CASE REPORT

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An Overview of Immunoglobulin G4-related Ophthalmic Diseases Accompanied by a Case Report

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ABSTRACT Immunoglobulin G4-related diseases (IgG4-RDs) are immune-mediated, fibroinflammatory conditions that are characterised by affected organ enlargement, lymphocyte, plasma cell infiltration (determined with IgG4-positive plasma cells) and serum IgG4 level elevation. When the disease affects ocular adnexal tissues (such as the lacrimal gland, extraocular muscles, trigeminal nerve branches and orbital fat), it is called IgG4-related ophthalmic disease (IgG4-ROD). The diagnosis of IgG4-ROD is made by physical examination, biochemical findings and histopathological evaluation. It is characterized by elevated serum IgG4 levels and distinctive histopathological features, including IgG4+ plasma cell infiltration, the presence of fibrosis in the storiform pattern and the presence of a dense lymphoplasmacytic inflammatory infiltrate, including eosinophils. It is rare in the ocular region and cause diagnostic confusion. There is a high probability of misdiagnosis when the disease is not recognized. Here, a rare case of eye involvement is presented and IgG4-RDs are discussed with the literature.

Keywords: IgG4-related disease; orbital disease; plasma cell; pathology

Immunoglobulin G4-related diseases (IgG4-RDs) are immune-mediated fibro-inflammatory conditions that can affect any organ system. They are characterised by enlargement of the affected organ, lymphoplasmacytic infiltrate containing plasma cells expressing IgG4 and elevated serum IgG4 levels and typical morphologic findings.[1]

IgG4-RDs can be seen in any organ, but the most commonly affected tissues include the pancreas, salivary glands, kidneys, retroperitoneum, periorbital tissue, lymph nodes, central nervous system, thyroid, lungs, liver, gastrointestinal tract, prostate, skin, breast and ocular adnexal tissues.[2,3] When the disease affects ocular adnexal tissues such as the lacrimal gland, extraocular muscles, trigeminal nerve branches, and orbital fat, it is referred to as IgG4 related ophthalmic disease (IgG4-ROD). IgG4-ROD does not show specific clinical features and the characteristic histopathological features of systemic IgG4-RDs, such as obliterative phlebitis and storiform fibrosis, may also be absent.[2,4] So that, the diagnosis of IgG4-ROD depend on elevated IgG4 cell levels and IgG4+/IgG+ in biopsied tissues.[5]

CASE REPORT

A 53-year-old a man presented eye medical clinic with a right eye proptosis. He had a painless swelling of both eyes for 20 years and proptosis of right eye for 12 years. Bilateral orbital mobile, solitary masses were found on physical examination (Figure 1).

The patient had eosinophilia and basophilia on the hemogram. In the contrast enhanced computerized tomography images, pronounced and massive thickness increase and tortiosis was observed in all extraocular muscles. The superior rectus muscle is

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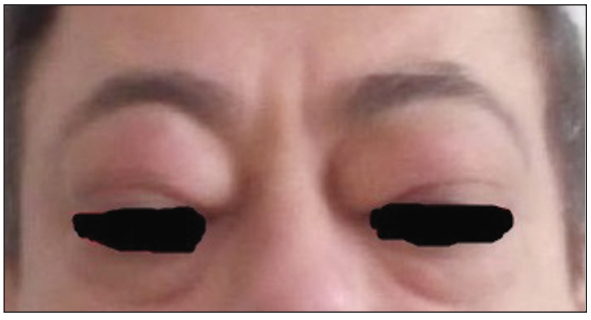

FIGURE 1: Proptosis of both eyes.

compressed by the superior oblique muscle, retroorbital fatty tissue were prominent. The findings were monitored symmetrically for both orbits. Both of the globes were anterior to the interzygomatic line and proptosis was observed (Figure 2). Pseudotumor, thyroid orbitopathy, sarcoidosis and systemic deposit diseases were considered in the initial radiologic diagnosis and neurofibroma was considered in clinical diagnosis.

Incisional biopsy was performed from the right orbital mass. It was encapsulated, hard and measuring 18×15×10 mm. Microscopically, the material had features of lymphoid tissue. A hyalinized-collagen ground was observed in nodulated focal areas starting from the capsule to make towards the center of the lymph node. There were numerous reactive follicles with distinct germinal centers. A large number of plasma cells, histiocytes and sparse eosinophils with lymphocytes were observed. Inflammation was accompanied by marked fibrosis. Because of the presence of collagen bands and a mixed cellular population on the ground, considering the possibility of Hodgkin's lymphoma analyzed in serial section but no typical Reed Stenberg cells or variant (Figure 3A, Figure 3B, Figure 3C). Morphologic and immunohistochemical findings were not found in favor of a low grade non Hodgkin's lymphoma. Orbital mass had features of lymphoid tissue and locally showed infiltration around nerve tissues. IgG4-related orbital disease was included in the differential diagnosis and in IgG4/IgG immunohistochemical staining, IgG4 was found to be significantly increased. Immunohistochemically IgG was positive, IgG4/IgG ratio was >60%, and IgG4 positive cells were found approximately 50-60/HPF (high power field) (Figure 3D, Figure 3E, Figure 3F).

Clinical, radiological and biochemical correlations were suggested for IgG4-ROD. Subsequently, blood biochemistry was examined. In blood biochemistry, eosinophil 11.6%, basophil 1.7%, IgG 2,369 mg/dL, IgG4 1,600 mg/dL were detected.

All clinical, radiological and biochemical findings were found to be compatible with IgG4-ROD. The patient was followed up under oral steroid treatment and his complaints subsided.

DISCUSSION

IgG4-RD is an autoimmune fibro-inflammatory condition that has recently affected many organs and tissues. It is characterized by elevated serum immunoglobulin IgG4 levels and distinctive histopathological features, including IgG4+ plasma cell infiltration and a fibroinflammatory response.[6,7] IgG4-RD can be seen in many organs such as pancreas, retroperi-

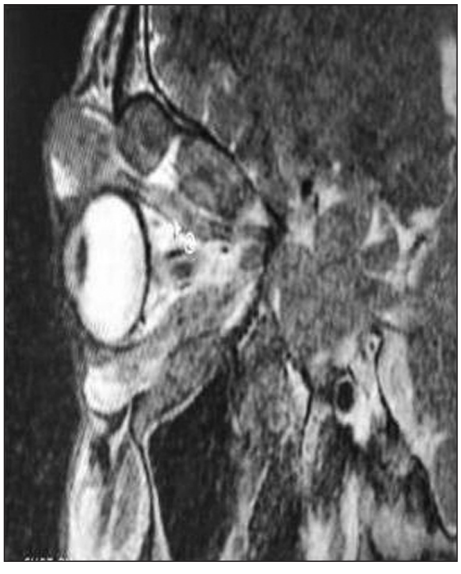

FIGURE 2: Magnetic resonance imaging of the orbit. a) In the axial T2 weighted image, it is seen that both globes are located clearly anterior to the interzygomatic line, consistent with exophthalmos. b) Bilateral size increase and tortiousness in the superior oblique muscles in the axial T2 weighted image are shown by arrows. c) In contrast-enhanced coronal section, marked increase in thickness and enhancement in extraocular muscles are observed almost symmetrically on both sides (arrows). d) Homogeneous enhancement of soft tissue masses in the pterygopalatine fossa are shown by arrows. e, f) Diffusion restriction in the pterygopalatine fossa (arrows) in diffusion-weighted axial image and apparent diffusion coefficient (ADC) mapping, respectively.

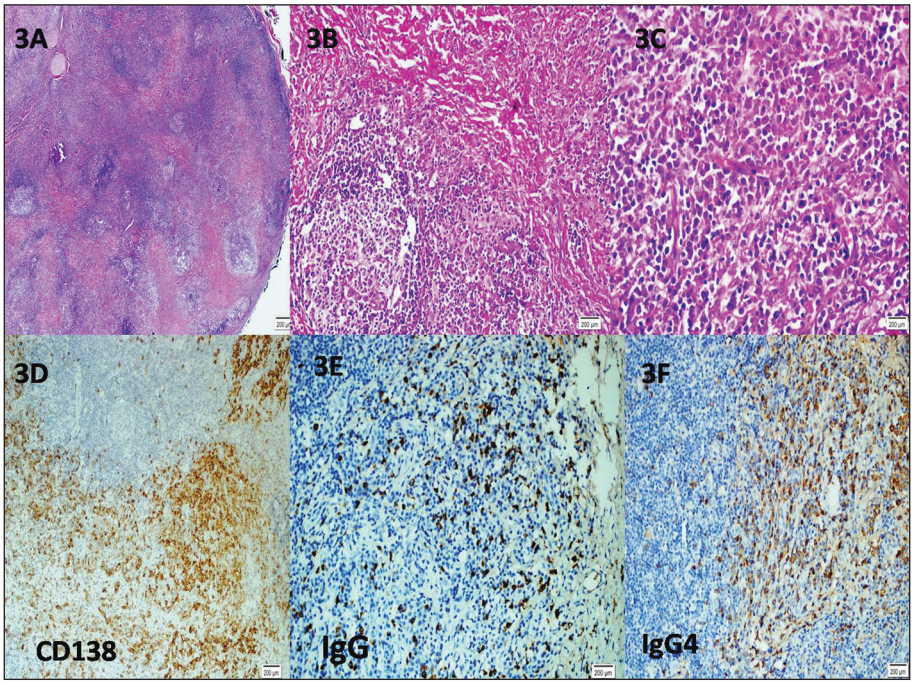

FIGURE 3: (A) Microscopically, the material had features of lymphoid tissue. A hyalinized-collagen ground was observed in nodulated focal areas starting from the capsule to make towards the center of the lymph node (HE, x20). (B) There were numerous reactive follicles with distinct germinal centers (HE, x200). (C) A large number of plasma cells, histiocytes and sparse eosinophils with lymphocytes were observed (HE, x400). (D) Numerous plasma cell infiltration (CD138, x100). (E) IgG expression in plasma cells (IgG, x200). (F) IgG4 expression in plasma cells (IgG4, x200).

toneal tissue, salivary glands, kidneys, periorbital tissue and lymph nodes. When the disease occurs in the periocular tissues, this condition is referred to as IgG4-ROD.[3] IgG4-ROD most commonly affects the lacrimal gland, but orbita, extraocular structures, nasolacrimal drainage and nerves may also be affected.[8,9] Bilateral orbital mobile, solitary masses were found in our patient.

The diagnosis of IgG4-RDs is made by physical examination, biochemical findings and histopathological evaluation. Diagnostic criteria for IgG4-RDs are as follows; there is organ involvement, serum IgG4 levels are higher than 135 mg/dL, the number of IgG positive plasma cells is greater than 10 per HPF and the plasma cell ratio of IgG4+/IgG+ is at least 40-50% in histological tissue sections.[10,11] Serum IgG4 level higher than >135 mg/dL suggests IgG4-RDs but is not specific for this disease, it may also be increased in other autoimmune diseases, chronic inflammatory diseases such as pneumonia, otitis, sinusitis and some malignancies. Therefore, correlation of biochemical findings with histopathological findings is important.[12] However, it should be kept in mind that IgG4 positive plasma cells may also be increased in diseases such as sarcoidosis, thyroid-related ophthalmopathy, idiopathic orbital inflammatory syndrome lymphoma, Rosai-Dorfman disease and rheumatoid arthritis.[13]

Our patient also had an orbital mass. Serum IgG4 levels increased up to 1,600 mg/dL and in histological tissue sections, IgG4+/IgG+ plasma cell ratio was above 60%.

Ophthalmologically IgG4-related ophthalmic disease may occur with various symptoms such as dacryoadenitis, myositis, hypophysitis, pachymeningitis causing cranial neuropathies. Bilateral lacrimal gland involvement is most common.[14]

The histologic pattern of IgG4-RDs is characteristic.The main histopathological features of the disease are the marked increase of IgG4+ plasma cells in the tissue, the presence of fibrosis in the storiform pattern (but not always), the presence of a dense lymphoplasmacytic inflammatory infiltrate, including eosinophils. Obliterative vasculitis or phlebitis may also be seen.

In our patient the biopsy specimen had features of lymphoid tissue. A large number of plasma cells, histiocytes and sparse eosinophils with lymphocytes were observed. Inflammation was accompanied by marked fibrosis and Immunohistochemically IgG was positive, IgG4/IgG ratio was >60%, and IgG4 positive cells were found approximately 50-60/HPF.

In most cases, two of the three major histological features are required for diagnosis. IgG4 immunostaining is strongly recommended. Plasma cell number and ratio should be as previously stated. The number of IgG4 plasma cells usually varies according to the anatomical region. Various organ specific cut off values have been proposed.[3,12]

Most accepted treatment consists of steroids. Orbital IgG4-RDs usually shows dramatic response with steroids but relapses are common so long-term use of immunosuppressive therapy is recommended.[14]

In conclusion, IgG4-ROD should be kept in mind in inflammatory eye lesions that can be confused clinically and pathologically with many lesions including malignancy. Correct diagnosis and correct treatment save lives.

Informed Consent

The patient was informed about the procedures, the disease and that he would be presented as a case report.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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