Review Article

CD36 immunization causing platelet transfusion refractoriness: narrative review

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Objective: This narrative review aims to describe the clinical and laboratory approach to patients with platelet transfusion refractoriness (PTR) from CD36 immunization.

Background: The most common cause of PTR is non-immune and within the immune-mediated causes, antibodies against CD36 are rare but clinically significant. CD36 deficiency is more common in African, African American, Chinese and Japanese populations. Immune-mediated PTR from CD36 antibodies almost exclusively affects individuals with type I deficiency, affecting both platelets and monocytes.

Methods: We describe a general approach to identify and manage patients with CD36 immunization as the cause of PTR. An overview of cases reported in the literature with emphasis in the clinical characteristics and outcomes is presented.

Conclusions: Approaching patients systematically, with post-transfusion counts, antibody screening and confirmatory testing to identify the antigen(s) involved is key in selecting the platelet units that are most likely to provide an adequate transfusion yield. Due to the high frequency of CD36 in the general population, CD36 negative platelet units are not readily available, and procurement of these units relies on related donors or units from reference blood banks around the world. Even when CD36 negative platelet units are available, other immune and non-immune mediated causes of PTR can be present simultaneously making platelet transfusions of little clinical utility. Additional interventions to increase transfusion yield such as administration of polyvalent immunoglobulin and addition of immunosuppression have also been described. The management of patients with PTR from CD36 antibodies remains challenging despite wider access to testing and antigen negative platelet units.

Keywords: Platelet transfusion; CD36 antigens; platelet glycoprotein IV deficiency (platelet GP IV deficiency)

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Overview of platelet transfusion refractoriness (PTR)

PTR is commonly encountered in clinical practice (1). Most cases [over 80% (2)] are due to non-immune mediated mechanisms that increase the consumption of transfused platelets, while a smaller proportion is due to immune-mediated mechanisms, where transfused platelets are rapidly cleared from circulation. Alloimmunization most frequently involves class I human leukocyte antigen (HLA) antigens, but platelet antigens such as glycoprotein (GP) IV (CD36) can be implicated. With clinically significant bleeding present in over 1/3 of patients with immune-mediated platelet alloimmunization and a bleeding-related mortality rate of around 8% (3), identifying the specific antigen involved is crucial for providing effective transfusion support. From the perspective of blood product utilization and cost, up to 2/3 of all transfused platelet units

are administered to patients with PTR and PTR is associated with longer hospitalization and higher cost per admission (4). This review aims to describe the clinical and laboratory approach to patients with PTR from CD36 immunization and provide tools for clinicians and laboratory specialists to care for patients with this rare and challenging presentation. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/aob-21-36).

Establishing the diagnosis of PTR

Following the observation of a platelet transfusion yield lower than expected, systematic evaluation of post transfusion counts will confirm the diagnosis. Most studies use the corrected count increment (CCI) as a standardized measure, which adjusts for body surface area and dose of platelets administered (5). To distinguish non-immune *vs.* immune-mediated causes, a platelet count within 1 hour of transfusion is obtained. A CCI <5,000 or an absolute increase of under 10,000/μL immediately after transfusion (confirmed in duplicate) is suggestive of immune-mediated PTR, however concomitant non-immune mediated causes should always be investigated.

Suspecting CD36 immunization as the cause of PTR

Once immune-mediated PTR has been established, a work-up to determine the specific antigen(s) involved is initiated. The type of laboratory studies obtained, turnaround time of results and transfusion strategy pursued while awaiting results, vary across facilities and countries and depend greatly on availability of local resources and geographical distance to reference testing and blood banks.

The prevalence of platelet GP IV deficiency varies across ethnicities. In the Sub-Saharan African population, CD36 negativity is as high as 7.7% (6). Chinese (7-9) and African American (10) populations have a CD36 negativity prevalence between 2.2% and 2.4%, followed by the Japanese population at 1% (11) and is lowest for Western Europeans where it approaches 0% (6). The patient's ancestry can increase the pre-test probability of PTR being from antibodies against CD36.

Platelet crossmatching is used in some centers to select the most compatible platelet units while awaiting results from antibody screening assays. Considering the very low frequency of CD36 negative individuals in most populations, a CD36 antibody is expected to lead to incompatibility of most (if not all) platelet units crossmatched. An incompatible crossmatch with multiple units will not be exclusive to CD36 immunization as it can be seen with class I HLA antibodies and antibodies to other common platelet antigens.

Since class I HLA antibodies are the cause of the majority of immune-mediated PTR, testing for class I HLA antibodies and finding HLA-matched platelets in the event an HLA antibody is present, can greatly improve platelet survival. In patients without class I HLA antibodies or those that continue to have a low platelet transfusion yield with HLA-matched platelet transfusions, investigating platelet antigen related refractoriness is indicated.

Confirming CD36 immunization

Antibody screening assays, including the PakPlus (LIFECODES, Waukesha, WI; Immucor GTI Diagnostics, Inc.) detect class I HLA, CD36, and GP IIb/IIIa, GP Ia/IIa and GP Ib/IX antibodies. Antigen capture assays, including modified antigen capture ELISA (MACE) and platelet antibody bead assay (PABA) (12) will delineate specificity of platelet antibodies and will not have interference from non-HPA antibodies (*Figure 1*). In rare instances, the CD36 mouse anti-human monoclonal antibody can block human antibody binding by competing for the same nearby epitope which prevents proper antibody detection and can lead to false negative results (13). Using a second CD36 monoclonal antibody can ameliorate this issue and increase the sensitivity of the assay.

Once CD36 reactivity (antibody) is detected, immunophenotyping of the patient's platelets and/or monocytes by flow cytometry should be considered. There are two types of CD36 deficiency, type I where both platelets and monocytes lack CD36 and type II in which only platelets do not express CD36. Type II deficiency is more common (7). It is widely accepted that only type I deficient individuals can produce antibodies, and hence it may only be necessary to test platelets (as absence of CD36 on monocytes would be assumed). However, patients with type II CD36 deficiency and detectable antibody have been reported in the literature (6). It is worth noting that the detection of CD36 antibodies is performed at reference laboratories and flow cytometry immunophenotyping is not widely available. Genotyping of the *CD36* gene is expected to reveal either homozygous or compound heterozygous variants and support the diagnosis of CD36 deficiency.

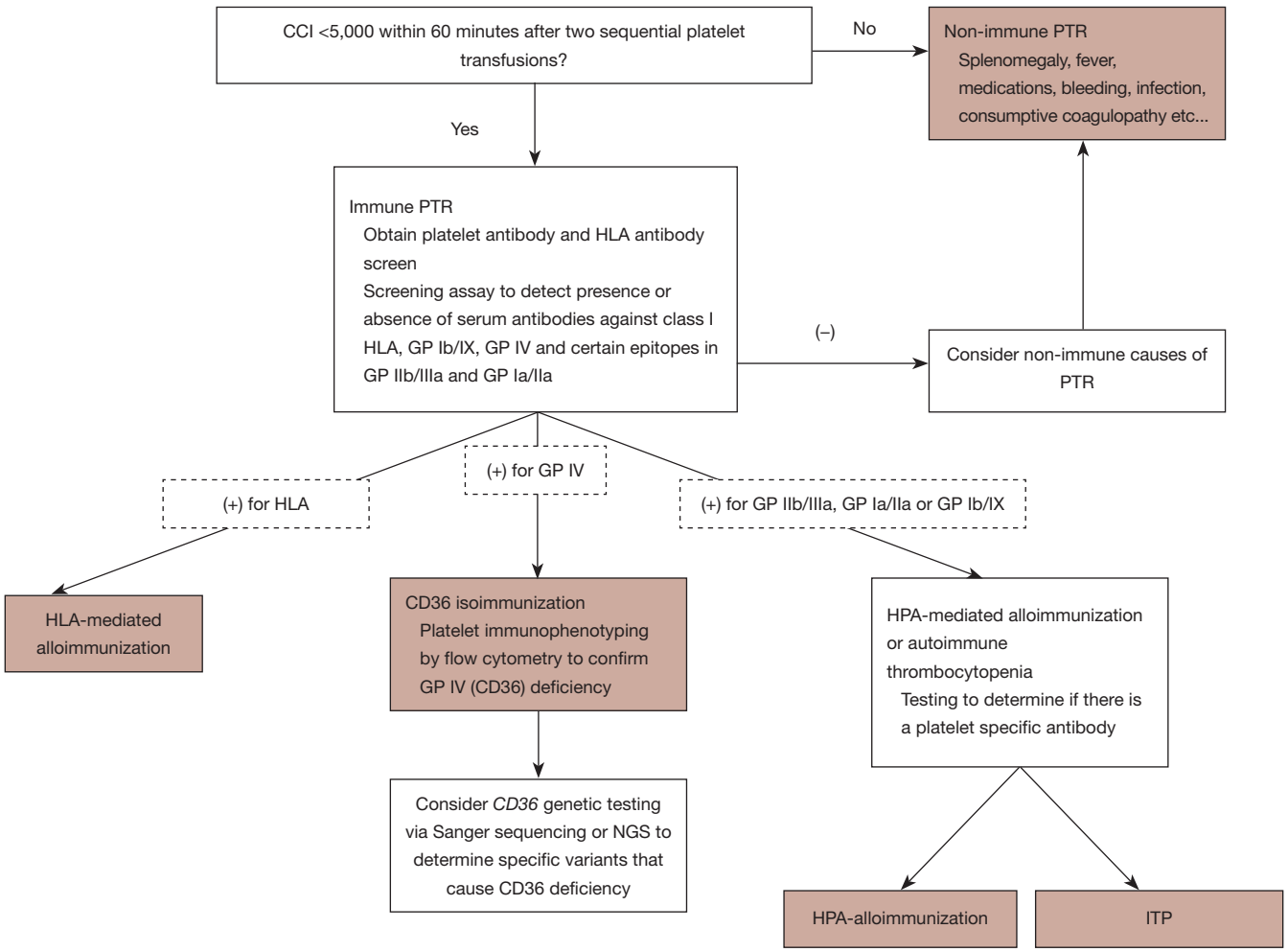

Figure 1 Testing approach to the patient with suspected PTR. CCI, corrected count increment; PTR, platelet transfusion refractoriness; HLA, human leukocyte antigen; GP, glycoprotein; NGS, next-generation sequencing; HPA, human platelet antigen; ITP, immune thrombocytopenia.

A large number of population estimates of CD36 deficiency have been established by phenotypic studies on platelets of blood donors and do not distinguish between the two types of deficiency (1). Studies that have reported phenotyping of both platelets and monocytes using flow cytometry demonstrate that while PTR is expected to affect almost exclusively those with type I deficiency, individuals with type II deficiency are suitable donors for patients with PTR caused by CD36 antibodies.

The identification of clinically relevant anti-CD36 antibodies is best accomplished in the context of immune-mediated PTR where *in vivo* data supports that the antibody is not only present but actively participating in clearance of CD36 positive transfused platelets.

In some clinical contexts, platelet antibody screens are obtained prior to intensive chemotherapy (such as that required for allogeneic stem cell transplantation) and CD36 antibodies are identified, yet the individuals are subsequently found to have adequate response to transfused platelets (14).

Transfusion support for the patient with PTR from CD36 antibodies

Platelet transfusions from CD36 negative donors are the main modality of support for patients with PTR from CD36 immunization. These platelets units are difficult to obtain, especially in geographical regions where the

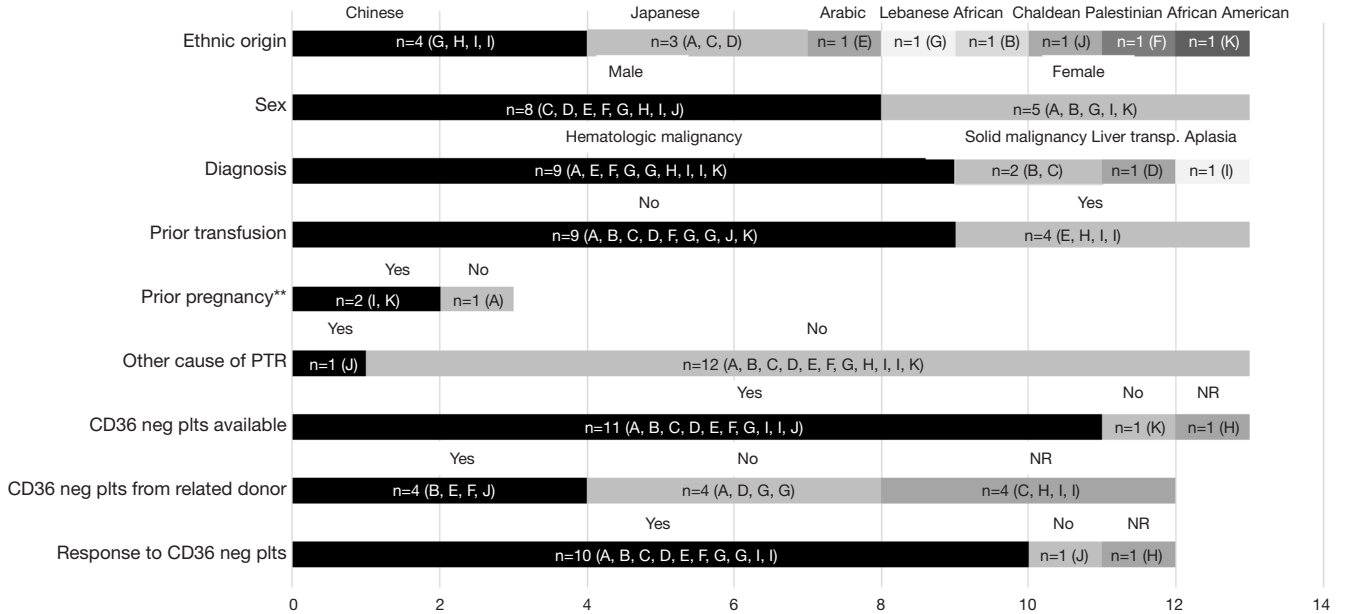

Figure 2 Clinical characteristics, transfusion availability and outcomes of 13* patients with PTR and CD36 isoimmunazation. (A) Ikeda *et al.* (15); (B) Lee *et al.* (6); (C) Fujino *et al.* (16); (D) Ogata *et al.* (17); (E) Flesch *et al.* (18); (F) Broderick *et al.* (19); (G) Saw *et al.* (20); (H) Xu *et al.* (21); (I) Xia *et al.* (22); (J) Khatri *et al.* (23); (K) Schmidt *et al.* (24). *, does not include all reports of PTR from CD36 isoimmunization, only those in which complete clinical history is reported; **, applies only to females in or past reproductive age. PTR, platelet transfusion refractoriness; transp, transplant; neg, negative; plts, platelets; NR, not reported.

donor population has a low prevalence of CD36 deficiency. Screening family members to identify those who may also be CD36 deficient and suitable to serve as platelet donors should be considered (*Figure 2*).

While globalization has facilitated exchange of therapeutic products, geographical distance from a large/reference blood bank can significantly limit access to CD36 negative platelet products. Patients in Canada have successfully been transfused with CD36 negative platelets from the United States (20), while a patient in Germany was unable to receive platelet units from Japan, as the 18- to 24-hour travel time would have compromised viability of the product (25). For the patient in Germany, autologous hematopoietic stem cell transplant conditioning was postponed until four CD36 negative family members were identified and traveled to Germany to provide directed platelet donations.

Even when CD36 negative platelet units are available, the presence of concomitant class I HLA antibodies or non-immune platelet refractoriness may lead to continued lack of response to platelet transfusion. Obtaining ABO compatible, HLA-matched and CD36 negative platelets becomes extremely difficult, if not impossible (26).

Clinical characteristics of patients with PTR from CD36 antibodies

Cases of PTR from CD36 immunization have been described in patients of various ethnicities and affecting males and females alike. Most have malignancy, in particular a hematologic malignancy, as the underlying cause of their need for platelet transfusions and many (but not all) had been previously transfused and most responded to CD36 negative platelets. *Figure 2* summarizes the clinical data of 13 cases of PTR from CD36 immunization reported in the literature. While more cases have been reported, only those with detailed clinical information are presented.

Other therapies

When CD36 negative platelets are not available or patients are immunized against multiple antigens, adjuvant treatments can be considered. Strategies to increase transfusion yield in the context of anti-CD36 immunization

leading to PTR such as polyvalent immunoglobulin (IVIG) to increase the half-life of transfused platelets and B-lymphocyte selective immunosuppression with rituximab have been described (26). The use of additional immunosuppressive agents to specifically address PTR is more likely to be utilized in patients who are not already undergoing treatment regimens that suppress the immune system. De-escalation of treatment intensity in the case of patients with hematologic malignancies has also been described, with the goal of allowing endogenous platelet count renewal in a shorter timeframe, albeit compromising the long-term outcomes in terms on control of the underlying malignancy (27).

Future directions

Despite wider access to testing and antigen negative platelet units, the management of patients with PTR from CD36 antibodies remains challenging. Continuing efforts to assure that the population of blood donors adequately reflects the racial makeup of the population it serves is key to the bility to adequately meet the needs of patients that need transfused products.

Advances in genome editing technology allowing for the engineering of antigen negative/universal platelets using technologies such as CRISPR/Cas9 promises to change the way we support patients who require special products (28).

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