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CASE REPORT

Paradoxical embolic strokes in a liver transplant recipient with atrial septal defect undergoing therapeutic plasma exchange

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Abstract
Therapeutic plasma exchange (TPE) is a technique used to separate blood components into layers based on their density difference, thus removing plasma and exchanging it with replacement fluids. A variety of adverse reactions has been described during TPE. Thrombotic events, especially strokes, are extremely rare complications of TPE. Our patient was a 55-year-old female with history of decompensated nonalcoholic steatohepatitis (NASH) liver cirrhosis. She underwent an orthotopic liver transplant (OLT) that was complicated with asystole during reperfusion. Cardiac workup revealed a new atrial septal defect (ASD) with left to right flow. Within the first 5 days after surgery, she developed refractory and persistent hyperbilirubinemia, with total bilirubin levels as high as 42 mg/dL. Our plasmapheresis service was consulted to initiate TPE. Towards the end of the first and only session of TPE, the patient developed hypoxia and left-sided hemiplegia. Stroke response was initiated, and the patient was intubated. MRI done 24 hours after the incident showed multiple acute small embolic infarcts scattered within the bilateral cerebral and cerebellar hemispheres. Bilateral lower and upper extremities venous duplex studies were positive for acute left internal jugular (IJ) vein thrombosis. Patient was treated with anticoagulation and the IJ catheter was removed. Patient also had closure of her ASD. On last follow up, she was doing well with complete reversal of neurologic deficits and stable liver function. Our patient had an uncommon complication of TPE. Her thrombosis manifested with multiple embolic strokes that would not have happened without an ASD with left to right flow.

KEYWORDS
atrial septal defect, embolic strokes, liver transplantation, paradoxical, plasma exchange

1 | INTRODUCTION

Therapeutic plasma exchange (TPE) is a technique performed with centrifugation- or filtration-based devices. TPE using centrifugation separates blood components into layers based on their density difference, thus removing plasma with the protein bound substances from the blood. The plasma is usually exchanged with replacement fluids such as albumin or thawed plasma.1
Although TPE is a relatively safe and well-tolerated procedure, different kinds of associated adverse reactions have been described. These adverse events have been attributed to the procedure itself, replacement fluid, anticoagulation used, or intravenous catheter access. The frequency of complications ranges from 4 to 30%.\textsuperscript{2-5} Frequently, the reported complications are mild and can be quickly managed. Rarely, severe events occur, mainly related to vasovagal reactions or severe citrate toxicity; these have been mostly reported in thrombotic thrombocytopenic purpura, leukostasis syndrome, and septic shock.\textsuperscript{2} TPE can affect patients' hemostasis due to the reduction of coagulation factors, which is further compounded in patients with an underlying risk for bleeding or thrombosis.

Thrombotic events, especially strokes, are extremely rare complications of TPE.\textsuperscript{6-8} We hereby report our experience with a case of paradoxical embolism resulting in stroke during TPE, which was complicated by the presence of an atrial septal defect (ASD).

2 | CASE HISTORY

Our patient was a 55-year-old Caucasian woman with a history of hypertension, hypothyroidism, end stage liver disease and cirrhosis secondary to non-alcoholic steatohepatitis (NASH) who underwent orthotopic liver transplantation (OLT). Cardiac echocardiogram and catheterization before transplant were negative. Her laboratory parameters showed a Model for End-Stage Liver Disease (MELD) score of 35 at transplant. During transplant, patient became coagulopathic with an estimated blood loss of 14 L and required transfusion with multiple blood components. She went into asystole during reperfusion and was revived with chest compressions and sent to the surgical intensive care unit. Cardiac workup revealed a new ASD with left to right flow and without evidence of pulmonary hypertension. Within her first postoperative week, she developed refractory persistent hyperbilirubinemia, with total bilirubin levels as high as 42 mg/dL. Patient’s workup was negative for antibody-related graft dysfunction or mechanical cholestasis. Her postoperative course was further complicated by ascites, peritonitis (treated with antibiotics), and abdominal wall mesh closure. Patient eventually recovered and was doing well.

Transfusion Medicine service was consulted to initiate TPE for her refractory hyperbilirubinemia. Although there are no ASFA (American Society for Apheresis)\textsuperscript{9} guidelines for the use of TPE for liver graft dysfunction in the setting hyperbilirubinemia, the decision to proceed with TPE was based on our institution’s experience with managing similar situations and published literature demonstrating the utility of early TPE in liver graft dysfunction by removing excess bilirubin.\textsuperscript{10}

After obtaining informed consent, TPE was performed using the COBE Spectra apheresis system processing one blood volume with thawed plasma replacement (2600 mL) to reduce the risk of bleeding from worsening thrombocytopenia and coagulopathy. A central venous catheter was placed in the left internal jugular (IJ) vein for vascular access. Anticoagulant citrate dextrose solution, solution A (ACD-A) was used with a whole blood to anticoagulant ratio of 15 to 1. A total of 5 g of IV Calcium gluconate was infused throughout TPE to treat ACD-A-induced hypocalcemia, and 25 mg IV Benadryl was given before TPE to treat allergic reactions to plasma. The patient did well during the first session of TPE; however, at the end the procedure, she became unresponsive, tachyypneic, hypoxic and left-hemiplegic. The extracorporeal volume was not rinsed with saline, thus aborting the return of contents to the patient. Oxygen saturation failed to improve with nasal cannula or bag mask ventilation; thus, the patient was intubated, and a stroke response was initiated. After stroke code activation, patient developed left upper extremity and left lower extremity hemiplegia with right-gaze deviation. Immediate CT head without contrast and CT angiography of head/neck with contrast were obtained (part of the acute stroke protocol) and were negative for acute findings. The patient’s neurological symptoms resolved within 30 minutes, leaving only mild residual deficits. Complete blood counts and basic electrolytes drawn within 10 minutes of the acute event showed persistent thrombocytopenia (Table 1). Therefore, due to her severe thrombocytopenia and resolving symptoms, she was not a candidate for any interventions including IV tissue plasminogen activator (tPA) or mechanical thrombectomy.

MRI of the brain without contrast 24 hours after initial symptom onset and resolution revealed multiple acute infarcts bilaterally in the cerebral and cerebellar hemispheres thought to be presumably embolic in nature (Figure 1). Subsequent transthoracic echocardiogram and transesophageal echocardiogram revealed preserved ejection fraction, a moderate size patent foramen ovale with bowing of the atrial septum to the right, and left to right shunting with no left atrial appendage thrombus. Telemetry monitoring did not show any atrial fibrillation. Bilateral upper and lower venous duplex studies were positive for an acute left internal jugular vein thrombosis; although it was unclear whether this was a consequence of the plasmapheresis or a culprit of thrombosis. The presumed etiology of the patient’s acute embolic infarcts was paradoxical emboli related to ASD. In the setting of acute ischemic infarcts, the patient was placed on
anticoagulation, so the closure of her ASD was delayed 5 days after stroke. It is worth noting that the transplant team was concerned about the ASD before starting plasmapheresis given the patient’s intraoperative course; however, the cardiology team did not anticipate an increased risk with plasmapheresis and recommended closing the ASD after the patient has been stabilized.

Our patient had no personal or family history of thrombosis. Thrombophilia workup was not pursued for two reasons. First, her management will not change based on the thrombophilia results. Second, there was concern that the results of the workup, especially for natural anticoagulants activities, would reflect the patient’s donor liver, instead of her pretransplant dysfunctional liver, and her initial recovery from a challenging surgery.

The patient had a prolonged and complicated course following her stroke. She had infectious complications, renal impairment, and she required intubation more than once. She also underwent ERCP with sludge removal and biliary sphincterotomy. Her liver function tests improved gradually. On last follow up after 24 months from the incident, the patient was doing well with stable liver function and without neurologic deficits from the strokes.

### DISCUSSION

Despite significant advances in orthotopic liver transplantation (OLT), graft dysfunction continues to be a serious complication that is associated with high morbidity and mortality.\textsuperscript{11,12} Biliary complications are the most common adverse events after OLT and can be seen in 10% to 25% of cases.\textsuperscript{12} Hyperbilirubinemia is a serious, significant determinant of early graft dysfunction following OLT. Without recovery of the liver graft, the mortality from early graft dysfunction is high. Retransplantation is considered a treatment for severe graft dysfunction; however, only a small number of patients would be rescued due to shortage of organ donors and possibly the unfavorable retransplantation outcomes among the severely ill.\textsuperscript{11} Thus, other methods of graft rescue and support are needed.

TPE is an extracorporeal blood purification procedure designed for the removal of pathogenic antibodies and proteins, immune complexes, cryoglobulins, endotoxins, and other high-molecular weight substances. The basis of TPE is that the removal of these substances will help reverse the pathologic processes caused by these

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Prior to TPE</th>
<th>Post TPE</th>
<th>Normal reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>13.4</td>
<td>13.7</td>
<td>12-15 g/dL</td>
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<tr>
<td>Platelet count</td>
<td>40,000</td>
<td>48,000</td>
<td>150-450 K/μL</td>
</tr>
<tr>
<td>PT</td>
<td>19</td>
<td>17</td>
<td>12.1-14.5 seconds</td>
</tr>
<tr>
<td>PTT</td>
<td>30</td>
<td>29</td>
<td>22-36 seconds</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>177</td>
<td>Not done</td>
<td>200-450 mg/dL</td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>36.5</td>
<td>20.2</td>
<td>&lt;1.2 mg/dL</td>
</tr>
</tbody>
</table>

**FIGURE 1** A, Diffusion weighted imaging (DWI) and B, FLAIR magnetic resonance imaging (MRI) revealing areas of acute ischemic infarcts in bilateral cerebral and cerebellar hemispheres.
“substances.” TPE can remove toxic substances including plasma bilirubin. Most of the coagulation factors are synthesized in the liver; thus, by replacing with fresh frozen plasma (FFP) TPE can also replace coagulation factors which are required in patients with liver failure and coagulopathy. A few reports have suggested the efficacy of TPE in liver support.10,14-17 In this regard, TPE can be used as a temporary support in liver failure until graft recovery or retransplantation.

According to a report from Johns Hopkins Hospital, TPE provided an effective treatment option for dysfunctional liver allograft in four of five patients, and all four patients had functioning grafts 1 year after liver transplantation.14 Akdogan and colleagues assessed the efficacy of TPE in 39 patients with fulminant hepatic failure.15 TPE was performed daily until adequate clinical response was obtained, the patient passed away, or transplantation occurred. Their findings suggested coagulopathy and hyperbilirubinemia were significantly improved through daily TPE. Twenty-one patients survived (54%), 12 required liver transplantation, and 18 patients expired. TPE was realized to be very effective in correcting coagulopathy and improvement of liver function. In another study from Japan, 11 patients with progressive liver failure after liver transplantation showed improved liver function after TPE, particularly in those with total bilirubin levels of 13 to 24 mg/dL.17

More recently and of more relevance to our case study, Choe et al10 published their experience evaluating the effects of TPE in early liver graft dysfunction. They defined early liver graft dysfunction as a sustained hyperbilirubinemia (≥10 mg/dL) within 30 days of liver transplantation without concurrent biliary complications. In a 13-year period, 107 early liver graft dysfunction patients underwent TPE while 36 patients did not. Patients managed with TPE had 82.2% and 53.8% survival rates at 1 month and 1 year respectively, whereas the non-TPE managed patients showed significantly lower survival rates of 58.3% and 22.2%, respectively (P < .001). In the TPE group, total bilirubin and INR statistically significant decreased after the final TPE session. TPE improved patients’ survival and decreased the hazard risk of death. Adverse events were documented in 44/1132 (4%) TPE sessions. Hypotension was the most common type of adverse events. Other minor adverse events comprised chills, abdominal pain, itching, and tingling. Alveolar hemorrhage was documented once. None of the patients had any thrombotic events or strokes from TPE.10

Although there are no ASFA (American Society for Apheresis) guidelines for the use of TPE for liver graft dysfunction in the setting hyperbilirubinemia, the decision to proceed with TPE for managing our case was made based on our institution experience with managing similar cases. This decision was further supported by published evidence in the medical literature on the utility of TPE to remove excess bilirubin from plasma to help reduce any damage caused on the liver graft.10,14,15,17 Bilirubin is associated with toxicity and its removal by TPE may help decrease its adverse effects.14,16,17 High levels of bilirubin can interfere with regeneration of the biliary duct cells. Therefore, hyperbilirubinemia has been considered a significant determinant of early graft loss in liver transplant patients.10,19 Thus, it seems reasonable to remove the excess bilirubin that cannot be processed by the transplanted liver especially during the early stage after transplantation.

Two distinct mechanisms have illustrated how ASD can cause cerebral embolic events: paradoxical embolism or atrial fibrillation. Our patient underwent extensive cardiac monitoring and imaging, revealing no evidence of atrial fibrillation or left associated atrial appendage thrombus; thus, the etiology of the patient's acute ischemic strokes was hypothesized to be due to a paradoxical embolism, in which her known left to right shunt was temporarily reversed to a right to left shunt, allowing for the formed embolisms to travel from her venous system to her brain. Perhaps this change in shunting was due to the flow of the plasmapheresis procedure, or a transient increase in abdominal pressure due to coughing or Valsalva maneuver that was enough for the right sided heart pressure to overcome the pressure within the left heart. Our patient had an uncommon complication of TPE, most likely fragmented thrombi from the thrombosed IJ vein although we cannot rule out thrombosis triggered by the patient's coagulopathy. Thrombosis manifested with multiple embolic strokes that would not have happened without an ASD.

Patients with liver disease including liver transplant patients are usually considered at risk for bleeding complications as reflected in their prolonged PT/aPTT. However, recent evidence suggests that the balance between prohemostatic and antihemostatic factors can be disrupted with a compensation for deficient liver-derived procoagulants resulting in a relative hypercoagulable state which may cause thrombotic complications. This is why coagulopathy in liver transplant patients is often coupled to thrombosis and it can extend for months following transplantation.20,21

In our patient, thrombosis manifested with multiple embolic strokes that would not have happened without an ASD. Our review of the literature yielded a single case report of a 68-year-old woman who developed a paradoxical embolism during discontinuous-flow plasmapheresis through a right jugular venous access.6 Her workup revealed a patent foramen ovale (PFO) with interatrial shunt. The authors hypothesized that the presence of the
venous catheter could have triggered an increase in the right atrium blood pressure, thus driving a paradoxical embolic stroke through the PFO. Our patient might have had the same mechanism of increased atrium blood pressure leading to a paradoxical embolism through the ASD.

Our case report is intended to caution physicians about thrombosis as a rare complication of TPE. The question remains whether ASDs should be corrected before TPE in the setting of increased risk of coagulopathy as in liver transplant patients. In our case, we decided to proceed with plasmapheresis as the priority was to treat the patient’s liver graft dysfunction and manage coagulopathy. We believe ASD correction before plasmapheresis would have been a risky procedure. We do not think ASD should be corrected before plasmapheresis especially in the setting of clinicially unstable patients with coagulopathy.

CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

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REFERENCES