



Case Report

Immunoglobulin G4-related chronic sclerosing dacryoadenitis

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ABSTRACT

A 47-year-old man had recurrent, episodic swelling of the right upper eyelid for about 2 years. There was a progressively enlarging, palpable mass over the superotemporal region of the right orbit without tenderness, local heat, or erythema. Ophthalmic examination revealed proptosis and ptosis of the right eye without vision decrease or ocular motility disturbance. An orbital computed tomography scan showed a huge lacrimal gland causing inferior displacement of the globe with proptosis. An anterior orbitotomy was done, and the pathological analysis revealed marked lymphoplasma cell infiltration with mild to moderate fibrosis surrounding the lobules of the lacrimal glands. No lymphoepithelial islands were seen. Immunohistochemically, about 40–50% of the immunoglobulin G (IgG)-positive cells were IgG4 positive, and the ratio of serum IgG4 to total IgG was 80.9%, compatible with a diagnosis of IgG4-related chronic sclerosing dacryoadenitis. IgG4-related chronic sclerosing dacryoadenitis may be a sign of Mikulicz disease, an IgG4-related systemic disease. Determination of the serum IgG4 concentration and IgG4/IgG ratio is necessary for clinical diagnosis. Long-term follow-up is also mandatory because of the possible complication of lymphoma.

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1. Introduction

Many orbital diseases can invade the lacrimal gland. In adults, infection, inflammation, and benign and malignant epithelial tumors can occur in the lacrimal gland fossa [1]. Clinical symptoms and signs combined with a pattern of neuroimaging abnormalities on computed tomography or magnetic resonance imaging are often very helpful in reaching the correct diagnosis. Those who present with a unilateral lacrimal gland mass without signs of inflammation may need surgical biopsy for definite diagnosis.

2. Case report

A 47-year-old man had multiple episodes of swelling of the right upper eyelid for about 2 years. There was a progressively enlarging, non-tender mass over the superotemporal region of the right orbit.

His best corrected visual acuity was 20/20 in both eyes. Proptosis and ptosis were noted in the right eye, and no ocular motility

disturbance was found. Orbital computed tomography without enhancement showed a prominent lacrimal gland with displacement of the globe and proptosis in the right eye (Fig. 1).

We performed an anterior orbitotomy, and the pathological results revealed the infiltration of heavy lymphoid cells with prominent germinal center formation. The lobular architecture of the lacrimal gland was still preserved, and there was marked infiltration of lymphoplasma cells with mild to moderate fibrosis surrounding the lobules of the lacrimal glands. No lymphoepithelial islands were seen (Figs. 2A and 2B). An immunohistochemical stain showed that the lymphocytes were polyclonal and composed of T cells (positive for CD3) and B cells (positive for CD20) (Figs. 2C and 2D). Immunoglobulin G4 (IgG4)-positive cells accounted for about 40–50% of the total IgG-positive cells (Figs. 2E and 2F). IgG4-related chronic sclerosing dacryoadenitis was impressed. The serum level of IgG was 1570 mg/dL (reference range, 1419.63 ± 279.84 mg/dL) and IgG4 was 1270 mg/dL (reference range, 3–201 mg/dL). The ratio of serum IgG4 to IgG (reference range, 3–6%) was 80.9%. Serum protein electrophoresis showed polyclonal gammopathy. IgG4-related chronic sclerosing dacryoadenitis was diagnosed, and long-term follow-up was advised because of the possible complication of lymphoma.

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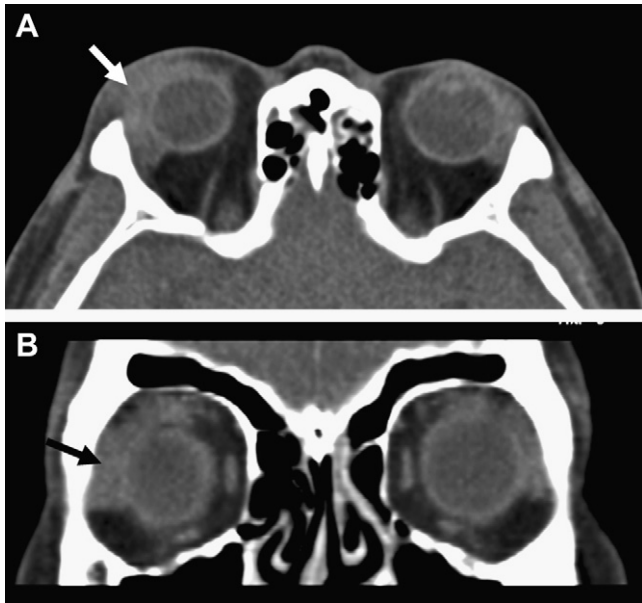


Fig. 1. (A) Axial view on orbital computed tomography (CT) showing a prominent right lacrimal gland (white arrow). (B) Coronal view on the orbital CT also shows gland enlargement (black arrow).

3. Discussion

Chronic dacryoadenitis represents any lacrimal gland inflammation in which there is hypertrophy and enlargement of the gland [2]. It usually develops insidiously, and as a general rule, causes no pain. Chronic dacryoadenitis is usually caused by inflammatory disorders, including idiopathic orbital inflammation, sarcoidosis, thyroid ophthalmopathy, Sjogren's syndrome, and benign lymphoepithelial lesions; it may also be caused by syphilis and tuberculosis. Neoplastic lesions may simulate chronic dacryoadenitis and must be considered in the differential diagnosis. Although the clinical diagnosis of chronic dacryoadenitis is relatively easy to establish, the actual etiology may be more difficult to identify; in many instances, it is necessary to biopsy the gland to verify the diagnosis [2]. Treatment can then be directed toward the underlying condition. We report a proven case of IgG4-related chronic sclerosing dacryoadenitis. Its presentation was similar to, but did not fully satisfy, the criteria of Mikulicz disease (MD).

MD is characterized by idiopathic, bilateral, painless, symmetrical swelling of the lacrimal and salivary glands. It was first reported in 1888 by Johann von Mikulicz–Radecki [3] and has been considered a part of primary Sjogren's syndrome (SS) because of its similarity with the pathological findings in Morgan and Castleman's report in 1953 [4]. However, this concept has been changed by recent studies; Tsubota et al. [5] reported that lacrimal gland acinar cells in cases with MD maintained their function and were not programmed for cell death, and sicca syndrome was not observed in MD patients. Yamamoto et al. [6,7] disclosed that MD had few autoimmune reactions and good responsiveness to glucocorticoids, leading to the recovery of the gland function. In their view, MD represented an IgG4-related systemic disease that differed substantially from SS. The histopathological features of IgG4-related sclerosing diseases are dense lymphoplasmacytic infiltration intermixed with fibrosis, obliterative phlebitis, and prominent infiltration of IgG4-positive

plasma cells [8]. By comparison, few IgG4-positive cells were seen in the tissues of patients with typical SS [7,9]. IgG4 is the rarest subclass of IgG in healthy subjects. Serologically, IgG4 is elevated in patients with IgG4-related diseases; in these patients, rheumatoid factor and antinuclear, anti-SS-A/Ro, and anti-SS-B/La antibodies are significantly lower than those in patients with typical SS [9].

It is still controversial whether a unilateral lesion of the lacrimal glands or swelling of the lacrimal glands alone without the involvement of the salivary glands eventually progresses to MD. Yamamoto et al. [7] experienced a case of bilateral involvement of only the lacrimal glands. They had the impression that some of the pathogenic features diagnosed in Küttner's tumor (chronic sclerosing sialadenitis) or chronic dacryadenitis are the same as those in MD. Cheuk et al. [10] reported six cases of IgG4-related chronic sclerosing dacryoadenitis, one of which involved a unilateral lacrimal gland and two of which involved the bilateral lacrimal glands without the swelling of the salivary glands.

Nowadays, MD is recognized as one of the new clinical entities [6,9,11]—the IgG4-related systemic disease (IgG4-positive multiorgan lymphoproliferative syndrome [9])—which involves one or more of the exocrine or extranodal sites with lymphoplasmacytic infiltrates and sclerosis, accompanied by an elevated IgG4 titer in the serum. Multiple diseases have been reported, including autoimmune pancreatitis; sclerosing cholangitis; Küttner's tumor; inflammatory pseudotumor of the lung, liver, and breast; retroperitoneal and mediastinal fibrosis; interstitial nephritis; autoimmune hypophysitis; and many other inflammatory conditions [9,11]. Dense infiltration of IgG4-positive plasma cells and elevated levels of serum IgG4 in these cases suggest that IgG4 plays a major role in the pathogenesis. However, the etiology and mechanism of development of IgG4-positive cells are still unknown. In Zen et al.'s [12] study, T helper 2 and regulatory immune reactions were upregulated in the affected tissues in cases of autoimmune pancreato-cholangitis and related disorders. Akitake et al.'s [13] study suggested the involvement of excessive T helper 2 responses to intestinal microflora in the development of IgG4-related sclerosing disease. In Kamisawa and Okamoto's [11] view, given the preponderance of the disease among elderly men and the marked, dramatic response to oral steroid therapy, the pathogenesis of autoimmune pancreatitis may not involve an autoimmune mechanism but might be caused by other mechanisms, such as an allergic reaction.

MD is mainly treated by the administration of steroids [7]. This leads to rapid improvement in glandular swelling as well as in lacrimal and salivary secretions. Glucocorticoid administration has also been shown to improve hypergammaglobulinemia [7]. According to Takahira et al.'s [8] experience, when steroid treatment was undesirable, excision of enlarged lacrimal glands (occasionally bilateral) was an alternative treatment for MD.

Cheuk et al. [14] reported three cases of ocular adnexal lymphoma arising in IgG4-related chronic sclerosing dacryoadenitis. One case was high-grade follicular lymphoma and the other two cases were extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type. In their series, the frequency was 10% among 30 cases of IgG4-related chronic sclerosing dacryoadenitis, but this figure may have been overestimated. However, the association with malignant lymphoma is an important issue in the clinical management of these patients. Therefore, long-term follow-up is essential in patients with IgG4-related chronic sclerosing dacryoadenitis for early detection of lymphoma transformation.

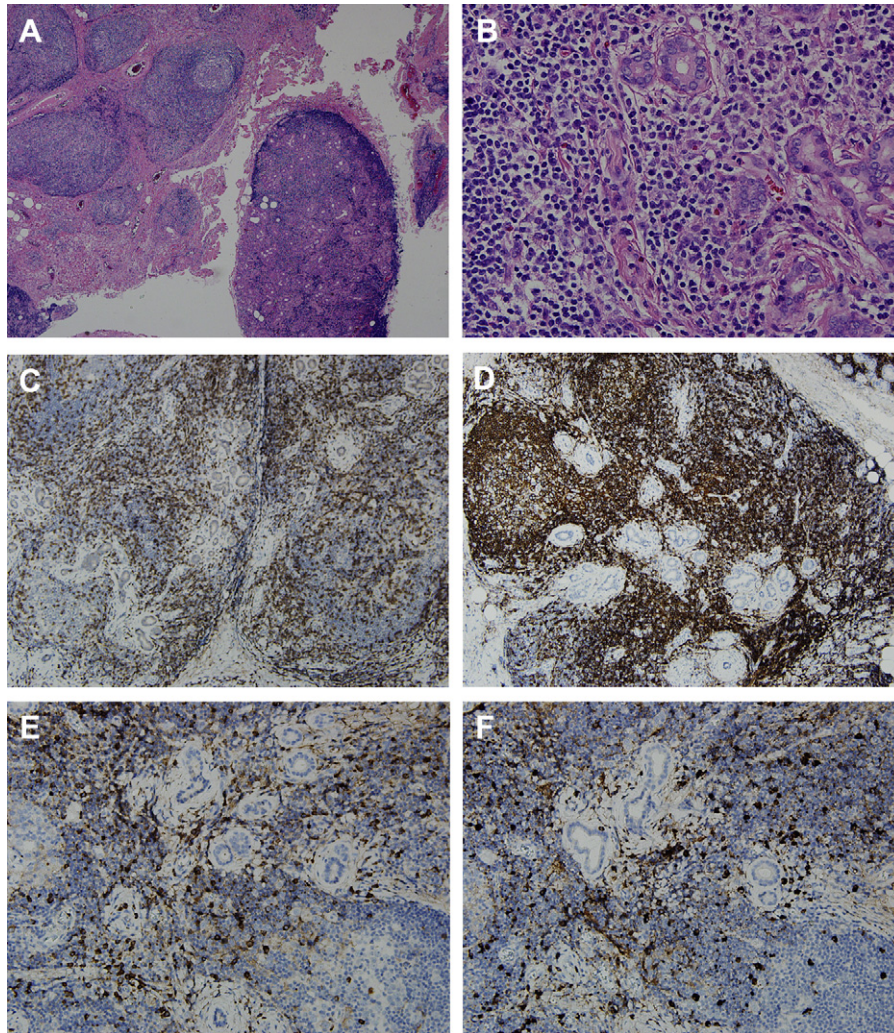


Fig. 2. Histopathological pictures of the lacrimal gland mass. Hematoxylin and eosin stain with low magnification (A, magnification 40 \times) and high magnification (B, magnification 400 \times) showing heavy lymphoid infiltration with prominent germinal center formation. The lobular architecture of the lacrimal gland is still preserved. Moreover, there is marked infiltration of lymphoplasmacytic cells (green arrows in B indicate plasma cells) with mild to moderate fibrosis surrounding the lobules of the lacrimal glands. Immunohistochemical staining using anti-CD3 antibody (C: magnification, 100 \times) and anti-CD20 antibody (D: magnification, 100 \times) reveals that the lymphocytes are polyclonal and composed of T cells (positive for CD3) and B cells (positive for CD20). Immunohistochemical staining using anti-IgG antibody (E: magnification, 200 \times) and anti-IgG4 antibody (F: magnification, 200 \times) showing IgG-positive cells and IgG4-positive cells. IgG = immunoglobulin G; IgG4 = immunoglobulin G4.

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