Human Pathology (2018) 73, 82–88

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Immunoglobulin G4–related chronic rhinosinusitis: a pitfall in the differential diagnosis of granulomatosis with polyangiitis, Rosai-Dorfman disease, and fungal rhinosinusitis☆,☆☆

Yingshi Piao MD, PhD[a,b,1], Yuan Zhang MD, PhD[c,d,e,1], Changli Yue MD[a,b], Chengshuo Wang MD, PhD[c,d,*], Luo Zhang MD, PhD[c,d,e,**]

[a]*Department of Pathology, Beijing TongRen Hospital, Capital Medical University, Beijing, China*
[b]*Beijing Key Laboratory of Head and Neck Molecular Pathological Diagnosis, Beijing TongRen Hospital, Capital Medical University, Beijing, China*
[c]*Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China*
[d]*Beijing Key Laboratory of Nasal Diseases, Beijing Institute of Otolaryngology, Beijing, China*
[e]*Department of Allergy, Beijing TongRen Hospital, Capital Medical University, Beijing, China*

Received 12 September 2017; revised 15 December 2017; accepted 15 December 2017

Keywords:
IgG4-related chronic rhinosinusitis;
Plasma cell;
Granulomatosis with polyangiitis;
Rosai-Dorfman disease;
Fungal rhinosinusitis

Immunoglobulin G4 (IgG4)–related chronic rhinosinusitis (CRS) has recently been proposed to be a new clinical entity of nasal disease, with no consensually agreed criteria for diagnosis. Moreover, the pathological features of IgG4-related CRS often overlap with other sinonasal inflammatory and autoimmune diseases such as granulomatosis with polyangiitis (GPA), Rosai-Dorfman disease (RDD) and fungal rhinosinusitis (FRS). We aimed to explore the specific similarities and differences in clinicopathologic features between IgG4-related CRS, and GPA, RDD and FRS, in order that these conditions can be diagnosed more accurately. Biopsy specimens collected from nasal mucosa of 20 IgG4-related CRS, 10 GPA, 10 RDD and 10 FRS patients were assessed by hematoxylin and eosin staining and immunohistochemical techniques for specific histochemical differences. The number of IgG4-positive plasma cells /high-power fields (HPF) in biopsies from IgG4-related CRS patients (mean = 79.6 ± 51.59; range = 15/HPF to 230/HPF) was significantly higher than in biopsies from GPA (mean = 13 ± 9.428; $P < .0001$) and RDD (mean = 12.5 ± 8.267; $P < .0001$) patients, but not from FRS (mean = 47.4 ± 26.48; $P > .05$) patients. Similarly, the ratio of

☆ This work was supported by grants from the program for National Key R&D Program of China (2016YFC20160905200), Changjiang Scholars and Innovative Research Team (IRT13082), the National Natural Science Foundation of China (81420108009, 81570895, 81400444, 81470678 and 81630023), the Special Fund of Capital Health Development (2011-1017-06,2011-1017-02), the Special Fund of Sanitation Elite Reconstruction of Beijing (2009-2-007), Beijing Health Bureau Program for High Level Talents (2011-3-043), Beijing Municipal Administration of Hospitals' Mission Plan (SML20150203) and Capital Citizenry Health Program (z161100000116062).

☆☆ Conflict of interest: All authors declare no financial or commercial conflicts of interest.

* Correspondence to: C. Wang, M.D., Department of Otolaryngology - Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, No.1, Dongjiaominxiang, DongCheng District, Beijing 100730, PR China.

** Correspondence to: L. Zhang, M.D., Beijing Institute of Otolaryngology, No. 17, HouGouHuTong, DongCheng District, Beijing, 100005, PR China.
E-mail address: wangcs830@126.com

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.humpath.2017.12.011

IgG4/IgG-positive plasmacytes was >40% in 90% (18/20) of IgG4-related CRS patients, compared to >40% in 10% (1/10) of GPA patients, 20% (2/10) of RDD patients and 20% (2/10) of FRS patients. The sinonasal diseases GPA, RDD and FRS might present with similar histopathologic features such as the increased numbers of plasma cells and fibrosis, which are characteristic of IgG4-related CRS. A comprehensive consideration combining the clinical signs and symptoms with a histopathological assessment of IgG4-positive plasma cells may provide accurate diagnoses of these conditions.

1. Introduction

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a newly recognized fibro-inflammatory condition characterized by several features; including a tendency to form tumefactive lesions in multiple sites, a characteristic histopathological appearance and often, but not always, elevated serum IgG4 concentrations [1]. While the primary clinical feature in IgG4-RD is an inflammatory tumor-like presentation coupled with tissue-destructive lesions, the multitude of clinical manifestations makes differential diagnosis of an IgG4-RD particularly challenging. The disease entity, however, is thought to be a result of plasma cell–mediated over-production of the IgG4 subclass of immunoglobulin IgG [2]. A consensus statement on IgG4-RD by a group of international experts has indicated that the diagnosis of IgG4-RD rests on the combined presence of the characteristic histopathological appearance and increased numbers of IgG4-positive plasma cells. IgG4 and IgG immunostaining in tissue biopsies is an essential test for the pathological diagnosis of IgG4-RD. Although immunostaining may not be necessary for straightforward cases with increased serum IgG4 concentrations, IgG4 immunostaining is nevertheless strongly recommended even in these cases because it is a simple, highly reproducible test that provides strong confirmatory evidence for the diagnosis of IgG4-RD [1].

The characteristics of IgG4-RD in nose and sinuses have not been widely investigated, and the reports of IgG4-related chronic rhinosinusitis (IgG4-related CRS) available in the literature document mostly case reports [3-9]. We have recently demonstrated that in patients with Mikulicz's disease with concomitant CRS (CRS-MD), both the concentration of serum IgG4 and IgG4-positive plasma cells infiltration in the lacrimal/salivary glands and the nasal mucosa, was significantly higher than in patients with only MD or common CRS, respectively [10]. To date, there is no consensus regarding the exact organ-specific criteria for the diagnosis of IgG4-related CRS.

Moreover, several studies have indicated that IgG4-related CRS often overlapped with other nasal and sinonasal inflammatory and autoimmune diseases, such as granulomatosis with polyangiitis (GPA), Rosai-Dorfman disease (RDD) and fungal rhinosinusitis (FRS), in terms of similar pathologic features involving large numbers of lymphocytes and plasma cells infiltration, fibrosis, and IgG4-positive plasma cells infiltration [11-17]. Thus, when IgG4-related CRS is comorbid with these inflammatory nasal and sinus diseases, it may be misdiagnosed or missed altogether.

The aim of the present study was thus to explore the similarities and differences in the clinicopathological features between IgG4-related CRS patients and GPA, RDD and FRS patients, in order to improve differential diagnosis of IgG4-related CRS among these diseases.

2. Materials and methods

Twenty patients with IgG4-related CRS were recruited from the Pathology Department of Beijing TongRen Hospital. Diagnosis of IgG4-related CRS was made according to International comprehensive diagnostic criteria (CDC) for IgG4-RD, 2011 [18] and based on (1) Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs; (2) Hematological examination showing elevated serum IgG4 concentrations (≥135 mg/dL); and (3) Histopathologic examination showing (1) Marked lymphocyte and plasmacyte infiltration and fibrosis. (2) Infiltration of IgG4+ plasma cells; with ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells/HPF.

Diagnosis was classified as "Definite" when criteria (1) + (2) + (3) were demonstrable; "Probable" when criteria (1) + (3) were demonstrable and "Possible" when criteria (1) + (2) were demonstrable. In this respect, 7 patients were classified as definite cases, 6 as probable cases and 7 as possible cases.

Ten patients each with confirmed diagnosis of GPA, RDD and FRS, according to relevant internationally recognized standards [11-13], were analyzed retrospectively for comparison with the IgG4-related CRS patients. All the FRS cases belonged to fungus ball sinusitis; with *Aspergillus* being the main fungus type.

Written informed consent was obtained from each participant before the study began. The study was performed according to the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Beijing Institute of Otolaryngology (date: 2014-1-10, approval number: 2014-0110).

2.1. Serological test

Blood was drawn from all patients and assessed for serum levels of IgG, IgG4, IgE, IgA, IgM, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), C-reactive protein (CRP), complement C3 and complement C4.