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Case Report

Orbital progressive transformation of germinal centers as part of the spectrum of IgG4-related ophthalmic disease: Clinicopathologic features of three cases

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Abstract

Progressive transformation of germinal centers (PTGC) is a form of follicular hyperplasia recently associated with immunoglobulin G4-related disease (IgG4-RD), but the ophthalmic manifestations of this combination are poorly described. In this retrospective case series, we present three cases of IgG4-related orbital disease (IgG4-ROD) showing varying degrees of PTGC involving the orbit and lacrimal gland. Three adult women presented with ill-defined lacrimal gland enlargement. Histologic sections showed variable fibrosis and large, irregular lymphoid follicles with prominent mantle zones penetrating the germinal centers, highlighted by Bcl-2 and/or IgD immunostains. The interfollicular areas contained a mixture of plasma cells, scattered histiocytes and eosinophils. Mixed T and B-cells were present, and no signs of monoclonality were identified. All cases showed more than 100 IgG4 positive cells per high power field. Epstein-Barr virus in situ hybridization performed in one case was negative. The serum IgG4 level was tested in one case and showed elevation above the normal range. After 2–10 months of follow-up, the patients showed either near-complete resolution or no remaining signs of ophthalmic disease. Increasing awareness of these PTGC in extra-nodal locations, including the orbit, may provide a better understanding of the histologic spectrum of this disease.

Keywords: IgG4-related disease, Orbit, Lacrimal gland, Progressive transformation of germinal centers, Follicular hyperplasia

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Introduction

Progressive transformation of germinal centers (PTGC) is an idiopathic form of reactive follicular hyperplasia mainly presenting in the lymph nodes, characterized by enlarged and irregular follicles with a predominance of mantle zone lymphocytes. These mantle zone lymphocytes invade into the germinal centers and can result in follicle lysis. An association with immunoglobulin G4-related disease (IgG4-RD) has been recently described in lymph nodes, and PTGC is now recognized as one of the five histologic subtypes of IgG4-RD.[1–3] Epstein-Barr virus (EBV) infection has been identified in over 50% of IgG4-related lymphadenopathy, and its presence in the PTGC-subtype is associated with systemic lymphadenopathy and/or extra-nodal involvement.[4]

Although the true incidence is unknown, ophthalmic involvement by IgG4-RD is not rare, and a significant number of patients will have disease elsewhere at presentation, or develop it subsequently.[5] More than 50% have unilateral or bilateral lacrimal gland lesions, followed in decreasing frequency by trigeminal nerve, extraocular muscles, orbital fat, circumscribed orbital masses, eyelid lesions, nasolacrimal

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duct, lacrimal sac, and optic nerve.[6,7] Thus, for ocular adnexal and orbital disease, the term IgG4-related ophthalmic disease (IgG4-ROD) is recommended.

Consensus criteria for the histopathologic diagnosis of IgG4-RD proposed in 2012 required both morphologic and immunohistochemical features. Three major histologic features were: (1) dense lymphoplasmocytic inflammation, (2) fibrosis, which may be variably present and focally show a storiform pattern, and (3) obliterative phlebitis. Thresholds for IgG4-positive (IgG4+) cells and their ratio to IgG-positive (IgG+) cells, defined using immunohistochemistry, varied by site. In the lacrimal gland, the proposed numbers were over 100. Because the microscopic findings were not as commonly found in the periocular tissues as other sites, revised criteria specific to ophthalmic disease were subsequently put forward by a Japanese consensus group.[8] These include an IgG4:IgG plasma cell ratio of 40% or above and/or >50 IgG4+ plasma cells per high power field (HPF), and do not require storiform fibrosis or phlebitis.[8,9]

Rare cases of extra-nodal PTGC have been reported in the orbit, oral cavity, large bowel, and skin, and a few cases of systemic PTGC-type IgG4-RD affecting the lacrimal gland and orbit have been previously described.[3,13] Here we report three cases of isolated IgG4-ROD with varying degrees of PTGC.

Case reports

A retrospective review of the pathology records (January, 2009 – December, 2016), dating from our first report of IgG4 in the orbit, for specimens with increased IgG4+ cells was performed and identified 11 cases of IgG4-related ophthalmic disease. These cases were reviewed and three with varying degrees of PTGC were identified (Table 1).

Case 1

The patient is a 55-year-old African-American woman with history of human immunodeficiency virus (HIV) infection treated with highly active antiretroviral therapy (HAART), who presented with a right superolateral orbital lesion. A magnetic resonance imaging (MRI) scan showed an enlarged, right lacrimal gland measuring up to 2.3 × 1.1 × 2.2 cm, with low signal density on T1 and T2, and homogeneous contrast enhancement (Fig. 1A and B). An incisional biopsy was performed. Histologic sections showed lacrimal gland tissue with patchy fibrosis, diffuse lymphoplasmocytic inflammation, and numerous, irregularly enlarged lymphoid follicles with prominent mantle zones including lymphocytes extensively invading the germinal centers, as highlighted by Bcl-2 and IgD immunostains. Scattered eosinophils and histiocytes were also noted throughout the lesion. Immunohistochemical stains also showed a mixed T-cell (CD3) and B-cell (CD20) infiltrate. Flow cytometry did not identify a monoclonal population. IgG4 and IgG markers demonstrated an IgG4:IgG ratio over 70% and >100 IgG4+ plasma cells per HPF, which were mostly concentrated within germinal centers (Fig. 1C–H). EBV/EBER in situ hybridization was negative. Serum IgG4 levels were not tested. The patient was treated with prednisone (0.6 mg/kg daily for one month, then tapered 10% every two weeks) and the lesion was nearly completely resolved two months after surgery.

Case 2

The patient is a 71-year-old Asian woman with history of adenoid cystic carcinoma of the left maxilla and ethmoid 24 years ago treated with maxillectomy, radiation and reconstruction of the orbital floor, and a ''left neck lesion'' treated with excisional biopsy and diagnosed as Warthin tumor in 2013. Three years later, she presented with a lesion involving the right lacrimal gland and orbital tissue. An incisional biopsy was performed. Histologically, the lacrimal gland and fibroadipose tissue were diffusely infiltrated by chronic inflammation with numerous, enlarged, irregular lymphoid follicles with abundant mantle zone lymphocytes that focally invaded the germinal centers, highlighted by a Bcl-2 immunohistochemical stain. CD3 and CD20 immunostains showed a mixed T-cell and B-cell population. There was a greatly increased number of IgG4+ cells (>100 per HPF) with an IgG4:IgG ratio of over 80% (Fig. 2). Serum IgG4 levels were not assessed. The patient did not receive treatment and no residual signs of orbital disease were present at 10-months follow up.

Case 3

The patient is a 66-year-old Asian woman who first presented with bilateral eyelid swelling in 1997. She was treated with steroids and her symptoms resolved. In 2004, her eyelid swelling recurred and persisted, and she underwent biopsy of her left eyelid tissue, which led to a histopathological diagnosis of benign lymphoid hyperplasia. Nine years later, the patient presented with recurrent, persistent left eyelid swelling and computed tomography (CT) scan showed moderate, ill-defined enlargement of the left lacrimal gland with extension into the preorbital region and minimal adjacent stranding, suggesting an inflammatory process.

An incisional biopsy was performed. Histologic sections showed orbital fibroadipose tissue without significant fibrosis, but scattered, large, polarized lymphoid follicles with a prominent mantle zone focally penetrating the germinal

Table 1. Clinicopathologic features of cases of PTGC IgG4-ROD.

Case	Sex	Age (years)	Biopsy site	IgG4:IgG ratio	IgG4+ cells/ HPF	Serum IgG4 (normal 3.9–86.4 mg/dL)	Follow up
1	F	66	Left lacrimal gland and preorbit	NA	>100	126	No signs of active disease
2	F	71	Right lacrimal gland and orbit	>40%	>100	NA	No signs of active disease
3	F	55	Right lacrimal gland	>40%	>100	NA	Almost resolved after 2 months

NA = Not assessed.

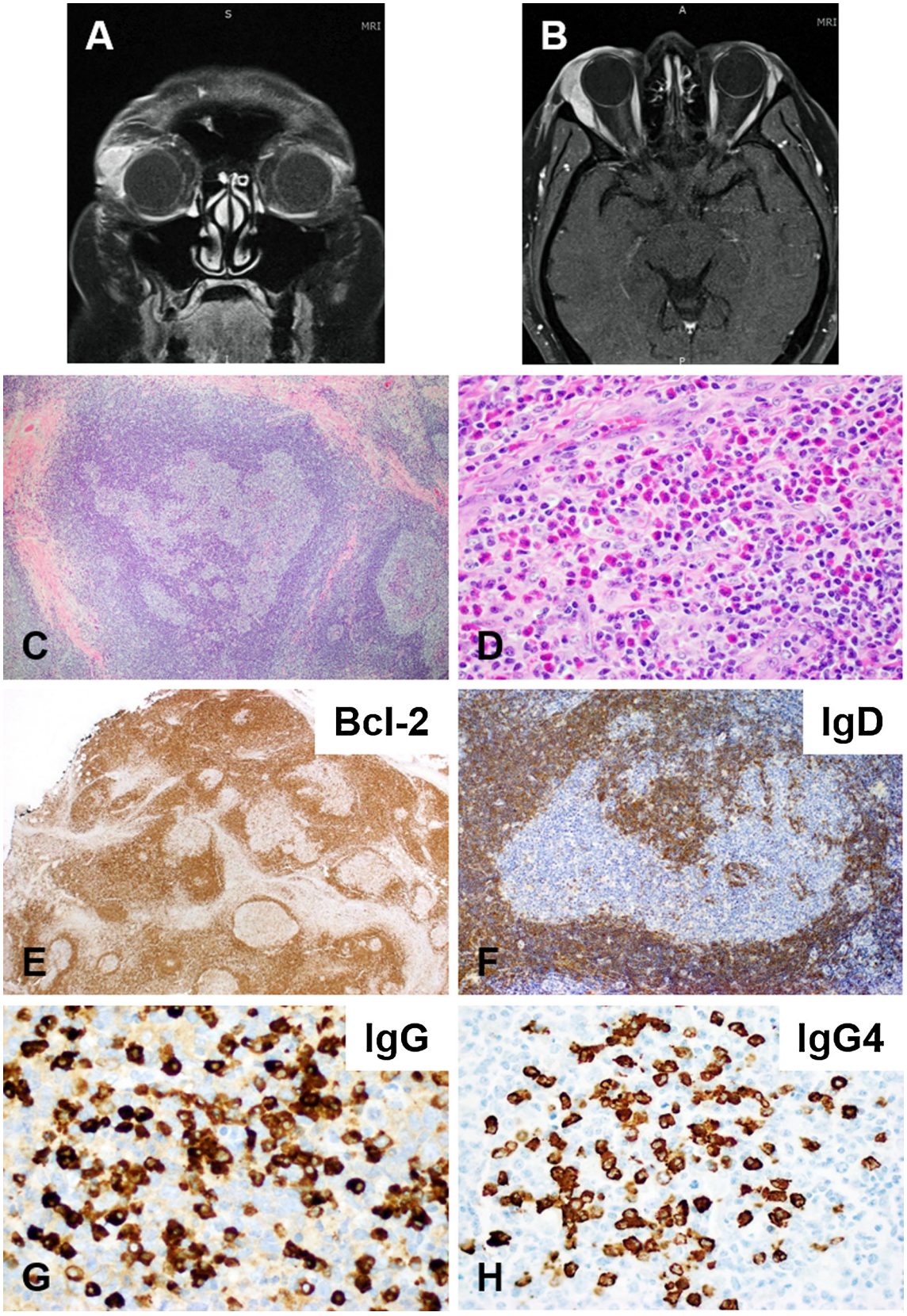

Fig. 1. Radiologic and histologic features of PTGC IgG4-ROD (Case 1). Post-contrast MRI scans in coronal (A) and axial (B) sections show diffuse, right lacrimal gland enlargement with homogeneous contrast enhancement. Microscopically, the lacrimal gland shows fibrosis and enlarged, irregular lymphoid follicles with prominent mantle zones invading germinal centers (C). Numerous eosinophils and histiocytes are also present in interfollicular areas (D). Bcl-2 and IgD immunohistochemical stains highlight mantle zone lymphocytes within germinal centers (E, F). IgG4:IgG ratio is over 70% and >100 IgG4+ plasma cells per HPF are noted (G, H).

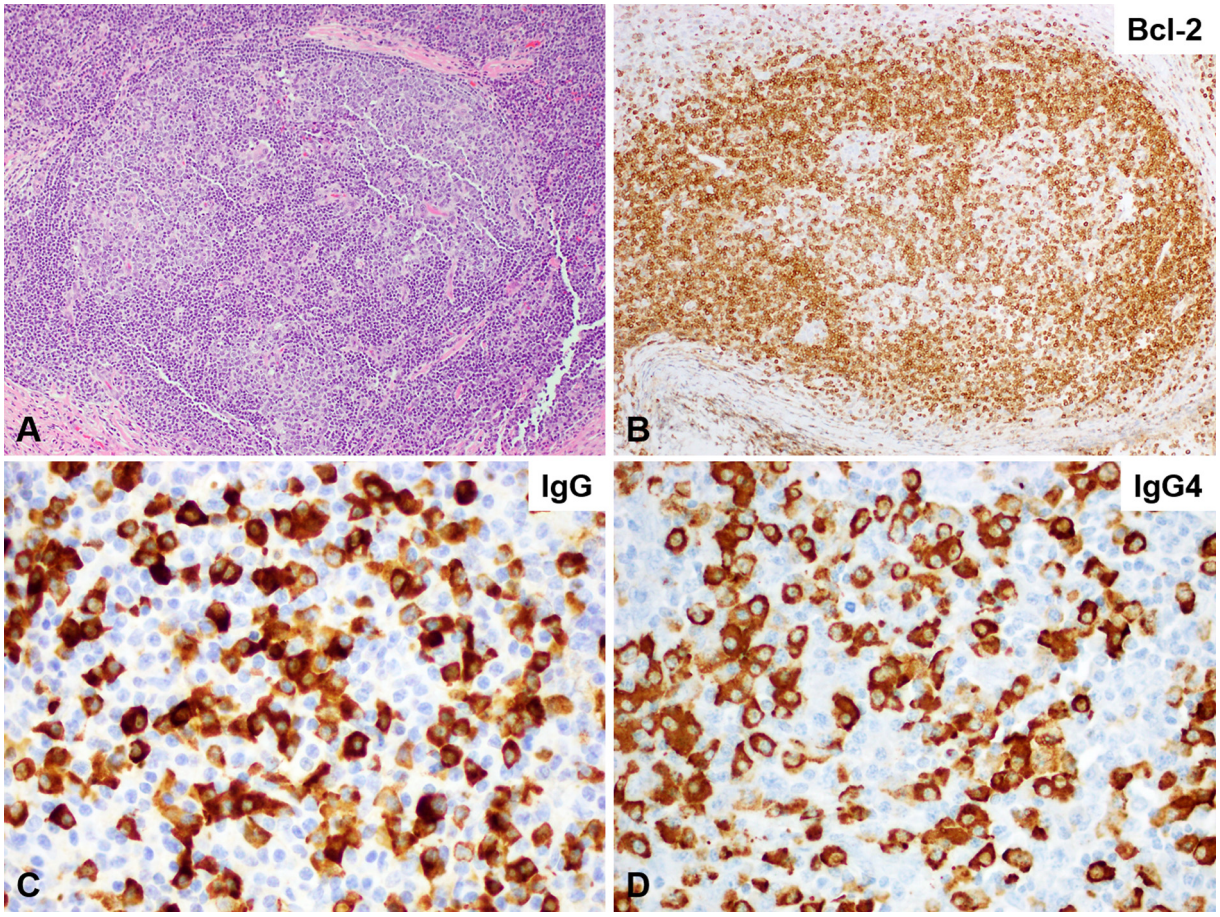

Fig. 2. Histologic features of PTGC IgG4-ROD (Case 2). The lacrimal gland and orbital tissue show focal fibrosis and is diffusely infiltrated by lymphoplasmocytic inflammation with prominent lymphoid follicles and abundant mantle zone lymphocytes penetrating germinal centers (A). Mantle zone lymphocytes are positive for Bcl-2 immunostain (B). More than 100 IgG4+ plasma cells are present per HPF, and IgG4:IgG ratio is over 80% (C, D).

centers, highlighted by bcl-2 immunohistochemical stain. The interfollicular areas contained a mixture of plasma cells and small lymphocytes with sparse histiocytes and eosinophils. An IgG4 immunostain demonstrated over 100 positive plasma cells per HPF (Fig. 3). The lymphocytes showed a mixed T and B-cell population with immunoreactivity for CD3 and CD20, respectively. No kappa or lambda light chain restriction was identified, and PCR studies for IgG gene rearrangements were consistent with polyclonality. IgG4 serum level was slightly elevated (126 mg/dL, normal 3.9–86.4 mg/dL).

In June 2016, she developed symptoms of dry eye, which were attributed to medication for glaucoma and no antibody testing was performed. However, she was also noted to have a nodule in the left submandibular gland. An excisional biopsy of the nodule was performed five months later and the diagnosis of low-grade B-cell lymphoma most consistent with marginal zone lymphoma was made. Analysis for t(14:18) was negative. Positron emission tomography (PET) scan showed no evidence of other regional or distant disease. At her 9-month follow up, the patient did not have systemic symptoms of lymphoma or signs of ophthalmic disease.

Discussion

Numerous conditions have now been recognized as part of the spectrum of IgG4-RD. In addition to autoimmune pancreatitis, they include Mickulicz disease, angiocentric fibrosis with eosinophilia, sclerosing sialadenitis (Kuttner tumor), Riedel thyroiditis, sclerosing cholangitis, and idiopathic retroperitoneal fibrosis, among others. In the orbit, IgG4-RD seems to account for a significant proportion of cases formerly diagnosed as idiopathic orbital inflammation (IOI) or reactive lymphoid hyperplasia (RLH).[5] Although IgG4-RD remains idiopathic as its etiology is unclear, the clinicopathologic criteria for its diagnosis seem sufficiently specific to distinguish it from other forms of IOI, RLH, and many other forms of orbital inflammation, such as Sjögren's syndrome, granulomatosis with polyangiitis, and sarcoidosis. Diagnosis depends on finding the appropriate histologic features and correlating them with the clinical history, imaging, and serum IgG4 levels. However, it is important to note that serum IgG4 levels may be normal in up to 40% of patients with IgG4-RD, which precludes its use as a sole diagnostic marker or as a measure of response to therapy in these patients.[5,8,9]

Progressive transformation of germinal centers is a variant of follicular hyperplasia described in the 1970s by Lennert and Muller-Hermelink.[10] It is present in less than 5% of patients with non-specific lymphadenopathy. Even though the PTGC variant is considered a benign, reactive condition, it has also been described in association with Hodgkin's lymphoma, particularly nodular lymphocyte-predominant Hodgkin lymphoma.[11] Histologically, PTGC is characterized by irregular enlargement of lymphoid follicles with prominent

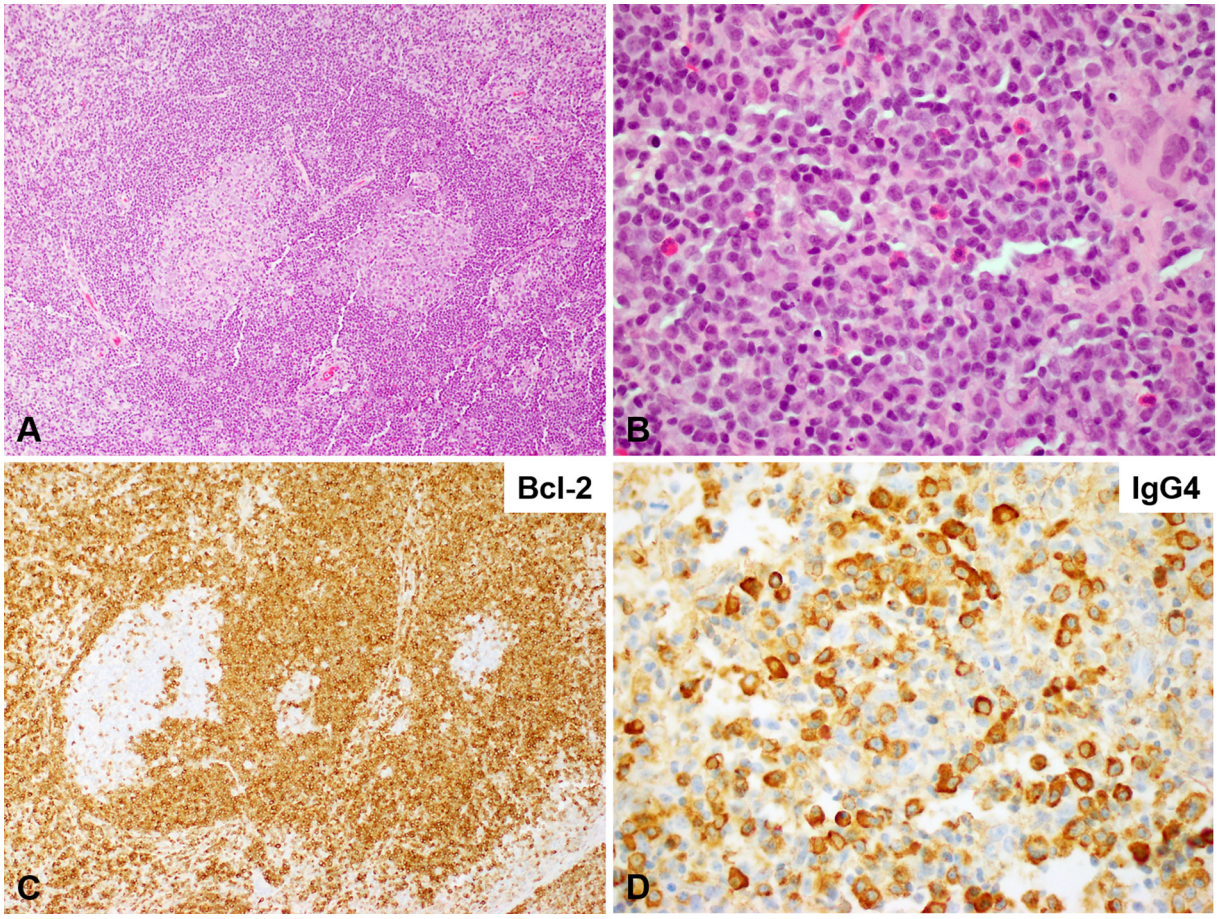

Fig. 3. Histologic features of PTGC IgG4-ROD (Case 3). The fibroadipose tissue shows scattered, enlarged lymphoid follicles with prominent mantle zones invading germinal centers (A). Sparse eosinophils, small lymphocytes and histiocytes were also identified within the lesion (B). Bcl-2 immunoexpression is present in mantle zone lymphocytes (C). Over 100 IgG4+ cells per HPF are present (D).

mantle zone lymphocytes that variably infiltrate germinal centers and may result in follicle lysis.[12] These findings can be highlighted by immunohistochemical stains such as bcl-2 or IgD.[3] Though it has been mostly described in lymph nodes, cases of extra-nodal PTGC have also been reported in the orbit, oral cavity, large bowel, and skin.[3,13] Interestingly, an association between IgG4-RD and PTGC has been recently identified, and PTGC is now recognized as one of the five histologic subtypes of IgG4-RD affecting lymph nodes.[1–3] EBV infection has been found in almost 60% nodal IgG4-RD compared to only 21% of extra-nodal IgG4-RD. Intriguingly, all patients with EBER+ PTGC-type IgG4-related lymphadenopathy had systemic lymphadenopathy and/or extra-nodal involvement.[4]

A few cases of systemic PTGC-type IgG4-RD also affecting the lacrimal gland and orbit have previously been described.[3,13] However, to the best of our knowledge, this is the first case series of extra-nodal PTGC-type IgG4-ROD with isolated lacrimal gland and orbital involvement at presentation. We reviewed 11 cases of ophthalmic IgG4-ROD and found three with features diagnostic of PTGC. In case 1, the changes were more prominent and extended throughout the specimen, while in cases 2 and 3 only a subset of follicles were involved. It is important to recognize PTGC, as it can be confused with other lymphoproliferative lesions such as Castleman's disease, rheumatoid arthritis-related lymphadenopathy, or even lymphoma. Moreover, there is a well-established correlation between extra-nodal IgG4-RD and the risk of developing lymphoma, especially mucosa-associated lymphoid tissue lymphoma (MALT). Therefore, identification of this entity is important to an accurate diagnosis and proper management and follow up.

Conflicts of interest

None of the authors have a conflict of interest.

Acknowledgments

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