Disseminated intravascular coagulation in malaria: A case report

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ABSTRACT

Disseminated intravascular coagulation (DIC) is seen in <5% of patients with severe *Plasmodium falciparum* malaria and is more common in cerebral malaria. Here, we report the diagnosis and management of a case of severe *P. falciparum* malaria with DIC.

Keyword: Cerebral malaria, cytokine storm, DIC, heparin

INTRODUCTION

In spite of the various efforts from the government to eradicate it, malaria continues to be a major health problem in the North Eastern parts of India. Disseminated intravascular coagulation (DIC)is a major complication of malaria besides those of renal failure, pulmonary edema and anaemia.[1-4] While the prevalence of malaria in India is 3697 per 100000 population, in the state of Meghalaya, it is 16656 per 100000 population, which is five times more than the national average and is also the highest among North Eastern States.[5] We report a case of *Plasmodium falciparum* malaria, in a patient with a history of recent travel to a village in Garo Hills (Meghalaya), who developed DIC with no other attributable illness.

CASE REPORT

A 45-year-old male patient was shifted to intensive care unit with history of 5 days fever, chills, rigor and body ache. He was restless, febrile (101°F), tachypneic (35/min) with heart rate 140/min, blood pressure 144/90 mm Hg and no focal neurological deficit or meningism or organomegaly. SpO_2 was 98% with 6 L/min oxygen by face mask, arterial blood gas analysis showed metabolic acidosis (base excess-9 mmol/L, lactate 7.5 mmol//L) and blood sugar 70 mg/dL. Immunochromatographic test was positive for falciparum malaria with ring forms of *P. falciparum* in peripheral blood smear.

Persistent backflow of blood from the peripheral intravenous (i.v.) infusion line was observed even after changing the sites of cannulation and blood sample clotted immediately in the syringe. So, initial bolus of 3,300 units (50 units/kg) of unfractionated heparin, followed by heparin infusion (10 units/kg/h[6]) was initiated. Only after heparin infusion parenteral treatment with fluids and artesunate (2.4 mg/kg body weight[7]) could be initiated.

Investigation results showed high serum creatinine (4.0 mg/dL), serum bilirubin 12.4 mg/dL and serum lactate 7.5 mmol/L along with a deranged coagulation profile (prothrombin time prolonged by 10 s, activated partial thromboplastin time prolonged by 13 s, International Normalized Ratio 1.7 and platelets 50,000/cubic mm). Fibrin degradation products (FDP), D-dimer and fibrinogen could not be sent on admission due to laboratory limitations.

Initially, two units of platelets and four units of fresh frozen plasma were transfused in view of the deranged coagulation profile. Cardiac enzymes (troponin T, troponin I and creatinine kinase MB) were normal. At 8 h after initiation of heparin therapy, D-dimer assay was strongly positive >8.0 μg/mL (ref <0.5) and FDP was also >80 μg/mL (ref <5.0). Serum creatinine, bilirubin, lactate and coagulation profile became normal by 36 h. Patient was fully conscious by the 8th day and was discharged to the ward on the 9th day while maintaining SpO_2 97% on room air.

DISCUSSION

Haemostasis represents a balance between anti-coagulant and procoagulant forces. Disorders in haemostasis occur when the hemostatic balance shifts towards one side or

the other, resulting in bleeding or thrombosis. In our case report, there was back flow of blood from i.v. cannula and clotting of blood sample in the syringe itself strongly suggestive of procoagulant forces setting in.[8]

Since the treatment of DIC consists of treating the underlying condition, low dose heparin had to be given to combat the clotting tendency. The formation of clots within the i.v. infusion line itself did not permit the initiation of anti-malarial treatment, as well as the correction of lactic acidosis and hypoglycemia till the venous line could be cleared by heparin bolus/infusion.

The thrombotic phase can lead to microangiopathic haemolytic anaemia. *P. falciparum* infection causes small protrusions or "knobs'' on parasitized red blood cell (RBC) membranes, which mediates their adhesion to the vascular endothelium. Rupture of schizont stage parasites exposes glycosyl phosphatidylinositol anchors on the parasite and RBC surface that induces macrophages and other inflammatory mediators including tumor necrosis factor (TNF), interleukin-1, kinins and reactive nitrogen to adhere to them. These cytokines play a role (cytokine storm) in activation of endothelial adhesion molecule type 1, E-selectin, enhancing cytoadherence of parasitised cells, mediating such pathologic processes as hypoglycemia, lactic acidemia, shock, gut mucosal damage and increased permeability and neutrophil aggregation in the lung.

These cascades lead to sequestration of parasitised RBC in the microvasculature causing sluggish flow and obstruction, resulting in impaired oxygen delivery and organ dysfunction. This may affect vital organs including brain, liver, heart, kidney, lungs and bone marrow. *P. falciparum* malaria infection influences blood coagulation by various interacting pathobiological mechanisms, most important being the cytokine storm.

DIC develops when there is sudden exposure of blood to procoagulants including tissue factor. Endothelial disruption, tissue damage, inflammatory or tumor cell expression leads to exposure to tissue factor in the circulation. This activates extrinsic pathway by VIIa complex forming tissue factor VII complex, which activates thrombin which converts fibrinogen to fibrin leading to platelet aggregation. Once thrombin generation is completed, it is regulated by multiple haemostatic mechanisms. Anti-thrombin is supposed to regulate the activity of thrombin, but it is consumed due to ongoing activation of coagulation. Protein C and protein S are other anti-coagulants which are incapacitated by cytokines, TNF, interleukins. Under normal conditions, protein C is activated by thrombin and is complexed on the endothelial cell surface with thrombomodulin. Activated protein 'C' combats coagulation via proteolytic cleavage of factors Va and VIIIa. But cytokines, TNF and so on incapacitate protein 'C' pathway. Protein 'C' levels are further reduced via consumption, leakage and reduced hepatic production and reduced circulating protein 'S'.

Tissue factor pathway inhibitor is another anti-coagulant mechanism that is disabled in DIC. It inhibits the tissue factor VIIa complex. Initial response to inflammation is the augmentation of fibrinolytic action, but this is reversed with the release of inhibitor for example, plasminogen activator inhibitor. Therefore, fibrinolysis cannot keep pace with the increased fibrin formation, leading to deposition of fibrin in vasculature.

The primary treatment of this condition includes treating the underlying cause, treatment of the DIC with heparin to prevent fibrin deposits in the capillary network which could further cause ischaemia and worsen the condition of the patient. After initiating the primary treatment of DIC, treatment for falciparum malaria was started. This case is being reported for the unusual occurrence of DIC in severe falciparum malaria. If the DIC is treated in time, the complications of severe falciparum malaria can be prevented and patient can be cured with the anti-malarial treatment.[1-4]

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