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Letter to the Editor

Corticosteroid-dependent tuberculous meningitis: A case report

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Dear Editor,

The effectiveness of adjunctive corticosteroids for treating tuberculous meningitis has been established in patients without HIV infection [1], and previous reviews have recommended some treatment regimens [2,3]; however, the optimum dosage remains unclear. Here, we present a case of tuberculous meningitis, wherein symptoms worsened with each reduction of corticosteroid administration, necessitating prolonged adjunctive use of high-dose corticosteroids.

1. Case report

A 16-year-old girl was admitted to our hospital with headache and pyrexia. She had no notable medical history or history of tuberculosis exposure and was conscious and alert. Her body temperature was 38 °C, and she exhibited neck stiffness; no other neurological abnormalities were observed. C-reactive protein was normal (≤0.05 mg/dL) and HIV test result was negative. Chest X-ray showed no signs of pulmonary tuberculosis. Cerebrospinal fluid evaluation revealed increase in cell count (136/μL; 94% mononuclear cells), mild increase in protein content (54 mg/dL) and adenosine deaminase (7.4 IU/L), and decrease in glucose (41 mg/dL; paired serum glucose: 95 mg/dL) with an elevated opening pressure (250 mmH_2O). Initial acid-fast bacteria cultures and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* in the cerebrospinal fluid were negative. Brain Gd-enhanced T1-weighted magnetic resonance imaging (MRI) revealed no disease-specific changes; however, contrast enhancement was observed in the pia mater (Fig. 1a). Acyclovir (1500 mg/day) and methylprednisolone pulse therapy were initiated because of the possibility of herpes simplex encephalitis or autoimmune encephalitis. *M. tuberculosis* sensitive to all antituberculosis drugs was detected in a follow-up cerebrospinal fluid sample collected on day 12 of admission. After confirmation by PCR, the patient was administered isoniazid (300 mg/day), rifampicin (450 mg/day), ethambutol (750 mg/day), and pyrazinamide (1.5 g/day) beginning on day 17 of admission according to the guideline [2]. The clinical course and treatment are summarized in Fig. 1.

Her headache and pyrexia resolved with repeated methylprednisolone for the first month, but both symptoms recurred following oral prednisolone administration [60 mg/day (1.5 mg/kg/day)]. We used anti-inflammatory agents including acetaminophen, loxoprofen, and diclofenac sodium; however, these had little or temporary effect. In addition, we repeated lumbar puncture to adjust intracranial pressure, but it also did not relieve the headache. Two additional courses of intravenous methylprednisolone pulse therapy comprising consecutive 1, 0.5, 0.25, and 0.125 g daily doses every 3 days for 2 months (month 1–2) were administered. Headache and pyrexia did not recur with subsequent oral prednisolone administration (60 mg/day) at the end of month 2. Prednisolone dose was reduced by 10 mg every 2 weeks starting from the beginning of month 3. In month 4, when prednisolone was administered at 30 mg/day, headache and pyrexia recurred and brain MRI revealed exacerbation of leptomeningeal enhancement because of paradoxical reaction (Fig. 1d). Headache and pyrexia resolved with methylprednisolone pulse therapy. Prednisolone (50 mg/day) was initiated in month 5, with reduction of 10 mg/day every 2 weeks; however, symptoms worsened at a dosage of 30 mg/day. Prednisolone was continued at 40 mg/day until month 10, during which symptoms were stable. Isoniazid and rifampicin were discontinued at 1 year because brain MRI showed near-complete resolution of leptomeningeal enhancement (Fig. 1f), and prednisolone was gradually reduced with close monitoring of brain MRI. The patient remains well without sequelae 2 years after onset.

2. Discussion

Our patient with corticosteroid-dependent tuberculous meningitis was refractory to the dose and duration of corticosteroids recommended in recent guidelines [2,3]. If clinical symptoms or brain MRI findings worsen during the treatment of tuberculous meningitis, clinicians generally consider paradoxical reactions, presence of drug-resistant tuberculosis, or formation of abscess or tuberculoma [4]. Insufficient dose and duration of drugs are believed to induce drug resistance in *M. tuberculosis* [5], and it is unlikely that *M. tuberculosis* acquires resistance during combination antituberculosis therapy. Recent reports have yielded conflicting results with respect to the survival benefit of

Abbreviations: INH, isoniazid; RFP, rifampicin; EB, ethambutol; PZA, pyrazinamide; ACV, acyclovir; MPDN, methylprednisolone; PSL, prednisolone; MRI, magnetic resonance imaging

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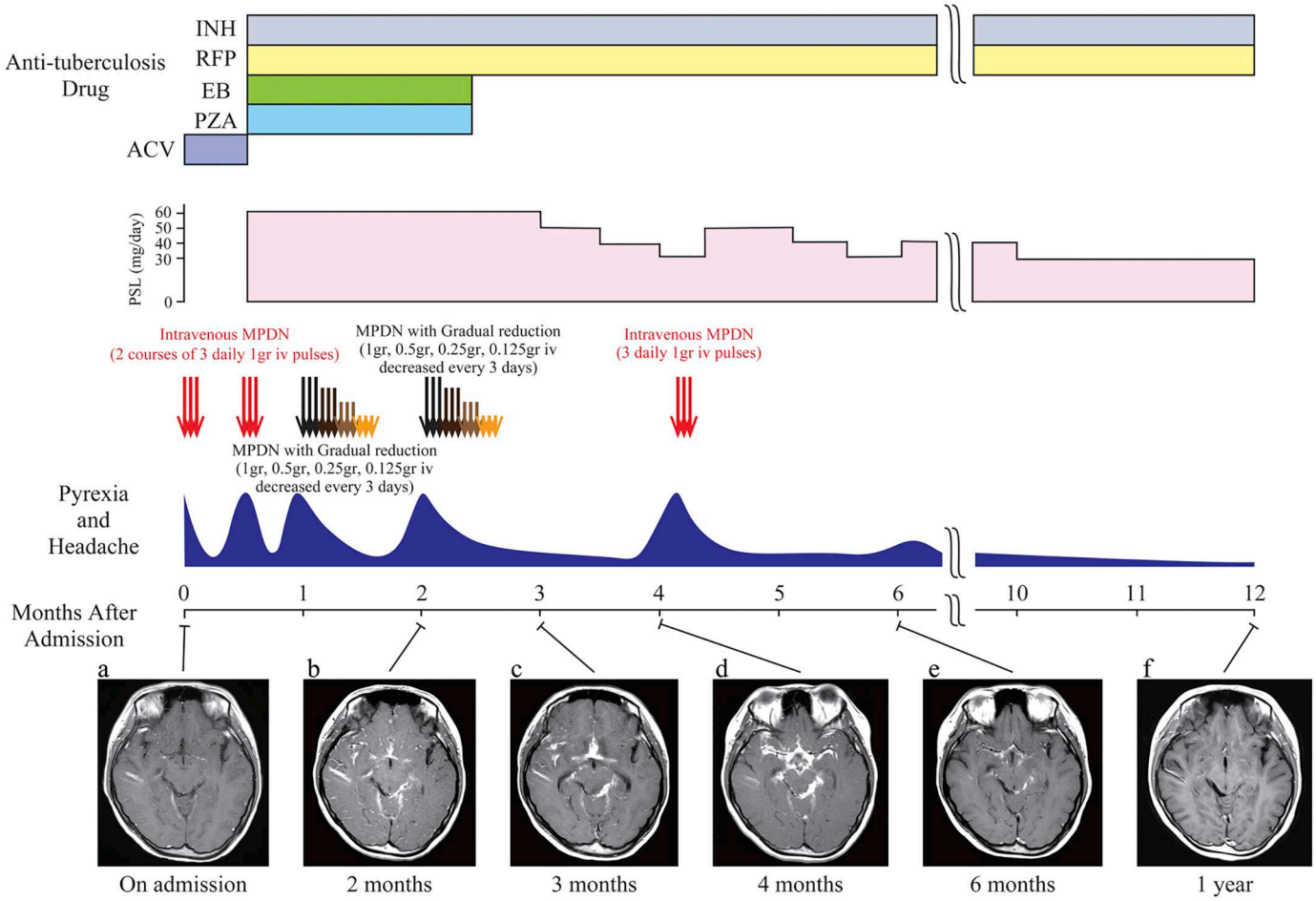

Fig. 1. Treatment, clinical course, and changes in brain MRI findings.
Administration of four antituberculosis drugs (INH + RFP + EB + PZA) was initiated on day 17 of admission. Headache and pyrexia initially resolved with three rounds of MPDN pulse therapy and two rounds of MPDN pulse therapy with gradual reduction over approximately 5 months. Gd-enhanced T1-weighted MRI revealed gradual exacerbation of leptomeningeal enhancement at month 4 (a–d). Based on the symptoms and brain MRI findings, we reduced PSL dosage carefully from 50 mg/day to 30 mg/day over a period of approximately 8 months (month 4–12), leading to the disappearance of leptomeningeal enhancement on brain MRI (e, f).

intensified antituberculosis therapy, and there is no definite and consistent evidence for the contribution of intensified antituberculosis treatment regimens [6,7]; these findings suggest that antituberculosis drugs alone cannot determine the prognosis in case of fully sensitive *M. tuberculosis*. Symptoms may deteriorate because of uncontrolled inflammation in response to *M. tuberculosis*, and increased corticosteroid administration is required for symptom alleviation. In fact, our patient's symptoms were relieved due to the control of inflammation with corticosteroids. The influence of other causes is unlikely because we did not insert ventriculoperitoneal shunt to control intracranial pressure nor change the antituberculosis drug dosages. In addition, rifampicin—the key drug for tuberculosis treatment—is known to reduce the effectiveness and bioavailability of prednisolone by approximately one-half to one-third [8]. The extent of this effect needs careful consideration in the treatment of each patient.

The duration of steroid administration must also be carefully considered. In a study by Thwaites et al., brain MRI showed persistent asymptomatic tuberculoma in approximately half of the patients at a mean follow-up of 270 days following recovery from tuberculous meningitis [9]. Tuberculoma may, thus, persist in one of every two asymptomatic patients following corticosteroids administered for the recommended interval. In our patient although the spread of leptomeningeal enhancement was strongly observed in the bottom part of the brain at 4 months, brain MRI at 12 months revealed near-complete resolution of leptomeningeal enhancement with corticosteroid administration for a longer period than that suggested in the guideline and reviews. There is no consensus regarding the management of asymptomatic post-treatment tuberculoma or leptomeningeal enhancement. We have previously treated a patient with residual tuberculoma and symptoms caused by late-onset paradoxical reaction 10 years after the discontinuation of antituberculosis drugs [10]. Steroid administration was also effective in that patient, which suggests that corticosteroid dose may be gradually reduced in patients with asymptomatic tuberculoma with consideration and monitoring of leptomeningeal enhancement.

In conclusion, some patients with tuberculous meningitis and no HIV infection may require higher doses of corticosteroids and/or longer duration of corticosteroid therapy than those generally recommended. Therefore, corticosteroid dosage should be individualized based on brain MRI findings and clinical symptoms. Further studies are warranted to identify indicators or tools to determine the optimum corticosteroid dosage and duration.

Conflict of interest

The authors declare that they have no conflict of interest.

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