American Journal of Clinical and Medical Case Reports

ISSN: 2771-4098

Case Report

Transjugular Intrahepatic Portosystemic Shunt as "Bridge Therapy" in a Case of Paroxysmal Nocturnal Hemoglobinuria

Maria Bindi[1], Francesca Puccini[1], Roberto Cioni[2], Sayla Bernasconi[3], Ana Filipovic[4], Chiara Paterno[5], Gabriella Casazza[3], Maurizia Brunetto[6] and Gian Domenico Biancofiore[7]*

[1]*UO Anestesia e Rianimazione Trapianti, AOUP, Italy*

[2]*UO Radiologia Interventistica, AOUP, Italy*

[3]*UO Oncoematologia Pediadrica, AOUP, Italy*

[4]*Scuola di Specializzazione Anestesia e Rianimazione, Università di PisaItaly*

[5]*UO Anestesia e Rianimazione Trapianti, Università di Pisa, Italy*

[6]*Department of Clinical and Experimental Medicine, University of Pisa and Hepatology, Unit Pisa University Hospital, Italy*

[7]*UO Anestesia e Rianimazione Trapianti, Università di Pisa, Italy*

Abstract

We describe the case of a young patient affected by paroxysmal nocturnal haemoglobinuria. This young lady developed acute severe liver failure due to a rare form of sinusoidal obstructive syndrome complicated by severe portal hypertension which was treated with the positioning of a Trans-jugular Intrahepatic Portosystemic Shunt (TIPS) as a bridge therapy in the aim to allow Eculizumab, the only effective therapy for patients with PNH, to achieve full control on the disease. The management of this clinical case was in some ways innovative and not previously described and outlines the importance of a continuous multidisciplinary consultation between the intensivists, the haematologists, the hepatologists and radiologists.

Keywords: Trans-jugular intrahepatic portosystemic shunt (TIPS); Haemoglobinuria; Hepatologist; Radiologist; CT scan

Introduction

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare bone marrow disorder that is characterized by hemolytic anemia, thrombosis, and peripheral blood cytopenia. The disease results from the expansion of a clone of hematopoietic cell that because of an inactivating mutation of the X linked gene *PIG-A* is deficient in two Glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, leading to uncontrolled complement activation that accounts for hemolysis and the other PNH clinical manifestations. According to available evidence, GPI-anchor protein deficiency is almost always due to somatic mutations in *Phosphatidylinositol Glycan Class A* (*PIGA*), a gene involved in the first step of GPI anchor biosynthesis. However, alternative mutations causing PNH have recently been discovered [1]. Thrombosis is the most common cause of mortality in patients with PNH and may occur at anybody district. Venous thrombosis is more common (85%) than arterial (15%) and, for unclear mechanisms, common sites include cerebral and intra abdominal veins with hepatic vein thrombosis (Budd-Chiari syndrome) being the most common manifestation leading to hepatic venous outflow obstruction, hepatic congestion, portal hypertension, hepatocyte necrosis, and possible liver failure [1-3].

We here in describe the case of a young patient with PNH who developed acute, severe, liver failure due to a sinusoidal obstructive syndrome, complicated by severe portal hypertension and who received a Trans-jugular Intrahepatic Portosystemic Shunt (TIPS) as a bridge therapy in the aim to allow Eculizumab, the only known effective therapy for patients with PNH, to achieve a full control on the disease [4].

Case Presentation

A 17 years old female was admitted to our ICU due to acute hepatic failure and pulmonary embolism. Two years earlier, she was diagnosed with acquired severe a plastic anemia, with a small PNH clone in the granulocyte lineage, without evidence of hemolysis or thrombosis at diagnosis.

She started, in absence of matched sibling donor, immunosoppressive therapy, with horse antithymocyte globuline plus ciclosporine. During treatment, the patient obtained a very good partial response (Hb>10 gr/dl ANC>0.5 × 10^9, PLTS>50.000, without red cells and platelet transfusion). At the same time, however, there was a progressive increase in the PNH clone activity with

Citation: Bindi M, Puccini F, Cioni R, Bernasconi S, Filipovic A, Paterno C, et al. Transjugular Intrahepatic Portosystemic Shunt as "Bridge Therapy" in a Case of Paroxysmal Nocturnal Hemoglobinuria. Am J Clin Case Rep. 2022;2(1):1011.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Sep 08th, 2022

***Corresponding author:** Bindi Maria, UO Anestesia e Rianimazione Trapianti, Azienda Ospedaliero Universitaria Pisana, Via Paradisa 2, Pisa, 56124, Italy, E-mail: l.bindi@ao-pisa.toscana.it

polymorphonuclear leukocytes and monocytes levels of respectively 94.9% and 95%, while red blood cells resulted at 3.9%. These laboratory results made possible the diagnosis of PNH with a largely prevalent GPI-negative myeloid cells population. This is a rare form of PNH which can be associated, in the absence of hemolysis, with severe thrombosis due to the presence of the GPI negative myeloid population [5]. At ICU admission, a whole body CT scan showed extensive peripheral pulmonary embolism, pleural and pericardial effusions, ascites with reversed, hepatofugal, portal vein blood flow. Laboratory admission data were as follows: aspartate Aminotransferase (AST) 11262 UI, Alanine Transaminase (ALT) 5389 UI, INR 4.96, serum lactates 85.7 mg/dL, arterial blood ph 7.24, serum creatinine 3.9 mg/dL, serum ammonia 127 mg/dL. Color Doppler sonography showed empty supra-hepatic veins with slowed portal blood flow (7 mm/s). Liver stiffness, measured by Transient Elastography (TE), showed a dramatic increase in 24 hours (from 22.5 to 66.4 kPa, normal value <5 kPa), suggestive of a rapid progression of the hepatic congestion [3].

In the ICU, the patient underwent hemodynamic stabilization with fluids and vasoactive medications, and received continuous renal replacement therapy. In the suspicion of sinusoidal obstruction SOS, we started therapy with Eculizumab (600 mg/once a week), Defibrotide (350 mg/6 hours every day), systemic anticoagulation with non-fractionated heparin and we stopped ciclosporine. In the following days, the patient showed some laboratory improvement (see Table 1 on day 5), including reduced stiffness of the liver (32.4 kPa on day 11). However, color Doppler sonography showed no improvement (10 mm/sec) with persistent hepatic venous outflow obstruction, hepatic congestion and portal hypertension. On day 14, in spite of a transient and mild transaminases elevation, lactates and INR suddenly worsened (Table 1) and TE values rose again from 32.4 kPa to 46.4 kPa. Moreover the patient's overall condition worsened quickly with clear clinical (severe drowsiness, multiple episodes of gastro-enteric bleeding) and laboratory (ammonia 94 mg/dL, blood lactates 111.1 mg/dL) features, strongly suggesting further progression of portal hypertension. A new CT scan was performed and it showed a significantly increased venous stasis in the domain of the superior mesenteric vein. Thus, in the consideration of such a global deterioration, on day 15 we decided to proceed to TIPS in the aim to reduce portal hypertension and "buy time" pending the therapeutic effects of Eculizumab. The procedure was uneventful and portal pressure decreased from 27 mmHg to 20 mmHg. In the following days, the patient recovered with dramatically improved laboratory data (see Table 1 on the 27th day) and liver stiffness (27 kPa). The patient was discharged to the hematologic ward on the 35th day with defibrotide three time/day and eculizumab 200 mg weekly as a treatment. At 36 months from hospital discharge, the patient receives Eculizumab 900 mg/15 days, oral anticoagulation and cyclosporin and is in optimal clinical situation with normal liver laboratory data and patent portal and sopra-hepatic veins. Moreover, TIPSS is perfectly functioning with a liver stiffness of 4.8 kPa.

Discussion

Patients with PNH show a thrombophilic state, that has not been fully explained in its physiopathology, but determines thrombotic episodes and this clinical feature has been recognized as a major clinical sign of the syndrome since it represents the most common cause of death in this class of subjects [1]. Our patient presented a severe post-sinusoidal portal hypertension, defined by empty supra-hepatic veins, reduced portal (<10 cm/sec) and no intrahepatic blood flows, associated with sudden development of ascites, severe liver damage and thrombocytopenia. Overall, the clinical picture was suggestive of a Sinusoidal Obstructive Syndrome (SOS), a clinical entity usually observed after hematopoietic stem cell transplantation and/or chemotherapy. However, in our case, the treatment with cyclosporine and the interplay between platelets, the clotting cascade and the dysfunctional endothelium characterizing PNH [6] could have triggered the intrahepatic multiple thrombotic event with damage of the sinusoid endothelium, ultimately leading to SOS that was associated with liver and progressive multiorgan dysfunction. According to the current recommendations, the patient started Defibrotide, a polydisperse oligonucleotide with local antithrombotic, anti-ischemic, and anti-inflammatory activity that binds to the vascular endothelium, modulates platelets activity, promotes fibrinolysis, decreases thrombin generation and activity and reduces circulating levels of plasminogen activator inhibitor type 1. The treatment improved the liver function, as indicated by the fast decline of transaminases values together with an increase of hepatic outflow. At the same time, Eculizumab, an anti-complement antibody targeting the CD5 complement component that since 2007 was approved by the US Food and Drug Administration (FDA) for PNH was started as specific treatment of the underlying disease. The drug, blocking the distal complement pathway, and protects PNH red cells from complement mediated lysis and it had been shown to reduce the thrombotic events, possibly by modifying some parameters of [7]. However, Eculizumab requires up to 3 weeks [8], to curb the Complement levels in the blood thus reducing the thrombotic risk. In our case, the placement of the TIPS was crucial and served as bridge treatment waiting for Eculizumab to achieve Complement inhibition. Thus, TIPS should be considered in patients with PNH and Budd-Chiari Syndrome induced life threatening liver failure.

References

1. Peacock-Young B, Macrae FL, Newton DJ, Hill A, Ariens RAS. The Prothrombotic state in paroxysmal nocturnal hemoglobinuria: a multifaceted source. Haematologica. 2018;103(1):9-17.
2. Hoekstra J, Leebeek FW, Plessier A, Raffa S, Darwish Murad S, Heller J, et al. Paroxysmal nocturnal hemoglobinuria in Budd-Chiari Syndrome: Findings from a cohort study. J Hepatol. 2009;51(4):696-706.
3. Bonino F, Arena U, Brunetto MR, Coco B, Fraquelli M, Oliveri F, et al. Liver stiffness, a non-invasive marker of liver disease: a core study group report. Antivir Ther. 2010;15(Suppl 3):69-78.
4. Strunk H, Marinova M. Transjugular Intrahepatic Portosystemic Shunt (TIPS): Pathophysiologic Basics, Actual Indications and Results with Review of the Literature. Rofo. 2018;190(8):701-11.
5. Sahin F, Akay MO, Ayer M, Dal MS, Ertop S, Ilhan O, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. Am J Blood Res. 2016;6(2):19-27.
6. Nishimura Ji, Kanakura Y, Ware RE, Shichishima T, Nakakuma H, Ninomiya H, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. Medicine (Baltimore). 2004;83(3):193-207.
7. Oyarzun CPM, Heller PG. Platelets as mediators of thromboinflammation in chronic myeloproloferative neoplasms. Frontiers Immunol. 2019;10:1373.
8. Griffin M, Munir T. Management of thrombosis in paroxysmal nocturnal hemoglobinuria: a clinician's guide. Ther Adv Hematol. 2017;8(3):119-26.

Table 1: Laboratory data.

ICU DAYS	1	3	5	7	9	11	13	14	15	17	19	20	22	27	28	31	35
Timing ICU	**Admission**								**TIPS**								**Discharge**
Continuosrenalreplacement Therapy	CRRT	CRRT	CRRT	CRRT		CRRT				CRRT							
Serum Ac. Lactates (mg/dL)	85.6	48	46	35.1	38.2	45.8	63.4	84.9	111.1	101.5	90.8	88	63.8	17.2	15.9	15.3	12.8
Creatinine (mg/dL)	3. 9	2.65	2.31	1.98	1.85	1.22	1.99	2.02	2.17	1	0.54	0.62	0.46	0.46	0.6	0.69	0.51
AST (mg/dL)	11262	1976	676	244	501	24	17	19	16	20	20	22	21	22	24	17	12
ALT (mg/dL)	5389	3015	1614	1009	263	206	84	66	54	58	59	59	61	46	44	38	36
LDH (mg/dL)	1789	466	428	308	263	224	234	255	308	388	401	435	594	356	365	325	322
Total bilirubin (mg/dL)	1.95	2.06	2.74	1.78	1.72	2.14	1.19	1.33	1.18	1.34	2.4	1.81	2.26	2.1	1.61	1.69	1.58
Platelets x $10^3/\mu L$	16	32	18	16	37	12	34	22	44	24	32	13	12	29	18	15	25
INR	5.36	4.14	2.67	2.22	2.11	2.12	1.78	3.7	2.09	1.44	1.35	1.32	1.18	1.43	1.39	1.37	1.39
Fibrinogen (mg/dL)	92	161	182	189	163	105	123	120	104	156	131	120	166		364	370	422
SerumAmmonia (mg/dL)	127	61	83		65	78	93	94	91		78	63	63			59	44
Fibroscan (kPA)	25.1	66.4		53.2	66.4	32.4		46.4	52	23.1				27		23.4	23.4
Portal Flow (cm/s)	7	13	10				11			30							