Case Report

Immunoglobulin G4-Related Ophthalmic Disease: A Case Report

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The authors reported a rare case with immunoglobulin (Ig) G4-related ophthalmic disease presented with chronic progressive bilateral complete ophthalmoplegia and blindness from orbital apex syndrome. MRI brain and orbit demonstrated ill-defined infiltrative lesions at bilateral orbital apexes, bilateral optic canals, and bilateral Meckel's caves, causing optic nerve compression and possibly optic neuropathy with generalized leptomeningeal enhancement at dura, cavernous sinus, and parotid gland. Lumbar puncture revealed few small lymphocytes, rare monocytes, very rare neutrophils with degenerative cells in background, and negative for malignancy. Serology titers for IgG subclass 4 (IgG4) had resulted in 5.959 grams per deciliter (g/dL). A dural biopsy revealed aggregate histiocytes with chronic inflammation and focal foreign body type giant cells. Motility improvement was achieved in the patient after systemic corticosteroids treatment. IgG4 serology should be considered for workup when patients present with chronic idiopathic orbital inflammation.

Keywords: IgG4-related ophthalmic disease, Ophthalmoplegia, Orbital apex syndrome

Received 4 Feb 2020 | Revised 13 May 2020 | Accepted 15 May 2020

J Med Assoc Thai 2020;103(7):719-24
Website: http://www.jmatonline.com

The term immunoglobulin (Ig) G4-related disease (IgG4-ROD) is an inflammatory condition characterized by proliferation of fibroblasts and lymphoplasmacytic inflammatory infiltrations and elevation of serum IgG4 level, IgG4-ROD may affect any ocular tissue but often presents as dacryoadenitis, myositis or orbital inflammation. Although it rarely affects the retrobulbar area, IgG4-ROD can present as orbital apex syndrome with enhancement of retrobulbar fat infiltration on magnetic resonance imaging (MRI) consistent with orbital inflammation. The differential diagnosis in IgG4-related orbital apex syndrome including idiopathic orbital inflammation (IOI), systemic vasculitis such as Wegener granulomatosis, orbital lymphoma, or metastasis[1].

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How to cite this article:

Thitiwichienlert S, Tangpagasit W, Sabsanhor S, Patarajierapun P. Immunoglobulin G4-Related Ophthalmic Disease: A Case Report. J Med Assoc Thai 2020;103:719-24.

doi.org/10.35755/jmedassocthai.2020.07.11128

Case Report

A 69-year-old Thai female presented with chronic headache and bilateral progressive painful visual loss during a 2-month period. She did not have nausea or vomiting, weakness, or numbness. She went to a secondary care hospital and a non-contrast computerized tomography (CT) brain showed bilateral chronic subdural hematoma (SDH) over the parietal lobes. She was referred to the neurosurgery department in the authors' hospital and underwent burr hole drainage and irrigation of chronic SDH on June 27, 2019. An ophthalmology consultation to evaluate the visual function was conducted after surgical intervention. Initial best corrected visual acuities (BCVA) were counting fingers (CF) at 1-foot oculus dexter (OD) and light projection (PJ) oculus sinister (OS). The external eye examinations revealed bilateral asymmetrical ptosis. The intraocular pressure, anterior segment, and dilated fundus examinations were normal in both eyes. The pupils were 5 mm in size and reacted sluggishly to light both eyes without relative afferent pupillary defect (RAPD). The ocular motility was completely limited in all direction in both eyes (Figure 1). The vestibule-ocular reflex (VOR) was impaired. The neurological examinations revealed decreased bilateral facial

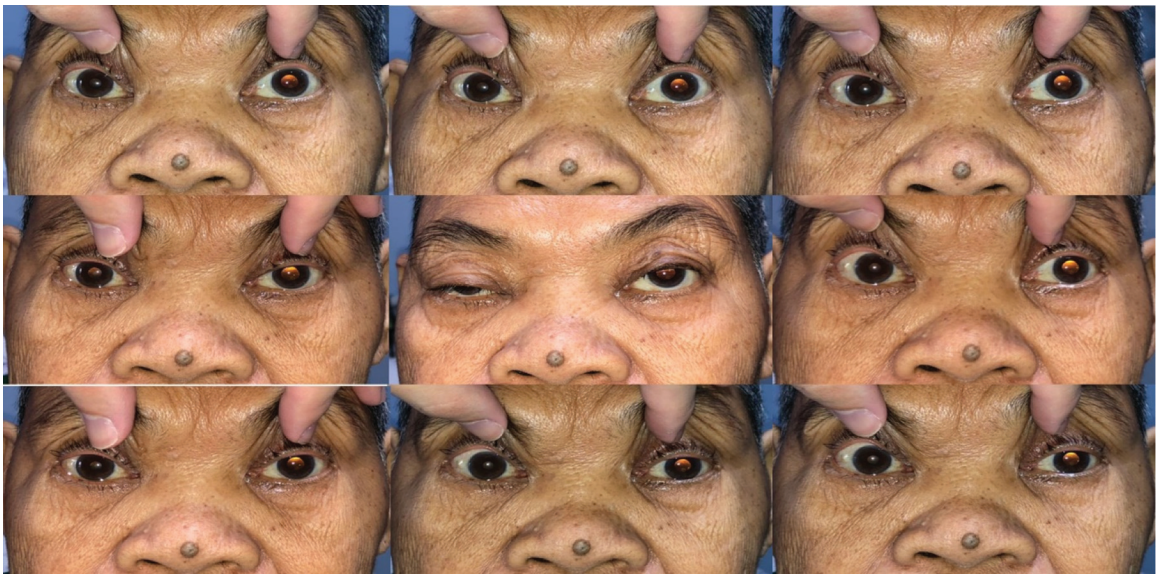

Figure 1. Nine diagnostic gazes show completely limited in all direction gazes in both eyes.

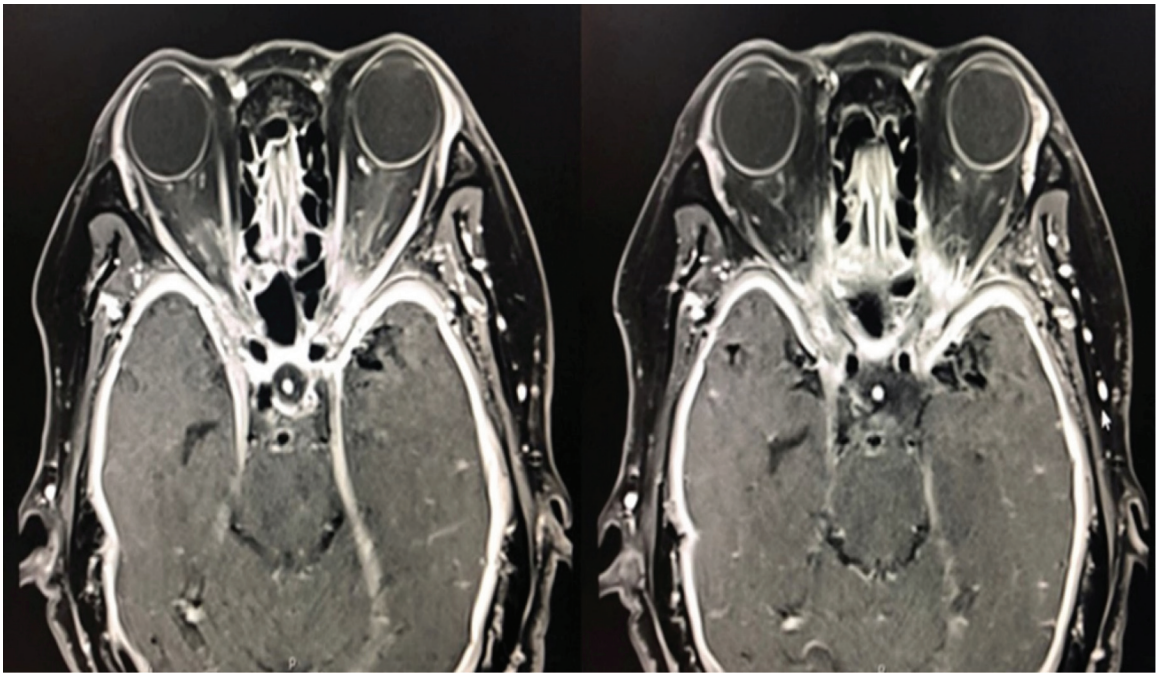

Figure 2. Contrast enhanced MRI brain and orbit revealed ill-defined infiltrative lesions at bilateral orbital apexes, bilateral optic canals and bilateral Meckel's caves.

sensation in the trigeminal nerve distributions with no decreased of body sensation, motor weakness, and other cranial nerves involvement. Deep tendon reflexes were normal and cerebellar signs were absent.

Contrast enhanced MRI of the brain and orbit revealed ill-defined infiltrative lesions at the bilateral orbital apexes, bilateral optic canals, and bilateral Meckel's caves, causing optic nerve compression and possibly optic neuropathy (Figure 2). Homogeneous enhancement of the bilateral cavernous sinuses showed subtle lateral convexity, probably from

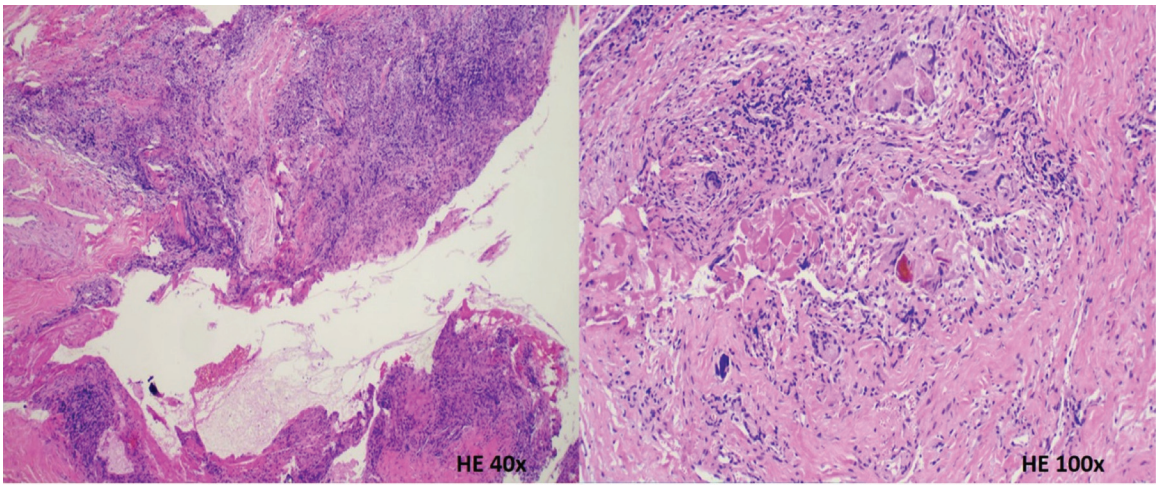

Figure 3. The hematoxylin and eosin (H&E) stained tissue revealed aggregate histocytes with chronic inflammation and focal foreign body type giant cells.

infiltrative lesion, or cavernous sinus thrombosis. Mild prominent size of superior ophthalmic veins was seen. Bilateral eye globes, bilateral orbital fat, extraocular muscles, and lacrimal glands were unremarkable. The radiological differential diagnosis was inflammatory lesions such as pseudotumor or lymphoproliferative disorder. The following laboratory analyses were unremarkable, complete blood count, blood urea nitrogen, creatinine, liver function test, fasting blood sugar, anti-HIV antibody, venereal disease research laboratory (VDRL), treponema pallidum hemagglutination (TPHA), chest X-ray, urine analysis, and stool concentration. Laboratory investigation of serum inflammatory markers showed a significant elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Serologic tests showed negative anti-double-stranded DNA (anti-dsDNA), positive antinuclear antibody (ANA), positive perinuclear antineutrophil cytoplasmic antibody (p-ANCA), and negative cytoplasmic ANCA (c-ANCA). Serology titers for IgG subclass 4 (IgG4) resulted in 5.959 grams per deciliter (g/dL) (normal range 0.03 to 0.86 g/dL).

During the investigation process, the patient complained of rapid decreased vision. BCVA were no light perception (NLP) in her both eyes. The pupils were 6 mm in size and did not react to light both eyes, which RAPD cannot be evaluated. The patient was referred to neurologist and underwent lumbar puncture procedure. The cerebrospinal fluid (CSF) analysis revealed normal opening pressure, normal sugar, and protein. The CSF cytology revealed few small lymphocytes, rare monocytes, very rare neutrophils with degenerative cells in the background and negative for malignancy. The most likely differential diagnosis was IgG4-ROD due to the increased serum IgG4 level. The patient did not have enlarged lacrimal or parotid glands. The authors discussed simultaneously with both the ear, nose, and throat (ENT) surgeon and neurosurgeon about tissue biopsy to make a diagnosis. The patient underwent frontal craniotomy with dural biopsy and duraplasty. The hematoxylin and eosin (H&E) stained tissue revealed aggregate histocytes with chronic inflammation and focal foreign body type giant cells (Figure 3). Acid-fast (AFB), gomori methenamine silver stains (GMS), and periodic acid-Schiff stains (PAS) were negative for organisms. Flow cytometry was normal for blood pattern representing around 9.8% of the total leukocyte population. These lymphoid cells were a mixture of B-cells (5.5% or 343 events), T-cells 76.4%, natural killer (NK) cells 16.3%, and B-cells express polytypic light chain Ig CD4:CD8 / 49:44.

The rheumatologists recommended systemic corticosteroids for the treatment of IgG4-ROD. After starting the treatment with oral prednisolone 0.6 mg per kilogram per day (MKD), she was discharged from the hospital. On follow-up at two weeks at the eye clinic, the patient still had blindness with some improvement of bilateral ptosis and ocular motility. Her eyes could move about 10% (Figure 4). The fundus examinations revealed mild pallor of bilateral optic discs. After the diagnosis was confirmed by a dural biopsy, the patient planned for long-term tapering of prednisolone.

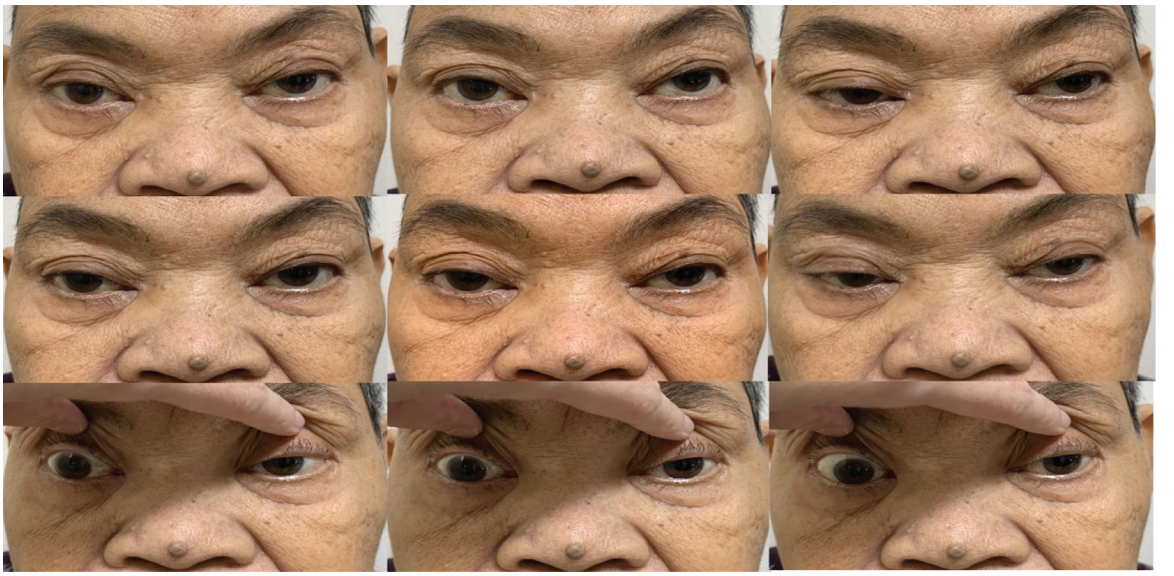

Figure 4. Nine diagnostic gazes show some improvement of ophthalmoplegia on the follow-up visit.

Discussion

Ig are Y-shaped glycoproteins antibodies secreted by activated B cells. Activated B cells form the humoral immune system and differentiated into plasma cells upon antigen recognition. Among five Ig isotypes (IgA, IgD, IgE, IgG, and IgM), IgG is the most long-lived isotype in the serum[2]. There are four subclasses, including IgG1, IgG2, IgG3, and IgG4. In 2004, the discovery of IgG4-related disease was identified in the fibroinflammatory condition characterized by widespread tissue infiltration by IgG4 rich plasma cells and elevation of serum IgG4 level. In 2011, the International symposium on IgG4-related disease recommended the term of IgG-related disease followed by the organ affected as the preferred nomenclature[3]. IgG4-related disease was first reported in autoimmune pancreatitis, and later in other organs included liver, salivary gland, nephritis, and interstitial lung disease, which are now recognized by the IgG4-related systemic disease spectrum[4-6]. IgG4-ROD was first reported in lacrimal gland involvement (dacryoadenitis), and there are generally two types of inflammation, acute and chronic inflammation, but the course of chronic inflammation is much more well-established. Ophthalmic symptoms can be unilateral or bilateral, and the involvement can affect any part of the eye and its adnexa.

Orbital apex syndrome is a rare neuro-ophthalmic manifestation of IgG4-ROD and is sight threatening if optic nerve dysfunction is not detected. In the present case, the patient had symptoms and signs of orbital apex syndrome, which is characterized as the dysfunction of the optic nerve and the ocular motor cranial nerves[7]. Orbital apex syndromes may result from variety of inflammatory, infectious, neoplastic, iatrogenic or traumatic, and vascular etiologies. Inflammatory etiology within the orbital apex may present as painful ophthalmoplegia with optic neuropathy. The onset of symptoms usually acute to subacute onset with progression within days to weeks. Associated systemic conditions include thyroid eye disease, IOI, Wegener granulomatosis, giant cell arteritis, sarcoidosis, orbital lymphoproliferative disease, orbital lymphoma, and orbital metastasis. The term IOI, also known as orbital pseudotumor is a heterogenous group of a non-specific inflammatory process characterized by proliferation of fibroblasts and lymphoplasmacytic inflammatory infiltrations. Clinically, IOI has been categorized as myositis, dacryoadenitis, anterior, apical, and diffuse process in various orbital regions[8]. Depending on the orbital site of involvement, IOI, IgG4-ROD, orbital lymphoproliferative disease, and orbital lymphoma can cause similar clinical manifestations and imaging findings. However, the clinical course of IgG4-ROD usually slowly progressive and chronic, the patients with IgG4-ROD have a mean disease duration of 21 months, but IOI had a mean disease duration of 10 months. IgG4-ROD often result in bilateral involvement (54% to 100%) and without any pain, and frequently associated with disease-specific extra-ophthalmic manifestations[9].

The diagnosis of IgG4-ROD is based on a typical clinical manifestation, laboratory investigations, radiological findings, and distinct histopathological and immunohistochemical findings. The patients with IgG4-ROD usually have high serum levels of IgG4 and serum IgG4 level had a sensitivity of 90% and specificity of 60%. However, approximately 20% to 40% of the patients with biopsy-proven IgG4-related disease have normal serum levels of IgG4, so the serum level of IgG4 is not a diagnostic marker[10]. The histopathological and immunohistochemical findings can provide strong supportive evidence for the diagnosis of IgG4-ROD. The International symposium on IgG4-related disease recommended that at least two of the three major histopathological findings are required for diagnosis of IgG4-related disease as following 1) dense lymphoplasmacytic infiltrate with predominance of T lymphocytes, 2) fibrosis, arranged at least focally in storiform pattern (spiral or whorled appearance), and 3) obliterative phlebitis. In immunohistochemical findings, an IgG4/IgG plasma cell ratio of more than 40% is also considered a strong supportive evidence for the diagnosis[11].

The current standard first line treatment consists of corticosteroids. The patients usually have a positive response to corticosteroids. However, the clinical course of the disease is variable and corticosteroids effect may not last, requiring the addition of immunosuppressive agents such as mycophenolate mofetil or rituximab to prevent long-term adverse effects of corticosteroids[12-14]. In the present case, the value of laboratory investigations and CSF analysis is the exclusion of infectious and neoplastic process. Serum IgG4 level was elevated at 5.959 grams per deciliter (g/dL) (normal range 0.03 to 0.86 g/dL). The dural biopsy was obtained and showed chronic inflammatory infiltrate. A diagnosis of IgG4-ROD was made. The patient then initiated treatment with long-term tapering prednisolone. At the 2-week follow-up visit, she still cannot see the light, but she would require a long-term regular follow-up for the response of corticosteroids with or without immunosuppressive agent.

Conclusion

The authors reported a rare case of IgG4-related orbital apex syndrome. IgG4-ROD must be considered in the differential diagnosis in patients presenting with chronic bilateral orbital inflammatory process. The diagnosis is established by clinical recognition, serum level of IgG4, and histopathological findings. The serum level of IgG4 should be performed when the disease is suspected.

What is already known on this topic?

IgG4-ROD is an uncommon entity of fibroinflammatory condition, but a serious sight threatening from orbital apex involvement. The clinical course of IgG4-ROD is usually slowly progressive and chronic. IgG4-ROD often results in bilateral involvement and without any pain and is frequently associated with disease-specific extra-ophthalmic manifestations.

What this study adds?

A very few patients with IgG4-ROD develop blindness from bilateral orbital apex involvement. Therefore, patients with a history of chronic bilateral orbital inflammatory process should be evaluated for IgG4-related disease.

Conflicts of interest

The authors declare no conflict of interest.

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