

# Mikulicz's Disease with Progressively Transformed Germinal Centers-type Immunoglobulin G4-related Lymphadenopathy Mimicking Sjögren's Syndrome

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Immunoglobulin G4-related disease (IgG4-RD) is a systemic disease, and lymphadenopathy is frequently observed in these patients. Among the 5 subtypes of IgG4-related lymphadenopathy, progressively transformed germinal centers (PTGC)-type IgG4-related lymphadenopathy possesses a unique characteristic that differentiates it from the other 4 subtypes. Here, we report on a rare case of PTGC-type IgG4-related lymphadenopathy accompanying Mikulicz's disease. A 39-year-old female complained of a left cervical mass and bilateral upper eyelid hypertrophy. The serum level of IgG4 was elevated, and computed tomography showed enlargement of the bilateral lacrimal and submandibular glands and left cervical lymph node. Excisional biopsy of a submandibular gland and cervical lymph node was performed, and the histopathologic findings revealed Mikulicz's disease accompanied by PTGC-type IgG4-related lymphadenopathy. After treatment of the patient with oral prednisolone and azathioprine, the patient's appearance improved. To the best of our knowledge, no case of PTGC-type IgG4-related lymphadenopathy has been previously reported in Korea. (*J Rheum Dis* 2015;22:395-400)

**Key Words.** Immunoglobulin G4-related lymphadenopathy, Progressively transformed germinal centers, Immunoglobulin G4-related disease, Mikulicz's disease

## INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a novel chronic inflammatory disease, which was first brought into attention in 2000. It is characterized by lymphoplasmacytic infiltrate, fibrosis with elevation of the serum IgG4 level, and abundant infiltration of IgG4-positive plasma cells to the internal organs [1,2]. IgG4-RD is a systemic disease that can involve almost all organs, including the pancreas, bile ducts, gallbladder, liver, stomach, salivary glands, lacrimal glands or orbit tissues, kidney, lung, lymph nodes, meninges, pituitary gland, aorta, breast, prostate, thyroid gland, pericardium, pleura, mesentery, retro-peritoneum, peripheral nerves, and skin [2,3]. IgG4-related lymphadenopathy can be divided into

5 types: multicentric Castleman disease-like, reactive follicular hyperplasia-like, interfollicular hyperplasia-like, progressively transformed germinal centers (PTGC)-type, and inflammatory pseudotumor-like [4]. Among these, no case of PTGC-type IgG4-related lymphadenopathy has yet been reported in Korea. Here, we report a rare case of PTGC-type IgG4-related lymphadenopathy accompanying Mikulicz's disease, which involved both the lacrimal and salivary glands.

## CASE REPORT

A 39-year-old female was admitted to our hospital with chief complaints of a left cervical mass and bilateral upper eyelid hypertrophy that had been progressing for 4 years.

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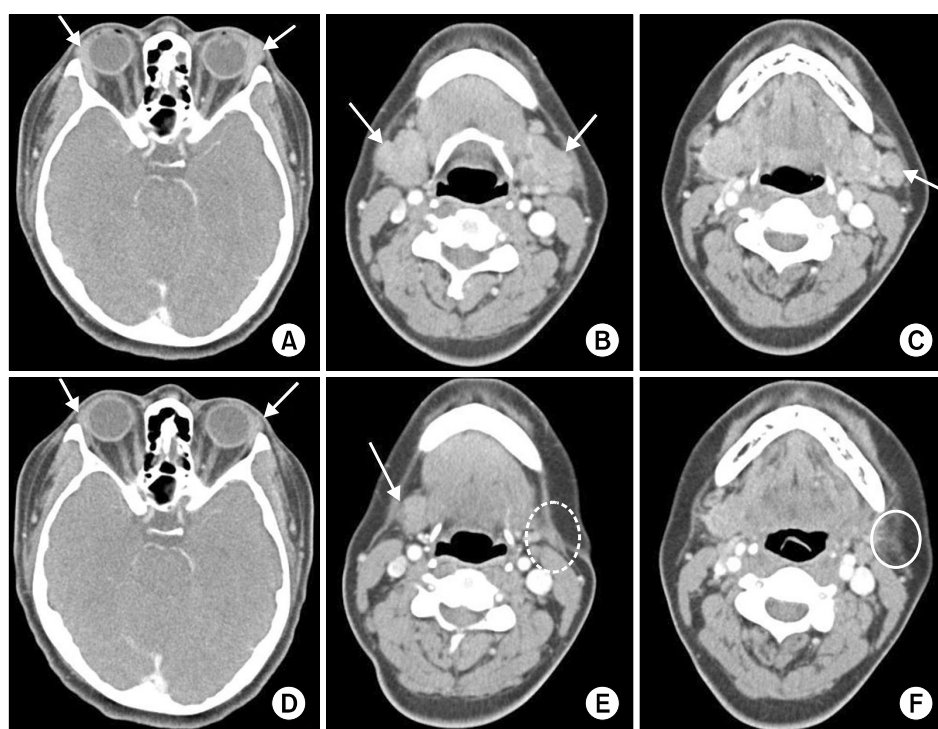
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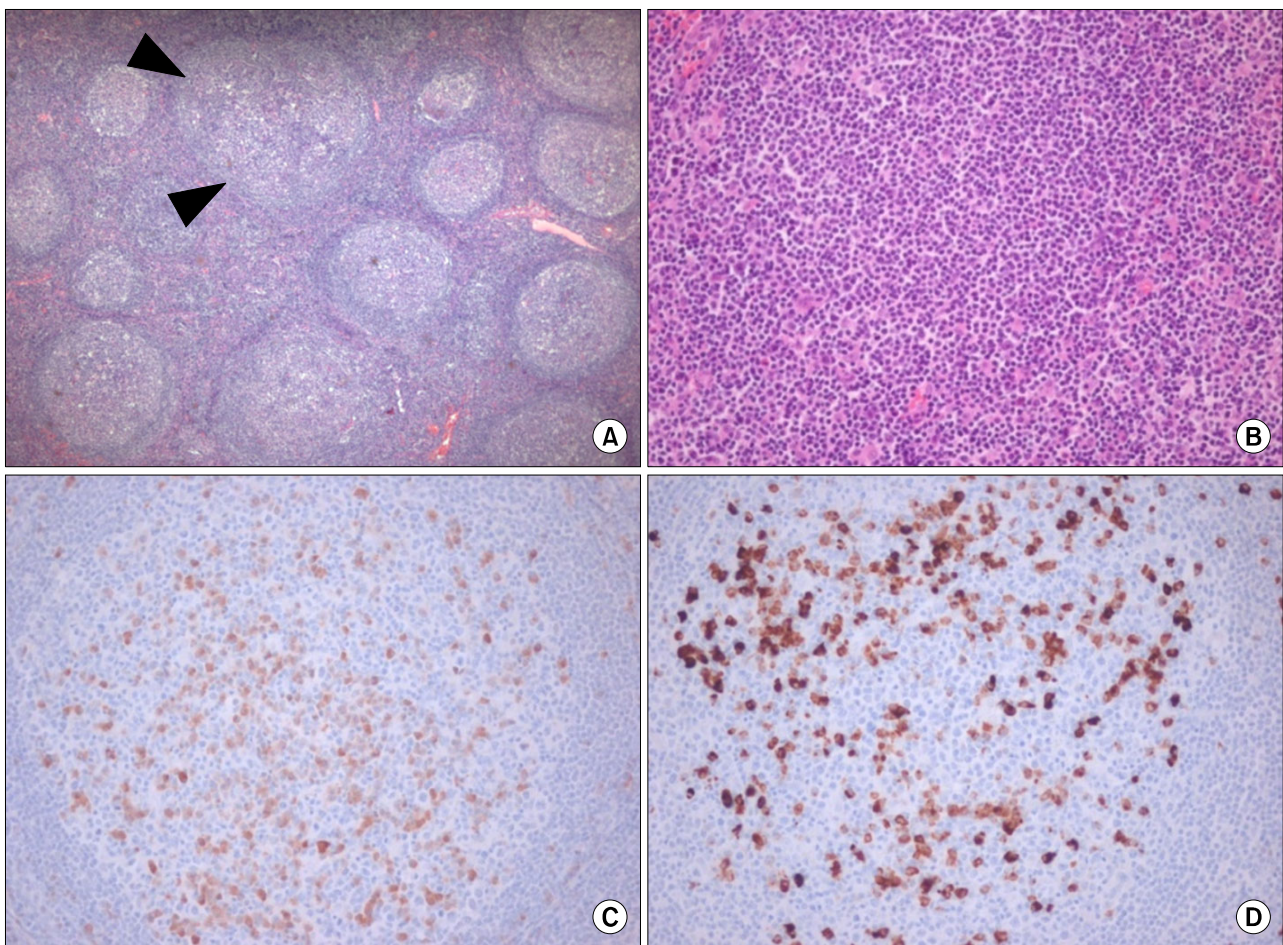
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She had a history of treatment with 2 mg methylprednisolone, 300 mg hydroxychloroquine, and 7.5 mg methotrexate for Sjögren's syndrome at another hospital 4 years earlier. Two years ago, she presented to our hospital with a chief complaint of pain at multiple sites. A 1.7-cm left cervical lymphadenopathy was observed upon cervical contrast-enhanced computed tomography (CT). Compared to the CT findings from the other hospital 4 years ago, no size change in the left cervical lymphadenopathy was observed. Moreover, a 3.8-cm right axillary lymphadenopathy was found upon CT, and an excisional biopsy was performed at that time. The biopsy results indicated reactive follicular hyperplasia with PTGC. Thereafter, the patient was followed-up conservatively for 1 year. However, as the aforementioned chief complaints progressed, she was consequently readmitted. At the time of admission, the patient showed blood pressure 120/70 mmHg, pulse 68 beats/min, respiration rate 20 breaths/min, and temperature 36.6°C, with clear consciousness. Swelling of the bilateral upper eyelids and enlargement of left cervical lymph nodes were observed. All other physical examination findings were unremarkable. The laboratory findings revealed that the complete blood cell count, blood coagulation test, and erythrocyte sedimentation rate were normal. The various biochemical and urine test results, and the C-reactive protein (CRP), C3, and C4 levels were also normal. Antinuclear and an-

ti-DNA antibodies were negative, and the levels of Ig were normal for IgE (70.1 IU/mL; normal range: <100 IU/mL), IgA (228.0 mg/dL; normal range: 70 to 400 mg/dL), IgM (90.0 mg/dL; normal range: 40 to 230 mg/dL), and IgG (1,178 mg/dL; normal range: 700 to 1,600 mg/dL). However, the IgG4 subclass was greatly increased to 304.6 mg/dL (normal range: 3.9 to 86.4 mg/dL). Upon cervical contrast-enhanced CT, slight enlargements of the bilateral lacrimal and submandibular glands were observed (Figure 1A and 1B), with not much difference in the left cervical lymphadenopathy noted compared to the CT results from 2 years ago (Figure 1C). Left submandibular gland and left cervical lymph node excisional biopsy was performed, and IgG/IgG4 immunohistochemical staining was performed on the above specimens as well as those previously obtained from the right axillary lymph node. In the cervical and axillary lymph nodes, round or oval follicles with a diameter 2 to 3 times larger than other reactive follicles were found (Figure 2A). The IgG4+/IgG+ plasma cell ratio was 90% and the IgG4+ plasma cells were counted as 180/high power field (HPF) (Figure 2C and 2D). Only a small number of IgG4+ plasma cells were present in the interfollicular zone, with most residing in the germinal centers (Figure 2C and 2D). Storiform fibrosis and obliterative phlebitis were observed in the submandibular gland specimens (Figure 2F and 2G). Further, the B cell receptor



**Figure 1.** Comparison of radiological features before and after excisional biopsy of the left submandibular gland and left cervical lymph node and medical treatment. (A~C) Contrast-enhanced computed tomography images revealing enlargement of the bilateral lacrimal and submandibular glands and left cervical lymph node. (D, E) After 2 months of medical treatment, the sizes of the bilateral lacrimal glands and right submandibular gland were decreased. (E, F) The dotted circle indicates the surgically removed left submandibular gland and the lined circle indicates the surgically removed left cervical lymph node by excisional biopsy.

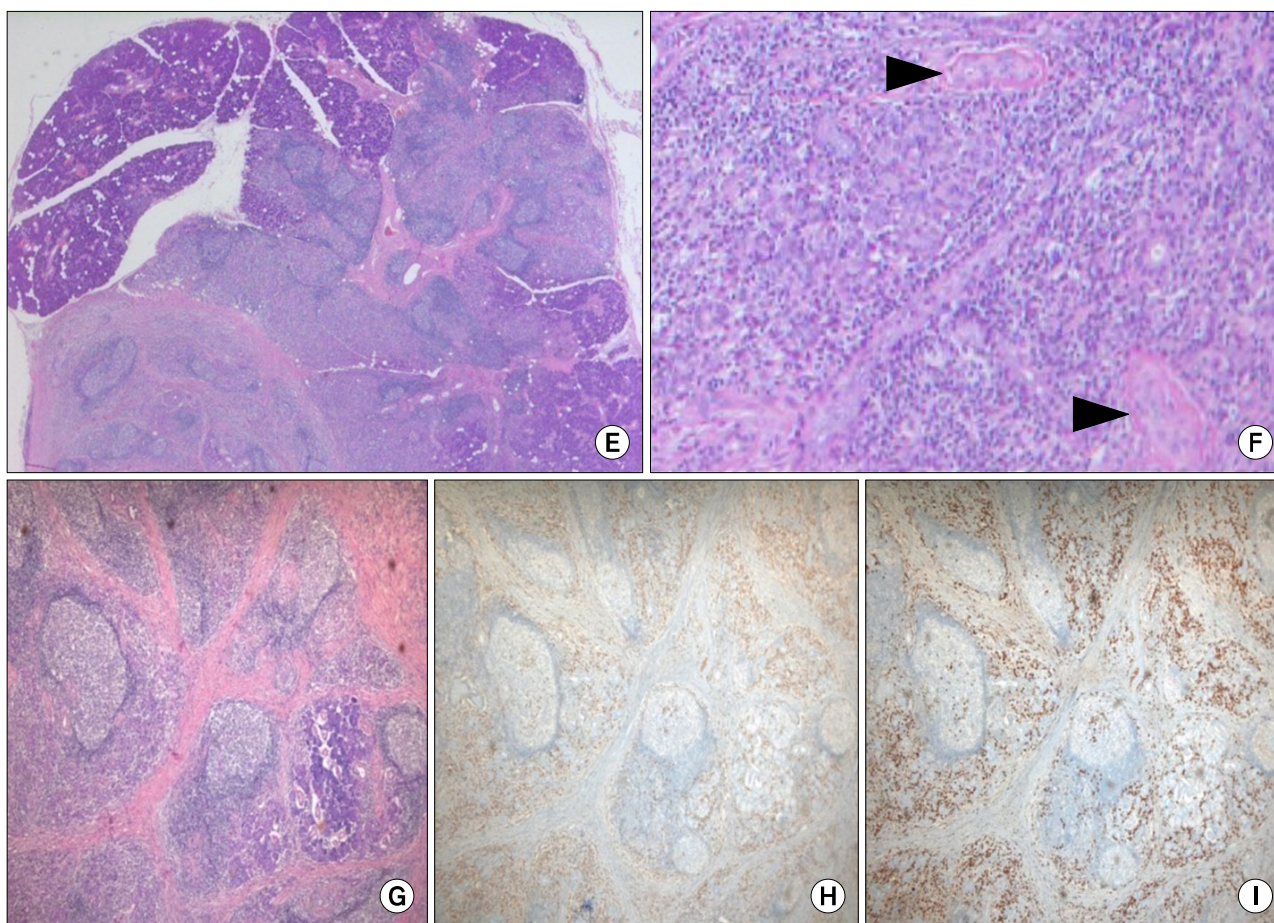


**Figure 2.** Histological and immunohistochemical features of the excisional biopsy specimens of (A ~ D) the lymph node and (E ~ I) submandibular gland. (A) The excised lymph node shows extensive reactive follicular hyperplasia and progressively transformed germinal centers (PTGCs) (arrowheads) (H&E,  $\times 100$ ). The PTGCs appear as round-to-oval structures, 2 to 3 times the diameter of the other reactive follicles. These large follicles show thickened mantles with inward extensions into the germinal centers but no expansion of the interfollicular zone. (B) The germinal centers are predominantly composed of lymphocytes, centrocytes, centroblasts, and numerous mature plasma cells and plasmacytoid cells (H&E,  $\times 200$ ). (C, D) The majority of immunoglobulin (Ig)G4+ plasma cells reside in the germinal centers, with a small number presenting in the interfollicular zone. This is a unique feature of PTGC-type IgG4-related lymphadenopathy, which distinguishes it from the other 4 subtypes. The IgG4+/IgG+ plasma cell ratio is 90%, and the IgG4+ plasma cells were counted as 180/high power field (C: IgG-immunostain,  $\times 200$ ; D: IgG4-immunostain,  $\times 200$ ). The features of the cervical lymph node are identical to those of the axillary lymph node specimen. (E) Acinar atrophy and destruction of the salivary gland are observed, along with marked lymphocytic infiltration with lymphoid follicles (H&E,  $\times 40$ ). (F) Veins occluded by inflammatory infiltrate composed of lymphocytes and plasma cells are noted, and indicate obliterative phlebitis (arrowheads) (H&E,  $\times 200$ ). (G) The storiform pattern of fibrosis is present, indicating dense fibrosis within which lymphocytes, plasma cells, and occasional eosinophils are embedded (H&E,  $\times 100$ ). Storiform fibrosis and obliterative phlebitis are usually absent in IgG4-related lymphadenopathy. (H, I) The IgG4+/IgG+ plasma cell ratio is estimated at 90% (G: IgG-immunostain,  $\times 100$ ; H: IgG4-immunostain,  $\times 100$ ).

and T cell receptor gene rearrangements showed polyclonal patterns. Based on the clinical findings, distinctive histopathologic results, and laboratory findings of IgG4 increase, the patient was diagnosed with Mikulicz's disease accompanied by PTGC-type IgG4-related lymphadenopathy and medical treatment was initiated with oral prednisolone 40 mg/d. As a result, the bilateral upper

eyelid hypertrophy was clinically improved and the prednisolone dose was tapered. Follow-up cervical contrast-enhanced CT after 2 months of treatment also showed decreased sizes of the lacrimal and salivary glands (Figure 1D and 1E), and finally, prednisolone was terminated after 3 months of treatment. However, the bilateral upper eyelid hypertrophy recurred, and pre-





**Figure 2.** Continued.

dnisolone 5 mg/d and azathioprine 100 mg/d were therefore administered. The patient again showed improvement of the symptoms and is currently under medication.

## DISCUSSION

Mikulicz's disease displays similar clinical symptoms to Sjögren's syndrome; however, unlike Sjögren's syndrome, Mikulicz's disease is a multi-organ lymphoproliferative disease characterized by IgG4 increases in the serum and tissues [5]. The patient in the present case showed symptoms of dry eyes and dry mouth, with a positive Schirmer's test and focus score of 1 in the histopathologic findings of the minor salivary gland biopsy, whereas the salivary gland scan revealed no abnormal findings and no anti-nuclear antibody and anti-Ro/La antibodies were found in the laboratory data from our hospital and the other hospital 4 years ago, fulfilling four of the six classification criteria for Sjögren's syndrome. However, a diagnosis of IgG4-RD should be ruled out to confirm Sjögren's syn-

drome; thereby, the patient can be diagnosed with Mikulicz's disease from the clinical and either the histopathological or serological criteria.

Hyper-interleukin (IL)-6 syndromes such as multicentric Castleman's disease and rheumatoid arthritis, as well as other immune-mediated conditions, should be differentiated from IgG4-RD, as they also present with elevated serum IgG4 levels secondary to the effects of the high IL-6 levels, sometimes fulfill the histological diagnostic criteria for IgG4-RD, and frequently involve the lymph nodes [4]. The laboratory findings are the most important to differentiate between IgG4-RD and hyper-IL-6 syndromes. In hyper-IL6 syndromes, the levels of IgG, IgA, IgM, and CRP are mostly elevated, and thrombocytosis, anemia, hypoalbuminemia and hypocholesterolemia are observed due to the effects of the high IL-6 levels.

It has been reported that lymphoma is relatively frequently found in IgG4-RD patients [6], indicating that the activation and proliferation of lymphocytes and chronic antibody stimulation in IgG4-RD may increase



the risk of lymphoma development. In particular, the PTGC has been reported to be associated with the onset of nodular lymphocyte predominant Hodgkin lymphoma [7]. Differentiating PTGC from this disease based only on the histological findings can be difficult; however, immunohistochemical staining using B cell and T cell monoclonal antibody panels is helpful for the differentiation [8]. In the present case, B cell receptor and T cell receptor gene rearrangements were performed, resulting in polyclonal patterns, thus excluding lymphoma.

PTGC-type IgG4-related lymphadenopathy possesses a unique characteristic that differentiates it from the other 4 subtypes [9]; according to a study with patients who satisfied the diagnosis of PTGC-type IgG4-related lymphadenopathy, it occurred most frequently in the submandibular lymph nodes, and some patients showed accompanying cervical lymph node involvement. Although the reason for the submandibular lymph nodes being frequently involved is not clear, they receive lymph fluids circulating the orbit tissues, nose, oral cavity, paranasal sinuses, and salivary glands. Therefore, it can be hypothesized that the submandibular lymph nodes relevant to lymphatic circulation are also influenced by this disease. In addition, during the follow-up, involvement of other organs besides the lymph nodes, or transition to systemic diseases, are observed in approximately half of the patients, with the most commonly involved organs being the lacrimal and salivary glands. In the present case, the cervical and axillary lymph nodes were involved, and IgG4-RD was also observed in the lacrimal and salivary glands.

Sato et al. [9] reported no cases with involvement of the axillary lymph nodes in PTGC-type IgG4-related lymphadenopathy patients, which suggests that the site of lymphadenopathy in this case is highly rare and that this case is therefore significant. In addition, IgG4+ plasma cells are found in the interfollicular zone in the other 4 subtypes of IgG4-related lymphadenopathy, while they are found in the intra-germinal centers in PTGC-type IgG4-related lymphadenopathy.

In terms of the mechanism of IgG4-RD occurrence, the immune responses of type 2 helper T (Th2) and regulatory T (Treg) cells play very important roles [1,10]. Together with the increases in the IL-4, IL-5, IL-10, and IL-13 levels, increased levels of the Th2-type cytokine can lead to elevation of the serum IgE and eosinophil levels. Moreover, IL-10 and transforming growth factor- $\beta$  are produced by activated Treg cells, which in turn can result

in increases in the IgG4 levels and in fibrosis [10]. Among the 40 cases with PTGC-type IgG4-related lymphadenopathy reported by Sato et al. [9], the serum IgE levels were elevated in 12 of 13 cases (92%), and the peripheral blood eosinophil count was increased in 18 of 34 (53%). However, in the present case, the IgE and eosinophil levels were in the normal ranges.

The diagnosis of IgG4-RD is based on the clinical patterns, histopathologic features, and serologic tests [11]. CT scan and ultrasonography can also be helpful [2]. The proposed diagnostic criteria are as follows [12]: clinical signs of organ involvement or damage, histopathologic findings of IgG4+/IgG+ plasma cell ratio >40% and IgG4+ plasma cells >10/HPF, and blood test results with an IgG4 value >135 mg/dL. Criterion 1 is essential in the diagnosis of IgG4-RD; when satisfying both criteria 2 and 3, the diagnosis can be confirmed as IgG4-RD. The present case satisfied all 3 criteria, and was thereby diagnosed as IgG4-RD.

As for the treatment of IgG4-RD, oral prednisolone is considered the primary treatment in the presence of symptomatic disease with organ involvement [13]. After maintaining the initial dose of 0.6 mg/kg for 2 to 4 weeks, the dose is generally reduced to 5 mg/d for 3 to 6 months, followed by 2.5 to 5 mg/d for 3 years. Alternatively, after maintaining the initial dose of 40 mg/d for 4 weeks, the dose can be reduced to 5 mg/d for 11 weeks and subsequently terminated. Recurrence is common during the reduction or termination of prednisolone, even when favorable treatment effects are noted. Such patients can be treated by administering 2.0 to 2.5 mg/kg of azathioprine, 750 mg of mycophenolate mofetil 2 times/d, or methotrexate as means of achieving additional immunosuppression and sparing the patients the effects of long-term glucocorticoid administration [1,13]. Rituximab, an anti-CD20 antibody that possesses B lymphocyte inhibition functions, may also represent an effective drug for patients with recurrence or no response to other drugs [3,13]. Because there are some cases of lymphadenopathy without symptoms and without changes for several years, or even decades, follow-up can be carried out through careful observation prior to commencing medication [1]. The present case showed appearance changes with involvement of the lacrimal and salivary glands; therefore, the patient received glucocorticoid treatment. However, she developed recurrence of the disease during the glucocorticoid tapering and was consequently treated with glucocorticoid plus azathioprine. Hart et al. [14] recently

showed in their observational study that immunomodulators and rituximab are reasonable alternatives for treatment of type 1 autoimmune pancreatitis. However, with no prospective, controlled studies currently available, the decision regarding what kind of immunomodulator to use for the treatment of recurrent and refractory disease must be made on an individual, case-to-case basis.

## SUMMARY

In the presence of lymphadenopathy in IgG4-RD, organ involvement other than to the lymph nodes can occur before, after, or concurrently as the lymphadenopathy; however, the order and exact mechanism of this occurrence are unclear. We here experienced a highly rare case of PTGC-type IgG4-related lymphadenopathy that presented as cervical and axillary lymphadenopathy with involvement of the lacrimal and salivary glands in IgG4-RD, known as Mikulicz's disease, and here reported the findings of this case along with a literature review.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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