Acute pain transfusion reaction in a regularly transfused Thalassemic patient: a case report

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Background/Introduction

Acute pain transfusion reaction (APTR) is a rare adverse transfusion effect of unknown etiology. Its defining characteristic is joint pain that appears during or shortly after blood product transfusions. It is usually registered in the haemovigilance records as unclassified reaction when all other causes of adverse reactions had been ruled out. **Cytokines** and **leukoreduction** filters have been linked to some APTR case reports; however, no underlying causes and mechanisms have been addressed in the limited literature.

Patient and Study Design

- **Patient:** 50-year-old, female, with transfusion dependent β-thalassaemia
- **Comorbidities:** secondary haemochromatosis, hypoparathyroidism, hypothyroidism, osteoporosis, atrial fibrillation, depression
- **Splenectomy:** 25 years ago
- **No previous** transfusion reactions or alloimmunization
- Usually exhibits **high haemoglobin increment** following transfusion (ΔHb 1.6 g/dL per unit)
- **APTR event:** the subject received complete-phenotype leucoreduced red blood cell (RBC) units. A serious adverse reaction with sudden moderate pain in the **neck and the lumbar back** appeared a few minutes after the onset of the second unit's delivery. The transfusion was immediately paused, and the patient was given corticosteroids and hydration. Following the international guidelines, the incidence of haemolytic or other adverse transfusion reactions was ruled out. Soon after the discomfort decreased, the patient was stable and released.
- **Study design:** Comparative assessment of RBC physiology, **storage lesion**, and **biological response modifiers' (BRMs)** levels in patient and RBC units' samples in APTR, previous, and next regular transfusions (Fig. 1).

Results

- **Subject's profile:** reportedly **increased PLT** count (500x109/L) and **D-dimers** (670μg/L) but normal RDW index and no nucleated RBCs (NRBCs).
- **Day before APTR:** normal lactate dehydrogenase (LDH), bilirubin, and C-reactive protein, but slightly increased **RDW (17.2%)**.
- **Immediately post APTR:** high **D-dimers** (739 μg/L), further increase in **RDW index** (18.5%), 15.2% **NRBC (**despite of improved Hb levels, 12.6 g/dL; ΔHb 1.9 g/dL), increased **cell-free Hb** (37.3 vs. 10.9 mg/dL), **susceptibility of RBCs to hemolysis, oxidative stress**, phosphatidylserine exposure (**PS⁺ RBCs**, 1.9 vs. 0.1%) (compared to a previous transfusion event).
- **APTR/RBC unit's examination**: **16-day-old**, **low Hb** concentration (15.8 g/dL), **high RDW** (15.5%), increased propensity to **hemolysis**, **oxidative stress**, but normal concentration of extracellular vesicles (EVs) compared to the average units, as measured by nanoparticle tracking analysis.
- **Next regular transfusion (15 days post APTR):** no more NRBCs but sharp increase in **D-dimers** (1058 μg/L), **EVs** (23x10^{10}/μL), **haemichromes**, and **oxidative hemolysis**. **RDW** remained high (17.7%), and **PS⁺ RBCs** reduced, albeit at still pathological levels (0.6%) that deteriorated post transfusion (1.1%).

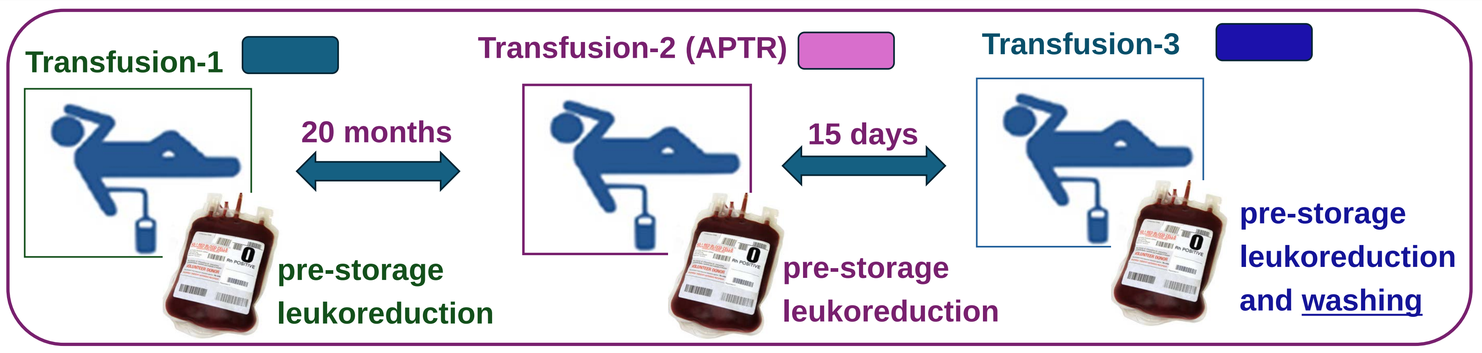
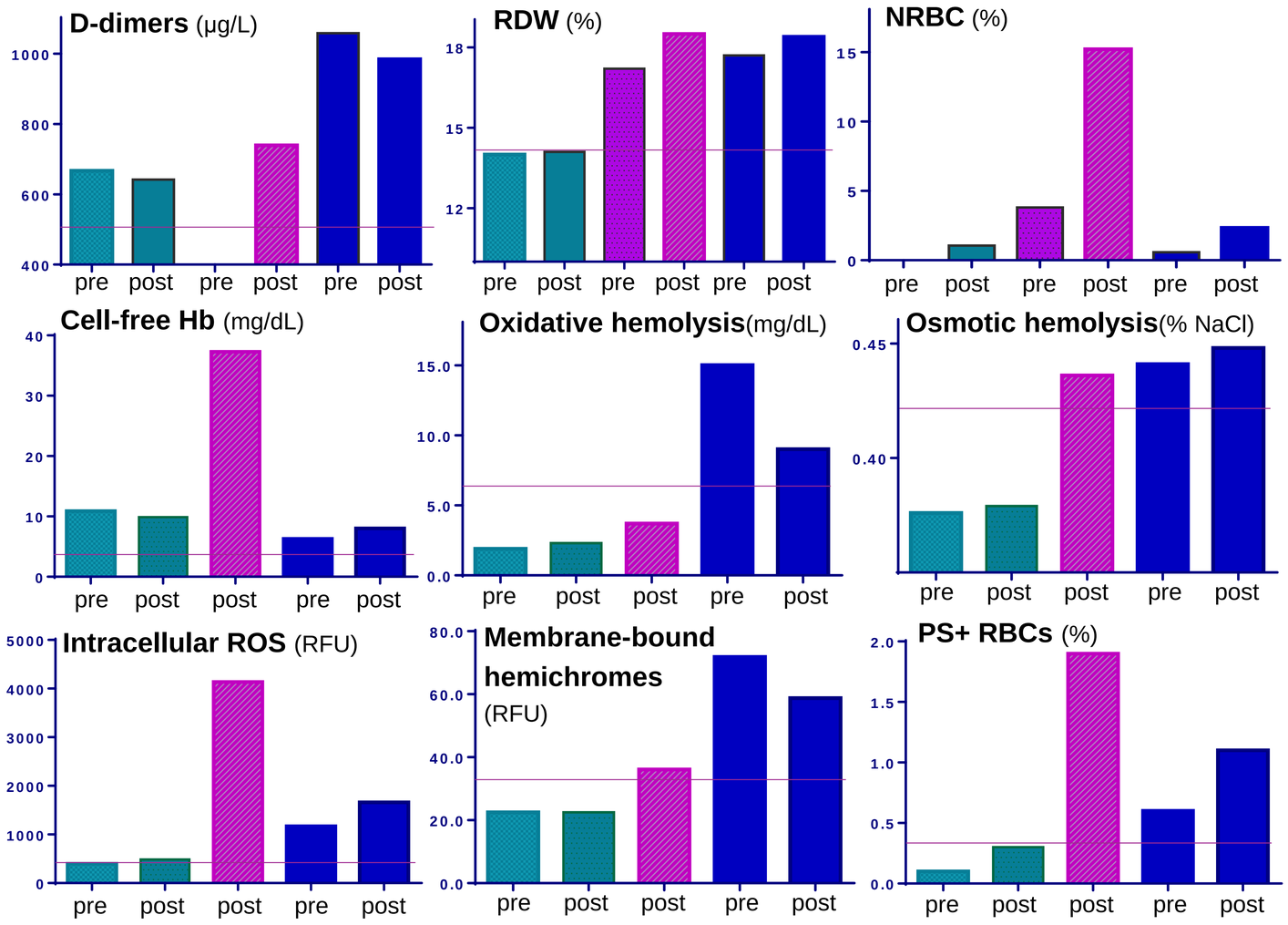


Fig. 1 Study design: clinical, serum biochemical, and RBC factors from the subject and the RBC units were assessed in the APTR event compared to the next regular transfusion. Data available from a previous (20 months ago) regular transfusion of the patient was also taken into consideration.



RBC units	TRF-1	TRF 2-APTR	TRF-3
Storage age (days)	6	16	17
RBC (x10e6/μL)	6,26	5,84	7,60
Hb (g/dL)	19,1	**15,8**	21,3
HCT (%)	62,5	55,3	72,4
MCV (fL)	99,8	94,7	95,3
MCH (pg)	30,5	27,0	28,2
MCHC (g/dL)	30,5	28,6	29,5
RDW (%)	12,7	**15,5**	13,5
fHb (mg/dL)	48	59	**134**
Osmotic hemolysis (MCF, %NaCl)	0,443	**0,501**	0,481
Mechanical hemolysis (MFI, %)	0,876	**1,248**	0,914
Oxidative hemolysis (mg/dL)	1,6	5,9	**38,1**
Membrane-bound hemichromes (μM)	19,3	17,6	**48,8**
intracellular ROS (RFU)	392	**1558**	825
intracellular Ca2+ (RFU)	nd	**7438**	4870
PS+ RBCs (%)	0,11	0,42	**0,53**
EVs (x10e10/μL)	2,5	1,4	2,2
RBC proteasome activity (RFU)	21191	8404	5617

Conclusions

The currently applied paired study design may lead to the successful detection of patient and RBC unit-related **stress markers** in linkage to the pathophysiology of APTR. Inclusion of **more events** and **further analyses** at cellular and molecular levels (e.g. omics, cytokines/chemokines, neurotransmitters) in patients and blood products are expected to shed light to this entity hoping to prevent it and increase the awareness of the transfusion clinicians to it.

References

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