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Case Report

Severe delayed haemolytic anaemia associated with artemether-lumefantrine treatment of malaria in a Japanese traveller☆

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ABSTRACT

Delayed haemolytic anaemia has been reported in association with intravenous artesunate treatment in patients with severe *Plasmodium falciparum* malaria, and furthermore, oral artemisinin-based combination therapies including artemether-lumefantrine (AL) have also been incriminated. However, definite cases of delayed haemolytic anaemia associated with AL appear to be scarce, as reported cases were often treated concomitantly with other anti-malarials. In this study, we report a severe case of delayed haemolytic anaemia following AL alone in a Japanese traveller with severe parasitaemia caused by numerous *P. falciparum* parasites and a few *P. vivax* parasites. We also stress the need by further studies to differentiate between delayed haemolytic anaemia and blackwater fever, the latter being another malaria-related haemolytic condition, more clearly than they are now.

1. Introduction

Parenteral artesunate, one of the artemisinin anti-malarials, was demonstrated to have superior efficacy and safety profiles than parenteral quinine in two large-scale trials on severe *P. falciparum* malaria conducted in Asia [1] and Africa [2]. Subsequently, intravenous (IV) artesunate has been increasingly used to treat severe malaria in travellers [3], occasionally reducing mortality when compared to IV quinine [4]. Since approximately 2010, delayed haemolytic anaemia following IV artesunate therapy has been documented, mostly in travellers, and it has become a concern because blood transfusion is often required [5,6]. In addition to parenteral artesunate, artemether-lumefantrine (AL), one of the artemisinin-based combination therapies (ACTs) that can be given orally, has also been incriminated as a cause of delayed haemolytic anaemia, despite very few definite cases reported to date.

In Japan, major anti-malarials were not licensed, unlike the situation in other industrialized countries, and therefore, the Research Group on Chemotherapy of Tropical Diseases was founded in 1980 by the Ministry of Health (later renamed the Ministry of Health, Labour and Welfare) with the aim of importing nationally unlicensed medicines for tropical and parasitic diseases and making them available for patients [7]. After such a medicine has been used sufficiently, the research group analyses the treatment data, and if satisfactory efficacy and safety are observed, the group assists the manufacture in licensing and marketing the drug in Japan.

The research group first introduced AL in late 2002, recommending its use primarily for uncomplicated *P. falciparum* malaria, and finally, the therapy was launched in Japan in March 2017 after its national approval. Among patients with malaria who were treated with AL provided by the research group, two cases of delayed haemolytic anaemia were reported [8], but only one could be regarded as a definite case. In this study, we report an additional definite case of delayed haemolytic anaemia following treatment with AL, which was also provided by the research group.

2. Case report

The patient was a 21-year-old male Japanese student who had no history of malaria or haematological disorders. He stayed in India for 10 days to attend a training course, but did not practice

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malaria chemoprophylaxis. Seven days after returning to Japan, he experienced abdominal pain and became febrile the following day. After the first consultation at a clinic, he consulted another hospital, at which a peripheral blood smear was prepared, and a diagnosis of malaria was rendered. Immediately, he was transferred to our hospital (Nagoya City East Medical Centre), eventually 6 days after symptom onset.

Upon arrival, the patient was conscious with the following vital signs: body temperature, 38.3 °C; blood pressure, 150/47 mmHg; and heart rate, 93 beats/min. The abnormal blood exam findings included a red blood cell (RBC) count of 2.88 × 10^6/μL, haemoglobin (Hb) level of 8.5 g/dL, haematocrit level of 24.8%, thus altogether showing slightly microcytic anaemia, platelet count of 30 × 10^3/μL, total protein level of 5.1 g/dL, albumin level of 2.6 g/dL, alanine aminotransferase level of 87 IU/L, aspartate aminotransferase level of 112 IU/L, lactate dehydrogenase (LDH) level of 754 IU/L and total bilirubin level of 4.4 mg/dL. A peripheral blood smear revealed numerous *P. falciparum* ring-form parasites (920 × 10^3/μL), as well as a smaller number of *Plasmodium vivax* parasites (3300/μL), thus indicating a mixed malarial infection (Fig. 1). Four AL tablets, each containing 20 mg of artemether and 120 mg of lumefantrine, were administered six times over a 3-day period starting on day 0 of treatment. Under this regimen, parasites became undetectable as early as day 2, and his Hb level was slightly increased at this time (Fig. 2).

Despite this slight improvement, the patient's Hb level started to decrease, eventually reaching 3.8 g/dL (normocytic anaemia) on day 9, whereas malaria parasites continued to be undetectable on blood smears. This profound anaemia made him feel disoriented while walking and necessitated a packed RBC transfusion. His LDH levels fluctuated in parallel with changes in his Hb levels, eventually reaching a second peak. His indirect bilirubin level increased to 1.5 and 1.9 mg/dL on days 7 and 11, respectively, and his reticulocyte level was 8.0% when first measured on day 13. Direct and indirect Coombs tests were negative, and no irregular antibodies were detected. Medicines other than AL used during the acute stage of malaria included loxoprofen, rectal diclofenac and zolpidem. Following the RBC transfusion, the patient's Hb level had increased to 8.3 g/dL when he was discharged on day 15, further rising to 9.4 g/dL 1 week later. The patient was recommended to take primaquine to prevent *P. vivax* relapses; however, this proposal was refused.

Seventeen days after discharge, he developed fever and visited our hospital the next day. A blood smear was first interpreted to contain a few *P. falciparum* parasites; however, the microscopic diagnosis was later corrected to a single *P. vivax* infection, at a concentration of 250/μL. Because of the initial suspicion of *P. falciparum*, he was administered mefloquine only and not primaquine. After 2.5 months, he was re-hospitalized with *P. vivax* at 4700/μL. A total of 1550 mg of chloroquine base was administered over 3 days, and no parasites were detected after treatment. After confirming a normal glucose-6-phosphate dehydrogenase level, 30 mg of primaquine base was administrated daily for 14 days, and he has experienced no further recurrence of malaria. His anaemia did not resolve completely for several months, probably affected by the *P. vivax* relapses, and finally, his Hb level was 15.0 g/dL as late as 5 months after the initial presentation.

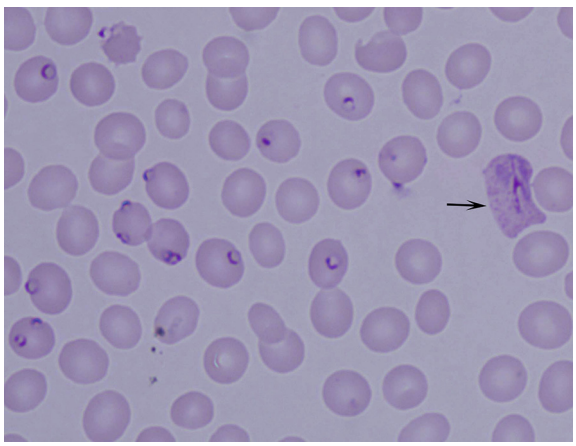

Fig. 1. Giemsa-stained thin blood film showing numerous *P. falciparum* ring-form parasites and a *P. vivax* amoeboid trophozoite (arrow) before treatment initiation.

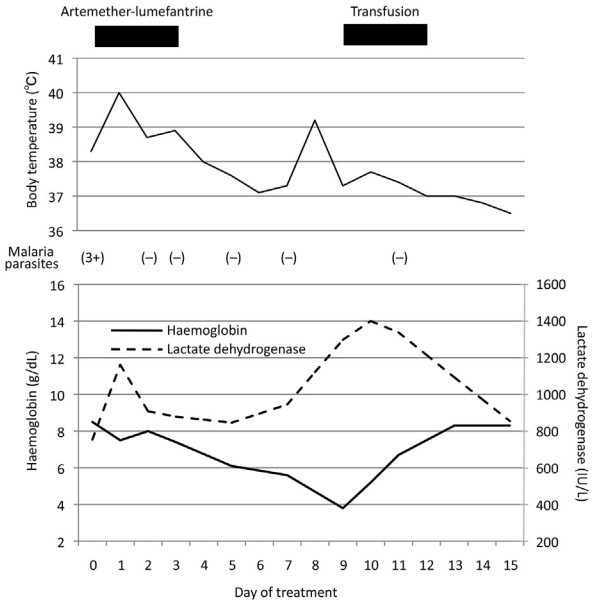

Fig. 2. Major clinical findings of our patient during the first hospital admission (16 days).

3. Discussion

Delayed haemolytic anaemia is becoming a significant concern in association with parenteral artesunate [5,6]. Previous reports suggested that oral artemisinins including ACTs such as AL were also associated with delayed haemolytic anaemia. However, some patients received anti-malarials other than AL concomitantly, making it difficult to conclude that AL could be the sole cause of delayed haemolytic anaemia [8,9]. To our knowledge, only two definite cases of delayed haemolytic anaemia associated with AL have been reported, one from Italy [10], and the other from Japan as previously mentioned [8]. The current patient was treated with AL alone, and he exhibited an initial decline in Hb levels followed by a short-term increase and gradual decline in Hb levels in parallel with an increase in LDH levels, while malaria parasites were eliminated. Around the observed nadir of anaemia, increases in indirect bilirubin levels and reticulocyte counts were noted. Thus, the entire clinical picture is consistent with that of delayed haemolytic anaemia as defined by Jauréguiberry et al. [11] and Arguin [12]. The nadir Hb level of 3.8 g/dL in this patient may be the lowest ever recorded among adult patients with delayed haemolytic anaemia, although an Hb level of 2.8 g/dL was documented in an African child [13]. Although the severe anaemia of this patient may have been related to the initial high parasitaemia as well as moderate anaemia existing prior to the start of treatment, it highlights

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