The Laryngoscope

Nasal Manifestations of Immunoglobulin G4-Related Disease

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Objectives/Hypothesis: Immunoglobulin (Ig)G4-related disease is a systemic syndrome, characterized by sclerosing lesions that mainly affect the exocrine tissue. Although some patients with IgG4-related disease complain of nasal symptoms, there are few reports concerning the nasal manifestations of this disease. We investigated the clinical and pathological features of the nasal manifestations of IgG4-related disease.

Study Design: Retrospective review in a tertiary referral hospital.

Methods: Twenty-three consecutive patients with IgG4-related disease, six allergic rhinitis (AR) patients, and eight healthy subjects (HS) were evaluated. Nasal symptoms, local findings of the nasal cavity, and laboratory data were examined. Mucosal tissues from the inferior turbinate were obtained from all subjects before treatment. The level of IgG4-positive plasma cells and other infiltrating cells, and the number of nasal glands in the nasal subjects were compared among the three groups.

Results: Ten (43.4%) of 23 cases had some nasal symptoms, such as nasal obstruction and nasal crusting. Thirteen cases (56.5%) had numerous IgG4-positive plasma cell infiltration in the nasal mucosa. IgG4-positive plasma cells, CD3, and CD4 were significantly higher in the IgG4-related disease group than in the HS and AR groups, whereas the number of nasal glands in the IgG4-related disease group was significantly lower than in the HS and AR groups.

Conclusions: The inflammatory lesions associated with IgG4-related disease exist on the nasal membrane. Thus, the nasal manifestations of IgG4-related disease were thought to be different from AR.

Key Words: Immunoglobulin G4-related disease, rhinitis, infiltrating cell, nasal gland.

Level of Evidence: 4

***Laryngoscope,* 123:829–834, 2013**

INTRODUCTION

Immunoglobulin (Ig)G4-related disease is a systemic syndrome, characterized by sclerosing lesions that mainly affect the exocrine tissue.[1] High serum concentrations of IgG4 and the infiltration of IgG4-positive plasma cells into the pancreatic tissue were first demonstrated in sclerosing pancreatitis in 2001.[2,3] At nearly the same time, the infiltration of numerous IgG4-positive plasma cells was observed in the salivary gland tissues from patients with Mikulicz disease,[4] which used to be considered to be a subtype of Sjögren syndrome (SS).[5] Currently, both sclerosing pancreatitis and Mikulicz disease are recognized as manifestations of IgG4-related disease. Later, the infiltration of IgG4-positive plasma cells into other organs, such as the kidneys,[6] bile duct,[7] prostate,[8] and the retroperitoneum,[3] was reported. IgG4-related disease has now been proposed as a new systemic syndrome.

Some patients with IgG4-related disease complain of nasal symptoms such as nasal crusting and nasal obstruction. However, there are few reports concerning the nasal manifestations of IgG4-related disease,[9] and the clinical and pathological features of the intranasal lesions associated with IgG4-related disease remain unknown.

The main pathological feature of IgG4-related disease is IgG4-positive plasma cell infiltration into the affected organs. Although some reports have focused on the number of IgG4-positive plasma cells in specimens from the affected organs, no study has counted the populations of other infiltrating inflammatory cells.

The purpose of this study is to investigate the clinical features of the nasal manifestations of IgG4-related disease. Moreover, we counted not only IgG4-positive plasma cells but also the infiltrating immunocompetent cells in nasal specimens from patients with IgG4-related disease.

MATERIALS AND METHODS

Patients

Twenty-three consecutive patients diagnosed with IgG4-related disease in the Department of Otolaryngology, Hokkaido University Hospital between September 2007 and August 2010 were examined. The diagnosis of IgG4-related disease was defined as satisfying following criteria: 1) elevated serum IgG4

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Editor's Note: This Manuscript was accepted for publication September 19, 2012.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.23792

levels (>135 mg/dL); 2) the presence of one or more lesions characteristic of IgG4-related disease (e.g., sclerosing sialadenitis, autoimmune pancreatitis, or sclerosing cholangitis); and 3) the exclusion of other diseases, such as sarcoidosis, Castleman disease, Wegener granulomatosis, and malignant disease.[1]

Nasal symptoms, local findings for the nasal cavity, laboratory data, and computed tomography (CT) findings were retrospectively examined on the basis of clinical records. The degree of nasal sinus lesions was evaluated using the Lund–Mackay staging system.[10]

Six patients suffering from allergic rhinitis (AR) and eight healthy subjects (HS) with no history of atopic or autoimmune diseases were also examined.

All subjects provided written informed consent. This study was approved by the institutional review board of the Hokkaido University Hospital for Clinical Research (011-0277).

Histopathology and Immunohistochemistry

Mucosal tissues from the inferior turbinate were obtained from all subjects before steroid therapy. Sections (4 μm) were cut for hematoxylin and eosin and immunohistochemical staining. The samples were used for immunostaining for IgG (rabbit polyclonal antihuman IgG; Cell Marque Corp., Rocklin, CA), IgG4 (mouse monoclonal antihuman IgG4; Zymed Laboratories, San Francisco, CA), CD3 (rabbit polyclonal antihuman CD3; Dako, Glostrup, Denmark), CD4 (mouse monoclonal antihuman CD4; Dako), CD8 (mouse monoclonal antihuman CD8; Dako), CD20 (mouse monoclonal antihuman CD20; Dako), c-kit (rabbit polyclonal antihuman CD117, c-kit; Dako), and myeloperoxidase (rabbit polyclonal antihuman myeloperoxidase, Dako).

Evaluation of IgG4-Positive Plasma Cell Infiltration

IgG4-positive plasma cells were counted in five high-power magnification fields (×400 HPFs, 1 HPF = 0.307 mm^2). The mean number of positive cells per HPF and the ratios of IgG4-positive to IgG-positive plasma cells were calculated. We classified the patients with IgG4-related disease into two groups (the high-infiltration group and the low-infiltration group) based on the following criteria: 1) >50 IgG4-positive plasma cells per HPF and 2) >40% ratio of IgG4-positive to IgG-positive plasma cells, according to a previous study.[11]

Evaluation of Other Infiltrating Cells and Nasal Glands

Positively stained nucleated cells showing immunostaining for CD3, CD4, CD8, CD20, c-kit, or myeloperoxidase were counted in three HPFs for all subjects. Eosinophils were also counted morphologically in three HPFs. The ratios of positively stained infiltrating cells to all infiltrating cells were then evaluated. The mean number of nasal glands in three low-power magnification fields (×200 LPFs, 1 LPF = 1.23 mm^2) was also calculated.

Statistical Analysis

All data are expressed as means ± standard error. Fisher exact test was used for comparisons of sex ratio and frequencies of nasal symptoms.

One-way analysis of variance followed by post hoc testing with Fisher Least Significant Difference was used for comparisons of age, CT scores, IgG and IgG4 serum levels, IgG4-positive plasma cell counts, other infiltrating cell counts, and nasal gland counts. Probability values of .05 or lower were considered statistically significant.

RESULTS

Clinical Features of Patients With IgG4-Related Disease

General symptoms. Six (26.1%) of the patients were women, and 17 (73.9%) were men (Table I). The mean age was 64.5 ± 2.55 years (range, 41–82 years). The mean IgG4 serum level was 697.9 ± 131.5 mg/dL. Twelve patients (52.2%) suffered from autoimmune pancreatitis, and 9 (39.1%) suffered from sclerosing cholangitis. Three (13.0%) and four (17.4%) patients, respectively, were diagnosed with retroperitoneal fibrosis and inflammatory pseudotumor. Eleven patients (47.8%) received oral corticosteroids, and three (13.0%) received intranasal corticosteroids.

Nasal symptoms. Ten patients (43.4%) showed some nasal symptoms, with eight (34.8%) suffering from nasal obstruction and seven (30.4%) from nasal crusting. In 12 patients, sinus CT scans prior to treatment were available. The mean Lund–Mackay score was 4.33 ± 1.21.

Comparison of Clinical Features Between the High-Infiltration and Low-Infiltration Groups

In most cases, IgG4-positive plasma cells were observed in the nasal specimens. Thirteen cases (56.5%) were classified as high infiltration, whereas the other 10 cases (43.5%) were classified as low infiltration. Clinical features were compared between the high-infiltration and low-infiltration groups, with no significant intergroup differences in age, sex, serum IgG4, frequency of nasal symptoms, or CT findings identified (Table II).

Comparison of Infiltrating Cell Numbers Among the IgG4-Related Disease, HS, and AR Groups

The number of IgG4-positive plasma cells in both the high-infiltration (218.4 ± 28.4/HPF) and low-infiltration (15.33 ± 5.49/HPF) groups was significantly higher than that in either the HS (1.41 ± 0.68/HPF) or AR (0.24 ± 0.19/HPF) group (Fig. 1).

The CD3-positive cell count in the high-infiltration group (28.43 ± 2.02%) was significantly higher than that in all other groups ($P < .01$, Fig. 2A). Furthermore, the CD4-positive cell count in the high-infiltration group (11.0 ± 1.21%) was also significantly higher than that in all other groups ($P < .01$, Fig. 2B). There were no differences in the number of CD8-positive cells among the four groups (Fig. 2C). There were also no significant differences in the number of CD20-positive cells among the IgG4-related disease, HS, and AR groups. However, the CD20-positive cell count in the high-infiltration group (10.70 ± 1.54%) was significantly higher than in the low-infiltration group (4.01 ± 1.11%; $P < .01$, Fig. 2D). The c-kit–positive cell count in the AR group (2.82 ± 0.39%) was significantly higher than in the other groups ($P < .01$, Fig. 2E), whereas the myeloperoxidase-positive cell count in the high-infiltration, low-infiltration, and AR groups was significantly lower than in the HS group ($P < .01$, Fig. 2F). In particular, very few myeloperoxidase-positive cells were observed in the IgG4-related disease group. Although some specimens from the high-infiltration group were infiltrated by a relatively greater number of eosinophils, there were no significant differences observed among the four groups (Fig. 2G).

TABLE I.
Main Clinical and Pathological Features of 23 Cases of IgG4-Related Disease.

No.	Sex	Age, yr	Serum IgG4, mg/dL	General Symptoms	Nasal Symptoms	CT Score	$IgG4^+$ Cells/HPF	$IgG4^+/IgG^+$ Cells	Degree of Infiltrate
1	M	69	312	SMG, AIP, SC	NO, NC	11	180	54.4	High
2	M	55	2,970	SMG, AIP, IPT, RPF	NO, NC	11	234	60.5	High
3	F	82	143	SMG	NO, NC	NA	2	75.2	Low
4	F	41	963	SMG	NC	NA	156	66.4	High
5	M	75	407	AIP, SC	NO, R	0	169.7	89.5	High
6	M	71	389	AIP, SC	NC	0	391.3	96.7	High
7	M	78	1,280	SMG	Absent	NA	300.3	94.8	High
8	M	57	284	SMG, AIP, SC	NO	6	335.7	88.6	High
9	M	55	414	AIP	Absent	NA	1	59.9	Low
10	M	65	511	SMG, AIP, SC	NO, NC	NA	135.7	50.4	High
11	M	77	277	SMG, AIP	Absent	NA	40.3	26.8	Low
12	F	79	328	PTG, AIP, SC, RPF	NO, NC	0	101	70.6	High
13	F	66	218	SMG, IPT	Absent	NA	350.3	94.4	High
14	M	65	338	SMG, SC	Absent	NA	6.7	28.2	Low
15	M	54	455	AIP, SC	Absent	0	107.3	53	High
16	F	55	330	AIP, SC	Absent	NA	7	34.4	Low
17	F	46	489	LG, PTG, SMG	Absent	4	4.3	23.6	Low
18	M	72	1,090	SMG	Absent	NA	46.3	71.7	Low
19	M	75	953	IPT	Absent	8	31.7	70.8	Low
20	M	67	1,720	SMG	Absent	NA	275.3	85.2	High
21	M	60	547	RPF	NO, R	6	13	73.6	Low
22	M	78	928	LG, SMG, IPT	Absent	1	102.3	73.8	High
23	M	41	706	LG, SMG, AIP	Absent	5	1	37.5	Low

AIP = autoimmune pancreatitis; CT = computed tomography; F = female; HPF = high-power field; Ig = immunoglobulin; IPT = inflammatory pseudotumor; LG = lacrimal grand; M = male; NA = not available; NC = nasal crusting; NO = nasal obstruction; PTG = parotid gland; R = rhinorrhea; RPF = retroperitoneal fibrosis; SC = sclerosing cholangitis; SMG = submandibular gland.

The number of nasal glands in the high-infiltration group (26.71 ± 4.22/LPF) was significantly lower than that in the HS (114.63 ± 5.70/LPF) and AR (94.92 ± 5.54/LPF) groups ($P < .01$, Fig. 3).

Representative Case

A 55-year-old man was referred to our hospital due to nasal obstruction and swelling of the bilateral submandibular region for a period of 2 months. He had a history of inflammatory pseudotumor in the lung, with infiltration of IgG4-positive plasma cells 4 months before his first visit to our department. Physical examinations

TABLE II.
Comparisons of Clinical Features Between the High- and Low-Infiltration Groups.

Characteristic	High-Infiltration Group, n = 13	Low-Infiltration Group, n = 10	*P*
Age, yr	65.77 ± 3.15	62.80 ± 4.34	.599
Sex, M/F	10/3	7/3	.536
Serum IgG, mg/dL	2,451 ± 337	2,016 ± 243.1	.192
Serum IgG4, mg/dL	828.1 ± 218.0	528.7 ± 96.0	.619
Nasal symptoms	8	2	.057
Nasal obstruction	6	2	.195
Rhinorrhea	1	1	.692
Nasal crusting	6	1	.077
CT score	3.63 ± 1.76	5.75 ± 0.85	.350

Data are mean ± standard error.
CT = computed tomography; F = female; Ig = immunoglobulin; M = male.

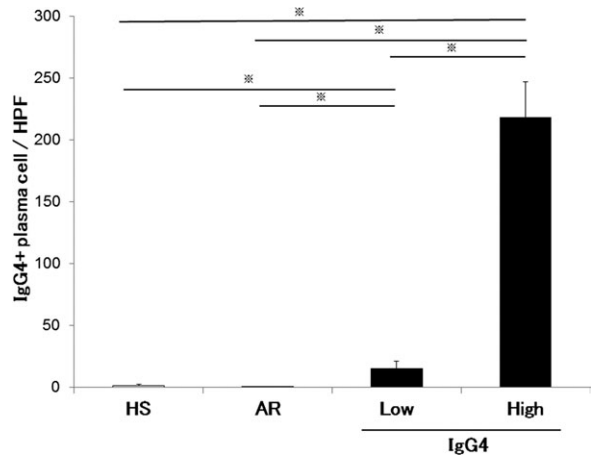

Fig. 1. Comparisons of immunoglobulin (Ig)G4-positive plasma cell counts per high-power magnification field (HPF; ×400) among the four groups. The number of IgG4-positive plasma cells in nasal specimens from patients with IgG4-related disease was significantly higher than that in the healthy subject (HS) and allergic rhinitis (AR) groups. High = high-infiltration group; Low = low-infiltration group. *$P < .01$.

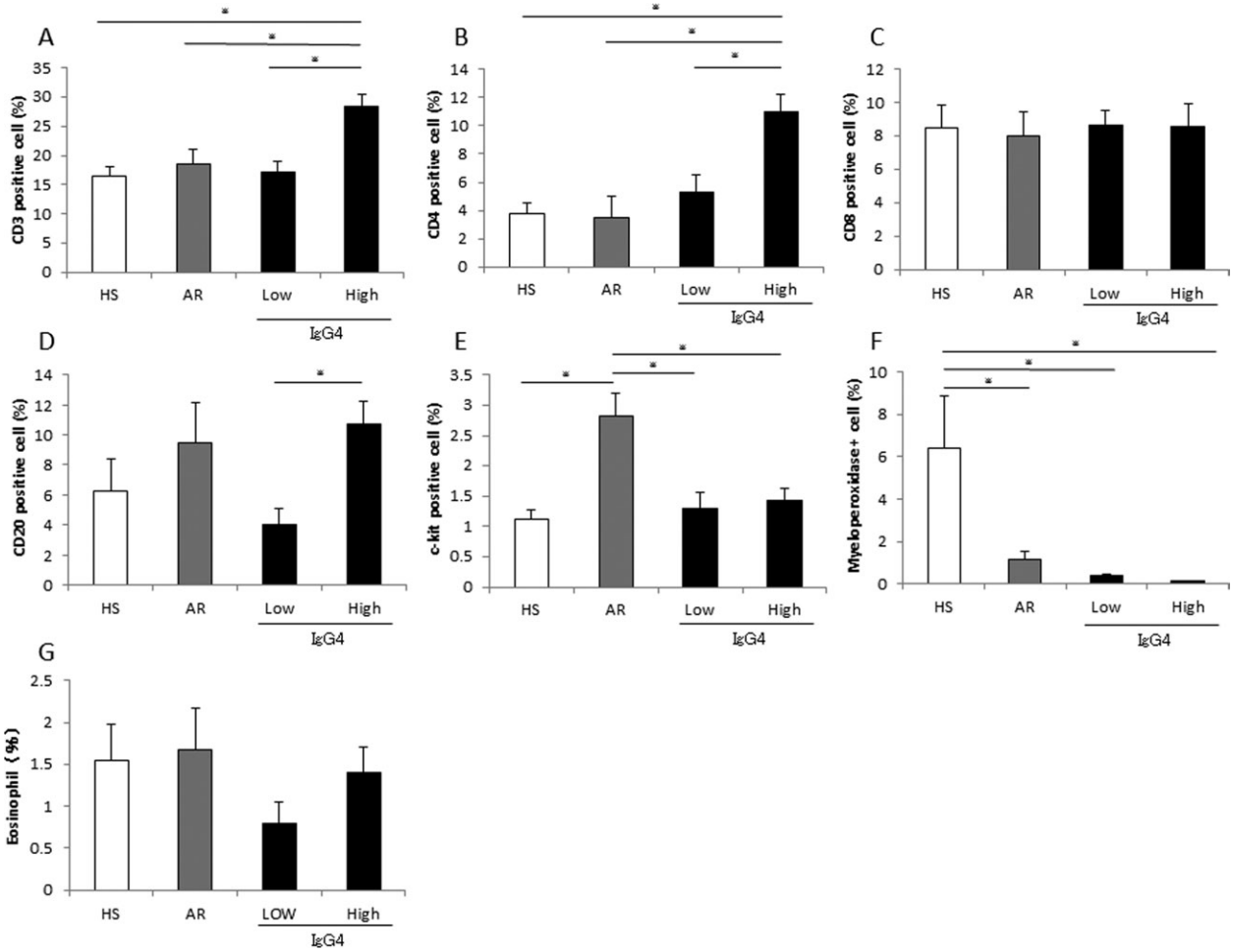

Fig. 2. Comparisons of the ratio of each infiltrating cell type to all infiltrating cells among the four groups. (A, B) CD3- and CD4-positive cell counts in the high-infiltration group were significantly higher than in the other groups. (C, D) There were no differences in CD8- and CD20-positive cell counts among the immunoglobulin (Ig)G4-related disease, healthy subject (HS), and allergic rhinitis (AR) groups. (E) The c-kit–positive cell count in the AR group was significantly higher than that in the other groups. (F) The myeloperoxidase-positive cell count in the HS group was significantly higher than that in the other groups. (G) There were no significant differences in eosinophil count among the four groups. High = high-infiltration group; Low = low-infiltration group. *$P < .01$.

revealed symmetrical enlargement of the submandibular glands, and diffuse nasal crusting (Fig. 4A). There were no other abnormalities in the head and neck region. Immunoglobulin analysis of peripheral blood showed elevated serum IgG (6,160 mg/dL), IgG4 (2,970 mg/dL), and IgE (1,402.5 IU/mL) levels. Autoantibodies, such as rheumatoid factor, proteinase-3–antineutrophil cytoplasmic antibody (ANCA), myeloperoxidase-ANCA, anti–SS-A antibody, and anti–SS-B antibody, were all negative. A sinonasal CT scan showed a slight soft tissue shadow in the maxillary and ethmoid sinuses (Fig. 5A). A nasal mucosa specimen was taken from the inferior turbinate, which on histopathologic examination showed chronic inflammation with dense lymphoplasmacytic infiltrates (Fig. 4C). Immunostaining for IgG and IgG4 (Fig. 4D, E) showed numerous IgG4-positive plasma cells (234/HPF) and a high ratio (60.5%) of IgG4-positive to IgG-positive plasma cells. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed foci of increased uptake in the bilateral submandibular glands, pancreas, bile ducts, and retroperitoneum (Fig. 5C). The patient was also diagnosed with autoimmune pancreatitis, sclerosing cholangitis, and retroperitoneal fibrosis.

After oral prednisolone (starting at 30 mg/day) treatment, the swelling of the bilateral submandibular glands improved, his nasal mucosa was normalized (Fig. 4B), and his sinonasal CT and FDG-PET findings were improved (Fig. 5B, D).

DISCUSSION

In this study, we revealed that 56.5% of patients with IgG4-related disease had marked IgG4-positive plasma cell infiltration in the nasal mucosa. Further, 43% of patients with IgG4-related disease had nasal symptoms such as nasal obstruction and nasal crusting. The nasal membrane is thought to be commonly affected by IgG4-related disease.

The IgG4-positive plasma cell count in the nasal specimens in the high-infiltration group was 218.4 ± 28.4/HPF. The IgG4-positive plasma cell count in chronic sclerosing sialadenitis and auto immune pancreatitis, which

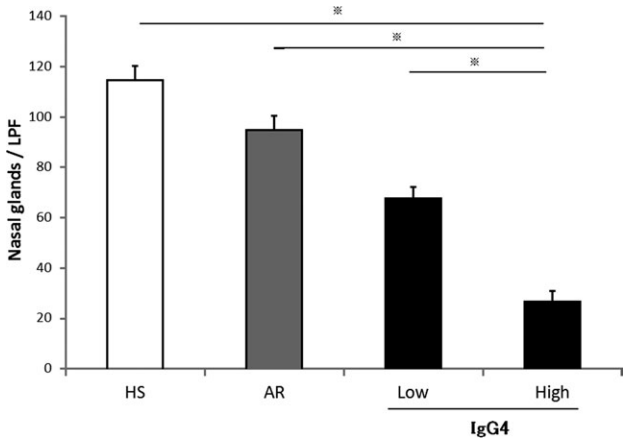

Fig. 3. Comparisons of the number of nasal glands per low-power magnification field (LPF; ×200) among the four groups. The number of nasal glands in the high-infiltration group was significantly lower than that in the healthy subject (HS) and allergic rhinitis (AR) groups. High = high-infiltration group; Low = low-infiltration group. *$P < .01$.

are recognized to be manifestations of IgG4-related disease, have been reported to be 118.2 ± 51.7 (mean ± standard deviation [SD])/HPF[12] and 149 ± 194 (mean ± SD)/HPF,[13] respectively. Thus, the number of IgG4-positive plasma cells in the nasal specimens in this study is greater than that in the salivary gland and pancreas.

In a previous report on IgG4-related chronic rhinosinusitis, no marked difference was noted in the magnitude of IgG4-positive plasma cell infiltration in the nasal specimens between the IgG4-related patient group and the control group.[9] That result was different from the results observed in this study. Possible reasons for this discrepancy are as follow. They classified IgG4-positive plasma cell infiltration in the nasal mucosa into three categories (mild, moderate, and severe) and compared only the distributions of these categories, whereas we directly compared the number of IgG4-positive plasma cells in the nasal mucosa between IgG4 patients and the control group. Moreover, as the number of patients in their study was relatively small, differences between the disease and control patients may have been missed in their study.

The number of nasal glands in the high-infiltration group was significantly lower in this study. We speculate that impaired secretory properties of the nasal cavity may lead to nasal symptoms such as crust formation and nasal obstruction in the patients with IgG4-related disease.

IgE and IgG4 syntheses are regulated by common mechanisms that include interleukin (IL)-4 and IL-13.[14–16] Therefore, in parallel to the IgE response, patients with allergic conditions, such as allergic rhinitis, have high levels of total and allergen-specific IgG4 antibodies.[17] However, the number of IgG4-positive plasma cells in the high-infiltration group in this study was 1,000 × more than that in the AR group. The c-kit–positive cell count in the AR group was significantly higher than

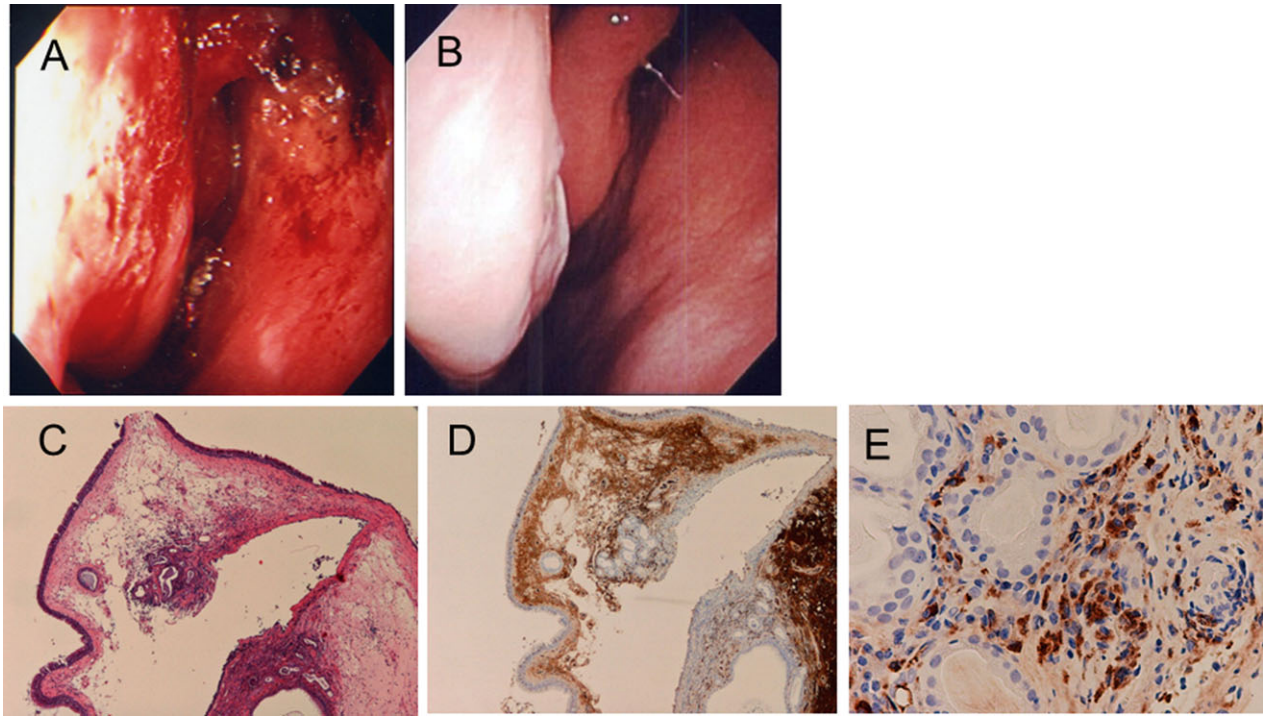

Fig. 4. (A) Endoscopic findings of the representative case at the initial visit. Diffuse nasal crusting was observed. (B) Endoscopic findings of the representative case after steroid therapy. The nasal crusting disappeared, and his nasal mucosa was normalized. (C) Hematoxylin and eosin staining of nasal specimens from the representative case. Histopathologic examination showed chronic inflammation with dense lymphoplasmacytic infiltration. (D) Immunoglobulin (Ig)G4 immunostaining of nasal specimens from the representative case (low-power magnification field). (E) IgG4 immunostaining of nasal specimens from the representative case (high-power magnification field). Immunostaining for IgG4 showed numerous IgG4-positive plasma cell infiltrates. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

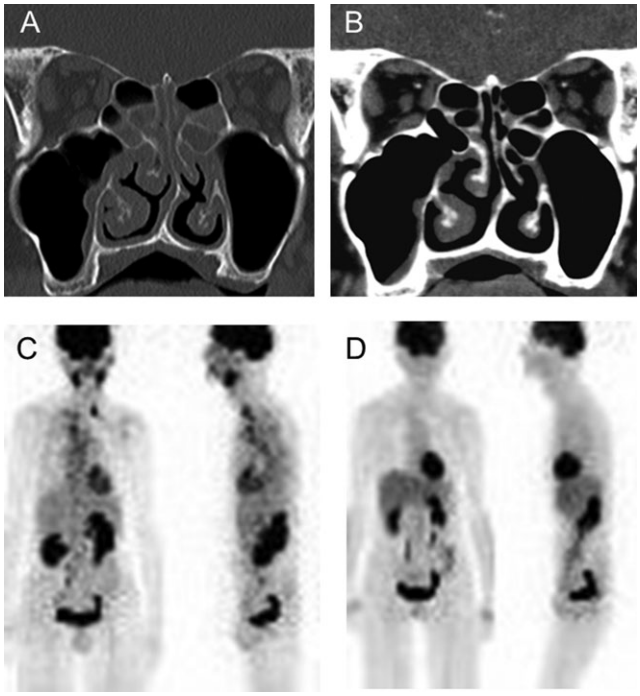

Fig. 5. Sinonasal computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) findings of the representative case. (A) A sinonasal CT scan showed a slight soft tissue shadow in the maxillary and ethmoid sinuses at the initial visit. (B) The soft tissue shadow in sinonasal CT disappeared after steroid therapy. (C) The FDG-PET findings before treatment showed foci of increased uptake in the bilateral submandibular glands, pancreas, bile ducts, and retroperitoneum. (D) FDG-PET findings post-treatment. The increased uptake in the bilateral submandibular glands, pancreas, bile ducts, and retroperitoneum was reduced by steroid therapy.

that in the IgG4-related disease group. In this regard, the nasal manifestations of IgG4-related disease appear as a different entity from AR.

In this study, greater CD3-positive and CD4-positive cell infiltration was observed in the nasal mucosa from subjects in the IgG4-related disease group than in those from the HS and AR groups. However, few neutrophil infiltrates were observed in the nasal specimens from patients with IgG4-related disease.

The infiltration of T cells is observed in the affected organs in IgG4-related disease, with CD4-positive T cells, in particular, being more common than CD8-positive T cells.[18] By contrast, little neutrophil infiltration is observed.[19] The results from this study, based on the absolute number of infiltrating cells, were in agreement with the pathological features of IgG4-related disease described in previous reports.[20]

IL-4 and IL-10 play important roles in the production of IgG4. The increase in CD4-positive cells observed in this study correlated well with the production of IgG4. Conversely, there were decreases in both the ratio and absolute number of neutrophils (data not shown). The mechanism underlying this decrease in neutrophils is unknown, and further investigation concerning neutrophils in IgG4-related disease is required.

In more than half of the patients with IgG4-related disease in this study, the nasal specimens shared pathological similarities with other organs affected by IgG4-related disease. As the nose is on the surface of the face and is ease to observe, nasal biopsy is safe and less invasive than that of the pancreas or biliary tract and should be considered for the diagnosis of IgG4-related disease.

CONCLUSION

In more than half of the patients with IgG4-related disease, numerous IgG4-positive plasma cells were observed in the nasal specimens. The nasal manifestations of IgG4-related disease differ from those of AR and share clinical and pathological similarities with those of other organs affected by IgG4-related disease. Thus, nasal biopsy is thought to be a safe and useful method for the diagnosis and evaluation of not only the nasal manifestations of IgG4-related disease, but also those of other affected organs.

Acknowledgment

We are grateful to Yuko Ishida and Jun Moriya for their expert technical assistance.

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