Ocular adnexal marginal zone lymphoma arising in a patient with immunoglobulin-G4-related ophthalmic disease: A 4-year delay in diagnosis

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Abstract:

Ocular adnexal marginal zone B cell lymphomas (MZBLs) make up the majority of lymphomas arising from the ocular adnexa. Immunoglobulin-G4 (IgG4)-related disease is a recently proposed entity with several unique clinicopathological features, such as enlargement of affected organs, elevated serum IgG4 level, and infiltration with IgG4-positive plasma cells. Ocular adnexal MZBLs are reported to arise in IgG4-related sclerosing dacryoadenitis, indicating a possible link between the two conditions. Here, we describe a 37-year-old Omani male who presented with right periorbital swelling and proptosis 4 years before presentation. He was diagnosed to have right orbital pseudotumor and exhibited good response to steroid therapy. However, 4 years later, rapid swelling of the right orbital mass was observed. The patient underwent lacrimal gland biopsy. Although the histology was consistent with IgG4-related disease, the infiltrating large atypical lymphoid cells showed that immunoglobulin light-chain restriction and dense lymphoplasmacytic infiltrate involving the soft tissue were seen. Consequently, he was diagnosed with extranodal marginal zone lymphoma with abundant IgG4-positive cells of the right lacrimal gland.

Keywords:

Immunoglobulin-G4-related disease, lymphoproliferative disorders, marginal zone lymphoma, ocular adnexa, orbital pseudotumor

Introduction

Lymphoproliferative disorders (LPDs) are a spectrum of manifestations, which include orbital inflammation with lymphoid hyperplasia, malignant lymphomas, and infiltration.

Immunoglobulin-G4 (IgG4)-related orbital inflammation which usually affects the lacrimal gland and surrounding orbital tissue must not be forgotten in the differential diagnosis.[1] When patients with suspected orbital LPDs are encountered, a tissue biopsy is recommended since imaging alone is not conclusive to distinguish inflammatory lesions from malignant.

Pathological examination can also detect whether the lesion is related to IgG4 or not. IgG4-related disease (IgG4-RD) often involves lacrimal glands, and recently, it was also elucidated that IgG4-related orbital inflammatory lesions include other ocular adnexal tissues such as extraocular muscles, periorbital membrane, and infraorbital nerve.[2] Therefore, IgG4-RD is a differential diagnosis in orbital LPD. In this case report, we show the importance of performing biopsy with the proper pathological examination and staining to reach the right diagnosis.

Case Report

A 37-year-old Omani gentleman was referred to our institution with painless protrusion of the right eye for the past 2 years before presentation [Figure 1a and b]. He had previously attended another hospital and was diagnosed to have orbital pseudotumor and started on oral prednisolone tapering dose. He did not undergo biopsy, IgG4 staining, or serum IgG4

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examination at that time. An ophthalmic examination revealed that visual acuity, pupillary reaction, intraocular pressure, and fundus reported as normal; right proptosis was confirmed as 23 mm by Hertels' in the right eye and 19 mm in the left. Initial magnetic resonance imaging (MRI) of the right orbit showed right orbital mass that has intraconal and extraconal components, involving the right lacrimal gland, superior rectus, and lateral rectus muscles [Figure 2a and b]. Images were discussed with a radiologist and impression of vascular lesion was highly suspected. He was advised to follow-up after 6 months in the clinic with a repeat MRI orbit. He was off steroid therapy at the time. The patient was doing well for up to 2 years later when he presented with right eye epiphora, discomfort, diplopia, and increase in eye protrusion. His vision at that time dropped to 0.6 corrected in the right eye from 1.0 corrected. He showed restriction in abduction elevation and depression. He had right proptosis measuring 30 mm by Hertels'. His anterior segment examination showed upper lid fullness, conjunctival hyperemia, and scleral show. However, his pupillary reaction, intraocular pressure, and fundus were normal. A diagnosis of relapse after remission of right orbital inflammatory mass therefore the patient was started on systemic steroids which he showed a good response to initially, followed by an urgent computed tomography (CT) and a scheduled biopsy. Orbital CT showed an increase in the right orbital mass which was seen on initial MRI. The patient opted for a second opinion and underwent an excisional biopsy abroad. Report came back as lymphoproliferative lesion with gesture suggestive of benign lymphoid reactive hyperplasia. No IgG4 staining or serum IgG4 examination was done at that laboratory. He was started on oral mycophenolate 500 mg twice daily and advised for intravenous methylprednisolone. He re-visited our clinic 4 months later with little improvement in his clinical presentation. The patient's histopathology slides were re-examined by our pathology department after receiving the biopsy block from the previous pathology laboratory. Histopathology slides of the right lacrimal gland showed storiform fibrosis and a dense lymphoplasmacytic infiltrate [Figure 3a]. Immunohistochemical staining revealed dense IgG4-positive plasma cells [Figure 3b] and an IgG4/IgG-positive plasma cell ratio of 60%. The right lacrimal gland also showed diffusely infiltrating, monotonous, small lymphoid cells which stained positively with CD20 [Figure 4a]. Light-chain restriction was seen(positive for Kappa and negative for Lambda [Figure 4]. A diagnosis of IGg4-positive extra-nodal marginal zone B cell lymphoma (EMZL) was made.

The patient was referred to an oncologist as a consequence to the pathology diagnosis. Examination revealed local disease with no lymph nodes involvement. Positron emission tomography scan was negative for systemic disease, only focal right orbit. Laboratory tests of thyroid function and autoantibodies were normal. Kidney function was appropriate for age, and pancreatic and hepatic enzymes were in the normal range. Viral serologies (hepatitis B and hepatitis C, and HIV) were negative. IgG4 was normal, and this was thought to be due to patient being on systemic immunosuppressant for a long time. He completed radiotherapy (total of 30 Gy) and was given follow-up appointment in the clinic.

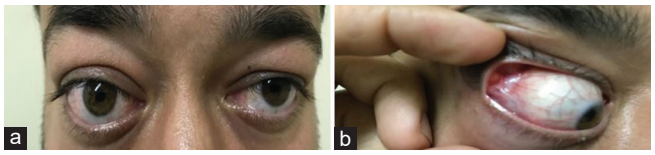

Figure 1: Clinical photographs of a patient with right eye proptosis. (a) Front view. (b) Lateral view.

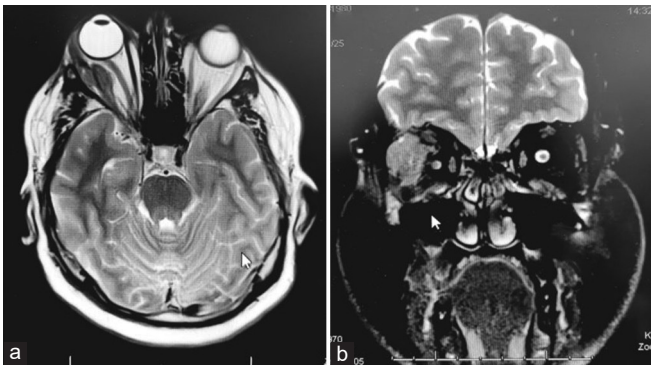

Figure 2: Magnetic resonance imaging scans showing a right orbital mass with intraconal and extraconal components and involving the right lacrimal gland and superior and lateral rectus muscles. (a) T2-weighted magnetic resonance imaging in the axial view. (b) Fat-saturated T2-weighted magnetic resonance imaging in the coronal view

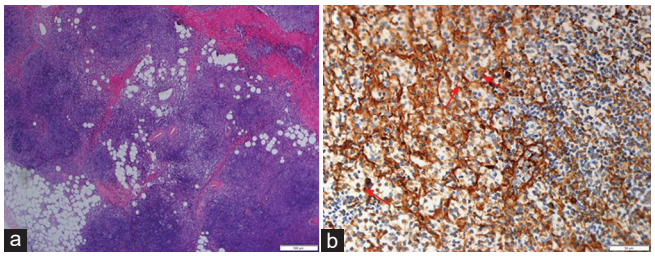

Figure 3: (a) Histopathology slide showing a dense lymphoplasmacytic infiltrate involving the soft tissue with scattered and disrupted lymphoid follicles (vague nodules). (b) Immunohistochemical stain showing positive immunoglobulin-G4 cells (red arrows)

Discussion

IgG4-RD is a recently proposed entity with several unique clinicopathological features, such as enlargement of affected organs, elevated serum IgG4 level, and infiltration with IgG4-positive plasma cells.[2] It was first identified in the pancreas at the beginning of this century. Subsequently, it has been identified to be a systemic and a chronic inflammatory disorder; patients show various symptoms according to the affected organs involved. Corticosteroid therapy has been shown to be effective in these patients, but disease relapse occurs frequently.[3] IgG4-related orbital disease is still an underdiagnosed condition in which the treatment may lead to remission and prevent significant morbidity and mortality.

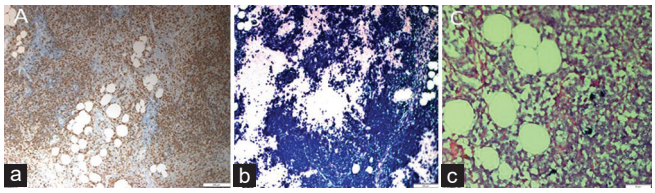

Figure 4: (a) Immunohistochemical stain confirming cluster of differentiation 20 positivity for B cells. (b and c) *In situ* hybridization kappa and lambda stains of the plasma showing kappa light-chain restriction

At present, diagnosis and proper treatment would not have been made without biopsy of the tissue involved and the proper staining. Although IgG4-RD forms a distinct clinical entity, many questions and problems remain to be elucidated, including its association with malignant lymphoma. Several studies have investigated a potential relationship between IgG4-RD and EMZL.[4-6] Although the exact relation between IgG4-RD and lymphoma is uncertain, they are close mimics of each other in the orbit. IgG4-positive plasma cells have been identified in orbital lymphomas or may arise in a background of IgG4-RD. Lymphoma may arise either concurrently with or subsequent to the diagnosis of IgG4-RD, and conversely, IgG4-RD may follow a lymphoma.[7] In the digestive organs, a subset of lymphomas has been found to develop via chronic inflammation, such as *Helicobacter pylori*-associated gastric MZL. Moreover, in the head and neck region, Sato *et al*. reported that a subset of ocular MZLs likely arises from pre-existing IgG4-RD.[8] Orbital IgG4-RD-associated lymphomas are usually of EMZL subtype, and those occurring at extraocular sites in association with IgG4-RD are usually of diffuse large B cell subtypes.[7] Speculations suggest dysregulation of B lymphocytes associated with autoimmune disease, leading to proliferation of abnormal B lymphocytes, culminating in the occurrence of malignant B cell lymphoma.[7] Lee *et al.* looked at the clinicopathological analysis of ocular adnexal EMZL with IgG4-positive cells. Five out of 50 ocular adnexal EMZL cases were categorized as IgG4-positive and predominantly located at the lacrimal gland. This group was also associated with a lower response rate to initial treatment compared with the IgG4-negative group.[9]

In conclusion, here, we have described a case of MZL with abundant IgG4-positive cells that may have arisen from IgG4-related ophthalmic disease in the same region. The details of this particular case suggest that IgG4-RD may be the underlying etiology in certain cases of MZL.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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