

## Delving into artemisinin's shadow: Insights from a unique case of artesunate – resistant complicated falciparum malaria

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World Journal of Biology Pharmacy and Health Sciences, 2024, 18(01), 408–412

Publication history: Received on 14 March 2024; revised on 24 April 2024; accepted on 26 April 2024

Article DOI: <https://doi.org/10.30574/wjbphs.2024.18.1.0220>

### Abstract

The emergence of drug-resistant malaria poses a formidable health challenge in emerging nations such as India. The ineffectiveness of the medicine artemisinin, which is essential for treating malaria, will quickly undermine the treatment and outlook for malaria patients. If, following a complete course of therapy with Artesunate Combination Therapy and without any instances of vomiting or diarrhoea, there is no clinical or parasitological improvement in the patient within 72 hours, resistance may be considered. Reports of artemisinin-resistant Plasmodium falciparum malaria are rare in the southern regions of India. This article details a case of rare Artesunate-resistant complex falciparum malaria.

**Keywords:** Artesunate Resistant Malaria; Complicated Malaria; Artemisinin compounds; Artemisinin combination therapy; Falciparum Malaria.

### 1. Introduction

The World Health Organization (WHO) reports that 3.2 billion individuals are still vulnerable to malaria, with around 249 million new cases and 608,000 fatalities occurring in 85 countries in 2022<sup>1</sup>. Since 2006, the World Health Organization (WHO) recommends intravenous artesunate (IVA) as treatment of choice for this condition since it has proven to be superior to intravenous quinine (IVQ) in reducing mortality in both adults and children in two well-known large randomized controlled trials performed in endemic countries<sup>2</sup>. The emergence and spread of drug-resistant malaria represents a challenging health problem in developing countries like India. The World Health Organization (WHO) advises the utilization of artemisinin combination therapy (ACT) as a treatment for Plasmodium falciparum (PF) malaria in order to achieve high rates of recovery and to inhibit the emergence of resistance to artemisinin compounds<sup>3</sup>.

Parasites with diminished susceptibility to artemisinin derivatives have become more widespread in South-East Asia (namely Cambodia, Thailand, Vietnam, Myanmar, and Laos) since 2008<sup>4</sup>. Signs of resistance to the ACT – artesunate sulfadoxine pyrimethamine in PF has been observed in north-eastern states of India<sup>5</sup>. This phenomenon, which leads to a delay in the clearance of parasites from the bloodstream of individuals treated with artemisinin derivatives, is currently a serious threat and may hinder efforts to tackle the disease. A significant apprehension is the potential dissemination of these drug-resistant parasites across Sub-Saharan Africa, the region most heavily impacted by malaria (accounting for around 94% of cases), similar to what occurred with prior iterations of antimalarial therapies (such as chloroquine and folic acid antagonists)<sup>6</sup>. Artesunate-resistant Falciparum malaria is infrequently reported in the southern states of India. In this report, we present a case of uncommon Artesunate-resistant complicated falciparum malaria.

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## 2. Case Report

A previously asymptomatic 14-year-old patient from Parvathipuram, Srikakulam, Andhra Pradesh has been admitted to the hospital presenting with a 4-day history of fever, 3-day history of yellowing of the eyes, 2-day history of abdominal pain, and 1-day history of shortness of breath. The vital signs indicated blood pressure of 100/70 mmHg, Pulse rate of 110/min, Respiratory rate of 45/min, Spo2 of 92% on Room Air, Temperature of 102 F. The patient had routine examinations and tested positive for *Falciparum malaria*, along with the presence of anemia and thrombocytopenia. The investigations indicated the presence of intravascular hemolysis, sepsis accompanied by acute liver injury, and acute renal injury. The patient received an initial intravenous loading dosage of 120 mg of Inj artesunate, followed by a subsequent dose of 60 mg of Inj artesunate. Suspected delayed parasite clearance was attributed to the onset of renal failure, so the patient's treatment with artesunate was prolonged.

On the second day, he developed disseminated intravascular coagulation and acute respiratory distress syndrome. The patient underwent intubation due to elevated respiratory rate and acute respiratory distress syndrome (ARDS). Administration of broad-spectrum antibiotics and supportive measures took place. Xray Chest AP Showed diffuse bilateral coalescent opacities and cardiomegaly (Figure: 1). Electrocardiogram showed sinus tachycardia and QTC prolonged (Figure: 2). 2D Echo showed global left ventricular hypokinesia, severe left ventricular systolic dysfunction, mild mitral regurgitation, moderate Tricuspid regurgitation, mild pulmonary artery hypertension with EF: 30-35 %. The abdominal ultrasound revealed significant enlargement of the liver and spleen. The HRCT scan revealed a mosaic attenuation pattern in both the hilar regions and lower lobe parenchyma, indicative of acute respiratory distress syndrome (ARDS). The patient received a 3-day course of intravenous Artesunate treatment, but did not show any improvement and continued to deteriorate. On investigation there is no parasite clearance. It was suspected that the patient may be resistant to Artesunate. Therefore, the patient was initiated on intravenous administration of 1200 mg of Quinine, followed by 600 mg of Quinine for a duration of 7 days, in addition to clindamycin and doxycycline. Serial investigations were conducted and parasitological clearance was confirmed after 10 days of treatment (Table 1). The patient's condition showed steady improvement following the administration of Quinine injection. The patient was slowly extubated on day 15. The patient had been discharged on the 28th day.

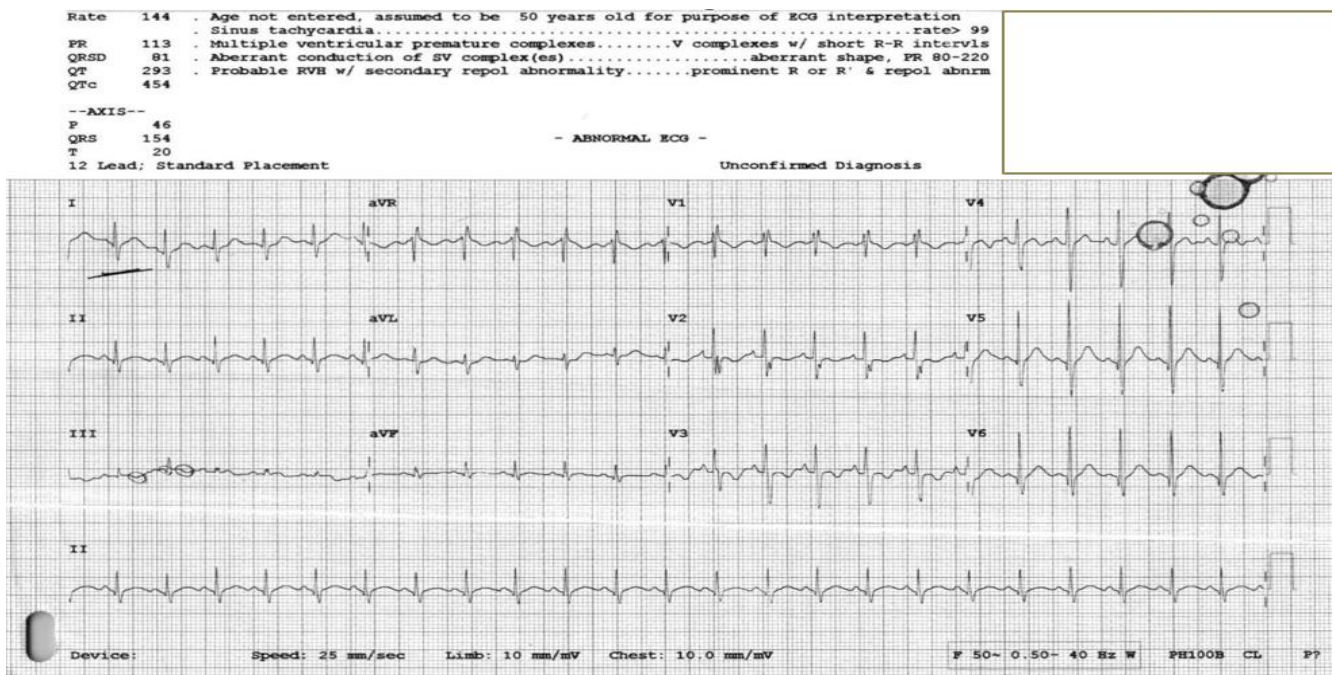
## 3. Discussion

Artemisinin compounds are highly potent drugs which are quickly eliminated from the body. They are particularly effective at eliminating parasites in the blood, faster than any other antimalarial medication. In 2005, the World Health Organization (WHO) advised the use of artemisinin-based combination therapy as the primary treatment for *falciparum malaria* in all areas affected by malaria. In 2010, India modified its antimalarial policy and advised the use of ACT for all instances of *falciparum malaria*.<sup>3</sup> The emergence of artemisinin resistance has occurred due to the massive utilization of the drug and has subsequently expanded significantly throughout Southeast Asia<sup>7</sup>. In a study conducted by Akunuri S et al., it was shown that out of the 4 patients who exhibited resistance to artesunate, 3 patients survived while 1 patient succumbed to complications associated with severe malaria. All four cases achieved parasitological clearance within four days of treatment with a combination of quinine and clindamycin. In a study conducted by Nair AA et al., it was shown that out of 4 patients who exhibited resistance to artesunate, 2 individuals survived while 2 individuals succumbed to the condition. After a duration of 4 days, subsequent examinations of peripheral smears revealed the continued presence of parasites. The resolution of organ dysfunction did not occur. Therefore, Injectable Quinine and clindamycin were initiated in all instances. On day 7 all obtained microscopic parasite clearance. In the present case at day 10 the peripheral smear showed negative for parasite. We could not confirm artemisinin resistance in our case due to lack of availability of gene testing in our area.

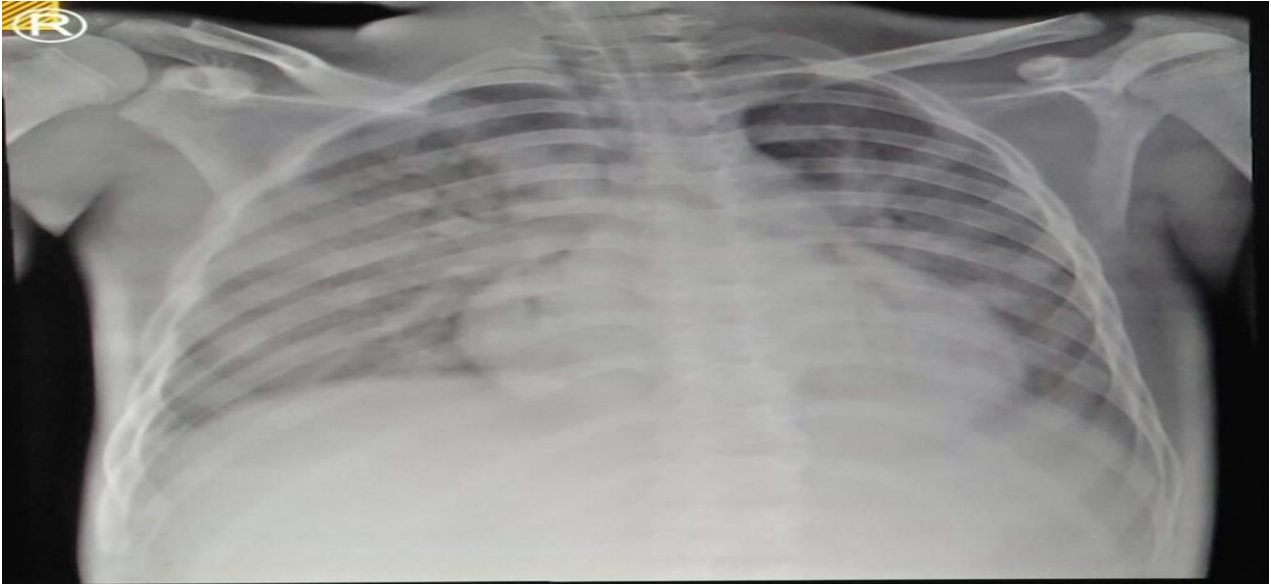
Potential causes include the broader accessibility of artemisinin monotherapies, the presence of poor-quality medications, the unregulated usage of antimalarial treatments, and the atypical genetic makeup of parasites. Delayed elimination of parasites, shown by the presence of detectable parasites on the third day, serves as an indicator of resistance to artemisinin. Suspect resistance to ACT if there is no clinical or parasitological response within 72 hours of starting the medication. However, the accuracy is compromised due to several factors that influence parasite clearance, such as the initial density of parasites, host-related factors such as impaired kidney function, previous splenectomy, and the existence of sickle cell disease. Instances of treatment ineffectiveness with ACT are infrequent. Nevertheless, in the event of a failure of ACT treatment, it is necessary to provide a combination of quinine and tetracycline/doxycycline/clindamycin for a duration of 7 days.

**Table 1** Serial Investigations with Smear tests

Investigation	Day 1	Day 2	Day 5	Day 7	Day 10	Day 20	Day 28
Hemoglobin (g/dl)	7.7	7.3	8.6	10.5	10.5	11	13
WBC	16000	14000	8200	7500	7000	6000	5500
Platelets	11000	41000	105000	200000	480000	530000	550000
S. Urea (mg/dl)	73	97	33	30	30	28	25
S. Creatinine(mg/dl)	1.4	1.9	0.6	0.6	0.5	0.5	0.5
S. Sodium (mmol/l)	140	135	137	136	140	138	140
S. Potassium (mmol/l)	3.8	3.5	4.0	3.7	3.8	3.7	4.0
Total Bilirubin (mg/dl)	18	8.0	5.9	4.7	4.0	1.5	1.1
Direct Bilirubin (mg/dl)	10	4.9	2.9	2.5	2.2	0.2	0.2
SGOT	277	232	243	240	200	40	40
SGPT	40	64	148	145	134	35	35
Alkaline Phosphatase	272	126	334	310	260	150	145
S. Albumin (g/dl)	2.6	3.4	3.6	3.8	4	4.5	4.5
PT with INR	57.7, 4.6				27, 1.7		
Smear for Malaria Parasite	Positive for Plasmodium Falciparum				Negative for Plasmodium Falciparum		



**Figure 1** Electrocardiogram Showing sinus tachycardia and QTC Prolongation



**Figure 2** Xray Chest AP View showing diffuse bilateral coalescent opacities and cardiomegaly

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#### 4. Conclusion

This paper highlights the necessity of enhanced surveillance to detect artemisinin resistance in India. Therefore, it is crucial to guarantee the logical utilization of the limited number of still effective medications, such as maintaining constant watchfulness to prevent the use of artemisinin monotherapy, ensuring complete treatment with primaquine, and verifying the effectiveness of the treatment through negative smear results on day 28. It will assist the physician in using drug combinations that are less prone to promote resistance.

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#### Compliance with ethical standards

##### *Disclosure of conflict of interest*

There are no conflicts of interest.

##### *Statement of informed consent*

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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