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Case report

Late onset acute pancreatitis in *P. falciparum* malaria – An adverse reaction to intravenous artesunate?

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Introduction

Malaria is a potentially life-threatening disease caused by *Plasmodium* spp. which are transmitted by female *Anopheles* mosquitoes. *Plasmodium falciparum* infection has a high mortality if untreated, but it has an excellent prognosis if diagnosed early and treated appropriately [1]. We report late onset pancreatitis occurring after treatment for severe *P. falciparum* malaria which was thought to be drug induced.

Case report

A previously healthy 34 year old Omani male who was admitted to the Royal Hospital (Muscat, Oman) with *P. falciparum* malaria after a travel to Tanzania without having taken malaria chemoprophylaxis. At admission he was febrile to 38.8 °C, heart rate of 110/min, respiratory rate of 24/min, blood pressure of 95/53 mmHg and Glasgow coma score of 14, initial parasite density of 230.000/ul (< 5%). His blood test showed hematocrit 25% (normal: 35–45), white blood count: 21×10^{12}/L (normal : 2.2–10 $\times 10^{12}$), platelets : 27×10^{9}/L (normal: 150–400 $\times 10^{9}$). Liver function test with lactate dehydrogenase of 1479 [IU]/L (normal : 125–240), bilirubin : 289 u mol/L (normal : 0–20), alanine aminotransferase : 192 [IU]/L (normal : 0–40), alkaline phosphatase : 131 [IU]/L (normal : 40–150), albumin : 17 g/L (normal : 35–50). Coagulopathy: PT : 14.5 s (normal : 9.8–11.9), APTT : 83.8 s (normal : 26.4–38.9), fibrinogen : 4.9 g/L (normal : 1.6–4), INR : 1.4 (normal : 0.8–1.05), lactate : 2 mmol/L (normal : 0.5–1.5) and he had acute kidney injury with a eGFR : 20 ml/min/1.73 m^2 (normal : > 90) and creatinine of 330 u mol/L (normal : 45–100).

He was initially kept on non-invasive ventilation (BIPAP mode), inotropic support, ceftriaxone 2 g empirically and artesunate 2.4 mg/kg were given after IV fluids (2 h after he arrived). After 48 h he became drowsy with Glasgow coma score of 7 and brain CT scan showed cerebral edema. He remained hypoxic and chest x-ray showed extensive bilateral lung opacities, then the patient was intubated, mechanically ventilated (PEEP of 7 and PaO2/FiO2 ratio of 74) and dialysis started 72 h after admission. While on ventilator he was sedated with fentanyl and propofol and paralyzed with rocuronium (a pure muscle relaxant). His antimicrobials were upgraded to piperacillin-tazobactam 2.25 g tid.

After he completed 5 doses of artesunate (2.4 mg\kg, IV at 0, 12, 24, 36 and 48) 72 h after the admission his pulmonary function improved, sedation could be lifted and he was extubated. 96 h after the admission his blood films showed no malaria parasites (72 h after starting artesunate).

While still on dialysis on day 8, he suddenly developed severe generalized abdominal pain associated with nausea and vomiting. Non-contrast CT showed diffuse enlargement of pancreas with loss of lobulation along with significant peripancreatic and retroperitoneal fat stranding, at the same time serum amylase was 1029 U/L (normal: 40–140). A follow-up MRI showed features of severe pancreatitis associated with a possible pseudocyst, No signs of cholecystitis or gallbladder stones. He was managed conservatively with crystalloid intravenous fluids and analgesia and kept nothing per mouth. He showed an excellent response and was discharged after 14 days of admission. After a month follow-up his serum amylase was normal and he had no abdominal pain (Fig. 1).

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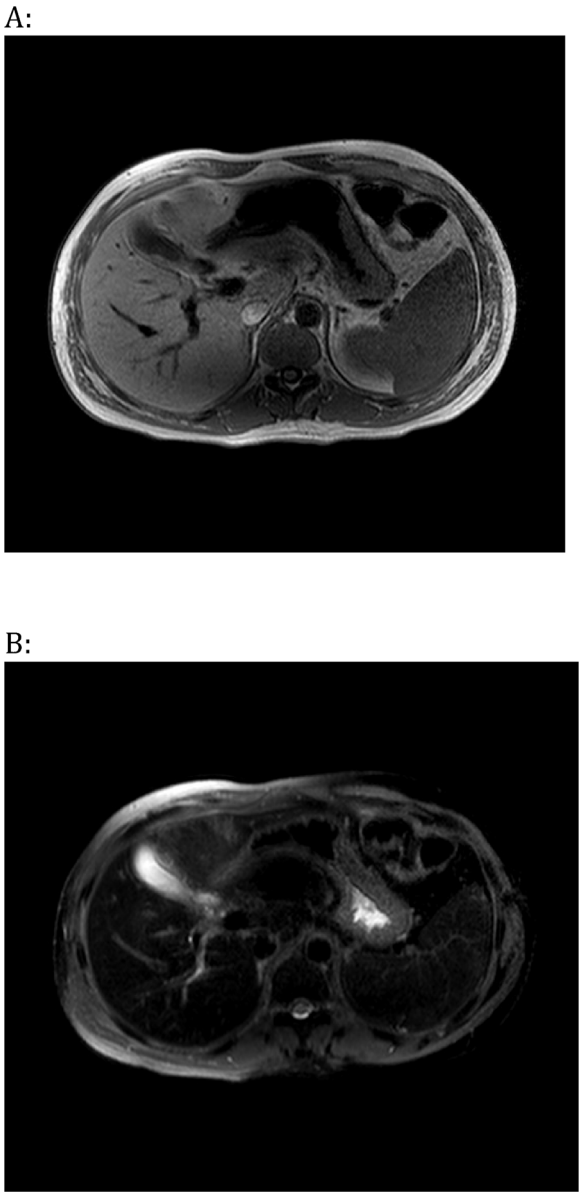

Fig. 1. A: T1 weighted MRI of the pancreas showing enhancement and collection. B: T2 weighted MRI of the same area.

Discussion

Our patient was non-immune to malaria and was admitted with severe malaria complicated with cerebral malaria, acute respiratory distress syndrome (ARDS) and renal failure. Thrombocytopenia is a common manifestation in malaria patients [2].

A meta-analysis of 11 observational studies showed an equal risk of developing severe and/or very severe thrombocytopenia between the patients with *P. vivax* malaria and those with *P. falciparum* malaria. [3].

Acute kidney injury, liver dysfunction, thrombocytopenia, cerebral malaria, disseminated intravascular coagulopathy (DIC) and ARDS are common in severe malaria. Metabolic abnormalities include hypoglycemia, hyponatremia and lactic acidosis. Bacterial infection may coexist in patients presenting with shock or ARDS and this along with a high parasite load has a high mortality [4,5].

Acute pancreatitis is a rare complication of *P. falciparum* malaria. A case series described five adult patients between 2005 and 2010 who were diagnosed with acute pancreatitis and *P. falciparum* malaria. All pancreatitis cases were diagnosed within 24 h after admission while the patients were still parasite positive by microscopy [6,7].

Our patient had no history of gallstones, ethanol abuse, hypercalcemia, hyper-triglyceridemia, or trauma thus he had no risk factors for pancreatitis. The pancreatitis occurred on day eight after admission (five days after his blood was parasite negative by microscopy) and this probably excluded that the pancreatitis occured due to impaired microcirculation because of parasite sequestration.

Late onset pancreatitis in severe complicated malaria has not previously described in malaria. Although pancreatitis is a rare complication but it has been described as an adverse reaction to many drugs. [8,9]. Potential mechanisms for drug-induced acute pancreatitis include pancreatic duct constriction, cytotoxic and metabolic effects, accumulation of a toxic metabolite or intermediary, and hypersensitivity reactions [10].

It is a possibility that the pancreatitis seen here is an adverse reaction to intravenous artesunate which also cause hemolysis for as long as four weeks after its administration even though the drug has long been excreted [11] and the mechanism behind this adverse reaction is not clear.

To assess the probability that the pancreatitis could be caused by intravenous artesunate we used the 'adverse drug reaction probability score' scoring system proposed by Naranjio et al. [12]. According to this scale our patient obtained a probability score of 7 which equal to 'probably event' (score 5–8). The pancreatitis responded rapidly to intravenous fluid and pain management and did not reoccur during a 2 months follow up period.

Conclusion

Delayed onset pancreatitis in severe complicated malaria should be distinguished from pancreatitis in acute parasitemia and it could be due to an intravenous artesunate side effect.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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None.

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