

Title: Spontaneous rupture of a mucinous cystic neoplasm of the liver resulting in a huge biloma in a pregnant woman: a case report

Answers to the Reviewers comments:

Reviewer Comments; in bold italics

Author comments; standard font

Response in article; Bold, italics, underlined, red

Reviewer #1:

Comments to the Author

This case is very interesting and novel in the literature, and in my knowledge, never reported priorly.

Response; We fully agree with the Reviewer and refer to this in the first sentence of the Conclusion (page 10). To the best of our knowledge, a symptomatic MCN-L in a pregnant woman has never been reported in the literature. Same is true for its spontaneous rupture during pregnancy. Here are our specific answers to the questions raised by the Reviewer:

1. Reviewer comment: I want to make sure that there were no other causes for the bile collection.

Response 1; The authors understand that any other potential causes for bile collection need to be excluded in such patients. The symptomatic cystic tumour of the liver hilum was the only pathology detected in our patient in October 2018 based on contrast-enhanced MRI. Importantly, within the following 6 weeks that is prior to the diagnosis of a large biliary collection, the patient did not have any diagnostic or therapeutic procedures performed nor sustained any abdominal trauma. Moreover, the communication between the cystic mass and the fluid collection was possible to be shown on oblique coronal T2-weighted MRI. Therefore, we assumed that spontaneous rupture of MCN-L with the formation of a biloma was the most likely diagnosis. We now added this

information in the manuscript together with a new Figure (1D) that we refer to responding to the Reviewer comment No 3:

Page 3, paragraph 1; line 12;

The patient did not have any diagnostic or therapeutic procedures nor any abdominal trauma in the preceding weeks. The fluid collection proved to be of biliary origin at percutaneous drainage. Therefore, we concluded this was a spontaneous rupture of MCN-L with the formation of a biloma.

Page 7, paragraph 1; line 8;

However, the communication between the cystic mass and the fluid collection was visible on coronal T2-weighted MRI study (Figure 1D). Moreover, the percutaneous fluid drainage revealed its mainly biliary content (fluid bilirubin of 18 mg/dl vs. serum bilirubin of 2 mg/dl) which lead to the diagnosis of the ruptured biliary cyst of the liver.

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2. Reviewer comment: Why perihepatic fluid was present on first MRI?

Response 2. Indeed, there was a slight amount of perihepatic fluid visible on first MRI, for which we do not have a clear explanation. We believe this might have been due to the increasing jaundice found at that time (serum bilirubin of 12 mg/dl) and the consequent distention within the MCN-L just prior to its rupture. As we described in “Case Presentation”, within a week the pain gradually decreased and serum bilirubin came down to 2 mg/dl which we believe could result from MCN-L rupture. However, we realize this is only our hypothesis.

3. Reviewer comment: Was the communication between the MCN and bile collection demonstrated at surgery?

Response 3. The bile collection was not present anymore intraoperatively as it was fully drained percutaneously 5 weeks prior to surgery. We now make it clear in the manuscript.

Page 8 ; paragraph 2; line 2;

Intraoperatively, no signs of residual biliary fluid collection were present following its percutaneous drainage 5 weeks before.

4. Reviewer comment: I wonder if on MRI axial images it was possible to see the connection between the MCN and the collection.

Response 4. We are grateful to this Reviewer for this important and interesting question. The fluid collection was directly adjacent to the MCN-L as demonstrated on axial T2-weighted images on Figure 2A (below).

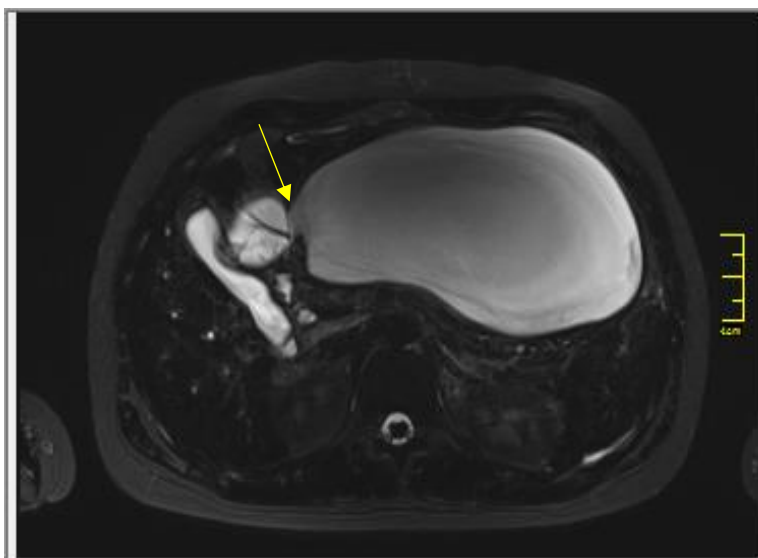


Figure 2A: Axial T2-weighted MRI showing the fluid collection directly adjacent to the MCN-L (arrow).

However, the communication (arrows) between the MCN-L, left hepatic duct and the fluid collection (star) was better depicted on oblique coronal T2-weighted images on Figure 2B (below)

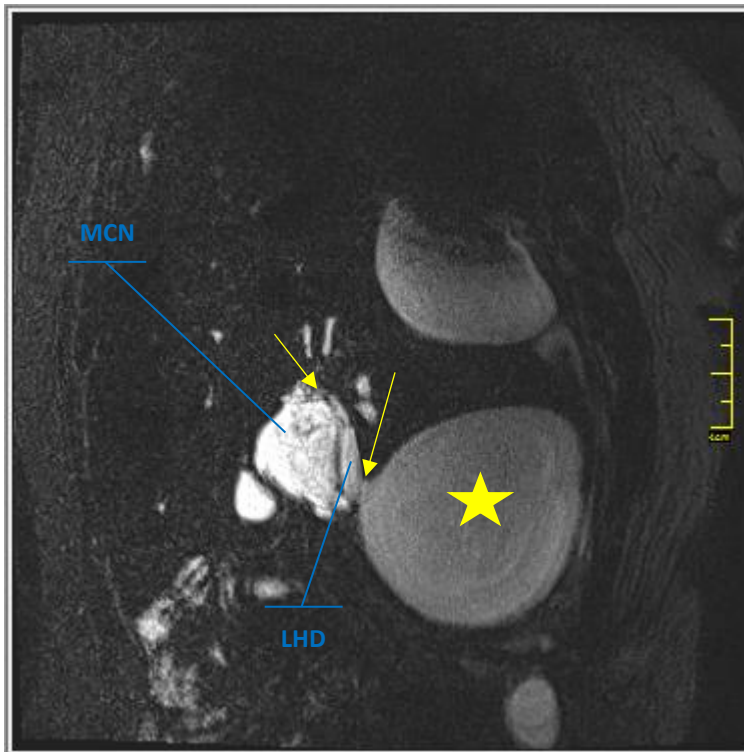


Figure 2B: Oblique coronal T2-weighted MRI indicating the communication (arrows) between the MCN-L, left hepatic duct and the fluid collection (star).

We now included this important information in the manuscript:

Page 7 ; paragraph 1; line 8;

However, the fluid collection was directly adjacent to the MCN-L as demonstrated on axial T2-weighted images (Figure 2A). Moreover, the communication between the cystic mass and the fluid collection was visible on coronal T2-weighted MRI study (Figure 2B).

We also added a new Figure 2A and Figure 2B (shown above) for better visualisation. As a result, Figure 2 (histopathological examination) became Figure 3 accordingly.

5. Reviewer comment: Did the MRI internal features of the cyst change from first to last MRI?

Response 5. Comparing the baseline with post-rupture MRI examinations, the shape as well as the architecture of the internal septations have changed which is shown on Figure below.

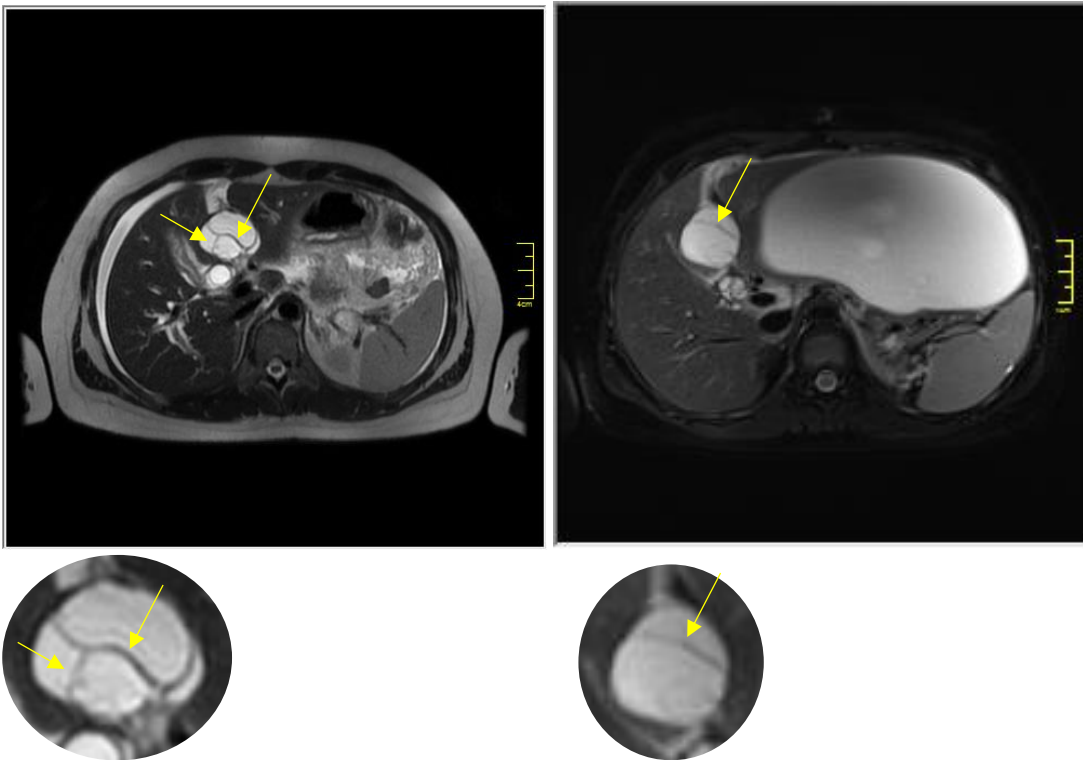


Figure 4. Baseline MRI study (left) showing an oval shape of MCN-L as compared to a more circular one (right) following its rupture. Some differences regarding the pattern of internal septations are also visible.

We now included this additional information in the discussion:

Page 10 ; paragraph 1; line 2;

Comparing the baseline with post-rupture MRI examinations, the shape as well as the architecture of the internal septations was clearly changed which is shown on Figure 3.

We also added Figure 4 (above) in our manuscript.

Reviewer #2:

Comments to the Author

It's a good case report. Some concerns were listed in the following.

1. Reviewer comment: On page 3 and 6: “ located between the left lateral sector (segments 2 and 3) and segment 4 of the liver” , needed to be specific to which segment of the liver.

Response 1; We agree with the Reviewer that the location of the lesion should be stated precisely.

We now altered the sentences on page 3 and 6 to provide precise information.

Page 3 ; paragraph 1; line 5;

Her first magnetic resonance imaging (MRI) of the abdominal cavity revealed a multilocular cystic tumour of the liver hilum (37 x 40 mm in diameter) located between the segment 3 and 4 of the left liver lobe.

Page 6 ; paragraph 6; line 2:

Her first magnetic resonance imaging (MRI) of the abdominal cavity performed in another hospital in October 2018 revealed a multilocular cystic mass of the liver hilum located between segment 3 and 4 of the left liver lobe (Figure 1A, 1B) which measured approximately 37x40 mm in diameter.

2. Reviewer comment: *On page 6: “jaundinced” should be jaundiced.*

Response 2; We would like to thank the Reviewer for indicating this spelling error. We corrected the wrong spelling:

Page 6 ; paragraph 4; line 2:

At admission to our unit, the patient was slightly jaundiced with a soft and tender mass palpable in the left upper abdomen.

3. Reviewer comment: *On page 4, 7: The word “lead” in “that lead to the tumour rupture with the formation of biloma in our patient.”, “that lead to the tumour rupture with the formation of biloma in our patient.” and “which lead to the diagnosis of the ruptured biliary cyst of the liver. ” should be “led”.*

Response 3; We are grateful for spotting this grammar mistake that appeared repeatedly in our manuscript. We corrected this mistake in all sentences:

Page 4; paragraph 2; line 7:

We believe the growth of this subepithelial stroma secondary to high levels of sex hormones produced during pregnancy might have been the main causative factor that led to the tumour rupture with the formation of biloma in our patient.

Page 4 ; paragraph 4; line 10:

We believe the growth of this subepithelial stroma due to high levels of sex hormones during pregnancy might have been the main causative factor that led to the tumour rupture with the formation of biloma in our patient.

Page 7 ; paragraph 1; line 12:

The percutaneous fluid drainage revealed its mainly biliary content (fluid bilirubin of 18 mg/dl vs. serum bilirubin of 2 mg/dl) which led to the diagnosis of the ruptured biliary cyst of the liver.

4. Reviewer comment: *On page 9: Reference 2 was not of the liver lesion, was it appropriate cited here?*

Response 4; We are grateful to the Reviewer for spotting our mistake. This particular reference indeed refers to ovarian-type stroma and not to the liver lesion. The sequence of the references was properly corrected.

5. Reviewer comment: *On page 9: “A growing body of evidence in the literature suggests that presence of the ovarian-type stroma within MCN-L may be affected by sex hormones [2].’ The reviewer believed that if more than one reference is given, it will be better to say that “A growing body of evidence”.*

Response 5; We appreciate very much this important suggestion raised by the Reviewer. This made us realize we need to clarify this issue more precisely. In fact, a growing body of evidence suggests that presence of ovarian-type stroma may be affected by sex hormones in case of MCN of the pancreas. Both MCN-L and MCN of the pancreas share the same ovarian-type stroma as the leading pathological feature required for diagnosis. Therefore, growth of both of them may be affected by elevated female hormones levels during pregnancy. However, this phenomenon has only been repeatedly observed in case of MCN of the pancreas which are much more common than MCN-L. We now explain this in the discussion. We also added an important publication by Revoredo F et al (Ref. No. 6 at present) which summarizes the current knowledge regarding the possible influence of pregnancy on growth of MCN of the pancreas

Page 10 ; paragraph 1; line 7:

The final diagnosis was made based on the presence of ovarian-type stroma at histopathological evaluation of the resected specimen (Figure 3A). Besides typical mucin-secreting biliary type

epithelium, the presence of dense subepithelial ovarian-type stroma with spindle cells expressing female sex hormone receptors is a characteristic feature of MCN-L [3, 4]. The presence of such stroma is also a defining feature of MCN of the pancreas [5], which have been observed to grow more rapidly achieving extraordinary size during pregnancy [5, 6]. This feminine hormonal influence might also explain the growth of MCN-L and its final rupture at the beginning of pregnancy (week 8-10) in our patient.

6. Reviewer comment: *On page 10: “MCN-L with associated invasive carcinoma that may not be fully excluded solely by imaging [2].” Reference 2 was not of the liver lesion, was it appropriate cited here?*

Response 6; We would like to thank to the Reviewer for spotting our mistake. This particular reference again refers to ovarian-type stroma. It was replaced by the proper one:

Zen Y, Jang KT, Ahn S, Kim DH, Choi DW, Choi SH, Heo JS, Yeh MM. Intraductal papillary neoplasms and mucinous cystic neoplasms of the hepatobiliary system: demographic differences between Asian and Western populations and comparison with pancreatic counterparts.

Histopathology 2014; 65 (2): 164-173.