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Antibiotic-Induced Thrombocytopenia in the ICU: Case Report of a Diagnostic Challenge

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Thrombocytopenia is the most common coagulation problem in ICU patients and is an independent predictor of death among critically ill patients.1 Thrombocytopenia is generally defined as a platelet count below 100,000/μL. The causation is highly multifactorial and driven by six distinct mechanisms:1 increased consumption, hemodilution, decreased production, sequestration, pseudo-thrombocytopenia, and increased destruction. The differential diagnosis of acute thrombocytopenia in an ICU patient is extensive. After eliminating the more common etiologies, drug-induced thrombocytopenia (DITP) should be considered as an often overlooked yet easily reversible cause of thrombocytopenia.1 Due to a lack of distinguishing clinical features and numerous other possible etiologies, diagnosis is often complex, requiring a multistep approach.2 We discuss the extensive workup of DITP in the context of this unusual case presentation.

Introduction

Thrombocytopenia is the most common coagulation problem in ICU patients and is an independent predictor of death among critically ill patients.1 Thrombocytopenia is generally defined as a platelet count below 100,000/μL. The causation is highly multifactorial and driven by six distinct mechanisms:1 increased consumption, hemodilution, decreased production, sequestration, pseudo-thrombocytopenia, and increased destruction. The differential diagnosis of acute thrombocytopenia in an ICU patient is extensive. After eliminating the more common etiologies, drug-induced thrombocytopenia (DITP) should be considered as an often overlooked yet easily reversible cause of thrombocytopenia.1 Due to a lack of distinguishing clinical features and numerous other possible etiologies, diagnosis is often complex, requiring a multistep approach.2 We discuss the extensive workup of DITP in the context of this unusual case presentation.

Patient Presentation

This is a 68 year old male with PMH of severe COPD, atrial fibrillation, and lung CA s/p upper lobectomy. He was admitted on four separate occasions to our institution over a two year period with COPD exacerbation and suspected pneumonia. On each admission his presentation, workup, and treatment were similar. Repeatedly he was empirically treated with vancomycin (Vanco) and piperacillin-tazobactam (pip-tazo) as an initial course, and in each circumstance he developed thrombocytopenia in a strikingly homogenous temporal sequence. In every instance, platelets recovered only after the cessation of pip-tazo. On the third admission platelets continued to fall after Vanco was stopped and pip-tazo was continued. On the final admission his platelets rose after cessation of pip-tazo while vanco was continued, strongly indicating that pip-tazo was the offending agent. Common and rare causes of thrombocytopenia were absent and anemia and neutropenia did not develop. Admissions during which he did not receive these antibiotics were not associated with thrombocytopenia.

Admission 1 3/22/10

- Admission notes: Coagulation profile, cultures negative, BP stable
- Initial Platelet Count: 163 230 168 289
- Days to nadir following Vanco and pip-tazo initial administration: 6 7 5 1
- Days to recovery following Vanco and pip-tazo initial administration: 15 >15 >15 >7

Admission 2 4/11/10

- Admission notes: Coagulation profile, cultures negative, BP stable
- Initial Platelet Count: 163 230 168 289
- Days to nadir following Vanco and pip-tazo initial administration: 6 7 5 1
- Days to recovery following Vanco and pip-tazo initial administration: 15 >15 >15 >7

Admission 3 3/16/11

- Admission notes: Coagulation profile, cultures negative, BP stable
- Initial Platelet Count: 163 230 168 289
- Days to nadir following Vanco and pip-tazo initial administration: 6 7 5 1
- Days to recovery following Vanco and pip-tazo initial administration: 15 >15 >15 >7

Admission 4 12/11/11

- Admission notes: Coagulation profile, cultures negative, BP stable
- Initial Platelet Count: 163 230 168 289
- Days to nadir following Vanco and pip-tazo initial administration: 6 7 5 1
- Days to recovery following Vanco and pip-tazo initial administration: 15 >15 >15 >7

Table 1: Note the pattern of thrombocytopenia across four admissions for similar clinical presentation and therapy.

Discussion

...when you have eliminated the impossible, whatever remains, however improbable, must be the truth.6 Sherlock Holmes4

After extensive investigation, the evidence points to DITP secondary to pip-tazo. DITP related to pip-tazo is exceedingly uncommon, appearing in only 3 case reports and in 13 patients specifically tested for antibodies at Blood Center of WI (BCW) over 10 years. Furthermore, in the absence of a positive drug-induced anti-platelet antibody test it is even more rare.10-11 Despite the lack of serological confirmation, a diagnosis of pip-tazo induced DITP can be made based on published clinical criteria.4-5 Our patient’s episodes of thrombocytopenia met all four of the criteria outlined by Rousan et. al. (figure 2) which constitutes “definite” probability for drug induced etiology.6-8 Additional support is seen with the utilization of an adverse drug reaction (ADR) probability scale.9 This case scored 11 out of a possible 13 points, where a score of 0 or 1 is equated with a “definite” probability that his thrombocytopenia is due to an ADR.

A blood sample failed to show pip-tazo or vanco related anti-platelet antibodies when tested by immunoassay; flow cytometry at BCW. However, there are several limitations to this test. These assays have high specificity but moderate sensitivity since a metabolite of the drug formed in-vivo may be responsible for DITP and not the primary drug itself.12-13 Piperacillin is known to form metabolites which are not normally tested. BCW does not routinely run a control along with a patient sample for piperacillin.14 Additional confounding elements are introduced by the need to test separately for piperacillin and tazobactam. Tazobactam induced antibodies are so rare that they are not normally tested for by BCW. Because piperacillin is essentially never administered without tazobactam, there is very low clinical relevance to testing these agents independently. Finally, piperacillin antibodies are known to have weak drug dependent interactions with normal platelets; however, there was no correlation shown between antibody strength measured by flow cytometry and the severity of thrombocytopenia.15 Therefore, a negative test is possible despite clinically relevant thrombocytopenia.

Ultimately, there may be value in re-testing this patient for drug-induced antibodies at his next clinical encounter. From a practical perspective, his providers should avoid pip-tazo or very closely monitor platelet count if a suitable alternative is unavailable.

References

5. Rousan TA, Aldoss IT, Cowley BD Jr, Curtis BR, Bougie DW, Aster RH, George JN. Recurrent acute thrombocytopenia in the hospitalized patient: sepsis, DIC, HIT, or...