

Role of IgG4 serology in identifying common orbital lymphoproliferative disorders

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Abstract

• **AIM:** To explore the role of IgG4 serology in identifying common orbital lymphoproliferative disorders.

• **METHODS:** Eighty –one patients with orbital lymphoproliferative diseases were treated in the Department of Ocular Oncology, Beijing Tongren Hospital, Capital Medical University between September 2010 and December 2012. Serum IgG4 levels were measured in 46 cases of idiopathic orbital inflammatory pseudotumor (IOIP), 17 benign lymphoepithelial lesion (BLEL), 12 cases of orbital mucosa-associated lymphoid tissue (MALT), and 6 cases of diffuse large B –cell lymphoma (DLBL) using immuno –scatter turbidimetry (ISTM).

• **RESULTS:** The frequency of elevated IgG4 levels in patients with IOIP, BLEL, MALT, and DLBL was 30.43% (14/46), 76.47% (13/17), 8.33% (1/12), and 0.00 (0/6), respectively. Among the patients with elevated serum IgG4 levels, all IgG –IOIP patients were male, and 92.31% of the IgG4 –BLEL patients were female (12/13). The mean serum IgG4 level of IgG4 –IOIP patients was lower than that of individuals with IgG4 –BLEL, but the variation in serum IgG4 levels was larger in IgG4 –IOIP than IgG4 –BLEL patients. Only one case of IgG4 –MALT with elevated serum IgG4 levels had a medical history >10y, which was significantly longer than the MALT patients with normal serum IgG4 levels. There was no significant elevation of serum IgG4 levels in patients with DLBL.

• **CONCLUSION:** Detecting serum IgG4 levels plays an important role in the differential diagnosis of orbital lymphoproliferative diseases.

• **KEYWORDS:** orbital disease; lymphoproliferative disease; IgG4

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INTRODUCTION

Orbital lymphoproliferative diseases are a common class of ophthalmic disorders, which broadly include reactive lymphoid hyperplasia, lymphoma, idiopathic orbital inflammatory pseudotumor (IOIP), and benign lymphoepithelial lesion (BLEL). Although these diseases have large variations in their treatment and prognosis, their clinical manifestations are very similar. As such, it is difficult to perform differential diagnosis based on clinical manifestations and radiographic examinations. Therefore, many patients have to go through histopathological examination for differential diagnosis after surgery.

IgG4-related disease (IgG4-RD) was discovered in recent years, and has received significant attention. It is a large class of diseases that are characterized by an abnormal elevation in the IgG4 levels in patients' blood or tissues. This IgG4 accumulation might occur in any tissue and organ, but it occurs only rarely in the orbital region [1-4]. Recent studies reported that IOIP and BLEL are IgG4-RDs [5-10]. The diagnostic criteria for IgG4-RD have not been unified to date. Nevertheless, elevated IgG4 serology or numerous IgG4-positive plasma cells in immunostaining contribute important clinical evidence [11]. This study measured the serum IgG4 levels in patients with common orbital lymphoproliferative diseases to determine their function in these diseases and also provide better guidelines for clinical therapy.

SUBJECTS AND METHODS

The study was a prospective study. Eighty-one patients with orbital lymphoproliferative diseases were treated in the Department of Ocular Oncology, Beijing Tongren Hospital, Capital Medical University between September 2010 and December 2012. The subjects included 46 cases of IOIP, 17 BLEL, 12 orbital mucosa-associated lymphoid tissue (MALT), and 6 cases of diffuse large B-cell lymphoma (DLBL). Post-operative histopathological examinations were performed to confirm the diagnosis of all patients. This study was approved by the Ethics Committee of the Capital Medical University Beijing Tongren Hospital, and written consent was given by all participating patients. All participants signed a detailed informed consent form, according to the Declaration of Helsinki.

Blood samples were collected from patients after an overnight fast the morning after admission to the hospital. Five milliliters of venous blood was collected *via* an aseptic median cubital vein puncture from each patient, and then centrifuged at 4000 rpm for 10min at 4°C. The extracted serum was stored at -20°C until use.

Serum IgG4 levels were detected using immuno-scatter turbidimetry (ISTM). The device (BN ProSpec full-automatic protein analyzer) and relevant kit were bought from Siemens of Germany.

Data were analyzed using SPSS17.0 statistical software (SPSS, Chicago, IL, USA). Data measurements (mean±SD) were used to indicate normality and homogeneity of variance tests. Independent sample *t*-tests were used to compare two groups, and *P* < 0.05 was used to represent statistically significant differences.

RESULTS

A total of 30.43% (14/46), 76.47% (13/17), 8.33% (1/12), and 0.00 (0/6) of patients with IOIP, BLEL, MALT, and DLBL had elevated serum IgG4 levels (Figure 1). All IOIP patients with elevated serum IgG4 levels were male, whereas 92.31% of IgG4-BLEL patients with elevated serum IgG4 levels were female (12/13). Only one patient with IgG4-MALT also had elevated serum IgG4 levels and an IgG4-MALT medical history >10y, which was significantly longer than other MALT patients with normal serum IgG4 levels. No significant elevation of serum IgG4 was found in patients with DLBL.

The serum IgG4 levels in the IgG4-IOIP (*n* =14) and IgG4-BLEL (*n* =13) patients were 917.43 ±862.32 and 363.48±236.72 mg/dL, respectively, which was significantly different (*P*=0.035). Serum IgG4 levels in IgG4-IOIP patients had large magnitude of changes (mean about 1000 mg/dL), whereas the change in serum IgG4 levels were lower in IgG4-BLEL patients than IgG4-IOIP subjects (mean <1000mg/dL) (Figure 2).

DISCUSSION

IgG4-RD is a new clinical entity that has been widely accepted and recognized by medical professionals. This disease can occur in any tissue and organ, and is most commonly found in the pancreas, followed by the parotid gland, bile duct, liver, lungs, and lymph nodes [1-4]. However, it is rare in the orbit [5-7]. To date, studies have reported that IgG4-related orbital diseases include IOIP and BLEL [5-10].

BLEL, also known as Mikulicz's disease, was first reported by a Polish scientist, Johann von Mikulicz-Radecki, in 1888. It describes the diffuse lymphocyte-infiltration of the lacrimal and salivary glands and a benign lesion caused by reactive hyperplasia of the ductal epithelial cells in the gland and intrinsic muscle [8]. Yamamoto *et al* [9] first reported elevated serum IgG4 levels in patients with BLEL in 2004, and many subsequent studies also supported that BLEL is an IgG4-RD. This study included 14 patients with orbital BLEL who were diagnosed histopathological examination. Their

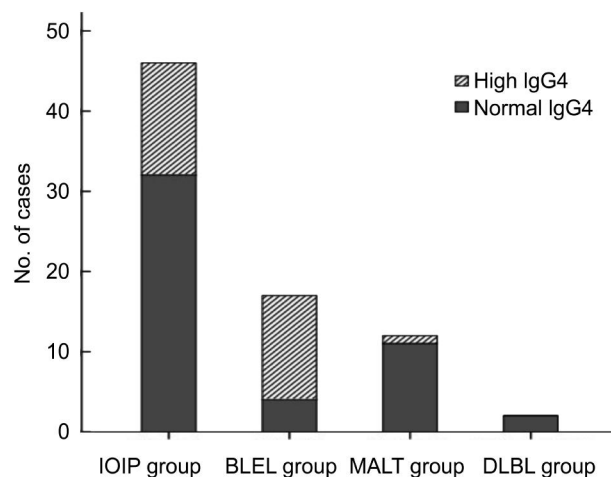


Figure 1 A total of 30.43% (14/46), 76.47% (13/17), 8.33% (1/12), and 0.00 (0/6) of patients with IOIP, BLEL, MALT, and DLBL had elevated serum IgG4 levels.

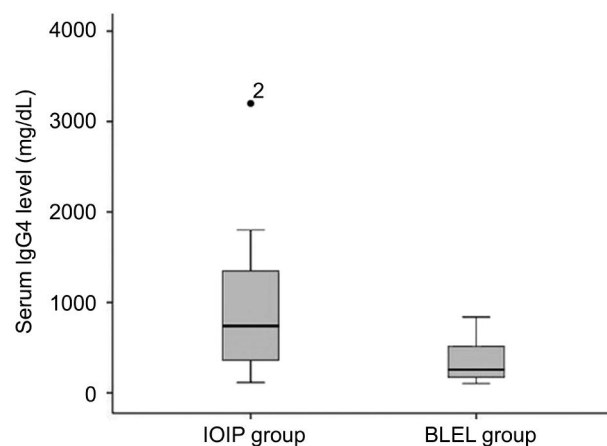


Figure 2 Serum IgG4 levels in IgG4-IOIP patients had large magnitude of changes (mean about 1000 mg/dL), whereas the change in serum IgG4 levels were lower in IgG4-BLEL patients than IgG4-IOIP subjects (mean <1000 mg/dL).

serum IgG4 levels were measured, and IgG4 immunohistochemical staining was performed. The results demonstrated that 13 patients met the current diagnostic criteria for IgG4-RD. However, the reason why only a small number of patients had low serum IgG4 will need to be determined in future clinical and basic studies with a larger sample size.

IOIPs affect any tissue and organ in the body. Few studies have suggested that orbital pseudotumors might be an IgG4-RD. Ahn *et al* [12] performed IgG4 immunohistochemical staining in 22 cases of hepatic IOIP, and showed that 17 cases stained negative for fibrosing IOIP, and four were positive for lymphocyte predominant IOIPs. This suggests that lymphocyte predominant IOIPs might be IgG4-RDs. However, the relationship between IOIP and IgG4-RD has only been reported rarely. The current study included 46 cases of IOIP that were confirmed by histopathological examinations, and measured their serum IgG4 levels. Thirteen patients met the diagnostic standard for IgG4-RD, accounting for one-third of the total number of IOIP patients.

Interestingly, these thirteen parents were all male, which might be due to bias caused by the small sample size in the current study. Nevertheless, these findings are consistent with the results of the male dominance of IgG4-RD reported previously.

MALT lymphoma is the most common form of clinical orbital malignant lymphoma. It has a low degree of malignancy, slow progression, and is confined to the orbit. MALT lymphoma is sensitive to radiotherapy. A small number of studies reported that patients with MALT lymphoma have elevated IgG4 levels in their serum and/or tissues^[13-16]. This study included 13 MALT lymphoma patients, one of whom had elevated serum levels of IgG4. This patient was a 56-year old male with a medical history >10y, which was significantly longer than that of the other MALT patients enrolled. According to his medical history, the patient underwent surgery in a local hospital, and the pathological report mentioned only inflammatory lesions of an unknown specification.

DLBL is a type of non-Hodgkin's lymphoma. It occurs at any age and is commonly found in elderly individuals. The clinical manifestation of DLBL is typically a painless mass that grows rapidly. The tumors mainly occur in the lymph nodes. Approximately 30% of patients show localized extranodal precursor lesions. These extranodal lesions are commonly found in the gastrointestinal tract, bone, and central nervous system, but rarely in the orbit^[17-19]. Only a few studies have reported that patients with DLBL might have elevated levels of IgG4 in their serum and/or tissues^[20]. However, in this study no patients with DLBL ($n=6$) had elevated serum IgG4 levels.

In conclusion, when ophthalmologists suspect orbital lymphoproliferative disease in clinical practice, they should consider the possibility of IgG4-RD. In addition to taking a comprehensive medical history, performing physical examination, and imaging tests, it is necessary to measure serum IgG4 levels. If serum IgG levels are elevated, ophthalmologists should consider the possibility of benign orbital lymphoproliferative disease. If the patient is male, ophthalmologists should focus on the possibility of IgG-IOIP and the systemic involvement of other organs. If the patient is female, ophthalmologists should consider the possibility of IgG4-BLEL. Finally, ophthalmologists should consider the possibility of IgG4-MALT in patients with a long medical history (particularly >10y).

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