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Case Report
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Treatment of Severe Hepatic Veno-Occlusive Disease after Bone Marrow Transplantation by Trans Jugular Intrahepatic Portosystemic Stent-Shunt (TIPS)

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Abstract

Severe Veno-Occlusive Disease (VOD) of the liver is an important cause of mortality after bone marrow transplantation. This paper reports the case of a child that underwent Transjugular Intrahepatic Portosystemic Shunt (TIPS) for life-threatening VOD after following haploidentical bone marrow transplantation for acute lymphatic leukemia. TIPS permitted regression of the hepatic symptoms as decreased aminotransferase levels and resolution of ascites. TIPS were an effective method for portal decompression.

Keywords: Veno-occlusive disease, Bone marrow transplantation, Treatment, Transjugular intrahepatic portosystemic stent-shunt (TIPS)

Introduction

Hepatic Veno-Occlusive Disease (VOD) is a complication after Hematopoietic Stem Cell Transplantation (HSCT). The development of VOD has been associated with high-dose and combination cytoreductive therapy, particularly regimens that involve busulfan, cyclophosphamide, carmustine, and etoposide, associated with total body irradiation, preexisting liver dysfunction, advanced disease status at time of transplant, HLA-mismatched or unrelated donor transplant [1-4].

The hepatic histology of VOD is characterized by a non-thrombotic obstruction of hepatic venules, sinusoidal congestion, sinusoidal fibrosis, and hepatocellular necrosis, which occurs predominantly in the centrilobular zone of the liver acinus. Portal hypertension with ascites frequently accompanies these histological changes and hallmarks the clinical manifestations of this syndrome [5].

Despite treatments, severe VOD is frequently fatal. It is important always to consider portal decompression in patients with life-threatening veno-occlusive disease [6].

Case Report

The 9-years-old boy was diagnosed with T acute lymphoblastic leukemia. He was treated with ALL BRM 2009. He had various chemotherapy toxicity including aplasia marrow and perianal ulcer. Cytomegalovirus and Fanconi Anemia research were negatives. He received conditioning regimen to three. Haploidentical bone marrow with fludarabine and TBI total dose decreased from 1200 to 1000 cGy. Prophylaxis to graft-versus-host disease was made with cyclophosphamide, tacrolimus and mycophenolate. He received ursodeoxycholic acid 600 mg/day in 2 divided doses to prophylaxis of VOD.

Twenty-two days after marrow infusion, the child presented abdominal pain, increase of serum aminotransferases, 23% weight gain, and impaired coagulation. Abdominal computed tomography showed marked hepatomegaly. ALT peaked 539 U/l, AST 1872 U/l and GGT 88 U/l. When TIPS was indicated total bilirubin was 1.55 mg/dl and he was anicteric. Hepatitis serologies were negatives. He had kidney failure with volume overload and creatinine clearance 69 mL/min/1.73 m2 possibly associated to increase abdominal pressure and/or renal hepatic syndrome. He required dialyze and paracentesis to release abdominal pressure and alleviate respiratory distress before TIPS. But despite the efforts, he needed mechanical ventilation support.

Twenty-six days after marrow infusion, TIPS was performed. Mean hepatic venous pressure gradient decreased from 14 mmHg to 2 mmHg after TIPS insertion. Following TIPS,

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Table 1: Level of aminotransferases levels. TIPS were performed in 08-08-17.

Date	AST U/l	ALT Ul/l	Total Bb mg/dl
8/2/2017	26	12	0.34
08-03--17	37	17	0.5
8/4/2017	96	38	0.5
8/5/2017	540	222	0.79
8/6/2017	1075	444	0.65
8/7/2017	1793	590	0.88
8/8/2017	1872	539	1.55
8/9/2017	1496	411	3
8/10/2017	675	283	2.63
8/11/2017	265	165	2.43
8/12/2017	165	136	2.12
8/13/2017	109	106	1.88
8/14/2017	104	104	2.72
8/15/2017	82	94	2.99
8/16/2017	66	90	3.08
8/17/2017	55	67	3.17

aminotransferases decreased. However, bilirubin increased. Six days after TIPS, he was extubated.

Discussion

In our patient, the risk factors for VOD were: unrelated donor transplant and cyclophosphamide associated with total body irradiation. The patient presented various systemic toxins during induction chemotherapy and after conditioning treatment to HSCT. It was interpreted as an indication that the cells are defective in the repair mechanism to tolerate the cross-links produced [4] in his DNA. Because of it, total dose of TBI was reduced. Nevertheless, he had toxicity with severe VOD and pneumonitis.

EBMT diagnostic criteria for hepatic VOD were used in this patient. It is the presence of two or more of the following: unexplained consumptive and transfusion refractory thrombocytopenia; otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain 45% above baseline value; hepatomegaly (best if confirmed by imaging) above baseline value, ascites (best if confirmed by imaging) above baseline value; rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥ 2 mg/dL within 72 hrs. This patient had four criteria: otherwise unexplained weight gain on three consecutive days despite the use of diuretics; hepatomegaly confirmed by imaging, ascites; rising bilirubin from a baseline value on 3 consecutive days (Table 1). He was icteric after TIPS.

This patient had many severity criteria to severe VOD: renal failure, impaired coagulation, necessity invasive pulmonary ventilation, increase of ALT and AST bigger than fivefold and need for paracentesis. However, Bilirubin was 1.55 mg/dl when TIPS was indicated. An icteric VOD was observed in 32% of patients in pediatric prevention trial, including those experiencing severe disease. An icteric VOD seems to be particularly prevalent in child. For this reason, pediatric European Society for Blood and Marrow Transplantation (EBMT) criteria recognize an icteric VOD as a frequent entity and consider hyperbilirubinemia as a non-mandatory criterion. Instead of a predefined level of hyperbilirubinemia in children, the EBMT criteria require the bilirubin level to rise from an individual baseline on 3 consecutive days, after the exclusion of competing causes [5,7,8]. Doppler ultrasound gives unspecific information by showing hepatomegaly, ascites, splenomegaly, periportal edema. It also helps ruling out biliary obstruction, infiltrative tumors or infectious lesions such as liver abscess, and detecting hepatic or portal vein obstruction. However, observer dependent factors may affect the result of Doppler Ultrasound. When clinical and imaging information is not sufficient to make a diagnosis of VOD in patients with moderate or severe disease, a liver biopsy is recommended. In patients with low platelets or severe ascites, a transjugular route is usually preferred. Complication and mortality rates related to this procedure have been 7% to 18% and 0% to 3%, respectively. We decided not to perform liver biopsy due to the risks of the procedure and the high probability of VOD.

A hepatic venous gradient (GHPV >10 mmHg) is highly specific for SOS in a context of exposure to myeloablative therapy [9]. The Hepatic venous pressure gradient value of this patient was 14 mmHg and decreased to 2 mmHg after TIPS.

VOD shares with the Budd-Chiari syndrome the same rationale for porta-caval decompression using the portal vein as an outflow tract. Compared to surgical porta-caval shunts, TIPS may be performed without laparotomy which is associated with the risks of infection in an immunocompromised patient and bleeding due to the coagulopathy. In addition, TIPS reduces the operative stress and the tissue trauma to a minimum [6].

In this case, TIPS showed hepatic benefits. The patient improved from ascites and hepatomegaly [6]. Data from literature favors precoce TIPS insertion in VOD patients. Nevertheless, after TIPS insertion the patient survived 10 weeks. This can lead us to hypothesize that TIPS insertion brought benefits to this specific patient.

Conclusion

TIPS may be an option of treatment of severe VOD.

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