Current Understanding of Post Transfusion Purpura: A Systematic Review.

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Abstract: Post-transfusion purpura (PTP) is an adverse reaction to a blood transfusion or platelet transfusion that occurs when the body produces alloantibodies to the introduced platelets' antigens. These alloantibodies destroy the patient's platelets leading to thrombocytopenia, a rapid decline in platelet count. PTP usually presents 5–12 days after transfusion, and is a potentially fatal condition. Though, It is rare, it has significant mortality rate. Alloimmunization is the main pathological mechanism of platelet destruction but autoimmunization process also happens. It should be kept in mind as a differential diagnosis in any patient presenting with thrombocytopenia, especially after transfusion. In this review article, we are focusing on describing one of very rare but yet, a serious complication of blood transfusion and proposing a new scheme of diagnosis which needs to be further studied in a big multicenter trial to prove its efficacy.

[Mohammed Albalawi, Mohammed Zolaly, Nawaf Alkhayat, Omer Al Sharif , Ghaleb Elyamany. **Current Understanding of Post Transfusion Purpura: A Systematic Review.** *J Am Sci* 2015;11(10):146-151]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 14. doi:10.7537/marsjas111015.14.

Keywords: thrombocytopenia, transfusion reactions, post transfusion purpura

Introduction

Post-transfusion purpura (PTP) is a rare but serious complication of blood transfusion, characterised by the sudden onset of severe thrombocytopenia within 5-10 days of transfusion of blood products. PTP was first reported in 1961 by Shuman *et al.* [1]. The exact incidence of the disease is unknown, but it is approximately occurring in 1:50,000–100,000 transfusions. PTP occurs primarily in women sensitized by pregnancy; the female-to-male ratio of the approximately 250 reported cases is 26:1. Blood components containing platelets, such as whole blood, red cells in additive solution, red cell concentrates and platelet concentrates have been implicated.

Post Transfusion Reactions are common; it is classified to acute and delayed reactions. It also can be classified as immunological and non-immunological reactions (Table 1). Underestimation of transfusion reactions is an important issue. This is usually because of many causes including overutilization and easily accessibility to blood products, lack of hospital-based policies for blood utilization in some hospitals and lack of awareness of such complications are other main causes. Transfusion reactions' are underreported by most clinicians.

Most references define PTP as a delayed reaction that occur within 1-2 weeks post transfusion with severe thrombocytopenia (platelets count below 20,000/μL). [1- 5]. There is no general consensus about the time of thrombocytopenia as PTP can occur after 24-hours of receiving blood components and this can occur up to 2-3 weeks. The degree of thrombocytopenia is variable as patients can have platelets count more than 10,000/μL and still have PTP. Thrombocytopenia in PTP can last for five weeks. (2). The literature reviews are very limited but are reporting PTP to be more common in women compared to men having significant morbidity and mortality in both sex. (1-6)

This is a systematic review of PTP and its clinical presentation to have a clear clinical path for its diagnosis and increase awareness among treating physicians for early diagnosis and management as appropriate treatment should be started as soon as a clinical diagnosis of PTP is made without waiting for the results of laboratory investigations.

Clinical manifestations

PTP is a rare cause of severe thrombocytopenia and purpuric skin rash that usually occurs 1 week after transfusion of blood products. (1- 3). Typical patients are multiparous women or male patients who had frequent history of transfusions. They can present any time post transfusion but usually from day 3 to 24, most commonly presenting between days 5-10. [1, 2, 7]. They present with thrombocytopenia and purpuric skin rash which is defined as small (less than 1 cm in diameter) purple to red color, raised skin spots that do not blanch away on pressure (figure 1). They can present with bleeding symptoms due to severe thrombocytopenia from any site but usually from mucous membranes. They can have CNS bleeding

which is the cause of high mortality rate in such patients reaching 10-20% [1, 2].

Pathogenesis

There are more than 33 platelet's antigens have been identified. Most of these antigens are located on glycoprotein complexes and are implicated in alloimmune platelet reactions. These antigens of platelet are classified to two types according to their specificity to platelets. Their expression on platelet surface is variable as some have high frequency and others have low frequency. Platelets also express other non-specific antigens including red blood cell antigens (ABO) and human leukocyte antigens (HLA) [2].

Platelet specific antigens are shown in (Table 2), which are considered to be the cornerstone of alloimmunization process. Human Platelet Antigen (HPA-1a) has a frequency of 97% in Caucasian population [1, 2, 4]. The antigen most commonly implicated is the platelet antigen PlA1, now known as human platelet antigen 1a, (HPA-1a) [7]. Non-specific platelet antigens are shared by other hematological cell lines and are important in platelet refractoriness and life span of post platelet transfusion. [2, 4, 5]

The mechanism of platelets destruction is related to platelet antigen/s antibody/s interactions (alloimmunization). Multiparous women or Patients with specific HPA who are receiving different HPA will produce an antibody against foreign HPA (Alloimmunization). These antibody will cross-react with patient own platelets and destroy them. The most common scenario is a patient with HPA-1b platelet who is receiving HPA-1a platelets. Such patient will develop antibodies against HPA-1a and upon re-exposure will develop anamnestic reaction against patient own platelets and consequently develop PTP. [7-15]

There are also different theories to support autoimmune destruction. These theories based either on soluble platelet specific antigen in donor plasma and platelet antibody in the patient, development of autoantibody on exposure to incompatible platelet antigen and soluble platelet antigen in donor plasma adsorbs to the recipient's platelet. [7-15]

Leucodepletion of whole blood reduces contaminating platelets by 100-fold[6] and in buffy-coat depleted and filtered red cell components, platelets are undetectable

Laboratory tests

Unexpected thrombocytopenia in a patient who had received a transfusion of a cellular blood component within the previous 2 weeks should be investigated for PTP.

In addition to severe thrombocytopenia, these patients will have no evidence of hemolysis and normal coagulation profile. Detection of the anti HPA in their serum is the only confirmatory test for the diagnosis.

Anti HPA antibodies can be detected in patient serum by platelet immuno-flourescence test (PIFT), immobilization of the platelets antigens with monoclonal antibodies (MAIPA assay), solid-phase red cell adherence assay, Flow cytometry. Flow cytometry technique has shown to be more sensitive compared to others. Few monoclonal antibodies against HPA antigens have been produced. Such antibodies have both diagnostic and potential therapeutic applications. [7-15]

In most cases, combination of tests is required to increase the sensitivity reaching the diagnosis but unfortunately, only few laboratories have these tests. Differential diagnoses should include other causes of thrombocytopenia (Table 3). History of recent heparin use as well as thrombosis rather than bleeding is probably suggestive of heparin-induced thrombocytopenia. History of infection and sepsis as well as abnormal coagulation profile may favor the diagnosis of disseminated intravascular coagulation while evidence of hemolysis is suggestive of other differential diagnoses as Thrombotic Thrombocytopenic Purpura however the history of recent blood transfusion is very important supporting point in establishing the diagnosis. [1, 4].

The laboratory tests to support and confirm the diagnosis are not available in in many laboratories and sending samples to advanced laboratories has some difficulties and time consuming. Another important factor is the rarity of the disease and the limited number of patients. For such reasons an algorithm is developed to help in diagnosing patient with PTP (figure 2) which is a clinical and laboratory approach as PTP is a diagnosis of exclusion especially in conditions of difficult accessibility to a confirmatory test.

A scoring system to categorize those patients into low, intermediate and high-risk categories based on combination of indicators is developed (Table 4). The scoring system is planned to be studied in a multi-center trial involving different hospitals in the Kingdom to prove efficacy and validity before it can be applied in clinical practice.

Management

PTP is a clinicopathological diagnosis. However, diagnosis should depend on clinical criteria, as the confirmatory test is not widely available and takes long time to be confirmed. Good history taking is very important initial step in management of such complication as it will rule out other causes of thrombocytopenia. It is very important to keep PTP in mind as a differential diagnosis in any patient presenting with thrombocytopenia post transfusion.

Treatment depends on the patient's presentation as it could vary from only observing patient with no bleeding to applying invasive interventions as plasma exchange in few cases. Intra-Venous Immuno-Globulin (IVIG) is considered to be the first line treatment in most patients given at a dose of 2 g/kg over 2 days or in split fractions over 5 days [2, 12, 13]. Other modalities of treatment include the usage of Steroids which is still controversial and the usage of plasma exchange which is shown to be effective in some published case reports [16].

The infusion of PlA1-negative platelets is generally not effective during the acute episode, because most platelets (ie, even antigen-negative platelets) are destroyed [17]. However, multiple platelet transfusions may be required in severe cases of bleeding to achieve a good increment in platelet count [2,13,15]. Preferably transfusion with antigen-negative platelets if available should be used in such patient especially in life threatening bleeds [14, 15, 16]. HPA-1a-negative patients diagnosed with PTP who require subsequent transfusion should receive only HPA-1a-negative blood products. Acceptable alternatives include red blood cells that are washed to remove contaminating HPA-1a-positive platelets and/or products from HPA-1a-negative donors [18] However, for patients who require a transfusion in the acute setting, avoidance of HPA-1a-positive components is prudent because it will limit the exposure to immunogenic antigens and may prevent additional allosensitization. During the recovery phase of severe thrombocytopenia, the platelet count of the patient should be closely monitored until normal levels are reached because of the possibility of rebound thrombocytopenia. A summary of PTP important clinical, laboratory manifestations and management are shown in (Table 5).

Table 1: Transfusion complications

Acute (Occur within 24 hours of transfusion)	Delayed (more than 24 hours after transfusion)
• Febrile non-hemolytic transfusion reaction	Alloimmunization •Red Cell Antigens •HLA •Leukocytes •Platelets
• Allergic reaction: Minor	•Graft versus host disease (TA-GVHD)
• Allergic reaction: Anaphylactic	•Post-transfusion purpura (PTP)
• Transfusion-associated circulatory overload (TACO)	•Hemosiderosis
• Acute hemolytic transfusion reaction	•Viral and parasitic infections
• Transfusion-related acute lung injury (TRALI)	•Transfusion-related immunomodulation (TRIM)

(Table 2): Platelet specific antigen & clinical significances.

Platelet-Specific Antigen	HPA-Nomenclature	Function	Clinical- Significance
GPIIb/III3a	HPA-1(a/b),3(a/b),4,6*,7*,8*,9* (a/b),10*,11*,14*,16*	Adhesion to fibrinogen & vWF	NAIT& PTP
GPIa/IIa	HPA-5(a/b),13*	Adhesion to collagen	NAIT
GP1b-IX-V	HPA-2* (a/b),12*	vWF receptor	NAIT
CD109	HPA-15(a/b)(Gov(a/b))	PI-membrane bound GP	Rare NAIT & PTP

* Associated with NAIT mainly

HPA: Human Platelet Antigen, vWF: Von Willebrand Factor, PI: Phosphoinositol, GP: Glycoprotein, PTP: Post-Transfusion Purpura, NAIT: Neonatal AlloImmune Thrombocytopenia.

Table 3: Differential diagnoses of Post-Transfusion Purpura

Idiopathic Thrombocytopenic Purpura (ITP)
Heparin-induced Thrombocytopenia (HIT)
Drug-induced Thrombocytopenia(DIT)
Neonatal Alloimmune Thrombocytopenia (NAIT)
Thrombotic thrombocytopenic purpura(TTP)
Disseminated Intravascular Coagulopathy(DIC)

Table 4: Proposed Scoring System of Post Transfusion Purpura:-

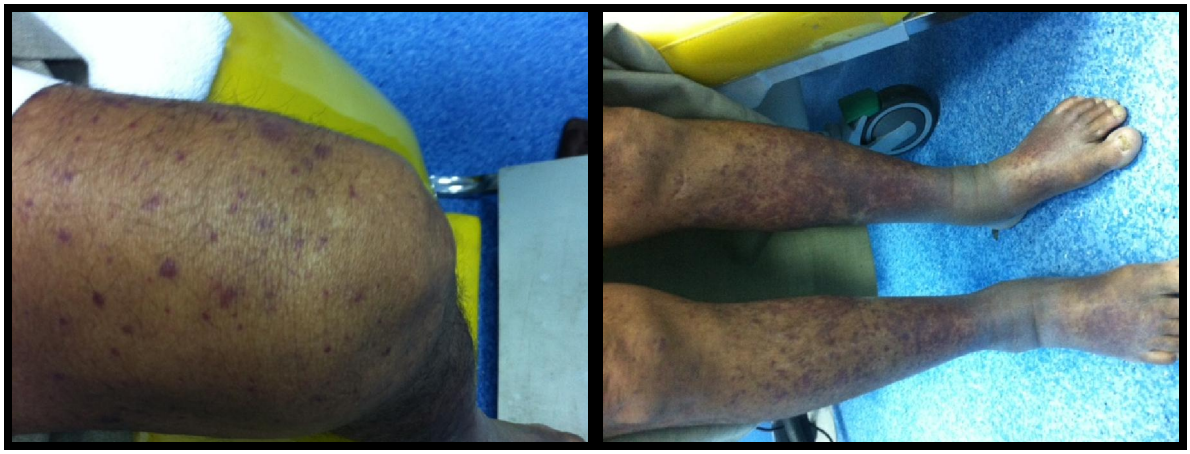
Scoring* / Clinical Characters	0	1	2
Recent blood product transfusion	NO	YES	NA
Multiparous women or Hx of frequent transfusions	NO	YES	NA
Purpuric skin rash	NO	YES	NA
Thrombocytopenia	>20000/µL	< 20000/µL	< 15000/µL
Normal coagulation profile& Fibrinogen level	YES	NO	NA
Positive HPA Antibody¥	NO	NA	YES

*6-8 High risk (Must include HPA positivity) *3-5 Intermediate risk (Not including HPA positivity)
*1-2 Low risk (Not including HPA positivity) HPA: Human Platelet Antigen
¥ These include detection of antibodies by immunofluorescence, Flowcytometric testing and enzyme-linked immunosorbent assay (ELISA)–based methods.

(Table 5): Summary of Post Transfusion Purpura

Causes and risk factors	Symptoms and signs	Laboratory test/s	Management
• Multiparous women • Frequent transfusion • HLA-DRw52a* • HLA-DRβ3-0101**	• Bleeding from any site • Purpuric skin rash	• Thrombocytopenia • Platelet antibody assay by PIFT & MAIPA&ELISA	• Observation • IVIG • Steroid • Plasma exchange • Platelets transfusion

*HLA-DRw52a: Human Leukocyte Antigen class II **HLA-DRβ3-0101: Human Leukocyte Antigen class II



(Figure 1): Purpuric skin rash (a, b) red to purple discoloration spots on the skin that are raised and do not blanch on applying pressure.

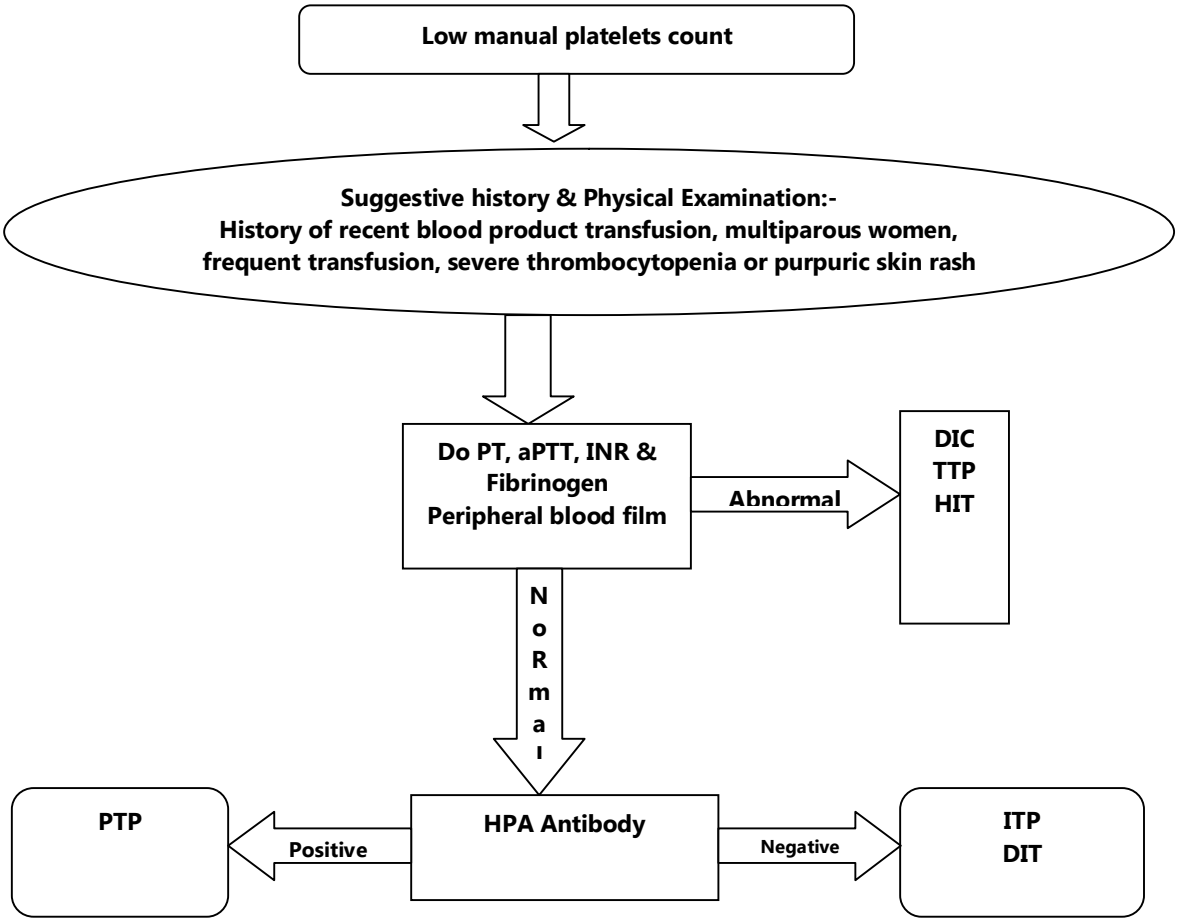
Conclusion

PTP is a rare transfusion reaction complication associated with severe thrombocytopenia. It is under-diagnosed mainly because of lack of awareness among treating physicians.

PTP has high mortality rate specially if associated with CNS bleeding. No clear consensus about its clinical criteria for diagnosis is available. Reporting of PTP is mandatory, as it will help in better understanding and forming evidence based management plans of such serious complication of common medical practice. The proposed algorithm and scoring system may help physicians to diagnose patient with efficacy but it needs further studying in a multicenter.

Disclosure of benefit:-

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper and we assure that the work was not supported or funded by any drug company and was not submitted or presented in any medical conference before.



(Figure 2): Algorithm for diagnosis of PTP

HPA: Human Platelet Antigen, PT: Prothrombin Time, aPTT: activated Partial Thromboplastin Time, INR: International Normalized Ratio, DIC: Disseminated Intravascular Coagulopathy, TTP: Thrombotic Thrombocytopenic Purpura, HIT: Heparin Induced Thrombocytopenia, PTP:Post Transfusion Purpura, ITP: Immune Thrombocytopenia, DIT: Drug Induced Thrombocytopenia

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11/10/2015