Advances in Medical Sciences 62 (2017) 393–397

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original research article

Clinical features of IgG4-related rhinosinusitis

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ARTICLE INFO

Article history:
Received 20 December 2016
Accepted 20 April 2017
Available online xxx

Keywords:
IgG4-related disease
Rhinosinusitis
IgG4
Steroid

ABSTRACT

Purpose: IgG4-related disease is a systemic disease that affects various organs of the body. Aim of this study is to elucidate the clinical characteristics of IgG4-related rhinosinusitis.
Material and methods: Clinical features, laboratory findings, radiological and endoscopic findings, associated disease, treatment and prognosis were retrospectively examined in 10 patients with IgG4-related rhinosinusitis.
Results: The age was 59.1 ±11.3 years old and male-to-female ratio was 1:1. The chief nasal complaints were hyposmia (n = 4), nasal obstruction (n = 3), and nothing (n = 3). Serum IgG4 levels were elevated in all patients and the value was 740.4 ± 472.4 mg/dl. Other IgG4-related diseases were associated in all 10 patients, including IgG4-related sialadenitis (n = 6), IgG4-related dacryoadenitis (n = 5), and autoimmune pancreatitis (n = 5). Imaging findings on CT/MRI were obstruction of the way of elimination (n = 10), thickening of the sinus mucous membrane (n = 10), and fluid in the sinus (n = 6). All of the cases had bilateral findings. Nasal endoscopic findings were chiefly deviated nasal septum (n = 5), polyps (n = 4), edema of the mucous membrane (n = 3). Histologically, abundant infiltration of IgG4 positive plasma cell and lymphocyte and an elevated IgG4+/IgG+ cell ration was detected in all 8 patients and 5 patients, respectively. Endoscopic sinus surgery was performed in 8 patients. Eight patients were treated with steroid therapy for other associated IgG4-related diseases. Symptoms improved in all 6 patients after an initial treatment (endoscopic surgery (n = 5) and steroids (n = 1)), but one patient suffered relapse.
Conclusions: IgG4-related rhinosinusitis is a distinct entity of IgG4-related disease, and is associated in patients with multiple IgG4-related diseases.

1. Introduction

IgG4-related disease is a newly recognized fibroinflammatory condition that is characterized by tumefaction consisting of fibrosis with dense infiltration of IgG4-positive plasma cells and lymphocytes, elevated serum IgG4 levels, and steroid responsiveness. It is potentially a multi-organ disorder, and has been described in various organ systems, including the pancreas, biliary tract, salivary gland, lacrimal gland, kidney, lung, lymph node, retroperitoneum, and others. Clinical manifestations are identified in a single organ in some cases, whereas in other cases effects are seen in two or more organs simultaneously or metachronously [1,2].

There are several papers about nasal manifestations of IgG4-related disease [3–11], but the papers other than 2 studies [6,9] are case reports. IgG4-related rhinosinusitis has not been established as a disease entity. We studied the clinicopathological features of IgG4-related rhinosinusitis based on cases that we experienced.

2. Patients and methods

A total of 108 patients with IgG4-related disease were treated in Tokyo Metropolitan Komagome Hospital from January 2005 to December 2014. Serum IgG and IgG4 levels were routinely examined in all patients suspected of IgG4-related disease. Twenty-seven patients of them were referred to the department of otorhinolaryngology for screening (n = 16), nasal symptoms (n = 7), or examination for salivary gland or neck tumor (n = 4). IgG4-related rhinosinusitis was diagnosed according to comprehensive diagnostic criteria for IgG4-related disease, that consisted

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http://dx.doi.org/10.1016/j.advms.2017.04.001
1896-1126/

Table 1
Comprehensive diagnostic criteria for IgG4-related disease, 2011.

1.	Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
2.	Elevated serum IgG4 concentrations (≥135 mg/dl)
3.	Histopathologic examination showing
	(1) Marked lymphocyte and plasmacyte infiltration and fibrosis
	(2) Infiltration of IgG4-positive cells: >10 IgG4+ plasma cells /high power field ratio of IgG4+/IgG+ cells >40%
Definite:	1) + 2) + 3)
Probable:	1) + 3)
Possible:	1) + 2)

of combination of clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs, elevated serum IgG4 concentrations, and histopathologic examination showing abundant infiltration of lymphocytes and IgG4-positive plasma cells and fibrosis [12] (Table 1). Clinical features, laboratory findings, radiological, endoscopic and histological findings, associated disease, treatment and prognosis were retrospectively examined in the patients with IgG4-related rhinosinusitis. The resected specimens were fixed in 17% formalin and routinely embedded in paraffin. Serial sections 3 micrometers thick were stained with hematoxylin and eosin for diagnostic evaluation. Sections were also immunostained using anti-IgG and anti-IgG4 antibodies with avidin-biotin-peroxidase complex. Sections of 3 resected specimens of chronic rhinosinusitis were immunostained using the antibodies as negative control. The number of immunohistochemically identified cells per high power field (hpf) in each specimen was counted. The findings of >10 IgG4-positive plasma cells/hpf and ratio of IgG4-positive cells/IgG-positive cells >40% are necessary for histopathological diagnosis.

Correlations between associated other IgG4-related diseases and serum IgG4 levels and nasal symptoms were statistically analyzed using Fisher's exact test and Chi-square test. A p value of less than 0.05 was regarded to indicate a statistically significant difference.

This study was approved by the institutional review board of Tokyo Metropolitan Komagome Hospital. Informed consent for invasive modalities was obtained.

3. Results

3.1. General data

A total of 10 patients were diagnosed as having IgG-4 related rhinosinusitis radiologically (n = 10), serologically (n = 10), and histologically (n = 5) according to comprehensive diagnostic criteria for IgG4-related disease [12]. Diagnoses of IgG4-related rhinosinusitis were definite (n = 5) and possible (n = 5).

The age was 59.1 ± 11.3 (mean ± SD) years old (39–72) and male-to-female ratio was 1:1. The chief nasal complaints were hyposmia (n = 4), nasal obstruction (n = 3), and nothing (n = 3). The outbreaks of the rhinosinusitis were acute in 8 cases, and the other 2 cases were acute aggravation of pre-existing rhinosinusitis.

Serum IgG4 and IgG levels were elevated in all patients, and the value was 740.4 ± 472.4 mg/dl (286–1820 mg/dl) and 2040.2 ± 537.2 mg/dl (1486–2840 mg/dl), respectively (Table 2).

Other IgG4-related diseases were associated in all 10 patients, including IgG4-related sialadenitis (n = 6), IgG4-related dacryoadenitis (n = 5), autoimmune pancreatitis (AIP, n = 5), IgG4-related retroperitoneal fibrosis (n = 4), IgG4-rerated sclerosing cholangitis (n = 3), IgG4-ralated lymphadenopathy (n = 2), and IgG4-related kidney disease (n = 1). The number of other associated IgG4-related diseases was 5 (n = 1), 3 (n = 3), and 2 (n = 6) (Table 3). There were no significant differences between associated other IgG4-related diseases and serum IgG4 levels and nasal symptoms.

Endoscopic sinus surgery was performed in 8 patients. Eight patients were treated with steroid therapy for other associated IgG4-related diseases. Symptoms (hyposmia (n = 4) and nasal obstruction (n = 2)) improved and a sense of contentment was achieved in all 6 patients with nasal symptoms after an initial treatment (endoscopic surgery (n = 5) and steroids (n = 1)). There were no adverse events by surgical and steroid therapy. However, one patient suffered relapse of the rhinosinusitis 5 years and 5 months after the first operation despite maintenance therapy with low dose prednisolone (4 mg/day), and reoperation was needed.

Table 3
Other associated IgG4-related disease in patients with IgG4-related rhinosinusitis.

Case	SIA	DAC	AIP	RF	SC	LYM	KID
1	+	+	+	–	–	–	–
2	+	–	–	–	–	+	–
3	–	–	+	+	–	–	–
4	+	+	–	–	–	–	–
5	+	+	–	–	–	–	–
6	–	–	+	+	+	–	–
7	+	–	+	+	+	+	–
8	+	+	–	–	–	–	–
9	–	–	+	–	+	–	–
10	–	+	–	+	–	–	+

SIA: sialadenitis, DAC: dacryoadenitis, AIP: autoimmune pancreatitis, RF: retroperitoneal fibrosis, SC: sclerosing cholangitis, LYM: lymphadenopathy, KID: kidney disease.

Table 2
Clinical findings of patients with IgG4-related rhinosinusitis.

Case	Age/Gender	Symptoms	Serum IgG4 (mg/dl)	Serum IgG (mg/dl)	Surgery	Steroid	Recurrence
1	48 M	nasal obstruction	286	1569	+	+	–
2	71 M	none	1820	2840	+	–	–
3	69 F	nasal obstruction	1100	2586	+	+	–
4	50 M	none	550	1539	+	+	–
5	39 F	hyposmia	495	1486	+	+	–
6	69 M	none	328	1685	+	+	–
7	54 M	hyposmia	687	2691	+	+	–
8	60 F	hyposmia	971	1950	+	+	+
9	59 F	hyposmia	323	1628	–	+	–
10	72 F	nasal obstruction	844	2430	–	–	–