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SHORT COMMUNICATION

Unusual presentation of *Plasmodium vivax*: a neglected human malaria parasite

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Abstract Severe and complicated malaria is usually caused by *Plasmodium falciparum malaria* (PF*)* but it has been increasingly observed that *Plasmodium vivax* malaria (PV), which was otherwise considered to be benign malaria, with a low case–fatality ratio, can also occasionally result in severe disease as with PF malaria. There is an urgent need to re-examine the clinical spectrum and burden of PV so that adequate control measures can be implemented against this emerging but neglected disease. We report a case of severe PV malaria with multi-organ dysfunction. Patients exhibited acute kidney injury, severe anemia/thrombocytopenia, jaundice, hypoglycemia, hyponatremia, and pulmonary edema. Peripheral blood microscopy by trained and expert pathologist and rapid diagnostic test showed the presence of PV and absence of PF. The patient recovered completely with antimalarial drugs, supportive measures, and hemodialysis. Recent microrheologic research that analyzed malaria severity in PV clearly demonstrated enhanced aggregation, erythrocyte clumping, and reduced deformability affecting microcirculation. Our case report highlights the fact that PV malaria is benign by name but not always by nature. PV can lead to unusual and potentially life-threatening complications. Further large-scale multi-centric studies are needed to define this less known entity.

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Introduction

Malaria remains a serious health problem in many parts of the world (Jensen and Mehlhorn 2009; Elsheikha and Sheashaa 2007; Richter et al. 2010). *Plasmodium vivax* malaria (PV) has the greatest geographic range and burden of disease. Worldwide, estimates of PV infections range between 130 and 390 million, with 2.6 billion individuals living at risk of infection (Hay et al. 2004). India is a major contributing country to the worldwide burden of PV. Severe and complicated malaria is usually caused by *Plasmodium falciparum* (PF*)* but it has been increasingly observed that PV malaria, which was otherwise considered to be a benign malaria, with a low case–fatality ratio, can also occasionally result in severe disease as with PF (Lampah et al. 2011). The reported severe manifestations included hepatic dysfunction, acute kidney injury (AKI), severe anemia, cerebral malaria, acute respiratory distress syndrome (ARDS),

shock, pulmonary edema, hemoglobinuria, retinal hemorrhage, and multiple organ involvement (Lampah et al. 2011; Kochar et al. 2005; 2009; Tanwar et al. 2011; Singh et al. 2011; Kochar et al. 2007; Prakash et al. 2003; Kochar et al. 2010; Carvalho et al. 2010; Mueller et al. 2009). PV-associated AKI is observed in 2–45% (Kochar et al. 2005; 2009; Prakash et al. 2003). In addition PV is known to cause relapsing human malaria (Richter et al. 2010). Even where reliable microscopic diagnosis confirms only PV, PF might still be presumed and its adherent properties might be cited as the basis of its apparent absence in peripheral blood film (PBF). Nonetheless, case reports of severe PF-like malaria attributed to PV have been published, including several using polymerase chain reaction (PCR) diagnostics (Kochar et al. 2009; 2007). In addition, the literature is almost silent on the mechanism of recent increase in incidence of PV and a shift towards multiple complications specifically in India. There is also an urgent need to re-examine the clinical spectrum and burden of PV so that adequate control measures can be implemented against this emerging but neglected disease.

Case report

An 18-year-old female was admitted with fever with chills/rigor, shortness of breath, and decrease urine output of 5 days duration. On examination, she was breathless with blood pressure of 110/58 mmHg, temperature 40°C, respiratory rate of 36 breaths per minute, heart rate of 116 bpm. Laboratory investigations revealed hemoglobin, 5.2 gm/L; total white cell count, $7.2\times10^3/\mu l$ (differential count: 60% neutrophils, 33% lymphocytes, 3% monocytes, and 4% eosinophils); platelet count, 12,000/μl; pack cell volume, 14%; serum creatinine (SCr.), 6 mg/dl; sodium,119 mmol/l; potasium, 4.5 mEq/l; blood urea, 132 mg/dl, alanine aminotransferase, 77 units/l (normal range, 0–40 units/l); aspartate aminotransferase, 194 units/l (normal range, 5–34 units/l); serum bilirubin, 4.5 mg/dl; serum albumin, 2.2 gm/dl; creatine phosphokinase, 90 units/l (normal range, 15–105 units/l); lactate dehydrogenase (LDH), 1,412 IU/l (normal range, 100–190 IU/l); and blood glucose, 44 mg/dl. The diagnosis of PV malaria monoinfection was confirmed by direct visualization of the parasite (Fig. 1a, b) in giemsa-stained PBF with parasitemia <2 % and rapid diagnostic test (RDT; negative histidine-rich protein 2 of *P. falciparum* and positive PV-specific LDH). The blood, urine, and sputum cultures were sterile. The serological tests for leptospirosis, dengue, and viral hepatitis were negative. The chest radiograph revealed bilateral, peripheral air space disease with air bronchograms. The patient was managed using anti-malarial drugs (artesunate and doxycyclin), fluid replacement and hemodialysis (HD). IV ceftriaxone 1gram BD was given initially until a bacterial infection (notably salmonella) was excluded. Supportive measures (e.g., antipyretics, oxygen, ventilator support, cardiac monitoring, and pulse oximetry) were instituted as needed. Heparin free intermittent hemodialysis was provided on an alternate days through temporary jugular dialysis catheter for 4 h for 11 times. Ten packed red blood cells and six platelet rich concentrates were transfused during HD sessions. On clinical improvement, she was discharged. On follow-up, 1 week later, her SCr. was 1.1 mg/dl.

Discussion

We reported a case of severe PV malaria with multi-organ dysfunction. In 2005, Kochar et al. reported 11 cases of severe PV in patients admitted to a malaria intensive care ward in Bikaner, India. Clinical presentations included ARDS, cerebral malaria, renal failure, bleeding diathesis, and jaundice. Two of the patients died, and one among the recovered developed post-malarial psychosis. A battery of diagnostic tests, including PCR, established infection with PV and ruled out co-infection with PF (Kochar et al. 2005).

Recently, in 2009, Kochar et al. reported 40 cases of severe PV malaria in patients admitted to the dedicated

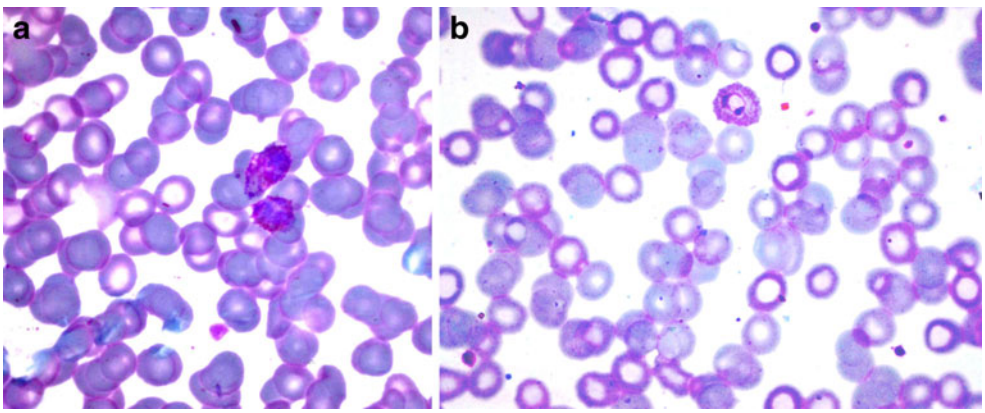

Fig. 1 **a** Schizonts of *Plasmodium Vivax*×1,000; **b** ring form of *Plasmodium Vivax*×1,000

malaria ward in Bikaner, India. Complications observed were hepatic dysfunction and jaundice in 23 (57.5%) patients, renal failure in 18 (45%) patients, severe anemia in 13 (32.5%) patients, cerebral malaria in 5 patients (12.5%), ARDS in 4 patients (10%), shock in 3 patients (7.5%), and hypoglycemia in 1 (2.5%) patient. Thrombocytopenia was observed in 5 (12.5%) patients, and multi-organ dysfunction was detected in 19 (47.5%) patients. The diagnosis of PV was established by PBF, RDT, PCR, and severe malaria was categorized as per World Health Organization guidelines (Kochar et al. 2009).

Twenty-three patients of PV monoinfection (PBF and/or RDT) were retrospectively analyzed by Singh et al. in 2011. Clinical presentations included thrombocytopenia (96%) with counts less than 50,000/μL in 39% patients, severe anemia (34%), cerebral malaria (13%), elevated liver enzymes (17.3%), jaundice (8.6%), hypernatremia (4.3%) while renal dysfunction (SCr. > 3 mg/dl) was present in 26% patients with two patients showing severely deranged renal functions (blood urea 168 mg/dl, 222 mg/dl and SCr. 5 mg/dl, 5.6 mg/dl, respectively). One patient expired within 12 h of presentation because of severely deranged hepatic and renal dysfunction (Singh et al. 2011). The association of thrombocytopenia was statistically significant with PV monoinfection in comparison to either PF monoinfection or mixed infection (Tanwar et al. 2011; Kochar et al. 2010). Our case report reminds the clinicians to the potential severity of PV malaria.

Exact pathogenesis and organ-specific morbidity caused by PV infection remains unrecognized and poorly studied because of a paucity of research in this area. PV is widely believed to be incapable of causing cytoadherence and microvascular sequestration and therefore is unable to cause organ dysfunction. Recent observations have shown evidence of sequestration of parasites in lung vasculature during evaluation of lung injury in PV (Kochar et al. 2009). Cerebral dysfunction in PV may occur through generation of nitric oxide. Cytokines and leukotrienes may be responsible for severe anemia and hemostatic complications (Carvalho et al. 2010). Recent microrheologic research that analyzed malaria severity in PV clearly demonstrated enhanced aggregation, erythrocyte clumping, and reduced deformability affecting microcirculation (Kochar et al. 2009).

There is no direct pathogenic linkage between PV and AKI, but the associated conditions such as hypercatabolic state, parasitemia, volume depletion, hyperbilirubinemia, intravascular hemolysis, renal ischemia, sepsis, antimalarial drugs, nephrotoxic drugs, dual infection, and DIC can contribute to AKI (Prakash et al. 2003). Hence, despite the association, cause and effect relationships remain doubtful. Hyperbilirubinemia may contribute to reduction in total peripheral vascular resistance and in renal blood flow due to left ventricular dysfunction. Although PV is widely believed not to mediate cytoadherence and microvascular sequestration of red cells, recent evidence in vivo challenges this theory (Carvalho et al. 2010). Carvalho et al. provide the first evidence that mature PV-infected erythrocytes are capable of cytoadhering to endothelial cells and placental cryosections (Carvalho et al. 2010; Mueller et al. 2009). Effects of mechanical, immunologic, cytokine, humoral, acute phase response, and hemodynamics factors in inducing malarial nephropathy have also been postulated Elsheikha and Sheashaa 2007).

Molecular technologies have been developed to improve the diagnosis of malaria, although these methods are limited by a number of factors including specialized equipment, continuing supplies, operator expertise, turnaround time, and cost (Bronzan et al. 2008; Torres et al. 2006; Kim et al. 2011; Cho et al. 2001). Detection of parasites on giemsa-stained blood smears by light microscopy is the gold standard for diagnosis of malaria. Identification of a schizont with >12 merozoites in the peripheral circulation is an important diagnostic clue for PV. In general, schizonts of PF are very rarely seen in blood films; they occur only in the setting of severe disease with hyperparasitemia. Repeat blood smears by trained and expert pathologist and RDT were also used to rule out mixed infection. The proteomic analysis of PV is hampered by limited parasitemia of usually <0.5%, seen in case of PV infections as it infects only reticulocytes, which comprise 1–3% of the total RBCs. This is in contrast to PF which is able to infect RBCs of all ages, resulting in a relatively higher average parasitemia of>5% (Acharya et al. 2011).

The shortcomings of the present case report included the lack of molecular technologies (PCR) to rule out dual infection due to resource limitation and economic constrains. Although PCR was not available it is unlikely that PF at a very low parasitemia would cause severe clinical malaria.

Conclusion

Our case report highlights the fact that PV malaria is benign by name but not always by nature. PV can lead to unusual and potentially life-threatening complications. Further large-scale multi-centric studies are needed to define this less known entity.

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