

# A Case of Hypertrophic Pachymeningitis with Elevated Serum IgG4

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## Abstract

Hypertrophic pachymeningitis is a rare disorder in which intracranial dura mater thickens focally or diffusely. To our knowledge, there are few reports of Immunoglobulin G4 (IgG4)-related hypertrophic pachymeningitis. Here, we report the case of such a patient. A 68-year-old woman was referred to our hospital complaining of visual disturbance in her left eye that had persisted for several weeks. There was a history of tuberculosis in her childhood. Brain magnetic resonance imaging showed dural thickening at the bilateral skull base and near the left orbital apex. Visual acuity in her left eye developed marked deterioration. The patient was treated with steroids combined with antituberculosis agents. Following steroid pulse therapy, her symptoms showed rapid amelioration and her visual acuity improved without reactivation of the tuberculosis. Thus, steroid combined with antituberculosis agents is a potential beneficial therapeutic option for patients with IgG4-related disease and tuberculosis.

**Keywords:** Immunoglobulin G4-related disease; Hypertrophic pachymeningitis; Tuberculosis

## Introduction

Immunoglobulin G4 (IgG4)-related disease is a recently defined disease entity, characterized by high serum IgG4 concentration and comprised of a spectrum of systemic disorders, including Mikulicz's disease; autoimmune pancreatitis; Riedel's thyroiditis; sclerosing cholangitis; retroperitoneal fibrosis; tubulointerstitial nephritis; and lung lesions, such as hilar lymphadenopathy, pseudotumor and interstitial pneumonia [1,2].

Recently, it was suggested that IgG4-related sclerosing disease might represent a subset of cases diagnosed as idiopathic hypertrophic pachymeningitis [3-5]. However, only a few cases of patients having IgG4-related disease and exhibiting pachymeningitis have been reported [4-10]. Here, we report the case of a patient with hypertrophic pachymeningitis with elevated serum IgG4 who had a history of tuberculosis; she was treated with a combination therapy of steroids and antituberculosis agents, which resulted in the rapid improvement of her symptoms.

## Case Report

A 68-year-old woman presented in July 2012 with a history of dull left-sided frontal lobe headaches that had persisted for 2 months and left eye visual disturbance that had persisted for 2 weeks. There was a history of tuberculosis in her childhood. On ophthalmic examination, best-corrected visual acuity in the right eye was 20/20 with -4.50D-1.25D $\times$ 125°, while the left eye visual acuity was 80/200 with -4.50D-0.75D $\times$ 35°. Ocular pressures were normal. The anterior segment of both eyes was unremarkable. Funduscopy of both eyes was unremarkable, with the optic disc appearing normal. The critical flicker frequency (CFF) was 38 Hz in the right eye and 7 Hz in the left eye. Visual evoked potentials in the left eye revealed an elongation of p100 latency and reduced amplitude. Chest radiograph revealed old pleuritis. Brain magnetic resonance imaging (MRI) demonstrated dural thickening at the bilateral skull base and near the left orbital apex (Figure 1). Laboratory findings were as follows: peripheral blood cell count was normal; C-reactive protein was 0.14 mg/dL (normal <0.06 mg/dL); erythrocyte sedimentation rate was 41 mm/h; total protein, 7.8 g/dL (normal range, 6.9–8.4 g/dL); and antinuclear antibody (autoantibodies to SS-A and SS-B) and antineutrophil cytoplasmic antibody tests were negative. IgG and IgG4 levels were elevated

to 1772 mg/dL (normal range, 870–1700 mg/dL) and 155 mg/dL (normal range, 4.8–105 mg/dL), respectively. Urinalysis was normal. Other biochemical examinations were within the normal range. The QuantiFERON® TB second-generation test (Cellestis Ltd., Australia) was positive with 0.44 IU/mL.

In late-August 2012, the patient developed marked deterioration in her left visual acuity to hand motion. She was hospitalized for further examinations and treatment. At the time of her admission, the patient was 150 cm tall and weighed 54 kg. Her temperature was 36.1°C; pulse rate was 74 beats/min; and blood pressure was 116/73 mmHg. Neurological examinations revealed no remarkable abnormalities except visual impairment. All other physical examination findings



**Figure 1:** Coronal T1-weighted gadolinium-enhanced brain MRI before treatment demonstrated linear enhancement at the bilateral skull base (red arrows) and near the left orbital apex (yellow arrow).

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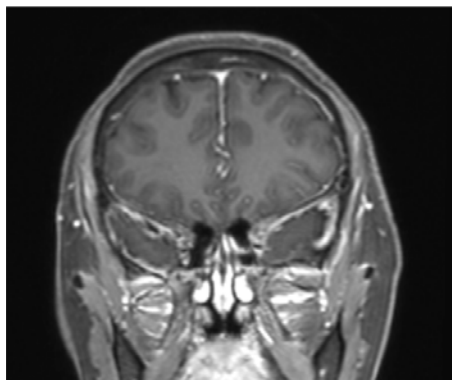


Figure 2: MRI showed improvement after treatment.

were unremarkable. Cerebrospinal fluid revealed no pleocytosis and normal protein and sugar levels. Following admission, the patient was treated for 3 days with intravenous methylprednisolone pulse therapy (1000 mg/day) and antituberculosis agents, including isoniazid 300 mg/day, rifampicin 450 mg/day, pyrazinamide 1 g/day, and ethambutol hydrochloride 750 mg/day. One week following steroid pulse therapy, the symptoms showed rapid amelioration and her visual acuity improved to 20/20, without reactivation of the tuberculosis. In the left eye, CFF also improved to 20 Hz. The cranial MRI finding of hypertrophic pachymeningitis was improved (Figure 2). The steroid dosage was gradually reduced over several months and tapered off in late-November 2012. The patient was doing well and there were no indicative signs of disease recurrence. Histological examination was not available in this case.

## Discussion

Cranial idiopathic hypertrophic pachymeningitis is a rare disease that causes dural thickening [11]. It is typically classified into 2 groups: diffuse linear and focal nodular types [5]. The majority of cases are the diffuse linear type, whereby symptoms are caused by fibrous entrapment of cranial nerves or ischemia. Symptoms include headaches with or without increased intracranial pressure, and cranial neuropathy. Immunosuppressants, such as steroids, azathioprine, and methotrexate are considered the main treatment options and are highly effective. The disease course is extremely variable, but it usually displays a chronic relapsing and remitting course. Typically, a diagnosis of idiopathic hypertrophic pachymeningitis is made by excluding all other possibilities. Undoubtedly, meningeal biopsy is the most confirmatory diagnostic tool; clinically, a diagnosis is made based on laboratory and radiological evaluation. In a patient with diffuse linear lesions, a diagnosis is also based on the effectiveness of steroids or immunosuppressive therapy.

In 2011, 2 IgG4 research teams in Japan proposed comprehensive diagnostic criteria for IgG4-related disease [2]. This diagnostic criteria is as follows: clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs; hematological examination showing elevated serum IgG4 concentrations ( $>135$  mg/dL); and histopathologic examination revealing marked lymphocyte and plasmacyte infiltration and fibrosis, and infiltration of IgG4+ plasma cells (ratio of IgG4+/IgG+ cells  $>40\%$  and  $>10$  IgG4+ plasma cells/high power field (HPF)). Thus, a diagnosis of IgG4-related disease is definitive in patients who fulfill all of the above criteria. A diagnosis of IgG4-related disease is also possible in patients who fulfill the first 2 criteria but not the last. A diagnosis of IgG4-related disease is probable

in patients with organ involvement who also fulfill the histopathologic criteria but who do not exhibit increased serum IgG4 concentration. The patient in the present case fulfilled the first 2 criteria. Thus, her condition represented a “possible” case of IgG4-related disease.

Recently, there have been an increasing number of reports focusing on the relationship of hypertrophic pachymeningitis and IgG4-related sclerosing disease [4-10]. These reports suggest that idiopathic hypertrophic pachymeningitis might be a part of the disease spectrum, although not all cases can be categorized as IgG4-related sclerosing disease. Response to steroid therapy and other organ involvement help the diagnosis as well. Thus, meticulous evaluation, including the serum levels of IgG4 and other autoantibodies, and imaging studies for other organs that may be affected are recommended. Yamashita et al. [4] proposed that the diagnosis of IgG4-related pachymeningitis should be based on the following points: elevated serum IgG4 level ( $>135$  mg/dL); infiltration of IgG4+ plasma cells into lesions (10 IgG4+ plasma cells/HPF) with fibrosis or sclerosis; a good response to steroid therapy; involvement of other IgG4-related diseases, such as autoimmune pancreatitis, Mikulicz's disease, retroperitoneal fibrosis, and IgG4-related sclerosing cholangitis; and exclusion of other diseases that could cause hypertrophic pachymeningitis. Regrettably, however, histological examination was not available in this case. According to these results, we diagnosed the disease as hypertrophic pachymeningitis probably due to IgG4-related disease. Including ours, there have been 8 cases of IgG4-related disease with hypertrophic pachymeningitis [4-10]. Serum IgG4 levels were measured in only 4 of these patients, including ours, prior to the initiation of steroid therapy [4,6,8]. Additionally, visual disturbance was presented in only 3 cases, including ours [6,8]. In our case, left-sided visual disturbance involved the left orbital apex and optic nerve.

In this case, we were hesitant regarding the treatment because of her history of tuberculosis. Thus, we selected a combined therapy of steroids and antituberculosis agents; this therapy improved her visual acuity without reactivation of the tuberculosis. Few reports are available regarding IgG4-related disease and tuberculosis [12,13]. Imai et al. [12] described a female patient with high serum IgG4 concentrations and tubulointestinal nephritis who had been treated for urinary tract tuberculosis 5 years previously. They suggested that an abnormal reaction to tuberculosis might be associated with a predominance of type-2 helper T-cell immunity, thus resulting in IgG4-related systemic disease. Kawano et al. [13] described a patient with IgG4-related disease concurrent with *Mycobacterium tuberculosis* infection. These reports suggest that some relationship might exist between IgG4-related disease and tuberculosis. However, in our case, her history of tuberculosis was certainly very old. So, we believe the association of hypertrophic pachymeningitis and tuberculosis was coincidental. Additionally, we think that the rapid improvement of clinical and radiological findings might be caused by steroid therapy.

This report has several limitations. Histological examination was not available in this case.

The IgG4-related pachymeningitis cannot be diagnosed just with the diffuse dural thickening on MRI and elevated serum IgG4 level without pathological confirmation [14]. However, her condition represented a “possible” case of IgG4-related disease [2]. For this reason, we considered to be hypertrophic pachymeningitis due to IgG4-related disease. Furthermore, the follow-up period of this case was too short. The long-term follow-up is needed considering the frequent relapse and remission of this disease.

In conclusion, when cases of IgG4-related disease with the history of tuberculosis are encountered, we suggest that steroid combined with antituberculosis agents in prophylactic purpose is one of the therapeutic options.

## Disclosure

The authors have no conflicts of interest to disclose for this paper.

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