CASE REPORT

Quinine-induced severe thrombocytopenia: the importance of taking a detailed drug history

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SUMMARY

Drugs can lead to severe life-threatening thrombocytopenia. The mechanisms of drug-induced thrombocytopenia are increased destruction by immune-mediated platelet destruction or decreased platelet production by bone marrow suppression. Quinine is a drug used for the treatment of malaria and nocturnal leg cramps and is also an important ingredient in some herbal preparations. Quinine can very rarely cause thrombocytopenia by immune-mediated platelet destruction. In a patient with thrombocytopenia, a detailed history of all the medications including over-the-counter medications and herbal preparations is very important.

BACKGROUND

This case report describes a patient who developed bleeding symptoms due to severe thrombocytopenia caused by the ingestion of quinine tablets. Only after asking specific question, the history of quinine ingestion was revealed. The tests for quinine-induced thrombocytopenia are technically demanding and not easily available in many countries. Hence, a thorough drug history including over-the-counter medications and herbal preparations is vital in the diagnosis of quinine-induced thrombocytopenia, and quinine should be stopped based on the history. If the history of quinine intake is positive, discontinuation of quinine alone is sufficient for the treatment of thrombocytopenia. This will help to prevent complications and avoid inappropriate treatments for thrombocytopenia.

CASE PRESENTATION

A 78-year-old Caucasian woman attended the emergency department of our hospital with symptoms of sudden onset of large bruises in the skin and haematuria of 2 days duration. There were no constitutional symptoms like night sweats or weight loss, flu-like symptoms and infections. She was taking pantoprazole for reflux disease, fluticasone and salbutamol inhalers for asthma and there were no known allergies. Full blood counts (FBC) conducted at emergency department revealed a very low platelet count ($1 \times 10^9/L$) with normal values of haemoglobin and white cell counts. There was no history of similar episodes and her historical FBC report 12 months prior to that episode showed a normal platelet count. On asking specifically if she took quinine, tonic water or herbal preparations, the patient admitted taking two quinine tablets 3 days prior for nocturnal leg cramps, which she did not remember initially. She had also taken quinine tablets 6 months prior to that episode without any adverse effects. Since quinine is the

presumed cause for her thrombocytopenia, the patient was advised to avoid quinine and quinine containing preparations.

INVESTIGATIONS

A repeat FBC confirmed marked thrombocytopenia with normal values of haemoglobin and white cell counts. A peripheral blood smear did not show any abnormalities in the red cells or white cells and there were no red cell fragments, platelet clumps or malignant blasts. Her coagulation assays, liver function tests and renal parameters were within normal limits. Tests for immune disorders like antinuclear antibody, antineutrophil cytoplasmic antibody, antibodies to anti-double stranded DNA, and rheumatoid factor were negative. Viral serologies for Hepatitis B and C, HIV and Epstein-Barr virus were also negative. Since quinine was the most likely cause of the patient's low platelet counts, a bone marrow biopsy was not performed. A blood sample for quinine-dependent antibody test was sent to a special platelet laboratory for confirmation.

DIFFERENTIAL DIAGNOSIS

- ▶ Idiopathic thrombocytopenic purpura (ITP)
- ▶ Secondary immune causes: systemic lupus erythematosus, antiphospholipid syndrome and rheumatoid arthritis
- ▶ Infections: falciparum malaria, HIV, Hepatitis B and C, *Helicobacter pylori* and bacterial sepsis
- ▶ Drugs: quinidine, sulfonamides, penicillin, heparin, abciximab and myelosuppressive drugs
- ▶ Bone marrow infiltration: leukaemia, lymphoma and myelodysplastic syndrome
- ▶ Disseminated intravascular coagulation
- ▶ Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome

TREATMENT

The patient was admitted to the hospital for management of severe thrombocytopenia and bleeding manifestations. Since ITP could not be excluded at that stage, she was treated with prednisolone at a dose of 1 mg/kg daily. After 3 days, her bleeding symptoms resolved completely and platelet counts improved to $78 \times 10^9/L$, and hence, prednisolone was ceased. She was discharged home and was advised to refrain from quinine or quinine containing preparations like tonic water. After a week her platelet counts increased to normal levels ($328 \times 10^9/L$).

OUTCOME AND FOLLOW-UP

The quinine-dependent platelet antibody test conducted by platelet immunofluorescence test (PIFT)

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was 100% positive and the results came 2 weeks after presentation. This confirmed that the patient had developed quinine-mediated thrombocytopenia. Severe thrombocytopenia can recur on re-exposure to quinine and can even cause life-threatening bleeding manifestations. Hence, she was warned not to take quinine or quinine containing preparations like tonic water for life. In her medical records, it was flagged as 'allergic to quinine'. She was followed up regularly for 12 months and the platelet counts were consistently normal.

DISCUSSION

The mechanisms of drug-induced thrombocytopenia are increased destruction by immune-mediated platelet destruction or decreased platelet production by bone marrow suppression. Quinine is a drug used for the treatment of malaria and nocturnal leg cramps and can lead to life-threatening thrombocytopenia by immune-mediated mechanism. Quinine-mediated thrombocytopenia is an extremely rare complication with the incidence of approximately 26/million users.¹

Quinine is also an important ingredient in many herbal preparations like tonic water and bitter lime.² The antibodies causing quinine-induced thrombocytopenia are immunoglobulins that usually recognise the platelet glycoproteins (GP) Ib/IX or GPIIb/IIIa.^{3,4} Quinine-dependent antibodies have significant affinity for these platelet antigens only in the presence of the drug at therapeutic concentrations.⁵ Hence in susceptible patients, these antibodies commonly attack the platelets on the second and subsequent exposure to quinine. Patients with quinine-mediated thrombocytopenia typically present with very low platelet counts (less than $10 \times 10^9/L$). The onset is usually abrupt and the time to develop thrombocytopenia after taking quinine is variable.⁶ The symptoms are often skin and mucosal bleeding; however, fatal bleeding manifestations have been reported.⁷ After ceasing quinine, the platelet counts generally show recovery after 7–10 days but occasionally can take a longer time.⁸

PIFT helps to demonstrate drug dependence in vitro by detecting antibodies binding to platelets in the presence but not in the absence of the drug.^{9,10} However, the test is a technically demanding test and highly specialised. A thorough drug history including over-the-counter medications and herbal preparations is important to differentiate quinine from other causes of thrombocytopenia. Early recognition and discontinuation of quinine are essential in the management of thrombocytopenia, which will help to prevent complications and avoid inappropriate treatments.

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Contributors MM as a clinician was involved in the treatment of the patient, and he also wrote the manuscript. RH as a biomedical scientist was involved in performing the patient's tests, and he also edited the manuscript.

Competing interests None.

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Learning points

- ▶ Awareness of the quinine-mediated thrombocytopenia is essential in patients presenting with an unexpected low platelet count.
- ▶ In some situations, other causes of thrombocytopenia can mimic quinine-induced thrombocytopenia (eg, falciparum malaria or idiopathic thrombocytopenic purpura can also cause thrombocytopenia). Continuing quinine in such instances can cause worsening of thrombocytopenia and may lead to fatal events.
- ▶ Only a few centres in the world have the facilities to test for quinine-induced thrombocytopenia. Hence, clinical judgement is necessary for the larger number of medical personnel who do not have access to such highly specialised tests.
- ▶ A thorough drug history including over-the-counter medications and herbal preparations is important. Sometimes specific questioning about intake of quinine, tonic water and bitter lime will be necessary to elicit the history.
- ▶ If the history of quinine intake is positive, discontinuation of quinine alone is sufficient for the treatment of thrombocytopenia. This will help to prevent complications and avoid inappropriate treatments for thrombocytopenia.

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