

## Case Report

# A case of compressive optic neuropathy putatively caused by IgG4-related idiopathic orbital inflammation.

Ai HARAGUCHI, Takao ANDO, Ikuko UEKI, Ichiro HORIE, Misa IMAIZUMI, Toshiro USA, Satoshi YAMASAKI, Tomoki ORIGUCHI, and Atsushi KAWAKAMI

Unit of Translational Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Nagasaki, Japan.

We report the case of a 58-year-old male presenting with an impairment of the left-sided visual acuity caused by compressive optic neuropathy, and marked bilateral proptosis. Blood test showed markedly elevated IgG4 (1830 mg/dl) and positive TSH receptor-stimulating antibodies (200%), but the thyroid function test were normal. Orbital MRI revealed abnormal soft tissue proliferation around the optic nerve and fusiform enlargement of the extraocular muscles. Systemic CT analysis detected multiple lymph node swelling, pseudotumor in the lung, retroperitoneal fibrosis, and kidney lesions. We considered that the eye manifestation was most likely caused by IgG4-related idiopathic orbital inflammation. Systemic administration of a moderate dose of prednisolone dramatically improved the compression of the optic nerve, as shown by the improvement of the visual acuity and the MRI findings. The clinical course made thyroid-associated ophthalmopathy unlikely. In conclusion, an overall consideration of the clinical picture and extensive work-up of any possible differential diagnosis including measurement of the serum levels of IgG4 was highly useful in making the diagnosis of the patient.

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## Introduction

Idiopathic orbital inflammation is an idiopathic benign inflammatory space-occupying lesion (1). Presenting symptoms include proptosis, oculomotor deficits, pain, lid swelling or mass, ptosis, and chemosis. The disease progression of idiopathic orbital inflammation can be acute to subacute or occasionally chronic and idiopathic orbital inflammation is usually unilateral but may occasionally be bilateral. A small subset of patients may have decreased visual acuity because of optic nerve compression (2). It has recently been suggested that idiopathic orbital inflammation is one of the components of IgG4-related disease (3-6). IgG4-related disease is characterized by dense infiltration of IgG4-positive

plasma cells into multiple organs or tissues in association with increased serum levels of IgG4 (>135 mg/dl). This disorder is frequently seen in older males, often older males with allergic disorders, and the most common organs involved are the salivary glands and pancreas. Among the endocrine organs, the pituitary gland (7, 8) and the thyroid (9) have been shown to be affected.

Here we present a patient with marked proptosis and compressive optic neuropathy putatively caused by IgG4-related idiopathic orbital inflammation with positive TSH receptor-stimulating antibodies.

**Address correspondence:** Takao Ando, M.D., Ph.D.

Unit of Translational Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Nagasaki, Japan, 852-8501  
Voice: 81-95-819-7268; Fax: 81-95-849-7270; Email: takaoando@gmail.com

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## Patient

A 58-year-old male smoker was referred to our hospital due to reduced visual acuity and bilateral proptosis. He had no allergic diathesis and no family history of thyroid disorders. He had had proptosis of the left eye for three years and had had glucocorticoids treatment with prednisolone starting from 30 mg per day for compressive optic neuropathy two years before the referral. There had been clinical improvement of proptosis and the visual acuity, but the patient terminated prednisolone by himself and then noticed gradual aggravation of proptosis and impairment of the visual acuity.

On physical examination, there was marked proptosis (35 mm, bilaterally, determined by an exophthalmometer) with intact eyeball movement. His visual acuity was 20/30 after correction and hand motion at 30 cm in the right and left eye, respectively. There were no enlarged thyroid or palpable superficial lymph nodes and no skin lesions identified. Ophthalmologic investigation did not reveal any signs suggestive of uveitis. Blood test revealed mild eosinophilia (10% of 8500 white blood cells /uL) and a marked increase of total protein (10.5 g/dl). Serum levels of IgG and IgE were increased to 4940 mg/dl (reference range 879-1700 mg/dl) and 1765.6 mg/dl (reference range <269 mg/dl), respectively. There was no monoclonal immunoglobulin. Subclass analysis of serum IgG disclosed a marked increase in IgG4 to 1830 mg/dl (>135 mg/dl being considered abnormally high (10, 11)). The serum level of soluble IL-2 receptor was increased (1463 U/ml; reference range 124-466 U/ml). Proteinase 3- and myeloperoxidase-anti-neutrophil cytoplasmic antibodies were negative. Thyroid function was normal: free T3 3.15 pg/ml (2.37-3.91 pg/ml), free T4 1.28 ng/dl (0.95-1.57 ng/dl), and TSH 4.044 uIU/mL (0.48-5.08 uIU/mL); however, TSH receptor-stimulating antibodies were 200% (<180%) and positive. The orbital MRI (Figure 1A and B) showed proliferation of aberrant soft tissue in both sides of the orbit and mild enlargement of the extraocular muscles.

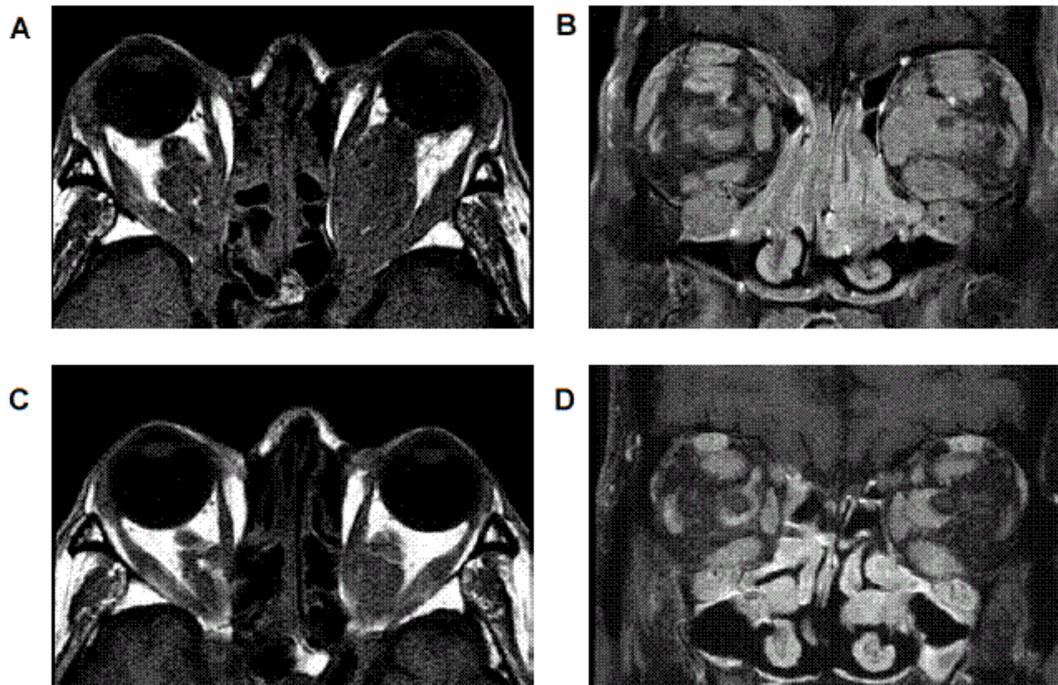
The marked elevation of serum IgG4 suggested IgG4-related idiopathic orbital inflammation. Since IgG4-related disease is known to show systemic involvement, we investigated putative lesions caused by IgG4-related disease by whole body CT. We were able to identify a lung pseudotumor, retroperitoneal fibrosis, and multiple less enhanced areas in the bilateral kidneys as well as swollen LNs from the neck to the mediastinum (not shown). Positron emission tomography-CT also documented fluorodeoxyglucose accumulation in the bilateral orbits, nasal sinus, mediastinal and hilar lymph

nodes and lung pseudotumor. Since the patient refused a tissue biopsy or surgical decompression of the left optic nerve, we were not able to make a definitive diagnosis. Considering the organs affected and the high levels of serum IgG4 and soluble IL-2 receptor, Wegener's granulomatosis and malignant lymphoma were the most important differential diagnoses. Wegener's granulomatosis was unlikely because of the negative anti-neutrophil cytoplasmic antibodies. His previous medical history of improvement of the visual acuity and proptosis by a moderate dose of prednisolone made malignant lymphoma unlikely. Based on the typical clinical findings, we considered that a diagnosis of IgG4-related disease including idiopathic orbital inflammation was most likely.

It was apparent that IgG4-related idiopathic orbital inflammation was the major element causing the proptosis and compressive optic neuropathy (Figure 1A and B), and thus the patient was treated with 20 mg of prednisolone. There was gradual improvement of the visual acuity (20/30 after correction and 20/1000 in the right and left eye, respectively) and dramatic amelioration of proptosis (17 mm, bilaterally), and there was also a decrease in the serum levels of IgG4 (468 mg/dl) and soluble IL-2 receptor (~500 U/ml). The aberrant orbital soft tissue dramatically declined and the extraocular muscles became slightly reduced in size (Figure 1C and D), and similar improvements in the lung and kidney were also noted in the follow-up CT (not shown). Therefore, the dose of prednisolone was tapered gradually down to 10 mg per day. However, there was symptomatic aggravation of the visual acuity shortly after the reduction of prednisolone. Therefore, a final maintenance dose of 13 mg was used, and resulted in no apparent relapse of the clinical symptoms.

## Discussion

IgG4-related disease is an emerging disease concept in which the affected organs or tissues may become tumorous as a result of a chronic inflammatory process, including IgG4-positive cell infiltration associated with fibrosis (10, 11). IgG4-related idiopathic orbital inflammation can occur alone or in association with other organ manifestation. The precise mechanism(s) by which IgG4-related disease develops have not been elucidated. It has been reported that IgG4 concentrations are closely associated with disease activity in IgG4-related disease (12). However, it is not known whether IgG4 has any pathogenic roles in IgG4-related disease. It has been shown that allergic rhinitis and



**Figure 1.** Ocular MRI before and after prednisolone treatment.

Panels (A) and (B) show massive proliferation of soft tissue around the optic nerve adjoining the extraocular muscles. The extraocular muscles show fusiform enlargement relatively sparing the tendons in the left eye. The soft tissue proliferation and extraocular muscle enlargement in the right eye are less prominent. There is also the marked mucosal thickening in the nasal sinus as well as the soft tissue swelling around the infraorbital nerves. Panels (C) and (D) show orbital MRI images obtained one month after prednisolone treatment. The dramatic reduction of the proliferating soft tissue in both the eyes and nasal mucosa was noteworthy, as well as the slight improvement of the extraocular muscle enlargement. T1-weighted images of the axial section are shown in panels (A) and (C) and T2-weighted images of the coronal section are shown in (B) and (D).

bronchial asthma are frequently associated with IgG4-related disease (10). The allergic aspect of IgG4-related disease may be further supported by the fact that a moderate dose of glucocorticoids has a favorable therapeutic response.

Thyroid-associated ophthalmopathy (TAO) is the major cause of proptosis seen in individuals suffering from Graves disease. TAO can develop in euthyroid patients without concurrent or previous history of Graves disease, but thyrotropin receptor autoantibodies are generally present in the sera of most such patients. In addition, increased volume of the orbital adipose tissue and/or extraocular muscles as retro-orbital alterations on CT and MRI are also always seen in patients with TAO (13). Several potential mechanisms have been put forward to explain the pathogenesis of TAO, including thyrotropin receptor autoantibodies and anti-insulin like growth factor-1 receptor autoantibodies interacting with its cognate receptor expressing in the orbital fibroblast (13). These findings support the idea of an autoimmune pathogenesis of TAO. Treatment of severe TAO consists of a high dose of glucocorticoids including steroid pulse

therapy with or without external beam radiation to the retro-orbital space, occasionally followed by surgery (14). Our patient reported herein showed the favorable clinical response to the moderate dose of prednisolone and, therefore, it was highly unlikely that TAO was the major component in making the extraocular muscle enlarged. This notion was also supported by the fact that TSH receptor-stimulating antibodies seen in our patient was only marginally positive and, therefore, too low to develop TAO since the levels of TSH receptor antibodies have been shown a tendency to correlate with the severity of TAO (15). Thus, positive TSH receptor-stimulating antibodies seen in our patient were, most likely, not more than coincidental. Although a clinical association between TAO and IgG4-related idiopathic orbital inflammation has not been reported so far, it is intriguing to consider that IgG4-related idiopathic orbital inflammation can expand and involve the orbital tissues, releasing the TSH receptor autoantigen locally which in turn generates the autoantibodies to the TSH receptor.

Here we reported a patient with compressive optic neuropathy and marked proptosis caused by IgG4-related idiopathic orbital inflammation with positive TSH receptor-stimulating antibodies. This case suggests an importance of overall consideration of the clinical picture and extensive work-up of any possible differential diagnosis.

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