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Otologic Manifestations of Immunoglobulin G4-Related Disease

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Abstract

Objective: Immunoglobulin (Ig) G4-related disease is systemic, and it has been reported that patients with IgG4-related disease complain of symptoms involving numerous organs. However, there are few reports concerning the otologic manifestations of IgG4-related disease. The purpose of this study is to investigate the clinical features of the otologic manifestations in IgG4-related disease.

Methods: We recruited 39 consecutive patients diagnosed with IgG4-related disease. Otologic symptoms, laboratory data, and audiogram findings were retrospectively examined. Mucosal tissues from the inferior turbinate were obtained from subjects before treatment. The serum IgG4 and eosinophil levels together with clinical features were analyzed.

Results: Five of the 39 cases had some otologic symptoms. Otitis media with effusion was present in 2 patients. Sensorineural hearing loss was also present in 1 patient. Eosinophilic otitis media was present in 2 patients with bilateral rhinosinusitis and bronchial asthma, and elevated serum eosinophil levels. Oral prednisolone was effective in the treatment of IgG4-related disease.

Conclusion: We revealed a new clinical entity associated with the otologic manifestations of IgG4-related disease.

Keywords

eosinophilic otitis media, IgG4-related disease, otologic manifestations, prednisolone

Introduction

Immunoglobulin (Ig) G4-related disease is a systemic disease characterized by the infiltration of IgG4-positive plasma cells into many organs, such as the pancreas, kidneys,¹ prostate,² retroperitoneum,³ and lungs.⁴ The majority of patients who present with IgG4-related disease limited to the head and neck region complain of problems with Mikulicz's disease.⁵

Recently, we have reported that patients with IgG4-related disease complain of nasal manifestations, such as nasal crusting and nasal obstruction. The nasal manifestations of IgG4-related disease differ from those of allergic rhinitis and share clinical and pathological similarities with those of other organs affected by IgG4-related disease.⁶ There is also report of rhinosinusitis associated with IgG4-related disease.⁷ However, there are few reports on the otologic manifestations of IgG4-related disease, and the clinical features of IgG4-related disease with ear involvement remain unknown.^{8–10} Difficulty in diagnosis often delays the initiation of treatment, and the disease occasionally progresses to the irreversible phase. Here, we report cases of IgG4-related disease that presented with mixed hearing loss and discuss the clinical features of the otologic manifestations associated with IgG4-related disease.

Materials and Methods

Patients

Thirty-nine patients were diagnosed with IgG4-related disease at Hokkaido University between September 2007 and August 2012. Their ages at the time of the disease onset ranged from 41 to 82 years.

A diagnosis of IgG4-related disease in the present study was made on the basis of the following criteria: (1) elevated serum IgG4 level (> 135 mg/dL); (2) the presence of 1 or more lesions characteristic of IgG4-related disease (eg, sclerosing sialadenitis, autoimmune pancreatitis, or sclerosing cholangitis); (3) the exclusion of other diseases, such as sarcoidosis, Castleman's disease, granulomatosis with polyangiitis (GPA), and malignant disease¹; and (4) $> 40\%$

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of IgG⁺ plasma cells being IgG4⁺ and > 10 cells/high powered field of biopsy sample.¹¹

Of the 39 patients, 5 patients (3 males, 2 females), ages 41 to 69 years (median, 60 years), had otologic symptoms (Table 1). Audiometric evaluation consisted of pure-tone thresholds by air and bone conduction. Each patient's pure-tone average is shown as the mean of the measurements obtained at 4 frequencies: 500, 1000, 2000, and 4000 Hz. All subjects provided written informed consent. This study was approved by the Institutional Review Board of the Hokkaido University Hospital for Clinical Research.

Histopathology and Immunohistochemistry

Nasal mucosa from the inferior turbinate was obtained from subjects before steroid therapy. Sections (4 μ m) were cut for hematoxylin and eosin (H&E) and immunohistochemical staining. Tissue samples were immunostained for IgG (rabbit polyclonal anti-human IgG; Cell Marque Corporation, Rocklin, California, USA) and IgG4 (mouse monoclonal anti-human IgG4; Zymed Laboratory, Inc, San Francisco, California, USA).

The numbers of IgG- and IgG4-positive plasma cells were counted in 5 high-power magnification fields ($\times 400$ HPF, 1 HPF = 0.307 mm²). The ratio of IgG4-positive plasma cells to IgG-positive plasma cells was calculated, with a ratio of more than 40% regarded as signifying IgG4-related disease (Table 1).

Treatment for IgG4-Related Disease With Otologic Manifestations

Three of the 5 IgG4-related disease patients with otologic manifestations were treated with oral prednisolone. Two patients were treated with steroid nasal spray only, due to either the presence of unstable diabetes mellitus or less severe symptoms. Oral prednisolone was started at 30 to 60 mg per day and reduced gradually (by 5 mg per week) to a daily dose of 5 mg.

Statistical Analysis

All data are expressed as means $\pm$ standard error (SEM).

Results

Clinical Features of Patients With IgG4-Related Disease With Otologic Symptoms

Thirteen (33.3%) of 39 IgG4-related disease patients were women and 26 (66.6%) were men. The mean age was 64.3 $\pm$ 1.69 years (range, 41-82 years). Twenty-eight (71.8%) patients suffered from Mikulicz's disease, 13 (33.3%) from sclerosing cholangitis, 4 (10.2%) from retroperitoneal

fibrosis, and 21 (53.8%) from autoimmune pancreatitis (AIP). Eleven (28.2%) patients suffered from rhinosinusitis, and 7 (17.9%) from rhinitis. The mean IgG4 level was 731.9 $\pm$ 86.9 mg/dL.

The clinical findings of the 5 patients (12.8%) with otologic symptoms are summarized in Tables 1 and 2. These patients presented with a variety of complaints including eosinophilic otitis media (EOM) in 2 patients, otitis media with effusion (OME) in 2 patients, and sensorineural hearing loss in 1 (case 4) who had developed vertigo at the onset of the disease. Bilateral rhinosinusitis and bronchial asthma were observed in both EOM patients, and serum eosinophil levels were increased. There was no relationship between the severity of otologic manifestations and serum level of IgG4.

Four of the 5 patients with ear disease had symptoms involving the nose or paranasal sinuses, and the ratio of IgG4-positive plasma cells to IgG-positive plasma cells was increased. Effusion in the middle ear was present in 4 patients, but no granulomatous lesions were observed. Elevated serum IgG4 was confirmed in all 5 patients at some time during their illnesses.

Effects of Steroid Treatment

Three patients were treated with oral prednisolone. In 2 of them, otologic symptoms were improved after starting oral prednisolone treatment. Case 4 was treated with oral prednisolone (40 mg/d) for sudden deafness with the dose tapered off after 2 weeks. His hearing level showed partial remission. After treatment, the serum levels of IgG4 were decreased in 2 cases treated with systemic prednisolone. Two patients (cases 1 and 2) were treated with local steroid nasal spray alone. No significant reduction in serum IgG4 levels was observed after nasal spray treatment. However, both their otologic and rhinologic symptoms were improved after treatment.

Discussion

In this study, we revealed that there is a new clinical entity associated with the otologic manifestations of IgG4-related disease. In the head and neck region, Mikulicz's disease was initially reported to be 1 of the manifestations of Sjögren's syndrome.⁵ However, the infiltration of numerous IgG4-positive plasma cells was observed in the salivary gland specimens from patients with Mikulicz's disease, and Mikulicz's disease is now considered to be a manifestation of IgG4-related disease.¹¹

Some patients with IgG4-related disease complain of nasal symptoms such as nasal crusting and nasal obstruction. Therefore, we analyzed patients with IgG4-related disease presenting with nasal symptoms. In more than half of the patients with IgG4-related disease, IgG4-positive

Table 1. Clinical Findings and Other Organ Involvement.

Case No.	Age, y/ Sex	Ear Findings	Mikulicz's Disease	Pathological Diagnosis	Vertigo	Other Organ Involvement	Serum IgG4, mg/dL	Serum Eosinophils, %	Serum IgE, IU/mL (0-295)	Rhinologic Findings	Asthma	IgG4/IgG
1	69/M	OME	+	Biliary tract		AIP, SC	312	10	53.8	Rhinosinusitis		54.4
2	41/F	EOM	+	Submandibular gland		–	963	10.6	763.7	Rhinosinusitis	+	66.4
3	60/M	OME	+	Nose		Orbital pseudo-tumor	547	8.6	1553.3	Rhinosinusitis	+	73.6
4	69/M	SNHL	+	Submandibular gland	+	Lung, pituitary gland	1820	4.9	7.5			80
5	61/F	EOM	+	Nose		Lung	692	9.7	699	Rhinosinusitis	+	NA

Abbreviations: AIP, autoimmune pancreatitis; EOM, eosinophilic otitis media; F, female; Ig, immunoglobulin; M, male; NA, not available; OME, otitis media with effusion; SC, sclerosing cholangitis; SNHL, sensorineural hearing loss.

Table 2. Treatment and Outcome.

Case No.	Treatment		Audiological Manifestation		Outcome		Serum IgG4, mg/dL (pretreatment)	Serum IgG4, mg/dL (posttreatment)
	PSL (oral)	Local	Right, dB	Left, dB	Right, dB	Left, dB		
1		+	50	45	23.8	27.5	312	NA
2		+	25	27.5	23.8	17.5	963	535
3	+		18.8	8.8	NA	NA	547	60.4
4	+ ^a		16.3	47.5	15	35	1820	630
5	+		40	13.8	25	17.5	692	NA

Abbreviations: Ig, immunoglobulin; IVCY, intravenous cyclophosphamide; NA, not available; PSL, prednisolone.

^aTreatment was short term (2 weeks).

plasma cells were increased in the nasal specimens. The clinical features of IgG4-related disease with nasal involvement differ from those of allergic rhinitis and share clinical and pathological similarities with those of other organs affected by IgG4-related disease.⁶ Moteki et al⁷ also reported that 32% of patients with IgG4-related disease had chronic rhinosinusitis.

However, there are few reports concerning the otologic manifestations of IgG4-related disease,⁸⁻¹⁰ and the clinical features of the otologic involvement associated with IgG4-related disease remain unknown. Among the patients with IgG4-related disease treated in our institution, 5 patients (12.8%) had otologic symptoms. These patients with otologic manifestations were divided into the following basic types: The first is OME, which may be due to Eustachian tube obstruction and nasopharyngeal involvement. In this study, both of the patients with OME suffered from rhinosinusitis. The second type is EOM, which is caused by eosinophil involvement in the middle ear and mastoid cavity. Both EOM patients suffered bilateral chronic rhinosinusitis with polyps and bronchial asthma. The serum eosinophil levels were also elevated. Eosinophilic otitis media is an intractable otitis media characterized by heavy eosinophilic infiltration and mucoid effusion, and it is found in patients with adult onset asthma.¹² Although the cause of EOM is unknown, eosinophilic inflammation is thought to be induced in the middle ear by some stimuli through the Eustachian tubes. It has been reported that Th2 and regulatory T cells might be involved in the pathogenesis of Mikulicz's disease.¹³ Eosinophilia observed in patients with IgG4-related disease might be mediated by Th2 cytokines. The third type is sensorineural hearing loss; although the etiology is unknown, there are reports of IgG4-related disease involving the central nervous system. Lindstrom et al¹⁴ described cases of meningitis that demonstrated increased numbers of IgG4-positive plasma cells. Inoue et al¹⁵ also reported histopathological examinations in perineural lesions and described that perineural soft tissue showed severe lymphoplasmacytic infiltration, fibrosis, and occasional eosinophils.

This type of hearing disorder is considered to be the primary form of involvement associated with IgG4-related disease; however, it is difficult to make a definite histological diagnosis, particularly when specimens are taken from the middle ear. As for GPA, we have reported that histological diagnosis is difficult using specimens from the middle ear and recommend that biopsy specimens be taken from the paranasal sinus or nose, because biopsy specimens from the nasal cavity showed a higher positive rate.¹⁶

In this report, the patients with OME due to Eustachian tube dysfunction in association with IgG4-related disease could be helped by steroid nasal spray. It has been reported that systemic steroid treatment was effective for AIP.¹⁸ In this study, sensorineural hearing loss was considered to be the primary form of ear involvement associated with IgG4-related disease, and early treatment with glucocorticoids can resolve these symptoms. However, there are reports of exacerbation of the disease during the tapering off of glucocorticoids.¹⁷ In such cases, the dose of glucocorticoids should be increased or combined therapy with immunosuppressive drugs should be considered. Case 4 was treated for sudden deafness, but only partial remission was achieved. There is a possibility that if he were to be treated with glucocorticoids long term, his hearing level might be recovered.

From our cases, it appears that the otologic manifestations may be 1 sign of IgG4-related disease. We should, therefore, consider the possibility of IgG4-related disease for patients presenting with a hearing disorder accompanied by elevated serum IgG4.

Conclusion

We presented the clinical features of the otologic manifestations of IgG4-related disease. The patients with otologic manifestations were divided into 3 categories: OME, EOM, and sensorineural hearing loss. Systemic steroid therapy is thought to be effective in the treatment of IgG4-related disease. We should consider the possibility of IgG4-related disease for patients presenting with otologic manifestations accompanied by elevated serum IgG4.

Declaration of Conflicting Interests

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