

BRIEF DEFINITIVE REPORT

Portosystemic shunt is an effective treatment for complications of portal hypertension in hepatic myeloid metaplasia and improves nutritional status

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Abstract

In patients affected by myelofibrosis with hepatic myeloid metaplasia (HMM), portal hypertension (PHT) complications may develop. In this case series, we analysed the efficacy and safety of transjugular portosystemic shunt (TIPS) in the treatment of PHT-related complications and its effects on the nutritional status. Six patients were evaluated and the average follow-up period after TIPS was 33 (IQR 5) months. None of the patients developed hepatic failure, nor any recurrence of variceal bleeding was recorded. No additional paracentesis or endoscopic prophylactic treatment for PHT-related complications were required. In all subjects, the average dose of diuretics was almost halved three months after TIPS. Three patients died during the follow-up, but none for liver-related causes. All patients showed an improvement in the global nutritional status. In conclusion, TIPS represent an effective and safe treatment option for patients affected by complications of PHT secondary to HMM and drives to an improvement of the nutritional status.

KEYWORDS

Hepatic myeloid metaplasia, Nutritional status, Portal hypertension, Portosystemic shunt, TIPS

Abbreviations: BCS, Budd–Chiari syndrome; BMI, body mass index; HMM, hepatic myeloid metaplasia; HVPG, hepatic venous pressure gradient; MPN, myeloproliferative neoplasms; PHG, portal hypertensive gastropathy; PHT, portal hypertension; PPG, portocaval pressure gradient; PVT, portal vein thrombosis; RFH-GA, Royal Free Hospital-Global assessment; SAAG, serum-ascites albumin gradient; TIPS, transjugular intrahepatic portosystemic shunt.

1 | INTRODUCTION

Myeloproliferative neoplasms (MPN) represent a group of chronic myeloid disorders including polycythaemia vera, essential thrombocythemia and primary myelofibrosis. Thrombosis, bleeding, evolution to acute myeloid leukaemia and progression to the fibrotic phase of the disease in case of polycythaemia vera and essential thrombocythemia are major complications of MPNs.¹ Myelofibrosis is a neoplastic disorder characterized by progressive dominance of a clone of haematopoietic stem cells associated with the gradual replacement of the bone marrow by reactive fibrotic tissue, which can result in extramedullary haematopoiesis in multiple organs, primarily affecting liver and spleen.² Hepatic myeloid metaplasia (HMM) may induce the development of portal hypertension (PHT), resulting in refractory ascites and/or gastrointestinal haemorrhage from varices rupture.^{3,4} Transjugular intrahepatic portosystemic shunt (TIPS) placement is a well-established procedure for the treatment of cirrhotic and non-cirrhotic PHT-related complications.⁵ Evidence in favour of the efficacy and safety of TIPS for the treatment of PHT-associated complications in HMM is limited to a few case reports,^{6,7} and no data are available concerning its effect on constitutional symptoms such as weight loss. In this case series, we analysed the efficacy and safety of TIPS in the treatment of HMM-related PHT complications and the effects of this procedure on the nutritional status. Indeed, treatment is largely based on palliation and improvement of quality of life. Therefore, TIPS could represent a rational approach to the management of this condition.

2 | METHODS

The study was approved by the Review Board of our Institution. We retrospectively evaluated patients affected by MPNs with associated HMM-related PHT, consecutively referred for TIPS to the Centers of Florence and Modena between January 2012 and December 2016. Diagnostic assessment of PHT included abdominal imaging (ultrasound and computed tomography or magnetic resonance imaging), echocardiography and hepatic venous pressure gradient (HVPG) measurement. A transjugular liver biopsy was performed in all subjects. Three needle passes within different liver segments were performed in each patient due to potentially patchy distribution of HMM. All specimens had at least 11 complete portal tracts. An upper-gastrointestinal endoscopy before and after TIPS was carried out in all patients. Efficacy of TIPS was evaluated by both the reduction of portocaval pressure gradient (PPG) and control of PHT-related complications. In order to assess the safety of TIPS in this setting, intra- and post-procedural complications, including development of hepatic encephalopathy and liver failure, were considered. Clinical and laboratory data were recorded at different time points for all patients. Nutritional status modifications following derivative procedures were assessed according to anthropometric and dietary parameters such as body mass index (BMI) corrected for fluid overload⁸ and those included in the Royal Free Hospital-Global Assessment (RFH-GA). The

RFH-GA can be used to determine the nutritional status of patients with liver disease and includes both anthropometric parameters and details of dietary intake. According to the RFH-GA, patients are stratified into three different subgroups: adequately nourished, moderately malnourished and severely malnourished.⁹ In addition, modification of nutritional biomarkers such as serum albumin and total cholesterol were also evaluated since they are easily available and have been used to develop a cachexia index for prognostic purposes in primary myelofibrosis.¹⁰ Variations in nutritional status were assessed at the time of TIPS placement and every 6 months.

Due to the small sample size, we only performed a descriptive analysis. Test of normality was used to assess the distribution of quantitative variables. Quantitative variables are expressed as median and interquartile range. Qualitative variables were expressed as counts and percentages. The data analysis was performed with SPSS (version 24, IBM, New York, NY, USA).

3 | RESULTS

Six patients (four from Florence and two from Modena) were enrolled. Clinical and laboratory features at the TIPS procedure are outlined in Table 1. Males were predominant and most of the patients were in their seventh decade at the time of the TIPS. Idiopathic myelofibrosis was the main aetiology (Table 1 and S1). Refractory ascites and severe splenomegaly were found in all patients. All patients received propranolol as primary (34%) or secondary (66%) prophylaxis of variceal bleeding. No patients had cirrhosis or advanced fibrosis or foci of nodular regenerative hyperplasia according to the histology. In all liver biopsies, varying degrees of extra-medullary haematopoiesis and infiltration of liver sinusoids, with an average percentage of haematopoietic cells of 60%, were found (Figure 1 and Table 1 and S1).

Refractory ascites was the main indication for TIPS. Moreover, TIPS was further indicated for secondary prophylaxis of variceal bleeding in four patients and hydrothorax in three patients. Large oesophageal varices with red wale marks and cherry-red spots, and severe portal hypertensive gastropathy (PHG) were detected in four (67%), and three (50%), patients, respectively. A pre-derivative paracentesis was performed in all patients showing an average serum-ascites albumin gradient (SAAG) above 1.1 g/L (median 1.6, IQR 0.4) which is indicative of PHT-related ascites and no haematopoietic cells were found in the peritoneal fluid. Derivative procedures were performed with the traditional transjugular approach in five patients. In one patient, HMM-related complications such as refractory ascites were further worsened by the development of complete portal vein thrombosis. In this case, TIPS was performed by a combined percutaneous transjugular and trans-splenic approach. This latter subject was the only on anticoagulant therapy (warfarin) before TIPS, and treatment was maintained after shunt placement. Endoprotheses (polytetrafluoroethylene-covered stent grafts, Viatorr, Gore, Flagstaff, AZ) were impacted at the intra-parenchymal tract at 6, 8 and 10 mm in one, three and two patients, respectively. Pre-derivative HVPG values were

TABLE 1 Clinical characteristics and laboratory values before TIPS and during the follow-up.

Gender n (%)				
Male				5 (83)
Female				1 (17)
Age (years), median (IQR)				64.5 (20)
Haematological treatment at TIPS positioning (%)				
Ruxolitinib				4 (67)
Duration (months)				8
				NA
				13
				6
PI3K inhibitor				1 (17)
Duration (months)				NA
Hydroxyurea				2 (33)
Duration (months)				32
				27
Myeloproliferative disease n (%)				
Polycythaemia vera				2 (33)
Essential thrombocythemia				1 (17)
Primary myelofibrosis				3 (50)
Myeloid metaplasia on liver biopsy, median (IQR)*				60 (20)
TIPS indication n (%)				
Acute variceal bleeding and secondary prophylaxis				4 (67)
Refractory/recurrent ascites				6 (100)
Hepatic hydrothorax				3 (50)
Portal vein thrombosis				1 (17)
Spleen size cm, median (IQR)				26.5 (6.2)
SAAG g/L, median (IQR)				1.6 (0.4)
Laboratory values median (IQR)	Pre-TIPS	3 months after TIPS	6 months after TIPS	Last follow-up
Total bilirubin mg/dL, median (IQR)	0.9 (0.2)	1.1 (0.6)	1.2 (0.5)	1.3 (0.2)
INR**, median (IQR)	1 (0.3)	1.1 (0.6)	1.1 (0.8)	1.1 (0.6)
Creatinine mg/dL, median (IQR)	1.3 (0.4)	0.9 (0.4)	0.8 (0.5)	0.8 (0.4)
Sodium mmol/L, median (IQR)	137.5 (4.7)	139.5 (5)	138.5 (7.5)	138 (3)
Albumin g/dL, median (IQR)	3.4 (0.4)	3.5 (0.4)	3.8 (0.3)	3.6 (0.3)
Cholesterol mg/dL, median (IQR)	113 (28)	120 (20)	123 (15.4)	123.5 (13.7)

NA, not available; SAAG, serum-ascites albumin gradient.

*Percentage of involved area in the biopsy slice.; **The patient on warfarin was excluded.

consistent with clinically significant portal hypertension and PPG was constantly higher at the time of TIPS. Median pre-TIPS HVPG was 19 mm Hg (IQR 5.2) while PCG was 26.6 mm Hg (IQR 6.5) and 9.3 mm Hg (IQR 4.9) pre- and post-TIPS, respectively, suggesting a pre-sinusoidal/pre-hepatic contribution to PHT in these patients. The median follow-up period was 33 (IQR 5) months. During the follow-up, no variceal bleeding was observed in any patient and no endoscopic prophylactic treatment for PHT-related varices was required. Upper-gastrointestinal endoscopy showed mild PHG in five patients (83%) and small vestigial oesophageal varices without red wale markings/cherry-red spots in two patients (33%). Only one patient developed a single episode of grade 3 hepatic

encephalopathy 13 days after TIPS in association with benzodiazepine intake. No patient developed hepatic failure (Table 1) and no additional paracentesis was necessary from 3 months after TIPS. The average dosage of loop diuretic was reduced by 63% (IQR 24) and by 72.2% (IQR 16.4) at 6 and 12-24 months, respectively. After two years one patient developed high-output cardiac failure (cardiac index 5.9 L/min/m²), facilitated by progressive spleen enlargement and persistent MPN-related anaemia as a consequence, cardiogenic ascites, requiring diuretic treatment escalation, developed and a splenectomy was performed. Three patients died during the follow-up but no death was liver-related (myocardial infarction and sepsis in one and two patients, respectively).

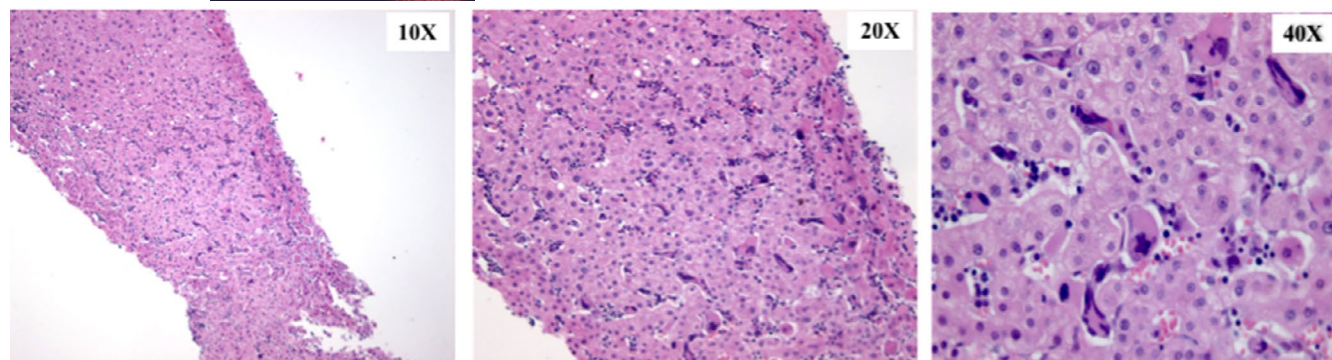


FIGURE 1 Representative liver biopsy showing myeloid metaplasia in a patient with MPN and refractory ascites. Megakaryocytes and immature lymphocytes within hepatic sinusoids are visible. Original magnification is shown in each panel

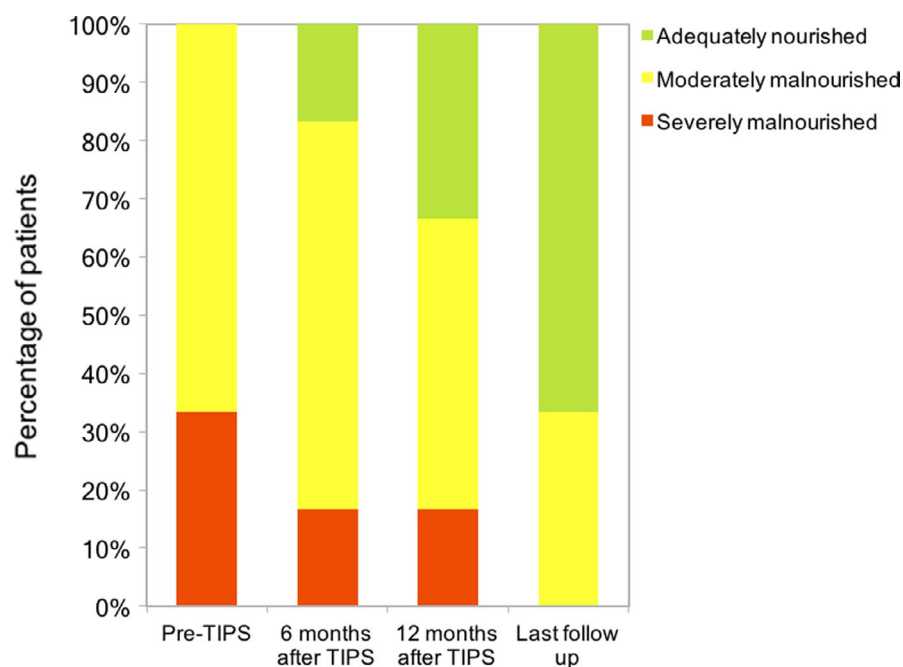


FIGURE 2 Modification of the nutritional status of patients with HMM after TIPS placement. Evaluation of the nutritional status performed with the RFH-GA algorithm before TIPS and during the follow up showing an overall improvement

All patients showed a nutritional benefit following TIPS. The median basal BMI, corrected for fluid overload, was 18.3 (IQR 0.9) kg/m^2 before TIPS and it increased to 21.3 (IQR 1.3) kg/m^2 during the follow-up. Albumin increased by 7.9% (IQR 3.5) in five patients and remained stable in one. Total cholesterol increased by 15% in five patients and by 7% in one patient who had the greater pre-TIPS level. The RFH-GA algorithm allowed to identify two patients (33%) as severely malnourished and four patients (67%) as moderately malnourished before TIPS. After the procedure, an overall nutritional status improvement and a general amelioration of some constitutional symptoms (Table S2) were observed. Four patients (67%) became adequately nourished while the remaining two patients moved to a moderately malnourished status (Figure 2).

4 | DISCUSSION

Myelofibrosis is a neoplastic disorder characterized by progressive reactive fibrotic bone marrow replacement that can result in

extramedullary haematopoiesis in multiple organs but primarily affecting liver and spleen.^{1,2} MPNs may therefore affect the hepatic circulatory system and the most common clinical manifestations are represented by Budd–Chiari syndrome, portal vein thrombosis and nodular regenerative hyperplasia. In addition, patients affected by myeloid disorders may develop PHT due to other mechanisms, including micro- and macro-vascular obstruction of the portal tracts and liver sinusoids by fibrotic tissue or clots, haematopoietic cell infiltration and increased portal in-flow due to massive spleen enlargement.¹¹ Notably, even in the absence of thrombosis, enhanced portal flow and intra-hepatic sinusoidal obstruction have synergistic effects and even a slight increase in resistance, combined with enhanced portal flow, might result in clinically significant PHT (ie PPG ≥ 12 mm Hg).

In this study, we report the largest series of patients with PHT related to HMM available to date (a list of previous studies is shown in Table S3). Patients were carefully characterized and evaluated for their outcomes after TIPS. In our population, the most common clinical presentation of PHT was refractory ascites (diuretic resistant

and diuretic intractable in 33% and 67%, respectively) and variceal bleeding. We provide evidence that TIPS is an effective and safe procedure to reduce portal hypertension secondary to HMM and to effectively control its complications, both from a haemodynamic and clinical point of view. Therapeutic paracentesis, which was required at short time intervals in all patients before TIPS, was no longer necessary three months after the procedure and thereafter. In addition, further episodes of bleeding due to PHT were not observed. These remarkable results were obtained in the absence of any significant deterioration of liver function. None of the patients developed hepatic failure during the follow-up period and no liver-related deaths were observed. Only a single episode of hepatic encephalopathy was recorded in the follow-up period and use of benzodiazepine was identified as a precipitating factor. Taken together, these data outline the advantages provided by TIPS on the best-known complications of PHT in this setting.

Malnutrition is a common aspect of patients with advanced chronic liver disease, and loss of muscle mass and sarcopenia are the most frequent phenotypes,¹² associated with a higher rate of complications. Sarcopenia and muscle mass depletion are also independent predictors of lower survival, increasing morbidity and mortality.¹² These features are also observed in patients with HMM, whose clinical features include signs and symptoms of a catabolic state (fever, fatigue and weight loss), marked splenomegaly and anaemia.¹³ Weight loss is often underestimated in myelofibrosis because of the coexisting fluid overload and splenomegaly, and the 'real' BMI of these patients during the disease is likely to decrease. In fact, weight loss remains common and represents a sign of advancing disease.¹⁴ The relevance of weight loss in MPNs is also highlighted by its presence in the main prognostic scoring systems adopted in the assessment of primary myelofibrosis.^{15,16} PHT can contribute to malnutrition that affects patients with MPN.¹⁷ PHT impairs gut motility, decreases nutrient absorption, provokes protein-losing enteropathy¹⁸ and finally malnutrition. Moreover, splenomegaly and ascites can worsen patient malnutrition because of their mass effect, causing early satiety and self-limitation of caloric intake. Therefore, PHT can worsen the constitutional symptoms and abdominal-related complaints that are an independent cause of morbidity and mortality¹⁹ in these patients. A novel and interesting finding of the present case series is the consistent improvement of the nutritional status after TIPS. In particular, during the follow-up, all patients showed an improvement in the global nutritional status according to the RFH-GA algorithm as well as to some biochemical markers. Probably, control of ascites might be one of the main mechanisms responsible for nutritional improvement, facilitating the dietary intake. Moreover, the drop in portal pressure following the derivative procedure may further improve the nutritional status through better nutrient absorption.

A further interesting disease-oriented approach to HMM concerns Janus kinase 1/2 inhibitor ruxolitinib administration. Indeed, ruxolitinib was shown to reduce liver volume and was associated with improvements in splenomegaly and metabolic status.²⁰ However, in the patients enrolled in this study in whom this line of information was available, disease-oriented treatment had been administered for

at least 6 months, without any effects on portal hypertensive complications (Table 1).

In conclusion, this case series clearly demonstrates that TIPS represent an effective and safe treatment for patients affected by complications of PHT secondary to HMM, preventing further bleeding episodes, limiting ascites and requirement of diuretic drugs, and driving to an improvement of the overall nutritional status.

CONFLICT OF INTEREST

FV, FS and FF have received lecture fees and FS has received research grant support from Gore.

AUTHOR CONTRIBUTIONS

Silvia Aspite, Filippo Schepis, Francesco Vizzutti and Davide Roccarina, were involved in the conception of the work, data analysis, drafting and critical revision of the article. Stefano Gitto, Michele Citone, Chiara Di Bonaventura, Francesca Campani and Marcello Bianchini were involved in data collection. Alessandro M. Vannucchi, Umberto Arena, Fabrizio Fanelli and Paola Guglielmelli were involved in the revision of the article. Fabio Marra and Francesco Vizzutti supervised the study. All authors contributed to the manuscript for important intellectual content and approved the submission.

ETHICS APPROVAL

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The institutional review board approved to collect retrospective clinical and haemodynamic data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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