Severe acute respiratory distress syndrome secondary to Plasmodium vivax malaria

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Abstract
Plasmodium Vivax malaria is generally considered as a benign self-limiting illness and is less often associated with more severe disease and complications. Amongst these, acute respiratory distress syndrome (ARDS) is a particularly rare complication. The few cases reported describe the onset of ARDS after initiation of anti-malarial therapy as a post inflammatory response. Here we report the case of a 45 year old male who was a victim of severe Plasmodium vivax malaria culminating into ARDS, prior to the initiation of anti-malarial therapy. He was treated with invasive ventilation and anti-malarial therapy and made a complete and uneventful recovery.

Keywords: Plasmodium vivax malaria, Acute respiratory distress syndrome.

Introduction
Malaria is a common parasitic infection and a major health problem worldwide. It is endemic in tropical and subtropical areas of Asia, Africa, North and South America.1 In Pakistan, 1.6 million cases are reported annually and Plasmodium vivax (P. vivax) is the most common pathogen.1,2 They are most commonly found in Khyber Pukhtunkhwa and Federally Administered Tribal Areas and have a seasonal predominance. Most cases occur between July and September.2

Typically, P. vivax malaria runs a benign course, with fever paroxysms every 48 hours accompanied by rigors and chills.3 However, in the recent past, there have been case reports of life threatening complications often associated with the more aggressive falciparum malaria. These complications include shock, severe anaemia secondary to haemolysis, acute renal and hepatic failure, seizures and very rarely the acute respiratory distress syndrome (ARDS).4 It has been hypothesized that ARDS is secondary to an exacerbated inflammatory response after commencement of anti-malarial therapy.5 Extremely rarely, however, ARDS may develop prior to initiation of treatment.6 Very few cases of the latter category have been reported and our case belongs to it. Only one case of ARDS secondary to P.vivax has been described in medical literature from Pakistan.4

We present the case of a middle aged male, who presented with respiratory failure secondary to ARDS and was found to have P.vivax infection.

Case Report
A forty four year old male patient presented to our hospital in January 2015 with high grade fever, productive cough and haemoptysis for one week. The fever was intermittent, associated with evening exacerbations, rigors and chills, extreme lethargy and temporary relief with antipyretics. The cough was productive of a whitish thick sputum admixed with blood. He was initially admitted to another hospital and received moxifloxacin for two days without any relief. He was an ex-smoker and had no other co morbidities. He had returned two weeks ago from a ten day trip to his village in an eastern province of India. He confessed not to have taken prophylactic medications advised by a family doctor.

On examination, he was a middle aged gentleman in...
significant distress. The pulse rate was 112/minute, blood pressure 100/60 mmHg, respiratory rate 30/minute, temperature 101°F and oxygen saturation 84% on 100% oxygen. Positive findings on examination included bilateral scattered fine crackles and an occasional wheeze.

Investigations performed on admission are shown in Table. Plasmodium vivax infection was confirmed by immune chromatographic assay (ICT). The thick and thin blood films also revealed presence of P. vivax. Blood cultures did not reveal any growth.

A chest x ray performed on admission is shown in Figure. It revealed dense air space consolidation with multiple confluent soft tissue nodular opacities.

Despite hundred percent oxygen via a rebreather mask and Bi level positive airway pressure (BiPAP) trials his respiratory rate increased and serial ABG reports revealed worsening hypoxaemia and metabolic acidosis. He was electively intubated and ventilated in the intensive care unit. The ventilation settings were kept at an assist control mode, tidal volume 400 ml, FiO2 100 %, peak end expiratory pressure (PEEP) 8 cm of water and respiratory rate 30/minute. An echocardiogram was normal. Our patient fulfilled the criteria of severe acute respiratory distress syndrome according to the Berlin definition and had a PO2/FiO2 ratio of less than 100 mm Hg.7

He was started on intravenous piperacillin-tazobactam 4.5 grams every 6 hours and moxifloxacin 400 mg once daily intravenously to cover for superimposed bacterial infections. Artemether and lumefantrine 80 mg /480 mg twice daily was begun for P. vivax. Intravenous hydrocortisone 100 mg eight hourly was also initiated.

Following treatment, he improved steadily and was extubated successfully on the fifth day. His C reactive protein levels progressively declined, renal functions normalized and he was oxygen independent 2 days after being extubated. He was discharged home 2 days later. Primaquine 15 mg once daily was prescribed for two weeks to clear the hypnozoite phase of P. vivax in the liver. This was done after assaying for Glucose 6 Phosphate Dehydrogenase (G6PD) to avoid drug induced haemolytic anemia.

**Discussion**

ARDS is an extremely rare manifestation of P. vivax malaria with just one fatal case documented from Pakistan.4 Despite the high prevalence of the disease, the low complication rate has some reasons. Firstly, P. vivax usually does not produce such an exuberant inflammatory response. Secondly, in endemic areas like Pakistan, patients often develop immunity against the pathogen. Non immune people are well recognized to develop severe vivax malaria.6 Unfortunately, data regarding this disease is scarce in Pakistan. Thus, its complications may be under diagnosed and under reported as stressed in the past by some authors.6,8

Lomar et al, in their review of the disease, described ARDS to be more common in those patients with vivax malaria who travelled to endemic areas, did not take recommended anti-malarial prophylaxis and had no past history of malaria.8 Unfortunately, our patient had all of the three aforementioned risk factors. This highlights the paramount importance of taking recommended anti-malarial prophylaxis while travelling to endemic regions. It also stresses that malaria should be actively thought and sought in travelers returning from endemic areas presenting with an acute febrile illness.

ARDS secondary to malaria has been postulated to be due to two reasons. Some researchers describe a post inflammatory response to the initiation of antimalarial therapy. Indeed, in most cases, ARDS developed within a week of commencing treatment.5,8 Extremely rarely however, ARDS has developed before initiation of the anti-malarial therapy.8 Our patient had a similar scenario and presented with ARDS without having received any treatment for malaria before.

The other theory regarding ARDS and malaria describes stasis of parasitized blood cells in the lung vasculature. The resulting activity of pulmonary monocytes increases the inflammatory response leading to ARDS. The general belief that P. vivax is incapable of cytoadherence to endothelial cells and microvascular sequestration has been offset.9 This response is much more pronounced in falciparum malaria. Thus, the disease may in fact be a combination of the processes described above.

ARDS is managed in the standard way with invasive ventilation and PEEP as required. P. vivax may be treated...
with chloroquine, hydroxychloroquine or artemisin based compounds. It is important to eradicate the hypnozoite stage by prescribing primaquine for two weeks. We used invasive ventilation, artemether-lumefantrine and primaquine in the management of our patient. Artemether-lumefantrine was used because of wide spread resistance to chloroquine frequently observed at our hospital. The antibiotics were stopped once blood cultures were negative. There are no studies that describe benefit of corticosteroid therapy in P. vivax malaria. However, a few past case reports have mentioned its use to good effect. We also observed a good response and swift patient recovery post addition of corticosteroids. This effect can be explained by the pathogenesis of the disease, as already described which is typified by a pronounced inflammatory response. Prognosis is usually good in patients with ARDS secondary to vivax malaria as compared to falciparum malaria.

**Conclusion**

Plasmodium vivax malaria may be associated with ARDS which is more common after initiation of anti-malarial therapy. In rare circumstances it may precede treatment. We stress on the importance of considering malaria induced ARDS in patients with respiratory symptoms and fever returning from malaria endemic regions, especially those who have never had malaria before and have not taken recommended prophylactic anti-malarial therapy.

**References**