Author's response to reviews

Title: Primary Ovarian Angiosarcoma in a 12-Year-Old Girl: a Case Report of an Exceptional Localization in a Context of Limited Resources Country

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Author’s response to reviews:

Dear Editor

Thank you very much for yours suggestions. We have taken in consideration the valuables comments made to improve our manuscript. We have addressed these comments in the manuscript.

We much hope our manuscript is now suitable for publication in your journal.

Best regards

Dr DARRE Tchin

Diane Bena (Reviewer 1)

1. First, because it will be in an English language journal, it should be edited by someone more familiar with English grammar and phraseology (for example, use the term "blood pressure" instead of "tension"). This should include a rephrasing of the title of the article.

R: Thanks for the suggestion. We had the manuscript read by two colleagues who have a good command of English
2. You make the statements that ovarian sarcomas are observed in adults; however, your case is that of a child, so you should say that these malignancies "usually" are observed in adults.

R: Thanks. We added this word.

3. Your conclusion in your abstract should be that this case report describes a rare example of a primary ovarian angiosarcoma in a child, diagnosed in a low-income country in a laboratory with limited resources. You should state that this case demonstrates that these uncommon tumors therefore are not exclusive to adults.

R: Thanks for the suggestion. We reviewed the conclusion of the Abstract.

4. In the last sentence of "Background," you state that the patient was 13 years old; elsewhere, you state that she is 12 years old.

R: Thanks. We corrected; it is 12 years.

5. Please be more specific regarding the metastatic work-up: which imaging methods were utilized to exclude the presence of metastatic disease?

R: We mentioned in the manuscript

6. Because you are making the point that this diagnosis occurred in a country of limited resources, it would be interesting to know your policy for sending cases to other laboratories for ancillary testing. How did you select the laboratory in France? Who paid for the immunohistochemical stains?

R: Thanks. We usually send the paraffin blocks by DHL in France and often to Pitier Salpetriere's pathological anatomy laboratory in Paris for immunohistochemistry.

We solicit colleagues in France to help us with Immunohistochemistry, when we have diagnostic difficulties. Usually, those are the same patients who pay the shipping fee and immunohistochemistry. But for this case, a colleague in France at the pathological anatomy laboratory Pitier Salpetriere in Paris accepted treated us gratuitously.

7. Please state whether there was any histologic evidence of teratomatous or other tumor elements in addition to the angiosarcoma.

R: Thanks. We have specified in the manuscript
8. Please mention proposed theories for development of angiosarcomas in the ovary. From where are they believed to arise? (For example, part of or dedifferentiation of teratomas, arising from carcinosarcomas....)

R: Thanks. We mentioned in the manuscript

9. The sentence in the Discussion beginning with "The main sites of angiosarcomas...." would be better placed earlier in the paragraph, after "head and/or neck [5]."

R: Thanks. We corrected the sentence in the manuscript

10. Likewise, the order of some of the sentences in the rest of the discussion should be changed, and the discussion text would be better divided into at least two paragraphs. (For example, "The main problem in the diagnosis of angiosarcoma" could begin a new paragraph.)

11. Please discuss prognosis and current treatment recommendations.

R: Thanks you for your comment. We have structured the discussion in three parts:

The first part on the frequency and the young age of the patient

The second part on histology data and immunohistochemistry

The third part on treatment and prognosis.

12. Again, because you are making the point that this diagnosis occurred in a country of limited resources, it would be interesting to know how much the recommended treatment would cost, and how much of a financial burden this would represent to the family. Is financial assistance available in these cases?

R: Thanks you for your comment. Our country will recess in 2014, health insurance for public officials. This insurance covers only workers in the civil service of the State. Concerning our clinical case, the parents are farmers with very little financial means, without health insurance unfortunately. The paraffin blocks we have in France for immunohistochemistry would cost 50,000fcf (75Eu).

In 2015, the Togolese state created a cancer institute, which until then was not functional.

13. In my opinion, there are 2 interesting aspects to this article: the first is the rare diagnostic entity and its occurrence in such a young patient, and the second is the issue of limited resources
for diagnosis and treatment. I think a more detailed discussion of the second issue (financial and resource limitations) would add a lot to this article's significance in the literature.

R: We have endeavored to improve the manuscript by strengthening all parts of the manuscript and especially the discussion.

Thank you for all the observations, corrections and suggestions made to improve this work.

Carla Bartosch (Reviewer 2):

My comments and suggestions are the following:

R: Thanks. We had the manuscript read by two colleagues who have a good command of English

-Introduction: Check is references are properly cited. Ref 1 does not mention ovarian angiosarcomas. Conversely ref 2 and 3 are about ovarian angiosarcomas case reports and not angiosarcomas in general as mentioned.

R: Thanks. We corrected the references in the manuscript.

- Clinical exam description: add BMI; page 2 line 48 "frequent" instead of "increased" urination;

R: Thanks. We added IMC

- Description of laparotomy findings are lacking: was disease limited to the ovary? At inspection the contralateral adnexa was normal? Uterus, peritoneum and remaining abdominal cavity contents?

R: Thanks. We have clarified in the manuscript

- Gross description: right adnexectomy was performed but there is no mention of Fallopian tube. Was the tumor solid and cystic like mention in ultrasound? Page 3, line 7 - "ovarian tumor" instead of "adnectomy"; line 11 - "she" instead of "he"; "no grossly apparent residual ovarian parenchyma"

R: Thanks. We have corrected in the manuscript

- In this context sampling is very important given that angiosarcomas can be represent a component of other tumors, like MMMT and, particularly in this patient age, a teratoma. Please provide details about how tumor sampling was performed including the number of sections taken.

R: Thanks. We corrected in the manuscript. We made 14 blocks of paraffin

- Histological description needs to be improved, namely by describing tumor features like low-power architecture and growth pattern, cellular density, stromal features, cellular morphology,
mitotic index... Importantly, angiosarcoma has a propensity for a varied histologic appearance and several growth patterns have been described that mimic other tumors.

-If your only two differentials were angiosarcoma and hemangiopericytoma (a controversial entity), how do you justified your immuno panel?

-Rather than just reporting positive/negative immunostaining results, describe extension and intensity of staining. Considering your figures, some of your markers appear to be focal/patchy.

-Tumor stage and follow-up should be reported.

R: Thanks you for your comment. We reviewed the histological and immunohistochemical description.

-Discussion is limited and needs focus. Literature review is poor. The discussion on young patient's age could be emphasized by comparing findings with others cases of ovarian angiosarcoma reported in children. It would be interesting to add a discussion on the tumor etiology, considering teratoma as reviewed by Contreras and Malpica (Int J Gynecol Pathol. 2009 Sep;28(5):453-7). Also, when discussing histological features, important pathology papers describing this entity should be cited (Nielsen GP, Young RH, Prat J, Scully RE. Int J Gynecol Pathol. 1997 Oct;16(4):378-82; Nucci MR, Krausz T, Lifschitz-Mercer B, Chan JK, Fletcher CD. Am J Surg Pathol. 1998 May;22(5):620-30). Brief considerations on treatment and survival could also be added (Int J Gynecol Cancer. 2014 Jan;24(1):4-12), following the discussion on financial therapeutic management restrictions.

R: Thanks you for your comment. We have structured the discussion in three parts,

The first part on the frequency and the young age of the patient

The second part on histology data and immunohistochemistry

The third part on treatment and prognosis.

-Figure 1 would benefit from an additional low-power illustration. Resolution is not sufficient to demonstrate that there is a mitosis next to the arrow as mention in the legend.

-Figure 2 and 3, describe in the legends what the arrows are indicating.

-references 3 and 8 are the same; references 5 and 10 are the same.

R: Thanks. We have reviewed the figures and the references