Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: This is a manuscript describing the usefulness of CEUS for the differential diagnosis of pathologies around the aorta. I have some concerns about the following issues. 1. The most important point in such a situation is the first diagnosis on admission of the patient. I think CEUS is really useful in this timing as authors mentioned. However, authors performed CEUS in the second admission. In this timing, tumorous pathology is easily expected by only CT scan, without needing of PET-CT or CEUS. It did not like endoleaks after EVAR. Even though, in discussion, authors mainly discuss about endoleaks after EVAR. I think this is unnecessary. Authors should mention about the usefulness in the differential diagnosis in the first admission, prior stent graft insertion. 2. CT scan on first admission revealed heterogenous enhancement in the mass. I suppose this enhancement does not like aortic hematoma. Why did not authors perform additional examination including CEUS or MR? Please note the reason. 3. Why did not authors perform endoscopic ultrasound-guided tissue acquisition (EUS-TA)? EUS-TA is a strong tool for differential diagnosis of tumor type. 4. How was the long-term survival of this patient? 5. Was surgery appropriate for the management of this patient, who had apparent metastatic lesions?

Responses

The author's team was mainly composed of ultrasound diagnostic physicians, and did not participate in the diagnosis at the first admission. Surgeons and radiologists agreed that aortic hematoma was the most likely diagnosis, so EVAR was performed. CEUS is a routine follow-up examination of the EVAR. And the ultrasound team first participated in the diagnosis was also at the second admission. Endoleak is the most common complication of EVAR, so we focus on the difference between this case and typical endoleak. The mass is more likely a malignant tumor with liquefaction and necrosis than endoleaks. That is why the patient underwent PET / CT examination.

Aortic hematoma was diagnosed during the first hospitalization, which was a non neoplastic condition and did not require EUS-TA.

EUS-TA is of course a strong tool, but also have risk of fatal hemorrhage and tumor seeding metastasis in this case.

The tumor is large in size, grows rapidly, and squeezes surrounding tissue. The patient was not expected to survive more than 3 months if surgery was not performed. However, according to the PET/CT detection, the tumor was sharply demarcated from surrounding tissue, and there was only one localized metastatic focus in the lung. The surgical team preferred to operate directly, skipping the EUS-TA.

The patient did not receive any chemotherapy or radiotherapy, and was discharged 10 days after the operation. There were no complications during the perioperative period. When discharged, the patient had no discomfort, and could walk with assistance. The first postoperative follow-up was scheduled a month later, and the follow-up treatment plan would be determined according to the test results. However, the patient did not come to our hospital for follow-up, and since hospital discharge, we had not been able to contact the patient.

So we do not know the long-term survival of this patient.

The usefulness experience from the case was that ultrasound and CEUS can provide valuable and unique diagnostic clues, should be performing by an experienced sonographer routinely and as soon as possible.

Reviewer #2:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: The manuscript entitled “Diagnostic value of contrast-enhanced ultrasonography in primary mediastinal leiomyosarcoma mimicking an aortic hematoma: case report and literature review” by Xiujing Xie et al. requires major revision before potential publication despite interesting case with potential diagnostic value. Major concerns are as follow: 1. The language quality of the manuscript is very poor and some parts of the text are completely unclear. 2. Phrases such as “We do not recommend performing PET/CT without any initial distinction but recommend performing CEUS by an experienced sonographer routinely and as soon as possible. “ should be avoided as this is the “only” case report and such strong recommendations should be avoided. 3. Please report what kind of stents were used for aorta repair. What was the final result of the repair? Did you perform control CTA after the treatment? Any sign of “leak”? 4. Please explain why did you perform CEUS over CTA? Which part of the aorta have you examined? The thoracic aorta is hard to visualize on the ultrasound. 5. Authors should avoid imprecise and descriptive words such as “huge tumor”. Please report size. “During surgery, the huge tumor grew in the mediastinum and retroperitoneum, surrounded the thoracic aorta, and invaded the left lung. There were lots of necrotic tissue and blood in the tumor.” 6. Sentences such as “Leiomyosarcoma is considered the primary mediastinum because it does not adhere to the aorta, and the mediastinum volume is larger than that the retroperitoneum volume.” is not precise. Please specify where the tumor was located. Furthermore, specify what kind of operation was performed? What was removed? How was the aorta reconstructed? Where and why do you believe the primary tumor location was? 7. Authors are referring to guidelines for CEUS In AAA but the case described primary sarcoma in the mediastinum (?). As mentioned before, more clarification on tumor precise localization, extent, and size is mandatory.

Responses：

1. The language quality of the manuscript is very poor and some parts of the text are completely unclear.

The article has been revised again by the editorial company.

2. Phrases such as “We do not recommend performing PET/CT without any initial distinction but recommend performing CEUS by an experienced sonographer routinely and as soon as possible. “ should be avoided as this is the “only” case report and such strong recommendations should be avoided.

Ultrasound and CEUS can provide valuable and unique diagnostic clues.

3. Please report what kind of stents were used for aorta repair. What was the final result of the repair? Did you perform control CTA after the treatment? Any sign of “leak”?

4. Please explain why did you perform CEUS over CTA? Which part of the aorta have you examined? The thoracic aorta is hard to visualize on the ultrasound.

7. Authors are referring to guidelines for CEUS In AAA but the case described primary sarcoma in the mediastinum (?).

The author's team was mainly composed of ultrasound diagnostic physicians, and did not participate in the diagnosis at the first admission. Surgeons and radiologists agreed that aortic hematoma was the most likely diagnosis, so EVAR was performed.

However,the patient’s abdominal pain was not alleviated, and was hospitalized again approximately 1 month after. We first performed CEUS over CTA, because CEUS is also routine follow-up examination of the EVAR according the guidelines. And the ultrasound team first participated in the diagnosis was also at the second admission. Endoleak is the most common complication of EVAR, so we focus on the difference between this case and typical endoleak. The mass is more likely a malignant tumor with liquefaction and necrosis than endoleaks. After the patient underwent PET / CT examination, there's little value in having a second CTA. No signs of aortic dilatation and endoleak were observed during the second operation.

The mediastinal area that can be detected by ultrasound is affected by the heart, lung, sternum, ribs and spine. There may be a blind spot in the posterior mediastinum and thoracic segment of descending aorta. In this case, we used ultrasound to examine the lower thoracic aorta and abdominal aorta. From the first CTA and PET / CT, we can see that the tumor was just around the lower thoracic aorta and upper abdominal aorta.

5. Authors should avoid imprecise and descriptive words such as “huge tumor”. Please report size. “During surgery, the huge tumor grew in the mediastinum and retroperitoneum, surrounded the thoracic aorta, and invaded the left lung. There were lots of necrotic tissue and blood in the tumor.”

The size of the resected tumor tissue was about 12×7×4.5cm, with hemorrhage and necrosis.

6. Sentences such as “Leiomyosarcoma is considered the primary mediastinum because it does not adhere to the aorta, and the mediastinum volume is larger than that the retroperitoneum volume.” is not precise. Please specify where the tumor was located. Furthermore, specify what kind of operation was performed? What was removed? How was the aorta reconstructed? Where and why do you believe the primary tumor location was?

During surgery, an incision was made from the 6th intercostal space to the outer edge of the left rectus abdominis. The costal arch and diaphragm were severed after into the thoracic cavity and retroperitoneum. The tumor grew in the mediastinum and retroperitoneum, surrounded the thoracic aorta, and invaded the left lung. The tumor and the lung metastasis were all completely removed. No treatment was done for the aorta as it was not invaded by the tumor. No signs of aortic dilatation and endoleak were observed during the operation.

We tend to agree that the primary leiomyosarcoma is located in the mediastinum because it does not adhere to the aorta, and the mediastinal volume is larger than the retroperitoneum volume.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear Author, I read with interest the manuscript entitled " Diagnostic value of contrast-enhanced ultrasonography in primary mediastinal leiomyosarcoma mimicking an aortic hematoma: case report and literature review". This was a case report reporting the relevance of CEUS in the diagnosis of primary mediastinal leiomyosarcoma. Although I consider the manuscript relevant for the research context, I have the following comments: Major 1. Title: the term literature review should be obviated. Alternatively materials, methods and results of the performed narrative review should be clearly reported. Minor 1. Case presentation: Pain was radioactive --> Please revise. 2. Case presentation: It is generally supposed that, hyperechoic regions were mainly composed of solid tissue, whereas hypoechoic regions contained more liquid component --> add citation. 3. Case presention: The high-density mass part had increased fluorodeoxyglucose (FDG) metabolism, while the low-density part had decreased FDG metabolism. --> please add standardized uptake value (SUV). 4. Case presentation: please add more details regarding the performed surgical operation. 5. Discussion and conclusions: These characteristics help differentiate leiomyosarcomas from thrombi as thrombi usually have high signal intensity on both T1 and T2 sequences no enhancement after gadolinium administration --> the sentence is poorly understandable; please revise. 6. Discussion and conclusions: The term “liquid hypoechoic” should be modified as follow: “liquid anechoic”.

Responses:

Diagnostic value of contrast-enhanced ultrasonography in primary mediastinal leiomyosarcoma mimicking an aortic hematoma: case report

A 63-year-old femalewoman visited our hospital for recurrent abdominal radicular pain for approximately 2 months.

According to the principles of ultrasound, solids reflect ultrasound more strongly than liquids, thus presenting a higher signal. The principle of medical ultrasound imaging is also based on this

theory. This implies that hyperechoic regions are mainly composed of solid tissue, whereas hypoechoic regions have more liquid components.

PET/CT showed that the mass with high FDG metabolism surrounded the descending aorta. The max standardized uptake value (SUV) was 28.8. A nodule with high FDG metabolism was observed in the left upper lobe, the max SUV was 9.5.

During surgery, an incision was made from the 6th intercostal space to the outer edge of the left rectus abdominis. The costal arch and diaphragm were severed after into the thoracic cavity and retroperitoneum. The tumor grew in the mediastinum and retroperitoneum, surrounded the thoracic aorta, and invaded the left lung. The tumor and the lung metastasis were all completely removed. No treatment was done for the aorta as it was not invaded by the tumor. No signs of aortic dilatation and endoleak were observed during the operation.
Rapid freezing pathology: pleomorphic soft tissue tumors rich in sinusoids. Routine pathology: The size of the resected tumor tissue was about 12×7×4.5cm, with hemorrhage and necrosis.

These characteristics help differentiate leiomyosarcomas from thrombi, because thrombi usually have a high signal intensity on both T1 and T2 sequences, and have no enhancement after gadolinium administration

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors demonstrate the diagnostic value of contrast-enhanced ultrasound in a patient with rare mediastinal leimiosarcoma. It is an important article in terms of the use of contrast ultrasound and may contribute to the literature. However, the authors need to make some changes. Case presentation; Q1. The mass showed heterogeneous enhancement on the enhanced scan Use ''contrast-enhanced CT scan'' instead of ''enhanced scan'' Q2. Figure 1 has both CT images and PET/CT images. However, PET findings were not mentioned in the sentence in which Figure 1 was referred to in the article. A/B and C/D in Figure 1 can be separate figures. The sentences in which the Figures are cited in the article should describe the findings in the relevant Figure. Figure 1 and Figure 2 legends are insufficient. Please describe it more clearly and adequately for the reader to understand. Q3. As above, write Figure 4 and other Figure legends more clearly for the reader Q4. I suggest describing the pathological findings in the last part of the case presentation. For example, which immunostainings made the diagnosis of leimyosarcoma? Which were positive? Write more clearly Q5. Discussion and Conclusions Write only "Discussion" in the title Q6. Look out for punctuation where references are cited. For example, in the sentence below, a point is used twice. please edit. ...but the most common location is the posterior mediastinum.[1, 10, 11].

Responses:

Q2, 3

PET findings were mentioned in the followed part in which Figure 1 was cited for the second time in the article. “No abnormal increase in FDG metabolism was observed in the rest of the body, including the brain (Figure 1. and Figure 3).”

A/B and C/D in Figure 1 can be separate figures.

We think that the combination of the these pictures can facilitate readers to compare the changes of tumor size after one month in the similar CT sections. However, if the reviewers think it is better to separate, we will accept the comments in the final version.

The sentences in which the Figures are cited in the article should describe the findings in the relevant Figure.

“On initial CTA, a thick circular mass with patchy high density enhanced signal was found around the lower thoracic aorta and upper abdominal aorta. The mass showed a heterogeneous enhancement on the contrast-enhanced CT scan (Figure 1).”

“ On CEUS, the ultrasound contrast agent (SonoVue®, Bracco Imaging) was injected as bolus through the peripheral vein. A delayed contrast filling was observed in the part with the lesions, and the contrast filling process was dispersion rather than cord or clump sign. No contrast medium filling was found in the hypoechoic area, and this was different from typical endoleaks. The contrast-enhanced images closely like the malignant tumor (Figure 2.).”

“Positron emission tomography/computed tomography (PET/CT) showed that the mass surrounded the descending aorta and had a heterogeneous but clear boundary. The part of the mass with high-density mass part had an increased fluorodeoxyglucose (FDG) metabolism, whereas that with the low-density part had a decreased FDG metabolism. Malignant tumors were initially considered. A nodule with high FDG metabolism was observed in the left upper lobe, and was also considered as metastatic foci. No abnormal increase in FDG metabolism was observed in the rest of the body, including the brain (Figure 1. and Figure 3).”

“Under microscopy (H&E staining), atypical, short fusiform or epithelioid cells, and multinucleated, pleomorphic giant tumor cells were seen. Mitosis was also present, which indicated rapid cell growth. Immunohistochemistry revealed that the tumor was positive for SMA, desmin, and caldesmon, which suggested that the tumor originated from the smooth muscle. The tumor was negative for cytokeratin, epithelial membrane antigen, synaptophysin, S-100, chromogranin A, and CD56, which indicated that it was not epithelial, neurogenic, neuroendocrine, or neuroectodermal in origin. Overall, these findings suggested that the tumor was a highly malignant soft tissue sarcoma, specifically a pleomorphic leiomyosarcoma(Figure 4).”

“Under ultrasound, endoleaks are composed of liquid anechoic and solid hyperechoic regions. The anechoic regions contained flowing arterial blood, which showed an enhancement upon the administration of the contrast agent. In contrast, the solid tissue was either coagulated or an

organized thrombus with less blood supply; thus, there was no obvious contrast agent signal in the enhancement phase (Figure 5)."

We have rewritten all the figure legends, adjusted the order of the figures.

Figure 1. CTA and PET/CT transverse section images

CTA: computed tomography angiography; FDG: fluorodeoxyglucose; PET/CT: Positron emission tomography/Computed tomography

Figure A and B are the initial CTA findings. Figure A is CT scan, Figure B is contrast-enhanced CT scan in approximately the same anatomic level. A circular mass with patchy high density enhanced signal is found around the lower thoracic aorta. The mass shows heterogeneous enhancement on the contrast-enhanced CT scan.

Figure C and D are the PET/CT findings one month later, Figure C is CT scan, Figure D is PET scan in the same anatomic level. The mass increased significantly, still surrounding the lower thoracic aorta. The high-density mass part had an increased FDG metabolism, whereas the low-density part had a decreased FDG metabolism.

Figure 2. Ultrasound and contrast-enhanced ultrasonography images

Figure A: Two-dimensional ultrasound image. The marked circular area is the mass. Figure B and C are synchronous contrast-enhanced ultrasonography pictures, figure B is in the harmonic mode, and figure C is in the basal mode. Figure D and E are synchronous contrast-enhanced ultrasonography pictures at different times and levels compared to Figure B and C. Figure D is in the harmonic mode, and figure E is in the basal mode. In the harmonic mode, the contrast signal can be highlighted. In the basal mode, only the tissue signal is displayed like normal ultrasound, and the contrast agent signal is not highlighted. Solids have stronger properties of reflecting ultrasound than liquid material, which will present as a higher signal and show higher brightness in the basal mode picture. In the harmonic mode, the higher the content of contrast agent in the tissue, the stronger the signal and the higher the brightness in the image. As seen in Figure A, the echo of the mass around the artery is uneven and is supposedly comprised of liquid anechoic and solid hyperechoic areas. By comparing B and C, D and E, it can be observed that the contrast medium predominantly diffusely fills in the hyperechoic areas, rather than in the hypoechoic

areas. There is no enhancement signal of the contrast medium in the liquid anechoic area, but a rich signal of the contrast medium in the solid hyperechoic area is present. It is suggested that the hyperechoic regions in this study are solid tissues rich in blood supply and capillaries. It was like a malignant tumor with liquefaction and necrosis.

Figure 3. Median sagittal and coronal section images of PET/CT

PET/CT shows that the mass with high FDG metabolism surrounds the descending aorta. The maximum standardized uptake value (SUV) is 28.8. A nodule with a high FDG metabolism is observed in the left upper lobe, with a max SUV of 9.5. The high metabolic signal in the bladder should be the excreted drugs. No abnormal increase in FDG metabolism was observed in the rest of the body.

Figure 4. Postoperative pathological picture

HE: hematoxylin and eosin–stained. SMA: smooth-muscle actin.

The size of the resected tumor tissue is about 12 × 7 × 4.5 cm, with hemorrhage and necrosis. Under the microscope (H&E staining), the tumor cells are short fusiform or epithelioid with obvious atypia. Multinucleated and pleomorphic giant cells are also present. Mitosis indicating active growth is present. Immunohistochemistry reveals that the tumor is positive for SMA+, Desmin+ and Caldesmon+, suggesting a smooth muscle origin, and negative for cytokeratin, epithelial membrane antigen, synaptophysin, S-100, chromogranin A and CD56, suggesting that the tumor is not epithelial, neurogenic, neuroendocrine and neuroectodermal tumor. Ki-67, an antigen index of cell proliferation, has a value of 60%. The higher the index, the higher the risk of malignancy. Cytokeratin, epithelial membrane antigen, Synaptophysin, S-100, Chromogranin A and CD56 were all negative in this case (picture didn't shown), suggested that the tumor was not epithelial, neurogenic, neuroendocrine and neuroectodermal tumor.

Figure 5. Typical type 2 endoleak contrast-enhanced ultrasonography findings

In Figure A, B, and C, the areas referred to by the white arrows are approximately the same anatomical location, as are the areas referred to by the red arrows. Figure A: two-dimensional ultrasound image. The region pointed by the white arrows are hypoechoic areas, presumed to be

flowing blood, and the areas pointed by the red arrows indicate patchy hyperechoic areas, presumed to be clotted thrombi. Figure B and C are synchronous contrast-enhanced ultrasonography pictures. Figure B indicates a harmonic mode pattern. In this mode, the contrast signal can be highlighted. The areas pointed by the white arrows indicates the fascicular contrast signal, presumed to be flowing blood with rich contrast medium. The areas pointed by red arrows have no contrast signal and are presumed to have very little blood supply. Figure C is in basal mode. In this mode, only the tissue signal is displayed like normal ultrasound, and the contrast agent signal is not highlighted. The areas pointed by white arrow are hypoechoic areas, the area indicated by the red arrow has a patchy hyperechoic area. On comparing Figure B and C, it can be seen that the contrast medium fills the hypoechoic area in bundles.

Q4.

The size of the resected tumor tissue is about 12 × 7 × 4.5 cm, with hemorrhage and necrosis. Under the microscope (H&E staining), the tumor cells are short fusiform or epithelioid with obvious atypia. Multinucleated and pleomorphic giant cells are also present. Mitosis indicating active growth is present. Immunohistochemistry reveals that the tumor is positive for SMA+， Desmin+ and Caldesmon+, suggesting a smooth muscle origin, and negative for cytokeratin, epithelial membrane antigen, synaptophysin, S-100, chromogranin A and CD56, suggesting that the tumor is not epithelial, neurogenic, neuroendocrine and neuroectodermal tumor. Ki-67, an antigen index of cell proliferation, has a value of 60%. The higher the index, the higher the risk of malignancy. Cytokeratin, epithelial membrane antigen, Synaptophysin, S-100, Chromogranin A and CD56 were all negative in this case (picture didn’t shown), suggested that the tumor was not epithelial, neurogenic, neuroendocrine and neuroectodermal tumor.

Reviewer #5:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: I have read this manuscript with great interest as I have worked on a manuscript recently regarding leiomyosacomas. In general, I found the subject quite interesting and the present manifestation quite rare. There are a lot of issues regarding grammar, 6他仍然非常 the overall quality of the manuscript. Furthermore, I have attached a file with some commnets I have attached on the manuscipt. Could you please explain if there were cclear indication for EVAR on the first time? Please use literature guidelines.

Responses:

In this study, initial CTA results were not typical, and the presence of aortic calcification, hypertension, and warfarin history made the diagnosis more confusing. Aortic hematoma was considered to be the most likely diagnosis. However, the inability to directly visualize the lesion and obtain a biopsy led to a 1-month delay in diagnosis. EVAR with stenting is currently the primary treatment standard for aortic hematoma[34]. So, the initial purpose of aortic stenting in this patient was not to treat leiomyosarcoma.

REFERENCES

34.Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, Timaran CH, Upchurch GR, Jr., Veith FJ. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. Journal of vascular surgery 2009; 50(4 Suppl): S2-49 [PMID: 19786250 DOI: 10.1016/j.jvs.2009.07.002]

Reviewer #6:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear author; 1)The limitations of the ultrasound and CEUS examinations in mediastinal masses should be mentioned. 2) Abbreviations to be used in the text should be used in parentheses just after the first use of the abbreviated words in the text.

Responses:

It is difficult to clearly detect all the mediastinal masses using ultrasound. The mediastinal area that can be detected by ultrasound is affected by the heart, lung, sternum, ribs and spine. There may be a blind spot in the posterior mediastinum and thoracic segment of descending aorta.

Reviewer #7:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors have not given detail of the surgery. Was the tumour resectable totally? What was done for the lung deposit? Was any post operative chemotherapy started? How much time has elapsed after the surgery? What is the morbidity status of the patient post operatively. These details will make the paper more scientific. There are certain grammatical corrections noted in the reviewed file returned. They may be incorporated.

Responses:

TREATMENT

During surgery, an incision was made from the 6th intercostal space to the outer edge of the left rectus abdominis. The costal arch and diaphragm were severed after into the thoracic cavity and retroperitoneum. The tumor grew in the mediastinum and retroperitoneum, surrounded the thoracic aorta, and invaded the left lung. The tumor and the lung metastasis were all completely removed. No treatment was done for the aorta as it was not invaded by the tumor. No signs of aortic dilatation and endoleak were observed during the operation.

OUTCOME AND FOLLOW-UP

The patient did not receive any chemotherapy or radiotherapy, and was discharged 10 days after the operation. There were no complications during the perioperative period. When discharged, the patient had no discomfort, and could walk with assistance. The first postoperative follow-up was scheduled a month later, and the follow-up treatment plan would be determined according to the test results. However, the patient did not come to our hospital for follow-up, and since hospital discharge, we had not been able to contact the patient.

For “C and D” in Figure 3. By compare B and C, D and E,

What we want to express is figure B compare to C. figure D compare to E. There is no need to compare figure C and D.

Is figure C contrast enhanced or basal mode? Please clarify.

Figure B and C were synchronous contrast-enhanced ultrasonography pictures. Figure B was a harmonic mode pattern. In this mode, the contrast signal can be highlighted. Figure C was in basal mode. In this mode, only the tissue signal is displayed like normal ultrasound, and the contrast agent signal is not highlighted.