Immunoglobulin G4 Positive Mucosa-associated Lymphoid Tissue Lymphoma of the Lacrimal Gland

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To the Editor: Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a multisystem autoimmune disorder that can involve the pancreas, liver, salivary gland, ocular adnexa, and other organs.[1] More recently, IgG4-positve mucosa-associated lymphoid tissue (MALT) lymphomas have been described in ocular, thyroid, dura, and other tissues.[2] It has remained unclear, however, whether IgG4-RD predisposes the patient to develop MALT lymphoma. Here, an unusual case of IgG4-positive MALT lymphoma of the lacrimal gland with a 12-year history of benign inflammatory lesion is documented. A 56-year-old Chinese man presented to our Department of Ophthalmology with continuing slow exophthalmos of right eye going back 12 years. He had undergone a right orbit biopsy in another hospital 10 years ago with a diagnosis of benign inflammatory lesion of the right orbit. He did not undergo IgG4 staining or serum IgG4 examination at that time. He had no diplopia, xerophthalmia, or xerostomia. He had noticed no other lumps and was otherwise well. Upon examination, the right eye demonstrated proptosis (Hertel's exophthalmometry measured the right corneal surface position at 22 mm and the left at 17 mm). There was no superficial lymphadenopathy. The chest was clear. Magnetic resonance imaging (MRI) examination of the orbit showed that the right lacrimal gland was enlarged with a distinct margin. It was predominantly isointense on T1-weighted images and T2-weighted images. A mild heterogeneous enhancement was visible on contrast-enhanced MRI images [Figure 1]. The serum IgG4 was 43 mg/dl (normal: <135 mg/dl). The patient was advised to undergo an orbital biopsy. Intraoperative frozen sections were reported to be consistent with a tumor of low malignancy. A complete resection was undertaken. Histopathological examination demonstrated small, diffusely infiltrating lymphoid cells [Figure 2a]. Upon immunohistochemical examination, these small monotonous lymphoid cells were stained positively with CD20 and Bcl2 and were negative for CD3, CD5, CD10, and CD23. Plasma cells expressed IgG and showed a kappa light chain restriction. A significant proportion of plasma cells and small lymphoid cells expressed IgG4. There were over 40 IgG4+ cells per high-power field in many areas [Figure 2b]. In these areas, the IgG4/IgG ratio was over 40%. The kappa light chain restriction was noted in areas with highest concentration of IgG4+ cells implying expression of IgG4 in the light chain restricted plasma cells. A proportion of small lymphoid cells also showed weak IgG4 expression. Ki-67 expression outside the follicles was about 10%. A diagnosis of IgG4-positive MALT lymphoma of the right lacrimal gland was made. The patient was discharged following his surgery and treated with 25 mg/d prednisone for 4 weeks, after which the dose was then reduced by 5 mg/d every 2 weeks. His symptoms gradually improved. Serum IgG4 levels dropped to 89 mg/dl after 2 months. There was no sign of recurrence during the 12 months of regular follow-up.

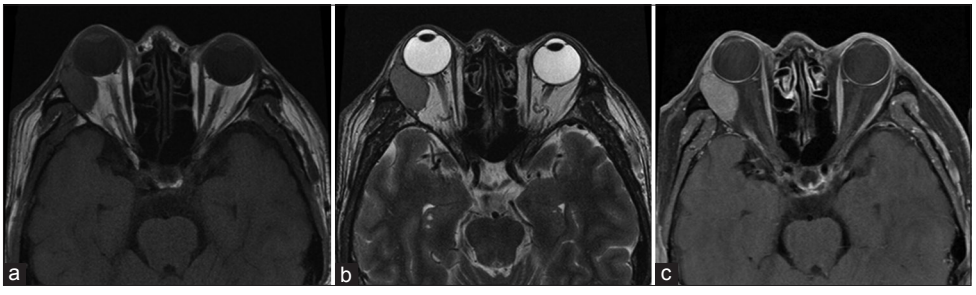

Figure 1: (a-c) Magnetic resonance imaging (MRI) examination of the orbit showed that the right lacrimal gland was enlarged with a distinct margin and was predominantly isointense on T1-weighted images and T2-weighted images and a mild heterogeneous enhancement on contrast-enhanced MRI images.

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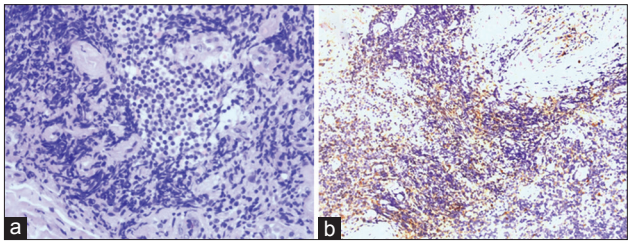

Figure 2: (a) Histopathological examination demonstrated diffusely infiltrating, monotonous, small lymphoid cells. (b) Immunoglobulin G4+ cells amounted to >40 per high-power field in many areas. Original magnification, 2a ×400, 2b ×200.

Whether the lymphoma arises from neoplastic IgG4 cell population or as a transformation of chronic IgG4-related inflammation to tumor tissue remains unclear. It has been reported that patients with IgG4-RD are at a higher risk of developing lymphoma: In one study, it was detected in 3 of 111 patients with IgG4-RD upon follow-up.[3] A large study involving 1014 cases of orbital lymphoproliferative disorders concluded that 44 (4.3%) had IgG4-positive MALT lymphoma.[4] Mulay and Aggarwal reported the first documented case of bilateral IgG4-related dacryoadenitis evolving into a MALT lymphoma on one side.[5] The current case demonstrates the overlap between IgG4-related autoimmune disease and MALT lymphoma. Although relatively rare, as clinical doctors, especially ophthalmologists, we should recognize the possibility of occurrence of MALT lymphoma with increased serum levels of IgG4 and test for light chain restriction to exclude the possibility of MALT lymphoma. In light of possible progression to MALT lymphoma, a diagnosis of IgG4-RD mandates strong clinical suspicion and continued surveillance at regular follow-up visits.

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