2012-03-24

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

Spiro Khoury
University of Massachusetts Medical School

Et al.

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[1]. Thrombocytopenia is generally defined as a platelet count below 100,000/μl[1]. The causation is frequently multi-factorial and driven by six distinct mechanisms: increased consumption, hemodilution, decreased production, sequestration, pseudo-thrombocytopenia, and increased destruction[1]. 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[2]. Due to a lack of distinguishing clinical features and numerous other possible etiologies, diagnosis is often complex, requiring a multi-step approach[3]. 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 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 incident, 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:	3/28/10	4/17/11	12/11/11	3/6/12
Admission Notes	COPD exacerbation, ?PNA, cultures negative, BP stable	COPD exacerbation, eColi PNA, BP stable	COPD exacerbation, eColi PNA, BP stable	COPD exacerbation, ?PNA, cultures negative, BP stable
Initial Platelet Count	163	250	168	289
Platelet Nadir (% drop from initial)	45 (73%)	118 (52%)	47 (75%)	109 (63%)
Days to nadir following vanco and pip-tazo initial administration	6	7	5	1
1 day drop in platelet count after exposure to vanco and pip-tazo	18%	40%	12%	57%
Days to recovery to baseline platelet count	15	>15	>15	>7

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

Figure 1. Thrombocytopenia & Antibiotics on Multiple Admissions

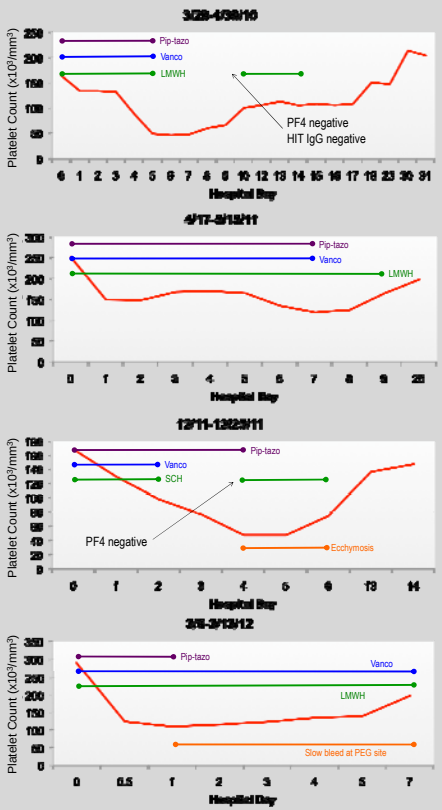

Figure 2. Method of Investigation

Criteria for evaluating a causal relationship between a drug and thrombocytopenia[4]:

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.

☑**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 exonerating them as the cause. Thrombocytopenia resolved and remained normalized while heparin products were administered, and HIT 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:

Potential Etiology[1]:	Excluded on basis of:
Sepsis	Failed to meet criteria for two admissions. Met sepsis criteria for one day on each of two admissions. Clinically unlikely to be explanation as sepsis was either very mild or not present.
Disseminated Intravascular Coagulation	No change in coagulation values on any admission, suspicion clinically low
Thrombotic Thrombocytopenic Purpura	Smears from each admission show no evidence of microangiopathic hemolysis; absence of anemia, hct stable during thrombocytopenia
Heparin-induced thrombocytopenia[5]	Multiple HIT tests negative on different admissions, eliminated HIT type II. HIT type I (non-immune mediated) would be unlikely to drop platelets below 100K and would be more transient than documented. Patient had 3 admissions without thrombocytopenia while receiving heparin (data not shown).
Dilution by fluid infusions	Magnitude and persistence of platelet drop too great. Platelet count dropped while hematocrit stabilized, which is not consistent with dilution.
Dilution by transfusions	No transfusions during critical platelet drops.
Sample clotting/ EDTA-induced clot	Platelet drop consistent across multiple samples at different times.
Bone marrow suppression	Could be caused by pip-tazo or vanco, but time course from meds to platelet drop likey too rapid to be explained by marrow suppression. No leukopenia or anemia on any admission.
Idiopathic Thrombocytopenic Purpura	Diagnosis of exclusion. ITP marked by chronically low platelets, not acute drops and recovery. Patient on steroids at baseline, which would be treatment for ITP if he had it.

☑**Criteria 4**. Re-exposure to vancomycin and to piperacillin-tazobactam was immediately followed by falling platelet count.

Discussion

"*…when you have eliminated the impossible, whatever remains, however improbable, must be the truth.*" Sherlock Holmes[6]

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[7-10]. Despite the lack of serological confirmation, a diagnosis of pip-tazo induced DITP can be made based on published clinical criteria[12]. 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[10]. Additional support is seen with the utilization of an adverse drug reaction (ADR) probability scale[11]. This case scored 11 out of a possible 13 points, where a score of ≥9 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 immunofluorescent 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 sample along with a patient sample for piperacillin[13]. 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[12]. 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

1. Hui P, Cook DJ, Fraser GA et al. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. Chest 2011;139:271-278.
2. George JN, Aster RH. Drug-induced thrombocytopenia: pathogenesis, evaluation, and management. Hematology Am Soc Hematol Educ Program. 2009:153–8.
3. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost. 2009;7(6):911-8.
4. George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: A systematic review of published case reports. Ann Intern Med 1998;129:886-890.
5. Franchini M. Heparin-induced thrombocytopenia: an update. Thromb Jour 2005;3:14.
6. Doyle AC. The Sign of Four. Filiquarian Publishing, LLC, Minneapolis, 2007.
7. Pérez-Vázquez A, Pastor JM, Riancho JA. Immune thrombocytopenia caused by piperacillin-tazobactam Clin Infect Dis. 1998 Sep;27(3):650-1.
8. Olivera E, Lakhani P, Watanakunakorn C. Isolated severe thrombocytopenia and bleeding caused by piperacillin. Scand J Infect Dis. 1992;24(6):815-7.
9. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, Vondracek T. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med. 1998 Dec 1;129(11):886-90.
10. Rousan TA, Aldous IT, Cowley BD Jr, Curtis BR, Bougie DW, Aster RH, George JN. Recurrent acute thrombocytopenia in the hospitalized patient: sepsis, DIC, HIT, or antibiotic-induced thrombocytopenia. Am J Hematol. 2010 Jan;85(1):71-4.
11. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions Clin Pharmacol Ther. 1981 Aug;30(2):239-45.
12. Reese JA, Li X, Hauben M, Aster RH, Bougie DW, Curtis BR, George JN, Vesely SK. Identifying drugs that cause acute thrombocytopenia: an analysis using 3 distinct methods Blood. 2010 Sep 23;116(12):2127-33. Epub 2010 Jun 8.
13. Curtis, Brian. Technical director of Platelet and Neutrophil Immunology Laboratory, Blood Center of Wisconsin. Personal Communication 3/8/12.

Abbreviations

BCW: Blood Center of Wisconsin Platelet & Neutrophil Immunology Laboratory
DITP: drug induced thrombocytopenia
ELISA: Enzyme Linked Immunosorbent Assay
PMH: Past medical history
PNA: pneumonia
COPD: Chronic Obstructive Pulmonary Disease
CA: Cancer
s/p: status post