A case of co-infection: First reported case of severe *plasmodium knowlesi* malaria and dengue co-infection in Sabah, Malaysia

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SUMMARY

We report a rare case of severe *Plasmodium knowlesi* malaria and dengue co-infection in a 36-year-old lady with hyperparasitaemia, metabolic acidosis, haemolysis and acute kidney injury. She was in shock requiring inotropic support and elective intubation. She had pericardial tamponade which necessitate pericardiocentesis to allow for haemodynamic stability during haemodialysis. She underwent haemodialysis, was ventilated for six days and stayed in hospital for 29 days. She was discharged home well with almost complete renal recovery. Physicians must have a high degree of suspicion for dengue co-infection in malaria patients with plasma leakage such as pericardial effusion to allow for prompt management.

INTRODUCTION

The incidence of zoonotic malaria of *Plasmodium knowlesi* is increasing in Sabah, Malaysia, and it has overtaken human malaria in recent years.[1] Dengue incidence in Sabah, Malaysia is also rising and in 2018, is predominantly dengue virus serotype 3 (DENV-3). Concurrent *P.knowlesi* malaria and dengue infections are rare due to the different habitats and activities of the mosquito vectors.[2,3] These two diseases share similar symptoms such as fever, headache, abdominal pain, myalgia, arthralgia, rash, nausea, vomiting and diarrhoea. Diagnosing dengue and malaria co-infections therefore remains a challenge as the clinician needs to be vigilant about such rare possibilities and is important as the management of each infection is vastly different. Here we describe a rare case of severe *P.knowlesi* and dengue co-infection which was successful treated with early diagnosis and aggressive treatment.

CASE REPORT

We present a case of a 36-year-old housewife with underlying hypertension and gestational diabetes mellitus who was referred from Tungku district clinic in Lahad Datu, Sabah, Malaysia. She presented with fever, chills, rigor, epigastric pain, generalised myalgia and lethargy for four days. She also vomited four times per day and developed jaundice for one day. She had brief period of loss of consciousness prior to arrival to the Emergency Department. She had no history of jungle trekking or coming in close contact with macaques. Upon arrival, she was in shock with blood pressure 64/40mmHg, pulse rate 136 beats per minute, oxygen saturation 100% on ambient air and temperature 36.6°C. Her GCS was 15/15 and respiratory rate was 28 breaths per minute. She had capillary refill time of three seconds, cold peripheries, weak pulse volume and appeared lethargic and dehydrated. Other examinations were unremarkable.

She was initially resuscitated with intravenous normal saline and was empirically started on intravenous Ceftriaxone 2gm stat at Emergency Department. Her dengue NS1 antigen was negative, IgM was negative, and IgG was positive which were suggestive of secondary dengue infection. Further investigations revealed the presence of malaria parasite resembling *P.knowlesi* with parasitaemia of 160,000/µL of blood and she was promptly started on IV artesunate 170mg (2.4mg/kg). Both blood and urine cultures were negative. Viral hepatitis B, hepatitis C and HIV screenings were negative. The investigations were as below (Table I).

Despite initial resuscitation, she developed worsening acute kidney injury and metabolic acidosis. She was intubated for respiratory distress and required four inotropic support. Bedside echocardiogram showed 2.5 cm massive pericardial effusion from apical region. Her right atrium and right ventricle were collapsed signifying pericardial tamponade. Pericardiocentesis was done under platelets transfusion. 220ml of pericardial fluid was aspirated and the catheter was left in situ for two days. Her haemodynamic improved after pericardiocentesis and we managed to taper down the inotropic support and she underwent haemodialysis. Her malaria parasite count dropped rapidly from 160,000/µL to 84,210/µL after 24 hours, then 906/µL after 48 hours and subsequently became negative. She was successfully extubated on day sixth and stayed in ICU for ten-day duration. Her total inpatient stay duration was 29 days. She underwent nine haemodialysis sessions while inpatient and had another outpatient haemodialysis in view of slow renal recovery. Her subsequent fortnightly outpatient review showed almost full renal recovery. She remained well during her last review in August 2018.

Dengue PCR was sent since plasma leakage with pericardial tamponade was rarely seen in severe malaria alone and revealed dengue virus serotype 3 (DENV-3) infection. *P.knowlesi* malaria DNA was also detected via PCR.

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Table II: Summary of number of patients in age group, mean kidney length and mean kidney volume

Investigations	Normal Range	Day 1	Day 3	Day 5	Day 7	Day 9	Day 22	Day 27	Day 46	Day 68
WCC (x10³/L)	[4-11]	12.3	16.3	15.8	10.8	6.4	-	-	15.0	10.4
Hb (g/dL)	[11-16]	14.2	12.9	8.9	10.0	9.4	-	-	8.5	8.8
HCT (%)	[37-47]	30	26	28	31	30	-	-	32	31
Platelet (x10^9/L)	[150-450]	11	44	33	83	206	-	-	248	298
Sodium (mmol/L)	[137-148]	125	142	143	140	135	138	136	135	138
Potassium (mmol/L)	[3.5-5.1]	3.9	4.8	4.3	3.7	3.4	4.3	4.5	4.3	3.7
Urea (mmol/L)	[1.7-8.3]	9.6	20.3	29.2	25.4	11.4	19.7	26.7	5.6	6
Creatinine (µmol/L)	[44-88]	143	377	477	411	396	1107	1098	118	101
LDH (U/L)	[140-280]	561	1915	-	-	-	-	-	-	-
Bilirubin (mmol/L)	[0-17]	29	57	37	-	18	-	-	-	1
ALT (U/L)	[0-31]	52	1817	408	-	12	-	-	-	12
ALP (U/L)	[35-104]	149	115	173	-	91	-	-	-	65
Albumin (g/L)	[34-48]	26	14	24	-	23	-	-	-	37
Globulin (g/L)	[20-35]	34	22	24	-	34	-	-	-	39

DISCUSSION

The incidence of *P.knowlesi* malaria and dengue co-infection is likely to increase as both infections are associated with human activities including deforestation. Therefore, in dengue and *P.knowlesi* malaria endemic area in Malaysia, clinician should suspect concurrent dengue infection especially if the clinical presentation of malaria is more severe than usual and in those who present with plasma leakage and pericardial tamponade. It is often difficult to differentiate between both because they share similar clinical features and laboratory findings especially thrombocytopenia. Even though dengue NS1 antigen test, dengue serology and blood film for malaria parasite (BFMP) tests are easily available in Malaysia, dengue NS1 antigen and dengue IgM are often negative in secondary dengue infection as illustrated in our case. Since plasma leakage with pericardial effusion is seldom encountered in malaria infections alone, further dengue tests are warranted to exclude concomitant dengue infection. These are reported in two similar cases of dengue and *P.knowlesi* malaria co-infection and highlight the dangers of accepting a single diagnosis alone.[2 3]

The severity of this case is multifactorial as our patient had hyperparasitaemia with multiorgan failure. Besides, dengue plays an important role as it triggers exaggerated immune responses in a host with secondary dengue infection. In addition, concurrent infections have been suggested to be more severe than isolated infections alone.[4] Therefore, a timely diagnosis of dengue infection would provide significant impact towards treatment as patient needs adequate fluid resuscitation. Untreated *P.knowlesi* malaria is rapidly fatal as they have a twenty-four hours replication cycle and thus need prompt intravenous artesunate.[5] We seek to help to improve the understanding of dengue and malaria co-infections and this area warrants further studies.

CONCLUSION

In summary, clinicians should always suspect dengue co-infection especially in malaria endemic areas and *vice versa* especially when the clinical picture does not fit the typical presentation of malaria or dengue alone.

REFERENCES

1. William T, Jelip J, Menon J, Anderios F, Mohammad R, Awang Mohammad TA, Grigg MJ, et al. Changing epidemiology of malaria in Sabah, Malaysia: increasing incidence of Plasmodium knowlesi. Malar J 2014; 13: 390.
2. Chong SE, Mohamad Zaini RH, Suraiya S, Lee KT, Lim JA. The dangers of accepting a single diagnosis: case report of concurrent Plasmodium knowlesi malaria and dengue infection. Malar J 2017; 16(1): 2.
3. Che Rahim MJ, Mohammad N, Besari AM, Wan Ghazali WS1.. Severe Plasmodium knowlesi with dengue coinfection. BMJ Case Rep 2017; 2017: bcr2016218480.
4. Epelboin L, Hanf M, Dussart P, Ouar-Epelboin S, Djossou F, Nacher M, et al. Is dengue and malaria co-infection more severe than single infections? A retrospective matched-pair study in French Guiana. Malar J 2012; 11: 142.
5. Cox-Singh J, Davis TM, Lee KS, Shamsul SS, Matusop A, Ratnam S, et al. Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening. Clin Infect Dis 2008; 46(2): 165-71.