

## A case of immunoglobulin G4-related chronic sclerosing sialadenitis and dacryoadenitis associated with tuberculosis

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**Abstract** We describe a 64-year-old woman with chronic sclerosing sialadenitis and dacryoadenitis, which developed during treatment for cervical lymph node tuberculosis. Anti-tuberculosis treatment did not improve the swelling in the lacrimal and submandibular glands, and a biopsy specimen of the lacrimal gland showed inflammation, with abundant lymphoid follicles with fibrosis and granuloma without caseous necrosis. Immunohistological examination of a repeat biopsy specimen showed abundant immunoglobulin (Ig) G4-positive plasma cell infiltration. Corticosteroid therapy improved the salivary gland swelling without

reactivation of the tuberculosis. This case suggests that an abnormal immunological reaction to tuberculosis may be one of the etiological candidates for IgG4-related disease.

**Keywords** Immunoglobulin G4 (IgG4) · Mikulicz's syndrome · Sclerosing dacryoadenitis · Sclerosing sialadenitis · Tuberculosis

### Introduction

Mikulicz's disease (MD) is a chronic inflammatory disorder of unknown etiology [1]. For many years, MD and Sjögren's syndrome had been considered to be the same clinical entity [2]. However, recent advances have revealed that these two disorders are histopathologically extremely different with respect to immunoglobulin G4 (IgG4) involvement [3].

Mikulicz's original patient had symmetrical swelling of the lacrimal, parotid, and submandibular glands [1], and recently proposed diagnostic criteria for MD include bilateral swelling of the lacrimal and salivary glands [3]. However, Morgan reported that more MD cases were confined to the salivary glands in the absence of lacrimal gland swelling, and slightly more than half of cases showed unilateral involvement [4]. In this respect, IgG4-related chronic sclerosing sialadenitis [5] and/or dacryoadenitis [6] encompasses a wider disease spectrum than Yamamoto's criteria for MD, with the former including the latter.

Recently, many inflammatory conditions have been reported to have common histological features of abundant IgG4-positive plasma cell infiltration with fibrosis, and the concept of IgG4-related disease was proposed [5–8].

In this report, we describe a case of IgG4-related chronic sclerosing sialadenitis and dacryoadenitis possibly

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associated with latent or reactivated tuberculosis infection, and we discuss the possible etiological involvement of tuberculosis infection in IgG4-related disease.

## Case report

### Patient

A 64-year-old woman was admitted to our hospital because of a swelling in her right lacrimal gland. Three years before admission, she had noticed swelling of her right cervical lymph nodes. Cervical ultrasound showed swelling in the right cervical and right supraclavicular lymph nodes and bilateral swelling in the submandibular lymph nodes. In addition, a small swelling in the left cervical lymph nodes was detected. A computed tomography (CT) scan of her chest showed neither lung lesions suggestive of tuberculosis nor hilar or mediastinal lymph node swelling. Histological examination of the right cervical lymph node revealed epithelioid granuloma with multinucleated giant cells and caseation necrosis compatible with tuberculosis. Although *Mycobacterium* spp. were not detected in the lymph nodes, reactivation of latent primary tuberculosis was highly suggested, and anti-tuberculosis therapy with isoniazid, 300 mg/day, rifampicin, 450 mg/day, and ethambutol, 750 mg/day, was started and continued for 8 months. One month after she had started the anti-tuberculosis therapy, the swelling in her right supraclavicular lymph nodes disappeared. Two months later, swelling in the right lacrimal gland appeared. Three months after the initiation of triple therapy for tuberculosis, the size of the left cervical lymph node had increased, in spite of continuing anti-tuberculosis therapy. Nineteen months before entry, a mass in her right lacrimal gland had been resected because of a gradual increase in size. Histological examination revealed that it was not lymphoma but inflammation with abundant lymphoid follicles with fibrosis. There were scattered eosinophils and obliterative phlebitis. Granuloma without caseous necrosis was also noted (Fig. 1). Despite the surgical removal of this mass, the swelling in the right lacrimal gland gradually recurred, and she consulted our hospital for further examination. At the time of her admission, the bilateral submandibular glands were also swollen. Laboratory study revealed a white blood cell count of  $4,500/\text{mm}^3$ , with a slightly increased percentage of eosinophils (7.9%), a platelet count of  $189,000/\text{mm}^3$ , and a hemoglobin value of 13.9 g/dl. C-reactive protein (CRP) level was 0.1 mg/dl, and erythrocyte sedimentation rate was 8 mm/h. Findings for rheumatoid factor, anti-nuclear antibodies, anti-Sjögren's syndrome A (anti-SSA) antibodies and anti-Sjögren's syndrome B (anti-SSB) antibodies were all negative. Serum IgG level was 1,820 mg/dl, including 486 mg/dl of IgG4

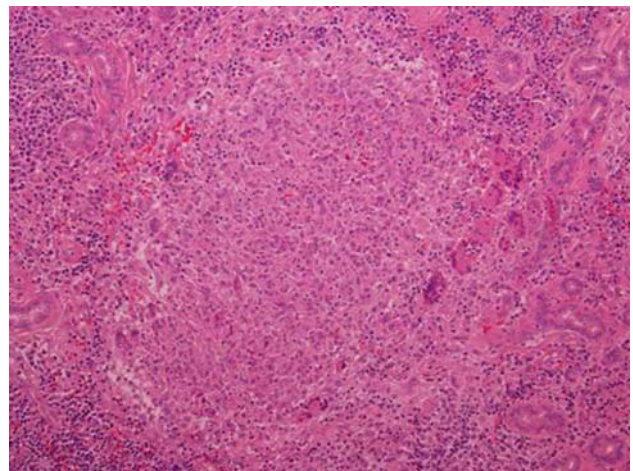


**Fig. 1** A biopsy specimen from the right lacrimal gland. Granuloma without caseous necrosis is noted. Hematoxylin and eosin (H&E)  $\times 100$

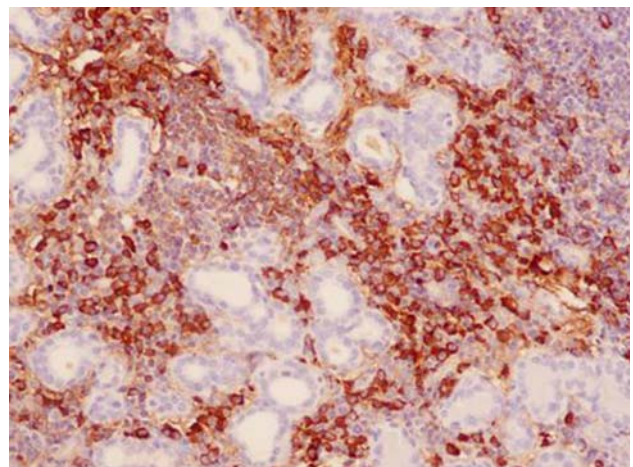


**Fig. 2** IgG4 Immunostaining of biopsy specimen from right lacrimal gland. Abundant IgG4-positive plasma cells have infiltrated around the lacrimal glands.  $\times 200$

(26.7% of IgG), IgA 221 mg/dl, IgM 59 mg/dl, and IgE 90 U/ml. Tuberculin skin test result was positive, and result of QuantiFERON<sup>®</sup>-TB gold test (Cellestis Ltd., Australia) was also positive, with 8 IU/ml of interferon gamma (IFN- $\gamma$ ) response to the early secreted antigenic target 6 kDa (ESAT-6) protein. However, findings from repeated smears and cultures for *Mycobacterium* spp. and the polymerase chain reaction (PCR) test for tuberculosis were all negative. To clarify whether the lacrimal gland swelling was related to tuberculosis, we repeated the biopsy of the right lacrimal gland. Histological examination showed severe lymphoplasmacytic infiltrates with fibrosis composed of abundant IgG4-positive plasma cells (Fig. 2). No granuloma was detected. These findings were compatible with IgG4-related chronic sclerosing sialadenitis and dacryoadenitis, and administration of 30 mg/day of corticosteroid was started.

Isoniazid was also administered, for tuberculosis prophylaxis, and the bilateral swelling in the submandibular gland decreased without reactivation of tuberculosis.

## Discussion

In this report we have described a case of IgG4-related chronic sclerosing sialadenitis and dacryoadenitis with increased serum IgG4 levels, in which latent or reactivated tuberculosis infection was highly suggested.

Our case did not fulfill the criteria for MD, proposed by Yamamoto et al., i.e., (1) persistent (for more than 3 months) symmetrical swelling of more than two lacrimal and major salivary glands; (2) prominent mononuclear infiltration of lacrimal and salivary glands; and (3) exclusion of other diseases presenting glandular swelling, such as sarcoidosis and lymphoproliferative disease [3], because our patient had only unilateral swelling in the lacrimal gland and bilateral swelling of the submandibular glands. However, Morgan reported that more MD cases were confined to the salivary glands in the absence of lacrimal gland swelling, and slightly more than half of cases showed unilateral involvement [4]. Thus, although our case did not strictly fulfill the diagnostic criteria of Yamamoto et al., it did meet those of Morgan.

Histological analysis of a lacrimal gland revealed IgG4 producing plasma cell infiltration with fibrosis and partial granuloma formation with giant cells. In addition, reactivation of latent tuberculosis infection was highly suggested, because histological analysis of the cervical lymph node had revealed granuloma with caseation necrosis. Decreased size of the supraclavicular lymph node after anti-tuberculosis therapy also supported reactivation of tuberculosis. Several reports are available about lacrimal gland granuloma in patients with sarcoidosis [9] or Crohn's disease [10]. Tuberculous dacryoadenitis is also known as a disease with lacrimal gland granuloma, though it is a very rare condition [11]. However, granuloma has not been reported in MD. In our case, neither sarcoidosis nor Crohn's disease was detected. These findings suggest that some relationship might have existed between lacrimal gland inflammation with IgG4-positive plasma cell infiltration and tuberculosis in this patient.

After the original description of MD, many cases of enlargement of the lacrimal or salivary glands resembling MD were accumulated. However, while the etiology of MD remains unknown, it had been recognized that many systemic diseases such as leukemia, lymphoma, sarcoidosis, and tuberculosis can also induce similar bilateral swelling of the lacrimal and salivary glands, and systemic disease associated with MD-like symptoms were separated as 'Mikulicz's syndrome' [12]. In this respect, our case might be considered as Mikulicz's syndrome associated with

tuberculosis. The relationship between Mikulicz's syndrome associated with tuberculosis and tuberculous dacryoadenitis is not well recognized, and tuberculous dacryoadenitis is usually unilateral [11]. Although no report is available about the relationship between Mikulicz's syndrome associated with tuberculosis and IgG4, our case suggests that tuberculosis-associated Mikulicz's syndrome shares the same immunopathological findings with MD.

In association with host defenses against tuberculosis, activation of T helper (Th)1 cells and production of Th1-associated cytokines, such as IFN- $\gamma$  and interleukin-12 (IL-12), are critical [13]. However, recent reports suggest that Th2 activation may also be elicited by tuberculosis, resulting in increased IgE production [14]. In particular, the fact that successful treatment for tuberculosis reduces serum IgE concentration [15] supports this hypothesis. IgG4 is also produced under the condition of Th2 activation [16]. The underlying mechanism in our case can be explained by latent or reactivated tuberculosis inducing Th2 activation, resulting in IgG4-related MD.

Although the clinical entity of IgG4-related disease is widely accepted now, and many cases have been accumulated [5–8], the etiology of IgG4-related disease is still unknown. In our case, the clinical and histological features were those of typical IgG4-related disease, while the strong T cell response to the mycobacterial antigen, ESAT-6, shows that this patient was in an immunologically active state against *M. tuberculosis*. In addition, granuloma was not only detected in the cervical lymph node but also in the lacrimal gland, where IgG4-positive plasma cell infiltration was noted. These findings suggest a causal link between IgG4-related disease and tuberculosis as a possible pathogen that can induce IgG4-related disease through an allergic mechanism. Further analyses of a larger number of cases are needed to clarify whether tuberculosis plays a significant pathogenetic role in IgG4-related disease.

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