



IgG4-related disease: association between chronic rhino-sinusitis and systemic symptoms

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Abstract

Purpose The objective of this study is to analyze the relationship between chronic rhino-sinusitis (CRS) and systemic symptoms in patients with IgG4-related disease (IgG4-RD).

Patients and methods The patients with IgG4-RD, confirmed by restrict association with clinical and histopathological manifestations between March 2013 and July 2016, were enrolled and followed-up for 1 year at the Tongren Hospital, Capital Medical University. The patients were divided into two groups: the case group included IgG4-RD patients with CRS confirmed by clinical and imaging, while the control group included IgG4-RD patients without CRS confirmed by clinical and imaging. Age, gender, clinical manifestations, the percentage of eosinophils in peripheral blood, sedimentation (ESR), C-reaction protein, serum IgE and IgG4 levels, histopathology, and treatment drugs at the baseline and 1 year of follow-up were compared between the two groups.

Results A total of 46 cases met the diagnostic criteria for IgG4-RD. A total of 30 patients (65.2%) had IgG4-RD complicated with CRS, and were aged 49.7 ± 13.4 years, with male:female ratio = 2:1. The disease duration in the case group was longer than that in the control group (3.0 versus 0.8, $p = 0.009$). The ratio of ocular involvement was higher (86.7 versus 60%, $p < 0.001$), and allergic manifestations including drug allergy, asthma, and allergic skin were more common (56.5 versus 20%, $p = 0.004$), with a higher percentage of eosinophils in peripheral blood (8.5 versus 3.3%, $p = 0.018$) and more sensitive to glucocorticoids (6.0 versus 3.5, $p = 0.004$) than those in the control group.

Conclusions CRS in patients with IgG4-RD was closely associated with IgG4-related ocular lesions, which was more prone to allergic manifestations accompanied by raised percentage of eosinophils in peripheral blood. The treatment of patients with IgG4-RD complicated with CRS was more effective than those with IgG4-RD without CRS.

Keywords IgG4-related disease · Chronic rhino-sinusitis · Clinical manifestation

Introduction

IgG4-related disease (IgG4-RD) is an autoimmune disease that was first described in a cohort of Japanese patients with ‘sclerosing pancreatitis’ [1], and has now been reported across ethnically diverse populations and in nearly every organ [2–5]. Autoimmune pancreatitis is the most common phenotype, and the organs in the head and neck region are typically involved in patients with IgG4-RD [6]. The sub-mandibular and parotid glands, orbit, and thyroid are some of the more common sites involved in IgG4-RD. Mikulicz disease and Riedel thyroiditis are also members of the IgG4-RD family [6, 7]. Chronic rhino-sinusitis (CRS) was often observed in patients with IgG4-RD [6, 8, 9]. Secretory glands are an important part of the nasal membrane and core clinical manifestations of secretory glands are

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frequently seen in patients with IgG4-RD [4]. Therefore, CRS may be theoretically involved in patients with IgG4-RD. In 2011, Moteki et al. [10] first suggested that sinus lesions such as CRS could be one of the extrapancreatic manifestations of autoimmune pancreatitis and/or Mikulicz disease. However, very few studies [11, 12] have analyzed the clinical manifestations of CRS in IgG4-RD, and reported the relationship between CRS and IgG4-RD [9]. Regardless of the organs involved, the gold standard for the diagnosis of IgG4-RD is the identification of typical histopathological features (e.g., a rich lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis) in the context of a significant IgG4+ plasma cell infiltrate, but the association between CRS confirmed by nasal sinus biopsy and systemic clinical manifestations in patients with IgG4-RD confirmed by extra-CRS organ biopsy has not been analyzed.

To identify the association between CRS and clinical features of IgG4-RD, 46 patients with IgG4-RD were examined in this study. Thirty cases of these patients were confirmed with CRS by clinical and imaging, and their nasal cavity membrane biopsy met the pathological criteria of IgG4-RD. Of these biopsies, 11 nasal biopsies were collected from tissue waxes in the past surgery, and 19 nasal biopsies were made for definitive diagnosis after admission.

Patients and methods

Cohort overview

The patients with IgG4-RD confirmed by restrict association with clinical and histopathological manifestations between March 2013 and July 2016 were enrolled and followed-up for 1 year at the Tongren Hospital, Capital Medical University. The patients with CRS confirmed by clinical and imaging in the nasal region were enrolled in the case group. The patients without CRS confirmed by clinical and imaging of the nasal region were enrolled in the control group.

Disease diagnostic criteria

The diagnostic criteria for IgG4-RD were previously described [13]. All enrolled patients met the diagnostic criteria and had at least one organ tissue biopsy. The definitive diagnosis was made after strict association between clinical manifestations and histopathological features. Patients with malignancy and other autoimmune diseases were excluded. This study was approved by the Medical Ethics Committee of Tongren Hospital and all patients signed written informed consent forms.

Diagnoses of CRS were based on patients' histories, clinical examinations, nasal endoscopies, and computed tomographic scans of the sinuses in accordance with the

"European position paper on rhino-sinusitis and nasal polyps 2012" guidelines [14], and the diagnosis was made by an ENT physician.

Disease definition for the groups

IgG4-RD complicated with CRS was defined as those patients with IgG4-RD that met the diagnostic criteria of CRS, and the tissue biopsies of the nasal cavity met the pathological features of IgG4-RD, together with the ratio of plasmacyte of IgG4+/IgG+ $\geq 40\%$, and IgG4+ plasmacyte ≥ 50 /high-power field based on the diagnostic criteria of IgG4-RD [14] and pathological criteria for IgG4-RD CRS of the pathology department of Tongren Hospital [15].

IgG4-RD without CRS was defined as those cases that met the diagnostic criteria of IgG4-RD but not of CRS.

Methods

The cases and their clinical data were retrospectively analyzed.

Data pertaining to demographics, prior treatment, and laboratory findings at the baseline evaluation were recorded.

Evaluation of organ involvement

Organ involvement was evaluated by a review of the patient's past history, physical examination findings, imaging results, laboratory studies, and biopsy tissue samples.

Serum IgG4 assays

Serum IgG4 concentrations were measured by scattering turbidimetry using a Siemens BN II instrument and reagent sets obtained from Siemens Healthcare Diagnostics Products GmbH. Normal level was < 1.35 g/L.

Pathology results

Pathology samples were independently evaluated by two pathologists with experience in the pathological diagnosis of IgG4-RD. The cases that were confirmed by both pathologists were enrolled. Any case that was confirmed by both pathologists after discussion was also enrolled.

Disease activity evaluation

Disease activity was measured using the IgG4-RD Responder Index (RI) [16] as follows: unaffected or remission in organ (RI score of 0); improved during treatment (RI score of 1 in each affected organ); unchanged disease (RI score of 2); new/recurrent disease (RI score of 3); or worsened despite treatment (RI score of 4). Each affected

organ was scored separately in the RI and all individual organ scores were added to calculate the overall RI. RI was evaluated every year.

Treatment and follow-up

The use of corticosteroids, maximum doses, duration of maximum dose administration, and duration of dosage decrease were noted. Other treatments like immunosuppressive agents were also recorded. The clinical manifestations and laboratory findings at the follow-up were recorded.

Table 1 Organ involvement of 46 patients with IgG4-RD in our cohort

Organ involvement	Case number	% of all cases
Orbit	32	69.6
Sinus/nasal cavity	30	65.2
Lymph nodes	21	45.7
Submandibular glands	20	43.5
Lung	10	21.7
Pancreas	9	19.6
Retroperitoneal fibrosis	7	15.2
Skin	6	13.0
Thyroid	5	10.9
Inner ear	4	8.7
Kidney	3	6.5
Mediastinum	3	6.5
Pericardium	3	6.5
Bile duct	3	6.5
Duodenum	3	6.5
Pituitary	2	4.3
Breast	2	4.3

Statistical analysis

The data were analyzed by SPSS version 17.0 for Windows (SPSS Inc, Chicago, IL, USA). Continuous variables with normal distribution were presented as mean $\pm$ standard deviation (SD); non-normal variables were reported as median (interquartile range). Statistical differences for continuous, normally distributed data were analyzed by independent-sample Student's *t* test; all continuous, non-normally distributed data were analyzed by the Mann–Whitney *U* test. Categorical variables were assessed by χ^2 test. $p < 0.05$ was considered to be significant.

Results

Organ involvement of 46 patients with IgG4-RD

A total of 46 cases met the diagnostic criteria for IgG4-RD and organ involvement was seen in 17 different known anatomical sites of disease. Table 1 lists the range of organs involved. The most commonly involved organs were orbit, sinus/nasal cavity, lymph nodes, and submandibular glands in the head and neck region. Nine out of forty-six (19.6%) cases with the past history of CRS actively disclosed the disease during history-taking.

Demographic characteristics and clinical findings of IgG4-RD with CRS at baseline

Of the 30 patients (65.2%) with IgG4-RD complicated with CRS, 66.7% cases (20/30) were male. There was no difference in demographic characteristics between the case group and control group. As compared to patients with IgG4-RD without CRS, disease duration was longer and ratio of eye lesion was higher in patients with IgG4-related

Table 2 Demographic characteristics and clinical manifestations in patients with IgG4-RD complicated with CRS before treatment

Items	Case group ($n = 30$)	Control group ($n = 16$)	$t/z/\chi^2$ value	p value
Gender (F/M)	10/20	9/7	2.260	0.133
Age (years) (mean $\pm$ standard deviation)	49.7 $\pm$ 13.4	54.8 $\pm$ 14.8	− 1.180	0.244
Disease duration (years)[M (P25, P75)]	3.0 (1.0,7.8)	0.8 (0.2,1.9)	2.613	0.009
Eye involvement % ($\pm$)	86.7% (26/4)	60% (6/10)	12.824	<0.001
Allergic manifestations% ($\pm$)	56.5% (17/13)	20% (2/14)	8.396	0.004
Skin allergy % ($\pm$)	20% (5/25)	0 (0/16)	1.519	0.218
Asthma % ($\pm$)	30% (9/21)	12.5% (2/14)	0.926	0.336
Drug allergy % ($\pm$)	10% (3/27)	0 (0/16)	0.464	0.496
IgG4-RD RI before treatment (mean $\pm$ standard deviation)	9.6 $\pm$ 3.5	7.4 $\pm$ 3.9	1.971	0.055

Allergic manifestations included skin allergy, asthma and drug allergy

IgG-RD RI IgG-related disease responder index

CRS. In case group, there was no difference between the disease duration of CRS and that of other organs affected ($z = 1.765$, $p = 0.078$). Allergies were more frequent in patients with IgG4-RD with CRS than that in patients with IgG4-RD without CRS. There was no difference in extra-ocular clinical manifestations between the case group and control group (Table 2).

Laboratory findings of IgG4-RD with CRS at baseline

There were a higher percentage of eosinophils in the peripheral blood of patients with IgG4-RD complicated with CRS than in patients without CRS. There were no differences in serum IgG4 and IgE levels, and inflammation index (eg: ESR and CRP) between the case group and control group (Table 3).

Previous misdiagnosis and surgery

A total of 17 out of 30 (56.7%) patients had undergone surgery before definitive diagnosis. The surgical procedures were generally performed for the purpose of diagnosis or

treatment of suspected or erroneous diagnosis of cancer. Before a definite diagnosis of IgG4-RD was made, the total number of surgeries of affected organs was 29 times, which was higher than IgG4-RD without CRS [surgery time 1 (1, 2) versus 0 (0, 1), $z = 3.829$, $p < 0.001$]. The most common misdiagnosis was pseudo-tumor (Table 4). The most common surgical procedures were nasal cavity surgery (11 patients), followed by lacrimal surgery (eight patients) and lymph nodes biopsy (three patients).

Treatment and effect

Glucocorticoids (GCs) were the most common and effective therapy administered to the patients. Prednisone dosage was 0.8 mg/kg day for 2 weeks, followed by gradual tapering. GCs were combined with GC-sparing medications (cyclophosphamide/methotrexate/azathioprine). No case used biological agents in this study. The patient's conditions were evaluated by IgG4-RD RI at the initial diagnosis and 1 year of follow-up, respectively. The change in IgG4-RD RI was considered to be the treatment effect. IgG4-RD RI before the treatment was comparable between the two groups. The treatment effect was better in cases with IgG4-RD

Table 3 Laboratory findings of patients with IgG4-RD complicated with CRS before treatment

Items [M (P25, P75)]	Case group (n=30)	Control group (n=16)	Z value	p value
Eosinophils (%) [M (P25, P75)]	8.5 (3.5, 12.1)	3.3 (0.7,8.5)	2.365	0.018
IgG4 level (g/L) [M (P25, P75)]	6.7 (3.7, 6.2)	4.3 (1.6, 4.9)	0.643	0.520
IgE level (g/L) [M (P25, P75)]	4.3 (2.3, 5.8)	3.0 (0.3, 8.8)	0.364	0.716
ESR (mm/h) [M (P25, P75)]	21 (10, 56)	26 (14, 61)	-0.600	0.548
CRP (mg/L) [M (P25, P75)]	3.8 (1.6,8.5)	9.2 (2.0, 35.8)	-1.838	0.066

IgG immunoglobulin G, *IgG4* immunoglobulin G4, *ESR* erythrocyte sedimentation rate, *CRP* C-reaction protein

Table 4 Misdiagnosis and previous surgery in IgG4-RD patients with CRS before definitive diagnosis

Surgery organ	Case number of surgery		Surgery times		Misdiagnosis
	Case group (n=30)	Control group (n=16)	Case group (n=30)	Control group (n=16)	
LN	3	2	3	2	Pseudo-tumor
SMB	2	3	2	4	Pseudo-tumor
LM	5	3	8	3	Pseudo-tumor
Lip	1	1	1	1	Sjogren syndrome
Duodenum	1	0	1	0	Intestinal tumor
Pancreas	1	1	1	1	Pancreatic cancer
Sinus	1	0	2	0	Sinusitis/allergic sinusitis
NC	11	0	11	0	Nasal polyps
Mediastinum	0	1	0	1	Thymoma
Retroperitoneal	0	2	0	2	Tumor
Bile duct	0	1	0	1	Choledochotumor
Total	25	14	29	15	

LN lymph nodes, *SMB* submandibular, *LM* lacrimal, *NC* nasal cavity

Table 5 Changes in the clinical and laboratory findings of patients with IgG4-RD complicated with CRS after treatment

Items [M (P25, P75)]	Case group (n = 30)	Control group (n = 16)	Z value	p value
Change in eosinophils (%)	4.7 (1.0, 10.4)	1.4 (−0.5, 5.9)	1.027	0.104
Change in IgG4 level (g/L)	3.1 (1.2, 5.1)	2.4 (0.2, 5.2)	0.554	0.580
Change in ESR (mm/h)	0.7 (−8.3, 18.0)	−1.0 (−15.0, 14.5)	1.015	0.310
Change in CRP (mg/L)	0 (−1.1, 5.2)	2.4 (−2.0, 30.7)	0.727	0.467
Change in IgG4-RD RI	6.0 (4.0, 8.8)	3.5 (2.3, 5.5)	2.860	0.004

complicated with CRS than in the cases with IgG4-RD without CRS (treatment effect 6.0 versus 3.5, $z = 2.860$, $p = 0.004$) (Table 5).

Discussion

IgG4-RD is a multi-organ immune-mediated condition [3, 17, 18]. Its organ involvement was seen in 17 known anatomical sites in this study. The most commonly involved organs were orbit, followed by sinus/nasal cavity. Orbit involvement in patients with IgG4-RD has been widely reported [19, 20].

CRS is an inflammation of the nasal and paranasal sinuses, and upper airways characterized by 12 weeks of persistent symptoms including congestion, stuffiness, nasal discharge, pain or facial pressure, impairment or loss of sense of smell (anosmia), cough, and fatigue. Unremitting inflammation can last for several years [14], and CRS affects approximately 10% of the population in China. CRS is sometimes ignored by patients and doctors. Very few studies of patients with IgG4-RD complicated with CRS have been reported till date, most of which were small sample size case reports [12, 21] or reported by pathologists [15]. Only three reports have described cohorts of IgG4-RD with CRS. Moteki et al. [10] and Piao et al. [15] focussed on the pathological features of IgG4-RD with CRS rather than the clinical characteristics or laboratory features of IgG4-RD. Takano K et al. [9] described the clinical features of patients with IgG4-RD complicated with CRS in Japan, but only 4 out of 79 cases underwent nasal sinus membrane biopsy. In this study, the baseline clinical and laboratory features of 46 patients with IgG4-RD diagnosed by strict clinical pathological correlation have been described. Definitive diagnosis was made in majority of the cases in this study by involved organs biopsy from extra-nasal cavity. We also found the same pathological features as IgG4-RD through reviewing nasal cavity membrane biopsy tissues of patients with IgG4-RD complicated with CRS. Our study differs from previously published studies of patients with IgG4-RD complicated with CRS and suggests that CRS was committed as a part of involved organs in these patients.

Middle-aged male patients were more susceptible to IgG4-RD, which was different from other autoimmune

diseases [3, 17, 18, 22, 23]. The demographic characteristics in our study were in accordance with these features. A total of 30 out of 46 (65.2%) patients with IgG4-RD were affected by CRS in this study, which was similar to Takano K et al. report [9], but higher than other reports [5, 17, 23]. One of the reasons was that the ratio of involved ocular cases was higher in this study than in other studies. Since ocular lesions and CRS were closely associated, it might be one of the reasons for the high ratio of CRS in this study. Another important reason was that only 19.6% (9/46) of cases with a past history of CRS in our cohort actively reported the disease during history-taking. CRS is so common and frequent in China that both patients and doctors ignore the association between CRS and systemic conditions. Therefore, the incidence rate of CRS in patients with IgG4-RD might be underestimated.

Major differences could be seen in the percentage of cases afflicted with ocular lesions, which was similar to the report of Li et al. [24]. Association between orbital mass and saddle nose was reported in patients with GPA [25], which may be contiguous, secondary to spread of granulomatous disease from the nasal passages or paranasal sinuses [26]. Therefore, we speculated that the possible cause for the close association between eye and nasal/sinus lesion in patients with IgG4-RD was that orbital lesion may be contiguous, secondary to spread of inflammation lesion from the nasal passages or paranasal sinuses because of close anatomical position. The close association between eye and nasal/sinus lesion needs further study.

The disease duration in patients with CRS was longer than that in patients without CRS. We reviewed our data further and found that in patients with CRS there was no difference between the disease duration of CRS and that of other involved organs; it indicated that CRS might develop at any time during the disease process of IgG4-related CRS.

In our cohort, allergic manifestations were more common in patients with IgG4-RD complicated with CRS, due to a raised percentage of eosinophils in peripheral blood, which was also observed in other studies [23, 27]. Differences in disease pathogenesis and mechanisms of damage might explain some of these differences that were found in this disease phenotype. High-serum IgG4 is present in 60–70% of patients, but these IgG4 antibodies are not directly pathogenic [28]. Eosinophils are multifunctional granulocytes

that contribute to initiation and modulation of inflammation. Their role in asthma and parasitic infections is well recognized. Eosinophils are also involved in autoimmune diseases; for example, eosinophilic granulomatosis with polyangiitis [29], inflammatory bowel diseases [30], bullous pemphigoid [31], etc. Humoral immunity is involved in the specific local immunity (membrane immunity) of nasal cavity and sinus membrane [32]. The mature plasmocytes are enriched in the nasal membrane after allergic reactions due to the increased vascular permeability. The production of IgG4 antibodies appears to be driven in part by T helper 2 (Th2) cytokines that mediate allergic responses and IgE production. Then, the Fc section of elevated IgG4 could combine and activate mast cells and eosinophils [33], to release inflammatory substances that mediate the pathogenesis of IgG4-RD [3]. Eosinophils in peripheral blood might also play a crucial role in the mechanism of IgG4-RD with CRS. Therefore, several potential mechanisms have been hypothesized such as release of profibrotic factors and promotion of plasma cell survival for IgG4 production. An IgE-mediated allergic response, therefore, seems to develop in most patients with IgG4-RD. However, there was no difference in serum IgE level between the two groups in this study. The inconsistency change in IgE and EOS may be associated with the incomplete data of IgE due to the retrospective nature of the study or with the other reasons. Therefore, further forward-looking study will be needed to validate our hypothesis.

Our study also provided additional information about the surgery history before definitive diagnosis. Before IgG4-RD was definitively diagnosed, 56.7% (17/30) of patients had undergone surgery and the total number of surgery of affected organs in patients with CRS was 29 times, which was higher than that in patients with IgG4-RD without CRS. Although there was longer disease duration in patients with CRS than in patients without CRS, there was no difference in the inflammation level and IgG4-RD RI at baseline between the two groups. It indicated that patients in the two groups had similar disease severity. The three key histopathological features of IgG4-RD that are well established include lymphoplasmacytic infiltration, fibrosis arranged at least focally in a storiform pattern, and obliterative phlebitis. We collected the biopsy tissues from the previous surgery of the majority of patients with IgG4-RD in our study, which included eight lacrimal glands, three lymph nodes, two submandibular glands, one lip, one duodenum, and one pancreas. The biopsy tissues met the histopathological features but could not be stained for IgG4 because of limited quantity. Taken together, these data indicated a higher ratio of misdiagnosis due to lack of phenotypic knowledge of this subtype of IgG4-RD. Nasal cavity membrane biopsy is a minimally invasive and convenient procedure as compared to other organs. The positive rate of nasal cavity membrane tissue biopsy might be higher in patients with IgG4-RD

accompanied by ocular involvement and CRS. Careful consideration was required when diagnosing IgG4-RD by biopsy in CRS, because other inflammatory disease conditions were potentially associated with an elevated number of IgG4-positive plasma cells in the tissue, including common CRS [34].

In 2012, a tool named IgG4-RD responder index was designed [16] for detecting disease activity and identifying improvement or worsening in affected organs, which was modeled on the Birmingham Vasculitis Activity Score for granulomatosis with polyangiitis (BVAS/GPA) [35]. Our study suggested that IgG4-RD with CRS was not associated with disease activity as measured by the extent of organ involvement through the IgG4-RD RI at baseline. This could be due to comparable baseline conditions before treatment between the two groups. Glucocorticoids are the first-line drugs for remission induction in all patients with active, untreated IgG4-RD, unless contraindicated [36]. In our study, there was actually no difference between the two groups in the raised ESR, C-reactive protein level, and IgG4-RD Responder Index which were usually used to measure the inflammation severity and disease activity of IgG4-RD. It was a pity that we had no observation about the inflammation degree in the nasal biopsies. Therefore, we speculated that the treatment was effective in both groups, but was better in patients with IgG4-RD complicated with CRS, perhaps, due to more frequent allergic manifestations and more active eosinophils in these patients instead of due to the inflammation severity.

This study had several limitations. This was a single-center retrospective study with a small sample size. Future multi-center studies with large sample sizes are needed to confirm the findings of this study.

Conclusions

Herein, a cohort of patients with IgG4-RD complicated with CRS confirmed by strict association between the clinical manifestations and histopathological features is described. CRS was frequent in patients with IgG4-RD, and was closely associated with IgG4-related ophthalmic and allergic manifestations. The treatment for patients with IgG4-RD complicated with CRS was more effective than that in patients with IgG4-RD without CRS. This clinical subtype had its distinctive clinical manifestations in the spectrum of IgG4-RD. The misdiagnosis rate for this clinical subtype remains higher than in patients with IgG4-RD without CRS. ENT specialist should think about IgG4-RD in patient with CRS. Further understanding of this clinical subtype would facilitate correct diagnosis.

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Compliance with ethical standards

Ethical approval This study was approved by the Academic and Ethics Committee of Beijing Tongren Hospital in accordance with the principles of the Declaration of Helsinki.

Informed consent All participants provided written informed consent to participate in this study.

Conflict of interest The authors declare that they have no conflict of interest.

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