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CASE REPORT | LIVER

Microangiopathic Hemolytic Anemia Following Transjugular Intrahepatic Portosystemic Shunt Creation in an Adolescent

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ABSTRACT

Transjugular intrahepatic portosystemic shunt (TIPS) creation is an effective approach to address the complications of portal hypertension. This case report describes an adolescent boy who underwent TIPS creation with an expanded polytetrafluorethylene-lined stent graft for portal hypertension secondary to sinusoidal obstruction syndrome. He subsequently developed microangiopathic hemolytic anemia, an uncommon complication of covered stents that is not well reported in the pediatric population. Despite its rarity and typical conservative management, microangiopathic hemolytic anemia should be considered and regularly monitored in the months following TIPS creation in pediatric patients.

KEYWORDS: pediatric portal hypertension; transjugular intrahepatic portosystemic shunt; TIPS-induced hemolytic anemia; microangiopathic hemolytic anemia; MAHA

INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) creation is an effective approach to address the complications of portal hypertension (PH) by reducing the portosystemic pressure gradient within the liver. In the adult population, this procedure is well established with high technical success and low adverse event rate.[1] TIPS in pediatric patients, however, remains a less common practice, likely influenced by the relatively lower prevalence and heterogeneous PH etiology and technical challenges in operating on smaller livers.[2] Recently, the literature on TIPS creation in children and adolescents has shown the usage of expanded polytetrafluorethylene (ePTFE)-covered TIPS stent grafts improves patency when compared with bare metal stents.[2–5] Several pediatric studies have since demonstrated high technical feasibility, safety, and clinical effectiveness.[2,4,5] While several complications still persist with ePTFE-covered stents, the shift from bare metal stents has minimized the incidence of TIPS-induced hemolytic anemia, reported previously in 10% of patients.[6] This case report describes microangiopathic hemolytic anemia (MAHA), a lesser-known complication following TIPS creation with ePTFE-covered stents, in a pediatric patient.

CASE REPORT

A 13-year-old adolescent boy with a history of Pre-B-cell acute lymphoblastic leukemia presented for management of PH complicated by nonbleeding esophageal varices and splenomegaly. PH was first noted at the age of 3 years resulting from sinusoidal obstruction syndrome after 6-thioguanine use during delayed intensification. Despite completing chemotherapy and achieving remission at the age of 6 years, he developed thrombocytopenia and splenomegaly the following year. Subsequent liver biopsies demonstrated minimal periportal chronic inflammation at the age of 7 years that progressed to nodular parenchyma with septal formation at the age of 13 years, indicating evolving cirrhosis. Esophagogastroduodenoscopy also revealed 3 esophageal varices that worsened from grade 1 to grade 2–3 with red-wale sign, refractory to 1 session of banding, wherein 1 band was successfully placed, but eradication was incomplete (Figure 1). For concerns of further variceal formation and bleeding, propranolol was prescribed and titrated to 10 mg daily. Subsequent MRI

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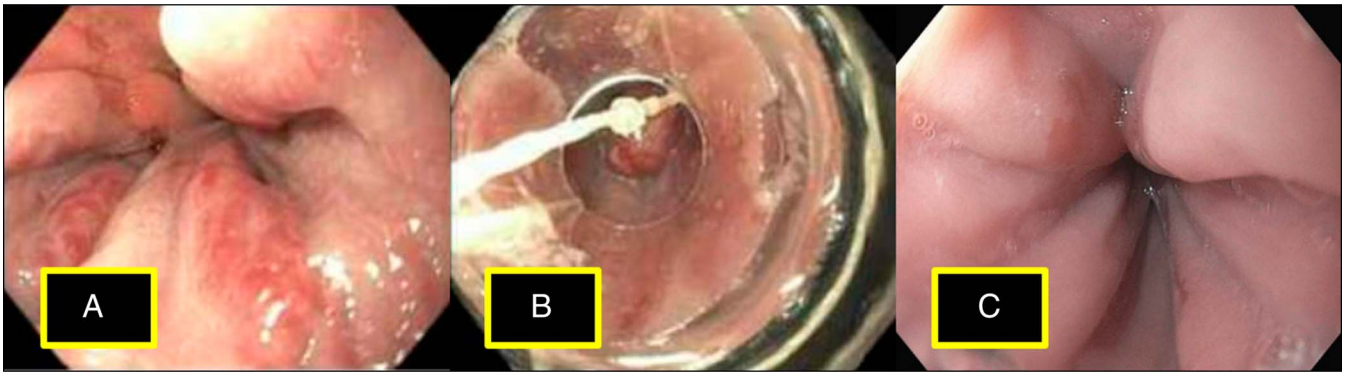

Figure 1. Lower third of the esophagus on endoscopy. (A) 5 months prior to TIPS procedure, Grade 2-3 varices were seen with red-wale sign, and (B) one band was placed as primary prophylaxis. (C) 7.5 months after TIPS creation, mucosal abnormality visualized, but varices were decompressed.

depicted small, tortuous portal systemic collaterals with splenomegaly (Figure 2). Vascular and interventional radiology consultation was requested.

The patient underwent successful endovascular TIPS creation from the right hepatic vein to the right portal vein with placement of a Viatorr stent graft (Gore Medical, Flagstaff, AZ). Portosystemic gradient decreased from 11 mm Hg to 4 mm Hg (Figure 3). Postprocedure laboratory results were notable for expected elevated transaminase (alanine aminotransferase 804 U/L, aspartate aminotransferase 863 U/L), bilirubin (total 2.3 mg/dL), and ammonia (122 μmol/L) levels (Table 1). Patient remained stable while admitted overnight with no interventions needed before his discharge on postoperative day 1.

At the routine 1-month follow-up, the patient demonstrated increasing unconjugated hyperbilirubinemia (total 3.4 mg/dL) with mild scleral icterus despite improved transaminase (alanine aminotransferase 53 U/L, aspartate aminotransferase 59 U/L) and ammonia (86 umol/L) levels. In addition, his baseline anemia before the procedure (hemoglobin 11.6 g/dL), unassociated with iron deficiency, appeared slightly worsened (hemoglobin 11 g/dL), suggesting a new onset hemolytic process. He was started on 300 mg of ursodiol twice daily and underwent an extensive evaluation, revealing reticulocytosis (absolute $173*10^3/\mu L$); elevated lactate dehydrogenase (345 U/L); low haptoglobin (<30 mg/dL); negative direct Coombs test; and negative peripheral blood smear for schistocytes. Urinalysis, while initially orange in color before resolving, contained elevated urobilinogen (8 mg/dL, normal < 2 mg/dL) but no red blood cells. Ultimately, the temporal association of TIPS creation to hyperbilirubinemia in the absence of other etiologies pointed toward a diagnosis of MAHA. TIPS patency was confirmed by Doppler ultrasound, and the patient had nonpalpable splenomegaly, improved thrombocytopenia, and esophagogastroduodenoscopy, showing resolution of esophageal varices (Figure 1). Reassuringly, he returned to his daily activities and did not develop symptoms concerning encephalopathy. He was subsequently managed conservatively with significant improvement in hyperbilirubinemia 7.5 months post-TIPS procedure (total 1.1 mg/dL) and continues to be monitored regularly.

DISCUSSION

This case highlights a time course highly suspicious for TIPS-induced hemolysis, an uncommon complication with covered stents. TIPS-induced hemolysis is often a diagnosis of exclusion. Nonetheless, in the absence of bleeding and preserved liver function, hemolysis was consistent with temporal onset of indirect hyperbilirubinemia, reticulocytosis, decreased haptoglobin, and elevated lactate dehydrogenase.

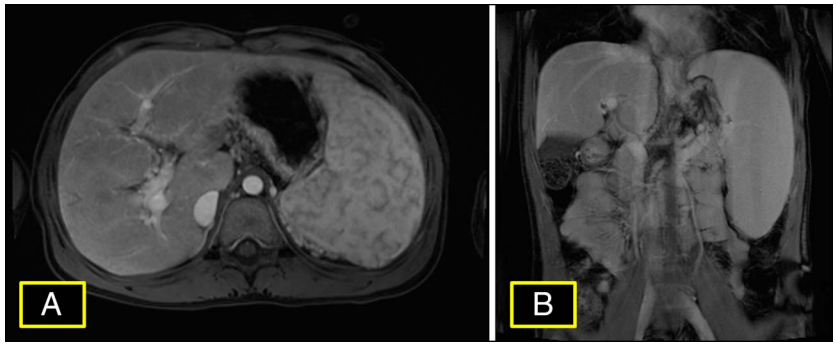

Figure 2. (A) Axial and (B) coronal views of abdominal MRI with IV contrast at the age of 13 years. Loss of hepatic volume. Heterogeneity and peripheral fibrosis, particularly in right hepatic lobe, with small, tortuous portosystemic collaterals. Markedly enlarged spleen with diameter increased from 14 cm at the age of 7 years to 16.7 cm at the age of 13 years.

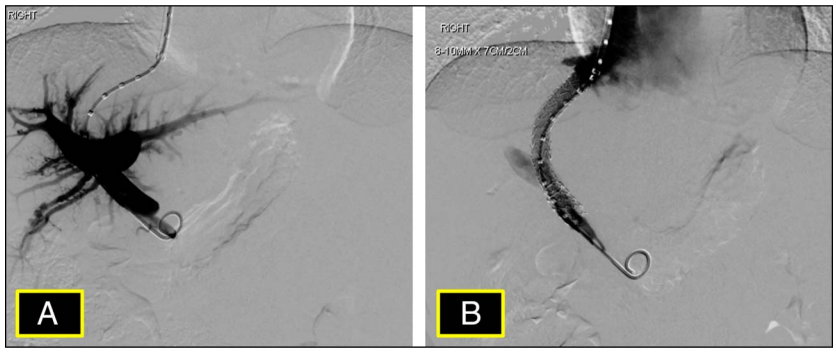

Figure 3. Portal venogram (A) before transjugular intrahepatic portosystemic shunt creation and (B) after placement of expanded polytetrafluorethylene-covered controlled expansion, endoprosthesis dilated to 8 mm. Portosystemic pressure reduction was achieved from 11 to 4 mm Hg.

Since the advent of ePTFE-covered stents, there are only a handful of case reports describing TIPS-induced hemolytic anemia, all observed in adults.[7–9] Although ePTFE-covered stents are mostly coated, there is a segment of stent that remains bare, extending into the portal vein; red blood cells (RBCs) may be injured during interaction with nonendothelialized bare metal stent. This concept was previously compared with the high-flow shear stress associated with artificial heart valves.[6] However, in this context, significantly lower mesenteric venous and TIPS flow and lack of schistocytes in peripheral smear argue against mechanical hemolysis as the sole reason for hemolysis following TIPS.[7,8] MAHA after TIPS is likely multifactorial: evolving or established cirrhosis is another consideration, frequently contributing to the abnormal RBC structure, life-span, and function from chronic liver disease and hypersplenism. It is possible that the fragility of RBCs in combination with stent-induced sheer stress may enhance susceptibility to a hemolytic process.

Patients with TIPS-induced hemolysis rarely require therapy as clinical sequela tends to be self-limited and resolve over time.[8] In the literature, the majority of TIPS-induced hemolysis resolves 12 weeks after placement, which corresponds to the formation of neointima lining the stent, reducing turbulence and therefore RBC trauma.[6,10] Regarding persistent hemolysis as seen in this patient, it is possible that more time is needed for further neointimal formation and endothelization, particularly on the uncovered area of the stent.

To our knowledge, pediatric TIPS-induced hemolytic anemia is under-reported in the literature. The mechanism proposed in adults is likely very similar to that in children. In both age groups, diagnosis requires new onset or worsening anemia after TIPS placement in addition to exclusion of alternate causes to lab abnormalities, such as hyperbilirubinemia from advanced liver disease. In addition, these patients should undergo hematology evaluation to support the presence of MAHA or potentially find rare thrombotic microangiopathic processes. The severity of change in anemia and clinical presentation, subclinical in this case, can further stratify which patients may benefit from extensive testing for MAHA or other underlying complications. Although usually a benign complication, TIPS-induced anemia can be severe enough to require blood transfusion.[7] MAHA as a differential for hyperbilirubinemia and anemia following TIPS creation in the setting of supportive

Table 1. Pertinent laboratory values before TIPS creation and the months following

Lab test (normal range)	Pre-TIPS	POD1	1 mo post-TIPS	1.5 mo post-TIPS	5 mo post-TIPS	7.5 mo post-TIPS
Hemoglobin (13–16 g/dL)	11.6	12.8	11	11	13.4	12.5
Total bilirubin (0.3–1 mg/dL)	1.0	2.3	3.4	4.4	3.6	1.1
Direct bilirubin (0–0.2 mg/dL)	—	—	0.8	0.8	—	0.3
Alanine aminotransferase (8–36 U/L)	22	804	53	39	32	26
Aspartate aminotransferase (13–38 U/L)	27	863	59	49	43	32
Ammonia (<47 μmol/L)	44	122	86	—	—	—
Absolute reticulocytes (33–126 *10^3/μL)	—	—	—	173	153	—
Lactate dehydrogenase (115–257 U/L)	—	—	—	345	297	—
Haptoglobin (44–215 mg/dL)	—	—	—	<30	<30	—
Direct Coombs test	—	—	—	—	Negative	—
Platelet count (150–350*10^3/μL)	72	101	78	106	107	205

POD1, postoperative day 1; TIPS, transjugular intrahepatic portosystemic shunt.

blood studies is thus crucial in the monitoring and longevity of the intervention.

DISCLOSURES

Author contributions: All authors provided substantial contributions to the conception and the acquisition, analysis, and interpretation of data for the work. Specifically, JY Khoo drafted the work, revising it critically for important intellectual content under the review and guidance of VV Gopalareddy. ML Lessne aided with image acquisition and interpretation and manuscript editing. Final version for publication was reviewed and approved by VV Gopalareddy and ML Lessne. VV Gopalareddy is the article guarantor.

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Informed consent was obtained for this case report.

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