Post-artesunate late haemolytic anemia in a 17-month-old infant followed for severe malaria at the yalosase health center, isangi, DR Congo.

ABSTRACT

Artesunate is an artemisinin derivative with rapid and potent parasiticidal power. However, cases of delayed hemolytic anemia described in the literature can be fatal, especially in children. We report a rare case of late hemolytic anemia in an infant. This was a 17 month old infant with a history of severe malaria treated with artesunate two weeks ago, seen in consultation for hemolytic anemia with negative GE. Both HBsAg and anti-HCV serology were negative. Considering the context, the diagnosis of post-artesunate late hemolytic anemia was retained and the patient had progressed well after transfusion.

Keywords: Late hemolytic anemia, Severe malaria, Artesunate injection, Isangi.

Introduction

Since March 2013, Artesunate has been considered the gold standard treatment for severe malaria [1]. It is an artemisinin derivative (quinghaosu) with rapid and potent parasiticidal power on circulating plasmodial strains. Its superiority over quinine in the treatment of severe forms of malaria is evident [2,3]. However, rare cases of delayed hemolytic anemia have been described in patients taking this drug [3, 4,5]. Unknown, the latter can be fatal for patients who in most cases are already at home. Our observation is one of the rare cases reported in a rural infant.

Case présentation

It was a 17 month old male infant weighing 9kg treated with artesunate for severe malaria in its algid form with good progression. On discharge, the hemoglobin level was 12.5g / dl. There was no leukocytosis and renal function was normal. Two weeks later, he was brought back for consultation by his mother with severe physical asthenia as well as a yellow coloration of the mucous membranes. She has also not reported any notion of medication or herbal medicine since her son's last hospitalization. No notion of hemoglobinopathy has been reported in children or in the family.

On physical examination, the general condition was preserved, the consciousness clear, the mucous membranes pale and jaundiced. The temperature was 37.1 ° C, BP was not collected due to lack of pediatric cuff, pulse at 130 beats per minute and respiratory rate at 40 cycles per minute. The neurological and pleuropulmonary examination was unremarkable. The abdomen was flexible, painless, with no collateral venous circulation and no hepatosplenomegaly. On digital examination, the anal margin was clean and the finger cot was soiled with normal-looking stools. At the paraclinical, severe anemia was noted at 6.6g / l. RDT and GE came back negative, as did HBsAg and HCV antibodies. In search of a particular ground, the retroviral and syphilitic serologies were negative. The rest of the classical biological and imagery assessment for jaundice exploration was not carried out due to a lack of a reduced technical platform. The diagnosis of Artesunate-induced late haemolytic anemia was most likely and the patient did well after blood transfusion and was discharged one day later.

Discussion

Two large studies (AQUAMAT, SEAQUAMAT) have shown substantial advantages of Artesunate over quinine [2, 3]. Thus, since March 2013, Artesunate has been considered the gold standard treatment for severe malaria [1]. Delayed hemolytic anemia has been described in 20 to 25% of patients on Artesunate [6]. Indeed, it has been proven that artesunate potentiates the original splenic mechanism of defense against malaria called "pitting" or splenic splenosis. It involves the expulsion of the dead parasite from the host erythrocyte as it passes through the interendothelial cleft. However, these fragile "pitted" erythrocytes returning to the general circulation will be lysed within 2 weeks following treatment and be responsible for anemia. Little known, the latter can be fatal especially in rural areas where the technical platform and qualified human resources are lacking. A recent experience of the team aiming to evaluate in vitro pitting on microbead filters showed that a minimum duration of 6 hours of exposure to Artesunate seemed necessary to induce a pitting phenomenon [7]. Our observation is one of the rare cases reported in a rural infant.

One can only be struck by the synchronized aspect of the onset of the loss (from the second week) and the prolongation of it sometimes for several weeks thereafter (for 2 or even 3 to 4 weeks [8]. This makes suspect an element triggering the destruction

which would occur from the second week and not before. The temporality of this one pleads for a destruction linked to the presence of antibodies (2 weeks on average for the establishment of a specific immune response) [8]. In our study, the patient presented with an anemic syndrome associated with jaundice on day 14. Our patient was successfully managed. We gave him a transfusion This resembles the observation by Zoller et al. [9] in Europe in 2011, where they found that out of 25 patients in the study, episodes of hemolytic anemia occurred in 6 patients, which was detected between 15 and 32 days (i.e. a median of 15.5 days rs). On the other hand SAGARA et al. [10] in Mali, in 2014, found a delay in the onset of late anemia on the seventh day, in patients treated with artemisinin and its derivatives per os for simple malaria attacks. Several studies have had a similar outcome, including a study by De Nardo et al in 2013, Anaba et al in 2012 observing hemolytic anemia on the sixth day of treatment for Plasmodium falciparum malaria treated with the artemeter - oral lumefantrine [11,12]. In contrast, hemolytic anemia induced by a dose-dependent artemisinin and its derivatives was controversial by the study by Rolling et al in 2012 [13]. ; On the one hand, the delayed reactivation of the pro-inflammatory reaction triggered by the rapid and massive destruction of malaria parasites by Artesunate and on the other hand an increase in the presentation of parasitic antigens have been suggested as a plausible explanation [13]. However, before the twelfth day, it is difficult to decide the part between the malaria itself and the imputability of the drug. Indeed, during the first week, malaria is responsible for the anemia.However, in our case, we believe that this is seen in the idea that the finding of a negative parasitemia excluded the involvement of plasmodium falciparum in the reappearance of hemolysis in the second or even the third week as well as late hemolytic anemia. induced by injectable artesunate was established.

The mechanisms of late haemolytic anemia are multiple and are not fully understood. The anemias are either constitutional and related to corpuscular abnormalities of pyruvate kinase deficiency, G6PD deficiency, hereditary sperocytosis, ...) or extra-corpuscular anemias where hemolysis of the red blood cells is secondary to an extrinsic factor (an infectious agent, mechanical or toxic, immunological disorder etc). This study has the merit of documenting a rare case of post-treatment hemolytic anemia. Its only limitation is that it has experienced methodological shortcomings for financial reasons, we have not been able to explore the other causes of anemia. This shows the importance of setting up a committee responsible for collecting information on the use and monitoring of patients treated with Injectable artesunate, in order to provide regular analyzes of this data.

Conclusion

Late haemolytic anemia is a reality in tropical countries, including the Democratic Republic of Congo: an adverse effect of artemisinin and its derivatives. A case of late haemolytic anemia has been observed following treatment with injectable artesunate. The benefit of artemisinin and its derivatives is not compromised by episodes of late hemolysis (rarely severe and generally of moderate intensity). Our results underline the need for the development of a predictive marker, in particular the controls of the haematological parameters of this hemolysis at the end of the search, document and rapid management of adverse events.

References.

1. **WHO. Guidelines for the treatment of malaria –3rd edition. 2015**
2. **Dondorp A, Nosten F, Stepniewska K, Day N, White N: Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005, 366(9487):717- 725.**
3. **Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, Bojang K, Olaosebikan R, Anunobi N, Maitland K *et al*: Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010, 376(9753):1647-1657.**
4. **Guidelines for the treatment of malaria, second edition Geneva, 2011 for the French translation Geneva, World Health Organization, 2011**
5. **KEEFTME ,JER-VEGTER AR,VAN GENDEREN P.J et col.Traitement out come of intravenous artesunate in patient with severe malaria in the Netherlands and Melgium.Malar J2012;11:102.**
6. **Stéphane Jauréguiberry. Retention and splenic "pitting" of red blood cells in acute malaria treated with an artemisinin derivative. Parasitology. Pierre and Marie Curie University - Paris VI, 2015. French. FfNNT: 2015PA066047ff. Fftel-01146815**
7. **Ndour PA, Lopera-Mesa TM, Diakite SA, Chiang S, Mouri O, Roussel C. et al: Plasmodium falciparum Clearance Is Rapid and Pitting Independent in Immune Malian Children Treated With Artesunate for Malaria. J Infect Dis 2014.**
8. **Jaureguiberry S, Ndour PA, Roussel C, Ader F, Safeukui I, Nguyen M, Biligui S, Ciceron L, Mouri O, Kendjo E et al: Postartesunate delayed hemolysis is a predictable event related to the lifesaving effect of artemisinins. Blood 2014, 124(2):167-175.**
9. **Zoller T, JUNGRANSS,Kapaun A et al. Intravenous artesunate for severe malaria kin travelers,Europe.Emerg Inf Dis 2011;17:771-77.**
10. ***Sagara I,Piarroux R,Djimbe A , et al. Delayed anemia assessment in patients treated with oral artemisinin derivatives for uncomplicated malaria: a pooled analysis of clinical trials data from Mali.Malaria J 2014;13:358***

11. **De Nardo P , Olivia A, Giancola ML, ety al.Haemolytic anemia after oral artemether-lumefantrine treatment in a patient affected by severe imported falciparum malaria.Infection 2013;41:863-65.DOI 10.1007/s15010-013-0451-x**
12. **Anaba FC,Ahiante BO, Pepple DJ.In vitro haemolytic effect of sulfadoxine/Pyrimethamine and Artemeter /Lumefantrine on malaria parasitized erythrocytes of femele patients.Pak J Pharm Sci 2012;25:851-55.**
13. **T,SCHMIEDEL S,WICHMANND et al.,"Post treatment haemolysis in severe imported malaria after intravenous artesunate.case report of tree patients witch hyperparasitaemia Malar J 2012,11:169**