Original Article

Clinical Research on Benign Lymphoepithelial Lesions of Lacrimal Gland in 20 Chinese Patients

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Abstract

Background: Benign lymphoepithelial lesion (BLEL) is characterized by symmetric bilateral swelling of the lacrimal and salivary glands and considered a subtype of immunoglobulin G4 (IgG4)-related sclerosing disease, the etiology and pathogenesis of which has not been determined. The purpose of the present study was to analyze the clinical features of BLEL in the lacrimal gland and the relationship between the serum level of IgG4 and BLEL.

Methods: Twenty consecutive patients with BLEL diagnosed in Department of Ophthalmology at Beijing Tongren Hospital, Capital Medical University between January 2012 and December 2013 were observed. The clinical features, imaging findings, laboratory tests, treatments and follow-up status of these 20 consecutive patients were analyzed.

Results: In all 20 patients, the ratio of male to female was 1:4, the ages ranged from 28 to 57 years, the ratio of unilateral to bilateral eyes involvement was 1:4, and painless uncongested symmetrical swelling of the upper eyelid was the main clinical manifestation. Orbital magnetic resonance imaging (MRI) showed that all patients involved lacrimal gland, which were obviously enlarged with equal signals in T1W images and T2W images and obvious enhancement on contrast MRI. Extraocular muscles were involved in 5 patients, salivary gland in 8 patients, and frontal nerve in 3 patients. Serum IgG4 concentration was elevated in 18 patients. The treatment strategy mainly included surgery and steroid administration. Three patients were lost to follow-up, 17 patients reached complete response, and no recurrence was observed.

Conclusions: Eyelid swelling is the typical symptom of BLEL. Most of the patients involved bilateral lacrimal glands. High serum IgG4 level and abundant IgG4-positive plasma cell infiltration are the important features, which can be found in most of BLEL patients. Surgery combined with glucocorticoids is an efficient treatment strategy.

Key words: Benign Lymphoepithelial Lesion; Glucocorticoids; Immunoglobulin G4; Lacrimal Gland; Surgery

Introduction

Benign lymphoepithelial lesion (BLEL), also called Mikulicz's disease (MD), is characterized by symmetric bilateral swelling of the lacrimal and salivary glands and considered a subtype of immunoglobulin G4 (IgG4)-related sclerosing disease, the etiology and pathogenesis of which has not been determined. In 1888, Mikulicz reported a patient with bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands, and BLEL was first discovered.[1] Then Mason *et al*.[2] in 2003 found that the expressions of transforming growth factor-beta (TGF-ß) are different in different tissues, and the decreased expression of its subtype TGF-ß1 in the gland can explain the abundant lymphocyte infiltration and epithelial cell and lymphocyte proliferation. Therefore, they raised the TGF-ß hypothesis. Ihrler *et al*.[3] studied the salivary glands in 12 patients with MD and 8 normal individuals. They thought that the development of duct lesions in BLEL arises from basal cell hyperplasia of striated ducts with aberrant differentiation into a multi-layered and reticulated epithelium characterized by profound alteration of the cytokeratin pattern. This functionally inferior, metaplastic epithelium is similar to the lymphoepithelial crypt epithelium of palatine tonsils and the basal cell infiltration hypothesis. Recently, a novel clinicopathological entity of IgG4-related diseases (IgG4-RD) has recently been proposed, which is characterized by infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis. Although autoimmune pancreatitis (AIP), one of the organ characteristics of IgG4-RD, has been international reported, there are only a few reports of IgG4-related BLEL. The research on a large case series of BLEL is rare. The purpose of the present study was to clarify the clinical features of 20 patients with BLEL

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in the lacrimal gland and the relationship between the serum level of IgG4 and BLEL.

Methods

Patients and materials

Twenty consecutive patients with BLEL, who were diagnosed between January 2012 and December 2013 by histopathologic examination, were observed. All patients were hospitalized in Department of Ophthalmology at Beijing Tongren Hospital, Capital Medical University. Clinical data of all patients including age, sex, chief complaint, history of present illness, past history, clinical manifestation, and physical examination were analyzed. The research has been approved by the Ethics Committee of Beijing Tongren Hospital and conducted according to the principles in the *declaration of Helsinki*. Written informed consents have also been obtained from all participants.

Laboratory tests

Laboratory tests mainly included the following aspects: Blood and urine routine tests, blood biochemical examination, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum IgG, complement component 3 (C3), C4, antistreptolysin O (ASO), rheumatoid factor (RF), anti-Sjogren's syndrome (SS)-A, and anti-SS-B.

Imaging examinations

Imaging examinations mainly included chest X-ray, orbital magnetic resonance imaging (MRI), and upper abdominal computed tomography (CT).

Histology and immunohistochemistry

Surgically resected specimens of lacrimal gland were fixed in 10% formaldehyde and embedded in paraffin. Serial sections were cut from each paraffin-embedded tissue block, and several sections were stained with hematoxylin-eosin staining, and were immunostained for IgG and IgG4-expression cells. Immunostaining for IgG and IgG4 expression was performed using a rabbit monoclonal antibody against human IgG (abcam, ab109489, Hong Kong, China) and IgG4 (abcam, ab109493, Hong Kong, China). The extent of IgG4-positive plasma cell infiltration was evaluated independently by two pathologists. The degree of infiltration was scored as negative, mild, moderate or marked according to the number of IgG4-positive plasma cells seen on high-power field (HPF) in each specimen, and the areas with the highest density of IgG4-positive plasma cells were evaluated. For each tissue section, the mean number of IgG4-positive plasma cells was calculated from four examined HPF. Tissue sections were subdivided as follows: Negative ≤10/HPF; mild >10, and ≤30/HPF; moderate >30, and ≤100/HPF; marked >100/HPF.

Treatment and follow-up status

Treatment strategy was total excision combined with postoperative steroid administration, which was used as following: 80-120 mg intravenous methylprednisolone per day for 3 days and then changed to oral methylprednisolone administration with an initial dosage of 0.4 $mg \cdot kg^{-1} \cdot d^{-1}$, and then tapered slowly based on the response.

Results

General clinical data

In all 20 patients, the male-to-female ratio was 1:4, and the ages ranged from 28 to 57 years with a median age of 45 years. The ratio of unilateral to bilateral eyes involvement was 1:4, and painless uncongested asymptomatic symmetrical swelling of the upper eyelid was the main clinical manifestation and complaint [Figure 1 and Table 1]. In addition, 3 patients had a history of salivary gland surgery, and 1 patient had a history of hepatitis C.

Laboratory findings

Laboratory findings included elevated ESR levels in 6 patients (30%), an elevated CRP level in 1 patient (5%), decreased C3 levels in 9 patients (45%), decreased C4 levels in 3 patients (15%), elevated RF levels in 7 patients (35%), and normal ASO/anti-SS-A/anti-SS-B levels in all patients [Table 2]. Total serum IgG concentration was elevated in 12 of the 20 patients (60%), and the serum IgG4 the concentration was elevated (>135 mg/dl) in 18 patients (90%). The ratio of serum IgG4 to IgG concentration was higher than normal in 18 patients (90%), which ranged from 0.6% to 66.8% [Table 3].

Imaging findings of sites involved

Orbital MRI showed that all 20 patients involved lacrimal gland, which were obviously enlarged with equal signals in T1WI and T2WI and obvious enhancement on contrast MRI [Figure 2]. Extraocular muscles were involved in 5 patients, salivary gland in 8 patients and frontal nerve in 3 patients [Table 4]. Chest X-ray was normal in all patients. Nine patients underwent upper abdominal CT, and only one case was found to have an abnormally thickened gallbladder wall.

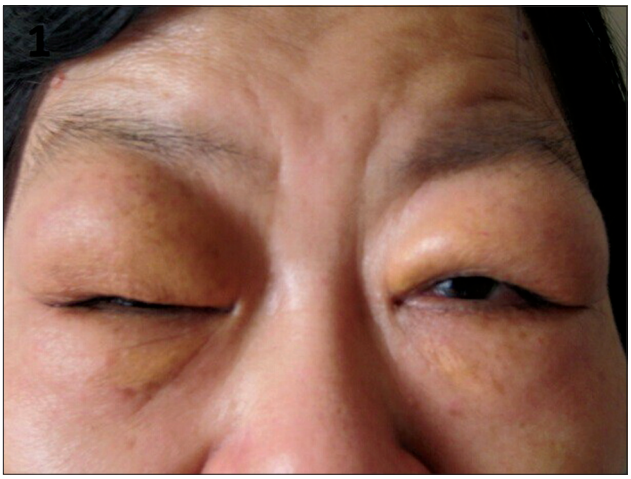

Figure 1: Clinical photograph (patient 18) showed bilateral uncongested symmetrical swelling of the upper eyelids, which was asymptomatic and nontender to palpation.

Table 1: General clinical data of 20 chinese patients with BLEL

Patient number	Age (years)	Sex	Duration (months)	Eye(s) involvement	Treatment	Treatment response	Follow-up period (months)	Follow-up status
1	36	Female	24	B	TE + steroid	CR	20	NR
2	46	Female	7	L	TE + steroid	CR	19	NR
3	57	Male	12	L	TE + steroid	–	–	–
4	48	Female	5	B	TE + steroid	CR	17	NR
5	43	Female	37	B	TE + steroid	CR	17	NR
6	42	Female	24	B	TE + steroid	CR	16	NR
7	44	Female	38	B	TE + steroid	CR	15	NR
8	37	Female	75	B	TE + steroid	CR	14	NR
9	40	Female	78	B	TE + steroid	CR	14	NR
10	56	Female	4	B	TE + steroid	CR	13	NR
11	39	Female	11	R	TE + steroid	–	–	–
12	48	Male	62	B	TE + steroid	CR	12	NR
13	49	Female	24	B	TE + steroid	CR	11	NR
14	53	Female	24	B	TE + steroid	CR	10	NR
15	28	Male	37	B	TE + steroid	CR	9	NR
16	38	Female	10	B	TE + steroid	CR	6	NR
17	54	Female	50	B	TE + steroid	CR	5	NR
18	54	Female	55	B	TE + steroid	CR	3	NR
19	39	Female	5	B	TE + steroid	CR	2	NR
20	48	Male	13	R	TE + steroid	–	–	–

L: Left; R: Right; B: Bilateral; CR: Complete response; NR: No recurrence; TE: Total excision; BLEL: Benign lymphoepithelial lesion.

Table 2: Laboratory findings in 20 chinese patients with BLEL

Patient number	ESR (mm/h, nl: 0–20)	CRP (mg/L, nl: 0–5)	C3 (mg/L, nl: 900–1800)	C4 (mg/L, nl: 100–400)	RF (U/ml, nl: 0–20)	ASO (U/ml, nl: 0–200)
1	34*	1.20	1222	219	4.10	30.30
2	13	1.25	1071.70	213.20	8.80	121.70
3	15	0.26	750.80†	215.50	7.80	34.50
4	11	0.95	688.10†	158.60	0.50	47.50
5	18	1.15	910.30	255.50	9.80	135.70
6	25*	3.50	1567.50	278.30	25.60*	126.40
7	14	2.24	1113.50	135.70	13.50	24.70
8	6	1.30	866.40†	204.50	27.80*	18.90
9	14	0.30	1073.30	189.50	20.50*	23.40
10	27*	4.58	1178.10	340.40	33.20*	87.30
11	16	0.47	725.30†	215.70	19.80	34.60
12	18	2.73	1162.20	277.80	35.00*	68.30
13	22*	0.22	673.60†	71.10†	6.00	48.50
14	25*	0.39	1522	272.20	92.20*	27.20
15	10	0.41	811.10†	151.20	4.70	76.70
16	19	0.51	879.20†	101.30	7.80	24.30
17	5	0.58	1018.80	259.50	10.40	20.50
18	12	1.14	1073.50	207.30	7.50	16.70
19	10	0.98	821.10†	89.70†	7.70	6.40
20	36*	21.21*	744.40†	79.90†	67.10*	13.80

*Higher than normal; †Lower than normal. nl: Normal level; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; C3 and C4: Component 3 and 4; ASO: Antistreptolysin O; RF: Rheumatoid factor; BLEL: Benign lymphoepithelial lesion.

Pathological findings

Prominent lymphoplasmacytic infiltration with lymphoid follicles was observed with the destruction and atrophy of the lacrimal gland lobules and periductal fibrosis [Figure 3a]. Immunostaining for IgG4 expression showed that numerous IgG4-positive plasma cells infiltrated the lesion [Figure 3b]. There were 16 patients of moderate (80%), 2 patients of marked, 1 patient of mild, and 1 patient of negative infiltration; and the degree of IgG4 expression in both tissue and blood was accordant [Table 3].

Treatment and follow-up status

Follow-up clinical data were available for 17 patients. The

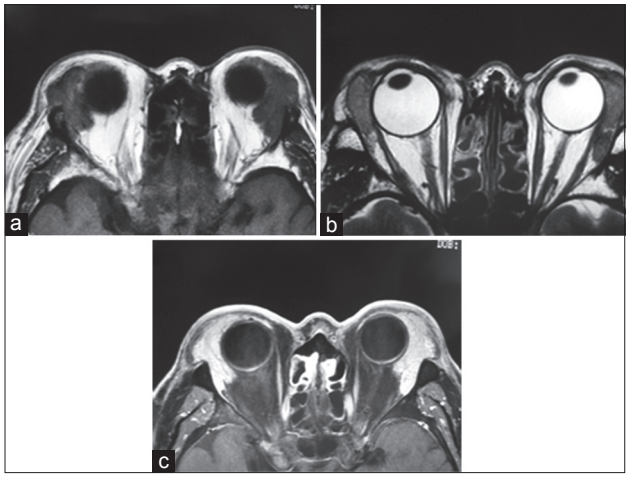

Figure 2: Axial orbital magnetic resonance imaging (patient 18) showed that bilateral lacrimal glands and right extraocular muscles enlarged obviously with equal signal in T1WI (a) and T2WI (b) and obvious contrast-enhanced image (c).

Table 3: Serum IgG and IgG4 concentrations and pathological results (before treatment)

Patient number	Serum IgG (mg/dl, nl: 751-1560)	Serum IgG4 (mg/dl, nl: 4-87)	Ratio of IgG4/IgG (%, nl<6%)	IgG4-positive plasma cells
1	1040	144*	13.8*	Moderate
2	1720*	270*	15.7*	Moderate
3	1620*	453*	28.0*	Moderate
4	2790*	839*	30.7*	Moderate
5	1280	136*	10.6*	Moderate
6	1040	104	10.0*	Mild
7	1210	177*	14.6*	Moderate
8	1450	535*	36.9*	Moderate
9	1720*	437*	25.4*	Moderate
10	1830*	515*	28.1*	Moderate
11	1730*	171*	10.0*	Moderate
12	2020*	1350*	66.8*	Marked
13	1840*	705*	38.3*	Moderate
14	2001*	242*	12.1*	Moderate
15	2140*	1250*	58.4*	Marked
16	1330	8.4	0.6	Negative
17	1010	423*	41.9*	Moderate
18	1560	155*	9.9*	Moderate
19	2563*	268*	10.5*	Moderate
20	1563*	240*	15.4*	Moderate

*Higher than normal. Negative: ≤10/HPF; Mild: >10, ≤30/HPF; Moderate: >30, ≤100/HPF; Marked: >100/HPF. HPF: High-power field; nl: Normal level; IgG4: Immunoglobulin G4.

duration of follow-up ranged from 2 to 20 months. All patients reached a complete response; no recurrence was observed [Table 1].

Discussion

The patients with BLEL in this study were mainly middle-aged females with a male-to-female ratio of 1:4. The median age was 45 years (range 28–57 years). The enlargement of the lacrimal

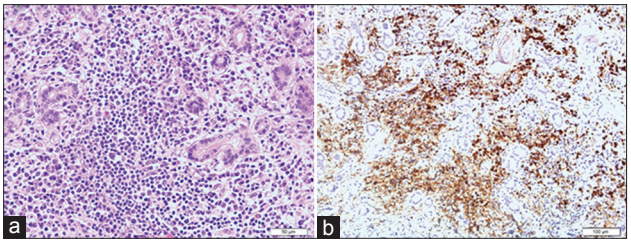

Figure 3: Histopathology of benign lymphoepithelial lesion (patient 2). (a) Marked lymphoplasmacytic infiltration with lymphoid follicles and the destruction and atrophy of the lacrimal gland lobules with periductal fibrosis were observed (hematoxylin-eosin staining, original magnification ×40). (b) Immunostaining for immunoglobulin G4 showed abundant IgG4-positive plasma cells infiltrated the lesion (original magnification ×20).

Table 4: Imaging findings of sites involved in BLEL patients

Patient number	Orbital MRI	Upper abdominal CT
1	Bilateral LG; bilateral UE; bilateral SG	ND
2	Left LG; left UE	Normal
3	Left LG	Normal
4	Bilateral LG; bilateral FN	ND
5	Bilateral LG	ND
6	Bilateral LG, bilateral SG	Normal
7	Bilateral LG; bilateral UE; bilateral SG	Normal
8	Bilateral LG; right EM; bilateral SG	Normal
9	Bilateral LG	ND
10	Bilateral LG; bilateral SG	ND
11	Bilateral LG	ND
12	Bilateral LG; bilateral UE; bilateral EM	Normal
13	Bilateral LG; bilateral UE; bilateral EM; bilateral FN	ND
14	Bilateral LG; bilateral EM; bilateral SG	ND
15	Bilateral LG; bilateral SG	Thickened wall of gallbladder
16	Bilateral LG; bilateral UE	Normal
17	Bilateral LG; bilateral UE	ND
18	Bilateral LG; bilateral SG	ND
19	Bilateral LG; bilateral UE; bilateral EM	ND
20	Bilateral LG; bilateral FN	Normal

LG: Lacrimal gland; UE: Upper eyelid; FN: Frontal nerve; SG: Salivary gland; EM: Extraocular muscle; ND: Not done; PNS: Paranasal sinus; MRI: Magnetic resonance imaging; CT: Computer tomography; BLEL: Benign lymphoepithelial lesion.

and (or) salivary glands in patients with BLEL was found to be uncongested and symmetrical as well as asymptomatic and nontender to palpation, which was consistent with the previous literatures.[4] The patients with BLEL might also suffer from other IgG4-RDs, including AIP, retroperitoneal fibrosis, tubulointerstitial nephritis, autoimmune hypophysitis or Riedel's thyroiditis.[5,6] However, none of the patients in our study showed any evidence of these diseases, and only one patient was found to have abnormal thickening of the gallbladder wall on CT. The reason may be associated with age, duration of disease, quantity of patients, and so on. All kinds of imaging examinations lacked specific features.

Recently, the phenomenon that patients with BLEL have a high level of serum IgG4 has been discussed more and more, and the concept that BLEL is a subtype of IgG4-related sclerosing disease has been increasingly accepted by doctors and scholars.[7,8] However, the role of IgG4 remains unknown. Our serological analysis revealed that 90% of patients with BLEL had elevated concentrations of IgG4, which has not been observed in any other connective tissue disease, including SS, systemic lupus erythematosus, rheumatoid arthritis, and polymyositis. Therefore, elevated serum IgG4 the concentration is a very specific and necessary index in the diagnosis of BLEL.

In addition, we found that the ESR level was elevated in 6 patients (30%), the CRP level was higher in one case (5%), the C3 levels were lower in 9 patients (45%), the C4 levels were lower in 3 patients (15%), the RF levels were higher in 7 patients (35%), and the ASO level was normal in all patients. The fact that hypocomplementemia existed in 45% of patients with BLEL was a very surprising finding, which needs more in-depth research to investigate the relationship between BLEL and hypocomplementemia. We suspected that low C3 concentration may be associated with a high IgG4 concentration.

In our study, imaging examinations mainly included chest X-ray, orbital MRI, and upper abdominal CT. Orbital MRI showed that all 20 patients involved lacrimal gland, which were obviously enlarged with equal signal in T1WI and T2WI and obvious contrast enhancement. In addition, extraocular muscles were involved in 5 patients, salivary gland in 8 patients, and frontal nerve in 3 patients, which was seldom reported in the previous studies. However, it was difficult to identify the involved sites whether they were primary or just an inflammatory response, and it needs further pathological examination of surgically resected specimens.

In this study, the lacrimal gland for anti-IgG4 antibody staining, and elevated concentrations of IgG4 were also detected in patients with BLEL. The infiltration of numerous IgG4-positive plasmacytes near acinar and ductal cells and around lymphoid follicles was confirmed in BLEL, which was completely consistent with the previous reports.[9-11] And, it was also found that the degree of IgG4 expression in both tissue and blood was accordant.

Benign lymphoepithelial lesion refers to idiopathic, bilateral, painless, and symmetrical swelling of the lacrimal, parotids, and submandibular glands. Its diagnosis needs comprehensive considerations and includes clinical manifestations, physical examination, imaging exams, serological exam, and so on. In addition, a differential diagnosis is necessary to distinguish BLEL from other distinct disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, and lymphoma, especially SS.[12] BLEL and SS are histologically similar; therefore, BLEL is considered a subtype of SS. However, BLEL and typical SS differ in some clinical features. Serologically, patients with BLEL lack anti-SS-A and anti-SS-B antibodies. It has also been confirmed that patients with BLEL show elevated serum IgG4 levels and infiltration of IgG4-positive plasmacytes in the lacrimal and salivary glands. Thus, BLEL is apparently different from SS. In our research, anti-SS-A and anti-SS-B were examined in all patients, and none of them showed abnormal level.

Benign lymphoepithelial lesion is mainly treated with administration of glucocorticoids, which has satisfied effect.[12] However, in our clinic, all patients had been treated by glucocorticoids administration, and relapsed on a reduced dose of glucocorticoids, so our treatment strategy changed to total excision combined with postoperative steroid administration, which was different from the literatures. In our study, the duration of follow-up was relatively short and ranged from 2 to 20 months. Follow-up clinical data were available for 17 patients (85%). It was so excited that all patients reached a complete response. We will certainly continue our study as long as we can to determine its long-term prognosis. There have also been reports on malignant transformation in BLEL.[13-15] However, none of the patients exhibited malignant transformation. Further analysis of complicating lymphoma in BLEL is necessary as there is no evidence on its long-term prognosis.

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