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Streptococcus bovis Septic Shock Due to Contaminated Transfused Platelets

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Although most physicians and the public are primarily concerned about the risk of transmitting human immunodeficiency virus (HIV) or hepatitis virus during a platelet transfusion, bacterial contamination is actually the most common infectious complication. Unlike red blood cells, platelets are stored at room temperature (20–24°C), which raises the risk of bacterial proliferation. The risk of bacterial sepsis is 2.5-fold higher for each unit of transfused platelets compared to each unit of red blood cells. We report an unusual case of *Streptococcus bovis* septic shock associated with a contaminated platelet transfusion. Am. J. Hematol. 77:282–286, 2004. © 2004 Wiley-Liss, Inc.

Key words: platelet sepsis; *Streptococcus bovis*; platelet transfusion

INTRODUCTION

For over 30 years, platelet transfusion therapy has played a major role in the management of patients with hematologic and oncologic disorders [1]. However, platelet transfusion poses a serious risk of bacterial sepsis. In the United States from 1986 to 1991, 29 episodes of fatal transfusion-associated bacterial sepsis were reported to the Food and Drug Administration (FDA) [2]. Twenty-one of the 29 deaths were due to platelet contamination. The other eight deaths were due to contamination of red blood cells. The largest prospective study of transfusion-transmitted bacterial infection in the United States (BaCon study) indicates that the incidence of bacterial contamination of platelets ranges from 0.04% to 1.0% [3]. Unlike red cells, platelets are stored at room temperature for up to 5 days. This room-temperature storage potentially allows a single platelet-contaminating bacterium to rapidly multiply to more than 10^5 organisms [4]. An inoculation of *Staphylococcus epidermidis* into a unit of platelets can result in colony counts of 10^4/mL at 3 days and 10^8/mL at 6 days. Although the minimum concentration of bacteria required to cause clinical symptoms is unknown, concentrations of at least 10^8 colony forming units/mL have been associated with fatal reactions [5].

CASE REPORT

The patient is a 21-year-old woman with clinical stage IIAE intermediate grade non-Hodgkin's gastric lymphoma diagnosed 17 months prior to admission. The patient underwent six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and then had 5 weeks of adjuvant radiation therapy to the gastric bed that was completed 6 months prior to admission. For the following 6 months, the patient

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did well and had no symptoms or signs of lymphoma recurrence.

However, during a routine oncology follow-up appointment, the patient complained of a 2-month history of bruising that had been worsening over a week and gingival bleeding while brushing her teeth. A complete blood count showed white cells of 28,000/mm^3, a hematocrit of 27.3%, and platelets of 7,000/mm^3. The patient was admitted to the hospital for further evaluation and treatment of symptomatic severe thrombocytopenia. She underwent a bone marrow biopsy, which revealed a cellular marrow, with decreased megakaryocytes, a mild left shift in myeloid precursors, dysplastic erythroid precursors, and no evidence of lymphoma. The results of the bone marrow aspirate were consistent with a myelodysplastic syndrome. Because the patient had active oral mucosal bleeding and because she had a bleeding groin wound from a previously placed femoral venous catheter, the patient was transfused with 2 units of single-donor platelets obtained by apheresis, over a period of 1 hr and 40 min. Both apheresis units of platelets transfused into the patient were no more than 48 hr old. During the first platelet unit transfusion, the patient became hypotensive, with a blood pressure of 72/35 mmHg, 45 min after initiation of the transfusion. At the completion of the second unit of platelets, the patient developed a fever to 38.8°C. An hour and half after the second transfusion ended, the patient had temperatures up to 40°C, rigors, and persistent hypotension unresponsive to intravenous fluids. Her exam was significant for tachycardia up to 130 beats/min, normal arterial oxygen hemoglobin saturation, and clear lungs. Chest X ray showed mild diffuse interstitial infiltrates. Two sets of blood cultures were drawn, and it was noted that the patient's white blood cell count had increased to 42,000/mm^3.

The patient was transferred to the intensive care unit for blood pressure support, and she required intravenous phenylephrine up to 240 μg/min. She was empirically started on intravenous triple antibiotic therapy with piperacillin/tazobactam, vancomycin, and levofloxacin to cover for presumed septic shock of unknown source. The platelet bags and saline tubing used during the transfusion were sent to the microbiology laboratory. After the surface of each of the platelet bags was disinfected, the remaining contents from both platelet bags were aspirated, Gram stained, and cultured individually. The Gram stain of plasma from the first platelet bag showed copious Gram-positive cocci. On the following hospital day, all four blood cultures grew pan-sensitive *Streptococcus bovis*. Also, cultures obtained from the first platelet transfusion unit and associated intravenous tubing grew out pan-sensitive *S. bovis*. Cultures drawn from the sealed donor pack tubing segment of the first unit also grew *S. bovis*. However, cultures from the sealed donor pack tubing segment of the second unit were sterile.

The patient received 10 days of appropriate intravenous antibiotic therapy, and she was discharged to home on oral amoxicillin and levofloxacin for another 4 days. She has subsequently received multiple additional units of single-donor platelets obtained by apheresis without adverse reactions. The patient was diagnosed, 1 month after this admission, with chronic myelomonocytic leukemia (CMML) which rapidly evolved into acute myeloid leukemia (AML).

TRANSFUSION INVESTIGATION

An investigation of our patient's platelet transfusion-associated bacteremia revealed that the two platelet units were derived from different donors. The donor of the first unit was a man who felt completely well at the time of his donation. The culture results from the platelet bags and from the sealed donor-pack tubing segment of each platelet bag implicate the first donor as the source of platelet contamination. Every platelet unit has sealed donor-pack segments, which are a portion of the tubing originally connected to the donor during collection. This tubing, with its blood product contents, is subsequently sealed into segments immediately after donation. Therefore, as *S. bovis* was cultured from the sealed donor-pack segment of the first platelet unit and not the second platelet unit, the first platelet unit probably was the original source of contamination. Although the contamination may have occurred during either platelet collection or processing, the unusual nature of the organism makes it much more likely that this case represents platelet contamination originating in the blood donor. Two months prior to the donation, the donor had seen his primary care doctor for a routine physical exam. At that time, it was recommended that he undergo a colonoscopy due to his age and prior history of a colonic polyp. At colonoscopy, a benign polyp was found and removed. Following documentation of our patient's receipt of contaminated platelets, surveillance blood cultures were drawn from this donor, which were subsequently sterile. The platelet donor had actually donated 2 units of platelets. The second unit was infused into a patient at a nearby community hospital with no clinical evidence of bacterial sepsis.

DISCUSSION

We report an unusual case of *S. bovis* septicemia secondary to contaminated donor platelets. *S. bovis* bacteremia has been associated with endocarditis, colonic polyps and carcinomas, urinary tract infections,

and biliary and peritoneal infections [6]. However, *S. bovis* bacteremia has not previously been associated with platelet contamination.

Historically, platelets were originally stored at 4°C, primarily to decrease the risk of bacterial contamination and proliferation during their shelf-life. In 1969, Murphy and Gardner [7] demonstrated that platelet storage at 22°C led to improved in vivo viability and function as compared to storage at 13, 20, and 37°C. These observations led to the current practice of storing platelets at room temperature (20–24°C) for up to 5 days [8]. Initial reports by several authors in the 1970s suggested that bacterial contamination might not be a significant problem for platelets stored at room temperature [9]. However, subsequent authors have reported an incidence of platelet bacterial contamination ranging from 0.04% to 10% [3]. Under the current guidelines for 5-day platelet storage, a platelet unit inoculated with 10 to 10^3 bacterial organisms can have rapid proliferation to 10^8 organisms per mL prior to transfusion [10,11]. In order to increase the availability of platelets, the FDA increased allowable platelet storage time from 5 days to 7 days in 1983, but this extension was associated with increased reports of fatal transfusion reactions from bacterial contamination [12]. As a result, the allowable platelet storage time was decreased to 5 days in 1986 [12].

Bacterial contamination of platelets is now the most common infectious complication following transfusion. The reported risk of bacterial sepsis after transfusion of a unit of platelets is approximately 1:50,000 [13]. This compares with a bacterial sepsis risk of 1:500,000 per transfused unit of red blood cells [13]. The risk of platelet-associated transfusion sepsis is about 24-fold greater than the transmission risk for hepatitis C and 28-fold greater than the transmission risk for human immunodeficiency virus [14]. In addition, a marked discrepancy between the incidence of culture-positive platelet units (1:2,000) [15], and the reported incidence of clinical bacterial sepsis following platelet transfusions (about 1:50,000) suggests that many instances of platelet transfusion-associated sepsis may be unrecognized or underreported.

The three main postulated mechanisms of bacterial contamination of blood products are (1) use of nonsterile tubing and collection bags due to improper manufacturing, (2) bacteria derived from the donor's skin or blood, and (3) unsterile handling of platelets during preparation and/or storage [16]. We will focus primarily on the second postulated mechanism because this is believed to be the most common etiology of platelet bacterial contamination. Bacterial contamination is believed to occur most often during phlebotomy secondary to insufficient skin sterilization or from a small contaminated skin core entering the phlebotomy needle at time of venipuncture [17]. The most commonly isolated bacterial contaminants of platelet concentrates are skin saprophytes such as *Staphylococcus epidermidis* and *Bacillus cereus* [17]. However, organisms not normally part of the skin flora may colonize the skin and can be responsible for platelet-associated bacterial sepsis. A fatal case of *Clostridium perfringens* sepsis secondary to a pooled platelet transfusion was linked to a donor who routinely held his naked infant child in the crook of his arm while changing the child's diaper [18]. Also, unusual cases of *Salmonella* sepsis from platelet transfusions linked to asymptomatic bacteremic donors have been reported [8,19,20].

The clinical presentation of patients who have received platelets contaminated with bacteria is variable [5,17,21]. Patients may remain completely asymptomatic or may develop fever and chills as soon as 1–40 min after initiation of the transfusion. Septic shock may occur several hours after the transfusion. Other potential signs and symptoms include nausea, vomiting, diarrhea, dyspnea and wheezing, and bleeding secondary to disseminated intravascular coagulation. The variable clinical presentation is dependent on multiple factors such as the immune status of the patient, whether the patient is already on antibiotics during the transfusion, the number of bacteria infused, the virulence of the contaminating bacteria, and the presence of endotoxin [5,21]. Transfusion-associated bacteremic episodes can mimic febrile–nonhemolytic transfusion reactions (FNHTR). In addition, because many patients who receive platelet transfusions often are immunosuppressed or leukopenic, many physicians may easily attribute septic episodes in platelet recipients to causes unrelated to a platelet transfusion [21].

The possibility of transfusion-associated bacterial sepsis should be considered if a fever of at least 38°C, or a 1°C rise in temperature, rigors, chills, or hypotension occurs shortly after transfusion of blood products [17]. However, on rare occasions, fever and chills may develop hours after the transfusion. In contrast to our patient, the transfusion should immediately be stopped when either hypotension or fever is detected during a transfusion, and an investigation protocol (see U.S. Bacterial Contamination of Blood Products web site [22]) should be initiated. The reaction should automatically be reported to the hospital blood bank. The platelet bag and its contents should be returned to the blood bank for inspection of bag defects and for Gram stain and culture. The patient should have blood cultures drawn. Broad-spectrum antibiotics active against Gram-negative organisms as

well as Gram-positive organisms should empirically be started in severe reactions while awaiting results of the cultures. The blood supplier should also be notified of possible bacterial contamination in order to recall and culture blood components from the same donation to prevent further potential morbidity and mortality [23].

Various methods have been proposed to decrease the incidence of transfusion-associated bacterial infection [5,17]. These approaches include expanding the donor screening questionnaire [21,24], improving the disinfection process of donor venipuncture sites [21], discarding the first aliquot of collected donor blood [21], reducing platelet storage temperatures [21], decreasing the storage time of platelets [21], transfusing single-donor platelets rather than pooled platelet concentrates [21], instituting methods for pretransfusion detection of bacteria [17], and pathogen inactivation [25]. The efficacy and cost-effectiveness of many of these approaches have been disappointing or are still under investigation.

A study from New Zealand found that expanding screening questions was ineffective in identifying blood donors harboring *Yersinia enterocolitica* [24]. Reducing platelet storage time to 3 days would likely decrease the prevalence of transfusion-associated sepsis, but this would also reduce the national platelet supply due to wastage [12]. The use of single-donor platelets rather than pooled platelet concentrates has not consistently shown to decrease the incidence of septic platelet transfusion reactions [3]. Gram staining, prestorage cultures, pH testing, and measurement of glucose levels have all been proposed to detect the presence of bacteria prior to transfusion [17], but none of these procedures is universally performed. However, beginning March 1, 2004, all platelets are being tested for bacterial contamination prior to transfusion, as required by both the College of American Pathologists and the Standards of the American Association of Blood Banks. Several strategies of pathogen inactivation with photodynamic or photochemical methods have shown some promising results, but none has to date been approved by the FDA [25].

In summary, platelet-transfusion-associated bacterial sepsis is now the most frequent infectious complication of transfusion medicine. It is likely underreported, and it is a serious cause of morbidity and mortality in transfusion medicine. As patients at greatest risk for this complication are often immunocompromised, it is important for clinicians to consider blood product transfusions, especially platelet transfusions, as a potential source of sepsis. However, the most important strategy to prevent transfusion-associated bacterial sepsis is to transfuse only when medically necessary. In addition, it is equally important to stop and not re-start transfusion when febrile and hypotensive reactions occur. Confirmed cases need to be reported to the hospital blood bank and relevant blood-processing center and to the Investigations and Prevention Branch, Hospital Infections Program, A-07, Centers for Disease Control and Prevention [5]. Fatalities must also be reported to the Food and Drug Administration [5]. Increased awareness of such reactions and rapid diagnosis would not only benefit the recipient of the bacterially contaminated blood product but may also benefit the donor and potential recipients of other blood products obtained from the donor. The promising role of pathogen inactivation and the new requirements to test for bacterial contamination prior to transfusion may well result in a decreased incidence of platelet-transfusion-associated sepsis in the future [25].

REFERENCES

1. Pisciotto PT, Benson K, Hume H, et al. Prophylactic versus therapeutic platelet transfusion practices in hematology and/or oncology patients. Transfusion 1995;35:498–502.
2. Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. Transfusion 1990;30:583–590.
3. Kuehnert MJ, Roth VR, Haley NR, et al. Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. Transfusion 2001;41:1493–1499.
4. Jacobs MR, Palavecino E, Yomtovian R. Don't bug me: the problem of bacterial contamination of blood components—challenges and solutions. Transfusion 2001;41:1331–1334.
5. Krishnan LG, Brecher ME. Transfusion-transmitted bacterial infection. Hematol Oncol Clin North Am 1995;9(1):167–185.
6. Siegman-Igra R, Schwartz D. Streptococcus bovis revisited: a clinical review of 81 bacteremic episodes, paying special attention to emerging antibiotic resistance. Scand J Infect Dis 2003;35: 90–93.
7. Murphy S, Gardner FH. Effect of storage temperature on maintenance of platelet viability—deleterious effect of refrigerated storage. N Engl J Med 1969;280:1094–1098.
8. Heal JM, Jones ME, Forey J, et al. Fatal *Salmonella* septicemia after platelet transfusion. Transfusion 1987;27:2–5.
9. Katz AJ, Tilton RC. Sterility of platelet concentrates stored at 25°C. Transfusion 1970;10:329–330.
10. Punsalang A, Heal JM, Murphy PJ. Growth of Gram-positive and Gram-negative bacteria in platelet concentrates. Transfusion 1989; 29:596–599.
11. Heal JM, Singal S, Sardisco E, Mayer T. Bacterial proliferation in platelet concentrates. Transfusion 1986;26:391–393.
12. Morrow JF, Braine HG, Kickler TS, et al. Septic reactions to platelet transfusions. A persistent problem. J Am Med Assoc 1991; 266:555–558.
13. Blajchman MA. Incidence and significance of the bacterial contamination of blood components. Dev Biol (Basel) 2002;108:59–67.
14. Strong D, Katz L. Blood-bank testing for infectious diseases: how safe is blood transfusion? Trends Mol Med 2002;8(7):355–358.
15. Reading FC, Brecher ME. Transfusion-related bacterial sepsis. Curr Opin Hematol 2001;8:380–386.
16. Hogman CF, Engstrand L. Serious bacterial complications from blood components—how do they occur? Transfus Med 1998;8(1): 1–3.

17. Goldman M, Blajchman MA. Bacterial contamination of platelets. In: Seghatchian J, Snyder EL, Krailadsiri P, editors. Platelet therapy. Current status and future trends. Amsterdam, The Netherlands: Elsevier Science B.V.; 2000. p 401–414.
18. McDonald CP, Hartlet S, Orchard K, et al. Fatal *Clostridium perfringens* sepsis from a pooled platelet transfusion. Transfus Med 1998;8:19–22.
19. Rhame FS, Root RK, MacLowry JD, Dadisman TA, Bennett JV. *Salmonella* septicemia from platelet transfusions: study of an outbreak traced to a hematogenous carrier of *Salmonella choleraesuis*. Ann Intern Med 1973;78:633–641.
20. Jafari M, Forsberg J, Gilcher RO, et al. *Salmonella* sepsis caused by a platelet transfusion from a donor with a pet snake. N Engl J Med 2002;347(14):1075–1078.
21. Blajchman MA, Goldman M. Bacterial contamination of platelet concentrates: incidence, significance, and prevention. Semin Hematol 2001;38(Suppl 11):20–26.
22. U.S. Bacterial Contamination of Blood Products (BaCon) website: www.cdc.gov/ncidod/hip/bacon
23. Heltberg O, Skov F, Gerner-Smidt P, et al. Nosocomial epidemic of *Serratia marcescens* septicemia ascribed to contaminated blood transfusion bags. Transfusion 1993;33:221–227.
24. Grossman BJ, Kollins P, Lau PM, et al. Screening blood donors for gastrointestinal illness: a strategy to eliminate carriers of *Yersinia enterocolitica*. Transfusion 1991;31:500–501.
25. Corash L. New technologies for the inactivation of infectious pathogens in cellular blood components and the development of platelet substitutes. Baillieres Best Pract Res Clin Haematol 2000;13(4):549–563.