

Case Reports

Diffuse alveolar hemorrhage due to *Plasmodium falciparum*: A rare entity—Are steroids indicated?

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Severe falciparum malaria is common in tropics, patients usually present with any of the following manifestations or combination of cerebral manifestations, circulatory failure, liver failure, acute lung injury and acute kidney injury. Pulmonary manifestations in falciparum malaria usually include acute respiratory distress syndrome (ARDS) and acute lung injury (ALI)¹. Here, we present two cases of *Plasmodium falciparum* malaria manifesting as diffuse alveolar hemorrhage (DAH). The reports on DAH are scarce. The use of steroids improved DAH in both the cases. Mechanism of diffuse alveolar hemorrhage in falciparum malaria is still not clear, and further research is needed regarding the pathophysiology and therapeutic intervention. This case report emphasizes on future research.

Case report 1

A 40-yr old male patient was admitted to ICU with complaints of high grade fever associated with chills and rigor since 15 days. There was history of yellowish discoloration of eyes for last 10 days, along with altered sensorium. He also had low urine output for last seven days and breathlessness for last five days prior to admission.

At the time of admission, his glasgow coma scale (GCS) was E3V2M4, heart rate (HR) = 110/min, and blood pressure (BP) = 110/60 mm Hg. He was tachypnoeic with respiratory rate of 36/min with diffuse bilateral crepts. His investigations revealed Hb (5.5 g/dl), WBC count (23,000 mm³), platelets (70,000 mm³), serum creatinine 4.3 mg/dl, serum bilirubin (5.08 IU/L) and SGOT/SGPT (154/43 IU/L). Histidine rich protein (HRP)-2 based antigen test (ParaHIT F) and microscopy was positive for *P. falciparum*. Chest X-ray revealed bilateral diffuse infiltrates (Fig. 1). CT scan of brain found was normal.

Diagnosis of severe falciparum malaria was made. He was intubated and initiated on mechanical ventilation. In view of acidosis, hyperkalemia, low urine output, high

serum creatinine levels, hemodialysis was initiated. Both antibiotics and antimalarials were administered, namely artesunate, doxycycline and ceftriaxone. Serological analysis for other infective etiologies like leptospira and dengue were negative.

He was severely hypoxemic and arterial blood gas analysis revealed pH (7.30), PaO₂ (60 mm Hg), PaCO₂ (52 mm Hg), HCO₃ (19.6 meq/L), BE (4.8) and SpO₂ (91%) on FiO₂ (1.0) (PaO₂/FiO₂ < 100). He was ventilated as per ARDS net protocol and proning sessions were also done. By Day 6, his ABG revealed a slight improvement in the form of pH (7.40), PaO₂ (88 mm Hg), PaCO₂ (42 mm Hg), HCO₃ (23 meq/L), BE (2.3), SPO₂ (97%) on FiO₂ (0.4); Na 143 (meq/L), and K⁺ (3.9 meq/L) (Table 1). Thereafter, the

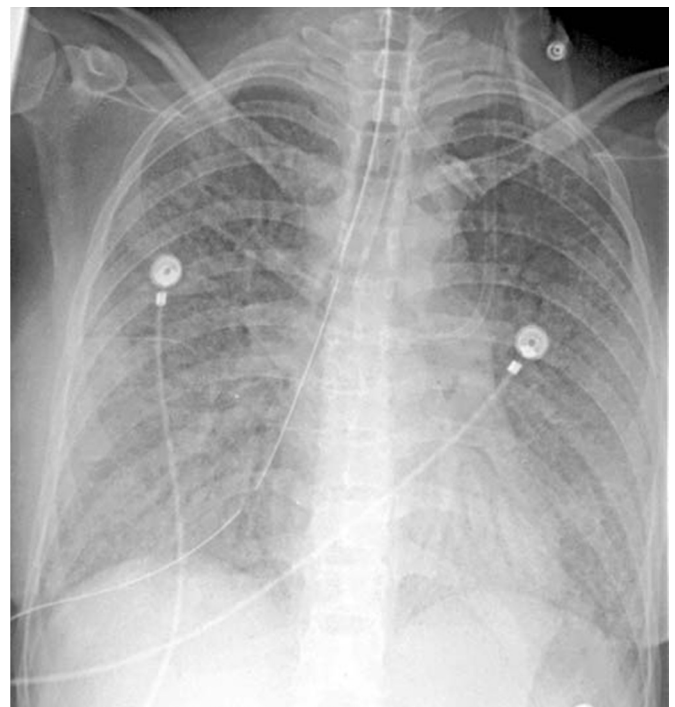


Fig. 1: Case 1: Chest X-ray showing bilateral diffuse infiltrates.

Table 1. Serial arterial blood gas analysis of patient

ABG parameters	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
pH	7.3	7.34	7.38	7.41	7.43	7.4	7.42	7.38	7.4	7.42	7.43	7.46
PaO ₂	60	70	72	78	90	88	75	66	80	85	82	88
PaCO ₂	52	58	48	41	38	42	39	42	40	38	43	40
HCO ₃	19.6	22	25	22	24	23	24	22	23	23	25	23
BE	-4.8	-2.4	1.8	-1.8	0.2	-2.3	0.2	-1.8	-2	-0.8	1	-0.8
SpO ₂ (%)	91	93	94	95	98	97	98	93	94	95	97	98
FiO ₂	1	0.8	0.7	0.6	0.5	0.4	0.4	0.4	0.5	0.5	0.4	0.4
P/F ratio*	60	88	103	130	180	220	189	165	160	170	210	220

P/F ratios*= PaO₂/FiO₂ ratios are used to define the severity of ARDS; Mild ARDS: P/F ratio = 200–300; Moderate ARDS: P/F ratio = 100–200; Severe ARDS: P/F ratio <100.

patient was given weaning trial, which subsequently failed and percutaneous tracheostomy was done.

On Day 8, of ICU stay endotracheal bleed was noticed and his PaO₂ dipped to 66 mm Hg on FiO₂ = 0.4 (Table 1). At that time his platelet count and coagulation parameters were within normal limit (Platelet count 170,000 mm³, prothrombin time (PT)-16 sec, fibrinogen-324 mg/dl and D-dimers-Negative). Bronchoscopy revealed diffuse alveolar hemorrhages, the entire tracheal tree including the carina with right and left bronchial tree was normal. The finding was further confirmed by Prussian blue staining of broncho-alveolar lavage centrifugate which revealed hemosiderin-laden macrophages (Siderophages). Possibility of post-inflammatory state was thought of and for anti-inflammatory action, steroids in dose of hydrocortisone 50 mg intravenous eight hourly (i.v. Q8) for five days was added. After one week patient's tracheal bleed settled and he was gradually weaned off ventilator.

Case report 2

A 50-yr old male patient, resident of Aurangabad, Bihar, with no history of addiction, no comorbidity, developed high-grade continuous fever and admitted to a local hospital. He was found to be *P. falciparum* malaria positive on microscopic examination along with deranged renal and liver parameters. Treatment was initiated with artesunate and piperacillin-tazobactam but mean while he developed respiratory distress. The patient was intubated and initiated on mechanical ventilation. Next day he was referred to our intensive care unit (ICU).

At the time of admission in ICU, he was sedated on mechanical ventilation, tachycardic with HR (146/min), and hypotensive with BP (90/60 mm Hg). His initial ABG revealed pH (7.28), PaO₂ (78 mm Hg), PaCO₂ (53 mm Hg), HCO₃ (16 meq/L), BE (6.3) and SPO₂ (93%) on FiO₂ (0.6). His investigations revealed Hb (6.7 g/dl), total leucocyte count (13,600 mm³), serum bilirubin (5.3 mg/dl),

SGOT (231 IU/L), SGPT (353 IU/L), creatinine (3.9 mg/dl), PT-12.6 sec (c-13.2 sec) and fibrinogen (376 mg/dl). So provisional diagnosis of falciparum malaria with septic shock with metabolic acidosis with acute kidney injury and thrombocytopenia was made. Patient was resuscitated with intravenous fluids and blood products. Vasopressors were initiated and renal replacement therapy was also started. Over next 24 h, vasopressors were tapered off. On Day 3 of admission to ICU, bleeding was noticed through endotracheal tube. Though, coagulation parameters— [PT-13.9 (c12.6 sec); fibrinogen (326 mg/dl) and platelet count (156,000 mm³) were normal. However, bleeding continued from endotracheal tube and bronchoscopy revealed alveolar hemorrhage with normal tracheobronchial tree. Prussian blue staining of broncho-alveolar lavage centrifugate confirmed the presence of hemosiderin laden macrophages. Anti-inflammatory agent in the form of steroids hydrocortisone 50 mg i.v.Q8H was added for a period of five days. Tracheal bleed settled but patient developed ventilator associated pneumonia with septic shock. Endotracheal tube aspirate culture revealed multi drug resistant klebsiella for which meropenem was added according to sensitivity profile. Patient's lung function continued to deteriorate, requiring increased ventilatory support for the same. Blood product transfusions and alternate day dialysis were continued but patient succumbed to multiorgan dysfunction despite all possible efforts.

DISCUSSION

Intra-alveolar hemorrhage in patients with malaria was found to be a rare finding, after intensive literature search. Though, this manifestation is common in patients with leptospirosis, mechanism being vasculitis².

Mechanism of diffuse alveolar hemorrhage in cases of malaria could be multifactorial. Massive intravascular hemolysis with the release of thromboplastic substances

is a well-known trigger mechanism for diffuse intravascular coagulation (DIC)³. In addition, DIC may be initiated by poor microcirculation secondary to rheological abnormalities and aggregation of platelets following damage to blood vessel walls. Generally in DIC, fibrin thrombi are removed by reticulo-endothelial fibrinolytic system. In acute malaria, the reticulo-endothelial system is probably already overloaded. Therefore, the process of DIC continues and serious clinical complications develop.

Another mechanism for diffuse alveolar hemorrhage (DAH) could be post-inflammatory state of alveolar capillary membrane⁴. The potential mechanisms include endothelial injury with alterations in endothelial permeability leading to interstitial and alveolar edema, and intravascular sequestration of leukocytes. Probably, this leads to inflammation of capillaries and thus, leading to intra-alveolar hemorrhage.

The falciparum malaria is notorious in causing cerebral manifestations and acute kidney injury (AKI). Extensive literature review has reported few cases of alveolar hemorrhage due to vivax malaria but falciparum malaria has never been reported as causing alveolar hemorrhage⁵. An inflammatory cause is seen in autopsy studies in patients with vivax malaria showing increased alveolar-capillary monocytes, and increased pulmonary phagocytic cell activity 1–2 days after the commencement of treatment for vivax malaria⁶.

DAH in vivax malaria reflects a post-treatment intravascular inflammatory response to the death of parasites or reperfusion and could be extrapolated in cases with falciparum malaria. This is consistent with the fact that both of our patients had diffused alveolar hemorrhage post-treatment. In both the cases, DIC was ruled out as patients had normal PT, activated partial thromboplastin time (APTT), and platelet count and was negative for D-dimers. Possibility of post-inflammatory state of alveolar capillary membrane was also thought, as this complication of tracheal bleed was noted after 24 h of initiation of antimalarial treatment. Post-hydrocortisone treatment DAH settled in both patients which were confirmed bronchoscopically. Steroids and agents like cyclophosphamide are being used in patients with DAH secondary to vasculitis^{2, 7}.

There is no evidence regarding the role of steroids in

the management of pulmonary complications of malaria. The use of steroids in a single case of vivax malaria complicated with bronchiolitis obliterans organizing pneumonia (BOOP) is reported in literature⁸.

This could be an area of research where steroids can be of help by suppressing the post-inflammatory state. Like in bacterial meningitis where dexamethasone 10 mg i.v. Q 8H is added prior to first shot of antibiotic to suppress the post-inflammatory response⁹, similar approach can be adopted in patients with falciparum malaria with lung involvement. In falciparum malaria patients with lung involvement in the form of poor oxygenation or bilateral diffuse infiltrates on chest X-ray; we suggest steroids can be added along with antimalarials at the time of initiation to suppress the post-inflammatory state. Future interventional studies are warranted to look for the role of steroids in this disease.

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