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 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 levels. This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

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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 extracanal
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 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.

**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. 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. IgG4-related orbital disease is still an
underdiagnosed condition in which the treatment may lead
to remission and prevent significant morbidity and mortality.
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. 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. 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. 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. 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. 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.

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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**Conflicts of interest**
There are no conflicts of interest.

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