG4-related sclerosing cholangitis," "Diagnostic criteria for IgG4-related nephropathy."

Common diagnoses based on diagnostic criteria for each organ in the otolaryngology area include IgG4-related Mikulicz's disease and dacryoadenitis. Diagnostic criteria for IgG4-related Mikulicz's disease (enlargement of glands in the head and neck) are shown in Table 2 [5]. It should be noted that serum IgG4 levels or tissue findings may not meet the criteria even in cases with suspected IgG4-related Mikulicz's disease. In case of high serum IgG4 levels and symmetric enlargement of at least two of the following: lacrimal, parotid, and submandibular glands, in some cases, when Schirmer test/fluorescent assay, gum test, or biopsy of lacrimal glands/minor salivary glands meets the diagnostic criteria for Sjögren syndrome, diagnosis of IgG4-related Mikulicz's disease is impossible because of the exclusion criteria. This makes the interpretation of diagnoses difficult. Our department also encountered such a case. The characteristic differences between IgG4-related Mikulicz's disease and Sjogren's syndrome are as follows. However, in addition to elevated serum IgG4 levels, patients with IgG4-related Mikulicz's disease have good response to steroid therapy, a good recovery of gland function and, in some cases, symptoms (e.g., dry mouth and reduced tear production) similar to those in patients with Sjögren syndrome.

There are only a few case reports of IgG4-related disease in the otolaryngology area. Only cases of chronic otitis media, with symptoms like abnormal tympanic membrane findings, swelling of middle ear mucosa, and a clear tympanic cavity shadow, and cases of inner ear ossification can be found reported in the literature [6–8]. There are summary reports of head and neck signs in Japanese patients with IgG4-related disease, but studies on otologic signs are scarce [9,10]. To our knowledge, none of these studies mentioned a shadow inside the mastoid air cells or the slow-progressing decalcification, mainly of the auditory ossicles, without inflammation of the entire tympanic cavity, or performed follow-up of symptom changes over time.

Serum IgG4 levels of the patient in this study did not increase at any time during follow-up blood test in our department. By conventional definition, a diagnosis of IgG4-related disease could not even be considered for the patient in this study because the findings did not meet the comprehensive diagnostic criteria for IgG4-related disease and IgG4-related dacryoadenitis and sialoadenitis. She was previously diagnosed with epithelioid granuloma lesions in the lacrimal gland using a biopsy (IgG4/IgG >50% for the same site) in another hospital. Previous systemic diagnosis in the Division of Rheumatology, Department of Medicine, Showa University School of Medicine did not indicate sarcoidosis, granulomatosis with polyangiitis, Castleman's disease, malignant lymphoma, or cancer lesions. Therefore, although a blood test showed normal serum IgG4 levels, she was diagnosed with IgG4-related disease. After a comprehensive evaluation of symptoms showing IgG4+ plasma cell infiltration in the lesions of auditory ossicles, the possibility of IgG4-related disease was considered. In addition, lesions in the auditory ossicles and their changes over time in the patient may not directly explain the acute severe sensorineural hearing loss during the course. However, the relationship between acute sensorineural hearing loss and IgG4-related disease cannot be denied. Takagi et al. [9] reported a case which had severe acute-onset sensorineural hearing loss during the course. Acute sensorineural hearing loss may have contributed to IgG4-related disease in the patient in this study as well. If that is the case, she is at greater risk of hearing loss of the right ear, which is unaffected till now, and new-onset multiple organ failure. She may require continued follow up. The significance of infiltration of IgG4+ plasma cells in the left auditory ossicles of the patient in this study is unclear. However, based on our literature review, there is no other case report of a patient with a shadow inside the mastoid air cells, slow-progressing decalcification, mainly of the auditory ossicles, without inflammation of the entire tympanic cavity, and infiltration of IgG4+ plasma cells in the tissue of the auditory ossicles. Therefore, this case report is a significant addition to the literature. However, future similar case reports are necessary to further validate our findings.

Table 2
IgG4-related dacryoadenitis and sialoadenitis (IgG4-related Mikulicz's disease) (quoted from Reference 5).

1. At least two of the following: symmetrical enlargement of lacrimal, parotid, and submandibular glands (persisting for at least three months)
2. High serum IgG4 level (≥135 mg/dL)
3. Infiltration of lymphocytes and IgG4+ plasma cells with characteristic fibrosis and sclerosis (IgG4/IgG > 0.5)
***Diagnosis is based on 1 and 2 or 1 and 3.**

Declaration of interest

The authors have no conflicts of interest directly relevant to the content of this article.

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