CASE REPORT

Worsening Proptosis: Diffuse Large B-Cell Lymphoma associated with Chronic Inflammation arising within IgG4-Related Orbital Disease

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ABSTRACT

The IgG4-related disease (IgG4-RD) is an established fibroinflammatory condition, characterised by tumefactive lesion with elevated serum IgG4 level and characteristic histopathological features. The malignant potential of IgG4-RD has been questionable. Low-grade lymphomas are commonly reported orbital malignancy that occurs in IgG4-RD. We describe a case of diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation arising within IgG4-RD of the orbit. The case highlights the association of high-grade lymphoma in chronic inflammatory condition, focussing on IgG4-RD, that is rarely documented in the orbital region, and the importance of biopsy reassessment in patients with longstanding and worsening proptosis.

Keywords: IgG4-related disease, Orbital neoplasms, Diffuse large B-cell lymphoma, inflammation

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INTRODUCTION

IgG4-related disease (IgG4-RD) is a recently emerging fibroinflammatory condition involving several organs. Most of the patients are men older than 50 years old, and its pathophysiology is poorly understood. The incidence of IgG4-RD remains unknown. However, IgG4-related ophthalmic disease is encountered in approximately 17 to 23 percent of patients with IgG4-RD. Clinically, patients present with tumefactive lesion and symptoms related to mass effect or focal deficits due to blood vessel compression.

The definitive diagnosis of IgG4-RD requires strong clinicopathological correlation, including serum IgG4 level and radiological examination. In diagnosing IgG4-RD, histopathologic examination of affected tissues is necessary. Characteristic histological features include dense lymphoplasmacytic infiltrate, dense fibrosis, obliterative phlebitis, and immunohistochemistry demonstrating increased IgG4-positive plasma cells and increased IgG4 to IgG-positive plasma cells ratio as depicted in the consensus criteria (1).

The malignant potential of IgG4-RD has been proposed and reported in several cases. The standardised incidence ratio (SIR) for malignant lymphoma in IgG4-RD is 16.0- fold higher than in the general population (2). Diffuse large B-cell lymphoma (DLBCL) and extranodal marginal zone B-cell lymphoma (EMZL) are the most common lymphomas described in literature (Table I) (3). However, the most common type of IgG4-related orbital lymphomas is low-grade lymphomas. To date, this is the first case reporting on IgG4-RD complicated with DLBCL associated with chronic inflammation.

CASE REPORT

A 60-year-old man presented in 2010 with two years history of bilateral proptosis and blurring of vision. Computed tomography (CT) of the orbit showed bilateral intraconal masses, raising the suspicion of lymphoma of the orbital soft tissue. Left eye incisional biopsy was performed and was reported as reactive lymphoid tissue secondary to chronic inflammatory changes.

He was treated conservatively, but his bilateral proptosis subsequently worsened with left eye vision became non-perceptive to light in 2013. Left eye tumour debulking surgery was performed and histopathological examination (HPE) revealed reactive lymphoid tissue with fibroinflammatory infiltration, suggestive of IgG4

Table I: Reported cases of diffuse large B-cell lymphoma occurring in IgG4-related disease

Case no	Authors	Age (years)/ Sex	Primary IgG4-RD	Interval to DLBCL
1.	Takahashi N, et al (2009)	72/M	Autoimmune Pancreatitis	5 years
2.	Takahashi N, et al (2009)	69/M	Chronic parotitis	3 years
3.	Mitsuyama T, et al (2013)	74/M	Ig-G4 related prostatitis	3 years
4.	Lightfoot N, et al (2013)	72/F	Ig-G4 related pachymeningitis	Concurrent
5.	Alan A, et al (2015)	51/M	Ig-G4 related ophthalmic disease	2 years
6	Nishimura Y, et al (2016)	61/M	Autoimmune pancreatitis	4 years
7.	Bledsoe JR, et al (2018)	66/F	Ig-G4 related salivary gland disease	Concurrent
8.	Marunaka H, et al (2018)	78/F	Ig-G4 related ophthalmic disease	NA
9.	Kawaji Y, et al (2019)	70/F	Ig-G4 related lymphadenopathy	4 years
10.	Wang H, et al (2020)	64/M	Ig-G4 related kidney disease	16 months
11.	Peng X, et al (2020)	44/M	Ig-G4 related ophthalmic disease	Concurrent

IgG4-RD= IgG4-related disease; DLBCL= Diffuse large B-cell lymphoma; NA= Not available

related sclerosing disease.

He presented again in 2016. The bilateral proptosis became even worse and right eye vision deteriorating further. A repeat CT of the orbit showed bilateral intraconal mass involving the optic canal with extraconal and left extradural space extension, as well as widening of the cavernous sinus (Fig. 1). Incisional biopsy of right eye mass revealed all the histopathological features of IgG4-RD, including the immunohistochemistry study findings (Fig. 2). The case was thus reported as highly suggestive of IgG4-RD. The patient was started on steroid therapy but later was withheld as he was diagnosed with pulmonary tuberculosis (TB).

In November 2018, the bilateral proptosis worsened further, and he was blind in both eyes. Left eye incisional biopsy was performed and showed nodular lymphoid tissue with a background of fibrotic stroma, consistent with residual features of IgG4-RD. The lymphoid tissue was composed of an admixture of plentiful large lymphoma cells and small reactive lymphocytes. Immunohistochemistry studies revealed large lymphoma cells which expressed B- cell markers (CD20, CD79a, PAX-5 and BCL6) and EBV-encoded small RNA (EBER). Ki67 proliferative index was around 60%. A few lymphoma cells were CD30+ (Fig. 3). These lymphoma

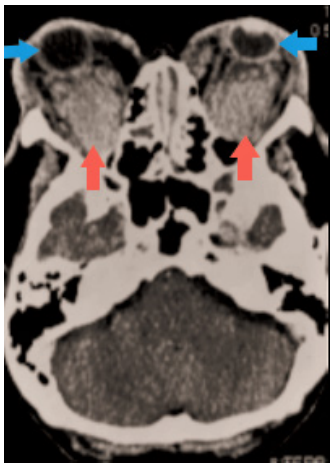

Figure 1: Bilateral enhancing intraconal lesions (red arrow) causing bilateral proptosis (blue arrow)

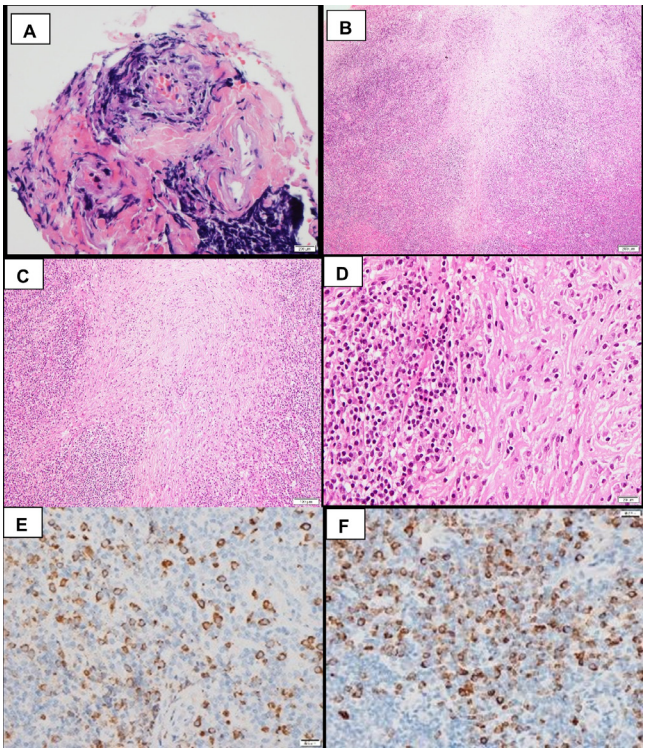

Figure 2: A, Obliterative phlebitis (H&E, 100x). B-D, Dense lymphocytes and plasma cells infiltration in the background of fibrosis (B, H&E 40x; C, H&E 100x; D, H&E 400x). E and F, Immunohistochemical staining shows IgG4+ plasma cells of >100 per hpf and IgG4+ : IgG+ plasma cells ratio of more than 40% (E, IgG, x200; F, IgG4, x 200)

cells were CD10-, Cyclin D1-, CD3-, and CD5-. The findings led to the diagnosis of DLBCL associated with chronic inflammation. The patient succumbed from ongoing lung infection before haematological referral for subsequent management was undertaken.

DISCUSSION

IgG4-RD is a recently emerging fibroinflammatory disorder involving multiple organs commonly lacrimal and salivary glands, pancreas and lymph nodes. In the orbit, nearly a quarter of orbital lymphoproliferative disorders are IgG4-related, mainly affecting the lacrimal gland (4). In this case, the intraconal mass had caused

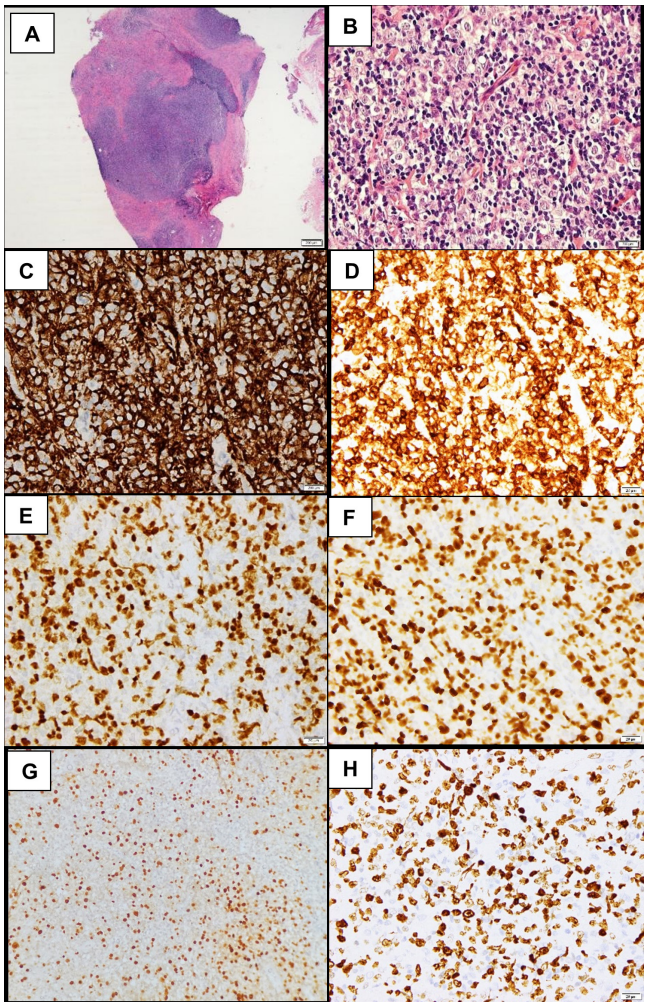

Figure 3: A, Lymphoid tissue arranged in nodules with background of fibrotic stroma (H&E, 20x). B, The lymphoid tissue is composed of numerous large lymphoma cells displaying vesicular nuclei with irregular nuclear membrane and prominent nucleoli. Smaller reactive lymphocytes are seen in between the lymphoma cells (H&E, 200x). C-H, Immunohistochemical stains show the lymphoma cells expressed CD20 (C, 200x), CD79a (D, 400x), PAX-5 (E, 400x), BCL6 (F, 400x) and EBER (G, 200x). Ki67 proliferative index is around 60% (H, 400x).

bilateral proptosis. The progressive blindness was possibly due to impingement of the optic nerve or retinal infarction caused by compression of the retinal vessels.

The characteristic histological features of IgG4-RD, namely, dense lymphoplasmacytic infiltrate, dense fibrosis (usually storiform pattern) and obliterative phlebitis, are all demonstrated in this case. Generally, at least two of these three features must be present for a confident histopathological diagnosis of an IgG4-RD. The diagnosis of IgG4-RD was not made on the earlier biopsies, probably due to lack of characteristic histological features.

Histopathological interpretation of this case as 'histologically highly suggestive of IgG4-RD' is based on the consensus criteria (1). These diagnostic terminologies are primarily based on the histological features mentioned above with the integration of organ-specific increase in the number of IgG4 positive plasma cells per high power field and IgG4 to IgG positive plasma cells ratio of more than 40%.

Apart from the distinctive histological features, elevated IgG4 positive plasma cells and IgG4: IgG ratio, a strong clinicopathological correlation was recommended. Thus, additional criteria, including high serum IgG4 >135 mg/dl and evidence of other organ involvement, as determined by the radiological or pathological assessment, must be fulfilled (1). A high serum IgG4 level (>135 mg/dL) is indicative of IgG4-RD but not specific. Some patients have normal levels of IgG4 despite characteristic IgG4-RD histological features. In this patient, serum IgG4 was not performed due to logistic reasons as the patient was referred patient from another state. It was also difficult to determine the patient's response to glucocorticoid therapy as it was withheld since he was diagnosed with pulmonary TB.

To date, very few cases of IgG4-related orbital disease associated with higher-grade and aggressive lymphoma have been identified (5). Other differential diagnoses of this present case are low-grade lymphomas such as MALT lymphoma, DLBCL not otherwise specified (NOS) and EBV positive DLBCL. The morphology of the lymphoma cells did not fit the features of low-grade lymphoma (small to medium size cells) or EBV DLBCL (variable number of immunoblasts and Hodgkin/Reed-Sternberg-like cells). Ki67 proliferative index was also high for low-grade lymphoma. EBER positive in most of the lymphoma cells excluded the diagnosis of DLBCL NOS. Large areas of geographical necrosis and angioinvasion were absent, which are characteristic of EBV positive DLBCL.

DLBCL associated with chronic inflammation is a lymphoid tumour arising from a longstanding chronic inflammation. The median age of patients at diagnosis is 65 to 70 years with male predilection. The time between predisposing inflammatory event and malignant lymphoma varies between 1.2 to 57 years. As in this case, the interval was around two years. The frequently involved area is the pleural cavity. However, any body cavities or confined spaces like the orbital region, as in this present case, are also possible. The histological features are similar to those of DLBCL NOS. The lymphoma cells are EBER positive as in this present case.

In this present case, the orbital lymphoma probably emerged from IgG4-RD instead of de novo because of the histological transformation from benign reactive lymphoid tissue with chronic inflammation to highly suggestive IgG4-related disease and finally became DLBCL associated with chronic inflammation. The pathogenesis of the development of IgG4-RD into malignant lymphoma remains unclear. Chronic

inflammation is a known predisposing factor for increased risk of malignant lymphoma, including DLBCL associated with chronic inflammation. Chronic inflammation at the local site is thought to aid EBV-transformed B cell proliferation by allowing them to get away from host immune surveillance by producing IL10 (an immunosuppressive cytokine) and providing autocrine to paracrine growth through IL6 and the IL6 receptor.

Since DLBCL associated with chronic inflammation is recognised as a high grade and aggressive lymphoma, it may arise from an IgG4-RD rather than an IgG4 expressing lymphoma. In addition, although IgG4 expressing lymphoma showed a high IgG4 level with IgG4/IgG > 40%, most of the cases do not meet the diagnostic criteria of IgG4-RD.

The treatment for DLBCL associated with IgG4-RD in most of the reported cases used the similar chemotherapy regime, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as in the de novo DLBCL. DLBCL associated with chronic inflammation is an aggressive disease with a 5-year overall survival rate of 20 – 35%, which can be improved to 50% with chemotherapy. Complete tumour resection has been reported to give good result.

CONCLUSION

High-grade lymphoma transformation in the setting of IgG4-related orbital inflammation is rare. Thus, clinician should have a high degree of suspicion of lymphoma transformation in IgG4-RD, especially in patients with worsening symptoms. Early detection of lymphoma would benefit the patients by providing appropriate treatment thus improving the clinical outcome.

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