Hemolytic Anemia following Stent-Graft Transjugular Intrahepatic Portosystemic Shunt Creation

Andrew Kuei, MD¹ Adam E. Mikolajczyk, MD² Matthew M. Niemeyer, MD^{1,3}

¹Department of Radiology, University of Illinois Hospital and Health Sciences System, Chicago, Illinois

²Division of Gastroenterology and Hepatology, University of Illinois Hospital and Health Sciences System, Chicago, Illinois

³Division of Interventional Radiology, University of Illinois Hospital and Health Sciences System, Chicago, Illinois

Address for correspondence: Matthew M. Niemeyer, MD, Division of Interventional Radiology, Department of Radiology, University of Illinois Hospital and Health Sciences System, 1740 West Taylor Street, MC 931, Chicago, IL 60612 (e-mail: mniemeye@uic.edu).

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Abstract

Keywords

- TIPS
- hemolytic anemia
- e-PTFE
- interventional radiology

Transjugular intrahepatic portosystemic shunt (TIPS) creation is a minimally invasive technique aimed at managing the complications of portal hypertension. Initially performed in the setting of variceal bleeding, the role of TIPS has expanded to treatment of medically refractory ascites, portal hypertensive gastropathy, hepatic hydrothorax, Budd-Chiari syndrome, portal vein thrombus, and hepatorenal syndrome. Potential complications from TIPS are well documented, and include hepatic encephalopathy, hepatic failure, and TIPS dysfunction. Hemolytic anemia is a lesser known complication related to TIPS creation. In this article, a case of hemolytic anemia following TIPS creation using a Viatorr stent-graft is described.

Transjugular intrahepatic portosystemic shunt (TIPS) creation is a minimally invasive technique aimed at managing the complications of portal hypertension. Historically, TIPS offered a safer alternative to surgical portocaval shunt creation for the treatment of acute variceal hemorrhage. In the early era of TIPS, bare metal self-expanding stents—such as the Wallstent (Boston Scientific, Marlborough, MA)—were utilized for the procedure.¹ In 2004, the Viatorr (W. L. Gore & Associates, Inc, Flagstaff, AZ) expanded polytetrafluoroethylene (e-PTFE) stent graft was introduced with the specific indication for TIPS. Its adoption brought significant improvements in shunt patency rates, and remains the preferred device today.^{2,3}

Initially performed in the setting of variceal bleeding, the role of TIPS has expanded to treatment of medically refractory ascites, portal hypertensive gastropathy, hepatic hydrothorax, Budd-Chiari syndrome, portal vein thrombus, and hepatorenal syndrome.⁴

Potential complications from TIPS are well documented, and include hepatic encephalopathy, hepatic failure, hemorrhage, biliary injury, TIPS thrombosis, TIPS dysfunction, and

TIPS migration.⁵ Hemolytic anemia is a lesser known complication related to TIPS creation. In the era of bare metal stents, the reported incidence was 10%,⁶ and has been described in multiple studies and case reports. In the stent-graft era, TIPS-associated hemolytic anemia occurs rarely. Here we describe a case of hemolytic anemia following TIPS creation using a Viatorr stent graft.

Case Report

A 55-year-old woman with a history of alcoholic cirrhosis was referred for TIPS creation. Her cirrhosis was complicated by nonbleeding esophageal varices and iron-deficiency anemia attributed to portal hypertensive gastropathy. She also had refractory chylous ascites complicated by frequent leakage of ascitic fluid from her umbilical hernia that was inadequately controlled with weekly large volume paracenteses and high-dose diuretics. Thus, to better address her ascites, she was placed on the liver transplant waitlist and a consultation for TIPS was requested.

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Preprocedure laboratory workup included a total bilirubin 2.0 mg/dL, indirect bilirubin 1.1 mg/dL, creatinine 1.36 mg/dL, hemoglobin 7.0 g/dL, platelet count 48,000 per microliter, and INR 2.0. Model for End-stage Liver Disease (MELD) score was 19. Echocardiography demonstrated normal right ventricular function and no tricuspid regurgitation.

The patient underwent successful creation of TIPS from the right hepatic vein to the right portal vein with placement of a 10 cm (8 cm covered + 2 cm uncovered) $\times$ 8–10 mm diameter Viatorr stent graft. The portosystemic pressure gradient decreased from 22 to 11 mm Hg (**Fig. 1**). She had an uneventful recovery. Her complete blood counts and liver enzymes remained stable, and she neither had encephalopathy nor did she require transfusions prior to discharge.

During routine 1-month follow-up, the patient demonstrated an acute worsening of her baseline anemia with a hemoglobin of 5.8 g/dL requiring blood transfusion. Initial workup demonstrated a borderline macrocytosis with mean corpuscular volume (MCV) of 101.1 fL/red cell. Serum iron, ferritin, and transferrin percent saturation were all normal, suggesting resolution of the previous iron deficiency. Vitamin B12 and folate levels were also normal. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) studies were negative for evidence of a monoclonal protein. A Coombs test was negative. Fecal occult testing was negative and CT of abdomen and pelvis was unremarkable for an intra-abdominal source of bleeding. Notably, reticulocytes were increased at 5.5%, lactate dehydrogenase (LDH) was mildly elevated at 184 units/L, haptoglobin had decreased from 36 to <10 mg/dL, and total bilirubin had increased to 3.9 mg/dL with an indirect bilirubin of 2.5 mg/dL. Erythropoietin levels were appropriately elevated to 64 mU/mL, suggesting increased loss of red cells. Peripheral smear did not reveal any schistocytes.

Over the next 2 months leading up to the present, she was readmitted multiple times with worsened anemia requiring blood transfusions. A bone marrow biopsy was negative for

myelodysplasia, only revealing increased erythropoiesis. Laboratory evaluation revealed progressive increases in the reticulocyte count to as high as 9.3%, and in the LDH to 304 unit/L. Strikingly, each time her anemia acutely worsened, her indirect hyperbilirubinemia would also simultaneously worsen. Having excluded other diagnoses during this extensive evaluation, the results were most consistent with an ongoing hemolytic anemia. At present, her anemia is managed with intermittent blood transfusions, and she awaits liver transplant.

Discussion

Hemolytic anemia is the primary hematologic complication of TIPS, characterized by reticulocytosis, indirect hyperbilirubinemia, decreased haptoglobin, and elevated lactate dehydrogenase. Anemia is a common complication of chronic liver disease and recognizing hemolysis as a complication of TIPS can be challenging. It also requires that other etiologies of anemia such as gastrointestinal hemorrhage, reduced erythropoiesis secondary to anemia of chronic disease, alcohol toxicity, and nutritional deficiency first be excluded.

Hemolytic anemia associated with creation of TIPS was first documented by Sanyal et al in 1992. In this case, a 48-year-old man listed for liver transplantation presented with hematemesis secondary to esophageal variceal bleeding. Following endoscopy and sclerotherapy to control the acute variceal hemorrhage, TIPS was performed using a 42-mm bare metal Wallstent. Over the next 10 days, the patient developed evidence of intravascular hemolysis with anemia, elevated serum bilirubin, decreased haptoglobin, and reticulocytosis. Hemolytic anemia persisted until liver transplant was performed 6 weeks later. Following transplantation, the hemolytic anemia resolved. It was hypothesized that hemolysis occurred secondary to blood passing through the un-endothelialized bare end of the Wallstent projecting into the portal vein. This was depicted *in situ* by images of the explanted liver.⁷

Fig. 1 (a) Preprocedural contrast-enhanced computed tomography of the abdomen demonstrates patent hepatic and portal veins with favorable anatomy for TIPS placement between the right hepatic vein (arrow) and posterior branch of the right portal vein (asterisk). Large-volume ascites is present. (b) Digital subtraction angiography after intravascular ultrasound-guided portal access confirms puncture of the posterior branch of the right portal vein (asterisk) from the right hepatic vein (arrow). There is hepatopetal flow within right and left portal veins. (c) Digital subtraction angiography after deployment of a 10 cm (8 cm covered + 2 cm uncovered) $\times$ 8–10 mm diameter Viatorr stent graft demonstrates a well-positioned stent with proximal uncovered end terminating in the right portal vein and distal covered end terminating at the confluence of the right hepatic vein and inferior vena cava. There is reversal of flow within the right portal vein.

In the following years, four cases were reported by Riggio et al and Cheng et al in 1994 followed by eight cases by Sanyal et al and Garcia-Rebollo et al in 1996. All studies propose a similar mechanism of hemolysis termed “naked stent syndrome.” Injury occurs as red blood cells collide with the unendothelialized bare wire mesh of the stent, particularly along the free hepatic and portal venous ends.^{7–10,14}

Hemolytic anemia related to other implanted devices is a known phenomenon, and traumatic red cell damage from high-flow shear stress induced by heart valve prostheses and aortic bypass grafts has been previously reported.¹¹ Flow models have shown that hemolysis by shear stress is found in flow velocities greater than 2,000 cm/s.¹² However, velocities within TIPS are typically far less by comparison. A notable difference in TIPS-related hemolysis compared with prosthetic valve-related hemolysis is the absence of schistocytes on peripheral blood smear, as demonstrated in our case report. A possible explanation for this is that the primary mechanism for injury is not simply rupture from high-flow shear stress, but rather collision injury of sufficient severity to induce erythrophagocytosis, in which damaged red blood cells are removed by the spleen or circulating phagocytes.^{6,13} Additionally, the red blood cells in TIPS patients often demonstrate intrinsic structural abnormalities and shorter half-lives secondary to cirrhosis and hypersplenism. These changes theoretically enhance the susceptibility for injury and subsequent erythrophagocytosis.⁶

Another distinguishing characteristic is the self-limited time course of hemolysis seen with TIPS, compared with a chronic hemolysis seen with prosthetic heart valves. Although a few of the previously reported cases of hemolysis resolved only after liver transplantation, the majority of cases resolved spontaneously by 12 weeks. It is postulated that the time course of spontaneous remission correlates with neointimal formation throughout the stent, which reduces collisions between red cells and stent interstices, thus diminishing injury.¹⁴

With the adoption of the Viatorr stent graft, TIPS-associated hemolytic anemia occurs rarely. This seems sensible, given the smooth e-PTFE lining the majority of the stent and limiting red cell collisions with bare metal interstices. While rare, our case illustrates that hemolytic anemia still remains a potential complication following TIPS placement in the stent-graft era. Although the majority of the length is covered by an e-PTFE lining, the Viatorr stents have a 2-cm bare metal segment to allow for portal perfusion (→ Fig. 2). This may represent a potential site of red blood cell injury, though this remains to be experimentally validated.

To date, our patient continues to have a prolonged and unresolved hemolytic anemia, despite being 12 weeks beyond TIPS creation. One potential explanation could be increased flow velocities within the TIPS, and thus increased collision forces between red cells and stent interstices at the free end. In our case, peak flow velocity in the distal stent increased from 204 to 277 cm/s at 1 and 2 months, respectively. The significance of portal venous velocity on hemolysis is unclear, however, and it has been shown that hemolysis subsides despite little change in portal venous

Fig. 2 The large bracket demarcates the intraparenchymal, covered portion of the expanded polytetrafluoroethylene (e-PTFE) lined Viatorr stent graft. The small bracket demarcates the 2-cm bare metal segment of the Viatorr stent positioned freely within the right portal vein, thus allowing unobstructed portal blood flow.

velocity within 12 weeks.⁶ A single case of self-limiting hemolytic anemia after TIPS using Viatorr stent was reported in 2008 by Fallon et al.¹⁵ This patient required multiple blood transfusions with peak indirect bilirubin at 4 months and eventual stabilization of hemoglobin at 5 months. With further endothelialization of the bare segment of stent, it is possible that our patient's hemolytic anemia will improve in a similar delayed fashion. If it does not, there is a paucity of literature available to guide therapy. In a case report from 2000, Abraham described resolution of hemolytic anemia

Fig. 3 The portal inflow angle is defined by the direction of inflow of blood from the portal vein with respect to the direction of flow within the intraparenchymal and hepatic outflow segment of the stent graft.

after embolization of the TIPS for hepatic coma.¹⁶ TIPS occlusion may decrease flow rates in the portal vein, mitigating the shear force on red cells as they pass through the bare segment. While less likely, TIPS occlusion could also reduce red cell injury if it occurs from turbulent flow through the intrahepatic, covered segment as a result of an acute portal inflow angle (►Fig. 3). This solution would result in the unwanted return of ascites. Alternatively, placement of a covered stent within the bare portion of the indwelling Viatorr may limit red cell collisions with the interstices and prevent red cell injury. The ultimate treatment for both hemolysis and underlying liver disease is liver transplantation. For our patient, the outcome is yet to be determined.

Disclosure

A.K., A.E.M., and M.M.N. have nothing to disclose.

Conflict of Interest

None.

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