Unusual association of diseases/symptoms

Piperacillin/tazobactam induced thrombocytopaenia—a delayed response

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Correspondence to Dr Jessica L Macwilliam, jmac@doctors.org.uk**Summary**

A 48-year-old lady who presented with sepsis secondary to a pelvi-ureteric junction obstruction was treated with an extended course of piperacillin/tazobactam. Four days after completing the course she developed thrombocytopaenia. Intravenous immunoglobulin was required to bring her platelet count back to normal. In the absence of other causes the authors believe that a delayed reaction to piperacillin/tazobactam was the cause of her thrombocytopaenia.

BACKGROUND

To our knowledge, thrombocytopaenia has never been previously reported as a delayed side effect of piperacillin/tazobactam (PT) therapy. There are however, a limited number of reported cases of thrombocytopaenia during patients treatment, with 21 cases reported via the Medicines and Healthcare products Regulatory Agency (MHRA) yellow card reporting system.^{1–3} Reaction to PT required further intervention in order to normalise serum platelet levels in this case. It is important to be aware of this delayed reaction as patients may be discharged before thrombocytopaenia may become apparent.

CASE PRESENTATION

A 48-year-old lady was admitted to urology department following the diagnosis of an obstructed infected kidney secondary to a pelvi-ureteric junction obstruction. A nephrostomy was inserted after a delayed diagnosis on day 23 of her hospital stay. Before this she had been receiving treatment for a fever of unknown origin with intravenous PT 4.5 g three times per day. She received a total of 18 days treatment. Four days after intravenous PT therapy was stopped, she was found to have a petechial rash on her legs and trunk along with a platelet count of $2 \times 10^9/l$ (normal range $140–450 \times 10^9/l$). Following this prophylactic

low molecular weight heparin (subcutaneous 2500 units dalteparin once daily) was suspended as it has been reported to be the most common causative agent in drug induced thrombocytopaenia.⁴

INVESTIGATIONS

Blood film examination revealed no clumps indicating true thrombocytopaenia. All other laboratory results were within normal limits and all culture samples were persistently negative. Heparin induced thrombocytopaenia screening, via PIFFA test, was negative.

DIFFERENTIAL DIAGNOSIS

The initial working diagnosis was one of drug induced thrombocytopaenia and consequently the low-molecular weight heparin was suspended. However, following a negative heparin induced thrombocytopaenia screen, and discussion with the haematology team, a diagnosis was made of PT induced thrombocytopaenia based on the exclusion of other causes.

TREATMENT

The patient was reluctant to receive steroid treatment when initial intervention with platelet replacement was unsuccessful, due to concerns regarding the potential side

Table 1 Criteria for assessing reports of drug induced thrombocytopaenia and levels of evidence for a causal relation between the drug and thrombocytopaenia¹²

Criterion	Description
1	1) Therapy with the candidate drug preceded thrombocytopaenia and 2) Recovery from thrombocytopaenia was complete and sustained after therapy with the drug was discontinued.
2	1) The candidate drug was the only drug used before the onset of thrombocytopaenia or 2) Other drugs were continued or re-introduced after discontinuation of therapy with the candidate drug with a sustained normal platelet count.
3	Other causes for thrombocytopaenia were excluded.
4	Re-exposure to the candidate drug resulted in recurrent thrombocytopaenia.
Level of evidence	
I	Definite: criteria 1, 2, 3 and 4 met
II	Probable: criteria 1, 2 and 3 met
III	Possible: criterion 1 met
IV	Unlikely: criterion 1 not met

Table 2 ADR probability questionnaire¹³

Question	Yes	No	Don't Know
1) Are there previous conclusive reports on this reaction?	+1	0	0
2) Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3) Did the adverse reaction improved when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4) Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
5) Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6) Did the reaction reappear when a placebo was given?	-1	+1	0
7) Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8) Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9) Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10) Was the adverse event confirmed by any objective evidence?	+1	0	0

Scoring: >9=Definite ADR5–8=Probable ADR1–4=Possible ADR0=Doubtful ADR

ADR, adverse drug reaction.

effects of steroids. She received treatment with intravenous immunoglobulin, 1 g/kg for 2 days.

OUTCOME AND FOLLOW-UP

Following intravenous immunoglobulin her platelet count began to increase. She was discharged 2 days later with a platelet count of $96 \times 10^9/l$. Further repeat blood testing by her general practitioner revealed a platelet count of 104×10^9 7 days postdischarge. She has now been recorded as having a PT allergy and a yellow card has been completed and sent to the MHRA.

DISCUSSION

Thrombocytopenia is defined as a platelet count of less than $100 \times 10^9/l$ or a drop in platelet count of more than 50% from baseline.^{4–5} In hospitalised patients, the most common causes identified are drugs, sepsis and disseminated intravascular coagulation.⁴ Thrombocytopenia is listed as an uncommon side effect of PT therapy ($\geq 1/1000$ to $< 1/100$). However, it is important that it is not overlooked as a potential cause for thrombocytopenia in hospitalised patients receiving treatment for sepsis.^{6–8} In this report, we present a case demonstrating a delayed reaction to the drug.

Delayed-type hypersensitivity (DTH) is defined as a reaction that does not manifest until more than 10 days of treatment; the DTH reaction most commonly associated with PT use is neutropenia, although the drug has also been associated with reversible myelosuppression.^{8–11}

Drug induced thrombocytopenia can be caused by numerous medications and establishing the causative agent in a patient who is taking several medications remains a challenge. A diagnosis can only be supported if thrombocytopenia resolves after the drug has been discontinued.^{11–12} In the case of piperacillin the mechanism of the thrombocytopenia is believed to be related to hapten-dependent antibodies.⁴ When patients are re-exposed to the drug it leads to platelet destruction and, in some cases, haemolytic anaemia.⁴

George *et al* conducted a review of cases of drug induced thrombocytopenia and produced criteria for establishing a causative relationship in cases of suspected drug induced thrombocytopenia¹² (table 1). This case meets criteria 1 and 3 however, it is not possible to fully assess criteria 2 and 4, other suspended medications were not reintroduced and the patient has not been re-exposed to the drug since this presentation. Using this system, our case therefore lies

between level II and level III evidence for a causal relationship which equates to a possible/probable causative effect. The Naranjo algorithm for detecting possible adverse drug reactions (ADRs) indicates that this is a probable ADR (table 2).^{9–13}

Our patient developed thrombocytopenia 4 days after PT had been discontinued. In previous cases thrombocytopenia developed while patients were still receiving treatment and management involved drug discontinuation.^{1–2} In our case, because there was a delayed reaction to the drug, and the patient was unwilling to take steroids, further intervention with intravenous immunoglobulin was instituted in order to restore a normal platelet count. We concluded that, as her platelet levels continued to rise upon leaving hospital, her thrombocytopenia was related to her extended course of PT and she is now listed as having an allergy to the drug. We recommended that she have her full blood count checked weekly in the community until her platelets were back to normal further advised her to be aware of the increased bleeding risk associated with this diagnosis. This case highlights the need for clinicians to be aware of this uncommon cause of thrombocytopenia and to consider it when producing a differential diagnosis for acute onset thrombocytopenia in a hospitalised patient.

Learning points

- ▶ Thrombocytopenia can present as a delayed reaction to drug therapy.
- ▶ In cases of delayed thrombocytopenia further intervention beyond suspending drug therapy, such as intravenous immunoglobulin, may be required in order to bring platelet count back to baseline levels.
- ▶ It can be difficult to establish, with complete certainty, the causative drug for the thrombocytopenia.
- ▶ Re-exposure to a causative agent can cause thrombocytopenia to recur.
- ▶ A yellow card should be completed and sent to the MHRA for all suspected life-threatening adverse drug reactions.

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Competing interests None.

Patient consent Obtained.

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