Steroid-Resistant Relapsing IgG4-Related Pachymeningitis Treated With Methotrexate

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INTRODUCTION
IgG4-related disease, which is newly recognized, is characterized by lymphoplasmacytic infiltration with increased IgG4-secreting plasma cells. Although a favorable response to steroids has previously been reported, the durations of follow-up to confirm the long-term benefits and clinical courses were limited. We describe long-term favorable response of oral methotrexate in a patient with IgG4-related pachymeningitis who was resistant to steroid therapy.

OBSERVATIONS
A patient in his mid-60s with pathologically proven IgG4-related pachymeningitis who was resistant to steroid therapy and experienced an exacerbation of symptoms 4 times is described. Low-dose oral methotrexate induced significant clinical and radiological improvement, with sustained remission of the disease over 2 years without complications.

CONCLUSIONS AND RELEVANCE
The long-term favorable response to oral methotrexate in the current patient suggests that methotrexate is a useful alternative treatment option in patients with IgG4-related pachymeningitis who are resistant to steroid therapy or who experience adverse effects from steroids.

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Steroid-Resistant Relapsing IgG4-Related Pachymeningitis

A man in his mid-60s first developed a subacute left-side visual disturbance and went to see the ophthalmologist. Without a clear diagnosis, he was initially prescribed 40 mg of oral steroids, which were tapered during 2 months, and his vision returned. Two days after cessation of steroids, he experienced the same visual disturbance. He was again prescribed 40 mg of oral steroids, which were tapered during 2 months again but his vision only partially returned. Additionally, he continued to have headaches and presented with cushinoid features as an adverse effect of the steroids. Two months after the steroid dose was tapered, he had a visual disturbance of the right eye, and orbital magnetic resonance imaging (MRI) revealed diffuse dural thickening and enhancement most prominently in the bilateral sphenoid and occipital dura, suggestive of chronic pachymeningitis (Figure 1A). Subsequently, his suspected diagnosis was optic neuritis, and he was treated with 1 g of intravenous methylprednisolone for 3 days. However, his visual disturbance did not improve even with a maintenance dose of oral steroids (60 mg), which was eventually tapered after 3 months. Six months after cessation of the oral steroids, a hearing disturbance of the left ear newly developed and his chronic headaches worsened. He visited our hospital for further evaluation 10 months after his initial ophthalmologist visit.

On admission, a neurological examination indicated a bilateral decreased visual acuity (right eye, 0.4/left eye, 0.3) with normal funduscopic findings and a left-ear sensorineural hearing loss. Brainstem auditory evoked potentials...
showed peripheral conduction defect in the left ear. Brain MRI revealed extensive dural thickening and enhancement, extending into the internal auditory canal and frontotemporal dura more severe than before (Figure 1B). An examination of the cerebrospinal fluid identified high protein levels (113 mg/dL) without pleocytosis. A polymerase chain reaction assay for *Mycobacterium tuberculosis* DNA and cerebrospinal fluid cytology findings were negative, but serum IgG (1820 mg/dL) and cerebrospinal fluid IgG (38.1 mg/dL) levels were significantly elevated. The erythrocyte sedimentation rate was 91 mm/h, and the C-reactive protein level was 11.53 mg/dL. Serology results for human immunodeficiency virus, hepatitis B surface antigen, Venereal Disease Research Laboratory, and vasculitic laboratory tests were all negative.

To investigate the cause of the pachymeningitis, a meningeal biopsy was performed. Neuropathological examination showed markedly thickened dura by lamellated collagen fiber deposition with perivascular infiltration of lymphoplasmacytic cells and many IgG4-positive plasma cells among infiltrated inflammatory cells (>50 IgG4-positive cells per high-power field), consistent with a diagnosis of IgG4-related pachymeningitis (Figure 2).

Evaluations for the involvement of other organs including abdominal computed tomography and echocardiography were unremarkable. Liver and renal function tests and serum amylase and lipase levels were normal, but serum IgG4 levels were elevated (2.34 g/L). Because the subject previously had an unfavorable response to steroids and steroid-related adverse effects, low-dose oral methotrexate (12.5 mg, weekly) was chosen. The patient became headache free, and no recurrence of cranial neuropathies was observed over the following 1 year of treatment. Subsequently, the dose of methotrexate was decreased to 10 mg/wk, and the patient remained relapse free for more than 2 years without adverse effects. Serial annual investigations of orbital MRI showed decreased dural thickening (Figure 1C and D). Serum IgG4 level measured yearly was within 0.85 g/L of the normal range during the first year with methotrexate and further decreased toward 0.65 g/L during the second year. The erythrocyte sedimentation rate and C-reactive protein level remained normal as well.

### Discussion

Previous reports found a favorable response of IgG4-RP to steroids, suggesting that this disease is benign and treatable. However, the long-term treatment response and clinical course remain unknown. A relapse of this disease at 4 years after discontinuation of steroid therapy was recently noted, and rituximab was proposed as a next-generation treatment. Nevertheless, the follow-up of rituximab treatment for only 2 months was too limited to evaluate the long-term response and prognosis. In the present case, the clinical course and response to steroids were different from those reported previously. Many relapses occurred for a short period, and neurological symptoms following the relapses were not recovered despite steroid therapy; furthermore, pachymeningeal thickening and enhancement identified by MRI worsened. Notably, here, significant clinical, serological, and radiological improvements and a sustained remission of the disease over 2 years were observed following low-dose oral methotrexate treatment.
Methotrexate is a specific antagonist of folic acid with anti-inflammatory and immunosuppressive characteristics that inhibit the proliferation of lymphocytes. In vitro models, methotrexate has been shown to suppress B-cell function. Furthermore, methotrexate affects the remission of other IgG4-related systemic diseases and idiopathic hypertrophic pachymeningitis. The long-term favorable response to oral methotrexate in the current patient suggests that methotrexate is a useful alternative treatment option in patients with IgG4-RP who are resistant to steroid therapy or who experience adverse effects from steroids. Further investigation is necessary to confirm the beneficial effect of oral methotrexate and to determine the treatment duration in patients with IgG4-RP.

**REFERENCES**


