

Orbital Mass With Features of Both Kimura Disease and Immunoglobulin G4-Related Disease

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Abstract: Kimura disease has been known as a chronic inflammatory disease of unknown etiology, since the first report in 1937 and characterized by an increased eosinophil fraction in peripheral blood, increased serum immunoglobulin E (IgE) levels, and lymphoid granuloma with eosinophilic infiltration on histopathological examination. The authors present a 30-year-old man who visited their clinic with a 3-month history of protrusion and conjunctival injection of the right eye. Surgical mass resection was performed, and initial histopathology revealed Kimura disease. Additional immunohistochemical examination revealed IgG4-related disease in another hospital, which showed more than 80 IgG4-positive plasma cells per high-power field and an IgG4+/IgG+ ratio more than 40%. There are histopathological similarities, and several reports have suggested a relationship between Kimura disease and IgG4-related disease. Thus, it is difficult to classify them as completely different diseases. Kimura disease and IgG4 can be considered a part of a clinical spectrum of abnormal immune reactions.

Kimura disease (KD) is a chronic inflammatory disease of unknown etiology, which has been reported frequently since the first report in 1937 and characterized by an increased eosinophil fraction in peripheral blood, increased serum immunoglobulin E (IgE) levels, and lymphoid granuloma with eosinophilic infiltration on histopathological examination.^{1,2} It is predominantly seen in young Asian men and occurs in the head and neck, subcutaneous tissue, and kidneys; it is rarely seen in the orbit or in the eye itself. Systemic symptoms such as fever, night diaphoresis, and weight loss are rarely reported.^{2,3}

Immunoglobulin G4-related disease (IgG4-RD) is characterized by significant infiltration of IgG4-positive plasma cells and T lymphocytes in various organs. Since the first report of serum IgG4 elevation in patients with pancreatitis in Japan in 2001, increased IgG4 levels have been associated with a variety of previously poorly understood diseases. The important findings in histopathological diagnosis for the IgG4-RD are storiform sclerosis with an increased IgG4+/IgG+ ratio, infiltration of IgG4-positive plasma cells, and obliterative vasculitis on biopsy.^{4,5} The commonly involved sites are the pancreas, biliary tract, retroperitoneum, kidney, lung, lymph nodes, salivary glands, prostate, and ocular adnexa. Cases of lacrimal gland and trigeminal nerve involvement have been reported.^{6,7}

A link between KD and IgG4-RD has been suggested several times in the literature as both are systemic diseases and have similar pathologic findings.⁷⁻¹⁰ We report a case of a

well-demarcated intraorbital tumor with characteristic histopathological features of both KD and IgG4-RD.

CASE PRESENTATION

A 30-year-old man visited our clinic with a 3-month history of protrusion and conjunctival injection of the right eye, associated with headache. There was no limitation of ocular movement. The intraocular pressure in the right eye was 30 mm-Hg by Goldman applanation tonometry. Hertel's exophthalmometry revealed that the right eye protruded approximately 3 mm more than the left. In contrast-enhanced computerized tomography of the orbit, a clearly demarcated 20 × 16 mm mass was noted between the lateral and inferior rectus muscles (Fig. 1). Laboratory tests showed elevated aspartate aminotransferase, alanine aminotransferase, and IgG4 antibody levels (50 IU/l, 115 IU/l, and 163 mg/dl, respectively).

Surgical resection was performed to remove the mass and to establish a definite diagnosis by histologic examination through a transconjunctival approach at inferior fornix after lateral canthotomy and inferior cantholysis, under general anesthesia. A white-yellow mass was identified behind the globe, firmly adherent to surrounding orbital tissue. The solid, oval mass was completely resected (Fig. 2A).



FIG. 1. The orbital computerized tomography of patient showing a well demarcated, round, enhanced mass attached to the inferolateral part of the right eyeball in sagittal (right) and coronal (left) views.

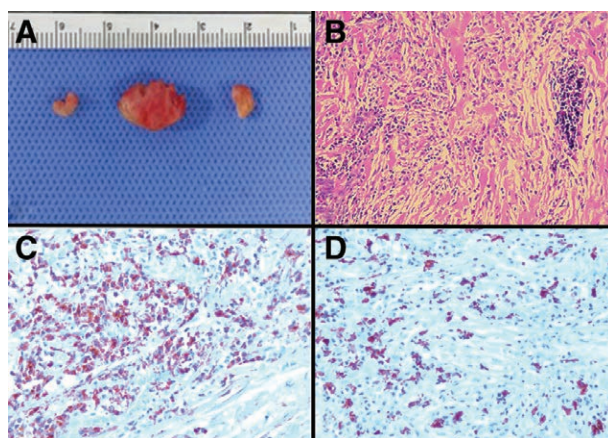


FIG. 2. The operative finding and pathology. **A**, Operative finding showing a 20 × 16 mm smooth, whitish mass after excision. **B**, Histopathology demonstrating dense lymphocytic aggregation with germinal center in hyalinized fibrous tissue, prominent eosinophilic infiltration in the stroma and capillary proliferation (hematoxylin-eosin stain, ×400). **C** and **D**, Immunohistochemical examination showing increased tissue IgG (**C**) plasma cells and IgG4 (>50/hpf) (**D**) plasma cells (×400).

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The patient whose histopathological examination showed eosinophilic infiltration around multiple germinal centers with lymphocytic infiltration, proliferation of capillaries around the nodule, and progressive fibrosis between the nodules had initially KD diagnosis (Fig. 2B). Additional postoperative testing showed elevated serum IgE levels (296.5 IU/mL) but no eosinophilia in peripheral blood. After surgical resection, protrusion and conjunctival hyperemia of the right eye improved. In order to improve the accuracy of the diagnosis, immunohistochemical staining was performed and IgG4-positive plasma cells were detected at a proportion of more than 40% among IgG-positive plasma cells, and more than 80 IgG4-positive plasma cells were detected per high-power field (Fig. 2C, D). These results indicated IgG4-RD. The patient was prescribed oral steroids for 1 week to reduce postoperative orbital inflammation and was observed, without recurrence or complications, for 3 months postoperatively.

DISCUSSION

This case had histopathological features of both KD and IgG4-RD. The authors reviewed the literature about KD and IgG4-RD to find out the characteristics of each disease and to discover if any similar case had been reported previously in the literature.

IgG4-RD has gradually come to include some different diseases and disorders. After a multinational research group coined the term IgG4-RD in 2012, various diseases, such as idiopathic orbital inflammation and reactive lymphoid hyperplasia, have been associated with IgG4-RD.¹¹ Many diseases such as autoimmune pancreatitis, Mikulicz disease, Kuttner tumor, Riedel thyroiditis, Ormond disease, retroperitoneal fibrosis, and eosinophilic angiocentric fibrosis, are also now classified under IgG4-RD.⁴ Thus, if diseases in eye, orbit, or the adnexa are related to IgG4, they could be classified as IgG4-related ophthalmic disease.⁴

In addition, since Tsubouchi et al⁹ reported the presence of numerous IgG4-positive plasma cells in lung biopsy specimens of KD patients, a relationship between KD and IgG4-RD has been suggested not only in ophthalmology but also in other fields. Kottler et al¹⁰ reported that KD had a similar clinical pattern to IgG4-RD based on the similarity of the clinical pathology of skin lesions in 25 KD patients to cutaneous IgG4-RD. Li et al⁸ hypothesized that IgG4-RD might be an epiphenomenon of KD, based on the reported presence of IgG4-positive plasma cells in KD and the results of immunohistochemical staining tests, in accordance with IgG4-RD

diagnostic criteria. Liu et al⁷ reported that a series of immune reactions due to chronic allergen exposure in KD patients may cause clinical manifestations of IgG4-RD. This hypothesis about the cause behind the association between KD and IgG4-RD could be significant.⁷

This present case also showed features of both KD and IgG4-RD on histopathological examination. The epidemiologic aspects of a young Asian male patient and elevation of serum IgE levels are consistent with KD, and serum IgG4 elevation and IgG4 immunohistochemical staining results are consistent with IgG4-RD. There have been several reports not only about KD cases which presented with increased serum IgG4 and histologic findings of IgG4-positive plasma cells but also of IgG4-RD cases which were associated with eosinophilic infiltration on histopathological examination. In conclusion, KD and IgG4-RD can be considered a part of a clinical spectrum of abnormal immune reactions. In addition, if KD is the histopathological diagnosis, diagnostic tests for IgG4-RD should be performed simultaneously.

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