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

Spiro Khoury
University of Massachusetts Medical School

Nicholas C. Watson
University of Massachusetts Medical School

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

Spiro Khoury M.D., Nicholas C. Watson M.D.
Department of Anesthesiology, University of Massachusetts Medical School, Worcester, MA

Introduction

Thrombocytopenia is the most common coagulation problem in ICU patients and is an independent predictor of death among critically ill patients. Thrombocytopenia is generally defined as a platelet count below 100,000/μl. The causation is frequently multifactorial and driven by six distinct mechanisms: 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. Due to a lack of distinguishing clinical features and numerous other possible etiologies, diagnosis is often complex, requiring a multistep approach. 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, AF, coronary artery disease, and lung CA slip upper lobe. 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 homogeneous temporal sequence. In every incident, platelets recovered only after the cessation of pip-tazo. On the first admission platelets continued to drop 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 none of the 3 admissions developed heparin-induced thrombocytopenia. Admission during which he did not receive these antibiotics were not associated with thrombocytopenia.

Admission: 3/28/10

- Platelet count: 163,290
- No transfusions during critical platelet drops.

Adoption Notes:

- C-reactive protein, leukocyte count, ALT, AST, serum creatinine, INR, PT, aPTT, D-dimer, fibrinogen
- Platelet count, total WBC, ANC

Initial Platelet Count: 163

Platelet/White (5% drop from admission)

<table>
<thead>
<tr>
<th>Days to read following vanco and pip-tazo initial administration</th>
<th>Platelet drop from admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>163</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>109</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
</tr>
</tbody>
</table>

Days to read following vanco and pip-tazo initial administration:

- Days to read following vanco and pip-tazo initial administration: 1.5 days to read following vanco and pip-tazo initial administration.
- Days to read following vanco and pip-tazo initial administration: 1 day to read following vanco and pip-tazo initial administration.

Platelet/White (5% drop from admission):

- Platelet count: 163
- Platelet drop from admission:
  - Days to read following vanco and pip-tazo initial administration:
    - Days to read following vanco and pip-tazo initial administration: 0 days to read following vanco and pip-tazo initial administration.
    - Days to read following vanco and pip-tazo initial administration: 1 day to read following vanco and pip-tazo initial administration.

Figure 1. Thrombocytopenia & Antibiotics on Multiple Admissions

- Figure 1. Thrombocytopenia & Antibiotics on Multiple Admissions:
  - Figure 1. Thrombocytopenia & Antibiotics on Multiple Admissions:
    - Initial platelet count: 163
    - Platelet drop from admission: 7
    - Platelet count: 109
    - Platelet count: 47

Figure 2. Method of Investigation

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    - Criteria 1a: Pip-tazo, vanco, and heparin products all preceded thrombocytopenia.
    - Criteria 1b: Thrombocytopenia resolved after discontinuation of vanco and pip-tazo in 3 admissions; however, on the 3/16/11 admission the thrombocytopenia improved after discontinuation of pip-tazo while vanco continued. On the 12/11/11 admission platelets declined after vanco was stopped and only recovered when pip-tazo was discontinued.
    - Criteria 2a: An extensive list of home medications was screened. Multiple home medications were continued throughout the admissions shown in figure 1 during the normalization of platelet count, thus exonerating them as the cause.
    - Criteria 2b: Thrombocytopenia resolved and remained normalized while heparin products were administered, while platelet count remained normal after discontinuation of suspected drug despite the resumption or continuation of other drugs.
    - Criteria 3a: Alternative etiologies of thrombocytopenia were excluded.
    - Criteria 3b: Re-exposure to the suspected drug was followed by thrombocytopenia.

Criteria for evaluating a causal relationship between a drug and thrombocytopenia:

1. Suspected drug administration preceded thrombocytopenia. Complete and sustained resolution of thrombocytopenia after suspected drug discontinued.
2. Platelet count remained normal after discontinuation of suspected drug despite the resumption or continuation of other drugs.
3. Alternative etiologies of thrombocytopenia were excluded.
4. Re-exposure to the suspected drug was followed by thrombocytopenia.

References

2. Doyle AC. The Sign of Four. Sherlock Holmes. 1891.

Discussion

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

After extensive investigation, the evidence points to DITP secondary to pip-tazo. DITP related to pip-tazo is exceedingly uncommon, accounting for 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. Despite the lack of serological confirmation, a diagnosis of pip-tazo-induced DITP can be made based on published clinical criteria. Our patient’s episodes of thrombocytopenia met all four of the criteria outlined by Russon et al. (figure 2) which constitutes “definitive” probability for drug-induced thrombocytopenia. Additional support is seen with the utilization of an adverse drug reaction (ADR) probability scale. This case scored 11 out of a possible 13 points, where a score of 9 is equated with a “definitive” 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 immunofluorescent flow cytometry at BCW. However, there are several limitations to this last; 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. Piperacillin is known to form metabolites which are not normally tested. BCW does not test separately for piperacillin and tazobactam. Antibody testing was negative on several tests; thus eliminating heparin as the causative factor.

Ultimately, there may be value in re-testing this patient for drug-induced antibodies at his next outpatient visit.

Abbreviations

- COPD: Chronic obstructive pulmonary disease
- LMWH: Low molecular weight heparin
- PEG: Percutaneous endoscopic gastrostomy
- PNA: Pneumococcal
- EColi PNA: E. coli Pneumococcal
- BCW: Blood Center of Wisconsin Platelet & Neutrophil Immunology Laboratory
- ASO: Antibody screening assay