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Marked effectiveness of low-dose oral methotrexate for steroid-resistant idiopathic hypertrophic pachymeningitis: Case report

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ABSTRACT

Idiopathic hypertrophic pachymeningitis (HP) is a rare clinical entity characterized by thickening of the dura mater without obvious underlying disease. High-dose steroid therapy is considered to be the first line for idiopathic HP, but half of patients show resistance for steroid therapy and suffer progressive clinical course. We describe low-dose methotrexate (MTX) administration for recurrent and steroid-resistant idiopathic HP resulting in noticeable improvement without severe adverse effects. A 51-year-old Japanese woman with dermatomyositis first presented with right retro-orbital pain caused by dural thickening in the sella and upper clivus involving the right trigeminal nerve, which was diagnosed as idiopathic HP by transsphenoidal biopsy. High-dose methylprednisolone therapy led to remission, and she remained healthy with low-dose dexamethasone. Three years after the initial therapy she presented with right facial nerve and lower cranial nerve palsies caused by diffuse and significant dural thickening in the posterior cranial fossa. Second high-dose methylprednisolone therapy was introduced, but the effect was transient and she suffered aspiration pneumonia. Low-dose oral MTX therapy was begun, and her symptoms were almost resolved and dural thickening was remarkably improved without severe adverse effects. Lowdose MTX may be a more appropriate choice for idiopathic HP than steroid administration. Randomized controlled clinical trials are now needed.

1. Introduction

Idiopathic hypertrophic pachymeningitis (HP) is a rare clinical entity characterized by chronic inflammation causing thickening of the dura mater, with a prevalence of 0.949/100000 persons [1]. The most common characteristic on clinical imaging is dural thickening in the posterior cranial fossa [2]. The symptoms depend on the location of the dural thickening. Headache is the most common initial symptom, followed by ophthalmological symptoms, such as visual loss and diplopia [1]. If the lesion has spread to all areas of the posterior cranial fossa, polyneuropathy occurs including lower cranial nerve palsy, such as dysarthria, hoarseness, and dysphagia. Steroid treatment can elicit a favorable response, but the duration of follow up to confirm the long-term benefits has been limited [1,2]. About half of the patients treated by steroid therapy have shown relapsing-remitting or progressive course [1]. However, no standard therapy for idiopathic HP has been established because of the low prevalence.

We present a case of recurrent and life-threatening severe steroid-resistant idiopathic HP, which was successfully treated with low-dose oral methotrexate (MTX) therapy with remarkable improvement on neuro-imaging studies.

2. Case report

A 51-year-old Japanese woman with dermatomyositis first presented with right retro-orbital pain. Magnetic resonance imaging (MRI) showed hypertrophic change in the dura mater of the sella and upper clivus involving the trigeminal nerve. *Treponema pallidum* antibody hemagglutination test was negative. Immunoglobulin G4 (IgG4) was normal (36.3 mg/dL). Anti-neutrophil cytoplasmic antibody and rheumatoid factor were negative. Dermatomyositis was in the remission phase. Chest radiography did not show bilateral hilar lymphadenopathy. She did not have malignant disease. Since the cause of dural thickening was not revealed, transsphenoidal biopsy was performed.

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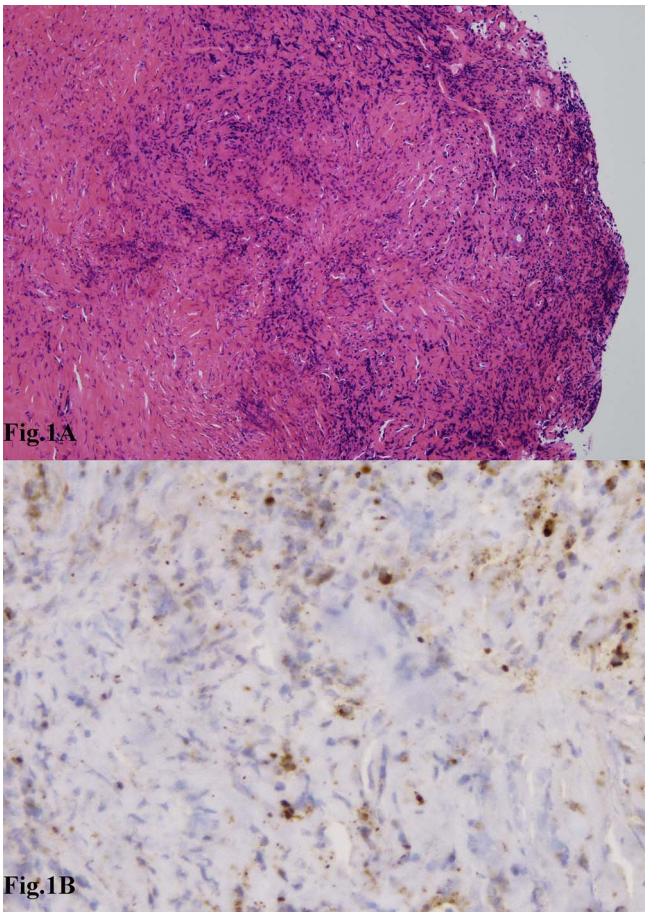

Fig. 1. Photomicrographs of the surgical specimen showing massive infiltration of plasma cells into dense fibrous and hyalinized tissue, which strongly suggests chronic inflammation. Hematoxylin and eosin staining (A) × 100. Immunohistochemistry revealed only a slight reaction for IgG4 (B) × 200.

Histopathological examination showed massive infiltration of plasma cells into dense fibrous and hyalinized tissue, which strongly suggested chronic inflammation. Immunohistochemistry revealed only a slight reaction for IgG4, and the diagnosis was established as idiopathic HP (Fig. 1). High-dose methylprednisolone therapy (1000 mg × 3 days) followed by low-dose dexamethasone treatment resulted in complete remission. Low-dose dexamethasone was continuously administered during the follow-up period. Three years later, she presented with progressive retro-orbital pain, and incomplete facial nerve and lower cranial nerve palsies on the right side. The patient had difficulty in eating and suffered from aspiration pneumonia due to dysphagia. MRI showed diffuse and significant hypertrophic change of the dura mater in the sella, entire clivus, and cerebellar tentorium (Fig. 2). Serum examination found the following: White blood cell count 9700/μL, red blood cell count 389 × 10^4/μL, hemoglobin 11.5 g/dL, hematocrit 35.6%, platelet count 33 × 10^4/μL, total protein 7.2 g/dL, aspartate transaminase 11 IU/L, alanine transaminase 16 IU/L, lactate dehydrogenase 179 IU/L, blood urea nitrogen 14.6 mg/dL, creatinine 0.59 mg/dL, C-reactive protein 17.92 mg/dL, and IgG4 76.3 mg/dL.

Second high-dose methylprednisolone therapy was introduced combined with antibiotic agent. Rapid improvement of pneumonia was observed with transient improvement of her neurological dysfunction, but diffuse hypertrophic change of the dura mater persisted. Two weeks after the high-dose methylprednisolone therapy, her symptoms worsened again and low-dose oral MTX therapy (12 mg/week) was introduced. Her symptoms gradually improved after 3 weeks, and MRI revealed noticeable improvement in the dura mater and her symptoms remained in remission after 16 weeks (Fig. 3). Her retro-orbital pain and lower cranial nerve palsies were diminished and she could eat, although slight facial nerve palsy remained. During the second high-dose methylprednisolone therapy and the introduction of MTX, serum C-reactive protein level was well correlated with pathophysiological state. Moderate liver dysfunction occurred, which was considered as a side effect of low-dose oral MTX therapy, but could be controlled by additional oral intake of folic acid (5 mg/week). She returned to normal life with the same dose of oral MTX, and oral intake of dexamethasone has been gradually withdrawn. During the 2-year follow-up period, no exacerbation of idiopathic HP has occurred with MTX treatment.

3. Discussion

High-dose methylprednisolone therapy has been widely used as the first line treatment for idiopathic HP, excluding infectious cases [3]. However, some series of idiopathic HP cases have suggested that steroid therapy without other immune modulating agents led to temporary but never sustained improvement in symptoms [2]. In our case, the initial steroid therapy maintained remission for only 3 years, and the second steroid therapy was ineffective.

Immunosuppressive agents, such as MTX, rituximab, azathioprine, and cyclophosphamide, have been used in a few cases of steroid-resistant idiopathic HP [1,2], and MTX therapy has also been reported in a few cases of idiopathic HP [3,4]. However, case series and/or cohort studies of MTX therapy for idiopathic HP have not been reported. Low-dose oral MTX therapy has been widely applied for steroid-resistant inflammatory disease, such as rheumatoid arthritis, psoriasis, and ulcerative colitis. In particular, MTX therapy for rheumatoid arthritis has become an immunosuppressive anchor drug, and the long-term effectiveness and safety have been established. In our case, the administration of low-dose oral MTX resulted in noticeable improvement in symptoms and remarkable change in the diffuse thickening of the dura mater on MRI without any severe adverse effect. Long-term administration of MTX requires weekly intake of folic acid to prevent adverse effects of MTX, such as gastrointestinal symptoms, increased liver enzyme levels, and pancytopenia. Further case experience and randomized clinical trials are required to elucidate the most effective choice of immunosuppressants.

In order to diagnose idiopathic HP, systematic examination is essential to exclude other causes of dural thickening such as intracranial hypotension, infections, systemic autoimmune/vasculitic disorders, malignancy, and meningioma [3]. Diagnosis of intracranial diffuse lesion with small biopsy specimen continues to be difficult [5], but transsphenoidal biopsy can be quite informative with less invasiveness for midline skull base lesion, and lead to diagnostic confirmation as idiopathic HP in our case.

4. Conclusion

Low-dose oral MTX therapy for idiopathic HP may be more effective therapy than high-dose administration of methylprednisolone. Long-term follow up and randomized controlled trials are required to establish validation of this procedure.