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A case of complicated falciparum malaria from coming back from Myanmar-India border presenting with cerebral malaria, black water fever, acute kidney injury, metabolic acidosis, hypocalcemia, severe anemia, thrombocytopenia and hepatitis having early parasitological failure on Day 14: Awareness on dihydroartemisinine-piperaquine combination therapy

Khin Phyu Pyar[1]*; Moe Zaw Myint[2]; Sai Aik Hla[2]; Soe Win Hlaing[2]; Soe Min Aung[2]; Zar Ni Htet Aung[2]; Nyan Lin Maung[2]; Aung Phyoe Kyaw[2]; Thurein Win[2]; Aung Aung[2]; Thein Tun Myint[2]; Kyaw Thet Maung[2]; Han Lin Aung[3]; Myo Thant Kyaw[3]; Zay Phyo Aung[3]; Kyaw Thuyein Lwin[4]; Lynn Htet Aung[5]; Lay Maung Maung[4]; Ye Min Hein[4]; Moe Tun Zaw[4]; Myo Maung Maung[4]; Thein Aung Moe[2]; Kaung Myat Oo[4]; Myat Ko[5]; Htet Aung[5]; Zin Min Htet[6]

[1]Professor and Head/Senior Consultant Physician, Department of Medicine/ Department of Nephrology, Defence Services Medical Academy/ No.(1) Defence Services General Hospital (1000-Bedded), Myanmar.

[2]Consultant Physician, No. (1) Defence Services General Hospital (1000-Bedded), Myanmar.

[3]Assistant Lecturer / Consultant physician, Defence Services Medical Academy, Myanmar.

[4]Consultant Nephrologist, No. (1) Defence Services General Hospital (1000-Bedded), Myanmar.

[5]Consultant Pathologist, No. (1) Defence Services General Hospital (1000-Bedded), Myanmar.

[6]Consultant Microbiologist, No. (1) Defence Services General Hospital (1000-Bedded), Myanmar.

***Corresponding Author: Khin Phyu Pyar**
Department of Medicine, Defence Services Medical Academy, Mingalardon 11021, Myanmar.
Email: khinphyupyar@gmail.com

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Abstract

A-39-year-old migrant worker coming back from Palatwa (Sagaing Division) and Myanmar-India border area (Rakhine State) developed cerebral malaria, acute kidney injury and metabolic acidosis. He was treated with intravenous artemisinine followed by ACT (artemisinine combination therapy); Dihydroartemisinine- piperaquine, hemodialysis, fresh blood transfusion. He had early parasitological failure on Day 14; therefore, different ACT (Artemether-lumefantrine) was initiated. He had adequate clinical and parasitological response till Day 42.

Keywords: Migrant worker; Border area; Complicated falciparum malaria; Early parasitological failure.

Introduction

Malaria is caused by Plasmodium species; severe clinical manifestation is commonly seen with *Plasmodium falciparum* and extremely rare with *Plasmodium vivax*. The incidence of malaria has been falling in Myanmar as well as South East Asia for nearly one decade. In fact, Myanmar has been trying for malaria free by 2030 [1,2]. Artemisinin resistance has been threatening not only to SEA but also to Western countries; containment of artemisinine was done in 2014 with many challenges [3].

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Case presentation

A-39-year-old migrant worker was transferred from Sittwe (Rakhine State) in state of unconsciousness, anuria and severe anemia following 3 days history of fever. He was from Htarwei (Tanintharyi State); and, he visited to Palatwa (Sagaing Division) and Myanmar- India border area (Rakhine State) for 3 months.

On arrival, his Glasgow Coma Scale was 6/15 with equivocal plantar response with loss of eye lid reflexes; he was very pale; temperature was 37^0C; SaO_2 92% on air; respiratory rate was 32/minutes; blood pressure was 110/70 mmHg; pulse rate was 110/minutes; lungs were clear; abdomen was soft; liver was enlarged 3 cm; spleen was not enlarged; and, indwelling urinary catheter had only 20 cc of brownish urine.

Blood for malaria parasite was 4224/UL; random blood sugar was 154 mg%; blood urea was raised 5 times (247 mg/dl); serum creatinine was raised 5 times (6.7 mg/dl); electrolytes were normal; hemoglobin was low (9.8 gm%); Hct was 27.1%; Total WBC was normal (8.85 x 10^9/L) with relative monocytosis (10.7%); platelet count was very low (30 x 10^9/L) normal differential count; AST was raised three times (82.7 U/L); serum calcium was low (8.7 mg%); and, CRP was normal. His blood was inspected for evidence of severe intravascular hemolysis; the serum was brownish with low red cell part. Serial estimation till day 3 revealed improvement in hemolysis and serum was yellowish reflecting jaundice.

He was treated as cerebral malaria, acute kidney injury, metabolic acidosis, hypocalcemia, severe anemia, thrombocytopenia and hepatitis with intravenous artemisinine. Renal replacement therapy (hemodialysis) was done on arrival to combat metabolic acidosis. Fresh blood was transfused to correct thrombocytopenia and anemia. Initial intravenous artemisinine was followed by ACT (artemisinine combination therapy); Dihydroartemisinine-piperaquine.

He was apyrexial throughout hospital stay. The color of black urine gradually faded and it was normal on Day 7. He became fully conscious and orientated on Day 10 and renal recovery on Day 14. Blood for malaria parasite was done daily to monitor parasitological response; it was negative on Day 5. Then, it was done weekly after 3 consecutive negative for 3 days. He had early parasitological failure on Day 14 with the parasite count of 5,000/UL; therefore, different ACT (Artemether-lumefantrine) was initiated. After 48 hours, blood for malaria parasite was negative; he had adequate clinical and parasitological response till Day 42.

Discussion

The incidence of malaria has been falling in Myanmar; therefore, diagnosis can be missed if travel history is not clerked. Moreover, severe manifestation of Plasmodium falciparum was rarely seen. History of travelling is important as well as awareness of diagnosis of cerebral malaria. Otherwise, the patient cannot be saved and diagnosis can be made only in autopsy [4]. Mortality rate of severe falciparum malaria is high even with treatment. This is the main reason for presenting case.

This patient did not have high parasite count; however, he did have severe manifestation and multi-organ involvement. Several studies pointed out that the higher the parasite count, the more severe the disease manifestation; hyper parasitemia itself is one of the criteria of complicated alaria. The severity of disease may be exacerbated by both higher parasite burdens and the tissue-specific patterns of infected RBC [5].

The mortality rate of cerebral malaria was high [6]; and the patient recovered. Falling conscious level in cerebral malaria was due to various pathological changes: mechanical microvascular obstruction by sequestered infected erythrocytes, activation of immune cells and release of pro-inflammatory cytokines, endothelial dysfunction, dysregulation of coagulation pathways, derangement in Blood–Brain Barrier (BBB) permeability, and brain swelling [7,5,3]. In this patient, CT scan of head was normal; MRI brain was not performed though it could detect changes in cerebral malaria [8,9]. The patient gained fully conscious and oriented only on Day 12. Regarding the duration and severity of unconsciousness in cerebral malaria, it is difficult to say exactly because it was influenced by several factors: the severity of parasitemia in peripheral blood as well as that of microcirculation; the degree of cytokine storm; electrolytes particularly intracellular sodium; hypocalcemia; hypoglycemia; metabolic acidosis in cellular level; CSF lactate; secondary effects from other organ involvement like acute kidney injury; degree of hepatitis; anemia; hypoxia; acute lung injury; concomitant septicemia; hyperpyrexia; hypoxic effect if the patient has convulsion; and effects of drugs like anti-convulsant and sedatives.

Black water fever in malaria became recurring according to some reports. Having black water fever in children from Uganda was reported to have high risk of death [10]. The patient had anuria for 48 hours and the urine color was black/prune juice. Black water fever was due to massive intravascular hemolysis of parasitized RBC both young and old; it was more pronounced in those with G6PD deficiency [11]. Some reports mentioned possible immune mechanism and it was related with anti-malaria drugs; artemisinin derivatives (Dihydroartemisinine-piperaquine) [12]; lumefantrine [13]; and quinine [14]. G6PD enzyme level was normal in this patient; his parasite count was not high. One report pointed out thatblack water fever was not frequently seen in patient with low parasite count; the mechanism was not clearly understood [15]. It also aggravated acute kidney in several ways: acute tubular necrosis; dehydration; hypotension; and possibly direct damage effect on kidney. Thus, the patient required renal replacement therapy till Day 11.

The overall mortality of adult cerebral malaria was reported as 15-20% and it was also influenced by associated vital organ dysfunction. The risk of death increased 3-fold in the presence of acidosis and renal failure [16]. Therefore, it is another reason for case presentation.

The patient had moderate anemia which was refractory and required correction with blood. Moreover, presence of thrombocytopenia also reflected bone marrow depressant effect of falciparum malaria. Having normal BT, CT, PT and D dimer excluded DIC in this patient.

Inspection of clotted blood in clear test tube was very informative in this patient particularly in correlation with urine color;

Table 1: Clinical progress.

Parameter	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
GCS	6	6	6	8	8	8	8	12	12	12	14	14	15
Urine output (cc/24 hr)	5	5	5	100	500	950	900	1650	2100	2700	2050	2500	3200
Urine color	Black	Black	Black	Black	Black	black	Brown	Brown	Brown	brown	Yellow	Yellow	Yellow
Hemodialysis	+	+		+				+				+	
Blood/blood product transfusion	+						+					+	
Fits		+		+				+					
Anemia	+	+	+	+	+	+	+	+	+	+	+	+	+
Jaundice													

Table 2: Changes in hematological parameter

Parameter/Day	D0	D1	D2	D3	D6	D8	D9	D11	D13	D14	D16	D17	D19	D30	D38	D50
Blood transfusion	+				+			+								
Hb (gm%)	9.8	10.4	9.3	8.3	7.8	8.3	7.9	7.8	7.1	7.4	6.6	8.0	8.1	8.0	10.0	12.3
Hct (%)	27.1	29.5	26.2	23.2	22	24.2	22.6	22.3	20.8	21.0	18.7	23.6	23.6	23.0	29.6	35.5
TWBC (x10^9/L)	8.6	11.6	10.1	11.6	8.9	9.8	13.9	9.2	6.8	7.6	6.3	5.7	7.9	9.0	6.0	5.9
N%	72.4	71.6	63.3	67.1	75.1	69.3	83.9	72.9	63	66.5	65.9	63.4	66.3	71.9	55.6	61.6
L%	16.9	21.3	28.6	27.7	20.5	24.7	12.2	21.9	30.5	26.2	28.1	30.4	28.3	23.2	37.7	31.8
M%	10.7	7.1	8.1	5.2	4.4	6	3.9	5.2	6.5	7.3	6	6.2	5.4	4.9	6.7	6.6
E%																
Platelet (x10^9/L)	31	75	111	172	259	398	394	390	338	348	273	248	214	271	265	204

Table 3: Renal profile.

Parameter/ Day	D 0	D 1	D 2	D 3	D 6	D 8	D 9	D 11	D 13	D 14	D 16	D 17	D 19	D 30	D 38
Sugar (mg%)	154		160												
Hemodialysis	+	+		+		+		+							
Urea (mg/dl)(10-50)	247	166.2	222	207	209	140	93	114	96.5	110	57	38.4	34	52	19.9
Creatinine (mg/dl) (0-1.3)	6.7	5.4	6.2	6.2	7.4	7.0	6.1	7.2	4.5	3.8	1.9	1.5	1.5	1.3	0.88
Na (mmol/L) (135-145)	143	142	142	142	138	141	142	141	137	138	133	140	136	136	137
K (mmol/L) (3.5-5.5)	5.2	4.1	5.5	5.2	4.9	4.7	3.9	3.9	3.5	3.2	3.3	3.9	3.9	4.2	4.2
Cl (mmol/L) (95-105)	111.8	105.9	104.3	103.2	101.7	104.2	103.1	106.3	97.6	103	98	104	102	98.5	101
Ca (mg/dL) (8.6-10.2)			7.36					7.85							
Corrected Ca (8.6-10.2)			8.4					9.2							
PO4 (mmol/L) (0.81-1.45)			2.03					2.3							
CK (U/L) (39-308)		3041		640		378									
Total protein (gm/L) (62-80)			51.8					55							
Albumin (gm/L) (38-54)							23.5	21.3							

Table 4: Liver profile.

Parameter	D 0	D 1	D 2	D 3	D 6	D 8	D 9	D 11	D 13	D 14	D 16	D 17	D 19	D 30	D38	D 50
Total Bilirubin (mg/dL) (0-1)										0.9						
AST (U/L) (0-37)	82.7	115										32				
ALT (U/L) (0-40)	21.2	24.7		15		7.7						18				
rGT (U/L) (11-43)		30														
Alkphos (U/L) (40-106)	96	94		121		122						111				
LDH (U/L) (135-225)	677									301		303				
Total protein (gm/L) (62-80)			51.8					55								
Albumin (gm/L) (38-54)							23.5	21.3								

USG -mild hepatosplenomegaly, kidneys. Echo – normal, CT head - normal.

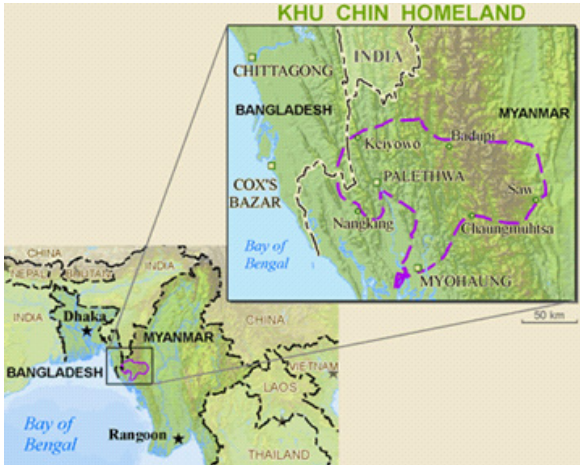

Figure 1: Geographical distribution of Paletwa township and Myanmar-India border.

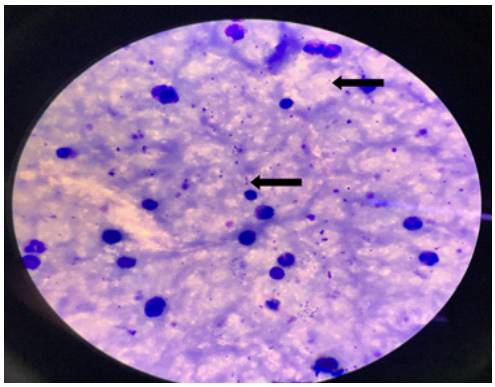

Figure 2: P f ring form thick film on Day zero.

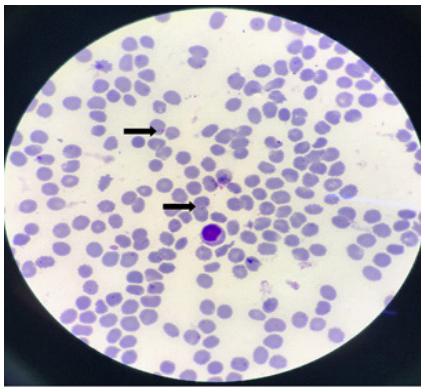

Figure 3: P f ring form thin film on Day zero.

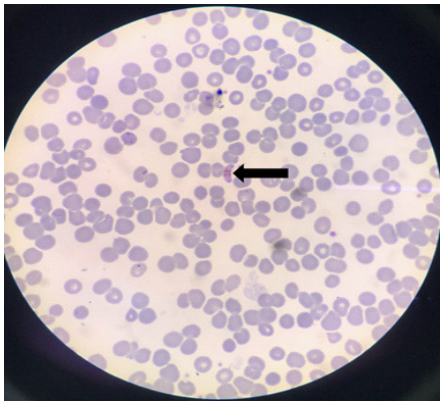

Figure 4: P f gametocyte thin film on Day 2.

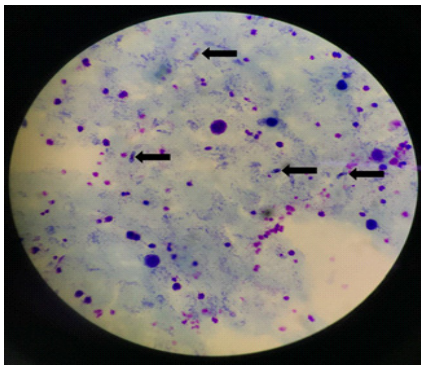

Figure 5: P f gametocyte thick film on Day 2

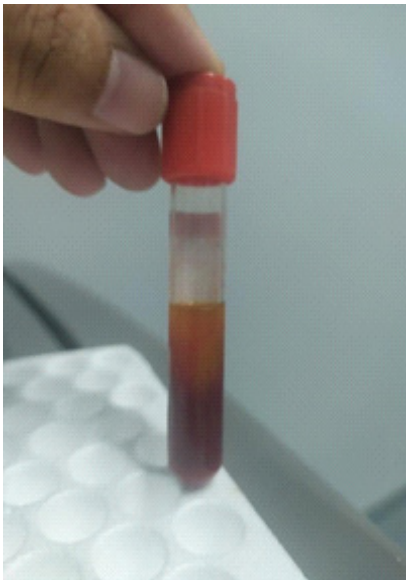

Figure 6: Hemolyzed serum due to massive intravascular hemolysis on arrival.

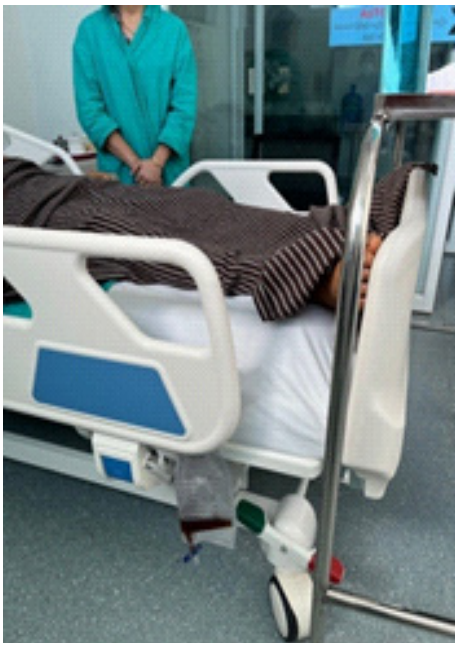

Figure 7: Black urine (Black water fever) and oliguria due to massive intravascular hemolysis and acute kidney injury on arrival.

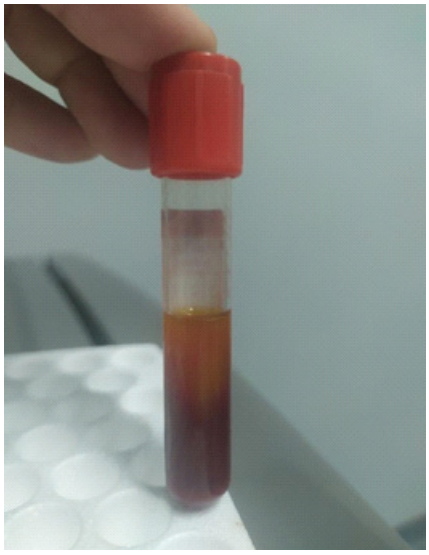

Figure 8: Hemolyzed serum with yellowish color due to less intravascular hemolysis on Day 2.

Figure 9: Black urine (Black water fever) and oliguria due to massive intravascular hemolysis and acute kidney injury on arrival and Day 2.

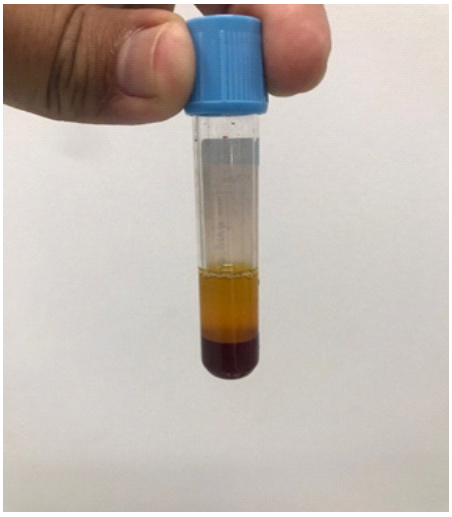

Figure 10: Yellowish serum due to improved intravascular hemolysis on Day 3.

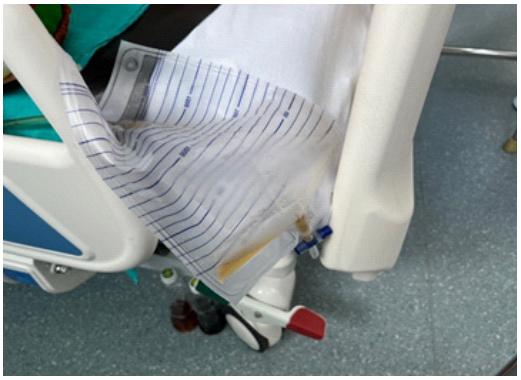

Figure 11: Normal urine color and oliguria due to improved intravascular hemolysis and acute kidney injury on Day 3.

Figure 12: Normal urine color and improved oliguria on Day 7.

Figure 13: Eye open spontaneously without eye lid response (E 4), no motor response (M1) and no verbal response (V1); GCS (6/15) and conjunctival oedema due to acute kidney injury on arrival.

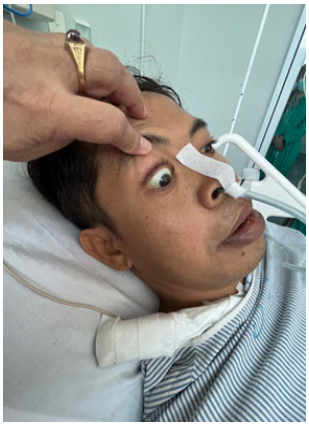

Figure 14: Jaundice and conjunctival oedema improved on Day 7.

Figure 15: Patient on hemodialysis 10 session over 3 weeks.

it was very useful in low resource setting. Having low red cell column indicated degree of anemia; brownish plasma revealed presence of hemolyzed RBC; daily inspection signified clinical improvement; improvement in RBC column showed improvement in anemia; less brownish color of plasma revealed less intravascular hemolysis. In addition, yellowish color at the top demonstrated increased bilirubin in serum. Combination of clinical changes, urine color and amount and serial inspection of clotted blood specimen in bed side gave excellent remarks. It is extremely useful in remote areas where malaria is endemic. This is the important reason for sharing bed side examination.

Having parasitological relapse in Day 14 after ACT (Dihydroartemisinine-piperaquine) was alarming although parasite count was not high. Containment of artemisinine resistance was done in 2014 with many challenges [3]. The recommendation from this case is "to contain ACT resistance". He made good response to different ACT (Artemether-lumefantrine) till Day 42. It is very good news because Artemether-lumefantrine combination therapy has been introduced in Myanmar over 10 years.

Conclusion

Importance of asking travel history in medicine is highlighted. Awareness of diagnosis of malaria is important particularly to those coming back from malaria endemic areas. Recognition of severe features of falciparum malaria and timely treatment can save lives. ACT resistance in Myanmar-India border area is alarming; it may be iceberg phenomenon.

Declarations

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