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TRANSFUSION

Platelet refractoriness associated with platelets stored in platelet additive solution

To the Editor,

The randomized prospective trial Evaluation of the Efficacy of Platelets Treated with Pathogen Reduction Process (EFFIPAP) reported a 54% rate of platelet (PLT) transfusion failures (24-h corrected count increment [CCI] <4.5) with pathogen-reduced (PR) PLT (PAS/PR-PLT), which was 40% higher than PLTs stored in plasma (PLS-PLT; 31%).[1] Although less dramatic, PLT stored in platelet additive solution without PR (PAS-PLT) also showed a shortened survival and higher rate of transfusion failures (40%).[1] An older randomized study also found a small but significant decrease in post-transfusion PLT response and survival with PAS-PLT compared to PLS-PLT.[2]

We present three patients with PLT refractoriness to PAS-PLT and PAS/PR-PLT, who were successfully managed with standard plasma PLT concentrates (PLS-PLT). All three patients underwent a formal PLT refractory consult that included a review of their medical history, medications, physical exam and radiology findings, transfusion history, PLT ABO type, and laboratory studies including 1-h post-transfusion PLT counts and HLA antibody testing (%PRA): PLT crossmatching was performed for two patients. To compare the transfusion response by PLT type, the absolute 1-h PLT increment and CCI for 6 weeks or hospital discharge were calculated for each patient and compared by student *t*-test.

Our first patient was a 16-year-old, atopic, group O male with Kostmann's congenital neutropenia, who was admitted for an allogeneic, hematopoietic stem cell transplant (HSCT) from an HLA-matched, ABO-incompatible (ABOi) sibling donor (group A; 10/10 HLA). He had no history of blood transfusion prior to his HSCT and was negative for HLA antibodies. He was transplanted with plasma- and RBC-depleted, cryopreserved bone marrow and cord blood, which was complicated by an anaphylactic reaction to the HPC-cord blood infusion. Given his history of atopy and recent infusion reaction, PAS-PLT were specifically ordered from the blood supplier, who had just begun offering PAS-PLT on a limited basis. On transplant day +10, the patient received three prophylactic PLT transfusions. He initially received two sequential group O PAS-PLT, from two different donors, with only a 1 K/μL increase in PLT count per unit (12 to 14 K/μL; CCI 0.45). Pre-pooled PLS-PLT were provided for his third transfusion on day +10 with an appropriate PLT increment (14 to 37 K/μL; CCI = 13) but complicated by a mild allergic reaction. For the remainder of his admission, he was supported with plasma-reduced, saline-suspended apheresis PLS-PLTs with no further transfusion reactions and improved CCIs (Table 1, Figure 1A), despite the adverse impact of washing on platelet recovery.[3] Because the patient responded well to PLS-PLTS, no platelet crossmatching or repeat HLA testing was pursued.

The second patient was a 33-year-old, group A female with chronic myelogenous leukemia who was readmitted 6 weeks after an allogeneic, ABOi (O donor), HLA-matched unrelated donor [MUD] HSCT for new pancytopenia despite molecular evidence of engraftment (100% donor). In addition, she had new PLT refractoriness with documented PLT decrements to three PAS/PR-PLT (CCI −0.5). She had no palpable splenomegaly or non-immune etiologies for refractoriness. She was negative for HLA antibodies pre-HSCT and upon re-testing (class 1 PRA = 0%, x 2). She was crossmatch-compatible with 14/14 PLT donors. Upon review, it was noted that she had responded well to PLS-PLT during her prior HSCT but had only developed refractoriness with PAS-PLT and PAS/PR-PLT during this admission. She was given a trial of apheresis PLS-PLT with an appropriate transfusion response (Table 1, Figure 1B). She was maintained on PLS-PLT with good responses until her final admission and death from infection and recurrent leukemia.

The third patient was a 54-year-old, group B female with myelodysplastic syndrome, who was admitted for an ABOi (O donor), MUD HSCT. She had no evidence of HLA antibodies pre-HSCT (PRA = 0%, x 2) and had historically responded well to PLS-PLT transfusion at an outside facility. In contrast, she was immediately refractory to PAS-PLT and PAS/PR-PLT (CCI 2.7) at HSCT admission (day-7). Repeat HLA testing was again negative (PRA = 0%) and she was crossmatch-compatible with 14/14 PLT donors. She was trialed with PLS-PLT

TABLE 1 Transfusion response by platelet product

	PAS-PLT and PAS/PR-PLT[a]				PLS-PLT[b]				PLS-PLT vs PAS-, PAS/PR-PLT	
	Transfusion response				Transfusion response					
Patients	No. units	ABO type	Increment[c] (median)	CCI[d] (median)	No. units	ABO type	Increment[c] (median)	CCI[d] (median)	Increment (P)[e]	CCI (P)[e]
Case 1[b]	2	O	1 ± 0 K/μL (1)	0.45 ± 0 (0.45)	5	O	15 ± 3.8 K/μL (18.5)	8 ± 1.6 (8.3)	0.024	0.00067
Case 2	3	A	−1.7 ± 2 K/μL (−1)	−1.4 ± 1.2 (−0.5)	13	A	17.4 ± 1.2 K/μL (19)	8.1 ± 0.6 (8.8)	<0.0001	<0.0001
Case 3	4	B	5 ± 0.7 K/μL (5.5)	2.5 ± 0.4 (2.7)	5	B	13.2 ± 3 K/μL (11)	6 ± 0.8 (5)	0.049	0.009
All cases	9	A,B,O	1.9 ± 1.1 K/μL (1)	0.78 ± 0.7 (0.45)	23	A,B,O	16 ± 5.9 K/μL (18.5)	7.5 ± 0.4 (8.3)	<0.0001	<0.0001

[a]PAS-C was the platelet additive solution for PAS-PLT and PAS/PR-PLT.

[b]PLS-PLT included pre-pooled, whole blood derived platelets (5 units group O/pool; $n = 1$) and single donor apheresis (case 1; $n = 4$). Cases 2 and 3 received single donor apheresis PLT only.

[c]Absolute PLT increment at 1-h post-transfusion (post − pre PLT count; K/μL). Results reported as mean ± SE (median).

[d]CCI, corrected count increment at 1-h post-transfusion ([post − pre PLT count] × patient size (m^2)/no. PLT transfused). Results reported as mean ± SE (median).

[e]Student *t*-test.

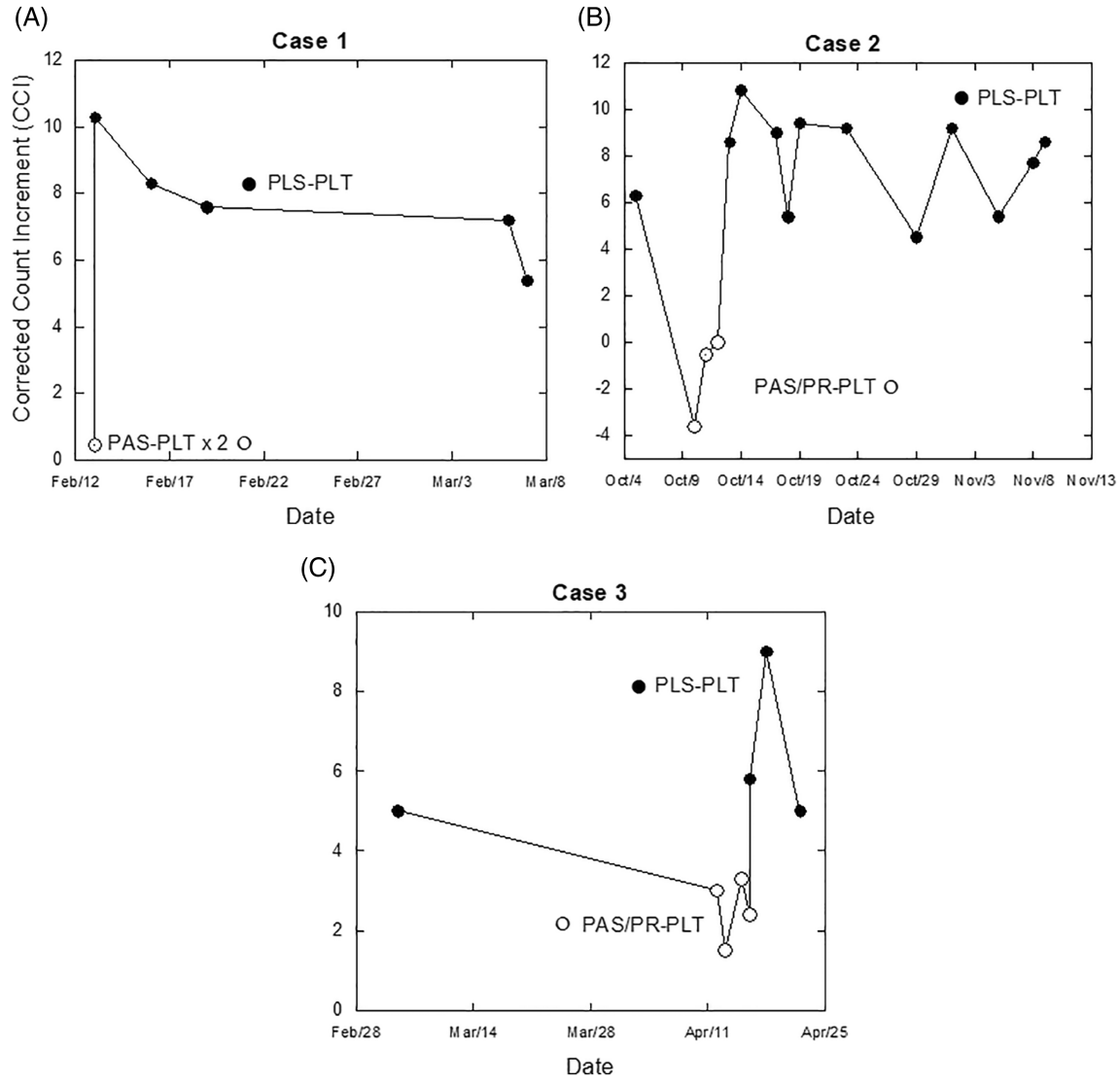

FIGURE 1 The corrected count increments for transfusions with a 1-h post-transfusion platelet (PLT) count for case 1 (pane A), case 2 (B) and case 3 (C). Results plotted over time by PLT-type infused: PLS-PLT (—•—) and PAS-PLT or PAS/PR-PLT (—○—)

with a two-fold increase in absolute PLT increment and CCI (Table 1, Figure 1C).

In summary, we documented specific refractoriness to PAS-PLT and PAS/PR-PLT, but not PLS-PLT, in three ABOi allogeneic HSCT recipients. Interestingly, Yale recently reported an increase in PLT alloimmunization testing and PLT refractoriness after adoption of PAS/-PR-PLT.[4] The EFFIPAP trial, which included PLT refractoriness and HLA alloimmunization as secondary measures, may provide further data.[1] We suspect refractoriness in our cohort reflects a combination of patient immune dysregulation, increased macrophage activation and acquired PLT senescent/neoantigen expression.[5] A trial of PLS-PLT may be indicated in patients with inexplicable non-immune PLT refractoriness following transfusion of PAS- or PAS/PR-PLT.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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Mortality in cold agglutinin disease shows seasonal pattern

We have with great interest read the recent publication by Röth et al. illustrating that patients with cold agglutinin disease (CAD) have persistent biochemical hemolysis all year round.[1] The study supports that anemia, hemolysis, and directly related symptoms like fatigue persist through seasons. Despite these findings, we have recently shown a remarkable seasonal variation in the incidence of CAD diagnosis in Norway, Denmark, and Italy indicating that symptoms may be aggravated and become clinically overt during colder months.[2] We, therefore, speculated whether mortality in cold agglutinin disease likewise shows seasonal variation, not seen in other acquired hemolytic diseases.

In order to address this we used our cohort including all patients diagnosed in Denmark with CAD or autoimmune hemolytic anemia (AIHA), and for each patient in the two categories up to 50 age-sex-matched comparators from the general population.[3] Denmark has nationwide health registers deriving from a universal, tax-funded health system providing a complete inclusion and minimal loss to follow up.[4] We included patients diagnosed from 1980 to 2016 for AIHA and 1994 to 2016 for CAD. A Danish adaptation of the International Classification of Diseases revision 10 in 1994, allows the separation of CAD (D591A) from unspecified AIHA (D591) in the Danish National Patient Register.[3–5] The unspecified AIHA category consists of warm-type AIHA and less frequently mixed-type AIHA.[2,3,5] Follow-up started on the date of diagnosis of either CAD or AIHA, the same start date was allotted to the corresponding comparators, and continued to the first of death, emigration, or December 31, 2017.

The main outcome was the date of death, grouped into the calendar seasons: *Spring* (March, April, May), *Summer* (June, July, August), *Autumn* (September, October, November), and Winter (December, January, February). The rarity of CAD made it impossible to analyze by month or assess seasonal patterns in causes of death.

We used Cox proportional hazard regression to estimate the risk of death in each disease or comparator group with respect to calendar season. We estimated unadjusted hazard ratios (HR) in a combined model including all diseases and comparator groups, applying interaction between each group and season, with the groups of comparators for the patients with CAD as a global reference, and summer as a local reference for mortality within each of the three remaining groups (CAD, AIHA, and AIHA comparators). Subsequently, adjusted HRs were estimated, including age at diagnosis, sex, and year of diagnosis in the model.

We identified 114 patients with CAD and 5311 comparators, who accumulated 45 and 1074 fatalities, respectively. In addition, we identified 2889 patients with AIHA and 143,269 comparators, experiencing 1809 and 64,954 fatalities. The two groups of patients with CAD and AIHA differed in mean age at diagnosis and sex distribution, but patient groups and corresponding comparator groups were similar by study design, Table S1.

Adjusted estimates are depicted in Figure 1, all adjusted and unadjusted HRs are presented in Table S2. When comparing patients with CAD to their age-sex-matched comparators there was no significant difference in the risk of death during spring and autumn. However, winter was associated with a 4.5 (95% confidence interval [CI] 2.00; 10.08) times increased risk of death, adjusted for age, sex, and year of diagnosis, Table S2. The unadjusted risk of death during winter was 3.2 (95% CI 1.43; 7.18). Amongst patients with AIHA or corresponding comparators, no significant seasonal effect was observed, Table S2.