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Thrombocytopenia-associated multi-organ failure after Fontan operation successfully treated with plasma exchange: A case report

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ABSTRACT:

Introduction: Thrombocytopenia-associated multi-organ failure (TAMOF) is a rare but life-threatening subtype of multiple organ dysfunction syndrome caused by thrombotic microangiopathy and decreased A Disintegrin and Metalloproteinase with a Thrombospondin type 1 motif, member 13 (ADAMTS-13) activity. Although commonly associated with sepsis, TAMOF is rarely reported after cardiac surgery.

Case presentation: We report a 10-year-old girl with right atrial isomerism and complex congenital heart disease who developed TAMOF following extracardiac Fontan surgery. She presented with distributive shock, persistent thrombocytopenia, acute kidney injury requiring continuous renal replacement therapy, transaminitis, and encephalopathy. Laboratory findings demonstrated thrombotic microangiopathy with elevated inflammatory markers. Plasma exchange (PLEX) was initiated based on clinical suspicion and later confirmed by reduced ADAMTS-13 activity. After two PLEX sessions, the patient showed rapid improvement, including platelet recovery, resolution of neurological, hepatic, and renal dysfunction, and successful extubation.

Conclusions: Early recognition of TAMOF in post-cardiac surgery patients with unexplained thrombocytopenia and multi-organ dysfunction is critical. Prompt PLEX may result in clinical recovery and improved survival.

Keywords: Thrombocytopenia-associated multi-organ failure; Plasma exchange; Post-cardiac surgery; Cardiopulmonary bypass; Right atrial isomerism

INTRODUCTION

Thrombocytopenia-associated multi-organ failure (TAMOF) is a rare but life-threatening complication characterized by thrombocytopenia and dysfunction of at least two organs, caused by disseminated microvascular thromboses [1]. While TAMOF has been well documented in patients with sepsis, it is uncommon in those undergoing cardiac surgery. TAMOF is considered a subtype of multiple organ dysfunction syndrome (MODS) associated with secondary thrombotic microangiopathy. The underlying pathophysiology involves a deficiency of A Disintegrin and Metalloproteinase with Thrombospondin type 1 motif, member 13 (ADAMTS-13), an enzyme responsible for cleaving ultra-large von Willebrand factor (ULVWF) multimers. Reduced ADAMTS-13 activity results in the accumulation of ULVWF, promoting the formation of platelet-rich microthrombi in small and medium-sized vessels throughout the body [2, 3].

TAMOF is associated with high morbidity and mortality. Systemic hyperinflammation triggered by conditions such as severe infection, cardiopulmonary bypass (CPB), or autoimmune disease can further suppress ADAMTS-13 activity. Inflammatory mediators such as interleukin-6 (IL-6) and plasma-free hemoglobin have been shown to inhibit ADAMTS-13 function, thereby contributing to thrombotic microangiopathy [4, 5].

Early recognition of TAMOF is crucial, especially in post-cardiac surgery patients, where its presentation may be mistaken for other coagulopathies. Timely intervention with plasma exchange (PLEX) has been associated with improvements in organ function and reduced mortality [6, 7]. Here, we report a rare case of TAMOF following Fontan operation that was successfully treated with PLEX.

CASE PRESENTATION

Case description

A 10-year-old female with a known diagnosis of right atrial isomerism, asplenia, situs ambiguous, dextrocardia, and unbalanced atrioventricular septal defect had previously undergone a left bidirectional Glenn (BDG) procedure at 11 months of age. Subsequently, she was scheduled for Fontan completion. Her pre-Fontan evaluation demonstrated acceptable Fontan physiology, with a pulmonary vascular resistance index of 2.14, mean pulmonary artery pressure (mPAP) of 15 mmHg, and well-developed bilateral pulmonary arteries (McGoon ratio 2.57). Transthoracic echocardiography revealed good single ventricular function, mild atrioventricular valve regurgitation, and a patent BDG anastomosis. She underwent extracardiac Fontan completion with fenestration. Intraoperative findings included moderate adhesions from prior surgery; postoperative mPAP was 17–18 mmHg, and transesophageal echocardiography demonstrated good ventricular contraction. After separation from cardiopulmonary bypass (CPB time 130 min, aortic cross-clamp time 9 min), she developed massive bleeding with hypotension (70/40 mmHg), requiring massive transfusion. Ongoing postoperative hemorrhage via the chest tube (total 45 mL/kg) prompted mediastinal re-exploration 12 hours later. Prior to reoperation, total blood component transfusion was 160 mL/kg, and hemostasis was achieved despite no focal surgical bleeding source being identified intraoperatively.

Diagnostic assessment

On postoperative day (POD) 1, she developed signs of distributive shock, likely due to sepsis, including fever, tachycardia, wide pulse pressure, and leukocytosis with a white blood cell (WBC) count of 17,000/ μ L and 20% band forms. Inflammatory markers were markedly elevated, with procalcitonin (PCT) >100 ng/mL and C-reactive protein (CRP) 53 mg/L. She required escalating vasopressor support, with a maximum vasoactive-inotropic score of 70 (epinephrine 0.3 mcg/kg/min, dopamine 10 mcg/kg/min, and norepinephrine 0.3 mcg/kg/min). Empiric broad-spectrum antimicrobials, including meropenem and vancomycin, were initiated following a comprehensive septic work-up. By POD 2, she exhibited clinical deterioration with the development of multi-organ dysfunction. Liver function tests

KEY MESSAGES:

- TAMOF is a rare but highly lethal condition in pediatric patients after cardiac surgery, even following low-risk procedures.
- Differentiating TAMOF from disseminated intravascular coagulation in the postoperative setting is challenging but critical, as preserved fibrinogen levels, mild PT/APTT prolongation, thrombosis-predominant features, and brain-kidney involvement favor a thrombotic microangiopathy phenotype.
- Systemic inflammation related to cardiopulmonary bypass and sepsis may suppress ADAMTS-13 activity, promoting platelet-rich microthrombi formation.
- Early clinical recognition and prompt initiation of plasma exchange may reverse organ dysfunction and improve survival in this high-risk population.

revealed severe transaminitis, with aspartate transaminase (AST) peaking at 4,692 U/L and alanine transaminase (ALT) at 1,396 U/L. Acute kidney injury (AKI) was also evident, with blood urea nitrogen (BUN) of 36.3 mg/dL and serum creatinine of 1.8 mg/dL, accompanied by an oliguria refractory to loop diuretics (furosemide infusion at 0.4 mg/kg/h). Progressive lactic acidosis was noted, with lactate peaking at 16.8 mmol/L.

On POD 3, continuous renal replacement therapy (CRRT) was initiated in continuous veno-venous hemodiafiltration mode at an effluent rate of 40–50 mL/kg/h using the Prismaflex M100 system (Baxter International Inc., Deerfield, IL, USA). Blood flow rate was 4 mL/kg/min. Replacement fluid was administered pre-filter and post-filter in a 50:50 ratio with a total dose of 20 mL/kg/h, and the dialysate flow rate was set at 20 mL/kg/h. Despite adequate heparin anticoagulation, maintaining activated partial thromboplastin time (APTT) between 65–80 seconds (as per institutional protocol), recurrent filter clotting occurred within 24 hours for three consecutive days. This necessitated repeated circuit replacements due to pressures exceeding acceptable limits.

On POD 5, TAMOF was suspected based on clinical and laboratory findings. There was a progressive decline in platelet count, reaching a nadir of $19 \times 10^3/\mu$ L, in association with multi-organ dysfunction including AKI requiring CRRT, transaminitis, and persistent encephalopathy (Glasgow Coma Scale score E1Vt M3) despite sedation cessation.

There was also evidence of a thrombotic microangiopathic process, including: markedly elevated lactate dehydrogenase (LDH), peaking at 2,241 U/L; low haptoglobin (<10 mg/dL); and elevated D-dimer at 19.83 mg/L. A peripheral blood smear revealed a few schistocytes and fragmented red blood cells. Non-blanching purplish petechiae were noted on the fingertips, suggestive of peripheral microthrombi (Figure 1). Despite the throm-

botic microangiopathic picture, coagulation studies showed a mildly prolonged prothrombin time (PT) of 16.2 seconds and international normalized ratio (INR) of 1.4, with a normal fibrinogen level of 150. Inflammatory markers were persistently elevated, with PCT >100 ng/mL for over five consecutive postoperative days, CRP peaking at 79.3 mg/L, and IL-6 at 50 pg/mL.

Therapeutic intervention

On POD 6, PLEX was initiated using the Baxter TPE 2000 device (Baxter Healthcare Corporation, Deerfield, IL, USA). ADAMTS-13 activity, measured prior to PLEX, was 49%, supporting a diagnosis of TAMOF. After two PLEX sessions (each exchanging $1.5\times$ plasma volume with fresh frozen plasma), the platelet count rose from 19,000 to 55,000/ μ L, normalizing to 128,000/ μ L within five days post following the last PLEX session. Neurologic status returned to baseline, and the patient was extubated three days post-PLEX. Liver function returned to normal by post-PLEX day 5. Renal function recovered, allowing CRRT discontinuation with sustained diuresis on diuretics alone. Inflammatory markers normalized, and all vasoactive support was discontinued by post PLEX day 8.

All cultures (blood, tracheal aspirate, urine) were negative. She was managed as culture-negative sepsis with a seven-day antibiotic course. She was discharged home in stable condition, neurologically intact. The clinical timeline is summarized in Figure 2.



Figure 1. Non-blanching purplish petechiae observed on the fingertips, suggestive of peripheral microthrombi.

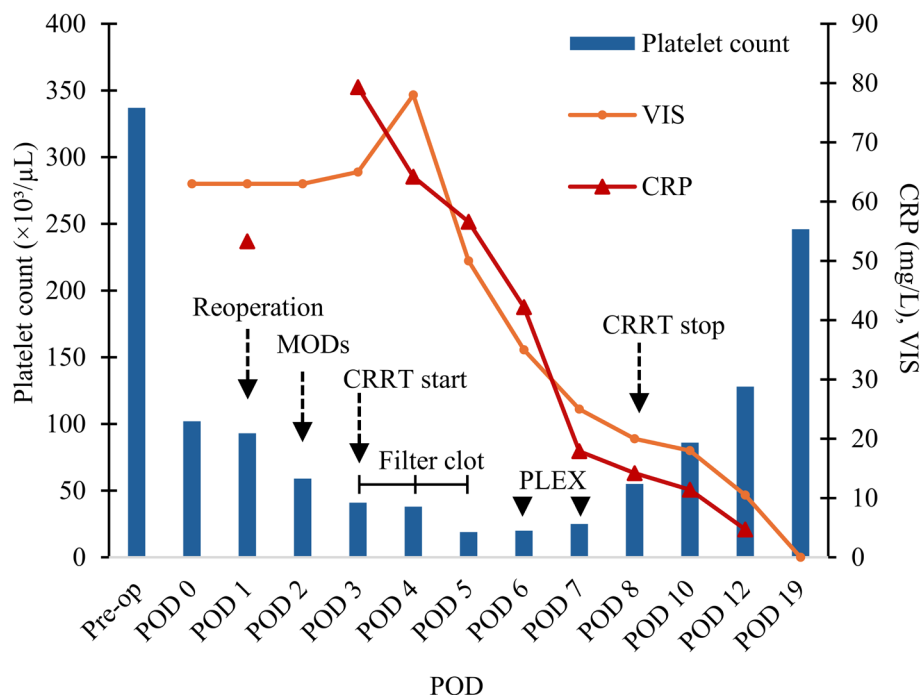


Figure 2. Daily platelet counts are shown. VIS and CRP were measured intermittently therefore the lines are intentionally discontinuous on days without measurements. Vertical dashed lines indicate major therapeutic interventions.

Abbreviations: POD: postoperative day; VIS: vasoactive inotropic score; CRP: C reactive protein; CRRT: continuous renal replacement therapy; PLEX: plasma exchange; MODs: multiple organ dysfunction syndrome.

DISCUSSION

Although data on the incidence of TAMOF in pediatric critical care units are limited, and scarcer still in the post-cardiac surgery population, morbidity and mortality remain significantly high, reaching nearly 40% [7]. A Multicenter Network Assessment reported that approximately 10 to 15 percent of patients with severe sepsis exhibited a TAMOF phenotype [8, 9]. In patients undergoing cardiac surgery with CPB, Very few studies have investigated TAMOF, reporting an incidence of 2 to 4 percent [10, 11]. The systemic inflammatory response following CPB contributes to elevated inflammatory markers, particularly IL-6 and PCT, which can destabilize hemodynamics and suppress ADAMTS-13 activity [12].

The Fontan operation is generally considered a low-risk procedure, classified as The Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery (STAT) Category 1, with a reported mortality rate of 1.3% (95% CI: 0.9%–1.9%), consistent with our institutional data over the past five years, where mortality remained below 1% [13]. Despite this, our patient developed TAMOF, a condition with substantially higher mortality. Early recognition of this condition was essential to initiate PLEX in a timely manner, which may have improved the outcome.

In our case, differentiating between TAMOF and overt disseminated intravascular coagulation (DIC) was particularly challenging, as both present with thrombocytopenia and multi-organ failure. In the postoperative setting, thrombocytopenia was initially attributed to common causes, including consumptive coagulopathy from surgical bleeding, cardiopulmonary bypass–related platelet consumption, or sepsis-associated DIC. Although the patient had early postoperative bleeding, the platelet count continued to decline markedly without evidence of ongoing hemorrhage. There was no identifiable source of infection; cultures were negative, and septic shock was not clearly evident. Importantly, several clinical clues favored a TAMOF phenotype: 1) thrombosis-predominant features, as demonstrated by frequent clotting of the CRRT membrane despite adequate anticoagulation; 2) severe thrombocytopenia with only mildly elevated PT and APTT, and normal fibrinogen levels; and 3) predominant involvement of the brain and kidneys, whose capillaries are highly sensitive to shear stress, resembling the pattern seen in thrombotic thrombocytopenic purpura (TTP) [1, 2, 7]. In contrast, overt DIC involves fibrin-rich microthrombi within small and medium-sized vessels across multiple organs, triggered by tissue factor activation and consumption of coagulation factors. This typically results in prolonged PT and APTT, along with significantly reduced fibrinogen levels [2].

Our patient met the diagnostic criteria for TAMOF, including thrombocytopenia (platelet count $<100,000/\mu\text{L}$), dysfunction of at least two organs, including AKI, transaminitis, encephalopathy, and elevated LDH and evidence of a thrombotic microangiopathic process, including reduced ADAMTS-13 activity and schistocytes on peripheral smear [6].

We postulate that, in addition to the inflammatory response following CPB, the patient was particularly prone to sepsis. A previous study reported that about 25% of patients with heterotaxy syndrome developed sepsis, with a mortality rate of 44% [14]. Sepsis may have further amplified the systemic inflammatory response. The patient demonstrated a hyperinflammatory state, evidenced by markedly elevated levels of PCT, CRP, and IL-6. These cytokines are known to reduce ADAMTS-13 activity, resulting in the accumulation of ULVWF and promoting platelet-rich microthrombi formation. This pathway leads to non-consumptive secondary thrombotic microangiopathy, unlike DIC, which is driven by a fibrin-based consumptive coagulopathy. Accordingly, laboratory findings consistent with consumptive coagulopathy were not observed in this patient [2, 3].

In the management of TAMOF, PLEX can improve organ dysfunction and reduce mortality by removing inflammatory mediators and ULVWF, as well as restoring ADAMTS-13 activity, thereby mitigating dysregulated inflammation. The number of PLEX sessions, based on studies in patients with sepsis, is typically guided by clinical response, particularly the recovery of organ function and improvement in platelet count [15]. According to the Thrombocytopenia-Associated Multiple Organ Failure Network Prospective Experience, an initial exchange of 1.5 times the plasma volume is performed on day 1, followed by single-volume exchanges on days 2 through 5 [7].

Our patient showed significant improvement in end-organ function and platelet count after two sessions of PLEX, eventually leading to successful extubation and discontinuation of CRRT. Although it is difficult to definitively determine whether TAMOF in this case was driven by sepsis or by the post-cardiac surgery inflammatory response associated with CPB, early recognition and prompt intervention with PLEX were critical, given the high mortality risk associated with this condition. Timely treatment may improve survival outcomes.

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: TP; (II) Data curation: TP; (III) Formal analysis: TP; (IV) Funding acquisition: TP; (V) Methodology: TP; (VI) Project administration: TP; (VII) Visualization: TP; (VIII) Writing – original draft: TP; (IX) Writing – review & editing: TP, SL.

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