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Acute myocardial infarction associated with severe *Plasmodium vivax* malaria

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ABSTRACT

Malaria is still a major public health problem, even after many preventive strategies. *Plasmodium vivax* is also a major health concern now due to the addition of new unusual manifestations day by day in its clinical profile. Herewith, we report a case of a 15-yr-old male of severe *P. vivax* malaria (complicated with thrombocytopenia, hepatitis, acute lung injury, and shock), who developed chest pain. Later, he was confirmed to have acute myocardial infarction based on electrocardiography, cardiac enzymes, and echocardiography. PubMed and Google-based literature search found that it was the first confirmed case of this type. Fortunately, timely diagnosis and appropriate management saved his life.

Key words Acute lung injury; complicated malaria; Hepatitis; thrombocytopenia; shock

Background

Malaria, transmitted by the bite of infected female *Anopheles* mosquito still remains one of the major health problems worldwide. It causes significant morbidity and mortality especially in sub-Saharan Africa, Southeast Asia, and Latin-America[1]. In endemic regions, malaria can present with a wide range of systemic complications including atypical manifestations. The majority of unusual manifestations or complications are reported with *Plasmodium falciparum* infection[1–2]. Cardiac manifestations have recently been observed in a few cases of severe *P. falciparum* malaria but it is extremely rare with *Plasmodium vivax* infection[3]. There are a few cases that have reported acute myocardial infarction in *P. falciparum* infection but there was only one case of *P. vivax* reported with an unusual presentation mimicking acute myocardial infarction[4]. Subsequently, a PubMed and Google-based literature search led us to believe that this is the first confirmed case report of acute myocardial infarction in severe *P. vivax* infection.

Case presentation

A 15-yr-old male student presented in the emergency department, Popular Multispecialty Hospital, Varanasi, Uttar Pradesh, India in August 2018, with high-grade fever, chills and rigors, nausea and generalized weakness for five days. He was fully conscious and oriented but restless. His general and systemic examinations were unremarkable except for crepitations in the bilateral chest. Blood Pressure (BP) in the right arm was 100/70 mm Hg, pulse rate 102/min, respiratory rate 22/min and temperature was 102.2°C. His past and family history were not significant. The differential diagnosis based upon history and clinical examinations were kept as complicated malaria, leptospirosis, atypical pneumonitis, severe dengue fever and complicated enteric fever.

Following standard protocol, management was started immediately empirically. Intravenous ceftriaxone 1g 12 hourly, artesunate 120 mg at 0, 12 hours, 24 hours then once daily with adequate fluid resuscitation and other supportive therapy was given on Day 1. Blood was sent for investigations. The relevant laboratory parameters during hospitalization are summarized in Table 1. Serum amylase, lipase, lipid profile, cortisol level, and glucose-6-phosphate dehydrogenase level were normal. Serology for Hepatitis A, B and C were negative. Dengue serology for NS1 antigen and IgM antibody by MAC ELISA, IgM Leptospira, IgM Salmonella typhi, IgM Scrub typhus and IgM Cytomegalovirus were negative. Blood and urine cultures were found sterile. Thick and thin peripheral blood smear revealed trophozoites of *P. vivax* and the antigen detection test was also positive (kit used - Malaria Pf/Pv Ag Rapid Test-CTK, Athenese-Dx Private Limited, Chennai, Tamil Nadu, India). Parasite density of *P. vivax* was calculated as 7190/µL and it became negative on 3rd day. Ultrasonography of the abdomen was normal.

Thirty hours following admission, he developed breathlessness, palpitations and chest pain with progressive worsening of his clinical condition. His antibiotic was upgraded to intravenous piperacillin and tazobactam 4.5g 8 hourly empirically.

At 48 hours after admission, his heart rate was between 60 and 64 per min, BP 80/60 mm Hg and decreased urine output was noticed. Electrocardiogram (ECG) was

Table 1. Summarized laboratory parameters

Parameters	Normal range	During hospitalisation					Follow up	
		Day 1	Day 3	Day 5	Day 8	Day 11	2nd week	8th week
Hb (g/dl)	13-16	12.4	12.2	11.8	11.6	11.8	12.0	13.2
TLC (/Cu.mm)	4000-10000	13300	11000	12800	8400	7800	4300	4830
PC (Lac/Cu.mm)	1.5-4.5	101	90	25	92	110	158	160
RBS (mg/dl)	70-150	103	112	100	148	130	115	-
S.Na+(mmol/L)	138-150	133.9	132	137	138.4	138.2	139	-
S. K+ (mmol/L)	3.5-5	4.65	4.45	3.58	4.0	4.2	4.0	-
B. Urea (mg/dl)	15-45	33.4	30.6	24.0	24.6	21.5	20	22
S.Creat (mg/dl)	0.6-1.4	1.18	1.1	0.9	1.11	0.8	0.8	0.82
S.Cal (mg/dl)	8.5-11	8.68	8.6	8.5	9.0	8.8	-	-
S.Bil-T (mg/dl)	0.3-1.2	0.8	0.58	0.9	1.0	0.9	0.8	0.8
ALT (IU/L)	<50	187.6	201.	142	38	42	40	41
AST (IU/L)	<50	148	150	143	40	36	38	32
S.ALP (IU/L)	30-90	151.6	162	161	58	62	70	53
S.Protein (g/dl)	6.4-8.3	6.8	6.65	5.8	6.5	6.8	7.8	-
S.Albumin (g/dl)	3.5-5.2	3.4	4.9	3.8	3.5	3.5	4.1	-
PT (seconds)	9.7-12.62	11.2	12.8	11.0	-	-	-	-
INR	<1.2	1.1	1.2	1.0	-	-	-	-

Hb–haemoglobin; TLC–total leucocyte count; PC–platelet count; S.Cal–serum calcium; S.Bil-T–serum bilirubin-total; ALT–alanine transaminase; AST–aspartate transaminase; S.ALP– serum alkaline phosphatise; RBS–random blood sugar; PT–prothrombin time; INR–international normalized ratio

suggestive of acute anteroseptal myocardial infarction. Cardiac biomarkers such as CPK-MB [42 ng/mL (normal <20)] was raised and troponin T was positive [103 pg/mL (normal <14)]. Echocardiography and color doppler showed mildly hypokinetic anterior wall with borderline left ventricle (LV) ejection fraction of 50%, borderline dilated right atrium and ventricle with severe TR, mild PR, trace MR and mild PAH (Fig. 1). He was still on intravenous artesunate and intravenous doxycycline 100mg 12 hourly was started. Aspirin 75mg and clopidogrel 75mg with atorvastatin 30 mg were added after a cardiology consult. Noradrenaline infusion was added after volume resuscitation with rapid infusion of isotonic saline. Aspirin was stopped due to progressively decreasing platelets count and appearance of mild subconjunctival hemorrhage in the left eye. Intravenous hydrocortisone 100mg 8 hourly was added on the 4th day due to persistent hypotension that was non-responsive to inotropes, to which the patient responded well. Fortunately, his vitals and clinical condition began improving. Coronary angiography was performed after the boy was stable and was normal (Fig. 2).

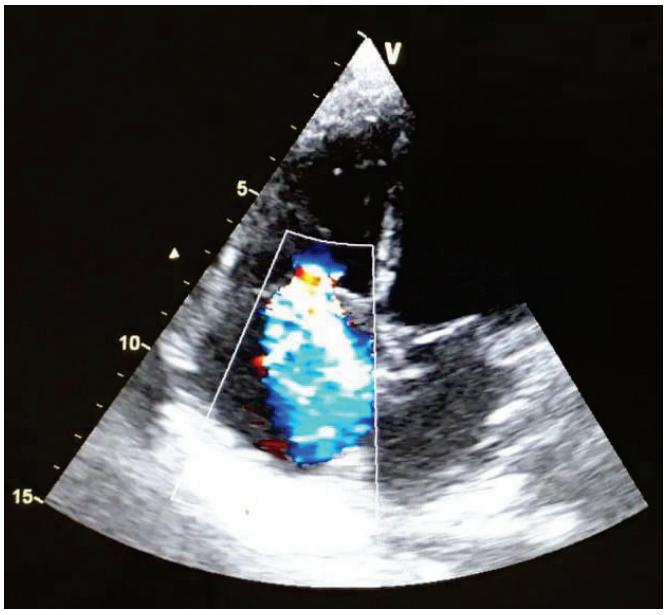

Fig. 1: Echocardiogram (ECG) showed mildly hypokinetic anterior wall with borderline left ventricle (LV) ejection fraction of 50%, borderline dilated right atrium and ventricle with severe TR, mild PR, trace MR and mild PAH.

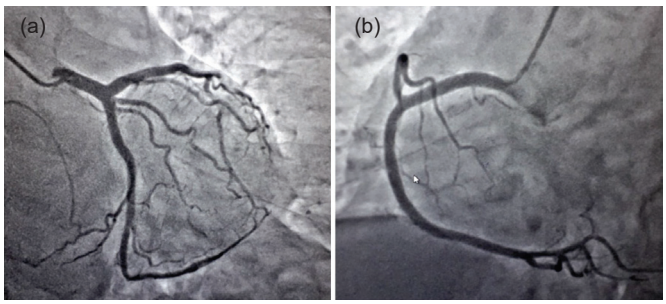

Fig. 2: Normal coronary angiogram for right coronary artery, left anterior descending artery, left main stem artery and left circumflex artery.

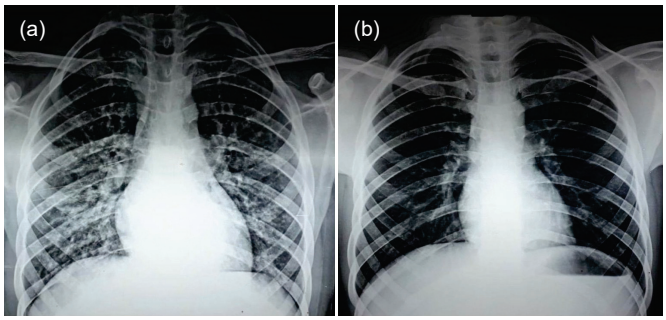

Fig. 3: Chest X-ray showing (a) infiltrates in bilateral lung fields during hospitalization and (b) normal lung fields after treatment.

On the 11th day of admission, all vitals were stable with normalization of laboratory parameters except echocardiography (Fig. 3b). He was discharged on the 13th day of admission in stable condition with hemetenics and clopidogrel 75mg with atorvastatin 20mg. All medications were stopped in the 2nd month after cardiac consultation. He was doing well 3 months later during follow-up.

DISCUSSION

World Health Organization (WHO) reported approximately 207 million cases of malaria and 627,000 deaths in the year 2012[5]. Malaria is common in tropical and subtropical areas, especially in South East Asia and India. It is estimated that *P. vivax* contributes nearly 50% of total malaria cases from more than two-thirds of the Indian population living in malaria-endemic zone[1, 3].

The typical features of malaria are fever and shivering, poor general condition, diarrhoea, nausea, and vomiting but during the course of malignant malaria, it affects different organ systems of the body[1]. WHO has outlined the criteria for severe malaria as severe anaemia, cerebral malaria, coma, multiple seizures, acute kidney injury, acute lung injury, acute respiratory distress syndrome, hypotension, circulatory collapse, acute hepatitis including fulminant hepatic failure, blackwater fever or haemoglobinuria, rhabdomyolysis, disseminated intravascular coagulation, acral gangrene, splenic rupture, splenic infarction, splenic torsion, and pancreatitis[1-2,7]. Besides this, few studies have described various cardiac complications such as bundle branch block, pericardial effusion, cardiomyopathy, and myocarditis[3,7]. However, studies showed conduction abnormalities and non-specific ST-T segment elevation but rarely elevated the cardiac biomarkers[4]. It is important to note that most of the literature regarding atypical presentation or complication is limited to *Plasmodium falciparum* malaria. In contrast to previous literature, atypical presentations due to *Plasmodium vivax* infection have been frequently reported during the last few years. Even though, cardiac complications due to *P. vivax* have rarely been described in the literature[3]. In this case, there was chest pain and breathlessness which may be due to acute lung injury but palpitations and ST-T segment elevation in ECG clinch cardiac involvement. Furthermore, positive cardiac enzymes (CK-MB and troponin T) and echocardiographic findings confirm acute myocardial infarction. In this scenario, echocardiography many times becomes very helpful to explore more about myocardial dysfunction.

Pathogenesis

Though the exact pathophysiological link between myocardial damage and malaria remains unclear, but previous literature proposed some hypothesis. [I] Cytoadherence-based theory - The possible cause of myocardial ischemia is related to blockage of capillaries due to cytoadherence by parasites and parasitized red blood cells to capillary endothelium mediated by strain-specific erythrocyte membrane adhesive protein and this sequestration of red blood cells may also interfere with the microcirculatory flow of heart[1, 8–9]. However, cytoadherence is characteristically reported in *P. falciparum* and not in *P. vivax* malaria, possibly due to low parasite density[10]. [II] Cytokines-based theory - Some studies strongly supported cytokine-mediated endothelial activation linked to complicated *P. vivax* malaria which might be a possible cause for transient myocardial ischemia. This is a better explanation in our case as how to involve lungs and myocardial injury. Various cytokines (tumor necrosis factor alpha, interleukin-10, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1) and *vivax*-specific "malaria toxins" are released in complicated *P. vivax* malaria and are supposed to cause organ-specific inflammation, increased alveolar-capillary membrane permeability, capillary leakage, and leukocyte aggregation[11-12]. [III] Catecholamine-based theory - Raised catecholamine observed in malaria induces vasoconstriction, which may further aggravate the myocardial damage[9]. [IV] Another theory stated that ischemia, acidosis, toxic effects of substances similar to *P. falciparum* glycosyl-phosphatidylinositol or Plasmodium-triggered mechanisms in severe malaria leads to apoptosis and this may cause myocardial damage[13].

Fever can rarely induce ST-segment elevation in the right precordial leads which is characterized as Brugada-like ECG changes[14]. In this condition, cardiac markers and transthoracic echocardiography remain normal. These Brugada-like ECG changes generally disappeared after the resolution of fever. Severe thrombocytopenia in

our case might be due to thrombostasis and microvascular thrombosis contributing to micro vascular obstruction which could have led to coronary ischemic symptoms.

CONCLUSION

Focus on cardiac complications reported so far; how the availability of biochemical labs, echocardiography, and cardiologist on call enabled you to help the patient to recover. This is often not available in all malaria-endemic regions. Though ARDS is known, pulmonary edema due to cardiac dysfunction needs attention. In the current study, authors have aimed to draw attention to this rare condition.

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Conflict of interest: None

Ethical Statement

Patient consent was obtained.

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