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Severe Malaria Therapeutic Impasse: Management of a Patient with Drug Eruption to Artesunate and Long QT Syndrome to Quinine

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Abstract **Case Report**

Severe malaria is a medical emergency with high mortality. Injectable Artesunate is the recommended first line treatment of severe malaria. It was shown it have fewer adverse effects, decrease parasite clearance time, and reduce mortality from severe malaria when compared with IV quinine that comes on the second line. We describe in this rare clinical case of severe malaria the observation of a patient with drug eruption to Artesunate and long QT syndrome to Quinine. We discuss furthermore the management of such therapeutic impasse.

Keywords: Severe malaria, intravenous Artesunate, Drug eruption, Quinine, Safety, Alternative.

INTRODUCTION

Severe malaria is described as a complex syndrome, affecting many organ systems, which has many features in common with sepsis syndrome. If not appropriately treated, severe malaria often leads to death or irreversible sequelae [1].

Severe and fatal malaria are predominantly caused by P falciparum principally due to endothelial cyto-adherence causing sequestration of mature-staged infected red blood cells in vital organs. This results in microcirculatory obstruction and end-organ dysfunction.

Injectable Artesunate (AS) is the recommended first line treatment of severe malaria and quinine comes on the second line [11].

We describe in this clinical case of severe malaria the observation of a patient with drug eruption to Artesunate and long QT syndrome to quinine. We discuss furthermore the management of such rare case.

CLINICAL CASE

On Sunday 26 March 2023 at 22:00 pm, at Level two Hospital of Bunia, DRC. We admit Mr. MM, a 40-year-old patient, an Indian working since three years as merchant in DRC with no medical history for impaired unconsciousness with spread skin eruption following drug intake of IV Artesunate in a private clinic for febrile syndrome diagnosed as a severe Malaria.

Admission clinical examination find an unconscious patient with GSC at 9/15, no deficit, equal and reactive pupils. He was hemodynamically stable with a BP at 140/70 mmhg and HR at 95 bpm. His saturation was at 96% on room air and the respiratory rate at 22. His temperature was at 38 °C, the capillary glycaemia at 1.3 g /l. The abdomen was flexible, the pulmonary and cardiac auscultation were without abnormalities.

Moreover, we note a diffuse skin eruption involving arms, upper back, thighs, eyelids and forehead with positive Nikolski sign following IV Artesunate intake consistent with the diagnostic of drug eruption (Figure 1).

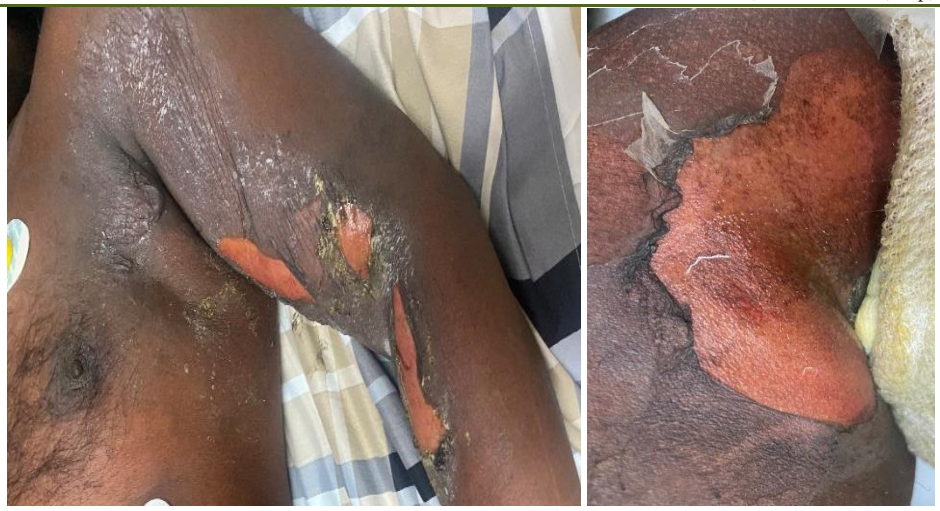

Figure 1: Skin eruption of the left arm and the upper back

Sudden diffuse skin eruption as an erythema in mass with positive Nikolski sign following IV Artesunate intake consistent with the diagnostic of drug eruption.

The primary EKG was normal but the second have shown a long QT syndrome after administration of quinine once Artesunate stopped with hemodynamic instability avoiding the use of this drug indicated in second line treatment of severe malaria (Figure 2).

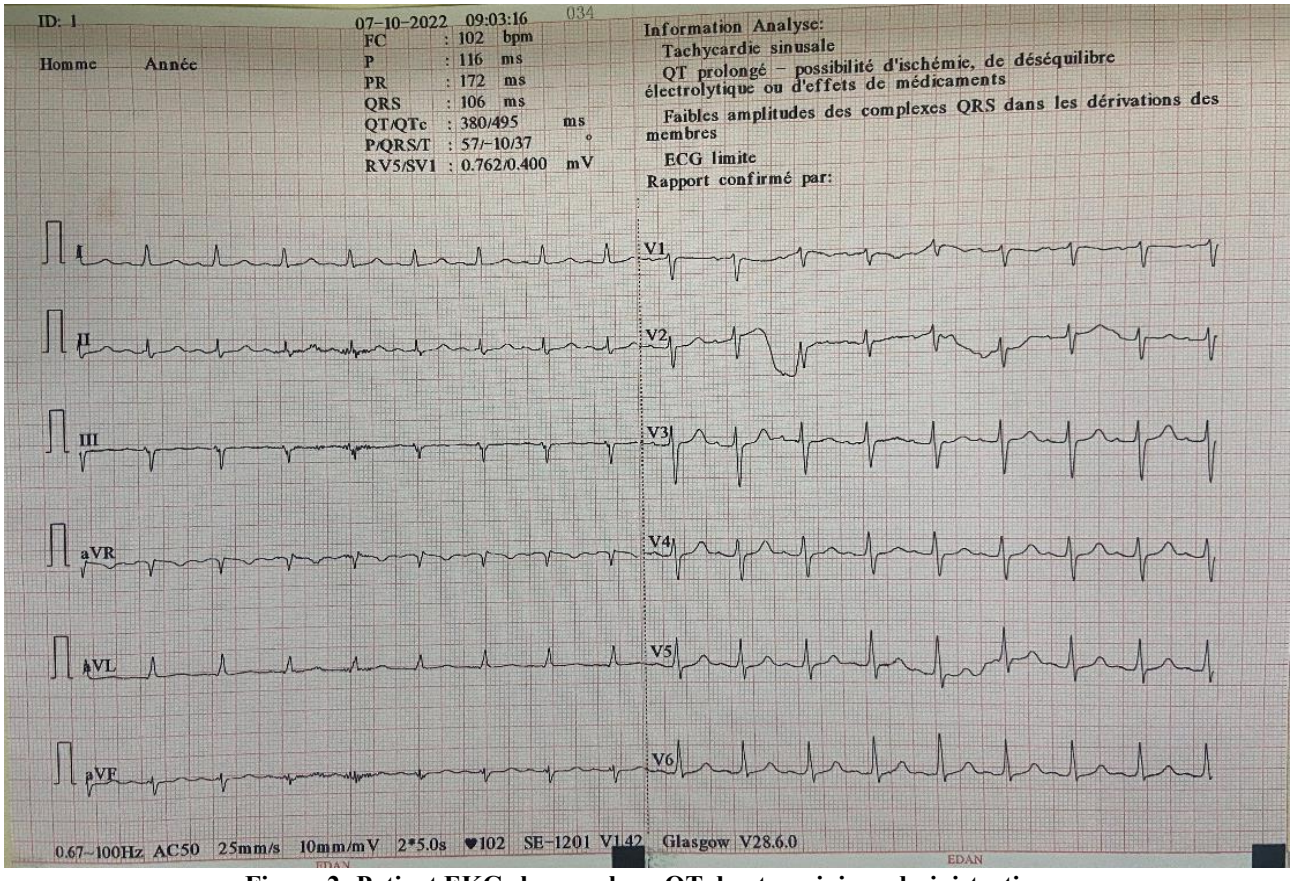

Figure 2: Patient EKG shown a long QT due to quinine administration

The abdominal ultrasound and the chest x-ray were with no abnormalities. The brain CT scan shown brain edema and no intracranial hemorrhage.

The blood samples was as follow: Hg = 16.9 g/dl HTC= 39.4% WBC= 12790 cel/µl PLQ= 32000 plq/µl Glycaemia 1.59 g/l Urea = 1.76 g/dl Creatinine = 12.6mg/dl Albumine = 26g/l AST= 120 UI/l ALT= 94

UI/l Bilirubine = 75mg/dl PAL = 70 UI/l GGT= 121 UI/l INR 1.

The Malaria test was positive to plasmodium falciparum. After conditioning monitoring and cleaning, a Sulfadiazine dressing was applied under general anesthesia.

For the malaria treatment, we decide to make the patient under Atovaquone-Proguanil by gastric tube as an alternative to Artesunate and Quinine formally contraindicated with no amelioration.

The worsening of the renal and hemodynamic failure marked patient's evolution. The casualty died 2 days later on multisystem organ failure despite mechanical ventilation and renal replacement therapy.

DISCUSSION

Severe malaria is a life-threatening medical emergency that requires prompt and effective treatment to prevent death. Mortality from severe malaria is still 10% to 20% despite optimal treatment and reaches 100% if left untreated. It is mainly caused by P falciparum, but also observed in P vivax and P knowlesi infections. It is rarely seen with the other Plasmodium species [1].

Diagnostic criteria for Falciparum severe malaria are prostration, convulsions, coma, respiratory distress, shock, pulmonary edema, abnormal bleeding, jaundice, anuria, hemoglobinuria, repeated vomiting, anemia, acidosis, hypoglycemia, renal impairment or hyper-parasitemia >10% [2].

Parenteral Artesunate is now recommended by the WHO as first-line treatment for severe malaria worldwide caused by any Plasmodium species in both adults and children [11]. Artesunate should be given at admission then at 12 and 24 h, and once a day thereafter until the patient can take and retain oral medication [3]. Treatment must then be completed with a full course of Artemisinin based combination therapy (ACT). If parenteral Artesunate is not available, Artemether or quinine are acceptable alternatives [4].

Two landmark randomized controlled trials (RCTs) showed that intravenous Artesunate is superior to intravenous quinine, reducing mortality by 35% (95% CI 18.5–47.6) in Southeast Asian adults and by 22% (95% CI 8.1–36.9) in African children [13, 14].

Artesunate is a semisynthetic drug derived from artemisinin, a compound obtained from the plant sweet wormwood, *Artemisia annua* [5].

Artesunate is well tolerated and rapidly metabolized to its active metabolite dihydro-artemisinin, reaching peak concentrations within 10 minutes and is rapidly eliminated (half-life 45 minutes). Artesunate dose does not need to be adjusted if renal impairment or liver dysfunction present [6].

It has broad stage specificity, killing young circulating ring-staged parasites up to late-staged sequestered parasites [7]. This activity against circulating ring- stage parasites is considered its critical advantage over quinine, as Artesunate kills parasites before they can mature and sequester in the microvasculature [8].

ARTESUNATE may cause serious side effects including hemolytic anemia and severe allergic reactions. The most common side effects are kidney failure requiring dialysis, hemoglobinuria and jaundice.

To the best of our knowledge, this is the first case report describing a drug eruption to IV ARTESUNATE.

Quinine has more adverse drug effects, including hypoglycemia, hyperinsulinemia, cardiotoxicity, and hypotension, particularly if given as a rapid injection rather than infusion [9]. Quinine requires dose adjustment according to renal dysfunction after 48 hours of full dosage [10].

In our patient the injection of quinine as an alternative to Artesunate have caused hemodynamic instability with long QT syndrome in EKG and was immediately stopped.

In our case, the contraindication of the two main drugs indicated in severe malaria leads us to use an alternative medicine free from Artemisinin or quinine derivatives that is Atovaquone-Proguanil by gastric tube without efficiency.

WHO has recommended that Artemisinin is a safe and effective alternative to quinine for the treatment of severe malaria especially in areas where quinine resistance is suspected; and to improve efficiency of the drug and delay onset of resistance, artemisinin should always be used in combination with another effective antimalarial [12].

CONCLUSION

Artesunate has been shown to be particularly effective in reducing mortality rates among patients with severe malaria; nevertheless, its use is not without risks as well as his alternative Quinine [11].

The choices if these two drugs are contraindicated are limited as described in our clinical case. Finally, the importance of preventing malaria warrants greater emphasis.

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