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Case report

A case of post-malaria neurological syndrome (PMNS) after treatment of falciparum malaria with artesunate and mefloquine

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Abstract: Post-malaria neurological syndrome (PMNS) is a rare complication after the treatment of falciparum malaria. We describe a case of a 56-year-old man who developed ataxia, tremor, and confusion 16 days after a successful treatment of falciparum malaria with artesunate followed by mefloquine. Magnetic resonance imaging of the brain revealed no abnormality, and he recovered spontaneously without any specific treatment including corticosteroids. Inflammatory changes were found in the cerebrospinal fluid, suggesting a localized inflammatory reaction as the cause of the syndrome.

INTRODUCTION

Post-malaria neurological syndrome (PMNS) is a rare complication of falciparum malaria, and was first described by Nguyen et al. in 1996 [1]. This postinfectious syndrome was reported to occur within 2 months (median 4 days) after the eradication of parasitemia and not as a manifestation of cerebral malaria. It presents variable neurological symptoms including acute confusion, generalized convulsion, motor aphasia, fine postural tremor, and cerebellar ataxia [2, 3, 4]. Only one case has been described in Japan to date [5]. We present a probable second case in Japan. In our case, PMNS occurred 16 days after the completion of treatment for falciparum malaria with sequential use of artesunate and mefloquine. The findings of cerebrospinal fluid examination suggested a localized inflammatory process as the cause of this syndrome.

CASE PRESENTATION

A 56-year-old Japanese man was admitted to our hospital because of falciparum malaria. He had stayed in Sierra Leone for 4 days and returned to Japan 16 days before the admission to our hospital. Before going to Sierra Leone, he had been healthy except for a slight increase in gamma-GTP level disclosed at a medical checkup, and he had been free from any neurological disorder. He had been well until 7 days earlier, when he began to suffer from chills, diarrhea, and appetite loss. He was admitted to another hospital 3 days earlier, when his temperature rose to 40℃, and profound thrombocytopenia (11,000/mm^3) was noted. He was treated with antibiotics, flomoxef (FMOX) for 2 days and then meropenem (MEPM) plus ciprofloxacin (CPFX) for 1 day. However, his symptoms did not improve and ten units of platelet were transfused one day before the admission to our hospital. He also developed atrial fibrillation. On the fourth day at the previous hospital, *Plasmodium falciparum* was found in the blood smear and he was transferred to our hospital for appropriate treatment.

On admission to our hospital he appeared a little confused. Laboratory examinations of the blood revealed thrombocytopenia (34,000/mm^3), mild anemia (Hb 11.7g/dl), and slight increases in liver enzymes (AST 67IU/mm^3, ALT 43IU/mm^3), but a normal level of creatinine (0.8mg/dl). A peripheral blood smear showed ring forms of *P. falciparum* with parasitemia level of 4.8% of RBCs. Atrial fibrillation continued and chest X-ray showed mild congestion, but echocardiography revealed no significant abnormality in the heart.

He was treated with 200mg (2.8mg/kg bw) of artesunate suppository twice on the first day and then 200mg once for four days. (The use of artesunate for this case was approved by the IRB of the Institute of Medical Science, the University of Tokyo, No.16-32.) On the morning of the sec-

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ond day, his confusion appeared to become more severe, but he recovered to a state of alertness in the evening. Diarrhea and atrial fibrillation were resolved on the third day. Platelet count also recovered to 67,000/mm^3 on the third day and 106,000/mm^3 on the fifth day. Clearance of parasitemia was demonstrated on the fifth day (i.e., day 4 in Figure 1).

On the sixth day he was given 1100mg of mefloquine for the completion of treatment, although the blood smear no longer showed any parasitemia. He showed no symptoms for the following ten days and was discharged with only mild anemia (Hb 10.6g/dl) remaining. He was free from all symptoms at the follow-up visit four days later.

However, 11 days after the discharge, the patient was readmitted to our hospital because of acute confusion and ataxia. He had noticed limb tremors and gait disturbance 5 days before readmission, i.e., 17 days after the clearance of parasitemia and 16 days after the completion of treatment (Figure 1). He had no recollection of his actions during the three-day period before readmission, when his estranged wife noticed his inappropriate speech and brought him to our hospital. On examination, his body temperature was 37.6℃, and postural tremor of the arms and tongue was prominent, which caused him difficulty in writing and speech. Gait ataxia and disorientation were also noted, but neurological examinations did not reveal any other abnormalities. Serum CRP level (0.23 mg/dl), white blood cell count (6,800/mm^3), platelet count (211,000/mm^3) were all normal, and the blood smears were invariably negative for parasites (Figure 1).

The examination of cerebrospinal fluid (CSF) by lumber puncture showed normal opening pressure but slight increases in mononuclear cells and protein in CSF samples (Figure 1). Magnetic resonance imaging (MRI) of the brain with the administration of gadolinium revealed no abnormal lesion. The patient was treated empirically with intravenous acyclovir, but PCR examinations for HSV, JCV, measles virus, Japanese encephalitis virus and *Mycobacterium tuberculosis* from CSF sample were all negative. Serological tests for mumps, measles, HSV, and VZV infection were also negative. His serum CRP level continued to be normal (i.e., less than 0.25mg/dl) for the entire course of the second hospitalization. His symptoms gradually improved without any specific treatment including steroids, and he was discharged with no symptoms remaining on the twentieth hospital day.

DISCUSSION

Post-malaria neurological syndrome (PMNS) is defined as the acute onset of neurological or neuropsychiatric symptoms in patients who recently recovered from falciparum malaria and have no parasitemia at the time of onset. It was first described by Nguyen et al. in 1996 [1]. They studied 18,124 patients with falciparum malaria in Vietnam and Thailand and reported the overall incidence of this postinfectious syndrome to be about 1.2 per 1000 patients, but the

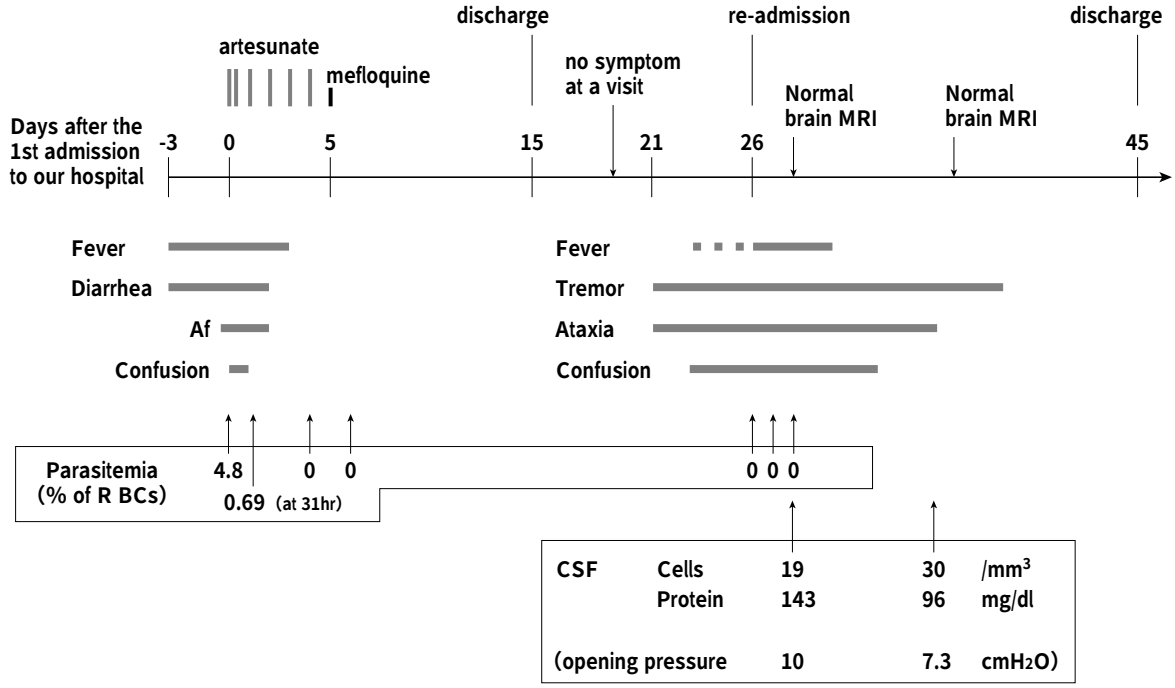

Figure 1: The entire clinical course showing biphasic occurrence of symptoms.
On day 0, the patient was admitted to our hospital for the first time.

incidence increased to nearly 1.8 per 100 in more severe cases. The reported cases occurred within 2 months (median 4 days, range 6 h to 60 days) after the eradication of parasitemia, and in a significant proportion of them oral mefloquine had been used for the preceding treatment. To our knowledge, only one case has been described in Japan to date [5]. The case we presented here had several features in common with the first reported case in Japan; both cases occurred after the sequential use of artesunate and mefloquine, showed inflammatory changes in the CSF, and recovered spontaneously.

PMNS was reported to present variable neurological symptoms such as acute confusion, generalized convulsion, motor aphasia, fine postural tremor, and cerebellar ataxia [1, 2, 3, 4]. Delayed cerebellar ataxia (DCA) occurring after falciparum malaria was also reported for 74 patients in Sri Lanka [6]. All patients of DCA showed gait ataxia but no signs of cerebral involvement. DCA can be considered a variant form of PMNS [7, 8], although one-third of the DCA cases occurred while parasitemia persisted [6]. Our case presented not only cerebellar symptoms (such as ataxia and postural tremor) but also confusion, which occurred 17 days after the clearance of parasitemia.

The etiology of PMNS remains unclear, and there may be some overlap with acute disseminated encephalomyelitis (ADEM) in its disease entity [9]. However, our case appears different from typical ADEM [10] in that repeated MRI examinations revealed no abnormality. Significant increases in mononuclear cells and protein were detected in the cerebrospinal fluid (CSF), suggesting some involvement of inflammatory reaction in the development of PMNS. However, there was no increase in serum CRP level, and the inflammation seemed to be locally contained. In some cases of DCA, elevation of serum and CSF concentrations of inflammatory cytokines (TNF-alpha, Il-6 and Il-2) were reported, also suggesting the involvement of the inflammatory process in the pathogenesis [11]. If the inflammation was more severe, the use of steroid could be considered, but the present case followed a self-limiting course without any specific treatment.

Artesunate is now used for the treatment of severe malaria more often than before [12, 13]. Oral mefloquine is also often used following artesunate, since artesunate has a very short half life (less than two hours) and combination therapy of a longer-acting anti-malaria medicine is recommended [14]. This sequential treatment of artesunate and mefloquine was used in both the first reported case in Japan [5] and our present case. It is not evident whether the side effects of these medicines, especially the neuropsychiatric side effects of mefloquine [15], are relevant to the symptoms of PMNS, but the use of oral mefloquine was reported to be most often associated with the occurrence of this syndrome [1]. Mefloquine has a long half life (about two weeks) and could predispose the patient to the delayed-onset neurological symptoms, although its exact role in the pathogenesis of PMNS remains to be clarified. In contrast, artesunate has a very short half life as described above, and is considered to be relatively safe in view of only short exposure, but its delayed neurotoxicity has also been suspected from animal studies [16]. Although no increase in adverse events was observed in the combination therapy of artesunate and mefloquine compared with mefloquine alone for treating uncomplicated malaria [17], the possibility of delayed neurological effects resulting from the combination treatment of severe malaria and its role in the development of PMNS may still be elucidated.

Under current trends in the treatment of severe falciparum malaria, clinicians should be aware of this delayed-onset neurological syndrome that could occur after the treatment completion. Most cases appeared self-limiting as the case we presented here, but the use of corticosteroid was reported to be effective in more severe cases [7, 8].

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