A Case Report: An Investigation into the Aetiology of severe Anaemia after Malaria Treatment from Turkey

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Abstract: Anaemia constitutes one of the main clinical manifestations of severe falciparum malaria, interestingly, anaemia may also be due to Artesunate related drug toxicity. A 42-year-old male patient with complaints of fever, difficulty in speaking, loss of balance and light headedness is presented to the clinic, extensive work up leads to a diagnosis of severe malaria. Initial parasitaemia is 20%. Upon receiving the treatment which is Artesunate, the patient witnesses massive improvement in his condition and parasitaemia is cleared. However, seven days post treatment and discharge, he returns to the hospital with classical signs of severe anaemia. Several aetiologies are suspected in the differential diagnosis, such as autoimmune haemolytic anaemia; a complication of severe malaria, the possibility of hemophagocytic syndrome is also taken into consideration. However, the final diagnosis was given as post Artesunate delayed haemolysis.

Introduction: Malaria can be a leading cause of mortality and morbidity in tropical regions and has been presenting a significant global health burden. Plasmodium falciparum is responsible for the most fatal type of Malaria infecting humans with having a mortality rate as high as 500 000 deaths each year. To gain better knowledge of the clinical course of severe malaria, one must first recognise what distinguishes severe malaria from other types of malaria. In this case report, we look at the clinical manifestations reported in this specific patient, treatment regimens and what consequences and complications the treatment can carry. One of the main clinical manifestations of severe malaria is anaemia with Hb levels falling below 8mg/dL. However, this complication can also be a case of drug adverse effects.

Case Report: A 42-year-old Turkish male was admitted with fever and chills, headache, difficulty in speaking, loss of balance and light headedness. His symptoms had started a week earlier with the fever being intermittent in nature. Physical examination revealed a noticeable level of somnolence and mild hepatomegaly. The patient reported a history of travelling to Africa which led us to perform a peripheral thin blood film microscopy and its result confirmed the presence of plasmodium falciparum with the 1544 parasites per µL. The rapid plasmodium antigen test was also positive for P. falciparum. The definitive diagnosis was severe malaria based on the given to data. On day one, the patient had creatinine values of 3.86 mg/dL, indicative of acute kidney failure. Furthermore, he also had severe jaundice confirmed by his bilirubin levels of 13 mg/dL with the direct bilirubin level being at a level 10 mg/dL.

The patient was started on intravenous Artesunate (2.4 mg/kg) (first two days)/ Arthemeter-lumefantrin (5 days) in addition to doxycycline (7 days), additionally, in addition to this, supportive care was provided. On day three, severe malaria was persistent. And the patient was now complaining of a serious headache. Cranial MRI was performed, and it showed cortical oedema localized in the occipitotemporal gyrus and inferior temporal gyrus, T2-weighted diffusion revealed hyperintense signal changes- cerebral malaria was the final diagnosis . Day seven was the third day with the patient being fever-free, he did however have rectal bleeding (history of haemorrhoid). No significant finding was reported in the colonoscopy and haemorrhoid treatment was initiated. On day eight, the patient was discharged with a 10 g/dL haemoglobin level.

On day 17, the patient was returned and fatigue was worsened, and, his severely pale status led to his re-admission to the hospital. Gastrointestinal haemorrhage is discarded. The patient had severe anaemia. Malaria related anaemia, gastrointestinal bleeding, hemophagocytic syndrome and drug-related anaemia were included in the differential diagnosis.

Further work up was done to find out the aetiology behind the anaemia and in the end, it was thought to be post-Artesunate related delayed haemolytic anaemia. The management plan included the administration of six units of erythrocyte suspension transfusion to the patient. (Table 1) demonstrates the laboratory values of haemoglobin, creatinine and bilirubin recorded throughout the patient stay.

	Day 0	Day 1	Day 4	Day 7	Day 12	Day 17
Reticulocyte	5.89					13.42
Hb	14.7	12.8	12	10	10	6.5
Htc	41.5	35.4	34	29	29	19
MCV		78	78	81	84	90
MCHC		36.2	38	28	34	34
Plt	44	26	44	133	202	193
Haptoglobulin					<10	
CRP	194	350	233	18	22	27
ALT	226	184		189	125	41
Ferritin						2698
Creatinine	1.2	3.86	4	2	1.6	1.42
LDH			828		876	1143
Bilirubin (T/D)	13	10	2.9	3.4	2.8/1.128	
Triglyceride						130

Table 1: demonstrates the laboratory values of haemoglobin, creatinine and bilirubin

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Discussion and Conclusion: A recent review of the available data obtained from non-immune and semi-immune patients reported post Artesunate related delayed haemolysis to have an incidence rate of 13%, additionally, the requirement for a blood transfusion was given as 9% of those reported cases. Our case report is of particular value because it is the first case of PADH to be reported from Turkey.

This patient met the major criteria required to be given a full diagnosis of severe malaria as set by World Health Organization (WHO) guidelines on Malaria as he had a positive peripheral smear test with a falciparum hyper-parasitaemia, in addition to this, the patient had severe jaundice with a plasma bilirubin level of 13mg/dL. His kidney function test was also showing some high level of impairment with a creatinine value of 3.86 mg/dL.

Artesunate is the internationally recommended first line treatment for severe malaria since 2010 [3]. The most up to date regimen of Artesunate (2.4 mg/kg) was administered intravenously a at time intervals of 12 hours for the first day, and then once daily afterwards. Although initially discharged, the patient came back with classic symptoms of severe anaemia.

Severe anaemia can be of many aetiologies and making the correct diagnosis can be complicated and challenging, for this reason, the differential diagnosis considered here include the malaria itself, the recovery process, or the side effects of Artesunate, another possibility is hemophagocytic syndrome which can produce similar signs and symptoms . To understand why we diagnosed this patient with post Artesunate delayed haemolysis, the pathophysiology behind the previously discussed aetiologies will be explained briefly and a comparison of our case will be given.

First disease to rule out in this specific clinical picture observed in our patient, was hemophagocytic syndrome, which is a heterogenic syndrome that can possibly lead to acute and fatal inflammatory reaction. It can be hereditary or acquired. The acquired form can be triggered by infection, it manifests itself by a consistent fever, cytopenia and splenomegaly. In the laboratory findings, the Histiocyte Society states that five out of eight criteria must be met to make a diagnosis of hemophagocytic syndrome. The criteria this patient met was hyperferritinemia with a value of 2698 on day 17, as well as a low platelet count of 44 on day 7, low haemoglobin and fever. This only adds up to four [6].

Malarial anaemia can be possibly due to the reason that the infected as well as the uninfected red blood cells are undergoing lysis, followed by their sequestration by spleen and irregularities in erythropoiesis followed by bone marrow suppression. According to the WHO stratifications, for severe malarial anaemia to be diagnosed the critical haemoglobin level should be below 6 g/dL whilst considering age, reticulocyte count, and checking for conjunctival and palmar pallor, if however, the cut off value is accepted as less than 5 g/dL, additional factors like mean corpuscular value and history of convulsions should be considered as well. In our patient, the haemoglobin level was 6.5 g/dL at its lowest and no additional factors indicative of severe malarial anaemia were observed.

This led to the final conclusive diagnostic possibility; post Artesunate delayed haemolysis. This is possible because Artesunate functions by rapidly lowering parasitemia via aiming at the ring stage malaria parasite inhabiting the erythrocyte and stimulating the removal of the parasite by spleen but at the same time sparing the host erythrocytes from being lysed. This complex process is called pitting, although spared, the erythrocytes are now deformed and reduced in size therefore their life span is also shortened resulting in their simultaneous destruction and this clearly causes the post Artesunate delayed hemolysis.

To conclude, intravenously given Artesunate acts rapidly against all stages of plasmodium falciparum throughout its whole life cycle. For all patients with severe malaria worldwide, Artesunate is considered as the first line treatment and it's classed as grade 1A drug, however there is data confirming the incidence of post Artesunate delayed hemolysis in as much as 10-15% of children and adult after the first week of drug admission and this risk continuing up until the third week. This was the first case report describing this event occurring in Turkey.