Post-Transfusion Purpura: A Challenging Diagnosis

Mordechai Shtalrid MD[1], Lev Shvidel MD[1], Eljakim Vorst[1], Eran E. Weinmann MD[3], Alain Berrebi MD[1] and Erica Sigler MD[1,2]

[1]Hematology Institute, [2]Blood Bank and [3]Department of Vascular Surgery, Kaplan Medical Center, Rehovot, Israel
Affiliated to Hebrew University-Hadassah Medical School, Jerusalem, Israel

Key words: post-transfusion purpura, HPA antibodies, human platelet antigen, thrombocytopenia

Abstract

Background: Post-transfusion purpura is a rare syndrome characterized by severe thrombocytopenia and bleeding caused by alloimunization to human platelet specific antigens following a blood component transfusion. The suggested incidence is 1:50,000–100,000 transfusions, most often occurring in multiparous women. The diagnosis is not easy because these patients, who are often critically ill or post-surgery, have alternative explanations for thrombocytopenia such as infection, drugs, etc.

Objectives: To describe patients with initially misdiagnosed PTP and to emphasize the diagnostic pitfalls of this disorder.

Patients and Results: During a period of 11 years we diagnosed six patients with PTP, four women and two men. The incidence of PTP was approximately 1:24,000 blood components transfused. We present the detailed clinical course of three of the six patients in whom the diagnosis was particularly challenging. The patients were initially misdiagnosed as having heparin-induced thrombocytopenia, systemic lupus erythematosus complicated by autoimmune thrombocytopenia, and disseminated intravascular coagulation. A history of recent blood transfusion raised the suspicion of PTP and the diagnosis was confirmed by appropriate laboratory workup.

Conclusions: PTP seems to be more frequent than previously described. The diagnosis should be considered in the evaluation of life-threatening thrombocytopenia in both men and women with a recent history of blood transfusion.

IMAJ 2006;8:672–674

For Editorial see page 709

Post-transfusion purpura is a rare acquired thrombocytopenia that occurs 7–14 days after transfusion of blood products. The affected patients produce alloantibodies against transfused platelet antigens, which paradoxically destroy their own platelets – negative for the antigen concerned [1,2]. The exact incidence of the disease is not known, but has been estimated to occur in 1:50,000–100,000 transfusions [2]. The typical patient is a middle-aged multiparous female, although PTP has also been reported, albeit rarely, in men. The majority of reported cases (90%) involve anti-HPA-1a antibodies in a homozygous HPA-1b patient. Occasionally the offending antibodies are directed against HPA-1b, 3a, 3b, 4a, 5a and 5b. The clinical course of PTP may be severe with a mortality rate of 10–20%. In particular cases, concurrently occurring diseases – such as infection, disseminated intravascular coagulation, autoimmune disorder – or heparin therapy could eventually produce severe thrombocytopenia and the diagnosis of PTP may therefore be temporarily ignored. The history of blood transfusion, the appropriate hiatus time until the appearance of thrombocytopenia, and its severity, must alert the physician to the correct diagnosis. Nonetheless, the final diagnosis is based on identification of antibodies against HPA not present on the patient's platelets. Laboratory workup includes detection of such antibodies and platelet genotyping.

PTP = post-transfusion purpura
HPA = human platelet antigen

Patients and Methods

During a period of 11 years (1994–2004) we diagnosed six patients with PTP, four women and two men. Platelet antibodies identification was performed using a solid-phase commercially available enzyme-linked immunosorbent assay (PakPlus, GTI, Brookfield, WI, USA). Platelet genotyping was performed by polymerase chain reaction as previously described [3]. Anti-heparin/PF4 antibodies were tested by a particle gel immunoassay according to the manufacturer's instructions (DiaMed SA, Cressier sur Morat, Switzerland).

Results

In our hospital approximately 13,000 units of blood components are transfused annually, so the frequency of PTP was 1:24,000 units. The antibody specificity and clinical characteristics of all the patients are depicted in Table 1. Five patients recovered after adequate therapy but patient no. 6 died of intracerebral hemorrhage despite therapy. In three patients PTP was initially misdiagnosed and their detailed clinical course is presented.

Patient 1

A 60 year old multiparous woman was hospitalized because of generalized purpura. The patient had been followed for 3 years in the nephrology department for progressive renal failure. Thirteen

Table 1. Clinical and laboratory features of the patients

Age / Gender	Platelet nadir x10^9/L	Differential diagnosis	Anti-platelet antibody	Platelet genotype	Therapy	Outcome
60 / F	5	HIT	Anti HPA-3b	HPA-3a/a	IVIG steroids	Recovered
71 / M	4	DIC	Anti HPA-1a Anti-HLA	HPA-1b/b	IVIG	Recovered from thrombocytopenia. Died of sepsis
54/ F	15	SLE, Evans syndrome	Anti HPA-3a Anti-HLA	HPA-1a/a HPA-3b/b HPA-5a/a	IVIG steroids	Recovered
50 / F	12	–	Anti HPA-1a	HPA-1b/1b	IVIG	Recovered
79 / M	10	–	Anti HPA-1a	HPA-1b/1b	IVIG	Recovered
74 / F	15	–	Anti HPA-1b	HPA-1a/1a	IVIG steroids	Died from hemorrhagic stroke

days before admission she received one unit of packed red cells, and a week before admission hemodialysis was started (including heparin anticoagulation). Physical examination revealed bleeding around the dialysis catheter, rectal hemorrhage, and extensive purpura and hematomas all over the skin and tongue. Blood tests showed hemoglobin 8.0 g/dl, white blood cells 4.7x10^9/L, platelets 5x10^9/L and serum creatinine 4.4 mg/dl. Prothrombin time, partial thromboplastin time, fibrinogen and D-dimer levels were within the normal range. Bone marrow examination revealed an increased number of megakaryocytes. Heparin-induced thrombocytopenia was suspected initially; however, the history of recent blood transfusion and the severity of thrombocytopenia and bleeding suggested the correct diagnosis. Heparin-induced platelet antibodies test was negative as well. Intravenous treatment with high dose immunoglobulin 0.4 g/kg/day for 5 days was started immediately. On the following day the presence of anti-HPA-3b antibodies was detected in the patient's serum. Platelet genotyping revealed HPA-1a/1a, HPA-3a/3a, HPA-5a/5a. The number of platelets started increasing after 3 days of treatment and reached normal levels in a week.

Patient 2

A 71 year old man was admitted because of an ischemic right foot. Three years earlier he had undergone a below-the-knee amputation of the left foot and aorto-bifemoral bypass and then received a blood transfusion. Because of the occlusion of the bypass, an axillo-bifemoral bypass was performed during the present hospitalization and two units of red packed cells were given. Gastrointestinal bleeding, bronchopneumonia and sepsis complicated the postoperative period. The platelet count abruptly decreased from 150x10^9/L to 10x10^9/L nine days after surgery. Blood tests revealed prothrombin time 17 seconds (control 12 seconds), partial thromboplastin time 35 seconds (control 27.9 seconds), fibrinogen level 205 mg/dl (normal 200–400 mg/dl), and D-dimer level 48.13 µg/ml (normal 0–0.5 µg/ml). Cultures of secretions from the right inguinal surgical wound and blood showed growth of E*nterobacter cloacae*, P*seudomonas aeruginosa* and K*lebsiella pneumoniae*. The diagnosis of DIC was made. Broad-spectrum antibiotic therapy, 3 units of fresh frozen plasma and 6 units of random donor platelets were administered. The platelet count further decreased to 4x10^9/L. PTP was suspected due to the recent blood transfusion, the very low platelet count and increment failure after platelet infusion. The patient was given IVIG 2 g/kg, resulting in normalization of the platelet count. However, his clinical condition deteriorated because of infection, and the patient died 1 month later of septic shock. An antibody with strong reactivity to HPA-1b along with an antibody with weaker activity against HLA class I antigens were found in the serum. The genotype of the patient's platelets was HPA-1a/1a.

Patient 3

A 54 year old multiparous woman was admitted for investigation of a prolonged fever. She had a previous history of systemic lupus erythematosus and autoimmune hemolytic anemia successfully treated with prednisone and blood transfusions 4 years earlier, and mitral valve replacement for mitral insufficiency. At the present admission hemoglobin was 13.0 g/dl, the direct Coombs' test was positive for anti-IgG and -C3d antisera, and indirect Coombs' test was negative; no clinical and laboratory signs of hemolysis were found. S*treptococcus viridans* grew on blood culture, and therapy with penicillin and gentamicin was initiated. After a week of treatment, hemoglobin suddenly dropped to 5.0 g/dl and the reticulocytes and indirect bilirubin rose to 4% and 3 mg/dl, respectively. Although penicillin-dependent red blood cell antibody test was negative, antibiotic therapy was changed to ceftriaxone, and two red blood cell units were transfused. A week later the platelet count dropped to 15x10^9/L. A bone marrow aspirate was normal. Therapy with IVIG 2 g/kg and prednisone 80 mg/day was started for suspected Evans syndrome complicating SLE. The platelet count rose to 56x10^9/L after 3 days and to 168x10^9/L after 7 days. Antibodies against HPA-3a were detected, along with anti-HLA class-1, confirming the diagnosis of PTP. The platelet genotype was: HPA-1a/a, HPA-3b/b, HPA-5a/a.

Discussion

We have described the clinical course of three patients with a challenging diagnosis of PTP. This condition appears in patients pre-exposed to foreign platelet-specific antigens by pregnancy or blood transfusion, and develops following a booster of incompatible platelets by producing high titer anti-HPA antibodies. These antibodies paradoxically destroy recipient platelets. Several mechanisms have been proposed to explain the destruction of the patients' own platelets along with transfused platelets: adsorption of antigen-antibody complexes, cross-reactive antibodies, or autoantibodies production [1,4]. The majority of PTP cases occur in patients with HPA-1b/b genotype producing anti-HPA-1a antibodies after transfusion of HPA 1a antigen; occasionally ex-

DIC = disseminated intravascular coagulation
IVIG = intravenous immunoglobulin
SLE = systemic lupus erythematosus

posure to other platelet antigens induces the disease. More than one species of platelet-specific antibodies may be implicated in rare cases of PTP [5].

Although 1.5% of the population has HPA-1b/b genotype and about 2% of transfused patients are at risk for PTP, the disorder is exceedingly rare – approximately 200 cases have been described in the literature [6]. The previously reported incidence of PTP is 1 case to 50,000–100,000 units of transfused blood components [2]. In our experience, the incidence is at least twice as high, raising concern for many misdiagnosed cases. The occurrence of PTP is not predictable and seems to be dependent on genetic HLA-linked capacity to form antibodies. It has been reported that patients who develop anti-HPA-1a have an increased incidence of HLA-B8, HLA-DRB3*0101, and HLA-DQB1*0201 genotype [5]. The platelet-specific antibodies detected in all our patients were anti-HPA-1a in two patients, anti-HPA-1b in two patients, anti-HPA-3a in one and anti-HPA-3b in one [Table 1]. Anti-HLA antibodies were also detected in two patients.

Despite the dramatic clinical presentation of extensive bleeding due to a low number of platelets, PTP is a self-limited disorder. However, because of the high fatality rate of about 10–20% early in the course of the disease, correct diagnosis and immediate treatment are essential. The treatment of choice is immunomodulation by administration of IVIG in a 2 g/kg dose with or without corticosteroids. A second modality is to remove antibodies by plasmapheresis or plasma exchange. Although some published reports suggest that patients do not respond to platelet transfusions, in rare cases of life-threatening hemorrhage, transfusion of platelets lacking the "guilty antigen" may temporarily increase the platelet number, stop the bleeding and save life [7]. Registries of HPA-1a-negative donors were established to limit future antigen-specific reactions.

We have reported three patients with PTP who were initially misdiagnosed. In the first case, severe thrombocytopenia appeared a week after administration of heparin during hemodialysis, so HIT was suspected. However, the very low platelet count, lack of thrombotic complication and anamnesis of recent blood transfusion led us to the correct diagnosis, appropriate treatment and prompt recovery. The differential diagnosis between HIT and PTP was discussed by Lubenow et al. [6]. According to their experience, patients with PTP are characterized by a very low platelet count (< $15x10^9$/L) with severe hemorrhagic symptoms, while patients with HIT have higher platelet counts (usually > $20x10^9$/L) and may develop thromboembolic complications; a cutoff of $15x10^9$/L and a different clinical presentation may help to distinguish between these two syndromes [8,9]. However, the differential diagnosis between PTP and HIT on clinical grounds alone is still difficult in cases with isolated thrombocytopenia, therefore screening tests for platelet-specific antibodies and platelet genotype are required. In severe cases it is indicated to start treatment with IVIG even before laboratory confirmation has been received.

HIT = heparin-induced thrombocytopenia

Although PTP is mainly found in multiparous women, the second patient was a male. This patient revealed laboratory signs of DIC but the number of platelets returned to normal only after infusion of high dose IVIG. A similar case report described a woman with consumptive coagulopathy who developed PTP after a transfusion of plasma [9]. She recovered after antithrombotic and fibrinolysis inhibitor therapy together with methylprednisolone, IVIG and plasma exchange. The third patient had a previous diagnosis of SLE and autoimmune hemolytic anemia. The acute hemolytic episode and subsequent thrombocytopenia were initially diagnosed as Evans syndrome. The patient received IVIG and corticosteroids therapy, fortunately effective in both disorders, and recovered.

In conclusion, because of the possible pitfalls in diagnosis, we assume that PTP might be an under-diagnosed condition. The cases reported emphasize the importance of being alert to the possibility of PTP, in an appropriate clinical setting, in women as in men, and that misdiagnosis of this syndrome might lead to the wrong treatment and a fatal outcome.

Acknowledgment. The authors thank Vered Yahalom MD of the Magen David Adom Blood Center (Sheba Medical Center, Tel Hashomer), for performing the platelet antibodies test, and Rima Dardik PhD of the Institute of Thrombosis and Hemostasis (Sheba Medical Center), for the platelet genotyping.

References

1. Rozman P. Platelet antigens. The role of human platelet alloantigens (HPA) in blood transfusion and transplantation. *Transpl Immunol* 2002;10:165–8.
2. Metcalfe P. Platelet antigens and antibody detection. *Vox Sang* 2004;87(s1):82–6.
3. Ficko T, Galvani V, Rupreht R, Dovc T, Rozman P. Real-time PCR genotyping of human platelet alloantigens HPA-1, HPA-2, HPA-3 and HPA-5 is superior to the standard PCR-SSP method. *Transfus Med* 2004;14:425–32.
4. Taaning E, Tonnesen F. Pan-reactive platelets antibodies in post-transfusion purpura. *Vox Sang* 1999;76:120–3.
5. Lucas GF, Pittman SJ, Davies S, Solanki T, Bruggemann K. Post-transfusion purpura (PTP) associated with anti-HPA-1a, anti-HPA-2b and anti-HPA-3a antibodies. *Transfus Med* 1997;7:295–9.
6. Lubenow N, Eichler P, Albrecht D, et al. Very low platelet counts in post-transfusion purpura falsely diagnosed as heparin-induced thrombocytopenia. Report of four cases and review of literature. *Thromb Res* 2000;100:115–25.
7. Loren AW, Abrams CS. Efficacy of HPA-1a (Pl^{A1})-negative platelets in a patient with post transfusion purpura. *Am J Hematol* 2004;76:258–62.
8. Araujo F, Sa JJ, Araujo V, Lopes M, Cunha-Ribeiro LM. Post-transfusion purpura vs. heparin-induced thrombocytopenia: differential diagnosis in clinical practice. *Transfus Med* 2000;10:323–4.
9. Welling KL, Taaning E, Lund BV, Rosenkvist J, Heslet L. Post-transfusion purpura (PTP) and disseminated intravascular coagulation (DIC). *Eur J Haematol* 2003;71:68–71.

Correspondence: Dr. E. Sigler, Blood Bank, Kaplan Medical Center, Rehovot 76100, Israel.
Phone: (972-8) 944-1577
Fax: (972-8) 944-1706
email: levsh@clalit.org.il