January 8, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: manuscript 1155-review.doc).

Title: Massive hepatic necrosis with toxic liver syndrome following portal vein ligation.

Authors: Aurélien Dupré, Johan Gagnière, Lucie Tixier, David Da Ines, Sébastien Perbet, Denis Pezet, Emmanuel Buc

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 1155

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 (highlighted in blue)

Major comments:

- The reason for massive hepatic necrosis is not completely clear. The authors suggested a liver congestion but the outflow was not modified by PVL and I am not sure that the hepatic artery flow increase can cause by itself congestion. Please comment. There was any sign of congestion at Doppler or CT scan?

We agree with this comment. The reason for hepatic necrosis after PVL is not completely clear, that's why we hypothesized acute congestion. PVL alone cannot induce hepatic necrosis. Hepatic artery obstruction (HAO) leads to interruption of arterial inflow with hypoxemia and secondary liver necrosis. In case of accidental HAO several reports have shown that arterioportal shunting could prevent hepatic necrosis through restoration of normal oxygen supply (Shimizy et al., 2000). Thus hypoxemia seems to be the basis of hepatic necrosis. In our observation, right hepatic artery was not dissected or traumatized at surgery and right arterial inflow is systematically assessed at the end of the procedure using intraoperative US. In

contrast, studies of right lobe grafts in living donor liver transplantation have shown congestion with sometimes necrosis of the anterior segment when grafts were harvested without the middle hepatic vein (Scatton et al., 2008, Lee et al., 2001, Yamamoto et al., 2003). A near-infrared spectrometry study has confirmed congestion and hypoxemia in this setting (Cui et al., 2001). As a consequence, portal veins can become the draining veins to ensure an adequate venous outflow.

So we hypothesized that compression of the right and median hepatic veins reduced the flow in these veins, with partial recovery of liver outflow through portal system. PVL in this condition has lead to acute congestion with secondary necrosis of the right liver. This phenomenon was probably worsened by increase hepatic arterial inflow due to hepatic arterial buffer response secondary to PVL.

We modified the final manuscript to better understanding (p4, lines 14-29).

- The authors reported that an abscess was drained. Was it in segment 4? It could be related to the non-selective ligature of P4 (arterial and portal branches). Isolated ligature of portal branches of P4 can be difficult.

The abscess was subcapsular in the segment 8, but close to both posterior segment and segment 4. Percutaneous drainage did not reveal biliary leak, with spontaneous favorable outcome without aggressive therapy.

We specified this point in the final manuscript (p3, lines 33-34).

Minor comments

- The authors reported a morbidity rate after PVE/PVL of 1%. They should specify "major morbidity". Further they stated, "Usually, planned hepatectomy can be performed even in case of such complications". It depends on complications. If a portal vein thrombosis occurs or there is severe embolization of non-targeted vessel sit could preclude surgery.

We agree with these comments. We modified the final manuscript (p4, line 3)

- The authors reported the technique of two-stage hepatectomy in the introduction. This is misleading because it was not the case. In the first surgical procedure they just performed PVL.

We agree with this comment. We modified this point in the final manuscript (p2, lines 24-27)

- Why the authors did not perform percutaneous PVE?

We did not perform percutaneous PVE for at least two reasons:

1) Assessment of resectability was mandatory concerning the metastasis close to the left hepatic vein. In such case intraoperative US can be more accurate than preoperative imaging;

2) Oncologic resection required right trisectionectomy and thus preoperative significant hypertrophy of the left lobe. Surgical ligation of the glissonian branches of the segment 4 appeared to be more secure as we know that embolization of the whole portal veins of the segment 4 can be difficult to achieve.

We specified these points in the final manuscript (p3, lines 18-22)

- What about postoperative bilirubin and PT/INR values?

Postoperative bilirubin increased since the first postoperative day and reached a plateau around 100 µmol/L. Prothrombin time fall rapidly to 47% at postoperative day 1, stabilized during 2-3 days, and increased again progressively.

We specified these points in the final manuscript (legend of the figure 2).

- Was the liver normal at the time of surgery? Any congestion or chemotherapy-related liver injury? Did the authors perform any biopsy (preoperative or postoperative)?

Liver was normal at surgery, with no congestion or chemotherapy-related liver injury. Preoperative biopsy was not performed because the patient received only six cycles of chemotherapy and because liver function tests were normal before surgery. Postoperative biopsy was not performed because of impaired coagulation and ascites.

We specified this point in the final manuscript (p3, lines 21-22 and 30).

3 References and typesetting were corrected

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

Sincerely yours,

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