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*Case Study*

# Ocular Adnexal IgG4-Producing Mucosa-Associated Lymphoid Tissue Lymphoma Mimicking IgG4-Related Disease

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IgG4-related disease is a recently proposed clinical entity with several unique clinicopathological features. A chronic inflammatory state with marked fibrosis, which can often be mistaken for malignancy, especially by clinical imaging analyses, unifies these features. In the present report, we describe a case of IgG4-producing mucosa-associated lymphoid tissue lymphoma mimicking IgG4-related disease. The patient was a 55-year-old male who was being followed for right orbital tumor over 1.5 years. The lesion had recently increased in size, so a biopsy was performed. Histologically, the lesion was consistent with IgG4-related disease ; however, $IgG4^+$ plasma cells showed immunoglobulin light-chain restriction and immunoglobulin heavy chain gene rearrangement was detected in the lesion. Therefore, the lesion was diagnosed as IgG4-producing mucosa-associated lymphoid tissue lymphoma. In conclusion, in histological diagnosis of IgG4-related disease, it is important to examine not only IgG4-immunostain but also immunoglobulin light-chain restriction. 〔*J Clin Exp Hematopathol 52(1) : 51-55, 2012*〕

**Keywords:** IgG4-related disease, IgG4-producing lymphoma, orbital tumor

## INTRODUCTION

IgG4-related disease comprises a recently recognized systemic syndrome characterized by mass-forming lesions in mainly exocrine tissue that consist of lymphoplasmacytic infiltrates and sclerosis.[1-4] There are numerous $IgG4^+$ plasma cells in the affected tissues, and the serum IgG4 level is increased in these patients. IgG4-related disease frequently involves the ocular adnexal region. Ocular adnexal IgG4-related disease is also called Mikulicz's disease or chronic sclerosing dacryoadenitis.[1,2,4]

Little is known about lymphomagenesis in the context of IgG4-related disease.[1,2,5] We recently reported ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphomas arising from IgG4-related disease for the first time.[2]

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Here, we report in detail on a case of ocular adnexal IgG4-producing MALT lymphoma mimicking IgG4-related disease.

## CASE REPORT

A 55-year-old Japanese male visited an ophthalmologist for examination of right eyelid swelling. Right orbital tumor was identified by enhanced magnetic resonance imaging (MRI) (Fig. 1a). The patient was followed up and the mass was found to increase gradually in size over 1.5 years (Fig. 1b).

Laboratory examination revealed lactate dehydrogenase, 163 IU/L (reference range, 120-240) ; and soluble interleukin-2 (IL-2) receptor, 448 U/mL (145-519).

The ophthalmologist suspected the lesion to be malignant lymphoma or idiopathic orbital inflammation and biopsied the right orbital tumor. After the pathological diagnosis was obtained, additional serological examinations were performed. The results of serological tests were as follows : IgG, 1,048 mg/dL (870-1,700) ; and IgG4, 122 mg/dL (4.8-105). The IgG4 subclass was 11.6% of the total IgG fraction (normally less than 6%).

Histologically, the lesion showed diffuse and dense infiltration by small lymphoid cells without atypia and scattered eosinophils. Aggregates of mature plasma cells without

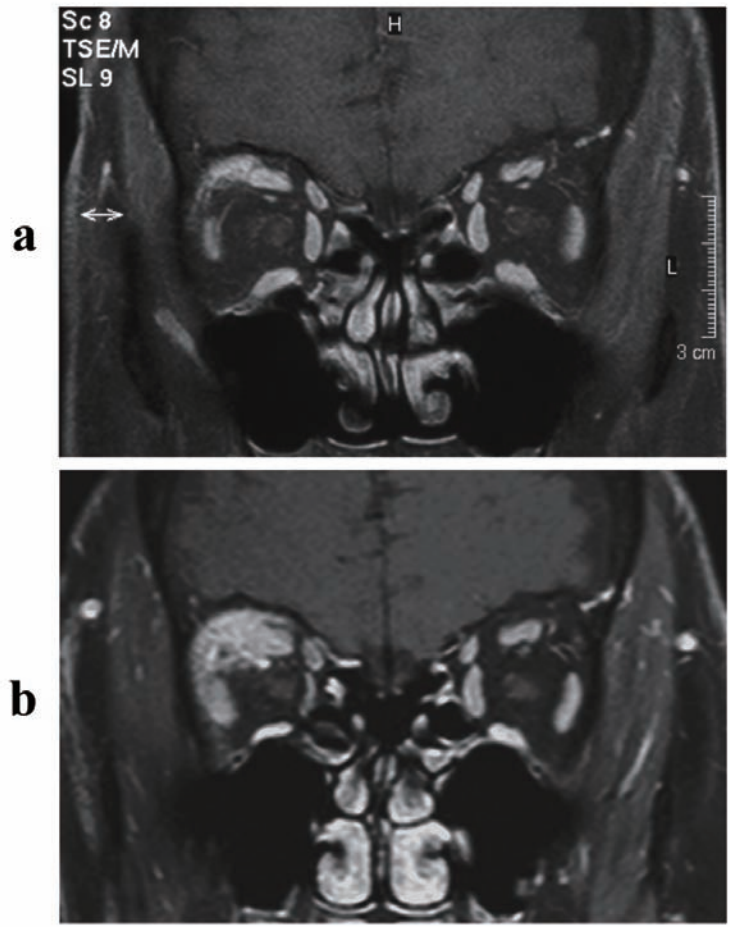


**Fig. 1.** Radiological images. (***1a***) Enhanced magnetic resonance imaging (MRI) revealed right orbital tumor. (***1b***) The orbital tumor had gradually increased in size over 1.5 years.

Dutcher bodies were also present. There were interspersed reactive lymphoid follicles and sclerotic bands (Fig. 2). The lymphoid cells were $CD20^+$, $CD3^-$, $CD5^-$, $CD10^-$, $CD23^-$, and cyclin $D1^-$. The lymphoid follicles were $CD10^+$ and $Bcl\text{-}2^-$. Abundant mature plasma cells were $IgG4^+$, and $IgG4^+/IgG^+$ plasma cell ratio was 63% (Fig. 3). These findings were compatible with IgG4-related disease. However, in *in situ* hybridization, $IgG4^+$ plasma cells showed immunoglobulin light-chain restriction ($\kappa$-monotype) (Fig. 3). Moreover, *immunoglobulin heavy* (*IgH*) *chain* gene monoclonal rearrangement was detected by southern blot hybridization analysis (Fig. 4). The histologic and immunophenotypic findings confirmed the diagnosis of an IgG4-producing MALT lymphoma.

## DISCUSSION

IgG4 is a unique immunoglobulin, which accounts for < 6% of all IgG. [1,2,4] Although its function has not been well determined, pathologic entities of IgG4-related disease are often systemic conditions, affecting more than one organ system, and usually show a good response to steroid therapy. [1,2,4]

In ocular adnexal IgG4-related disease, clinically, the lacrimal glands are involved, and bilateral lacrimal gland swelling is frequently observed.[1,2] In addition, histological findings are uniform : marked lymphoplasmacytic infiltration and lymphoid follicles, admixed with dense fibrosis, and infiltration of abundant $IgG4^+$ plasma cells as well as scattered eosinophil infiltration.[1,2] These histological findings are compatible with our case. In addition, our case showed elevated serum IgG4 level and serum IgG4/IgG ratio. Therefore, initially, we suspected IgG4-related disease. However, the IgG4-positive plasma cells showed immunoglobulin light-chain restriction, and *IgH*-gene monoclonal rearrangement was detected in the lesion. Therefore, we diagnosed our case as IgG4-producing MALT lymphoma.

We reported ocular adnexal MALT lymphomas with detected clonal rearrangement of the *immunoglobulin heavy*

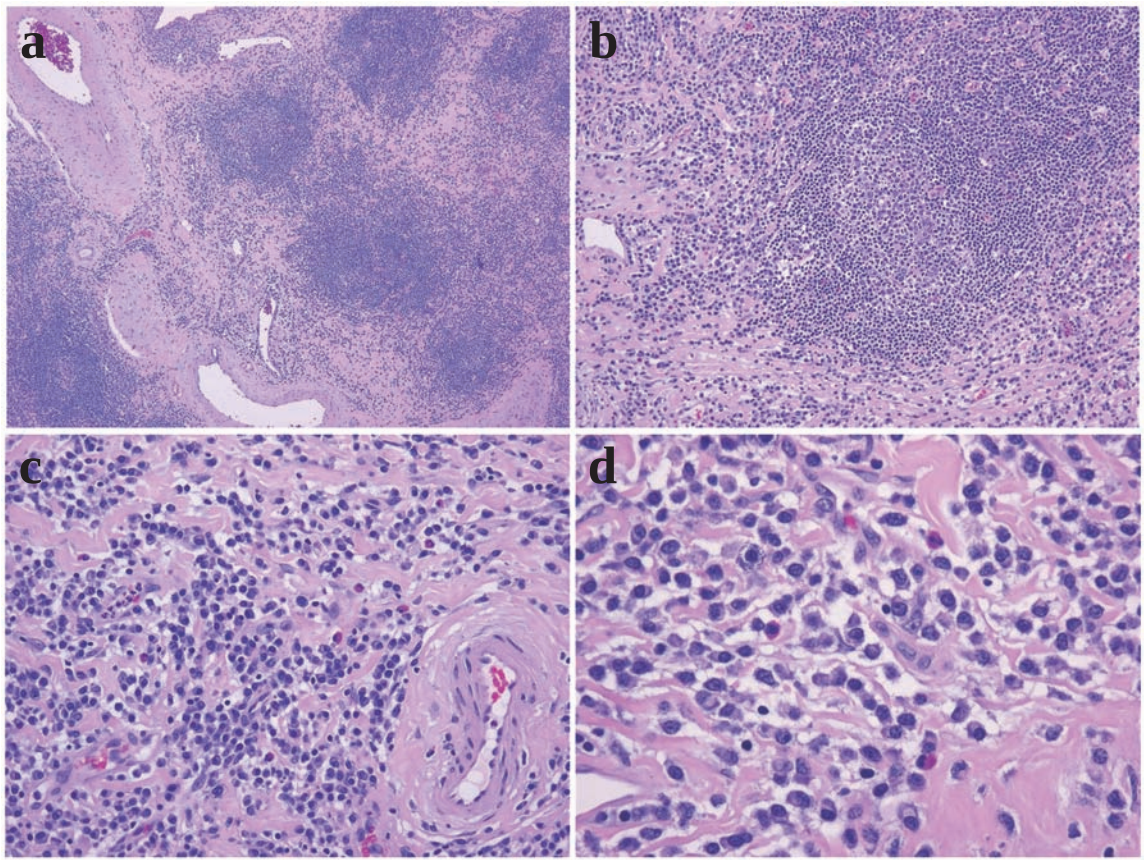


**Fig. 2.** Histological features. (***2a*** & ***2b***) The orbital lesion showed dense fibrosis, lymphoid follicle formation, and marked lymphoplasmacytic infiltration. (***2c*** & ***2d***) Inflammatory cells consisted of mature lymphocytes and plasma cells without any atypia, as well as scattered eosinophils (H&E stain : *2a*, ×40 ; *2b*, ×100 ; *2c*, ×200 ; *2d*, ×400).

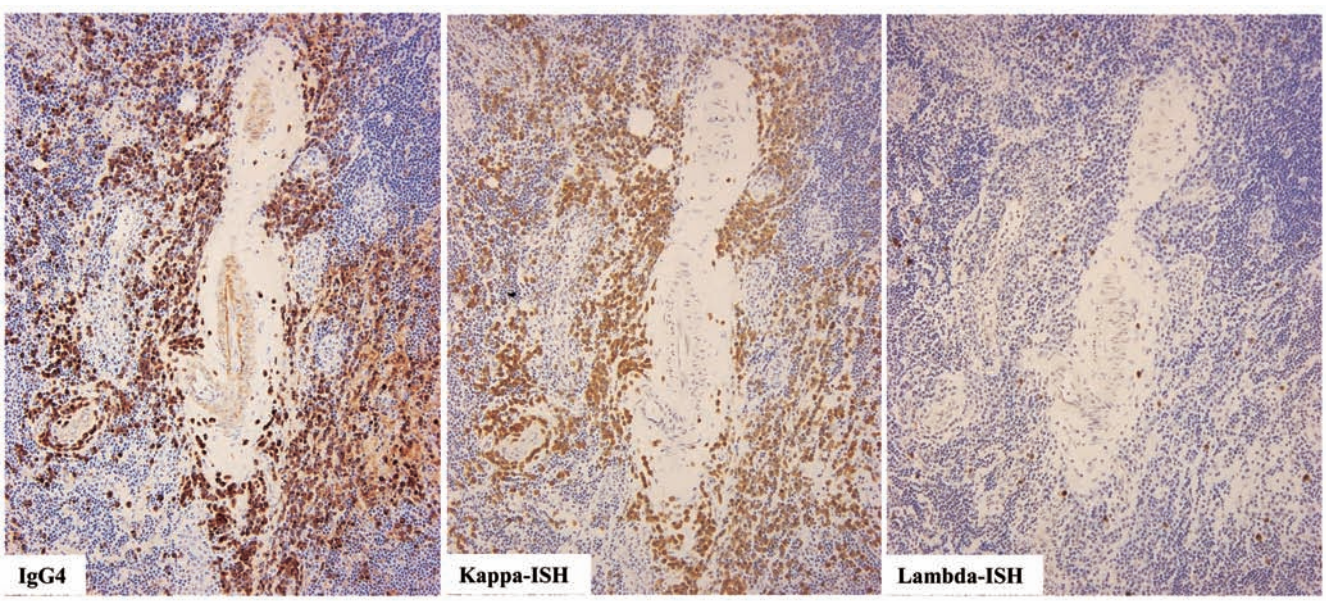


**Fig. 3.** Immunohistochemistry and *in situ* hybridization. Numerous plasma cells were IgG $4^+$ (IgG $4^+$/IgG$^+$ plasma cell ratio > 60%), and most of the IgG $4^+$ plasma cells exhibited $\kappa$-light chain restriction (×10).

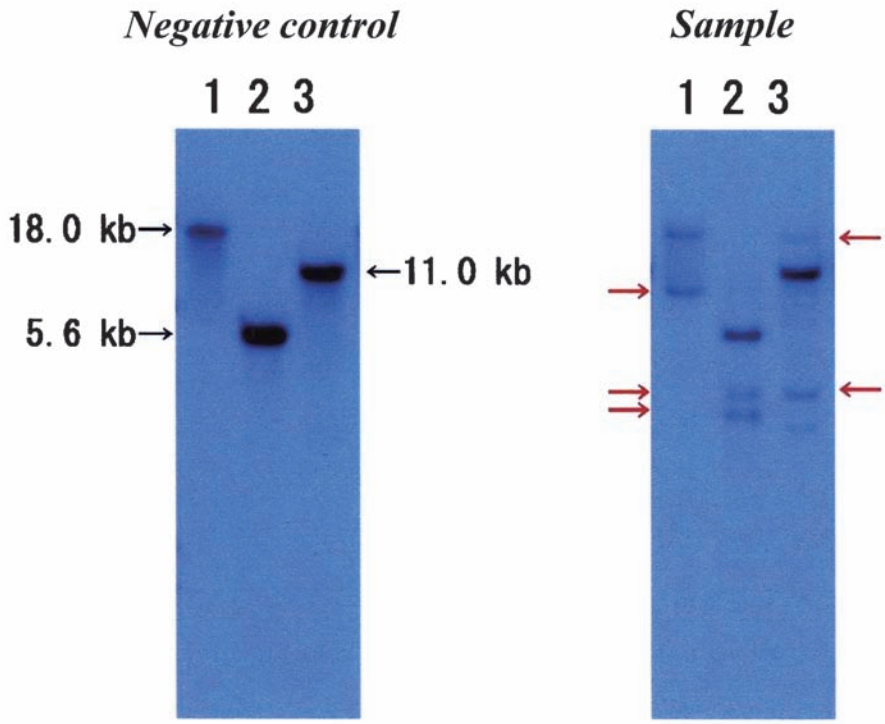


**Fig. 4.** Southern blot hybridization. *Immunoglobulin heavy chain* gene rearrangement was detected.

*chain* gene arising from IgG4-related disease of the ocular adnexa for the first time.[2] These results suggest that ocular adnexal MALT lymphoma arose against a background of IgG4-related chronic inflammation. Recently, Yamamoto *et al*. demonstrated that malignancies occurred in 10.4% of patients with IgG4-related disease, approximately 3.5 times higher than the incidence of cancer in the general population.[6]

Previously, we reported IgG4-producing marginal zone B-cell lymphoma of the lymph node.[7] This report indicates that, not only can malignant lymphomas occur in the setting of IgG4-related disease, but IgG4-producing cells can also be neoplastic. Cheuk *et al*.[8] also reported on ocular adnexal IgG4-producing MALT lymphoma. They concluded that it remains unclear whether ocular adnexal IgG4-producing MALT lymphoma arises from pre-existing IgG4-related disease or de novo IgG4-postive MALT lymphoma. We suggest that it may involve clonal expansion of $IgG4^+$ plasma cells occurring against a background of IgG4-related chronic inflammation. This is because our case showed marked lymphoplasmacytic infiltration and lymphoid follicles, admixed with dense fibrosis, and also elevation of serum IgG4 level and serum IgG4/IgG ratio was detected. These findings are compatible with IgG4-related disease.

In conclusion, we have reported a case of ocular adnexal IgG4-producing MALT lymphoma mimicking IgG4-related disease. Therefore, in histological diagnosis of IgG4-related disease, it is important to examine not only IgG4-immunostain but also immunoglobulin light-chain restriction.

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