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Case report

Severe imported malaria in an intensive care unit: A case series

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ABSTRACT

Introduction: Complicated malaria is a medical emergency with a high mortality if untreated.
Aim: To describe the clinical spectrum, treatment practices and outcome of severe malaria cases admitted to an intensive care unit.
Method: Thirteen severe malaria cases admitted to the ICU over a 6 years period (2012 – October 2018) were included. The data was retrospectively extracted from the hospital patient data management system.
Results: Nine patients had *P. falciparum* malaria, three had *P.Vivax,* and one had both. Only one had received malarial chemoprophylaxis. The median time of attending to medical health facility after symptoms started was 7 days (range: 2–21 days). All cases responded to antimalarial therapy and supportive management. Complications included shock 54%, kidney failure 38%, respiratory failure 69%, cerebral malaria 61%, hypoglycemia 23%, coagulation derangement 8%, and acidosis 23%. There were no fatal outcomes but one case had permanent brain damage and the rest recovered completely.
Conclusion: The median treatment delay of seven days explains why these patients ended in intensive care with multiple symptoms of severe malaria and often multiorgan failure. Pretravel advice and use of malaria chemoprophylaxis when visiting high risk areas would probably have prevented infection and timely attendance to healthcare once symptomatic would have reduced the morbidity associated with infection, reduced length of stay in hospital and hence resources.

Introduction

Severe malaria is a medical emergency and often need management in an intensive care unit (ICU) [1]. Criteria for the definition of severe malaria were amended by the World Health Organization (WHO) in 2006, 2010 and 2015, particularly with regard to the definition of hyperparasitaemia [2]. There is a correlation between the parasite density and the severity of the disease and its complications, especially among non-immune people. In such cases, the patients' clinical condition can deteriorate even after initial appropriate treatment due to exacerbation of systemic inflammatory response, leading to organ dysfunction [3].

Imported malaria remains an important clinical problem due to the rapid potential progression to severe and life threatening disease in non-immune patients [4]. A person from a non-endemic country who stays in malaria affected areas for less than two years is considered non-immune [5].

Oman has long been an area of *P. vivax* malaria transmission (33,000 cases in 1990), but control aiming at eradication was started in 1991 and in 2000 the annual parasite incidence had been reduced to less than 1 per 10,000 population. Interruption of malaria transmission was achieved in 2004 and maintained till September 2007 when a focus of local transmission was detected. However, due to the increase in the number of imported cases, foci of local transmission were detected the following years, which were controlled immediately. In 2017, a total of 1078 imported cases were recorded. The majority (56.8%) of the diagnosed cases were *P. vivax* and 42.0% of the cases were *P. falciparum* [6].

Malaria imported to Oman came from East Africa and the Indian subcontinent. Accordingly, appropriate prevention strategies need to be implemented especially easy access to prophylactic drugs for the travellers which is considered for a public-private partnership [6].

The purpose of this study was to describe the clinical spectrum, risk factors, treatment practices, outcome of severe malaria cases admitted to an ICU in a tertiary hospital in Oman.

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Methods

Patients and study period

The study was a retrospective, observational study reviewing the medical records of all malaria cases admitted between January 2012 and October 2018 to the Royal Hospital adult ICU; a 700 bed tertiary care referral hospital in Muscat, Oman. Age, gender, nationality, country of malaria exposure, duration of symptoms before admission, presence of co-morbidities, and days hospitalized were collected from the Al-Shifa patient data management system.

Malaria diagnosis

Malaria was diagnosed by microscopy of peripheral thick and thin blood films. Standard operation procedure of WHO was followed to prepare the smear. Giemsa-stained blood film was examined under the microscope with 100× oil immersion visual fields at a magnification of 1000× on both thick and thin smears. Microscopy reviewed100 high power fields of the thick blood film before the sample was considered parasite negative.

Clinical assessment

Clinical assessment at admission included the Glasgow Coma Score (GCS), quick sepsis-related organ failure assessment (qSOFA) [7], vital signs, inflammatory markers, and evidence of multi organ dysfunction. Re assessment during the first 24 h of ICU admission was by using different predictive scoring system such as SOFA and Acute Physiology and Chronic Health Evaluation (APACHE II) score. All patients included in this case series fulfilled the WHO 2015 criteria for severe malaria [8].

Biochemistry

The biochemistry analysis included total white blood cells and differential counts, C reactive protein, renal and liver function tests, coagulation profile, arterial blood gases, lactate, blood culture, and daily parasite count.

Supportive management

It included intubation and ventilation with a Drager Evita 4 Ventilator, vasopressor support with norepinephrine, antibiotics as indicated and renal support in the form of continuous renal replacement therapy.

Ethical approval for this study was obtained from Scientific Research Committee at Royal hospital (SRC#112/2018).

Results

From January 2012 to October 2018, thirteen patients with complicated malaria were admitted to the adult ICU, nine (69%) with *P. falciparum*, three (23%) with *P. vivax,* and one (7%) with a double *P.falcipaum* and *P.vivax* infection. Parasite count was registered for all 10 cases of *P. falciparum*. Out of 10, 6 (60%) had parasite count >100,000/ul with parasitemia percentage ranging between 3% and 24% and the rest had counts ranging between 800 and 72,000/ul (0.002%–0.2%).

The median age was 34 years (range of 18–59), with 9 males and 4 non-pregnant females. Half of the patients were Omani and the other half were from different ethnicity including, India, Pakistan, Sudan, Tanzania, South Africa, and Serbia. The Serbian patient was a resident of Oman working in the airline industry. All *P. falciparum* and one *P.vivax* infection were acquired in Africa and two cases of *P. vivax* were acquired each in India and Pakistan.

Twelve out of thirteen patients had not taken any anti-malarial chemoprophylaxis. Only one patient had received the prophylaxis as he had suffered from malaria in the past but it was not documented which drug had he received. Co-morbidities were presented in 3 patients and included; hypertension, chronic obstructive pulmonary disease (COPD), and hyperthyroidism.

Clinical features on admission

The median period of time from the start of the symptoms until the patient sought medical help was 7 days (range: 2–21 days). The delay was partly due to patients delay (not informing the physician about the travel history) and partly due to doctors delay (not asking for a travel history). It was documented that some patients had

Table 1
Patients status at admission.

Patient	Duration of symptoms	GCS[1]	Parasitemia[2]	GFR[3]	RR[4]	ALT[5]	Plt[6]	BP[7]	qSOFA[8]	SOFA Score[9]	APACHE II[10]
1	7	15	–	76	15	45	13	124/77	0	9	19
2	11	4	>100,000	30	20	53	75	80/40	2	14	29
3	7	15	–	73	16	27	27	90/45	1	10	12
4	10	15	–	>90	35	149	60	130/76	1	6	20
5	3	15	>100,000	41	18	395	60	124/76	0	15	28
6	11	13	11920	>90	25	108	121	70/40	3	13	26
7	12	15	>100,000	76	24	173	146	110/70	1	9	16
8	7	15	>100,000	39	19	32	47	86/40	1	9	23
9	2	15	800	>90	18	90	84	96/64	1	5	17
10	7	14	72000	20	16	192	24	96/53	1	12	27
11	5	14	>100,000	80	25	113	20	90/48	1	11	20
12	14	13	10560	27	20	20	55	110/65	0	9	24
13	21	15	>100,000	70	20	71	14	120/75	0	9	17

[1] GSC: Glascow Coma Scale.
[2] Parasites per microliter at admission.
[3] Estimated Glomerular filtration rate: ml/min/1.73 m^2.
[4] Respiratory Rate: breath/min.
[5] Alanine transferase: [IU]/L.
[6] Platelets: $\times 10^9$/L.
[7] Blood Pressure: mm/Hg.
[8] quick Sepsis-related Organ Failure Assessment.
[9] Sepsis-related Organ Failure Assessment. During 24 h of ICU admission.
[10] Acute Physiology And Chronic Health Evaluation 2. During 24 h of ICU admission.

rotated between several health care institutes before reaching to the definitive diagnosis. All patients had experienced fever for a median of 7 days (range 2–21days) prior to admission. Chills, headache, nausea, vomiting, and poor oral intake, were the most frequent symptoms. One patient presented with productive cough while two patients presented with hemoglobinuria. One patient had one episode of seizure, which was brief and witnessed. The patient's status at admission is summarized in Table 1.

At the time of admission, all patients were conscious with GCS of ≥13/15 with the exception of one patient who presented with altered mental status with GCS 4/15. Out of 13 cases, 3 (23%) presented with hypotension (blood pressure <90/60 mmHg) and one presented with respiratory distress.

Complications during admission

The interquartile range (IQR) of hospital stay duration was 7–18.5 days (total range: 2–130 days). According to the major WHO 2015 criteria of severe malaria, all patients had severe malaria at admission and half of them presented with four or more organ dysfunctions: pulmonary edema or acute respiratory distress syndrome (ARDS) in 69% of the patients (9/13), renal impairment in 38% (5/13), impaired consciousness or cerebral edema in 61% (8/13), hyperbilirubinemia in 53% (7/13), shock (defined as the need for inotropic support to maintain a systolic blood pressure over 90 mmHg) in 54% (7/13), severe anemia in 38% (5/13), hypoglycemia in 23% (3/13), metabolic acidosis in 23% (3/13), DIC in one and two patients presented with hyperparasitaemia (>10%). Out of the three patients with severe *P.Vivax* malaria, 2 were complicated with hyperbilirubinemia, 2 developed ARDS and 1 had shock (1/3).

Malaria treatment

Five (50%) patients with *P. falciparum* were treated with intravenous (IV) quinine dihydrochloride, with a 20 mg/Kg loading dose followed by 10 mg/Kg t.i.d, in a four-hour infusion along with oral doxycyline followed by artemether/lumefanthrine (A/L) for 3 days. However, after IV artesunate was introduced in June 2016 it became the drug of choice and was used to treat all 5 patients admitted after mid 2016, followed by a full course of oral A/L. At discharge a single dose of primaquine was administered to prevent transmission as per the WHO guidelines [9].

All patients with *P. vivax* were treated with chloroquine and primaquine which were effective except in one patient from Pakistan. He failed to clear his parasitemia, deteriorated clinically after three days of treatment and hence was changed to A/L which cleared the infection.

Critical care management

84% of cases were transferred to the ICU within 3 days of admission. The median APACHE II score (normal range 0–71, with higher scores indicating greater severity of illness) [10] was 20 (range: 12–29), and the median SOFA score (normal range, 0–24, with higher scores indicating more severe organ dysfunction) [10] was 10 (range: 6–16). Both APACHE and SOFA score was recorded during first 24 h of ICU stay.

The median length of stay in the ICU was 8 days (range: 2–41 days). Patients received supportive treatment in ICU according to the dysfunctions presented, which included IV fluids, vasopressors support, and antibiotics. Five (38%) patients who failed to response to IV Fluids alone needed inotropes to maintain a blood pressure over 90 mmHg. Invasive ventilatory support was needed in 8 (62%) patients for a period varying from 2 to 23 days (median 9 days) due to ARDS. One (7%) patient with cerebral edema and permanent brain damage became ventilator dependent and needed tracheostomy and prolonged ventilation. Four (31%) patients received packed red blood cell transfusion and one (7%) had an exchange transfusion. Three (23%) received platelets and fresh frozen plasma transfusions. Seven patients developed Acute Kidney Injury and five (38%) patients required continuous renal replacement therapy with median of 6 days duration (2–14 days). Treatment over the first 5 days is summarized in Table 2.

Bacterial co-infection

Six patients (46%) developed pneumonia, five cases were ventilator associated pneumonia and one case of influenza pneumonia was assumed infected outside the hospital. One patient developed candidemia with *Candida albicans* isolated from a peripheral blood culture once.

Outcome

All patients survived. 93% (12/13) had full recovery and were discharged home without any persistent complications and were back to work three months after discharge. One patient developed cerebral edema complicated by obstructive hydrocephalus and ischemic hypoxic encephalopathy and was discharged on family request after 130 days of hospitalization on home ventilator. Patients were also evaluated after hospital discharge for follow-up and neither other sequel nor medications side effects, e.g. artesunate delayed hemolytic anemia were noted.

Discussion

In spite of numerous attempts to control malaria, it remains one of the most important life threatening infectious diseases worldwide.

Table 2
Treatment over the first 5 days.

Patient	Invasive Ventilator	Dialysis	Artesunate i.v. for no. days	Inotropic support	Urinary catheter	Central line	ICU stay/ days	Hospital stay/day
1	No	No	No	Yes	Yes	Yes	2	4
2	Yes	Yes	Yes/1d	Yes	Yes	Yes	8	9
3	No	No	No	No	Yes	No	2	12
4	Yes	No	No	No	No	No	7	17
5	Yes	Yes	No	Yes	Yes	Yes	41	46
6	Yes	No	No	Yes	Yes	Yes	28	130
7	Yes	No	No	Yes	Yes	Yes	10	16
8	No	yes	No	Yes	Yes	No	9	13
9	No	No	No	No	No	No	2	3
10	Yes	Yes	Yes/3d	Yes	Yes	Yes	14	18
11	Yes	No	Yes/2d	No	Yes	Yes	3	15
12	Yes	Yes	Yes/3d	No	Yes	Yes	13	19
13	No	No	No	No	No	No	3	5

Once severe malaria develops and various vital organs are affected, even optimal intensive care may not prevent fatal outcome. Case fatality rate (CFR) of severe malaria cases admitted in ICU was reported in non-endemic countries; In France, Bruneel and his colleagues reported 5.2% CFR in 155 patients [11]. 4% CFR has been reported in UK among 124 patients [12]. In a cohort study in Portugal which included 59 patients with severe malaria admitted in ICU had a CFR of 15.2% [13]. In case of major delay in seeking medical help in patients with severe malaria, patients may soon develop multiorgan failure and even the best intensive care support may not prevent a fatal outcome. In our case series the mean time from the start of symptoms to diagnosis was 7 days, longer than a case series from Switzerland of imported *P.falciparum* cases with a fatal outcome where the median time to diagnosis was 5.5 days [14]. This could be explained by the lack of awareness of travelers' health.

The difficulties in treating severe complications underline the importance of prevention, ideally pre-travel advice with prescription of chemoprophylaxis to high-risk destinations [14].

We found that only one out of 13 patients had used malaria chemoprophylaxis, and hence compliance to prophylaxis measures were poor, which may be due to lack of pretravel information. Patient delay to access healthcare was significant with the median of 7 days. This delay could be reduced if the patients would be counseled before travel and instructed to seek immediate help in case of illness after travel. Doctor delay was not assessed properly due to missing data, but in the documented cases (3/13) it was mentioned that the diagnosis was delayed and the patient was rotating between different health care institutes before reaching the definitive malaria diagnosis. Implementing appropriate strategies for early diagnosis is important particularly in primary health care system where delayed or misdiagnosis could be explained by multiple reasons such as; primary care physicians typically face high patient volumes and make decisions amid uncertainty [15]. Furthermore, they need to carefully balance the risk of missing serious illness with the wise use of often scarce and costly referral and testing resources [16].

Principal symptoms found at time of admission were fever, chills, headache, nausea, and vomiting. The symptoms that were mentioned by cases were concordant with symptoms most frequently mentioned in medical literature [17]. Malaria diagnosis was suspected through signs and symptoms mentioned above, to confirm the diagnosis thick and thin smear were used.

IV quinine plus doxycyline followed by A/L have been used to treat severe *P.falciparum* malaria before 2016 at our hospital. Thereafter, IV artesunate was available and considered the treatment of choice for severe malaria patients according to WHO 2015 guidelines. There is substantial evidence in endemic countries for the superiority of intravenous artesunate over intravenous quinine with two large trials and a meta-analysis conducted in Africa and South East Asia demonstrating a mortality benefit, safety and rapid action in terms of parasite clearance [18,19]. Post artesunate delayed haemolysis (PADH) was defined by delayed haemolytic episodes occurring 7–30 days after treatment initiation. PADH has been reported in 15% treated patients [20]. All patients who received artesunate were followed with full blood counts weekly for one month, None developed PADH. Chloroquine resistance was suspected in one case of *P. vivax* from Pakistan, therefore, treatment was changed to A/L which cleared the parasitemia. Chloroquine-resistant *P. vivax* was present in most vivax-endemic countries. Data on chloroquine resistance from Pakistan is scarce [21]. Nevertheless, in 2013, the emergence of the F1076 L mutant of the pvmdr1 gene—the mutation responsible for chloroquine resistance—in P vivax in Pakistan highlights the imminent threat of resistant P.vivax [22]. In countries where there are high levels of chloroquine resistance, national guidelines have changed to artemisinin combination therapy as first-line therapy for P vivax [23].

Despite numerous studies, no adjunctive therapy has been shown yet to confer a survival advantage. ICU management remains supportive and improved outcomes may be attributable more to advances in multi-disciplinary team working with mechanical ventilation, careful fluid management, inotropic support, daily assessment of parasitemia, dialysis, and treatment of other infections [24]. In our series, the median ICU stay was 8 days in which the patients received specific supportive treatment and careful monitoring according to the organ dysfunctions. Bacterial co-infection is relatively common suggesting a low threshold for starting antibiotics, when supported by clinical and laboratory investigations, may be appropriate [12]. Almost all of our patients received empirical antibiotics to cover for possible co-infections or super infections.

The mortality rate in our series was 0%. All patients had good outcome and no subsequent complications persisted with the exception of one case, which developed cerebral edema which was subsequently complicated by obstructive hydrocephalus and ischemic hypoxic encephalopathy. Despite, being young (18 years), with no co-morbidites, and in spite of receiving appropriate management in ICU, she developed severe, irreversible brain damage as a result of cerebral edema. This was a *P. falciparum* case and there was a delay in seeking medical help after symptoms started eleven days before admission. Hence early administration of antimalarial therapy and good ICU care could have prevented this outcome.

The evaluation of quality of intensive care can be effectively determined only by scoring model which quantify the severity of illness [25]. One study found that the average APACHE II score in non-survivors (27.97; 95%CI $\pm$ 8.53) was higher than in survivors (15.82; 95%CI $\pm$ 8.79). [10] The average SOFA score in non-survivors (9.68; 95%CI $\pm$ 4.88) was higher than survivors (5.63; 95%CI $\pm$ 3.63) with statistically significant p value (< 0.001).The median of APACHE II and SOFA score in our series was high 20 and 10 respectively. Despite high predictive score in our patients, all patients survived without sequelae except the patient with severe brain damage. This could partly be attributed to the fact that our patients were young without major co-morbidities. However, as demonstrated here, severe outcomes can be seen and our patients were diagnosed late in the illness (median seven days) and chemoprophylaxis would have saved them from an intensive care admission for a life threatening infection.

Conclusion

Severe malaria can be prevented by avoiding patient and doctors delay. If diagnostic delay happens effective management of severe malaria include early institution of effective anti-malarial therapy, recognition of complications, and appropriate supportive management in an ICU. Travel medicine is very important to increase awareness among population and to establish good strategies to reduce communicable disease among traveler. It is extremely important to advise the traveler how to react in case of illness after the return as this will reduce the patient's delay in accessing healthcare. It is equally important that all health care staff should ask the febrile traveller for a history of visit to a malaria endemic area.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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