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Case Report
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Anaphylactic Reaction to Parenteral Artesunate

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Abstract

Severe malaria is a medical emergency requiring prompt diagnosis and treatment. For the treatment of severe malaria, WHO recommends artesunate above quinine. An 18-year-old male presented to a tertiary care hospital in India with severe and COVID-19 co-infection. Intravenous artesunate was administered to the patient for prompt management, following which he had an anaphylactic reaction in the form of sudden onset generalized erythematous maculo-papular blanchable urticarial rash, tachypnea & tachycardia immediately after drug administration. The drug-induced anaphylaxis was managed with 0.5 ml intramuscular adrenaline (1:1000) & 100 mg intravenous hydrocortisone. After 7 days of the adverse reaction, a positive intradermal skin test confirmed the diagnosis of artesunate-induced hypersensitivity. Anaphylaxis to parenteral artesunate is a sparce occurrence with limited data available. Whether co-infection with SARS-CoV-2 causes any hyper-susceptibility needs to be evaluated.

Introduction

Severe malaria is a medical emergency and it requires prompt diagnosis and treatment. The mortality associated with severe malaria is high if left untreated. According to the Global WHO malaria report 2021, India accounts for the highest burden of malaria cases in South-East Asia region accounting for an estimated 83% cases in the region and 1.7% cases globally [1]. The only intravenous formulation available for the treatment are artemisinin derivative and cinchona alkaloids (quinine, quinidine). The WHO revised guidelines 2nd edition started recommending parenteral artesunate over quinine for the treatment of severe malaria based on the SEAQUAMAT & AQUAMAT trials conducted by Dondorp et al. which showed a significant reduction in mortality with artesunate over quinine [2,3]. Artemisinin is the active principle of plant Artemisia annua and artesunate is the semi-synthetic water-soluble derivative of artemisinin [4]. The safety profile of artesunate is reasonably well defined and they are safe, well tolerated and some of the most commonly reported adverse reactions to artemisinin derivatives are nausea, vomiting, abdominal pain, anorexia, headache, dizziness and rash [5]. Very few serious adverse events have been reported other than delayed hemolysis starting more than one week after artesunate treatment specially in hyperparasitemia non-immune individuals [6].

FDA recently approved artesunate on May, 2020 for the treatment of severe malaria [6]. WHO strongly recommends the continued use of intravenous artesunate for treatment of severe malaria as it is generally well tolerated and life-saving. However, there is a paucity of data on anaphylactic reaction to artesunate with only a handful of case reports mentioning such adverse events. Herein, we report a case of severe allergic reaction to parenteral artesunate in a young male admitted with SARS-CoV-2 and malaria co-infection.

Case Presentation

An 18-year-old male from northern part of India without any significant past history was admitted to our tertiary care center with complaints of fever for the past 7 days prior to admission. Fever was high intermittent in nature relapsing every 24 h and was associated with chills and rigor. He also complained of holocranial headache which was not associated with vomiting or any focal neurological deficit. He denied any cough, shortness of breath or sore-throat. With a suspicion of SARS-CoV-2 infection due to the ongoing COVID-19 pandemic, the patient was referred from a private hospital to our tertiary care center for management.

At arrival, the patient weighed 58 kgs. He was mildly pale, febrile (101.4 F) with a heart rate of 94 beats/min, BP of 124/70 mm of Hg, respiratory rate of 18/min with a saturation of 98% on room air. On examination, patient had pallor with mild splenomegaly. Respiratory examination did not reveal

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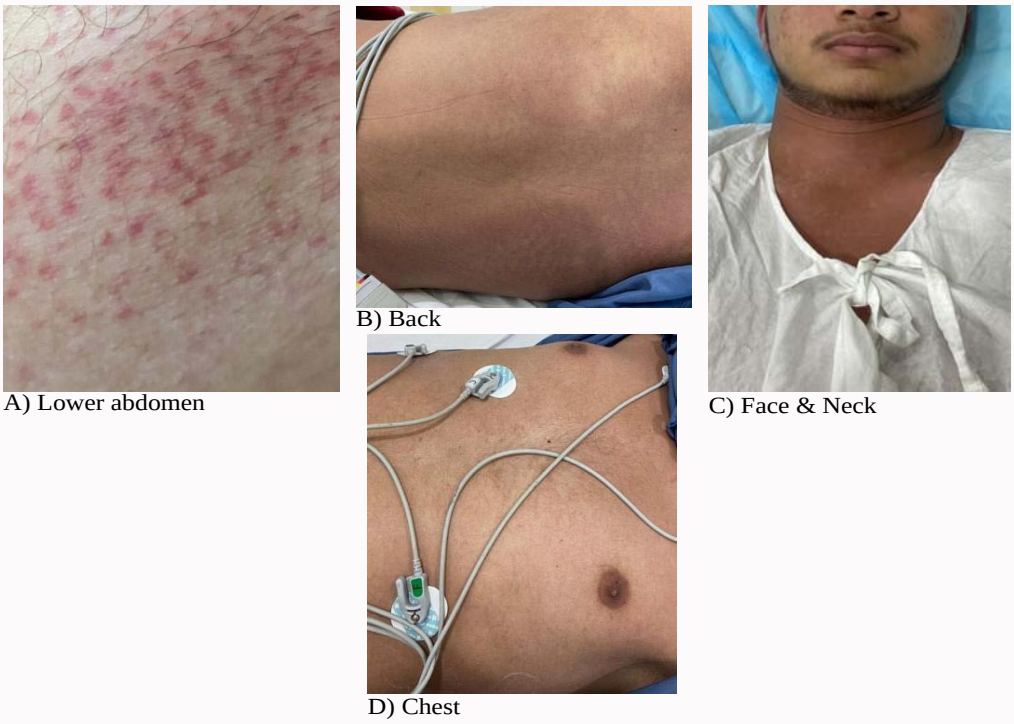

Figure 1: Rashes after 12 hours of anaphylaxis, over:

any abnormality and other systemic examination was unremarkable.

Due to the ongoing COVID-19 pandemic, PCR for SARS-CoV-2 infection from nasopharyngeal swab was done which was positive and he was classified as mild COVID-19 infection. The patient was shifted to COVID-19 dedicated ward for further evaluation.

As part of fever work up protocol, malaria rapid kit antigen came out to be positive for *Plasmodium falciparum* along with RT-PCR positivity for SARS-CoV-2 from the nasopharyngeal swab. His saturation on pulse oximetry was 98% at room air at the time of admission with a respiratory rate of 16/min & the patient was hemodynamically stable.

Initial blood investigations revealed no abnormalities in the complete blood count, liver & renal function tests.

With a suspicion of severe falciparum infection since the patient had concurrent COVID-19 infection, he was started on parenteral artesunate (140 mg per dose) with slow infusion over 1 min to 2 min planned at 0, 12 & 24 h followed by assessment for oral therapy. As planned, the first dose of parenteral artesunate was given under supervision. After 5 min of slow infusion, the patient had sudden onset generalized erythematous maculo-papular blanchable urticarial rash. It initially occurred over the genital region which progressed rapidly over the entire trunk followed by the limbs & face. Patient became tachypneic (Respiratory rate 24/min) & was also having tachycardia (Heart rate – 102/min) with a blood pressure of 118/74 mmHg.

Treatment

With the suspicion of anaphylaxis, the patient was immediately administered 0.5 mg adrenaline (1:1000) intramuscularly & 100 mg hydrocortisone intravenously. Due to unavailability of intravenous quinine formulation, the patient was started on oral therapy with artemether-lumefantrine (80/480 mg) twice daily for the next 3 days alongside supportive therapy for mild COVID-19 pneumonia as per national guidelines.

Outcome & follow up

With administration of IM adrenaline & IV hydrocortisone, his tachypnea settled along with decreased itch. The rash slowly faded within the next 48 h, with persistence over the back for further 24 h. He was discharged after completing the isolation period as per national COVID discharge protocol & was followed up after a month at OPD, he didn't have any residual symptoms & was doing well (Figure 1).

Discussion

A hydrophilic hemisuccinate derivative of artemisinin, artesunate, has been recognized as the treatment of falciparum malaria [7] for its rapid antimalarial effect, easy to administer dosage regimen & infusion volume, safety & reduction in mortality [8].

Antimicrobials has been reported as the most common drug causing anaphylactic reactions, of which artesunate is the second commonest [8]. Oral artesunate has been reported to cause allergic reactions, although anaphylaxis caused by parenteral artesunate is rare despite its widespread use. IgE mediated Type I hypersensitivity has been reported to be the mechanism of allergy to artesunate [8]. Based on the clinical presentation, assumption of an anaphylactic reaction to parenteral artesunate was made, this was further supported by a positive intradermal skin test for artesunate, after 7 days of the initial reaction. Literature search for the same shows two case reports of anaphylaxis to parenteral artesunate [9]. Whether co-infection with SARS-CoV-2 leads to any hyper-susceptibility in such patients needs to be evaluated. Early anticipation, prompt clinical diagnosis and immediate intervention should be done in the management of anaphylaxis. In malaria endemic regions, an anaphylactic reaction to

artesunate can be due to prior sensitization with previous exposure [9]. Prevention is better than cure, however, depriving a patient with a highly effective antimalarial agent like artesunate is not justified. Thus, an early anticipation & a timely intervention can lead to a favorable outcome.

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