Respiratory Distress in Nonimmune Adults with Imported Malaria

A. G. Habib, K. S. Singh

Abstract

Acute respiratory distress (ARD) in two nonimmune adults with imported mixed and vivax malarial infections with low and resolving parasite load is described. Malarial pulmonary edema exacerbated by hypoalbuminemia and fluid redistribution without overload occurred in the latter patient. ARD led to mortality in one of the two. ARD should be promptly recognized and managed.

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Introduction

Respiratory distress is an indicator of life-threatening malaria in the nonimmune patient [1]. In adults acute respiratory distress (ARD) secondary to pulmonary edema is a grave and frequently fatal manifestation of severe falciparum malaria first described in Africa and encountered throughout the tropics [2]. It often results from increased pulmonary capillary permeability with high-level falciparum parasitemia and acidosis, and is rarely reported in non-falciparum infections [2—4]. Here, we report on the development of respiratory distress in nonimmune adults with low-level parasitemia secondary to mixed and vivax malarial imported infections, respectively, with a view to highlighting the circumstances and contributory factors in the pathogenesis of the syndrome and its poor prognosis.

Patients and Methods

Over a 2-year period, 2002–2003, 53 patients were diagnosed with imported malaria at our unit (*Plasmodium vivax* 29; *Plasmodium falciparum* 18; mixed *P. vivax* and *P. falciparum* 3; and other or unspecified 3). Species identification, parasite load, and monitoring was done concomitantly with conventional thick and thin blood smears, quantitative buffy coat (QBC) and immunochromatographic (ICT) [Pf/Pv] assays. Routine laboratory investigations and glucose-6-phosphate dehydrogenase (G6PD) status of patients were performed. Two of these patients developed respiratory distress.

Case 1

A 48-year-old female who visited Moro Island, Indonesia, presented with a 3-day history of fever (38.5 °C), headache, vomiting, diarrhea, and shortness of breath. She was dehydrated and her blood pressure was 85/60 mmHg. Initial investigations at admission showed mixed *P. vivax* and *P. falciparum* infections with a parasite load of 0.65%; full blood count (FBC) – leukocytes count – 3.62×10^9/l (normal range [NR]: $4.00–11.00 \times 10^9$/l) (polymorphs – 73.8%), hemoglobin – 13.1g/dl (NR: 11.3–14.9 g/dl), platelet – 37×10^9/l (NR: $130–400 \times 10^9$/l); urea – 8.9 mmol/l (NR: 2.0–6.5 mmol/l), creatinine – 124 µmol/l (NR: 50–90 µmol/l); arterial blood gases (ABG) – pH – 7.50 (NR: 7.35–7.45), pO_2 – 77.2 mmHg (NR: 75.0–100.0 mmHg), pCO_2 – 22.5 mmHg (NR: 35.0–45 mmHg), HCO_3 – 17.0 mmol/l (NR: 23.0–33.0 mmol/l) and abnormal chest X-ray (CXR) (Figure 1). She was treated with quinine and doxycycline with a decline in parasitemia to 0.2% on the 3rd day and sustained disappearance of parasitemia by the 4th day onwards using daily slide smear, QBC, and ICT. Respiratory distress and CXR progressively worsened (Figure 1) and the patient was intubated by the 5th day. She was resuscitated with intravenous fluids and had a positive fluid balance of 1,850 ml on the day of admission but subsequently required hemodialysis for rhabdomyolysis-associated acute renal failure by the 7th day (creatine kinase [CK] – 6389 U/l [NR: 20–300 U/l], CK-MB – 7 µg/l [NR: 1–6 µg/l], aspartate aminotransferase [AST] – 2187 U/l [NR: 10–50 U/l], lactate dehydrogenase [LDH] – 26903 U/l [NR: 300–700 U/l], aldolase – 42.3 U/l [NR: 0–7.0 U/l], urea – 22.4 mmol/l [NR: 2.0–6.5 mmol/l], creatinine – 368 µmol/l [NR: 50–90 µmol/l]). Cardiac enzymes and troponin T were normal. Bronchoscopy and alveolar lavage culture were negative on culture for bacteria and for respiratory viral tests, as were serology for *Legionella* and *Mycoplasma*. She died on the 8th day due to persisting respiratory distress and metabolic complications (metabolic acidosis – pH – 7.16 [NR: 7.35–7.45], lactate – 8.4 mmol/l [NR: 0.7–2.1 mmol/l], HCO_3 – 14.4 mmol/l [23.0–33.0 mmol/l], hyperkalemia – 6.6 mmol/l [NR: 3.5–5.0 mmol/l] and hypoglycemia – 1.3 mmol/l [NR: 4.0–7.8 mmol/l]).

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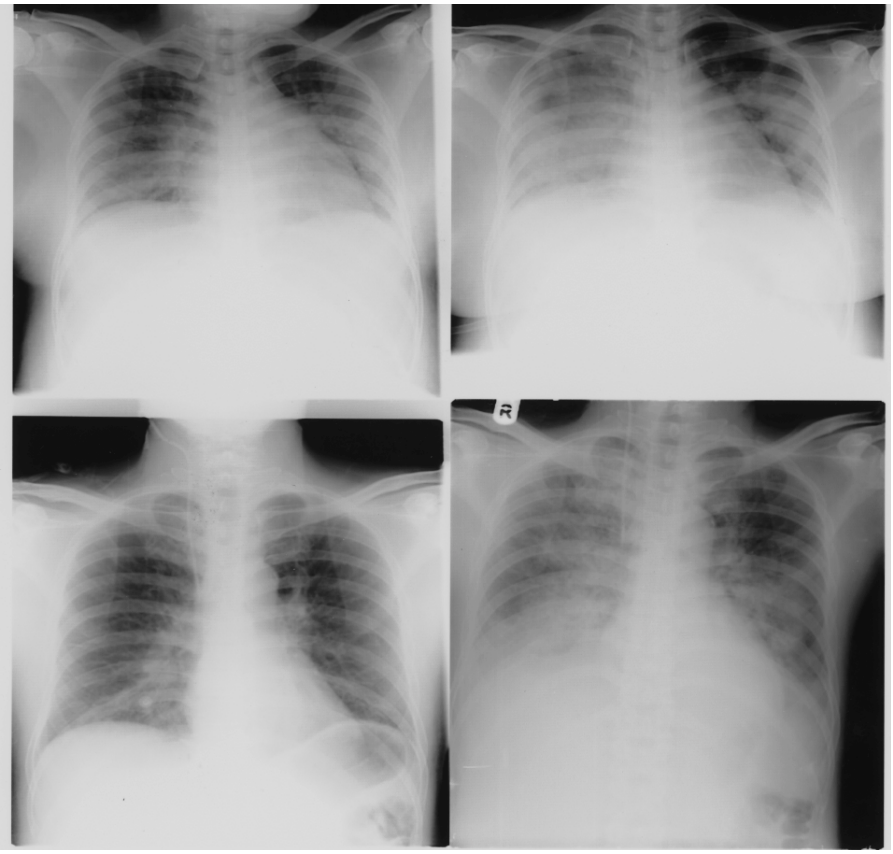

Figure 1. Radiographs of patient 1 (top panels) and patient 2 (lower panels) at admission (left vertical panel) and during hospitalization (right vertical panel).

Case 2

A 48-year-old offshore oil rig worker in Indonesia presented after a visit to an island with fever (39.7 °C), vomiting, dizziness and was found to be dehydrated and hypotensive, blood pressure 80/50 mmHg. Vivax malaria was confirmed and the patient was managed with quinine, doxycycline, and fluids. Admission CXR was considered normal but the patient developed shortness of breath, hemoptysis with worsening pulmonary edema radiographically by the 3rd day (Figure 1). Cardiac enzymes, bronchoscopy, and alveolar lavage bacterial cultures were negative or normal. Progression of parasitemia, fluid balance, and laboratory parameters are shown in Table 1. Intravenous furosemide 20 mg (on day 4) and 100 ml of 20% albumin (on days 4 and 6) were given. The patient improved with resolution of CXR by day 7, and was discharged on the 8th day on primaquine.

Discussion

Varied pulmonary manifestations like cough, chest pains, wheezing, and dyspnea have been reported in up to 18% of nonimmune subjects with mild *P. falciparum* malaria infection [5]. ARD and pulmonary edema with evidence of hypoxemia or radiographic opacities occurred in two out of 53 patients (3.8%). One patient died. These manifestations should be promptly recognized, especially in returning travelers as they are the most important pulmonary manifestations of malaria and carry a high mortality rate of 70%, particularly when there is concurrent adult respiratory distress syndrome (ARDS) [2—4]. Metabolic acidosis was noted only terminally in the fatal case but both pulmonary edema and acidosis are known major defining criteria of severity in adults with imported malaria [2, 6]. In nonimmune African children deep and labored breathing is often noted with dehydration, hyponatremia, organ hypoperfusion and lactate accumulation with acidemia [1, 7, 8]. Cautious volume repletion with improved organ function reduces the acidosis and distress [9], but overhydration can lead to pulmonary edema in malaria [2]. However, fluid imbalance is not essential for the development of pulmonary edema or ARDS and it occurs in some patients with acidosis and low mean central venous pressure without fluid overload [4]. Both patients presented initially mildly dehydrated clinically with slight hypoxemia in the former, while shortness of breath evolved later in the latter. The patients had increased gastrointestinal and fever-related water loss and were not overtly fluid overloaded, as also confirmed by the serum osmolality [10]. Cardiac functions were normal and both underwent bronchoscopy and lavage with no superadded nosocomial causes of pneumonia identified. The resulting parasitemia, sequestered parasitized pulmonary capillary erythrocytes, cytokine mediated increased pulmonary capillary permeability and impaired gas transfer have been known to lead to pulmonary involvement [2, 3, 11]. But other factors were also contributory, such as "uremic"

Table 1
Progression of parasitemia, fluid balance, and laboratory features

	Day 1	Day 2	Day 3	Day 4	Day 5 #	Day 6 #	Day 7	Day 8
Vivax parasite load (%)	1.2	0.4	0.2	0.05	Slide negative; QBC positive	Slide negative; QBC positive	Slide negative; QBC negative	Slide negative; QBC negative
Platelets [NR: 130 – 400 x 10^9/l]	77	67	74	107	154	234	392	558
Daily fluid balance (ml) (a) +	+1590	+1589	-350	-1866.8	-490	-85.6	-1563.2	-112
Apparent cumul. fluid balance (ml) (b)	+1590	+3179	+2829	+962.2	+472.2	+386.6	-1176.6	-1288.6
Approx. cumul. fluid balance (ml) (d)*	+890	+2479	+2129	+262.2	-227.8	-313.4	-1876.6	-1988.6
Albumin [NR: 38–48 g/l]	28	21	ND	26	24	ND	ND	30
Serum urea [NR: 2–6.5 mmol/l]	8.1	3.7	2.9	3.1	2.7	2.7	2.2	3.3
Serum sodium [NR: 135–150 mmol/l]	136	137	139	133	133	132	136	136
Serum osmolality [NR: 275–295 mmol/1g]	293	296	293	282	281	282	286	290

Slide negative smears and positive QBC equals parasite load ~< 0.05%; + Computed from actual input (oral and intravenous, including food, drinks, and medicines) and urinary output; * Unmeasured daily water loss [c] = 700 ml) was subtracted from daily apparent cumulative fluid balance (b) to give (d). (Normal range [c]: 700–1,000 ml per day; insensible loss from skin, 300–400 ml, and lungs, 300–400 ml, sweat 50–100 ml, feces 50–100 ml). See reference [10]; (d) = (b)–(c); (b) = cumulative daily fluid balance (a) from day 1 to day 8; ND: not done; (d) is an overestimation and (c) an underestimation in the initial days because of increased gastrointestinal loss (vomiting, diarrhea) and fever-related increased skin loss.

lung and hypoalbuminemia with low oncotic pressure as seen in our patients. This likely led to worsening of pulmonary capillary leakage and probable interstitial redistribution of fluid in the lungs and pulmonary edema without overt volume overload. Increasing the oncotic pressure therapeutically with exogenous albumin proved helpful in the latter patient. Indeed, subsequent recovery following supportive albumin and volume replenishment has been reported in severe falciparum malaria [9, 12] and it is likely that hypoalbuminemia from malnutrition may worsen pulmonary edema in some native patients.

Patients with pulmonary edema or ARDS often have severe malaria with high parasitemia and other complications [4], but both patients presented here had low-level parasitemia. Most reports of ARD have been with falciparum malaria and there have been only eight cases of ARD with vivax and one case in ovale malaria cited in the literature [11, 13]; our vivax patient increases to nine the total number of ARD reported with vivax malaria. Furthermore, both responded to treatment with consistent decrease and subsequent disappearance of parasitemia and normalization of platelet counts. In fact, the fatal case died due to metabolic complications after successful resolution of parasitemia. These cases show that distress can present initially or even after institution of therapy, with the latter suggesting either fluid imbalance, redistribution, the influence of therapy-related immune inflammatory changes, or other complications.

In conclusion, ARD should be promptly recognized and managed as it is an important cause of morbidity and mortality in nonimmune adults with malaria. It can occur in vivax malaria, with low parasitemia, or even after starting therapy with disappearance of parasitemia. Pulmonary edema can occur without overt fluid overload but hypoalbuminemia may exacerbate it by altering body water homeostasis and distribution.

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