

IgG4-related disease in the sinonasal cavity accompanied by intranasal structure loss



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ABSTRACT

IgG4-related disease was recently proposed under the classification of systemic chronic inflammatory disease. In the field of otolaryngology, organ-specific diagnostic criteria have been established for the occurrence of this condition in the salivary glands, but not in the sinonasal cavity. Here we report a case involving a 70-year-old man with IgG4-related disease in the sinonasal cavity. The patient, with the chief complaint of nasal bleeding, first visited a physician. However, the patient experienced recurrent bleeding with intranasal structure loss and was subsequently referred to our hospital. His IgG4 level was elevated, and histopathological examination of a tissue sample obtained from the edematous sphenoid sinus showed increased IgG4-positive plasma cells and storiform fibrosclerosis. A definitive diagnosis of IgG4-related rhinosinusitis was made on the basis of comprehensive criteria for IgG4-related disease. The disease showed a progressively destructive course that was clearly different from that of chronic sinusitis and represented a very rare case of IgG4-related rhinosinusitis. IgG4-related disease originating in the sinonasal cavity is rare, and, to the best of our knowledge, this is the first primary case of IgG4-related disease that originated in one side of the sinonasal cavity and showed progressive destruction.

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1. Introduction

IgG4-related disease is a systemic chronic inflammatory disease characterized by high serum IgG4 levels and histopathological findings of IgG4-positive plasma cell infiltration and fibrosis as well as tumor-like hypertrophic lesions. In the field of otolaryngology, this disease has been frequently reported in the salivary and lacrimal glands [1]. The incidence of salivary gland involvement is high, and relevant diagnostic criteria have been proposed for IgG4-related dacryoadenitis/sialadenitis or IgG4-related Mikulicz disease [2]. However, sinonasal cavity involvement is rare, and no diagnostic criteria have been established for sinonasal cavity. We recently observed an unusual case of unilateral IgG4-related sinusitis in a 70-year-old man. The patient, with the complaint of nasal bleeding, initially visited a physician, and the patient exhibited a unique clinical course with progressive sinonasal

structure loss. We describe the clinical course of this patient in the present report and discuss the relevant literature on IgG4-related disease involving the sinonasal cavity.

2. Case description

A 70-year-old man with the chief complaint of bleeding from the left nasal cavity visited a physician. At the first visit, bleeding in or around the middle turbinate was suspected, and the surrounding area was somewhat swollen. A tumor-like lesion was suspected after recurrent nasal bleeding; however, sinonasal computed tomography (CT) only detected sinusitis, while blood tests failed to identify the cause (Table 1). One year after the first visit, the bleeding recurred and the patient visited the same physician, who observed loss of the sinonasal structures, including the left middle turbinate. The patient was subsequently referred to our hospital for detailed examination. He reported a history of type 2 diabetes and was on oral medication for diabetes. There was no allergic disposition, such as bronchial asthma, pollinosis, or atopic dermatitis. Furthermore, the patient did not report any history of surgery in the sinonasal cavity or use of an intranasal spray. At the first visit to our hospital, the patient was asymptomatic, with

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Table 1

The blood test results.

	Unit	Mar, 2012	Jan, 2014	Dec, 2014
WBC	/ μ L	8100	8800	9500
Neutrophil	%	61.9	62.2	65.9
Eosinophil	%	2.5	2.1	1.3
Basophil	%	0.4	0.3	0.3
Monocyte	%	6.9	6.8	7
Lymphocyte	%	28.3	28.6	25.5
RBC	$\times 10^4$ / μ L	499	519	490
Hb	g/dL	14.4	15.3	14.5
CRP	mg/dL	0.24	0.3	0.1
IgG	mg/dL	no data	1424	1314
IgA	mg/dL	no data	142	128
IgM	mg/dL	no data	45	38
IgE	IU/mL	no data	88.7	111
IgD	mg/dL	no data	2.9	2.2
IgG4	mg/dL	no data	198	150
PR3-ANCA	U/mL	<1.0	<1.0	<1.0
MPO-ANCA	U/mL	<1.0	<1.0	<1.0
sIL-2R	U/mL	no data	184	179

no nasal bleeding, congestion, or pain. Visual examination of the nasal cavity showed complete loss of the middle turbinate, while the inferior turbinate was half the normal size. The lamella of the ethmoid sinus was not visible. The skull base and lamina papyracea were directly visible in the nasal cavity (Fig. 1). Sinonasal CT performed 3 months after the first visit to the previous clinic showed mild sinusitis with an intact middle turbinate and ethmoid sinus lamella, while that performed 7 months after the first visit showed initial destruction of the posterior end of the middle turbinate and the posterior ethmoid sinus. A year later, the outermost wall structure, including the nasal septum, skull base,

and lamina papyracea, was intact. The middle turbinate, lamella of the ethmoid sinus, and maxillary sinus were completely lost, and the inferior turbinate was completely atrophic. At the first visit to our hospital in the following month, the imaging findings were not significantly different (Fig. 2). Blood tests showed the following (Table 1): white blood cell (WBC), 8800/ μ L (neutrophils, 62.2%; basophils, 0.3%; eosinophils, 2.1%; lymphocytes, 28.6%; and monocytes, 6.8%); C-reactive protein (CRP), 0.3 mg/dL; amylase, 95 U/L; creatinine, 0.92 mg/dL; soluble IL-2 receptor (sIL-2R), 184 U/mL; myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) negativity; proteinase 3 antineutrophil cytoplasmic antibody (PR3-ANCA) negativity; antinuclear antibody negativity; squamous cell carcinoma (SCC) antigen, 1.1 ng/mL; and IgE, 88.7 IU/dL. Urinalysis revealed positivity for glucose and negativity for protein and occult blood. No abnormal findings were observed. However, his IgG4 level was high at 198 mg/mL (normal range, 5–105 mg/mL), while his IgG level was normal at 1424 mg/dL (normal range, 703–1540 mg/dL). Histopathological findings of both specimens obtained at our hospital and those obtained at the previous clinic revealed dense plasma cell infiltration and characteristic storiform fibrosis. Immunohistochemical staining indicated that the majority of plasma cells were positive for IgG; IgG4-positive cells accounted for 59% of the IgG-positive cells, with a density of 34 cells per high-power field (HPF) (Fig. 3). None of these findings indicated granuloma, necrosis, malignancy, or an apparent increase in atypical lymphocytes. On the basis of the swelling around the middle turbinate at the first visit to the previous clinic, high serum IgG4 level, and characteristic histopathological findings, a definitive diagnosis of IgG4-related sinusitis that met the comprehensive criteria for IgG4-related disease was established. Whole-body CT did not indicate apparent lesions in other organs. However, IgG4 level of this patient is still

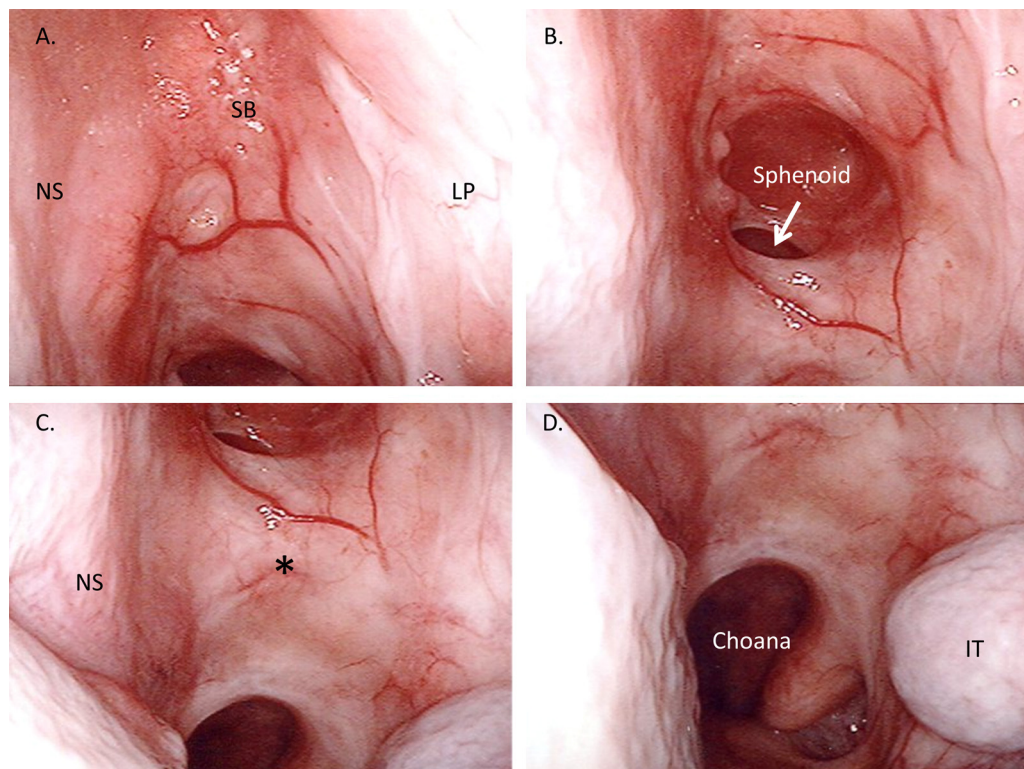


Fig. 1. Intranasal findings. (A) The skull base and lamina papyracea are retained, while the lamellae of the ethmoid sinus, middle turbinate, and superior turbinate are lost. SB, skull base; LP, lamina papyracea; NS, nasal septum. (B) The lamella of the ethmoid sinus is destroyed and the sphenoid sinus is directly visible. (C) It is visible from the anterior wall of the sphenoid sinus (*) to the choana, however the superior turbinate is not. (D) The inferior turbinate is half the normal size, while the posterior naris can be easily visualized. IT, inferior turbinate.

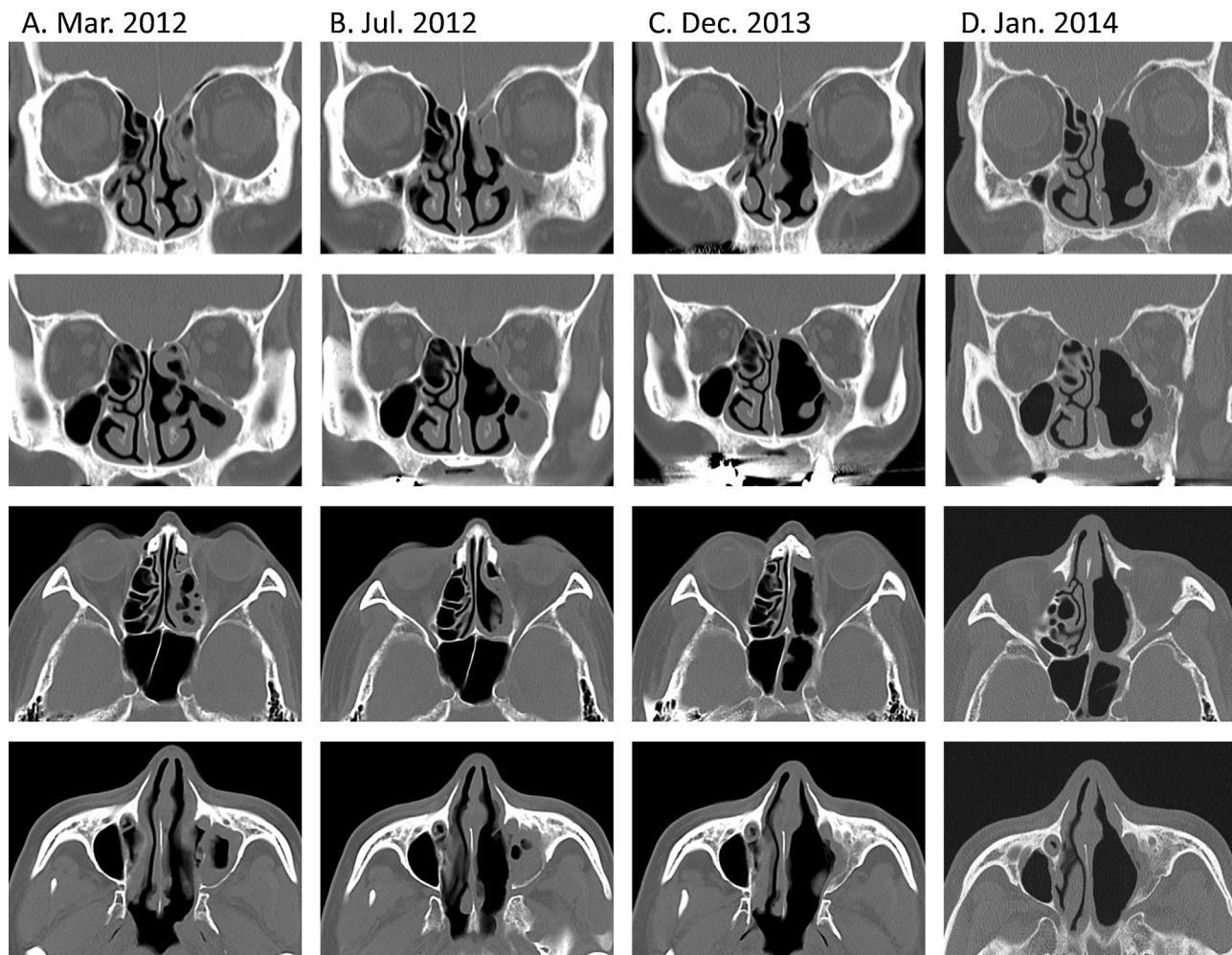


Fig. 2. Time course of computed tomography (CT) findings. (A) March 2012. The structural details are identified in both nasal cavities. (B) July 2012. The posterior end of the left middle turbinate and that of inferior turbinate are beginning to show destruction. (C) December 2013. The structural details in the left maxillary sinus, left middle turbinate and a part of inferior turbinate are lost, while the nasal septum, skull base, and lamina papyracea are maintained. (D) January 2014. There is no further destruction compared with December 2013.

higher than normal range (Table 1). The patient is currently asymptomatic, with no nasal bleeding or further destruction of sinonasal structures, and is being followed on an outpatient basis without medical treatment. The disease has not shown progression during an approximate follow-up duration of 1 year.

3. Discussion

IgG4-related disease was recently proposed under the classification of systemic disease, with comprehensive diagnostic criteria [1,3]. Although specific diagnostic criteria for this condition in the pancreas, lacrimal and salivary glands, kidneys, and bile ducts are available [4], those for the sinonasal cavity have not been established. For organs without specific criteria, the comprehensive diagnostic criteria for IgG4-related disease are helpful. According to these criteria, a definitive diagnosis is based on a combination of the following: (1) diffuse or localized swelling, mass, nodulation, or hypertrophic lesions in single or multiple organs; (2) high serum IgG4 levels (≥ 135 mg/dL); and (3) marked lymphocyte/plasma cell infiltration and fibrosis, an IgG4-positive/IgG-positive cell ratio of $\geq 40\%$, and an IgG4-positive plasma cell density of ≥ 10 per HPF. For organs with no established diagnostic criteria, characteristic histopathological findings such as marked lymphoplasmacytic infiltration, storiform fibrosis, and obstructive

phlebitis should be confirmed and other possible diseases may be ruled out. Chronic sinusitis should be considered in the differential diagnosis as a non-IgG4-related disease that accompanies an increased number of IgG4-positive cells in the tissue [4]. Our patient exhibited a clinical course that was clearly different from that of sinusitis and fulfilled the above-mentioned comprehensive diagnostic criteria for IgG4-related disease. In particular, the pathological findings showed dense plasma cell infiltration and characteristic storiform fibrosis, although obstructive phlebitis was absent, supporting a diagnosis of unilateral IgG4-related disease. In the region of the sinonasal cavity, IgG4-related disease has been reported in the maxillary sinus [5–8] but not in the ethmoid sinus, as observed in the present patient. Moteki et al. reported the cases of IgG4-related rhinosinusitis which occurred in sinonasal cavity, in detail [9]. There are such cases which occurred in ethmoid sinus or one side of the sinonasal cavity in their cases. However, these cases were complicated cases in Mikulicz disease or Autoimmune pancreatitis. It means that these were not the cases that occurred only from sinonasal cavity. In addition, some cases of sinonasal IgG4-related disease due to progression from the orbit, as detected on the basis of ocular symptoms [8], and destruction of the skull base [7] have been reported. Because our patient showed an intact lamina papyracea and did not show ocular symptoms, the disease was considered to have originated in

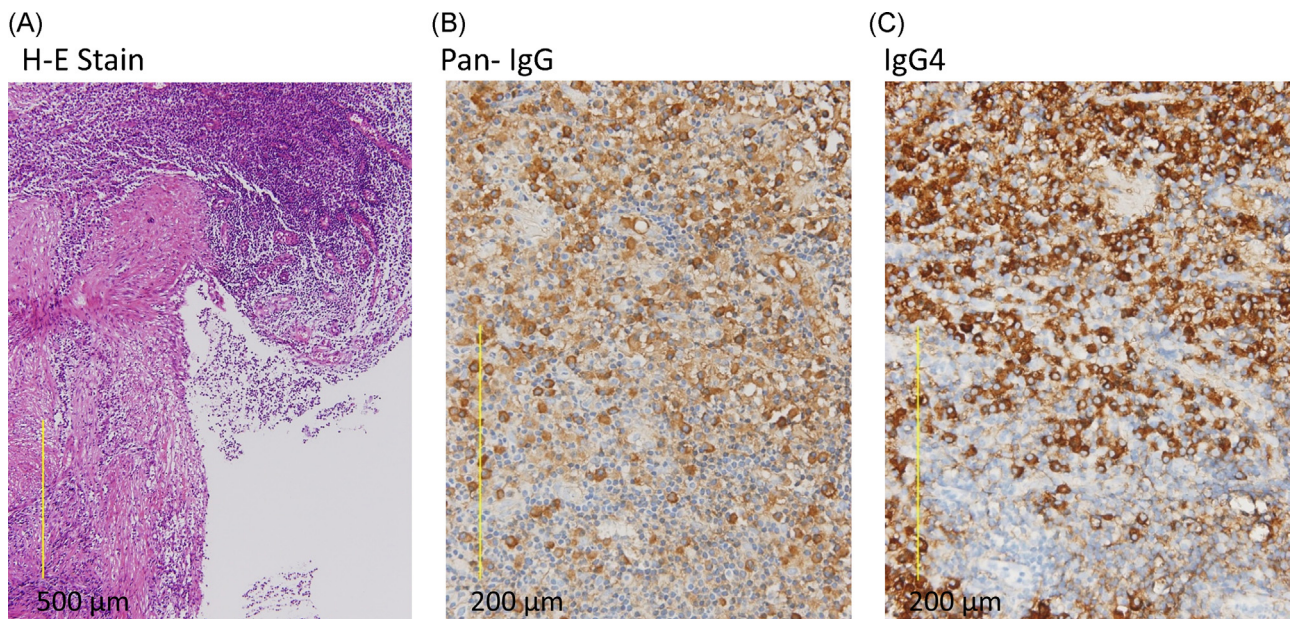


Fig. 3. Histopathological findings. (A) Hematoxylin and eosin staining. Intense plasma cell infiltration is observed along with a storiform fibrosclerosis. (B) Immunostaining (Pan-IgG). Most plasma cells are positive for IgG. (C) Immunostaining. IgG4-positive cells account for 59% of the IgG-positive cells, with a density of 34 cells per high-power field (HPF).

the sinonasal cavity. Several cases show accompanying parotid, submandibular, and lacrimal gland swelling [5]; however, our patient did not show involvement of any other organ in the entire body, as confirmed by CT and blood tests. This confirmed the presence of a single lesion on one side of the sinonasal cavity. The present case is also significant; in that, the time course of destruction was captured on CT. Taking into account the absence of pain, the possible underlying mechanism for sinonasal structure loss was that IgG4-related disturbances in blood flow caused nasal bleeding and that the tissue belonged to the nasal cavity, which is an open cavity. To the best of our knowledge, this is the first reported case of IgG4-related disease that originated on one side of the sinonasal cavity and showed progressive destruction.

The differential diagnoses of intranasal necrosis include ANCA-related vasculitis, malignant lymphoma, malignant tumor, and natural killer/T-cell lymphoma. Differential diagnosis requires the measurement of markers, such as PR3-ANCA, MPO-ANCA, and sIL-2R, and the examination of adequate tissue specimens obtained from the involved site. We considered and excluded these diseases during differential diagnosis.

There is no therapeutic consensus for IgG4-related sinusitis. The first-line therapy for IgG4-related disease is the administration of glucocorticoids, which often results in a complete response. Furthermore, cases of spontaneous remission have been reported, and physicians may choose simple observation over treatment if the patient is asymptomatic or does not have serious organ disorders [10]. The most common IgG4-related disease is sialadenitis, also known as Mikulicz disease, and the therapeutic strategy for this disease may be used as a reference. For symptomatic patients, prednisolone (PSL) treatment is initiated at 0.6 mg/kg/day and continued for 2–4 weeks, following which the dose is tapered to a maintenance dose of 5–10 mg/day over 4–6 months, considering the high incidence (approximately 20%) of recurrence [2,11]. However, the necessity of maintenance therapy remains controversial. Furthermore, immunosuppressants such as rituximab have been tested in cases where steroid tapering is difficult, although the validity of this therapy is yet to be established. During the follow-up phase, careful observation, including that of other organs, is necessary, considering the nature

of the disease and the occurrence of multiple lesions spatially and temporally. The present patient also requires careful follow-up observation, even though his symptoms have resolved and disease progression has ceased.

4. Conclusions

In conclusion, we reported a patient with a definitive diagnosis of unilateral IgG4-related sinusitis showing a unique clinical course with the progressive loss of sinonasal structures. IgG4-related disease originating in the sinonasal cavity is rare, and early diagnosis and treatment are important because of the potentially destructive nature of this condition, as observed in the present patient.

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Conflict of interest

All authors disclose no financial support or relationship that may pose a conflict of interest.

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