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Case Report

Plasmodium vivax infection causes acute respiratory distress syndrome: a case report

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Abstract

Plasmodium falciparum (*Pf*) is associated with numerous complications and high mortality, whereas *Plasmodium vivax* (*Pv*) infection is generally considered to be benign. However, severe complications, such as acute respiratory distress syndrome (ARDS) in *Pv* infection, are emerging. This case report highlights the complication of ARDS during the course of *Pv* infection in a 60-year-old woman. The diagnosis of the patient was made using microscopy, immunochromatography, and polymerase chain reaction assays for *Pf* and *Pv* species. The data indicated the presence of mono-*Pv* infection in the patient's blood, and *Pf* infection was specifically ruled out. The patient was discharged after intensive supportive care and antimalarial treatment. *Pv* infection is associated with ARDS and other complications such as sepsis and multi-organ dysfunction syndrome; this enhanced severity of *Pv* infection, if unrecognized, can lead to more deaths in malaria-endemic areas.

Key words: malaria; ARDS; PCR.

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Introduction

Malaria is a major infectious disease and remains a significant cause of morbidity and mortality worldwide. According to the World Health Organization (WHO)'s 2013 *World Malaria Report*, there were 207 million diagnosed cases of malaria in 2012, and the total number of malaria cases reported in India alone was 1.06 million [1]. The most common species being reported to cause malaria in humans so frequently are *Plasmodium vivax* (*Pv*) and *Plasmodium falciparum (Pf)*. *Pv* infection accounts for more than 80% cases in India [2]. However, the severity of malaria is higher in an infection caused by *Pf* as compared to one caused by *Pv*. Complications such as renal failure, severe anemia, acute respiratory distress syndrome (ARDS), shock, hypoglycemia, and central nervous system damage are common with *Pf* infection. Complications are rare during the course of *Pv* infection [3-5]. Usually, the presence of such complications with *Pv* infection is attributed to mixed infection by both *Pf* and *Pv* parasites, with *Pf* being unrecognized [6]. The retrospective data analysis of malaria cases in Udupi and Dakshina Kannada coastal districts of Karnataka was done by many authors, who presented an association of *Pv* infection with acute respiratory distress syndrome [7-11]. These retrospective studies do not include *Plasmodium* species identification by polymerase chain reaction (PCR) methods. However, studies using sensitive PCR methods have been more reliable in detecting mixed infections [12]. We report a severe case of *Pv* infection in an adult female with ARDS. The increasing drug resistance and lack of drug alternatives to kill dormant *Pv* hypnozoites in the liver gives us a great opportunity to document such unusual cases, which may be a result of climate conditions in the coastal districts of Karnataka state, which are surrounded by the sea and rivers.

Ethical statement

Written prior informed consent was obtained from the patient. The study was approved by the institutional ethics committee of Manipal University in Manipal, India.

Case Report

A 60-year-old woman with no known medical illnesses presented to the emergency triage with a sudden onset of breathlessness. She gave a history of fever with chills for five days prior to the onset of breathlessness, for which she had taken paracetamol for symptomatic treatment at home. On examination, she had tachypnea (24 breaths per minute) along with sinus tachycardia (110 beats per minute) and blood pressure of 100/70 mmHg. There was no fever at the time of presentation. Respiratory examination revealed bilateral crackles. Oxygen saturation by pulse oxymetry was 86%. Arterial blood gas (ABG) analysis done about 10 minutes after starting 60% oxygen inhalation by Venturi device revealed hypoxia (PO_2 66 mmHg, PCO_2 27.5 mmHg) with a PO_2/FiO_2 ratio of 110. Chest X-ray showed bilateral infiltrates (Figure 1). She was diagnosed with moderate ARDS and started on conservative management with mechanical ventilation on standby. Meanwhile, she was reported positive for *Pv* by a rapid immunochromatography test for malaria. She also had mild anemia, leucopenia, and thrombocytopenia (hemoglobin 9.9 g/dL, total white blood cell [WBC] count $3.2\times10^3/mm^3$, and platelet count $35\times10^3/mm^3$). Her renal and liver function tests were abnormal (serum creatinine 1.7 mg/dL, total bilirubin 5.5 mg/dL, direct bilirubin 4.4 mg/dL, aspartate aminotransferase [AST] 57 IU/L, alanine amino transferase [ALT] 21 IU/L, alkaline phosphatase 193 U/L). Serum electrolytes and prothrombin time were normal. Serum NT-pro-BNP was slightly elevated (2,808 pg/mL) and troponin-T was normal. A subsequent test for malaria using the quantitative buffy coat (QBC) method was also positive for *Pv* (reported as 4+, indicating severe parasitemia). A blood sample was also diagnosed by PCR to confirm the presence of *Plasmodium* species. Two sets of primer pairs were used to detect the malaria parasite, primer pairs for *pfcrt* (forward 5'-TGTGCTCATGTGTTTAAACTT-3' and reverse 5'-CAAAACTATAGTTACCAATTTTG-3') and *pvldh* (forward 5'-AAGAACCTGGGGGACGTAGT-3' and reverse 5'-TCTCGGTTCCATTCCTTGTC-3') genes specific for *Pf* and *Pv*, respectively [13], which showed a positive result for *Pv* infection and a negative result for *Pf*, as shown in Figure 2. In view of complicated *Pv* malaria, the patient was started on intravenous artesunate and oral doxycycline along with supportive therapy. She responded well to the treatment, and her oxygen requirement reduced gradually. Tachypnea and dyspnea also subsided in about three to four hours after the first dose of IV artesunate. A throat swab for influenza (H1N1, H3N2, and B) was negative. Cultures of blood, respiratory secretion, and urine were subsequently reported as sterile.

Figure 1. Figures A and B represent the portable chest X-ray in anteroposterior view of a patient with *P. vivax* malaria infection before treatment (A) and after treatment (B). Figure A shows bilateral infiltrates in the lung fields, suggestive of ARDS. Figure B shows resolution of lung infiltrates.

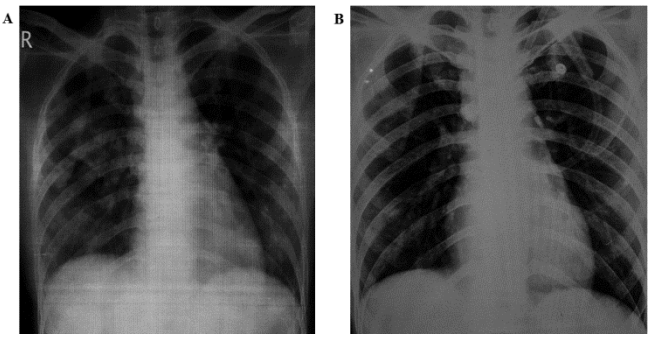
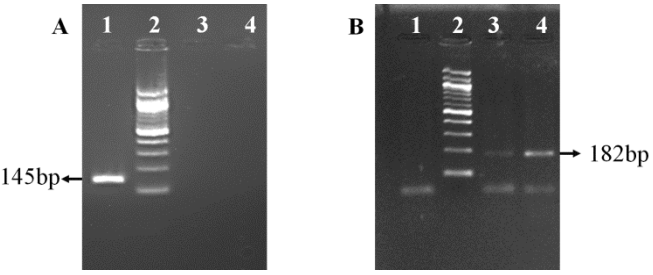


Figure 2. Figures A and B showing PCR amplification product of 145 bp and 182 bp by using *pfcrt* (specific for *P. falciparum*) and *pvldh* (specific for *P. vivax*) primers pairs, respectively. Lane 2 in Figures A and B represents 100 bp DNA marker. In Figure A, lane 1, lane 3, and lane 4 are *Pf*-positive PCR control, negative PCR control, and test sample respectively. In Figure B, lane 1, lane 3, and lane 4 are negative PCR control, test sample, and *Pv*-positive PCR control, respectively.



Discussion

It is known that *Pf* infection can lead to organ dysfunction and ultimately to death; however, complications in *Pv* infection are unusual. It is presumed that a patient with *Pv* infection with complicated malaria is suffering from a mixed infection of *Pf* and *Pv*. It is challenging to absolutely rule out the likelihood of *Pf* by using orthodox diagnostic tools, which may perhaps explain, in various cases, the use of anti-malarial therapy against both *Pf* and *Pv* infection [14-16]. It has been reported that *Pv* infection alone is also capable of causing sequestration and non-sequestration related

complications; such complications are commonly seen during the period of *Pf* infection [2]. Hence, it is very important to rule out the possibility of mixed infection by using sensitive and reliable methods such as PCR. It has been shown that the occurrence of mixed infection in our population is up to 2%, consistent with a malaria survey study in a Thai population [17], which used conventional diagnostic methods. However, another study on a Thai population put the incidence rate of mixed infection up to 30% by using sensitive PCR methods [12]. In the case patient, we have shown the complication of ARDS in mono-*Pv* infection, and specifically ruled out the presence of *Pf* by using PCR-based assays [13]. The exact mechanism of rarely noted ARDS with *Pv* is still unknown. However, there are chances it may follow the same pathophysiologic mechanism as ARDS in *Pf* infection, and this has been reported before as well [18, 19]. In most mixed infections with *Pf* being unrecognized, the patient is treated only for *Pv*. The inadvertently untreated *Pf* infection then gets worse in the background and is responsible for the complications. These complications of *Pf* are also often falsely attributed to *Pv*. The uniqueness of this case was that the patient developed ARDS with high parasitemia even before starting the treatment for uncomplicated *Pv*, which is quite unusual and has been reported before in a 43-year-old Brazilian woman [4]. In addition, our patient had features of sepsis (systemic inflammatory response syndrome with evidence of an infection) and multi-organ dysfunction syndrome (MODS) (pulmonary, hepatic and renal dysfunction), in the absence of any other demonstrable infection. These above-mentioned complications are uncommon complications of malaria caused by either *Pf* or *Pv* infection [20].

Conclusions

The presence of ARDS, sepsis, and MODS in *Pv* infection may lead to a greater number of deaths due to malaria. A high index of suspicion is needed to diagnose these complications, even in malaria-endemic regions like ours, as these complications can be life-threatening, and *Pv* malaria is not commonly recognized as a causative agent responsible for such severe presentations.

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