

Author's response to reviews

Title: Splenic rupture as the presenting manifestation of primary splenic angiosarcoma: a case report

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Author's response to reviews: see over
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Editorial Office,

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Dear Sir/Madam,

We are very pleased to be informed that you would be interested in evaluating a revised version of our paper entitled "Splenic rupture as the presenting manifestation of primary splenic angiosarcoma: a case report" (MS: 2274587151754306), which we have submitted for consideration for publication in Journal of Medical Case Reports, that addresses the reviewers’ comments. Please find attached the revised manuscript of our paper with all required revisions. In this cover letter we point out in detail how we have responded to each reviewer comment and all the changes that have been made.

We appreciate the reviewers’ comments and we believe that they really helped us to improve our text. The paper has been improved according to the suggestions of the reviewers and all the comments of the reviewers were addressed in the manuscript (Please see below).

Answers to Reviewers’ Comments:

Reviewers’ Comments:
Reviewer #1 (Comments to authors): “None”.

Answer: We would like to thank the reviewer for his/her comments.

Reviewer #2 (Comments to authors): “Primary angiosarcoma of the spleen is a very rare and aggressive neoplasm with poor prognosis. Primary tumors in the pediatric age group is even rarer. Splenic angiosarcoma rarely occurs in the pediatric group (18 years or younger). Survival duration for pediatric patients is often limited. In a recent pediatric surgery publication (aug 2007) a case of a 7-year-old boy with splenic angiosarcoma is reported. The postoperative course following splenectomy was uneventful. The patient was disease free at 16 years after surgery.”.

Answer: We agree with the reviewer. As stated in the revised manuscript, “Abstract” (Introduction section), 1st sentence, page 2: “Primary splenic angiosarcoma consists a rare neoplasm of vascular origin carrying a dismal prognosis, partly due to its high metastatic potential.”. In the same section, 3rd sentence, it is also mentioned: “We report the case of a 17 years old female patient, who presented with splenic rupture of a primary splenic angiosarcoma.”. In addition, in the “Abstract” (Case presentation), last sentence it is stated: “After an uneventful recovery, the patient was discharged on the 6th postoperative day.”. As also stated in the Conclusion section of the revised “Abstract”: “Primary splenic angiosarcoma constitutes an infrequent neoplasm. Although a malignancy of advanced age, there have been a few reported cases among younger patients. The reported case presented with splenic rupture, was treated with laparotomy and splenectomy, and is disease free after 16 months of follow-up.”.

Moreover, as stated in the “Introduction” in page 3: “Primary angiosarcoma or hemangiosarcoma of the spleen is an extremely rare malignancy of incompletely understood pathogenesis, with a high metastatic potential and exceedingly poor prognosis, regardless of
the treatment regimen. This aggressive disease entity presents in adults in their sixth to seventh decade with only 8 cases reported in the literature below 18 years of age. Reported median survival rates range from 4.4 to 14 months, depending on whether the diagnosis is made either after splenic rupture has occurred, or based on clinical findings, respectively [1,2]. Because of the poor clinical findings of these mesenchymal tumors, they can easily be overlooked and splenic rupture still represents their most encountered presenting manifestation. We herein report a case of splenic rupture in a 17 years old female patient due to angiosarcoma, which represents the ninth case of this disorder below 18 years of age and, to the best of our knowledge, the second case presenting with splenic rupture in this age group.”.

Additionally, in the 1st sentence of the revised “Case presentation” in page 4, it is mentioned: “A 17 years old female patient presented to the emergency department of our hospital with diffuse abdominal pain and distention.”. In the last paragraph of this section, in page 5, it is also stated: “After an uneventful recovery, the patient was discharged on the 6th postoperative day. The patient remains symptom and disease free after a follow-up period of 16 months, in contrast with the median survival of 4.4 months of patients with primary angiosarcoma of the spleen and splenic rupture [2].”.

Furthermore, in the revised “Discussion” section, 1st sentence, 1st paragraph, page 6, it is stated: “Angiosarcoma originating from the spleen is a very rare mesenchymal, malignant tumour of vascular origin, consisting of atypical and anaplastic endothelial cell concentrations.”. In the 4th sentence of the same paragraph it is mentioned: “Among the primary malignant splenic tumours, which affect 0.14-0.25 per million of population, angiosarcoma represents the majority of them.”. As also stated in the 6th and 7th sentences of the same paragraph: “Overall, since 1879 when Langhans described the first case of angiosarcoma of the spleen, there have been approximately 200 cases reported in the literature. Splenic angiosarcoma consists a disease entity of the adulthood, with a mean age of
presentation at 50-60 years among the various series, although pediatric population may be also affected at virtually any age [4,5].”.

In addition, in the “Discussion” of the revised version of our paper, in the last sentence of page 6 and 1st sentence of page 7, it is stated: “The high incidence of early metastasis of this tumour, hematogenous in their majority, is reflected by the fact that the reported rates are between 69 and 100% among various series, with the most common sites being the liver, lungs, bones or bone marrow, lymph nodes, gastrointestinal tract, brain, and adrenal glands.”.

Finally, in the “Conclusion” section, page 8 and 9 it is stated: “Splenic angiosarcoma, although rare, must be considered in the differential diagnosis of patients with hematologic abnormalities of unexplained origin and parenchymal lesions on spleen imaging. Definite diagnosis requires laparotomy and splenectomy, since the risk of splenic rupture is enhanced with percutaneous splenic biopsies. Since metastatic disease is encountered in the majority of cases in patients with splenic angiosarcoma, the surgical approach with splenectomy is a more diagnostic than therapeutic modality. Although no effective chemotherapeutic protocol for angiosarcomas has yet been established, combined treatment with cyclophosphamide, adriamycin, vincristine, and prednisone or other agents after splenectomy has been employed in a few cases, with fewer relatively good results [12]. Because of no evidence of metastatic disease, our patient was not treated with adjuvant chemotherapy, with excellent results at 16 months of follow up.”.

Comment #1: “The case is well written although the authors should have highlighted the physical findings along with vitals and labs on initial presentation given splenic rupture was the initial presentation.”.

Answer #1: We would like to thank the reviewer for this comment. In the revised manuscript, the physical findings along with the vital signs and laboratory results on initial presentation
have been highlighted. In particular, the 1\textsuperscript{st} and 2\textsuperscript{nd} sentence of the Case presentation of the “Abstract”, page 2, in the initial text: “The patient presented with severe tenderness of the left upper abdominal quadrant, diffuse abdominal pain, abdominal distention, and hemodynamic instability. Blood tests showed anemia and thrombocytopenia.” have been changed to: “The patient presented with diffuse abdominal pain and abdominal distention. Clinical examination revealed severe tenderness of the left upper abdominal quadrant, a palpable abdominal mass, and hemodynamic instability (systolic arterial blood pressure: 75 mmHg and heart rate: 135 beats per minute). Blood tests showed anemia (hemoglobin: 7.0 gr/dl) and thrombocytopenia (platelets: 70x10^{9}/l)” as stated from the 1\textsuperscript{st} to the 3\textsuperscript{rd} sentence, Case presentation in the “Abstract” section, page 2, in the revised version of our paper.

Furthermore, the 1\textsuperscript{st} sentence in the “Case presentation”, page 4 of the initial manuscript: “A 17 years old female patient presented to the emergency department of our hospital with symptoms of severe tenderness of the left upper abdominal quadrant, diffuse abdominal pain and distention, and hemodynamic instability, as it was apparent from decreasing blood pressure and the presence of tachycardia.” has been revised to: “A 17 years old female patient presented to the emergency department of our hospital with diffuse abdominal pain and distention. Physical examination revealed severe tenderness of the left upper abdominal quadrant, a palpable abdominal mass, and hemodynamic instability; in particular, the patient’s systolic arterial blood pressure was 75 mmHg and the heart rate 135 beats per minute.” as shown in the 1\textsuperscript{st} and 2\textsuperscript{nd} sentence, “Case presentation”, page 4, in the revised version. The 3\textsuperscript{rd} sentence of the initial “Case presentation”: “Apart from a moderate body weight loss and sporadic episodes of dizziness, reported medical history was unremarkable up to the day before admission, while laboratory investigations brought up anemia and thrombocytopenia.” has also been changed to: “Apart from a moderate body weight loss and sporadic episodes of dizziness, reported medical history was unremarkable up to the day before admission.
Laboratory investigations brought up anemia (hemoglobin: 7.0 gr/dl) and thrombocytopenia (platelets: 70x10^9/l).” as presented in the 4th and 5th sentences, “Case presentation”, page 4 of the revised version.

Comment #2: “In the 2nd paragraph under the case presentation section 'former' splenectomy needs correction.”.

Answer #2: We agree with the reviewer’s comment. The 3rd sentence of the 2nd paragraph of the “Case presentation” section in page 4 of the initial text: “A former splenectomy was performed and peritoneal lavage with worm saline for the evacuation of clots followed.” has been corrected to: “Splenectomy was performed and peritoneal lavage with warm saline for the evacuation of clots followed.” as stated in the 3rd sentence of the 2nd paragraph of the “Case presentation” section in page 4 of our revised paper.

Comment #3: “The case could have benefitted with slides of the CT although the authors have touched upon in the discussion section. CT may reveal an enlarged spleen with hypo- or hyperattenuating areas on nonenhanced scans. Areas of hyperattenuation are likely to reflect acute hemorrhage or hemosiderin deposits. On contrast-enhanced CT scans, the tumors may exhibit peripheral or heterogeneous contrast enhancement. Ill-defined nodular lesions with low- or high-signal intensity may be seen on both T1- and T2-weighted images depending on the age of blood products and presence of necrosis. High-signal intensity on both T1- and T2-weighted images is related to subacute hemorrhage or tumor necrosis, and low-signal intensity is related to chronic hemorrhage or fibrosis within the tumor. The appearance of splenic angiosarcoma on contrast-enhanced T1-weighted images consists of hyperintense masses with focal areas of nonenhancement depending on the hemorrhage and necrosis within the tumor.”.
**Answer #3:** We would like to thank the reviewer for this comment. In the revised paper, according to the reviewer’s suggestion, an image from the abdominal CT scan (“Figure 1”) has been included. Accordingly, the initial “Figure 1” and “Figure 2” have been renamed as “Figure 2” and “Figure 3”, respectively.

The 4th sentence, 1st paragraph, page 4, of the initial paper: “Abdominal ultrasound showed large quantity of intraperitoneal free fluid and an enlarged spleen, which were confirmed by the abdominal computed tomography that followed, with further demonstration of spleen originating hemorrhage and heterogenous and low-density signal within the splenic parenchyma which showed varying degrees of contrast enhancement.” has been revised as stated in the new “Case presentation” section, 6th sentence, 1st paragraph, page 4: “Abdominal ultrasound showed large quantity of intraperitoneal free fluid and an enlarged spleen, which were confirmed by the abdominal computed tomography (CT) that followed (Figure 1), with further demonstration of spleen originating hemorrhage and heterogenous and low-density signal within the splenic parenchyma which showed varying degrees of contrast enhancement.”.

The last sentence of page 4 and the 1st and 2nd sentence of page 5 of the initial “Case presentation”: “The splenic weight was 1530g, its greatest diameter was 19cm, and macroscopically it appeared nodular and spongy with hemorrhagic characteristics (Figures 1a & 1b), excluding the diagnosis of idiopathic rupture. The pathologic examination of the excised spleen demonstrated angiosarcoma presumably of splenic origin (Figure 2).” have been modified to: “The splenic weight was 1530g, its greatest diameter was 19cm, and macroscopically it appeared nodular and spongy with hemorrhagic characteristics (Figures 2a & 2b), excluding the diagnosis of idiopathic rupture. The pathologic examination of the excised spleen demonstrated angiosarcoma presumably of splenic origin (Figure 3).”
stated in the 1st and 2nd sentence of page 5 in the “Case presentation” section of the revised version of our text.

The legend of the computed tomography image is presented in the “Figure legends” section of the revised manuscript in page 13: “Figure 1. Abdominal CT demonstrated intraperitoneal free fluid (arrowhead) and an enlarged, anisoechoic spleen with hypoechoic areas representing focal necrosis (arrow).”.

The legend of the initial “Figure 1” in the “Figure legends” section in page 12: “Figure 1. Excision specimen of the enlarged spleen. Hemorrhagic and nodular lesions excluded the diagnosis of idiopathic rupture, while they prompted for further abdominal exploration for other pathologies.” has been changed to: “Figure 2. Excision specimen of the enlarged spleen. Hemorrhagic and nodular lesions excluded the diagnosis of idiopathic rupture, while they prompted for further abdominal exploration for other pathologies.” as shown in page 13 of the revised paper. Similarly, the legend of the initial “Figure 2” in page 12: “Figure 2. Histopathological findings of angiosarcoma of the spleen (H&EX80). Spindle-cell neoplasm has replaced the normal red and white pulp in spleen whereas ectatic vascular spaces lined with hypertrophied endothelial cells are apparent.” has been also changed to: “Figure 3. Histopathological findings of angiosarcoma of the spleen (H&EX80). Spindle-cell neoplasm has replaced the normal red and white pulp in spleen whereas ectatic vascular spaces lined with hypertrophied endothelial cells are apparent.” as appears in the revised “Figure legends” section in page 13.

Finally, the 1st paragraph of page 8 of the initial text: “Imaging modalities are an invaluable aid for the differential diagnosis between other benign and malignant tumors of the spleen, although diagnostic accuracy is lacking. Among them, computed tomography of the abdomen is capable of revealing an enlarged spleen with hypoattenuating lesions on non-enhanced scans. Contrast enhancement of angiosarcoma may be similar to that of hepatic cavernous
hemangioma, although the pattern of enhancement is variable. Massive splenic calcifications on computed tomography or magnetic resonance imaging have been reported as a prominent suggestive finding of angiosarcoma [10]; however, calcifications may also be apparent in patients with benign conditions such as hemangioma [11].” has been revised so as to describe more thoroughly the tumour imaging features on CT and also to discuss its appearance on MRI. In particular, as stated in the revised version of our paper, “Discussion” section, 1st paragraph, page 8: “Imaging modalities are invaluable for the differential diagnosis between other benign and malignant splenic tumours, although diagnostic accuracy is lacking. Among them, CT may reveal an enlarged spleen with hypo- or hyperattenuating areas on non-enhanced scans. Areas of hyperattenuation are likely to reflect acute hemorrhage or hemosiderin deposits. Contrast enhancement may be similar to that of hepatic cavernous hemangioma, although the pattern of enhancement is variable. On contrast-enhanced scans, it may exhibit peripheral or heterogeneous contrast enhancement. On magnetic resonance imaging (MRI), ill-defined nodular lesions with low- or high-signal intensity may be seen on both T1- and T2-weighted images depending on the age of blood products and presence of necrosis. High-signal intensity is related to subacute hemorrhage or tumor necrosis and low-signal to chronic hemorrhage or fibrosis in the tumour. Massive splenic calcifications on CT or MRI have been reported as a prominent suggestive finding of angiosarcoma [10]; however, calcifications may also be found in patients with benign lesions such as hemangioma [11].”.

Comment #4: “The immunopathological study of the resected specimen showed CD31 (positive), CD34 (positive), factor VIII related antigen (positive), and ulex europaeus agglutinin (positive) in a case report published recently. This case report does not mention of any immunopath findings.”.
**Answer #4:** We appreciate the reviewer’s comment. We would like to apologise for not mentioning the results of immunohistochemistry in the initial manuscript. On immunohistochemical examination, the resected specimen showed positive immunostaining for CD31 and CD 34. Immunostaining for factor VIII related antigen (FVIIIRAg) and ulex europaeus agglutinin (UEA) was not performed. As stated in the revised paper, “Case presentation” section, 3rd sentence, 1st paragraph, page 5: “On immunohistochemical examination, the resected specimen showed positive immunostaining for CD31 and CD 34.”.

All authors have contributed to, and read the paper, have given permission for their name to be included as a co-author, and take public responsibility for it. We also state that the present manuscript is original, is submitted solely to this Journal, has not been previously published, nor accepted for publication elsewhere, nor is it under consideration for publication elsewhere, and will not be submitted elsewhere. We declare that we do not have any financial support or relationships that may pose conflict of interest. In addition, written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

We would like to thank you for your interest in our paper. Please do not hesitate to contact us in case you have any further questions or comments.

Yours sincerely,

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