

## SUCCESSFUL TREATMENT OF HEPATIC VENO-OCCLUSIVE DISEASE IN A PERIPHERAL BLOOD PROGENITOR CELL TRANSPLANT PATIENT WITH A TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT-SHUNT (TIPS)

Javier de la Rubia,\* Ana Carral,\* Hortensia Montes,<sup>o</sup> Juan J. Urquijo,<sup>#</sup> Guillermo F. Sanz,\* Miguel A. Sanz\*

\*Bone Marrow Transplantation Unit, Department of Hematology; <sup>o</sup>Service of Vascular Radiology; and <sup>#</sup>Gastroenterology and Hepatology Service, La Fe University Hospital, Valencia, Spain

### ABSTRACT

Hepatic veno-occlusive disease (VOD) is a common cause of morbidity and mortality after BMT. Although treatment of VOD is primarily supportive, some success has been obtained recently with fibrinolytic therapy. However, for critically ill patients liver transplantation may be the only therapeutic option. Nevertheless, this procedure is associated with high mortality and can only be performed in a minority of cases. The transjugular intrahepatic portosystemic stent-shunt (TIPS) is a non-surgical, side-to-side shunt consisting of an intraparenchymal duct between a main branch of the portal vein and a hepatic vein. In this report we describe a patient who underwent TIPS placement for severe VOD following autologous PBPC transplant. No complications developed and gradual improvement in clinical status and liver function was observed early after this therapy. Nine months after TIPS, the patient is asymptomatic with normal liver function. TIPS provides an interesting alternative to invasive therapies for patients with severe VOD after bone marrow or PBPC transplants.

Key words: hepatic VOD, TIPS procedure, progenitor cell transplantation

Hepatic veno-occlusive disease (VOD) is a complication commonly observed following bone marrow transplantation (BMT) that affects the terminal hepatic venules and surrounding sinusoids and hepatocytes, and produces a syndrome of jaundice, painful hepatomegaly and fluid retention.<sup>1</sup> The reported incidence ranges from 3% to 53% depending on the type of BMT, conditioning regimen and patient selection, and is responsible for more than 15% of deaths.<sup>1</sup> Management of VOD includes supportive measures aimed at maintaining the intravascular volume, improving renal blood flow and minimizing the accumulation of extracellular fluids. Efforts to treat established VOD have focused on alleviating the obstruction to sinusal blood flow through the use of recombi-

nant human tissue plasminogen activator (rtPA)<sup>2</sup> or prostaglandin E1.<sup>3</sup> Surgical approaches, including side-to-side portacaval shunting<sup>4</sup> or Le Vein shunts,<sup>1</sup> have rarely been attempted due to their invasive nature and/or possible complications. Finally, in severe cases with life-threatening liver dysfunction, orthotopic liver transplantation may be the only effective therapy.<sup>5,6</sup>

The transjugular intrahepatic portosystemic stent-shunt (TIPS) is a relatively new technique for reducing portal hypertension. It is a non-surgical, side-to-side shunt consisting of an intraparenchymal duct between a main branch of the portal vein and a hepatic vein. Since its introduction in 1988,<sup>7</sup> it has been increasingly used as treatment for esophageal varices and hemorrhage and refractory ascites.<sup>8-10</sup> It has a low oper-

ative risk, even in critically ill patients, and does not interfere with subsequent liver transplantation. In this report we describe a patient with life-threatening VOD following autologous peripheral blood progenitor cell transplantation (APBPCT) for relapsed lymphoma successfully managed by TIPS placement.

### Case report

In August 1991, a 46-year-old male was found to have a diffuse large cell non-Hodgkin's lymphoma stage II-S-B. At diagnosis, he presented with enlarged diaphragmatic lymph nodes and spleen and pancreas infiltration. The patient was splenectomized, received six courses of CHOP chemotherapy and achieved CR. He was then administered 2 consolidation courses of OAP-BLEO (vincristine, cytarabine, prednisone, bleomycin). He relapsed in May 1995, presenting with an inguinal mass without involvement of other areas. At that time he was treated with three cycles of MINE-type chemotherapy (ifosfamide, novantrone, etoposide) and attained a second CR.

In September 1995, APBPCT was performed. The conditioning regimen consisted of cyclophosphamide 1.5 g/m<sup>2</sup> on days -7, -6, -5 and -4; etoposide 250 mg/m<sup>2</sup> on days -7, -6, -5 and -4; BCNU 200 mg/m<sup>2</sup> on days -7, -6, -5 and -4. The main complications observed posttransplant were skin toxicity secondary to etoposide, severe nausea and vomiting that required parenteral nutrition, and a febrile syndrome without clinical or microbiological documentation. No hepatic dysfunction was observed in this period. Engraftment was rapid (time to achieve  $0.5 \times 10^9$  neutrophils/L and  $20 \times 10^9$  platelets/L was 12 and 11 days, respectively) and the patient was discharged on day +14 in good overall clinical condition.

On day +40 the patient was readmitted because of anorexia, nausea, vomiting, ascites and moderate weight gain. A chest X-ray showed left pleural effusion. Hematological values on admission were normal except for mild thrombocytopenia. Coagulation parameters were normal and serum chemistry showed: bilirubin concentration 2 mg/dL (normal range

0.1-1.1 mg/dL), alkaline phosphatase 145 U/L (normal range 30-115 U/L),  $\gamma$ -glutamyl transferase 131 U/L (normal range 0-65 U/L), cholesterol 113 mg/dL (normal range 125-250 mg/dL). Transaminase levels were normal. Abdominal CT scan and ultrasonography confirmed ascites and hepatomegaly but showed no signs suggestive of lymphoma relapse. Upper gastrointestinal endoscopy revealed grade I/IV esophageal varices, congestive gastropathy, duodenal ulcers and erosions. Abdominal Doppler ultrasound showed ascites, hepatofugal flow in the portal vein, normal suprahepatic veins and a normal hepatic artery. Viral serology was negative. Supportive treatment with sodium restriction, diuretics and albumin was started and two paracenteses were performed with good initial response. Nevertheless, despite intensive medical treatment, the patient's clinical status and liver chemical values worsened, with progressive weight gain (from 73 to 79 kg), refractory ascites and signs of grade I encephalopathy on day +71. Serum bilirubin concentration rose, reaching a maximum value of 7.6 mg/dL on day +71, cholesterol level decreased to a minimum of 62 mg/dL on day +68, and coagulation parameters deteriorated (Quick index 37%). Transaminase values did not rise and no renal or respiratory failure developed. A transjugular liver biopsy performed on day +68 confirmed a diagnosis of VOD, with obliteration of the central veins and centrilobular necrosis. Thrombolytic treatment with r-tPA (50 mg/day, four days) plus a bolus of 1,000 U heparin was started on day +74, but had to be aborted after 24 hours due to severe bleeding.

In this situation the decision to perform a TIPS was made and the procedure was carried out in the radiological procedures room on day +88. After mild intravenous sedation and local anesthesia with 2 mg of midazolam and 45 mg of pethidine, a puncture needle was advanced intrajugularly in a catheter through the inferior vena cava into the middle hepatic vein. Subsequently, an intrahepatic branch of the portal vein was punctured and the shunt was established by implanting a Wallstent.<sup>8-10</sup> No major procedure-related complications developed. There was a very slight increase in aspartate

aminotransferase and alanine aminotransferase values, which peaked at 166 U/L and 145 U/L, respectively, on the fourth day after the procedure and declined thereafter. Early after the procedure, there was a gradual improvement in clinical status and liver function tests, diuresis increased, ascitic and pleural fluids progressively disappeared and jaundice diminished. Diuretic treatment was gradually reduced, and on day +104 the patient was discharged from the hospital with a bilirubin level of 4.38 mg/dL, cholesterol of 135 mg/dL and a Quick index of 45%. Follow-up showed further improvement in the hepatic function and nutritional status of the patient, and on day +131 bilirubin was 1.9 mg/dL, cholesterol 138 mg/dL and Quick index 83%. Three months after TIPS placement (day +176), thrombotic occlusion of the stent shunt was detected by Doppler ultrasound without reappearance of ascites or worsening of liver function tests. An additional stent overlapping the previous one was implanted, but again thrombotic occlusion was detected 48 hours later by sonography. This time balloon dilatation was performed with successful re-establishment of the shunt and oral anticoagulation was started. Currently, nine months post transplant and six months after TIPS placement, the patient remains in good general condition, with normal liver function and without medical treatment except for oral anticoagulation with warfarin (1 mg/day).

### Discussion

The ideal treatment for established VOD still remains to be defined. Conservative treatment approaches like the administration of fibrinolytics,<sup>2</sup> prostaglandin E1<sup>3</sup> or heparin<sup>11</sup> are only effective in the early stages of the disease, and their potential for fatal hemorrhagic complications cannot be emphasized enough. In severe cases associated with progressive hepatic failure, liver transplantation may be the only effective therapeutic option.<sup>5,6</sup> However, although the procedure may be technically successful, long-term survivors among patients given liver transplants for severe VOD are scarce,<sup>6</sup> and its use following BMT is obviously limited. Thus new

approaches to managing patients who developed severe VOD are needed.

TIPS can provide an alternative to these therapies. It is a non-surgical technique for the treatment of portal hypertension that shares with surgical shunts the therapeutic principle of decompressing the portal system, but avoids the risks of general anesthesia and surgery and does not interfere with subsequent liver transplantation, if indicated. It has been used mostly in patients with cirrhosis to treat variceal hemorrhage and intractable ascites.<sup>8,10</sup> It is generally well tolerated, with a direct procedural mortality rate between 1% and 2%.<sup>9</sup> In the patient reported herein, clinical deterioration, persistently altered coagulation parameters and rapidly falling cholesterol values suggested severe liver damage highly predictive of fatal outcome. r-tPA could not be administered due to bleeding diathesis, and the poor clinical status of the patient precluded more aggressive therapies, so the idea of placing a TIPS was considered. No procedure-related complications were observed, and the patient's clinical status and liver tests improved gradually after TIPS placement, demonstrating that the procedure had been beneficial. Another case of VOD resolution through the TIPS technique after allogeneic BMT was recently reported.<sup>12</sup> As in our patient, the clinical status and liver function tests of this person improved dramatically after TIPS placement; however, this patient died shortly thereafter of interstitial pneumonitis and no conclusions could be drawn regarding the long-term efficacy of the procedure.

Restenosis of the shunt is relatively common after the procedure (24%)<sup>9</sup> and requires surveillance with Doppler ultrasonography repeated at 3-month intervals to allow for shunt revision. Stenoses and occlusions can be treated successfully by redilatation or implantation of an additional stent.<sup>8,10</sup> Two shunt occlusions occurred in our patient. The first was detected during a Doppler check-up three months after TIPS placement, and was treated by implantation of an additional stent. The second developed 48 hours later, and patency was maintained by balloon dilatation. Low-dose oral anticoagulation (warfarin 1 mg/day) was started to try to avoid

further occlusion of the shunt. Heparin can be administered during and after TIPS placement to prevent thrombosis;<sup>8</sup> however, the use of heparin does not significantly affect occlusion rates, whereas it does increase perioperative morbidity<sup>8</sup> and therefore is not generally recommended.

To our knowledge, this is the first case of successful long-term control of severe VOD developing after APBPCT by means of TIPS placement. We suggest that TIPS is a feasible, safe and potentially beneficial procedure for patients with severe VOD after transplantation, and that it can delay or even avoid liver transplantation. Nevertheless, additional reports are needed to assess the definitive role of TIPS for severe VOD following bone marrow or PBPC transplants.

---

### References

1. Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. *Blood* 1995; 85:3005-20.
2. Bearman SI, Shuhart MC, Hinds MS, McDonald GB. Recombinant tissue plasminogen activator for the treatment of established severe venoocclusive disease of the liver after bone marrow transplantation. *Blood* 1992; 80:2458-62.
3. Ibrahim A, Pico JL, Maraninchi D, et al. Hepatic veno-occlusive disease following bone marrow transplantation treated by prostaglandin E1. *Bone Marrow Transplant* 1991; 7(suppl 2):53.
4. Murray JA, La Brecque DR, Gingrich RD, et al. Successful treatment of hepatic venoocclusive disease in a bone marrow transplant patient with side-to-side portacaval shunt. *Gastroenterology* 1987; 92:1073-7.
5. Rapoport AP, Doyle HR, Starzl T, et al. Orthotopic liver transplantation for life-threatening veno-occlusive disease of the liver after bone marrow transplant. *Bone Marrow Transplant* 1991; 8:421-4.
6. Schlitt HJ, Tischler HJ, Ring B, et al. Allogeneic liver transplantation for hepatic veno-occlusive disease after bone marrow transplantation - clinical and immunological considerations. *Bone Marrow Transplant* 1995; 16:473-8.
7. Rössle M, Richter GM, Noldge G, et al. New non-operative treatment of variceal hemorrhage (letter). *Lancet* 1989; ii:152.
8. Sanyal AJ. Tips: The new kids on the blocks. *Hepatology* 1994; 20:1092-5.
9. Miller-Catchpole R. Transjugular intrahepatic portosystemic shunt (TIPS). Diagnostic and therapeutic technology assessment. *JAMA* 1995; 273:1824-30.
10. Ochs A, Rössle M, Haag K, et al. The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites. *N Engl J Med* 1995; 332:1192-7.
11. Bearman SI, Hinds MS, Wolford JL, et al. A pilot study of continuous infusion heparin for the prevention of hepatic veno-occlusive disease after bone marrow transplantation. *Bone Marrow Transplant* 1990; 5:407-11.
12. Lévy V, Rio B, Azoulay D, et al. Successful treatment of severe venoocclusive disease of the liver after allogeneic BMT by transjugular intrahepatic portosystemic shunt (TIPS) (Abstract). *Bone Marrow Transplant* 1996; 17 (suppl 1):S80.