Case Report

IgG4-Related Mikulicz's Disease Associated with Thyroiditis: a Case Report and Review of the Literature

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Abstract

Purpose: To report an unusual case of IgG4-related Mikulicz's disease associated with thyroiditis.

Case report: We describe a 25-year-old Chinese man who presented with bilateral, painless swellings of the lachrymal glands, parotid glands, and thyroid nodules. The patient underwent left-sided dacryoadenectomy and the diagnosis of IgG4-related Mikulicz's disease was pathologically confirmed. The size of the right-sided lachrymal gland and parotid glands recovered fundamentally after one month of glucocorticoid therapy.

Conclusion: IgG4-related Mikulicz's disease associated with thyroiditis should be considered in the differential diagnosis of bilateral swellings of lachrymal glands, salivary glands, and thyroid nodules. Surgical excision is recommended in order to treat the tumor and to ensure the pathological diagnosis. Glucocorticoid therapy should be considered in association with surgery after removal. (***Eye Science 2014; 29:47-52***)

Keywords: IgG4-related disease; IgG4-related thyroiditis; Sjogren's syndrome; orbital lymphoproliferative disorders

Introduction

IgG4-related Mikulicz's disease (IgG4-related MD) is a very rare chronic fibrosis disorder of unknown etiology characterized by painless unilateral or bilateral swellings of the lachrymal and salivary glands without visual disturbances[1,2]. Riedel thyroiditis is another member of IgG4-related disease (IgG4-RD). Currently, Google Scholar and the PubMed literature surveys on IgG4-related MD have provided no publications on this condition associated with IgG4-related thyroiditis since the diagnostic criteria of IgG4-RD was initially promoted. Only 2 suspected cases of IgG4-related MD affecting thyroid glands are available in China[3].

Differential diagnosis of IgG4-related MD is difficult, due to similar clinical features with Sjögren's syndrome, orbital tumors, and pseudotumors. Histopathological and immunohistochemical features are considered hallmarks for diagnosis of IgG4-related MD[1,4]. Glucocorticoids are very effective and constitute the mainstay of the treatment.

Herein, we report a Chinese patient diagnosed as IgG4-related MD associated with thyroiditis. To the best of our knowledge, this is the first case report since the diagnostic criteria for IgG4-RD was developed in 2011[5].

Case report

A 25-year-old Chinese male patient referred to the Department of Ophthalmology, First Affiliated Hospital of Guangxi Medical University, in September, 2013. He came for a complaint of non-tender bilateral proptoses and swollen eyelids that had been present for approximately two years, without vision loss. Orbital computed tomography (CT) showed bilateral swellings of the lachrymal glands (Figure 1). Sonographic examinations of the thyroid revealed bilateral thyroid nodules and absence of vascular flow. The patient had undergone bilateral laser-assisted in situ keratomileusis for myopia 4 years previously. He

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had suffered from allergic rhinitis and the symptoms of dry mouth for 2 years, and had smoked 1 packet/d for 5 years. In the past 6 months, he had lost 5 kgs. He had no history of malignant or autoimmune diseases.

Physical examination revealed non-tender bilateral

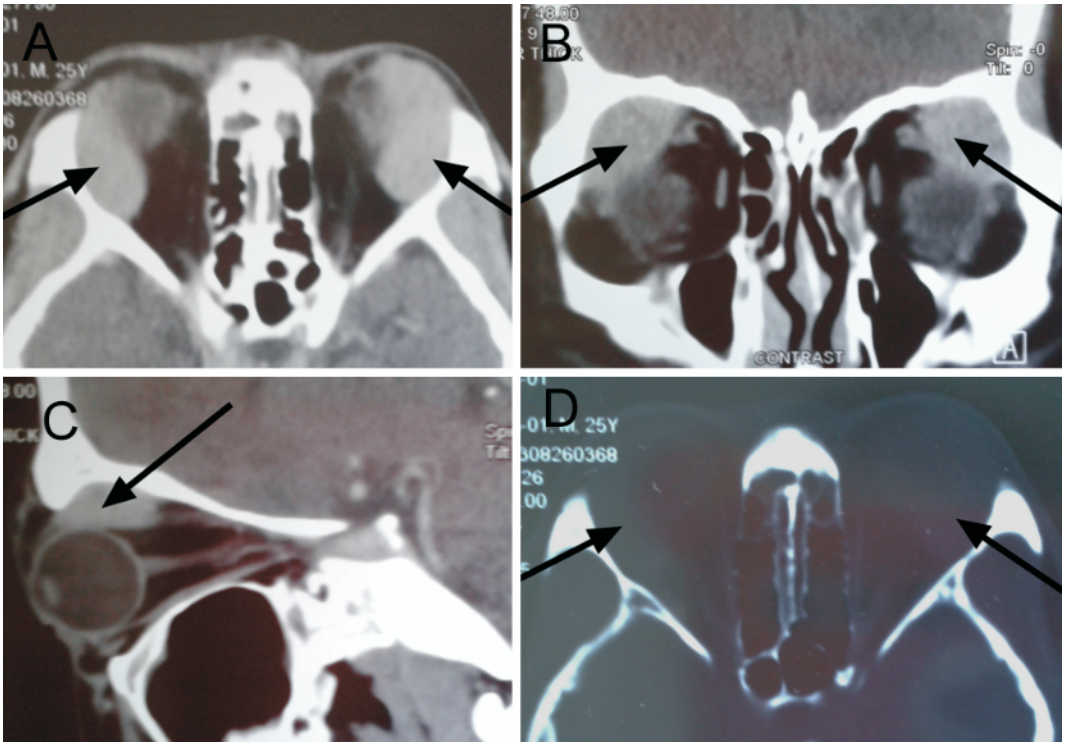

Figure 1 Computed tomography(CT) and contrast-enhanced computed tomography scans of a 25-year-old man with IgG4-related Mikulicz's disease and thyroiditis. In the CT scan, (A) axial view, (B)coronal view and (C) sagittal view (arrows) show bilateral swelling of the lachrymal glands, no hypertrophy of the extraocular muscles, and no compression of the optic nerves; In the contrast-enhanced CT scan, (D) axial view (arrows) shows no enhancement of the lachrymal glands.

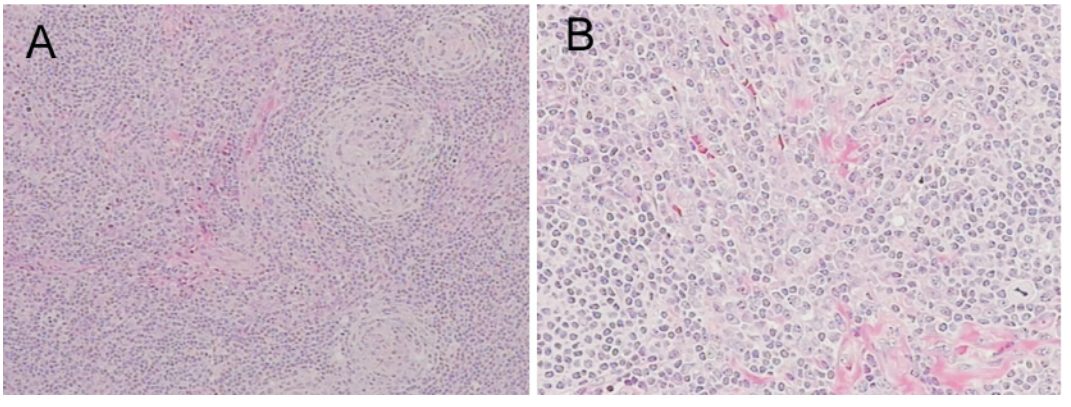

Figure 2 Microscopic sections from the left-sided dacryoadenectomy revealed (A) few atrophic acinar cells and a dense lymphoplasmacytic infiltrate and fibrosis, and (B) a mixed infiltrate of immature plasma cells, mature plasma cells, small lymphocytes and scattered eosinophils in lachrymal gland. hematoxylin-eosin; original magnification: (A)×100, (B)×400.

swellings of lachrymal and salivary glands and symmetric hard mobile thyroid nodules (about 5 mm in size). There was no pathological enlargement of the thyroid glands and cervical lymph nodes. The thyroid nodules were too small to perform FNAC according to the thyroid nodule guidelines[6]. Exophthalmometry

was 17 mm in the right eye and 19 mm in the left eye, with a base of 100 mm. Serum IgG was 14.510 g/L (normal range 11.520~14.220), IgM 0.402 g/L (normal range 0.840~1.320), thyroid function, anti-thyroid peroxidase antibody, anti-thyroglobulin anti body, anti-streptolysin O, rheumatoid factor, anti-nuclear antibody, anti-double-stranded DNA, and anti-centromere antibody were all within normal range.

The patient had undergone left-sided dacryoadenectomy. The size of the mass was 2.7 cm×1 cm×1 cm. The pathology examination revealed a few atrophic acinar cells and a diffuse dense infiltrate of lymphoid cells with lymphoid follicles and fibrosis (Figure 2). A proportion of IgG4/IgG-positive plasma cells >40% was identified on immunostaining, and the T cells in the lesion were positive for CD20, CD3, CD21, and Ki-67. The diagnosis of IgG4-related Mikulicz's disease was identified. The patient was given methylprednisolone (80 mg) for 3 days, followed by tapering to prednisone (40 mg) for 7 days and maintaining at a dosage of 30 mg. The swollen glands reduced to normal sizes in one month postoperatively. Our patient had surgical and glucocorticoid treatment without chemotherapy. By the time this report was completed, the patient had been followed for 5 months without evidence of recurrence.

Discussion

Historical cognition

IgG4-RD is a systemic disease characterized as fibrosclerosis affecting several organs, such as the lachrymal glands, salivary glands, thyroid glands, liver, pancreas, *etc*[5]. Since the first case reported in 1888[7], Mikulicz's disease (MD) had been proposed, which presents as idiopathic, bilateral, painless and symmetrical swellings of the lachrymal, parotid and submandibular glands. In January, 2012, Japanese researchers identified the well-established classification of IgG4-RD after an association of MD was reported with elevated serum IgG4 concentrations[1]. According to the classification, MD was renamed as IgG4-related MD and the disease affecting the thyroid glands was renamed IgG4-related thyroiditis[1].

The debate on nomenclature

In 1990, WHO proposed that MD be renamed benign lymphoepithelial lesion[8], which was characterized by painless enlargement of the lachrymal and salivary glands, histological infiltration of lymphocytes, and the formation of myoepithelial islands within the duct hyperplasia. The etiology and pathogenesis of the disease is hypothesized to involve IgG4[9]. However, whether the benign lymphoepithelial lesion should be renamed IgG4-RD remains controversial. Pathological changes in benign lymphoepithelial lesions do not show specificity for only the myoepithelial islands found in salivary glands and not the lachrymal glands, according to available reports[1]. At present, no diagnostic criteria exist for benign lymphoepithelial lesion, although acknowledged diagnoses are based on the following criteria[10]: 1) symmetric and persistent swelling of the lachrymal glands and either or both of the major salivary glands (parotid and substantival); and 2) the exclusion of other diseases that may mimic this presentation, such as sarcoidosis, viral infection, or lymphoproliferative disorders. The case in this report was considered to be diagnosed as IgG4-related MD rather than benign lymphoepithelial lesion.

Etiology and pathogenesis

IgG4-RD is generally accepted to represent a chronic inflammatory autoimmune disorder. However, the etiologic mechanisms and pathogenesis of IgG4-RD remain obscure, although current evidence suggests that proliferation and infiltration of plasma cells in tissues might be the major underlying mechanism. Recently, predisposing risk factors for IgG4-RD have been found to include the DRB1 * 0405-DQB1 * 0401 haplotype[11], CD4+ and CD8+ cells[12], Th2 and T-regulatory[13] cells, exposure to asbestos[14], allergy history[15], *etc.*

Pathogenetic characteristics

Japanese prevalence studies identified that 21.6% of orbital lymphoproliferative disorders were related to IgG4 in Japan[4]. The median age of IgG4-related MD was in the range of 55–65 years, and was extremely uncommon in people younger than 20 years of age[4]. No gender differences were noted in IgG4-related MD, which differed from the male dominance in IgG4-RD[4] and female dominance in benign lymphoepithelial lesion[9]. However, no similar prevalence study has been published in China or in any other countries. The incidence of IgG4-related thy-

roiditis varies between 0.04% and 0.30%, estimated from a large series of thyroidectomies[16].

Clinical examination

Typical symptoms of IgG4-related MD are symmetric, continuous, painless swellings of the lachrymal and/or salivary glands, with low incidence of dry eye, dry mouth, and vision loss. Apparent proptoses, ocular shifts to the nasal side, and limitation in eye movements can occur. Refractive error and vision loss appear when severe oppression exists. Sonographic examinations reveal a homogeneous and circumscribed mass. Computed tomography scan shows a circumscribed, hypodense mass in the lachrymal glands, but no accompanying bone destruction. Obliterative phlebitis has been identified as a histological feature of IgG4-RD; but it is rare in IgG4-related MD[17]. IgG4-related thyroiditis has no pathognomonic clinical features, presenting with a goiter of remarkably hard consistency, generally associated with a series of symptoms of oppression, while nodular goiter shows multiple soft adenomatous nodules without oppression. Sonographic examinations can distinguish IgG4-related thyroiditis from most malignant nodules. The hypoechoic nodules and complete absence of vascular flow are diagnosed as IgG4-related thyroiditis, whereas most malignant nodules show intense vascularization. Magnetic resonance imaging features of IgG4-related thyroiditis report a pathognomonic homogeneous hypointensity on both T1- and T2-weighted images, compared with hyperintensity characteristic of all other thyroid diseases[16].

Diagnosis

The comprehensive clinical diagnostic criteria for IgG4-RD which are suitable for all organs affected is definitive in patients with[5]: (1)organ enlargement, mass or nodular lesions, or organ dysfunction; (2) a serum IgG4 concentration >135 mg/dl; and (3) histopathological findings of>10 IgG4 cells/HPF and an IgG4+/IgG+cell ratio>40%. A diagnosis of IgG4-RD is definite in patients who fulfill criteria(1), (2) and (3), and is probably satisfied with both (1) and (3), and possibly qualified with both (1) and (2). In recent studies, serological features except serum IgG4 reveal no specificity. A few patients with IgG4-RD had positive serology for eosinophils in complete blood count and antinuclear antibody[18], and negative serology for IL-6, CRP and serum tumor marker[19]. No laboratory data are peculiar to IgG4-related thyroiditis. As noted, most patients with IgG4-related thyroiditis have normal triiodothyronine, thyroxine, and thyrotropin concentrations and antibody-negative results at the early stage, which differs from other forms of thyroiditis that exhibit abnormal thyrotropin concentrations. Hypothyroidism occurs if thyroid tissues are completely replaced by fibrous tissues[16]. No specific diagnostic criteria have been established for IgG4-related thyroiditis. More studies are needed to identify these criteria.

Differential diagnosis

IgG4-related MD is probably misdiagnosed as Sjögren's syndrome, orbital lymphoproliferative disorders, and idiopathic orbital inflammatory disease. Similar clinical features make the differential diagnosis of this syndrome from Sjögren's syndrome difficult, but less dryness of the eyes and mouth, negative serology of antinuclear antibody, and histopathological examinations can distinguish them[20]. IgG4-related MD, orbital lymphoproliferative disorders and idiopathic orbital inflammatory disease present similar imaging features, but differ clinically, histopathologically, and immunohistochemically[4]. IgG4-related thyroiditis is probably misdiagnosed as thyroid carcinoma and nodular goiter that can be differentiated according to thyroid function, ultrasonography, and biopsy of the thyroid glands[16]. Meanwhile, taking the affected multiorgans into consideration, the occurrence of thyroid disease is obviously unlikely to have arisen by chance in this disease entity.

Treatment and prognosis

At present, no treatment criterion exist for IgG4-related MD[1]. The surgical treatment is effective as swelling of lachrymal glands is removed. Glucocorticoid therapy is effective but may be followed by relapses and side effects. Corticosteroid therapy is a more classic treatment and is beneficial when the pathology is identified. In Japan, two glucocorticoid treatment regimens have been suggested: the standard of care is prednisone (0.6 mg/kg) for 2 to 4 weeks followed by tapering to 5 mg/d over 3 to 6 months. Prednisone therapy is then maintained at a dosage of 2.5 to 5 mg/d for about 3 years[2]. The ad-

justment of the dose and course of glucocorticoid treatment is based on serology and imaging examinations. Immunomodulating agents have also been suggested, such as azathioprine, methotrexate, tripterygium wilfordii, *etc.* Rtuximab has been evaluated in patients with IgG4-RD in refractory or inflammatory condition[21], but palindromia developed in 3 years[22]. No evaluation of Rtuximab for IgG4-related MD has been conducted.

The patients with IgG4-related thyroiditis respond swiftly to glucocorticoid if it is given early. Thyroxine has been the recommended treatment for IgG4-related thyroiditis to control the condition of hypothyroidism[23]. Tamoxifen has proved to be effective especially in patients who do not respond to glucocorticoid therapy[24]. The therapeutic response of IgG4-RD patients regarding various organs treated with Tamoxifen is not known.

IgG4-related MD and thyroiditis have a good prognosis. Recurrence or malignant transformation is rare[2]. Sato et al[17]. found a few IgG4-related MD patients that tended to develop malignant B cell lymphoma in the long-term follow-up of IgG4-RD. Therefore, in cases of deterioration, long-term follow-up is absolutely indispensable.

Conclusion

Thyroid associated IgG4-related MD remains rare. Due to the difficulty of this diagnosis, we present this case to increase awareness of the diagnosis upon presentation of symmetrical swelling of the lachrymal and salivary glands and thyroid nodules, meanwhile highlighting the pathological and serological features that can aid in the correct diagnosis. Surgical excision is considered the first line of treatment in symptomatic cases and to ensure the pathological diagnosis. Glucocorticoid therapy should be considered after surgical removal. Careful follow-up is needed in cases with multiorgan involvement.

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