**Case Report**

**Quinine Induced Thrombotic Microangiopathy (TMA)**

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**Abstract**

Quinine is the most common cause of Drug induced thrombotic microangiopathy (DITMA), being the offending drug in 33% of cases. We present a case of DITMA after only a single dose of quinine with no previous history of quinine exposure treated successfully with plasma exchange (PEX), oral corticosteroid followed by mycophenolatemofetil (MMF).

The diagnosis was made by the close temporal relationship of exposure of quinine to the onset of TMA and exclusion of other causes of TMA including aHUS, TTP, SLE. DITMA from quinine can be triggered either by a single ingestion occurring many months or up to 10 years in some case reports. Our case presented with a prolonged PT has previously been reported and makes the distinction from DIC more challenging.

The patient was managed with regular hemodialysis and PEX. Although the role of PEX is uncertain in Quinine induced DITMA-in this case PEX was associated with improving hematological parameters, rising platelet counts, resolution of hemolysis on the blood film and a gradual improvement in renal function.

This case highlights the need for a careful drug history in patients who present with TMA and provides evidence for the potential value of PEX in this condition. Although quinine antibody levels are not widely available, the use of immunosuppression with MMF to control the disease, through suppression and removal of quinine-dependent antibody production is supported. The evolution of Specialist Centers for TMA may help to concentrate experience in managing such acute case presentations and allow future research.

**INTRODUCTION**

Drug induced Thrombotic microangiopathy (DITMA) are classified as primary TMA with the characteristic clinical picture of microangiopathic hemolytic anemia (MAHA), thrombocytopenia and microvascular thrombosis. Quinine has been widely implicated in drug induced TMA's with a proven causal relationship of drug exposure and clinical manifestations of TMA [1]. Patients can present with a spectrum of clinical features ranging from isolated thrombocytopenia to severe clinical features of MAHA and/or disseminated intravascular coagulation and acute kidney injury [2,3]. Variable recovery has been reported in case reports with combination of supportive care, plasma exchange, hemodialysis, steroids and cytotoxics. We present a case of DITMA, following a single dose of quinine with no previous history of quinine exposure treated successfully with plasma exchange (PEX) and oral corticosteroids, followed by MMF. For patients who respond initially to PEX, immunosuppression may be required to achieve PEX independence.

**CASE REPORT**

A 47-year-old Caucasian female with background of hypertension, COPD and an active smoker of 20 cigarettes/day presented to her local hospital with a two-day history of sudden onset diarrhea, vomiting, shortness of breath and abdominal bruising. She had been prescribed quinine sulphate by her general practitioner for leg cramps and had received a single dose of 200mg quinine sulphate 5 days prior to admission. The patient denied use of any herbal remedies, other medications or previous quinine use.

At presentation the patient had a pyrexia of 38.4°C, she was alert and oriented, SaO2 92% on room air, BP 149/73 mmHg. Clinical examination revealed perioral ulcerations, bilateral expiratory wheeze, normal heart sounds, right upper quadrant abdominal tenderness and a non-blanching purpuric rash in the right hypochondrium with an area of necrotic skin on the right shin. The patient was anuric despite fluid resuscitation with a blood gas showing pH 7.36, pCO2 4.05, pO2 9.49 and Lactate 2.8 mmol/L (Figure 1).

Blood tests revealed AKI stage 3 with a creatinine of 468 umol/L, CRP 494 mg/L, Bilirubin 232 umol/L, GGT 352 U/L, ALT 287 U/L, LDH 3910 U/L, Complement C3 and C4 were normal,
platelets 19 x10^9/L, prothrombin time 17.7 secs, APTT 40.8 secs, Hb 97 g/L (Blood tests from a few days previous showed normal FBC, U/E). In view of the pyrexia, elevated CRP, AKI3, persistent anuria despite fluid resuscitation transfer to intensive care unit (ICU) was arranged with a working diagnosis of sepsicaemia and treatment with Meropenem and Cefuroxime was commenced. Computed Tomography (CT) of chest, abdomen, and pelvis showed bilateral atelectasis of lungs and an ovarian cyst but normal kidneys.

The blood film showed a persistent MAHA and after 3 days post admission and therefore the patient was transferred to a regional TTP specialist centre for further management. The patient was commenced on daily plasma exchange (PEX) by centrifugation technique (1.5 times calculated total blood volume) and steroid therapy. ADAMTS13 level was found to be normal at 95% however in view of improving blood parameters the patients continued daily plasma exchange for suspected Quinine induced TMA. Haemodiafiltration (standard dialysis modality provided for anuric renal failure in our unit) was also performed although the patient remains edanuric. On day 18 she developed increasing confusion and agitation, suspected to be steroid induced or due to an intercurrent infection. CT head showed no features of infarction or bleed. Clinically this confusion improved over the next 2-3 days with a prednisolone reducing regimen along with urine output.

Stool cultures and antibody testing for cryptosporidium and shiga toxin were negative along with lupus anticoagulant, ANCA, dsDNA and anti-GBM antibodies. A CT-PET showed no significant abnormality other than the previously identified ovarian cyst.

Direct sequencing of the entire coding regions for Complement Factor H (CFH), CFI, CFB, CD46, and C3 revealed no pathogenic mutation. Auto antibodies for anti-factor H were not detected in the plasma of the patient. It was concluded that the most likely diagnosis was quinine induced TMA.

When PEX was discontinued on day 21 the LDH levels started to rise after 4 days and the blood film showed a worsening MAHA (Figure 2).

Therefore, the patient recommenced plasma exchange (total 20 PEX sessions during the admission). The patient received her last dialysis on day 24 and received last PEX on day 33.

Testing for quinine associated antibodies was not possible but in view of the protracted and severe course of her illness the patient was commenced on MMF (Day 29) to suppress the presumed production of these antibodies (Figure 3).

At one month post discharge the patient remains dialysis independent with Hb 124 g/L, Platelets 263 x10^9/L, LDH 249 U/L. Normal blood film, Creatinine 146 umol/L, eGFR 22ml/min/1.73m2, on Mycophenolate mofetil 250mg BD.

**DISCUSSION**

Quinine is the most common cause of immune-mediated DITMA being the offending drug in 33% of cases [2]. It occurs more commonly in females, although no genetic cause has been found [4]. A retrospective review of 6 patients with quinine-induced TMA revealed all patients were females with an age range of 43 to 73 years and had taken quinine for leg cramps [5]. There is a distinct racial variation in patients with DITMA predominantly occurring in whites as compared to acquired autoimmune TTP, in which the relative incidence rate is seven-fold greater in blacks compared to non-blacks [6].

Though our patient denied any previous use of quinine the possibility of chronic low dose ingestion in beverages, such as tonic water cannot be fully ruled out. As the literature suggests DITMA from quinine can be triggered either by a single ingestion occurring many months or up to 10 years in some case reports [3,6].

In this case, though the clinical presentation was of acute anuric renal failure, thrombocytopenia and MAHA which occurred abruptly after quinine ingestion, leading to a consideration of the diagnosis of DITMA. ADAMTS13 levels taken prior to octaplas administration showed normal activity of 95% consistent with previous case reports [5]. Quinine induced DITMA associated with a prolonged PT has previously been reported [6] and makes the distinction from DIC more challenging.

Our patient was managed with daily PEX with intermittent haemodialysis. Although the role of PEX is unclear in Quinine induced DITMA, in this case withdrawal of PEX was associated with a deterioration of blood parameters. Introduction of MMF resulted in rising platelet counts, resolution of MAHA on the blood film and a gradual improvement in renal function (Figure 3).

Quinine dependent antibody levels were not analysed due to...
lack of availability of the assay. However, it has been proposed that checking quinine dependent antibodies in the early part of the presentation may show low levels or are not detected as they are consumed during this phase [2,3]. As the illness progresses there is a trend for rising antibody levels which may persist for months to years [2,6].

The mainstay of treatment in DITMA is withdrawing the causative agent along with supportive therapy. There is a paucity of evidence about the use of immunosuppression in these cases as there are no trials or case studies validating their use. However, in patients with post-transplant TMA who are receiving either calcineurin inhibitors or mTOR agents there are reports of successfully treating by switching the immunosuppression to Rituximab [7], IV Immunoglobulin [8] or MMF [9].

In summary we present a case of quinine associated DITMA. The diagnosis was made by the close temporal relationship of exposure of quinine to the onset of TMA and exclusion of other causes of TMA including aHUS, TTP, SLE. The case highlights the need for a careful drug history in patients who present with TMA and supports the use of PEX in this condition. Although quinine antibody levels are not widely available, the use of immunosuppression with MMF to control the disease, through suppression of quinine-dependent antibody production is supported here. The evolution of Specialist Centers for TMA may help to concentrate experience in managing such acute case presentations and allow future research of such cases.

REFERENCES


