ANSWERING REVIEWERS

April, 30 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10288-review.doc).

Title: Embolization of splenorenal shunt associated to portal vein thrombosis and hepatic encephalopathy

Author: Letícia de Campos Franzoni, Fábio Cardoso de Carvalho, Rafael Gomes de Almeida Garzon, Fábio da Silva Yamashiro, Laís Augusti, Lívia Alves Amaral Santos, Mariana de Souza Dorna, Júlio Pinheiro Baima, Talles Bazeia Lima, Carlos Antonio Caramori, Giovanni Faria Silva, Fernando Gomes Romeiro

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10288

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer:

- Answer to the rewier 00182860:

We thank the reviewer for the dedicated time reading and correcting our case report. We did a correction in the article to answer your comments cautiously.
The portosystemic shunt presented in the article was spontaneous, and this information is now inserted in the paper introduction.

- Answer to the rewier 01550345:

We thank the reviewer for the dedicated time reading our case report. We attempted to answer your comments the best we could.
We agree that our case report is about a complex situation. However, we have to disagree that this case could be only a difficult case without scientific interest, mainly because we have faced this problem in several patients and this is a challenge for any doctor who treats patients with liver cirrhosis. We tried to show it more clearly in the article now.
There is no doubt that liver cirrhosis is a major cause of portal vein thrombosis (PVT). The reported rates of PVT are in the range of 0.6%-15.8% in patients with liver cirrhosis, but these rates increase in relation to the patients' age and their liver disease severity, reaching

15% in patients awaiting liver transplantation (1). Unfortunately, liver transplantation for patients with advanced PVT (grades 3-4 according to the Yerdel classification) is a big challenge, and even in specialized centers the results are not as good as in patients without PVT (2). Thus, there is a significant amount of cirrhotic patients who can not be included in the liver transplantation list because they have PVT.
Since the prevalence of portal vein thrombosis rises in proportion to the liver disease severity, even among patients who are already waiting for liver transplantation there is a considerable amount who need to be removed from the waiting list. Once PVT occurs, these patients suffer an important raise on their portal pressure and this is a stimulus to the development of portosystemic shunts, which are a further predictor of poor prognosis and a cause of hepatic encephalopathy (3). Therefore, the question is: how these patients should be managed when the liver transplantation is not an option and they have PVT and hepatic encephalopathy?
Our case report is an example of this association, which gave her a dismal prognosis. She was worsening day-by-day and our hospital was not prepared to perform a liver transplantation in this situation. After the shunt embolization, she recovered too fast and her MELD score decreased. Worth mentioning, she never needed new hospitalizations.
As the rate of patients that are too sick to be submitted to the liver transplantation is high and keeps rising according to the time they are in the waiting list (4), we believe that are many other patients that could benefit of these kind of procedure. Being so, we need to show this case to other doctors, and this is the main reason to include this paper in the World Journal of Gastroenterology. We hope to achieve your agreement for this publication.

References

1) Kinjo N, Kawanaka H, Akahoshi T, Matsumoto Y, Kamori M, Nagao Y, Hashimoto N, Uehara H, Tomikawa M, Shirabe K, Maehara Y. Portal vein thrombosis in liver cirrhosis. World J Hepatol. 2014 Feb 27;6(2):64-71.

2) Ponziani FR, Zocco MA, Senzolo M, Pompili M, Gasbarrini A, Avolio AW. Portal vein thrombosis and liver transplantation: Implications for waiting list period, surgical approach, early and late follow-up. Transplant Rev (Orlando). 2014 Apr;28(2):92-101. doi: 10.1016/j.trre.2014.01.003. Epub 2014 Jan 27.

3) Kumamoto M, Toyonaga A, Inoue H, Miyakoda K, Morita Y, Emori K, Sakamoto Y, Oho K, Sata M. Long-term results of balloon-occluded retrograde transvenous obliteration for gastric fundal varices: hepatic deterioration links to portosystemic shunt syndrome. J Gastroenterol Hepatol. 2010 Jun;25(6):1129-35. doi: 10.1111/j.1440-1746.2010.06262.x.

4) Freeman RB1, Edwards EB, Harper AM. Waiting list removal rates among patients with chronic and malignant liver diseases. Am J Transplant. 2006 Jun;6(6):1416-21.

- Answer to the rewier 00182548:

We thank the reviewer for the dedicated time reading and correcting our case report. We tried to answer each of your comments cautiously.
Even patients with portal venous thrombosis without liver cirrhosis have signs of hepatic encephalopathy, and the proposed physiopathology is the presence of portal-systemic shunting, showing the relevance of the hepatic circulatory disturbances (1). Thus, the

mechanism of hepatic encephalopathy improvement after the splenorenal shunt embolization seems to be directly linked to the hepatic venous flow.
Although in our patient both the portal vein thrombosis and the ammonia levels persisted after the shunt embolization, the hepatic blood flow enhancement is the most conceivable reason to the hepatic encephalopathy improvement. As the hepatic blood flow depends mostly of the portal vein, before the embolization she had a serious limitation in her hepatic circulation, not only due to the portal vein thrombosis but mainly because the splenorenal shunt turning aside the portal flow. A partial correction of this flow steal was possible due to the fact that she had portal vein thrombosis with cavernomatous transformation, so even after the shunt embolization there were other veins that kept part of the venous flow around the portal vein.
Since Doppler abdominal ultrasonography can measure the blood flow only into the portal vein and not in other small veins that keep the flow to the liver, on cases like this patient´s the imaging exams performed could not provide evidence to this partial increase in the hepatic flow, but the decrease in the MELD score (without changes in creatinine levels) is a good marker of liver function improvement. The MELD score decreasing demonstrates that we re-established part of the hepatic venous flow by closing the shunt and increasing the flow into the other veins that kept the hepatic flow. Despite that, there is not a clear recommendation to perform portosystemic shunt embolization in patients with portal thrombosis, and this case was indeed an exception. This information was now inserted in the article discussion.
Another interesting issue is the possibility of prior prophylaxis and treatment of portal vein thrombosis as a modality of prophylaxis and treatment of hepatic encephalopathy.
First, regarding the treatment, as liver cirrhosis is a major cause of portal venous thrombosis, we need to be aware to confirm the presence of acute portal vein thrombosis in cirrhotic patients to begin the anticoagulation in order to re-establish the hepatic venous flow as soon as possible, because it is a marker of decompensated disease (2, 3). When the portal venous thrombosis is only diagnosed at the routine imaging exams, the evidence to indicate the anticoagulation is not so clear, since patients with cavernomatous transformation are excluded from the studies of anticoagulation treatment (2).
Unfortunately, most of these imaging exams are indicated just as a screening strategy to find hepatocellular carcinoma nodules at an early stage, so they are performed no more than twice a year. As a result, many diagnoses of portal thrombosis in these patients are confirmed only when the acute phase of thrombus formation was missed and the complications are already installed. To avoid these late diagnoses, doctors who attend cirrhotic patients must be aware of the possibility of portal venous thrombosis in any kind of cirrhosis decompensation with no evident trigger factor. Therefore, cirrhotic patients with abdominal pain, hepatic encephalopathy, esophageal variceal bleeding or newly diagnosed ascites without a comprehensible trigger factor should be submitted to abdominal ultrasonography before the hospital discharge. Doing this simple and non-invasive exam at time, much more cases of acute and subacute thrombosis could be found earlier, avoiding the late diagnosis and its complications.
We also could reflect on the anticoagulation treatment to some selected patients when the time of the portal thrombosis is not clear enough and they already have some signs of late diagnosis, but the better strategy in this setting is controversial.
Finally, the role of prophylactic treatment to avoid portal venous thrombosis is still more controversial because cirrhotic patients have a significant risk of bleeding. There is not a clear indication for this prophylaxis, but it also could be considered in selected patients who already have some kind of procoagulation disturbances. However, this is a complex issue that was not well evaluated yet. We hope that further studies can access this topic to raise more information about it.

References

1) Mínguez B1, García-Pagán JC, Bosch J, Turnes J, Alonso J, Rovira A, Córdoba J. Noncirrhotic portal vein thrombosis exhibits neuropsychological and MR changes consistent with minimalhepatic encephalopathy. Hepatology. 2006 Apr;43(4):707-14.

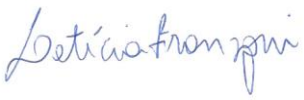
2) Delgado MG1, Seijo S, Yepes I, Achécar L, Catalina MV, García-Criado A, Abraldes JG, de la Peña J, Bañares R, Albillos A, Bosch J, García-Pagán JC. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol. 2012 Jul;10(7):776-83. doi: 10.1016/j.cgh.2012.01.012. Epub 2012 Jan 28.

3) Qi X1, Bai M, Yang Z, Yuan S, Zhang C, Han G, Fan D. Occlusive portal vein thrombosis as a new marker of decompensated cirrhosis. Med Hypotheses. 2011 Apr;76(4):522-6. doi: 10.1016/j.mehy.2010.12.007. Epub 2011 Jan 8.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,



Letícia de Campos FRANZONI, MD
Department of Internal Medicine
Division of Gastroenterology
Botucatu School of Medicine
Rubiao Junior District S/N, 18618-970
Sao Paulo, Brazil.
leticiafranzoni@hotmail.com