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Research Article

Pulmonary Complications in Falciparum Malaria: A Retrospective Analytical Study

Arun Kumar Maria[1], Rakendra Singh[2], Manjot Kaur[3]
[1,2] Professor Department of Medicine, Adesh Institute of Medical Sciences and Research, Bathinda-151101, India
[3]Professor Department of Radiology, Adesh Institute of Medical Sciences and Research, Bathinda-151101, India

***Corresponding author**
Arun Kumar Maria
Email: cooldoctor5@yahoo.co.in

Abstract: In spite of various successful measures in vector control and new treatment modalities, India still suffers from high malaria burden. Various studies have projected data of malaria morbidity and mortality though at variance with official figures with reports of 205 000 malaria deaths /year and 1·8% cumulative probability of death from malaria before age 70 years. All patients with Falciparum malaria were evaluated for pulmonary manifestations. Those with lung involvement were further differentiated into the type pf involvement. Out of 548 cases of malaria 42 patients presented with respiratory symptoms in the form of cough, dyspnoea, expectoration, and haemoptysis. The clinical presentations were in the form of bronchitis (6 cases), pneumonia (9 cases), and Acute respiratory distress syndrome (7 cases). Four out of 7 patients of ARDS died. Amongst various malarial complications, pulmonary involvement is a serious one because of high mortality associated with its complications. Even though cough has been described as a common feature in pulmonary involvement of malaria, the sinister complications are encountered more with the falciparum variety. We present a retrospective data analytical study of pulmonary involvement with falciparum malaria in hospitalized patients in our institution over a period of five years.
Keywords: Malaria, Falciparum, Acute respiratory distress syndrome (ARDS), Acute Lung Injury (ALI), Pulmonary oedema.

INTRODUCTION

Malaria remains a major health concern in tropical and subtropical countries. Reports from the National Vector Borne Disease Control Programme (NVBDCP) have indicated that two million confirmed cases and 1000 deaths are reported annually in the country [1]. However, the World Health Organization (WHO) South East Asia Regional Office (SEARO), India estimates that there are about 27 million cases of malaria and 42,000 deaths in 2012 in the region [2]. Total DALYs (disability adjusted life years) lost due to malaria were 1.86 million years in India [1]. Recent years have witnessed a shift in the profile of patients with complicated malaria. Multiorgan system failure, ALI (Acute lung injury) and ARDS (Acute respiratory distress syndrome) are being increasingly reported in falciparum malaria and also in malaria caused by the species hitherto considered benign (*P. vivax, P . ovale* and *P . malariae*) [3].

Apart from bacterial pneumonias, parasitic pneumonias are also being increasingly diagnosed from many parts of the world [4]. This could be the result of increased globalization and international travel or modern and newer investigative techniques. Amongst these parasitic pneumonias, malarial pneumonia is important. Human malaria, caused by five plasmodium species, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and the monkey malaria *Plasmodium knowlesi* [1], is transmitted by the female anopheline mosquito.

Humans are infected due to bite by an infected female *Anopheles gambiae* mosquito carrying these plasmodia. Plasmodium requires human erythrocytes as well as mosquito host for its life cycle [5]. Sequestration of erythrocytes containing mature forms of *P. Falciparum* in the microvasculature of organs makes *P. falciparum* malaria as the most severe type [6]. Quantification of the sequestrated parasites can be carried out by *P. falciparum*-specific histidine-rich protein 2 (HRP2) using a quantitative antigen-capture ELISA [7].

Lung involvement in malaria has been recognized for a long time. However, our knowledge of its pathogenesis and management is still limited. The pulmonary manifestations which have been described vary from mild cough to severe and rapidly fatal ARDS and ALI (mild ARDS according to the Berlin definition) [8]. Historically, three clinical types of pulmonary manifestations have been variously described in patients with falciparum malaria, namely *bronchitic*, *pneumonic* and *bronchopneumonic* forms

[9]. Pulmonary edema has been detected most often in malaria naïve individuals with *P. falciparum* infections as a part of severe complicated systemic illness or as the main feature of acute malaria, although it is uncommon . However *P. vivax* and *P. ovale* have also been reported to cause ARDS and pulmonary edema [10, 11]. As definitive evidence for the existence of true malarial pneumonitis has not been categorically established, it has been suggested that malarial pneumonitis is uncommon and these manifestations are probably due to coincident pneumonia, pulmonary oedema and, metabolic acidosis [11].

In India, about 70% infections are reported due to *P. vivax*, 25.3% due to *P. falciparum* and 4–8% due to mixed infections [12]. 5% patients with uncomplicated falciparum malaria and 20% –30% patients with severe and complicated malaria requiring ICU admission may develop ARDS [5].

We present our experience of pulmonary involvement in falciparum malaria as a retrospective data analysis of cases treated in our hospital.

MATERIALS AND METHODS

The patient population included in this study was adult malaria patients aged 18 years and above who had been admitted in medicine ward or attended the outpatient department due to Malaria during the period between July 2006 to July 2011.

A detailed clinical history including the history of episodes of malaria and the duration of illness before presentation, was properly taken. Cough was recorded as being present on the basis of the patient's history. Clinical assessments included general physical examination and the respiratory signs and symptoms. Daily monitoring of vital parameters were done during hospital stay. All patients underwent detailed laboratory investigation, which included hemoglobin, total and differential leukocyte count, platelet count, serum bilirubin, serum asparate aminotransferase [AST] and alanine aminotransferase [ALT], blood sugar, serum creatinine, blood urea, serum electrolyte, complete urine examination. PA view chest X-ray was done in all patients who complained of respiratory symptoms or had abnormal chest examination findings. ECG, ultrasound abdomen, pulse oxymetry, blood gas analysis and pulmonary function tests were done in selected patients.

The diagnosis of malaria was confirmed by examination of thick and thin smear/ OptiMal test. Only those cases with asexual forms of *Plasmodium* in the blood by smear examination or found positive in OptiMal test for *Plasmodium* were included. The peripheral blood films were prepared from prick of finger, stained by conventional Leishman's stain and Geimsa stain, seen under oil immersion microscope. A minimum of 100 fields were examined before declaring the slides negative for *Plasmodium*. The patients with any other systemic disease, chronic obstructive pulmonary disease, bronchitis, and pulmonary tuberculosis were excluded from study. Smokers, pregnant females and those unable to give informed consent were also excluded.

The diagnosis of ALI (mild ARDS) and ARDS were considered according to the Berlin definition published in 2012 [8]. ARDS is defined as the acute onset of bilateral pulmonary infiltrates with an arterial oxygen tension/fractional inspired oxygen ratio of 300 mmHg or less, a pulmonary artery wedge pressure of 18 mmHg or less, and no evidence of left atrial hypertension. ARDS is defined as acute lung injury and an arterial oxygen tension/fractional inspired oxygen ratio of 200 mmHg or less.

Table 1: Definitions of acute lung injury and acute respiratory distress syndrome (Berlin Definition)

Diagnostic criteria for ARDS/ALI (mild ARDS)
Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules
Respiratory failure not fully explained by cardiac failure or fluid overload.
Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
200 mmHg < PaO_2/FIO_2 ≤300 mmHg with PEEP or CPAP ≥5 cmH_2O[c] 100 mmHg < PaO_2/FIO_2 ≤200 mmHg with PEEP ≥5 cmH_2O PaO_2/FIO_2 ≤100 mmHg with PEEP ≥5 cmH_2O

All patients had been managed by the hospital clinicians as per their clinical judgement and national guidelines. The study was ethically approved by the institutional ethics committee. Patients with severe malaria were reviewed at 4, 7 and 28 days.

RESULTS

Baseline demographics

A total of 548 [Males = 548 (57.66%); Females = 232 (42.34%)] patients suffering from malaria were seen during this period. The vast majority were treated for vivax malaria or some as clinical malaria. Hence were excluded. (n = 331) 8 patients had mixed infections. 4 were pregnant females, 1 patient was lost to follow up and hence excluded. The falciparum malaria cases were 204 i.e. (37.23 %). A large percentage (55.80%) of these patients developed falciparum related complications. Most of the cases had neurological complications and some had developed evidence of hepatitis.

Maximum patients with falciparum malaria 52.94% were in the age group of 21–40 yr. The minimum number (7.84%) was < 20 yrs of age (Table 2).

Almost half of the cases had complicated falciparum malaria (n=108, 52.94%). The parasite load in these patients is shown in Table 3.

Out of these 204 Falciparum Malaria cases, 42 patients (20.59%) had developed features of Respiratory system. The different pulmonary manifestations are presented in Table 4.

Cough was the predominant respiratory symptom (n=36, 85.71%) with one-fourth having only dry cough. Dyspnea was the presenting symptom in 25 patients, (59.52%). Tachypnea with a respiratory rate > 30/min was observed in 38.09% of total cases (n=16). However, most patients had a normal respiratory rate (73.5%).

Two (2) patients had hemoptysis ranging from mild to life threatening. In the study ALI (mild ARDS) was seen in only 4 patients while severe ARDS (as per latest guidelines) was the presenting feature in 7 patients. Concurrent pneumonia was detected in 4 patients.

Radiological abnormality in the way of abnormal chest X-ray was presented in 18 patients infected with malaria. 6 patients had findings suggestive of bronchitis, 9 patients had pulmonary infiltrates (diffuse opacities), while 3 had inflammatory patches. Patients with ALI and ARDS were associated with diffuse lung infiltrates similar to that in bacterial pneumonia. The severity of respiratory involvement correlated with heavy parasitemia (Table 5).

Table 2: Age wise distribution of falciparum malaria and those with Pulmonary System involvement

Age	Number with falciparum malaria	Those with pulmonary involvement
11-20	16	2
21-30	42	11
31-40	66	15
41-50	41	8
51-60	22	2
>60	17	4

Table 3: Parasite load in the patients

% of parasitized RBCs	No.	Percentage
<5%	91	44.61%
6-10%	29	14.22%
11-15%	49	24.02%
16-20%	26	12.75%
>20%	09	04.41%

Table 4: Clinical manifestations of pulmonary involvement in falciparum malaria cases

Cough	36
Dyspnea	25
Haemoptysis	02
Tachypnea	22
Respiratory distress	15
Bronchitis	06
Pneumonia	09
ARDS	07

Table 5: Level of parasitemia in ARDS patients

Complication	Parasitemia <20%	Parasitemia >20%
ARDS	2(25%)	5(75%)
Acute Lung injury	3(75%)	1(25%)

Spirometry was performed in patients who were fit enough to perform the procedure and had respiratory symptoms. 28 patients had features suggestive of early airway obstruction. Reversibility testing with short acting beta agonist (salbutamol (200 µg) inhalation), showed reversible airway disease after two minutes in 5 patients. Twenty-three (23) patients showed no effect of medication. Repeating the

spirometry on follow up after showed that six (6) patients had persistence of early small airway obstruction.

In nine (9) patients, there was radiological evidence suggestive of consolidation/ pneumonitis. In all these cases productive cough, tachycardia and chest pain were the predominant features with radiological evidence of seven cases had evidence of ARDS out of which 3 developed features of ARDS even after cessation of therapy.

Metabolic acidosis was present in 14 malaria patients as assessed by blood gas analysis. Oxygen saturation in maximum number of patients ranged between 96 and 100%. Outcome of malaria patients with respiratory system involvement showed that 37 (88.10%) recovered and 5 (11.90%) expired.

The duration of hospitalization ranged from four to 19 days (median of 8 days). One patient who required almost three weeks stay needed prolonged ventilation and had to undergo tracheostomy. Six patients required ventilation while another 5 were managed with Non Invasive Ventilatory support.

Most of the patients presented with fever, chills and cough which was productive on examination. On sputum culture examination, this came out to be sterile. On examination wheeze was present on auscultation. Chest X-ray findings suggested of bronchitis. In all these patients, there was no previous history of any respiratory disease and the coughing coincides with onset of fever. Altered lung function was common. In patients with pulmonary symptoms, a marked decrease in PEFR and slowed recovery (9.6 days) was observed. Hence, we suspected that *Plasmodium* itself is capable of causing pneumonia. There were four deaths during the hospitalization.

DISCUSSION

The most frequent presentation of malaria is that of a pronounced febrile illness with rigors and chills. However, the clinical features of malaria can be extremely diverse because the parasitized red cell circulates to every organ and tissue within the body and therefore has the potential for producing a wide variety of pathology.

Involvement of lung in malaria has been noted and described since a long time. It was reported even a century back and in 1944 a US army officer published reports on association of pneumonic involvement in malaria [13]. Respiratory symptoms have multiple causes, including severe anemia, metabolic acidosis, concomitant pneumonia, fluid overload, and ALI/ARDS. It is seen in up to 25% of adults and 40% of children with severe falciparum malaria. Clinical and autopsy data have demonstrated that the clinical illness is mostly characterized by progressive deterioration. It is not only during the course of febrile illness, but patients with severe malarial infections are also reported to develop ALI and ARDS, many days after anti-malarial drug treatment is over [14]. Even in absence of fluid retention, or detectable cardiac decompensation; pulmonary edema has been found. This has been considered because of abnormalities of pulmonary microcirculation playing a major role in pathogenesis of pulmonary edema in malaria. But measurements of pulmonary capillary wedge pressure have revealed no evidence of raised hydrostatic pressure in the pulmonary microcirculation to support the presence of an Adult Respiratory Distress Syndrome (ARDS) - type lesion in malaria [15].

Though ARDS has been well documented, disease related changes in pulmonary function have not been defined well and underlying mechanisms are still not very well understood in both falciparum and vivax malaria. In most of the patients there has been evidence of self-limiting cough [16]. Other studies have also reported incidences of lung involvement in malarial infection. Cough was frequent in both patients with uncomplicated malaria (50%) and those with severe malaria (30%) which mostly resolved by day 14. In our study also cough was the commonest and most predominant symptom. However it was seen much more frequently in upto 85 % of patients. Microvascular sequestration of parasitized red blood cells (RBCs) underlies most extrapulmonary organ- specific manifestations of severe falciparum malaria [17].

ARDS usually commences during the first 5 days after the start of treatment, when peripheral parasitemia has decreased or disappeared [9]. It has therefore been hypothesized that lung injury following treatment of malaria may be predominantly an inflammatory response, rather than a purely microvascular mechanical obstructive phenomenon [16]. These patients present with abrupt onset of dyspnea, cough, and tightness of chest. On physical examination these patients presented with acute respiratory distress, expiratory wheeze and crepts. Cyanosis was also noticed.

Studies from India and abroad have amply demonstrated the prevalence of acute lung injury in falciparum infection. Malaria is an important treatable cause of acute respiratory distress syndrome (ARDS) in the tropics. ARDS is a major cause of death in adults with severe malaria [18, 19]. 9%-23% of hospitalized patients develop pulmonary edema [20, 21]. In a retrospective study, Gachot *et al*. described 40 patients with complicated falciparum malaria admitted to a medical ICU [22]. Patients with mild ARDS had more severe disease and had a higher simplified acute physiology score (SAPS) on admission and a longer mean time of treatment delay. Similarly in our patients, those with ARDS had a more severe disease.

The risk of developing ARDS/pulmonary edema in patients presenting with uncomplicated falciparum malaria has been found to be low: 0.1% (3 of 3,300) in US Army soldiers in Vietnam [23]. In severe malaria, reported incidence rates vary widely between < 2% to about 25% [37]. In our study, the respiratory distress was present in 35.7% cases with an incidence rate of ARDS and ALI in 16.67% and 4.21% respectively.

We found that the patients who developed ARDS had heavy parasitemia (75%) as also the patients with ALI. This indicates that the pathogenesis of ALI/ARDS in severe falciparum malaria is multifactorial and includes the effects of sequestration of parasitized erythrocytes, host immunologic reactions to lung-specific sequestration or systemic malaria infection, superimposed pulmonary infections. Respiratory symptoms were more common and severe in patients in whom parasitemia was more than 15% in peripheral smear. Though certain degree of correlation exists between the severity of the disease and parasitemia, but quantification of the asexual parasitemia does not accurately reflect the parasite load due to erythrocyte adherence and sequestration. In settings without mechanical ventilation, ARDS mortality was 80 -100% [24, 25]. Even with the availability of mechanical ventilation, ARDS is associated with > 95% deaths [26]. In our study 5 out of 7 patients with ARDS died showing a similar high mortality rate of 71.42%.

ARDS was seen in seven of our patients. In patients with severe malaria, acute respiratory distress syndrome usually develops after the start of drug treatment and is a major cause of death. Our findings were corresponding to that seen in similar studies. Mishra & Ray observed ARDS in 7 cases out of 45 patients with respiratory involvement [27]. Rajput *et al*. observed that ARDS was presented in 4 patients out of 29 patients with respiratory involvement [28]. Sarkar *et al*. reported three cases of sudden onset of ARDS from Kolkata as a complication of *P. vivax* malaria [29].

Respiratory symptoms and signs are common in plasmodium falciparum malaria with a frequency of 4% -18% in uncomplicated malaria. In our study respiratory manifestations were found in 20.59% in falciparum malaria which is consistent with earlier studies. A dry cough may be present in 20% to 50% of patients with malaria [28, 30]. Cough was the most common symptom in our study. Tachypnea may result from high fever, anemia, and lung involvement. In our study patients with respiratory involvement, 85.71% had cough, 59.52% had dyspnea while 52.38% were tachypneic.

In a study on 50 *P. falciparum* infected patients by Gozal et al, dyspnea was observed in two patients [31]. In a similar study by Mishra & Ray on 150 cases, 36 were due to *P. falciparum*. Forty-five patients had respiratory symptom involvement and 40% of these have dyspnea, of these 45 patients 42 (93.4%) were of *P. falciparum* malaria [27]. In a study done by Rajput *et al*. on 100 patients (53 *P. vivax*; 36 *P. falciparum* and 11 mixed infections), 26/ 100 had respiratory involvement [28]. Incidence of dyspnea in our study was comparable to those observed by Mishra & Ray and Rajput *et al*. [27, 28].

Contrary to ours, another study demonstrated that in most patients (19 of 25), pulmonary edema was noted on the first day of admission and was associated with higher parasitaemias and levels of acidemia. Most of these patients diagnosed with pulmonary edema developed signs of ARDS with associated high mortality [27, 28, 31]. Tong *et al*. [32] and Applebaum *et al*. [31] also suggested that pneumonia presented during malaria is directly contributed by the disease pathogen itself. Out of 60 patients with respiratory involvement, 6 (3%) presented with acute bronchitis. The previous study conducted by Mishra & Ray and Rajput *et al*. also observed the same incidence [27, 28].

In severe malaria pneumonia may be present concomitantly in up to 13% in those geographical areas where both the illnesses are common [17, 18]. O'Dempsey *et al*. showed that although certain signs like cough, chest wall recession, and crepitations, were more likely in radiographically confirmed pneumonia, none was sufficiently discriminating to exclude malarial pneumonia [33]. X-ray findings in these patients were suggestive of ARDS and O_2 saturation was quite low. Blood gas analysis done on these patients showed hypoxemia and metabolic acidosis.

Data from the African Quinine vs Artesunate in Severe Malaria (AQUAMAT) trial of young African children showed that there was a significant correlation between respiratory distress, respiratory rate, deep breathing, and metabolic acidosis (base excess) [34]. All four were risk factors for death in univariate analyses but only metabolic acidosis was an independent risk factor for death in a multivariate analysis. Similarly, in the large South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) study of adult severe malaria, 175 patients (12%) had respiratory distress (respiratory rate 32/min) [35]. In France, 25% of patients admitted with severe malaria were mechanically ventilated; 19% for ARDS [36]. The median duration of ICU stay was three days (range 0–15 days).

Mortality in patients of malaria with ARDS is very high. Acute respiratory distress syndrome (ARDS) is a major cause of death in adults with severe malaria [38, 39]. In settings without mechanical ventilation, the mortality for malaria-associated ARDS reaches 81% in Rajasthan, and upto 100% in Vietnam [24, 25], which is higher than the 15%-30% overall case-fatality rate

for severe malaria [17]. Even with availability of mechanical ventilation, ARDS accounts for 10% to 40% of malaria deaths. However the incidence but reached a phenomenal 95% (70 of 74) in Krishnan and Karnad ICU series, in which the risk of death was some 50-fold higher with ARDS [26]. Even we report a mortality rate of 71.43% in those with ARDS.

It can be surmised that pulmonary involvement in malaria especially so in cases of falciparum malaria is not only an uncommon occurrence, but also may cause serious life threatening emergencies with high resultant mortality. A clinician has to be on guard to recognize ALI/ARDS after cessation of anti malarial therapy which may suddenly strike a patient. Further studies will of course highlight the exact mechanism of such processes. The development of an effective, long lasting and easily available malaria vaccine will go a long way in preventing such fatal complications.

CONCLUSION

The awareness about the changing spectrum of severe malaria is of great importance to every level of health care provider. Our results suggest that pulmonary involvement is seen in a significant number of patients mostly 20–40 yr age group who are most susceptible.

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