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CASE STUDY

Quinine induced thrombotic microangiopathy and thrombocytopenia: A teaching hospital's perspective

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Abstract: Although quinine is an infrequently prescribed drug, with malaria treatment being its only FDA-approved indication, unwitting exposure via beverages (*e.g.*, tonic water), over the counter herbal remedies and illegal recreation drugs still occur. We present a unique case of a female patient who denied any known prior history of quinine exposure, who after being prescribed quinine tablets for restless leg syndrome, developed an immune-related thrombotic microangiopathy with thrombocytopenia and subsequent multi-organ failure. It was later elucidated that her only known potential source of prior quinine exposure was a remote history of crack-cocaine use. The patient survived this rare and severe inflammatory response with recovery of renal function and was able to discontinue dialysis.

Keywords: Quinine, TMA, drug reaction, DITMA, thrombocytopenia

1 Introduction

Thrombotic microangiopathy (TMA) represents a spectrum of clinical diseases defined by pathologic abnormalities in arteriole and capillary vessel walls, resulting in platelet-induced microvascular thrombosis.[1] Drug-induced TMA (DITMA) is a unique immune-mediated entity of this clinical spectrum, resulting from the formation of drug-dependent antibodies that interact with host cell immune regulators in the presence of the implicated drug (or breakdown metabolite). DITMA often presents a diagnostic dilemma, as specific laboratory tests to identify the culprit agent are often unavailable. Moreover, many of the implicated substance etiologies may either be illegal recreational drugs, or substances unintentionally ingested by the patient, leading to an incomplete history of present illness thereby making subsequent testing more difficult. Multiple pharmacologic agents have been recognized as causative agents in the literature; however, quinine remains the most commonly reported cause of immune-mediated DITMA.[2] The inciting quinine exposure may occur through ingesting quinine tablets or herbal products for intended therapeutic purposes (*e.g.*, malaria or leg cramps) or through quinine-containing beverages (*e.g.*, tonic water, bitter lemon or gin and tonic). In addition, quinine has been often implicated as an adulterant, or "cutting agent," in commonly used drugs of abuse such as cocaine and heroin, and their unwitting co-ingestion is not without potential clinical consequences. Quinine associated DITMA is dose-independent, often occurring after only a single ingestion, and because of the long half-life of their drug-specific antibodies, the clinical consequence of immune reactivation may transpire months to years after the initial exposure.[3] We present an interesting case of a patient who denied any history of quinine exposure (from any source), but did report a remote history of crack-cocaine abuse, and who survived a severe systemic inflammatory response and multi organ failure, eventually recovering her renal function and able to discontinue dialysis.

2 Case presentation

A 45-year-old Caucasian woman was transferred to our academic medical center for further evaluation and management of severe thrombocytopenia, acute renal failure, and acute liver failure. She initially presented to her local emergency department two days prior with a chief complaint of bilateral leg swelling and pain following commencement of quinine tablets prescribed by her primary care physician for restless leg syndrome (RLS)

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refractory to conventional therapy (dopamine antagonists). At that time she was informed that her symptoms likely represented an allergic reaction to her new medication, and she was discharged home with instructions to discontinue further use. The patient returned to her local ED less than 48 hours later with worsening painful lower extremity swelling, and with new reports of extreme lethargy, weakness, intractable headache and a noticeable decline in urine output. After initial triage and basic labs were drawn, she was immediately transported to our tertiary care medical center for further evaluation and management.

Her past medical history was significant for hypothyroidism secondary to RAI ablation for toxic multinodular goiter five months prior to presentation, fibromyalgia, and RLS. Her family history was significant for autoimmune thyroid disease in her biological father. She reported a 15 pack-year tobacco history, denied ever ingesting any alcoholic beverages but admitted to crack-cocaine use on multiple occasions in the last ten years. Upon further questioning, the patient was quite certain she had not ingested tonic water or had prior exposure to quinine products.

Physical exam revealed a lethargic, morbidly obese female in moderate distress secondary to pain in her lower extremities and back. Vital signs were significant for tachycardia (heart rate 110), hypotension (blood pressure 88/60 mmHg), and SpO_2 92% on room air; she was afebrile (37°C) and non-tachypneic (RR 12). Bilateral lower extremities had 2+ pitting edema, with dusky skin changes in distal metatarsal tips (Figure 1). Bilateral radial, dorsalis pedis and posterior tibial pulses were palpable, and cardiovascular, respiratory and neurological examinations were unremarkable.

Initial laboratory investigation upon arrival revealed thrombocytopenia (platelet count 10,000 cells/mm3), normocytic anemia (hemoglobin 11.9 g/dL, hematocrit 33%, MCV 93), elevated liver (albumin 3.0 g/dL, total protein 5.9 g/dL, total bilirubin 7.2 mg/dL, direct bilirubin 4.9 mg/dL alkaline phosphatase 131 U/L, ALT 288 U/L, and AST 584 U/L) and renal function tests (blood urea nitrogen (BUN)/creatinine 75/6.5 mg/dL, potassium 5.0 mmol/L), thyroid stimulating hormone (TSH 137 mIU/L) and creatine kinase (1944 U/L). Initial radiologic exams included a Chest X-ray (unremarkable) and abdominal ultrasound with Doppler (diffuse echogenicity without focal lesions, normal hepatic blood flow, and normal sized kidneys without hydronephrosis).

Further evaluation on admission included a coagulation panel (prothrombin time 16.1 s, INR 1.3, and activated partial thromboplastin time 42 s), direct antiglobulin (Coombs) test (negative), lactate dehydrogenase

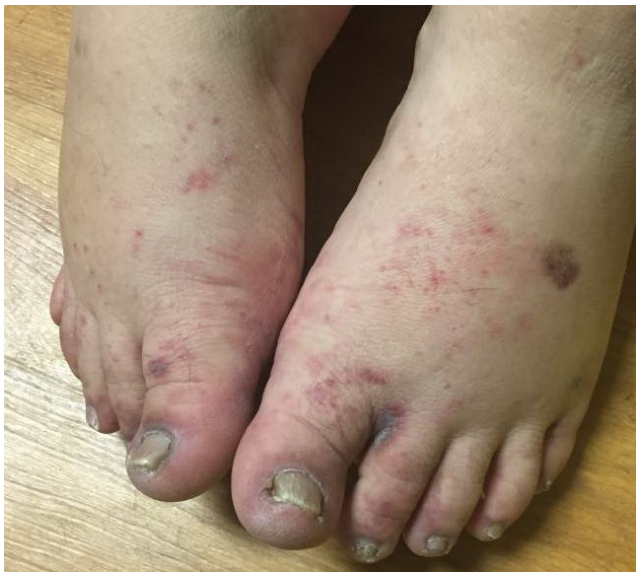

Figure 1. Bilateral lower extremity skin changes

(4927 U/L) and normal ADAMSTS13 level (89%). Review of peripheral blood smear showed 3 schistocytes per high power field, limited platelets, no platelet clumping, few target cells, limited spherocytes, and absence of nucleated red blood cells. Given the new onset of renal failure, thrombocytopenia, positive schistocytes on peripheral blood smear, and a normal ADAMTS13 level in the setting of recent short-term quinine exposure, a diagnosis of drug-induced thrombotic microangiopathy (DITMA) was suspected.

After 48 hours of ICU-level care the patient's vital signs stabilized, her pain, weakness and lethargy began to abate, and her liver function tests (AST/ALT, alkaline phosphatase, bilirubin, and INR) quickly downtrended towards baseline. However, the patient remained anuric with a progressively declining renal function (creatinine peak 10.63 mg/dL), complicated by multiple electrolyte (hyperkalemia, hyperphosphatemia, hyponatremia) and metabolic (uremia, anion-gap acidosis) abnormalities, requiring placement of a central venous catheter and initiation of hemodialysis (HD). She remained on HD (3 days/week) during her inpatient stay, but given the minimal improvement in renal function observed, Interventional Radiology placed a tunneled dialysis catheter and the patient was referred for continuation of renal replacement therapy (RRT) at a local outpatient dialysis center. Furthermore, her anemia and thrombocytopenia continued to worsen over the first seven days of hospitalization, requiring one transfusion of both packed RBCs and platelets, no clinically evident bleeding was observed. She responded appropriately to both transfusions and her cell counts remained stable, slowly trending up towards

baseline around hospital day 10, and required no further blood products. Serum drug specific antibody tests were sent to the Blood Center of Wisconsin laboratory to confirm the suspected diagnosis of DITMA, and results were positive for quinine-dependent red cell antibodies when tested in the presence of the drug.

Outpatient continuity was established as the patient elected to follow-up with our institution's Nephrology and Hematology clinics. After discharge, she continued to require RRT for approximately for one month before renal function started showing recovery. Review of the most recent nephrology clinic encounter, now five months post hospital discharge, showed her current renal function is stage G3aA3, with a creatinine plateau of 1.25 mg/dL Other than mild proteinuria (urine protein to creatinine ratio 600 mg/g), she is maintaining well with no metabolic or electrolyte abnormalities, no recent illness and no hospitalizations in the interim.

3 Discussion

Quinine associated thrombocytopenia is a rare immune related thrombotic microangiopathy (TMA) first described in 1865 with four patients.[4] Other mechanisms theorized include an idiosyncratic and direct toxic effect.[5] All cases necessitate a detailed history to uncover a possible medication exposure. Previous exposure is often absent from the patient's history due to unawareness (unlabeled herbal products) or intentional omission of ingestion (*e.g.* illegal drugs of abuse). The Oklahoma TMA registry reports 11% of patients were found to have a TMA associated with a drug, the most common being quinine ingestion.[2] Most documented cases of quinine induced reactions occur with prior exposure and due to a sensitization reaction.[6,7] Although ingestion of the medication for approximately one week is typically required to develop sensitization, drug-dependent antibodies may develop after only a single previous exposure.[3,8] These patients experience a diverse reaction to the drug and many have been shown to have a picture appearing of systemic inflammatory response.[7] What was interesting is that in our case the patient was adamant on not being exposed to any quinine during her lifetime including tonic water, yet after ingestion of one tablet of quinine, she developed signs of rhabdomyolysis, acute liver failure, severe hypothyroidism, progressive renal failure, and thrombocytopenia. The only possible substance noted in the detailed history obtained by multiple members of her inpatient care team was previous abuse of crack-cocaine, which as previously mentioned, may be unsuspectingly "laced" with quinine products. It has been shown that patients who require renal replacement therapy have higher risk of progression to long term CKD (chronic kidney disease), can lead to renal failure[9] and doubles the risk of long term death.[7] When the diagnostic confidence of DITMA is high based on history and laboratory values, the mainstay intervention involves supportive care and it is not recommended to initiate plasma exchange or anti-compliment therapy, as these therapeutic modalities have been shown to be ineffective or harmful in patients with quinine-induced TMA. For patients diagnosed with immune-mediated DITMA, it is imperative that the implicated agent be completely avoided for life, as even miniscule subsequent levels of exposure may result in death.[3] The drug should be clearly documented in the patient's medical record as an absolute contraindication secondary to severe drug reaction.

The highlights of our patient's hospital course include a very careful detailed history to uncover new medication administration, the fact that subjectively she denied any quinine exposure and yet we observed a dramatic response after ingestion of quinine leading to acute renal failure requiring RRT for two months, although her current renal function continues to improve off hemodialysis and she is doing well from a hematologic perspective.

4 Informed consent/ethics

Informed consent has been obtained and is available on request

5 Author contribution

All authors contributed to the preparation, writing, and editing of the manuscript.

6 Conflicts of interest and funding

On behalf of all authors, the corresponding author declares that there is no conflict of interest regarding the publication of this article. No funding was involved in the preparation or at any stage in the production of this manuscript.

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