3-24-2012

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

Spiro Khoury
University of Massachusetts Medical School, spiro.khoury@umassmemorial.org

Nicholas C. Watson
University of Massachusetts Medical School, nicholas.watson@umassmed.edu

Follow this and additional works at: http://escholarship.umassmed.edu/anesthesiology_pubs

Part of the Anesthesiology Commons

Repository Citation
http://escholarship.umassmed.edu/anesthesiology_pubs/116

This material is brought to you by eScholarship@UMMS. It has been accepted for inclusion in Anesthesiology Publications and Presentations by an authorized administrator of eScholarship@UMMS. For more information, please contact Lisa.Palmer@umassmed.edu.
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/\mu l. The causation is frequently multi-factorial 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 multi-step approach. We discuss the extensive workup of DITP in the context of this unusual case presentation.

Patient Presentation

This is a 66 year old male with PMH of severe COPD, atrial fibrillation, and lung cancer as/p two year period with COPD exacerbation and suspected pneumonia. 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 fall while 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.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission Notes</td>
<td>C/CPN, cultures negative, BP stable</td>
<td>C/CPN, cultures negative, BP stable</td>
<td>C/CPN, cultures negative, BP stable</td>
<td>C/CPN, cultures negative, BP stable</td>
</tr>
<tr>
<td>Initial Platelet Count</td>
<td>153</td>
<td>230</td>
<td>168</td>
<td>289</td>
</tr>
</tbody>
</table>

| Platelet/Admission (% drops from initial) | 45 (72) | 118 (52) | 47 (75) | 109 (83) |
| Days to readmit following vanco and pip-tazo initial administration | 0 | 7 | 5 | 1 |
| Pip-tazo continued for 1 day post admission before exposure to vanco and pip-tazo | 15% | 40% | 12% | 57% |
| Days to recovery baseline platelet count | 15 >15 >15 >7 |

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

Criteria for evaluating a causal relationship between a drug and thrombocytopenia:
1. Suspended 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.

Criteria 1. Vanco, pip-tazo, and heparin products all preceded thrombocytopenia.
Thrombocytopenia resolved after the discontinuation of vanco and pip-tazo in 3 admissions; however, on the 3/6/12 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 2. 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 exacerbating them as the cause. Thrombocytopenia resolved and remained normalized while heparin products were administered, while hirudin testing was negative on several tests, thus eliminating heparin as the causative factor.

Criteria 3. Any alternate etiology of thrombocytopenia would need to fit the time course of the acute drop in platelet counts shown in figure 1. Thus, many chronic and indolent causes of thrombocytopenia were eliminated from consideration. A number of potential etiologies remained that were excluded by logic and investigation.

Therapeutic Approach

Sepsis
Sepsis was either very mild or not present. Admissions during which he did not receive these antibiotics were not associated with thrombocytopenia.

Disseminated Intravascular Coagulation
No transfusions during critical platelet drops.

Thrombotic Thrombocytopenic Purpura
No transfusions during critical platelet drops.

Heparin-induced thrombocytopenia
No transfusions during critical platelet drops.

Potential Etiology
Excluded on basis of:

2. Potential Etiology1: Excluded on basis of:
   - Sepsis: Failed to meet criteria for two admissions. May explain for one drop in each of four admissions. Clinically unlikely to be the explanation as patient was not intentionally treated with antibiotics.
   - Disseminated Intravascular Coagulation: No transfusions during critical platelet drops.
   - Thrombotic Thrombocytopenic Purpura: No transfusions during critical platelet drops.
   - Heparin-induced thrombocytopenia: No transfusions during critical platelet drops.

Diagnosis of exclusion. ITP marked by chronically low platelets, not acute drops and recovery. Patient on steroids at baseline, which would very closely monitor platelet count if a suitable alternative is unavailable.

Potential Etiology

Sepsis
Sepsis was either very mild or not present. Admissions during which he did not receive these antibiotics were not associated with thrombocytopenia.

Disseminated Intravascular Coagulation
No transfusions during critical platelet drops.

Thrombotic Thrombocytopenic Purpura
No transfusions during critical platelet drops.

Heparin-induced thrombocytopenia
No transfusions during critical platelet drops.

Potential Etiology
Excluded on basis of:

2. Potential Etiology1: Excluded on basis of:
   - Sepsis: Failed to meet criteria for two admissions. May explain for one drop in each of four admissions. Clinically unlikely to be the explanation as patient was not intentionally treated with antibiotics.
   - Disseminated Intravascular Coagulation: No transfusions during critical platelet drops.
   - Thrombotic Thrombocytopenic Purpura: No transfusions during critical platelet drops.
   - Heparin-induced thrombocytopenia: No transfusions during critical platelet drops.

Diagnosis of exclusion. ITP marked by chronically low platelets, not acute drops and recovery. Patient on steroids at baseline, which would very closely monitor platelet count if a suitable alternative is unavailable.

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, appearing in only 3 case reports and in 13 patients specifically tested for antibodies at Blood Center of HI (BCR) 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 of the criteria outlined by Russon et al. (figure 2) which constitutes “definitive” probability for drug induced etiology. 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 BCR. 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. Piperacillin is known to form metabolites which are not normally tested. BCR does not routinely run a control sample along with a patient sample for piperacillin. 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 by BCR. 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. 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


Abbreviations

BCR: Blood Center of Wisconsin Platelet & Neutrophil Immunology Laboratory
IP: Intraperitoneal
PNA: pneumonia
BP: blood pressure
CA: cancer
COPD: chronic obstructive pulmonary disease
G-2: Gene 2
LTA: lipopolysaccharide
T: Tumor
SP: stable
CPN: cultures positive