

## Case Report

# A Case of Scleritis Associated with Immunoglobulin G<sub>4</sub>-Related Aseptic Meningitis

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**Abstract**

**Purpose:** The aim of this study was to report a case of scleritis associated with immunoglobulin G<sub>4</sub> (IgG<sub>4</sub>)-related aseptic meningitis.

**Case report:** A 63-year-old man, who was referred to our clinic with *refractory uveitis*, presented initially with severe headache, fever and ocular inflammations. Slit-lamp examination revealed bilateral scleritis, an increase of scleral thickness was also observed by anterior segment optical coherence tomography (CASIA SS-1000, Tomey, Japan). After the investigation for a fever of unknown origin, IgG<sub>4</sub>-related aseptic meningitis was diagnosed with a cerebrospinal fluid (CSF) examination and bone marrow biopsy. After the definite diagnosis, the patient was treated with oral prednisolone (initial dose 30 mg/day). After the treatments, all symptoms including inflammation of the sclera, headache, and laboratory data were improved. The scleral thickness also decreased markedly. With treatment, ocular inflammation was controlled during the following 7 months, but the scleritis recurred during steroid tapering. Currently, the patient continues to be followed untreated without complications.

**Conclusion:** The clinical findings of ocular inflammation strongly suggested scleritis in this patient. To our knowledge, this is the first report of scleritis associated with IgG<sub>4</sub>-related aseptic meningitis. It is necessary to consider the IgG<sub>4</sub>-related disease as a differential diagnosis of scleritis.

**Keywords:** Scleritis; Immunoglobulin IgG<sub>4</sub>; Meningitis

## Introduction

IgG<sub>4</sub>-related disease (IgG<sub>4</sub>-RD) is an unknown disease entity characterized by elevated serum IgG<sub>4</sub> concentration, tumefaction, a dense lymphoplasmacytic infiltrate rich in IgG<sub>4</sub>-positive plasma cells, storiform fibrosis, obliterative phlebitis, mild to moderate eosinophilic, and elevated serum IgG<sub>4</sub> levels [1]. IgG<sub>4</sub>-RD can affect almost any organ: the biliary tract, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin.

Diagnosis of IgG<sub>4</sub>-RD is based on identification of a combination of reported histologic patterns and increased numbers of IgG<sub>4</sub> polyclonal plasma cells [2]. The underlying pathologic mechanism of IgG<sub>4</sub>-RD is unclear; however, enriched lymphoplasmacytic infiltration of IgG<sub>4</sub>-positive plasma cells, fibrosis in the involved organs, and elevated levels of serum IgG<sub>4</sub> were thought to be involved in the pathogenesis. Glucocorticoid had been shown to have clinical efficacy [3,4]. Despite a good response to steroid therapy, the lesion often recurs during steroid tapering or following the withdrawal of steroid treatment [4,5] Rituximab (an anti-CD20 monoclonal antibody) has also been effectively used in patients with refractory to corticosteroids and immunosuppressive agents [5].

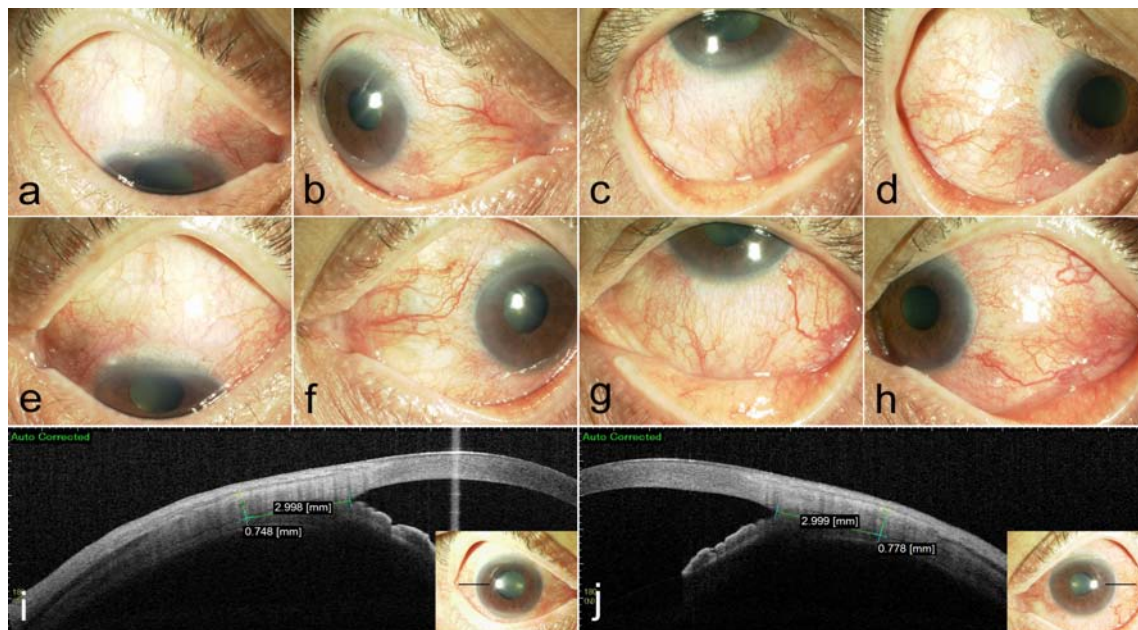
Mikulicz's disease, characterized by swelling of lacrimal and salivary glands, has been identified as part of the spectrum of IgG<sub>4</sub>-RD [6,7]. Since then, many studies on IgG<sub>4</sub>-RD in the ophthalmic region have focused to a large extent on the lacrimal gland. However, IgG<sub>4</sub>-RD has been reported to affect several ophthalmic

region not only the lacrimal gland but also other ocular adnexa, such as extraocular muscles, branches of the trigeminal nerve [8-11]. Ocular manifestations of IgG<sub>4</sub>-RD are reported to as external ophthalmoplegia, ptosis, exophthalmos, intraocular pressure elevation, and ophthalmalgia.

IgG<sub>4</sub>-RD also involves the sclera, it occurs bilaterally and presents with anterior chamber inflammation in middle age [12,13]. The prognosis is good, because systemic rituximab and steroid have been reported to well control ocular inflammation [13,14], however; its etiology still remained to be elucidated. There are few cases which IgG<sub>4</sub>-RD caused *scleritis* [13,15]. *However, to the best of our knowledge, there is no report of scleritis associated with IgG<sub>4</sub>-related aseptic meningitis. In the current study, we report and discuss a rare association with these diseases.*

## Case Presentation

The patient was a 63-year-old man with 1 month history of *refractory uveitis* and consulted a local ophthalmologist. He was diagnosed with scleritis and referred to our department. At first visit, he complained of severe headache, fever, blurred vision and bilateral inflamed eyes. There was no previous ophthalmic history and his general health was good. His best corrected visual acuity (BCVA) was 1.2 bilaterally and his intraocular pressures were normal. A slit-lamp examination revealed bilateral conjunctival/ciliary injection, scleritis, and 2+ anterior chamber cells (Figure 1a, b). Increase of scleral thickness was observed by anterior segment optical coherence tomography (AS-OCT) (CASIA SS-1000, Tomey, Japan) (Figure 1c).



**Figure 1:** Slitlamp photograph of the right eye (a-d) and left eye (e-h) showing engorged episcleral and scleral vessels. The sclera was imaged 3 mm from the detected scleral spur using an AS-OCT system (CASIA SS-1000, Tomey, Japan) showing the increase of temporal scleral thickness of the right eye (i) and left eye (j).

According to the previous report, the mean scleral thickness of forty normal healthy controls was  $0.53 \pm 0.08$  mm [16].

On peripheral blood tests, erythrocyte sedimentation rate and C-reactive protein were elevated. Serum autoantibody was all negative. There was no finding suggestive of inflammatory diseases and tuberculosis. And, there were no findings in head MRI, chest X-ray, and computed tomography. In spite of intensive examination, the etiology of the disease remained unclear. He was admitted into our hospital to investigate the cause of headache and unidentified fever. A cerebrospinal fluid (CSF) examination showed negative viral antibodies, increased protein concentration, lymphocytic pleocytosis, and presence of eosinophils. Hematological examination shows elevated serum IgG4 concentrations; histopathologic examination of bone marrow shows the fibrosis and infiltrations of IgG4-positive plasma cells (Figure 2), thus the patient was diagnosed with IgG4-related aseptic meningitis according to the diagnostic criteria [1].

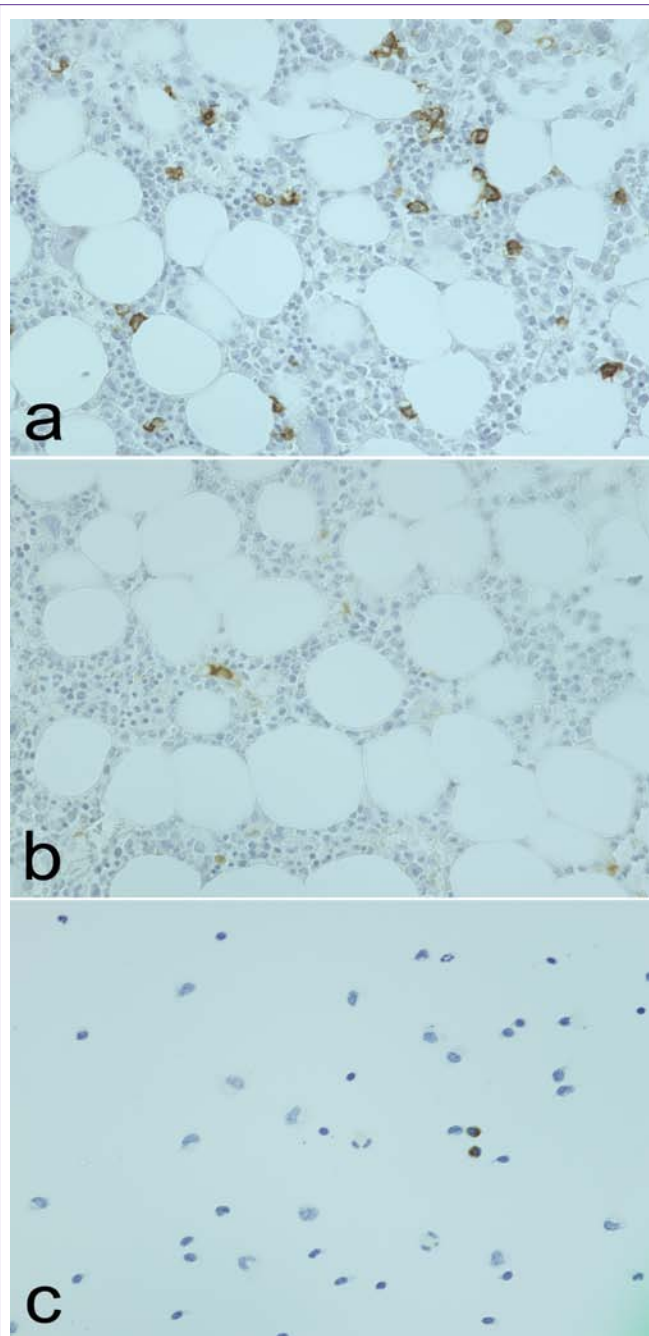
Initially, the patient was treated with topical steroids for eye symptom, but there was no improvement. After the definite diagnosis, the patient was treated with oral prednisolone (initial dose 30 mg/day). After the treatments, all symptoms including inflammation of the sclera and laboratory test results were improved (Figure 3). Two months after the therapy, systemic signs of inflammation and scleritis were alleviated, accompanied by reduction of serum IgG4 concentration to normal range. Unexpectedly, after seven months, headache, tinnitus and scleritis reappeared and systemic steroid was resumed, resulting in lesion and symptom control after ten months. At the last examination after sixteen months of follow-up, the BCVA was 1.5 with no evidence of active inflammation. The patient continues to be followed untreated without complications.

## Discussions

IgG4-RD is a novel clinical disease entity characterized by elevated

serum IgG4 concentration and tumefaction or tissue infiltration by IgG4-positive plasma cells. The diagnosis of IgG4-RD is based upon biopsy findings demonstrating the characteristic histopathologic findings and immune histological staining. A diagnosis of IgG4-RD is definitive in patient with clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs, elevated serum IgG4 concentrations, and marked lymphocyte and/or plasmacyte infiltration and fibrosis and infiltration of IgG4-positive plasma cells [1]. It is significant for the diagnosis of IgG4-RD to confirm swelling or thickening of the affected lesions. In the current case, we could observe the thickening of the sclera by using AS-OCT, the increase of eosinophils and infiltrations of IgG4-positive plasma cells in the cerebrospinal fluid, elevated serum IgG4 concentrations, and histological findings. Many systemic diseases such as rheumatoid arthritis, ANCA-associated vasculitis, and systemic lupus erythematosus had been reported to cause scleritis [17]. Moreover, there are a few reports of *scleritis* caused by IgG4-RD. However; to the best of our knowledge, this is the first report of scleritis associated with IgG4-RD aseptic meningitis.

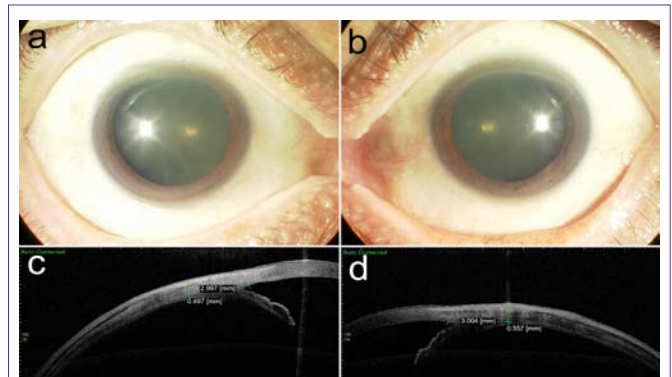
Glucocorticoids are typically the first line of therapy for IgG4-RD. Most patients respond well to oral glucocorticoid within several weeks [5], but the lesion sometimes recurs during tapering of steroid. For patients with recurrent or refractory IgG4-RD, B-cell depletion with rituximab has also been a useful approach [13,14]. And there is report of successful use of rituximab in a patient with IgG4-RD and refractory scleritis [12]. At first, we speculated that topical steroids only cannot prevent production of IgG4 because immunological reactions in bone marrow caused ocular inflammation. Therefore, we treated with topical steroids only for eye symptoms not to prevent intensive examination, but there was no improvement. After the definite diagnosis and starting treatment with systemic steroids, the improvement of symptoms including inflammation of sclera and



**Figure 2:** Histopathological analyses at 40X. (a) Immunohistochemistry for CD138, marker characteristically positive for plasma cells, shows numerous positive cells in bone marrow biopsy. (b) IgG4 immunohistochemistry demonstrating IgG4 positive plasma cells in bone marrow. (c) Immunohistochemical staining for *IgG4* in spinal fluid showing strong staining in plasma cells.

laboratory test results was achieved.

Pathologically, IgG4-RD is reported to be caused by T helper ( $Th_2$ )-cells immune responses stimulated with autoimmunity and infectious agents. In addition to  $Th_2$ -cells, activation of regulatory T cells ( $T_{reg}$ ) is also characteristic of IgG4-RD. Interleukin (IL)-4, 5, 10, 13, and transforming growth factor  $\beta$  (TGF- $\beta$ ) are over expressed through an immune reactions. These cytokines activate B cells, eosinophils,



**Figure 3:** Slitlamp photograph of the right eye (a,) and left eye (b) after the treatment, showing the local control of ocular inflammation. The sclera was imaged 3 mm from the detected scleral spur using an AS-OCT system, showing the significant decrease of temporal scleral thickness of the right eye (c) and left eye (d).

and fibroblasts which contribute to the eosinophilia, elevated serum IgG4, Ig E concentrations, and progression of fibrosis [5]. Meanwhile, pathogenesis of scleritis is reported to be caused by autoimmunity and infectious agents as well as IgG4-RD. Cytokines and chemokines produced by dendritic cells (DCs) attract T cells and B cells, and involved in the pathogenesis. IL-8, 17, 23, and TNF- $\alpha$  are produced and activate immune reaction. T cells, plasma cells, macrophages, DCs and fibroblasts localized in the sclera could release tissue-destructive matrix metalloproteinase (MMP) and inhibit tissue inhibitor of matrix metalloproteinase (TIMP), resulting in tissue destruction [17]. Concerning the pathogenesis of diseases, both diseases share the same mechanisms of immunological reactions such as the activation of T and B cells. It is likely that elevation of eosinophils followed by increases of  $Th_2$  and  $T_{reg}$  cells in IgG4-related aseptic meningitis lead to the activation of T and B cell and caused severe scleritis in this patient.

In conclusion, we here report the first case of scleritis associated with IgG4-related aseptic meningitis. And it suggests that *there is something in common immune mechanisms between IgG4-RD and scleritis.*

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