CASE REPORT

Vancomycin-induced thrombocytopaenia in a patient with severe pancreatitis

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SUMMARY

Vancomycin-induced thrombocytopenia is a rare side effect of a commonly used drug that may cause life-threatening disease. A 51-year-old man was treated for an episode of acute severe alcohol-induced pancreatitis complicated by development of a peripancreatic fluid collection. He developed fever of unknown origin and was treated with intravenous vancomycin and piperacillin with tazobactam. On day 6 of vancomycin therapy his platelet count dropped to $46 \times 10^9/L$ ($237 \times 10^9/L$ on day 1 of treatment) and by day 8 of therapy platelets had fallen to a nadir of $9 \times 10^9/L$. The patient at this stage displayed a florid purpuric rash and haematoma formation on attempted intravenous cannulation. A clinical diagnosis of vancomycin-induced thrombocytopaenia was made and the drug withdrawn. After 3 days a significant improvement in the platelet count was noted, rising to $56 \times 10^9/L$. Immunofluorescence testing (PIFT) ruled out teicoplanin and heparin as causes of drug-induced thrombocytopenia.

BACKGROUND

Vancomycin is a naturally occurring glycopeptide antibiotic traditionally indicated for treatment of penicillin-resistant *Staphylococcus aureus* infection. It is increasingly used for treatment of a broad range of Gram-positive infections. Thrombocytopenia is a rare side effect associated with vancomycin therapy. Although the clinical presentation has been described,¹ diagnosis may not be made until repeat exposure,²⁻⁴ which is associated with life-threatening thrombocytopenia. Knowledge of its clinical features is therefore important for early recognition and maintenance of patient safety. We presented a case that demonstrates the typical clinical progression of severe vancomycin-induced thrombocytopenia.

CASE PRESENTATION

A 51-year-old man of Indian descent presented to our emergency department with sudden onset severe epigastric pain, rated as 8 of the 10 severity, associated with two episodes of vomiting. He had no medical history other than mild hypertension. The patient reported drinking vodka equivalent to 10 units of alcohol a day for the previous 6 months, no use of recreational drugs and he did not smoke tobacco. He was febrile ($38.7^\circ C$) with an elevated blood pressure of 157/115 mm Hg, a heart rate 119 bpm, a respiratory rate 19 and an oxygen saturation of 95% on room air. The

laboratory workup included an elevated serum amylase 2059 IU/L, γ -glutamyl transferase 260 IU/L, white cell count (WCC) $16.9 \times 10^9/L$ (neutrophils $12.4 \times 10^9/L$), calcium 2.54 mmol/L, lactate dehydrogenase 178 IU/L, blood glucose 10.9 mmol/L and other parameters within normal limits. A diagnosis of acute pancreatitis was made and the patient was treated according to a standardised treatment protocol.

As part of his clinical follow-up, an outpatient CT of the abdomen was performed 4 weeks post-discharge. This demonstrated a large peripancreatic fluid collection. An 8.5 French locking pigtail catheter was inserted and pus was aspirated. Following culture and sensitivity of the aspirated pus, a heavy growth of *Enterococcus raffinosus* was demonstrated. The patient remained clinically well and was discharged with a course of oral ciprofloxacin 500 mg twice daily and intravenous teicoplanin 400 mg once daily. This was administered in the community by the district nurse.

Two weeks later the patient was referred by the district nurse for investigation of fever, noted on a routine medication visit. On presentation he had a temperature of $38.8^\circ C$ and was tachycardic with a heart rate of 103 bpm, but otherwise clinically well. A full septic screen was ordered including routine serology, blood and urine cultures, HIV and hepatitis screens, chest radiography and a transthoracic echocardiogram. The pigtail catheter was removed from the peripancreatic collection due to minimal output. Serology at this time showed WCC $4.5 \times 10^9/L$ (neutrophils $0.9 \times 10^9/L$), mildly elevated C reactive protein of 7 mg/L, haemoglobin 10.2 g/dL, platelets of $382 \times 10^9/L$. No source of sepsis was identified. Antibiotic therapy was withheld following advice from the infectious disease team and a 263 μg dose of granulocyte-colony stimulating factor was administered for treatment of neutropenia, following clinical review by the haematology team.

Forty-eight hours later the patient continued to suffer from fever of unknown origin. The case was reviewed by the infectious disease team who advised treatment with vancomycin 1 g twice daily and piperacillin with tazobactam 4.5 g thrice daily. Vancomycin levels were measured initially on a daily basis and were within therapeutic range. On day 6 of vancomycin therapy his platelet count dropped to $46 \times 10^9/L$ ($237 \times 10^9/L$ on day 1 of treatment), falling to a nadir of $9 \times 10^9/L$ on day 8

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Figure 1 Progression of platelet count in vancomycin-induced thrombocytopenia.

of vancomycin therapy (figure 1). Fibrinogen levels remained within normal limits. The patient at this stage displayed a florid purpuric rash and excessive bleeding with bruising and haematoma formation following attempted intravenous cannulation. There was no epistaxis or bleeding with oral hygiene. A clinical diagnosis of vancomycin-induced thrombocytopenia was made and the drug withdrawn on day 8 of therapy. After 3 days a significant improvement in the platelet count was noted, the nadir rising to $56 \times 10^9/L$ (figure 1). Once daily heparin therapy continued to be administered for prophylaxis of venous thromboembolism. The patient completed a further 2-week course of intravenous antimicrobials (meropenem and fluconazole) and was discharged with outpatient follow-up. His platelet levels had returned to normal reference ranges on discharge.

DIFFERENTIAL DIAGNOSIS

On the basis of clinical information alone, application of the Naranjo method for estimating the probability of adverse drug reactions demonstrated vancomycin as the 'probable' cause of thrombocytopenia.⁵ Use of the 4T score suggested a 'low' probability of heparin as the cause of thrombocytopenia. A 'low' 4T score has been demonstrated to be highly specific to exclude heparin-induced thrombocytopenia ('HIT').⁶ A blood film was subsequently reviewed, which demonstrated thrombocytopenia and neutrophilia with toxic granulation and vacuolated reactive lymphocytes. Immunofluorescence testing (PIFT) was used to rule out teicoplanin and heparin as causes of drug-induced thrombocytopenia. A standardised, validated test for detection of vancomycin-induced antiplatelet antibodies was not available. Given the severity of the drug reaction in this case, vancomycin rechallenge was not recommended.

DISCUSSION

Severe thrombocytopenia is a potentially life-threatening complication of Vancomycin therapy. It is thought to occur due to drug-induced platelet activation and apoptosis⁷; however direct toxicity may also be important in its pathogenesis. Previous studies have demonstrated an exposure-response relationship between vancomycin trough concentration and the severity of thrombocytopenia.⁸ Poor control of vancomycin trough levels and previous exposure may be risk factors for development of the condition. It is most frequently seen 7–10 days after starting of vancomycin therapy¹ and clinical features of the condition may include bleeding, ecchymoses, petechial rash and resistance to platelet replacement therapy.⁴ Gradual resolution of thrombocytopenia typically occurs over a period of approximately 7 days after stopping vancomycin (figure 1); however, recovery may be delayed, particularly in patients with concurrent renal failure.¹

Early diagnosis of vancomycin-induced thrombocytopenia is essential in order to avoid significant morbidity. In practice this is challenging and requires interpretation of the clinical picture and serological investigations within a multidisciplinary setting. Clinicians must have a high index of suspicion and an understanding of differential diagnoses, which in this case included HIT, disseminated intravascular coagulation (DIC) and teicoplanin-induced thrombocytopenia. In this case the diagnosis was made on clinical grounds, later confirmed by exclusion of differential diagnoses through immunofluorescence testing. In specialist centres early diagnosis may be made through detection of vancomycin-dependant IgG or IgM antiplatelet antibodies; however, these tests are not standardised and currently inaccessible to most.⁹

Learning points

- ▶ Vancomycin-induced thrombocytopenia is a rare complication of a commonly used drug.
- ▶ This case demonstrates the typical clinical picture and progression of the disease.
- ▶ Knowledge and understanding of the condition and its differential diagnoses is required in order to make an early diagnosis, which is essential in order to avoid life-threatening disease.

Contributors SPR obtained informed consent from the patient and carried out corrections to the manuscript. IR collected blood results and organised immunofluorescence testing. IR also helped in drafting the manuscript. HS provided advice in drafting the manuscript, supervision and held overall responsibility for clinical care.

Competing interests None.

Patient consent Obtained.

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