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Southeast Asian Journal of Case Report and Review

Journal homepage: https://www.sajcrr.com/

Case Report

Prolonged intravascular hemolysis and vitamin B12 deficiency after parasitic clearance in a case of complicated falciparum malaria

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ARTICLE INFO

Article history:
Received 12-08-2024
Accepted 14-09-2024
Available online 11-10-2024

Keywords:
Falciparum
Malaria
Intravascular hemolysis
Vitamin B12

ABSTRACT

Background: Malaria is still a very threatening disease to tackle in India. The potential array of complications which can arise due to this infection is appreciably wide and many of these complications pose a significant life risk.

Case report: Our patient, a 35-year-old gentleman presented with a complicated falciparum malaria infection. He developed an acute kidney insult, thrombocytopenia, septic shock, acidosis and anemia with a parasitemia of 3%. He was managed with artemisinin based therapy as per the latest guidelines and gradually his complications got tackled and he achieved parasitic clearance. But his anemia kept on worsening after fever resolution and parasitic clearance and he developed a picture of persistent intravascular hemolysis after recovery from the infection. Also, interestingly, his vitamin B12 level was significantly low despite being on a non-vegetarian diet and receiving oral B12 supplementation.

Conclusion: This case highlights the importance of monitoring hemoglobin levels even after complete parasitic clearance as the intravascular hemolysis can also arise due to the usage of artemisinin based therapy, an entity called as post artemisinin delayed hemolysis. Also, this case showed the coexistence of low B12 state and poor B12 absorption in a young gentleman who had previously normal B12 levels. The association between malaria and poor B12 absorption needs to be explored further by more studies. Any association found can help in recommendations of B12 supplementation in malaria cases.

1. Introduction

Malaria, a threatening parasitic infection transmitted by the Anopheles mosquito, is a deadly disease with a high number of possible complications. Recent statistics show that globally, there were an estimated 247 million malaria cases in 2021 in 84 malaria-endemic countries, with approximately 6,00,000 deaths each year.[1] India is a malaria-endemic region, and there is still a high number of cases being reported from India annually.

Malaria usually presents with a high fever, which may be accompanied by chills and headache. Patients with malaria may also experience a wide range of complications, including metabolic acidosis, electrolyte abnormalities, thrombocytopenia, acute renal injury, liver failure, respiratory distress, rapidly progressing cerebral malaria, manifesting as an altered sensorium, and, infrequently, seizures. The principal factors in the pathogenesis of complicated malaria are impaired microcirculation due to the sequestration of parasitized erythrocytes, systemic inflammatory responses, and endothelial activation.[2] For initial diagnosis, thick blood smears are performed; however, a single smear showing no

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https://doi.org/10.18231/j.sajcrr.2024.018

evidence of parasites is not sufficient to exclude malarial infection. To identify the type of parasitic species, thin blood smears are used.[3] Nowadays, immunochromatographic tests or rapid diagnostic tests are being widely used in clinical practice.

The severity of malaria infection is often determined by the causative species of Plasmodium. *Plasmodium falciparum* is known for causing the maximum mortality and morbidity and contributing to the maximum proportion of complicated malaria cases, although *Plasmodium vivax* and *Plasmodium knowlesi* also have the potential to cause severe disease.[4,5] Management of patients with severe malaria presents a broad array of clinical challenges given the complex pathophysiology of the infection involving multiple organ systems. The mainstay of therapy in complicated malaria cases nowadays is Artemisinin derivatives. Intravenous Artesunate is now the preferred agent in complicated malaria in most countries.[6] Anemia is a known complication of malaria and has a multifactorial etiology. Since plasmodium is an intraerythrocytic parasite, the destruction of parasitized RBC is a major contributor. However, an interesting observation is that there is side-by-side destruction of unparasitized RBCs as well.[7] This contributes to the hemolytic anemia commonly demonstrated in malaria cases. However, generally, this resolves after antimalarial therapy and after the achievement of parasitic clearance. In our case, a 35-year-old gentleman presented with complicated falciparum malaria. He received treatment with IV artesunate and was then shifted to oral antimalarials. After the clearance of parasitemia, hemolysis persisted for a prolonged period. Prolonged hemolysis after artemisinin-based combination therapy (PADH) is now a known entity; this phenomenon was suspected in our case.[8] This hemolysis is usually low grade, but in our patient it was severe enough to require repeated transfusions. Also, interestingly, the patient had severely low Vitamin B12 levels in spite of consuming a non-vegetarian diet and receiving oral B12 supplementation during a hospital stay. This indicates a low B12 absorption in falciparum malaria. A study conducted to explore the relationship between anemia, parasitemia, and vitamin B12 and folate levels in malaria showed the prevalence of folate and vitamin B12 deficiencies to be 26.0 and 26.6%, respectively.[9] Low B12 absorption in malaria is a topic to be explored as any correlation found can be used to supplement B12 prophylactically in complicated cases of falciparum malaria.

2. Case Report

A 35-year-old gentleman presented with a 7-day history of high-grade fever with chills, malaise, high-colored urine, and mild confusion for one day. He worked in the armed forces and was recently posted in a forest area in central India. He was diagnosed with falciparum malaria one day before his presentation to the tertiary care setting. He was admitted to the Intensive Care Unit. On admission, he was febrile, mildly confused, with slightly low blood pressure. Initial labs showed a hemoglobin level of 6.0 with 3 percent parasitized RBCs, thrombocytopenia with a platelet count of 70,000, evidence of acute kidney injury with a creatinine of 3.3, raised indirect bilirubin, and LDH. Clinically palpable splenomegaly was present. Immediate parenteral artesunate therapy was started in accordance with the latest guidelines. He received 3 doses of IV artesunate as per body weight, and then he was shifted to oral antimalarials in the form of artemether-lumefantrine. A prophylactic antibiotic was also continued alongside antimalarials. A single dose of primaquine was given after obtaining normal G6PD levels. After completion of IV artesunate therapy, he showed good clinical response; parasitemia became undetectable, indicating a complete clearance of the parasite from the blood. However, the patient continued to have highly colored urine, and his hemoglobin levels continued to drop. He was transfused with several units of PRBC in view of his persistent anemia. Even after the transfusion, his hemoglobin levels failed to stabilize. A thorough work-up for his anemia was initiated, which showed very low B12 levels, high corrected reticulocyte production index, rising indirect bilirubin, normal iron levels, and elevated LDH. Direct Coomb's test was negative, and the peripheral blood smear showed the absence of schistocytes. Urine analysis showed no RBC, but urine was positive for hemoglobin, thereby indicating an ongoing intravascular hemolysis. Artemisinin therapy-related hemolysis was suspected.

In view of his vitamin B12 deficiency, it is interesting to note here that the patient followed a non-vegetarian diet and hence did not have any obvious risk factor for such severely low B12 levels. Moreover, from the very first day of his hospital stay, he was receiving oral B12. Hence, probably, the disease state induced a state of reduced vitamin B12 absorption, the mechanism of which is poorly understood. He was started on IV vitamin B12 and PRBC transfusions were continued as per daily hemoglobin levels. Gradually, with treatment, he improved clinically. Although the hemoglobin levels were still low, the rate of decrease came down. His other lab parameters normalized, and the patient was discharged with advice for weekly monitoring of hemoglobin levels.

3. Discussion

Anemia is one of the most common complications of severe malaria and has a multifactorial etiology, the most common being intravascular destruction of infected RBCs.[10] Other causes can be extravascular clearance of uninfected RBCs by the spleen and liver, activation of the immune system, dyserythropoiesis, and the effect of other coinfections.[11] It has been postulated that red cell deformability is also reduced in severe falciparum and knowlesi malaria.[12] It usually occurs in severe malaria and is commonly caused by

Plasmodium falciparum. Some studies have demonstrated a definite correlation between malaria transmission intensity and anemia severity.[12]

Hemolysis in malaria can be broadly attributed to two mechanisms, one being the non-immune destruction mediated by the direct destruction of parasitized RBCs and the other being immune hemolysis. Artesunate, used as the treatment of choice in complicated malaria, has been shown to cause hemolysis. Few case reports of post-artemisinin delayed hemolysis have been published.[8] The mechanism of PADH is not fully understood but is thought to involve the process of pitting in which RBCs containing the dead parasites killed by artesunate are directed to the spleen for destruction.[13] PADH was strongly suspected in the present case, given the absence of other explanatory causes of hemolysis after parasitic clearance, normal G6PD levels, and the clinical context of recent artemisinin exposure.

4. Conclusion

As post-artesunate delayed hemolysis is now recognized, it is recommended that hemoglobin levels be checked at regular intervals post-therapy with these agents. Our patient had a similar occurrence of prolonged intravascular hemolysis after parasitic clearance. Also notably, in our patient, it occurred significantly earlier after parasitic clearance than in other reported cases.

Another unique feature was that he had severely low B12 levels despite oral supplementations. His B12 levels normalized after receiving IV B12 injections. Prior to this episode of malaria he never had anemia and maintained good hemoglobin levels with normal MCV in routine health checks. This association hints towards a low B12 absorption in malaria. This can be investigated in further studies and establishment of an association can lead to recommendations of supplementing B12 in acute malaria cases.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Cite this article: Chandra SK, Dastidar AG, Bandyopadhyay S, Dutta A, Samanta R, Ganguly S. Prolonged intravascular hemolysis and vitamin B12 deficiency after parasitic clearance in a case of complicated falciparum malaria. *Southeast Asian J Case Rep Rev* 2024;11(3):77-79.