

Response Letter

Dear editor and reviewers,

We would like to express our deep gratitude again for your careful review and invaluable advice, which helped us substantially in improving the manuscript. In this revised version, we checked our manuscript carefully and reconfirmed the postoperative pathological results according to the reviewer's suggestions. Also, we modified the language and polished the whole manuscript. The amendments are highlighted in the reviewer view in the Word office. Point by point responses to your comments are listed below. Thank you again for your patient and meticulous work!

In addition, during the process of revision and communication with pathologists, Professor Qingbo Fan made great contributions. Therefore, we would like to list Professor Qingbo Fan as the corresponding author after the unanimous decision of all the authors. And the original corresponding author, Professor Qi Yu, was changed to a co-author, and pathologist Dr. Xiannian Chen was added as a co-author. The author order change has been confirmed and unanimously agreed by all authors, and we sincerely apologize for the inconvenience.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: In this case report, a rare case of giant retroperitoneal lipoma is described in a very clear and detailed way. I have few comments: Page 2 Line 49: "tumor in the previous literature". The author should clarify which database was used to analyze the previous literature (PUBMED, EMBASE??) Page Line 93 "CT scanning demonstrated a ". Was the CT performed with or without contrast? And if contrast was used, what were the characteristics of the mass?

Comment 1:

Page 2 Line 49: "tumor in the previous literature". The author should clarify which database was used to analyze the previous literature (PUBMED, EMBASE??)

Answer 1:

Thank you for pointing out the unclear definition in this manuscript. We have revised our manuscript based on your suggestions in the corresponding part. There have been 22 published cases in the pubmed describing the retroperitoneal lipomas in adults since 1970. We have emphasized in the background part in the revised manuscript (Page2, Line 50-51) as following:

Page2, Line 50-51: Retroperitoneal lipomas are a rare condition, with just 22 case reports describing the tumour in adults in the previous literature of pubmed since 1970.

Comment 2:

Page Line 93 "CT scanning demonstrated a ". Was the CT performed with or without contrast? And if contrast was used, what were the characteristics of the mass?

Answer 2:

We apologize for the previous unclear expression about the CT examination. In this case, the patient had received computed tomography (CT) plain scan at outside hospital. And she refused to reassess with CT or MRI scans with contrast due to economic reasons. Hence, she was re-evaluated with ultrasonography in our hospital, resulting in a lack of enhanced CT scan data of retroperitoneal lipoma in this case. We have emphasized it in the revised manuscript as following:

Page 5, Line 89-90: The patient had received computed tomography (CT) plain scan at outside hospital, and was re-evaluated with ultrasonography in our hospital.

Page 5, Line 93-94: CT plain scan demonstrated a giant homogeneous mass mainly consisting of fatty tissue and thin septa.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an interesting case by Qi Yu and colleagues describing a rare retroperitoneal tumour with successful management. Despite the case being interesting, I have some concerns regarding the clinical workup and grammatical/spelling errors noted throughout the manuscript. Minor revisions are required. Good luck! What do the authors mean by 'left retroperitoneal area' in the case report section? Why did the authors think about lipoblastoma intraoperatively? Kindly provide the H&E images of lipoma and myelolipoma. Was it a mixed tumor or myelolipoma alone? Was IHC done for confirmation? What laboratory investigations could possibly point towards relapse? What is the difference between first line investigation and initial investigation as described in the discussion section? Some texts in the discussion section are repeated, specially in the radiological investigation part. Kindly be uniform. How will IHC detect molecular patterns like '12q13-15'? Some unremarkable details are there in the case report. Kindly put only relevant information in the text. Authors have not mentioned the figure legends in the case report.

Thank you so much for your reviewing and advice concerning our manuscript. Those comments are all valuable and pertinent for improving our paper, we have modified the language and enhanced the writings of the manuscript. The revised contents and the point-by-point responses to the reviewer's comments are as following.

Comment 1:

What do the authors mean by 'left retroperitoneal area' in the case report section?

Answer 1:

Thank you very much for your careful check of the article and pointing out the unclear statement. Actually, what we want to express was that during the operation, a bulky yellowish tumour originating from perirenal fatty tissues in the left retroperitoneal region was found to occupy the retroperitoneum. In addition, there is a major mistake after carefully re-checking on this manuscript, there were two lines (page4, line108-109) of right and left in the treatment part were careless written backwards. We have re-wrote this part in revised manuscript and the mistake has been corrected, which are shown (Page4, Line 105-110) as follows.

Page4, Line 105-110: During the operation, a bulky yellowish tumour originating from perirenal fatty tissues in the left retroperitoneal region was found to occupy the retroperitoneum. The uterus and adnexa were displaced by the mass. The mass adhered to the left psoas major muscle and wrapped around the left ureter, making it unfeasible to perform en bloc resection. After carefully separating the left ureter, we performed tumour debulking and left adnexectomy, which was also tightly adhered to the tumour.

Comment 2:

Why did the authors think about lipoblastoma intraoperatively?

Answer 2:

We gratefully appreciate for your meticulous work and insightful opinion. As the reviewer said, we must admit that we made a mistake here. The most suspicious differential diagnosis in this case is retroperitoneal liposarcoma rather than lipoblastoma.

As is well-known, Retroperitoneal benign lipomas are extremely rare and represent about 2.9% of all primary retroperitoneal tumors and about 80% of them are malignant neoplasms. The physical examination revealed a palpable giant abdominal mass of the patient. and the imaging examinations indicated its adipose origin. therefore, we opened the patient with suspicion of low-grade sarcoma, including retroperitoneal liposarcoma and lipoblastoma. Considering that lipoblastoma mainly occurs in children <3 years of age, therefore the most suspected intraoperative diagnosis of this case is retroperitoneal liposarcoma, rather than lipoblastoma. Again, we want to express our apology for the inconvenience brought to you. And we have revised this section and proposed a more potential differential diagnosis for this patient (Page4, Line103-105).

Page4, Line103-105: After completing the examinations and preoperative assessments, the patient underwent an exploratory laparotomy with the suspicion of malignancy, most likely retroperitoneal liposarcoma.

Comment 3:

Kindly provide the H&E images of lipoma and myelolipoma. Was it a mixed tumor or myelolipoma alone? Was IHC done for confirmation?

Answer 3:

We could not agree more with this pertinent and professional advice, we have added the missing H&E images of lipoma and myelolipoma correspondingly. After detailed discussion with the pathologist, it was confirmed that this was a mixed retroperitoneal tumour of lipoma, which was consist of multiple conventional lipomas and multiple myelolipomas. In this case, due to the pathologist's confidence in the final diagnosis, immunohistochemistry (IHC) was not performed for further evaluation. In the discussion section, we added a brief introduction about retroperitoneal myelolipoma to further understand the differential diagnosis of retroperitoneal fat-containing tumours. We have arranged a more clear and informative description of the discussion section as follows:

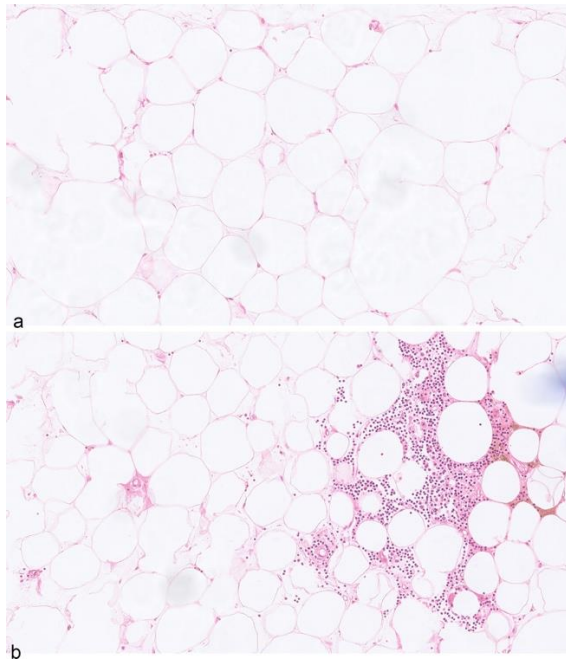
Page 5, Line 132-133: We reported a massive retroperitoneal tumour of lipoma, which was consist of multiple conventional lipomas and multiple myelolipomas.

Page 5-6, Line 137-145: According to the morphologic characteristics, lipomas can be subdivided into conventional lipoma, fibrolipoma, angioliipoma, spindle cell lipomas, pleomorphic lipomas and myelolipoma[7], of which, almost all myelolipomas have been identified inside the adrenal gland, with just about 50 cases myelolipomas being identified in extra-adrenal locations, such as the retroperitoneum[28]. The exact underlying aetiology of retroperitoneal lipomas is not well understood. Seeding after fibroid excision, exogenous hormone treatment, or chronic abnormalities in glucose homeostasis have all been blamed for these benign tumours. And genetic factors are thought to have an important role in adipocyte proliferation[5].

Page 12, Line 348-350:

Figure 4. Microscopical picture of the extracted tumours(H&E 20×)

- (a) lipoma was composed of mature adipocytes. (b) myelolipoma was composed of mature adipose adipocytes and hematopoietic cells, without necrosis, atypia and hyperchromatic cells.



Comment 4:

What laboratory investigations could possibly point towards relapse?

Answer 4: This is a very thoughtful and vigilant question. At present, our laboratory examinations revealed no obvious features that were indicative of the possibility of malignancy and future recurrence. However, the mass is too large to completely rule out the possibility of malignant sarcomas, which tend to develop a local recurrence and distant metastases.

Comment 5:

What is the difference between first line investigation and initial investigation as described in the discussion section?

Some texts in the discussion section are repeated, specially in the radiological investigation part. Kindly be uniform.

Answer 5: Thank you for your valuable comment. We are sorry for any inconvenience and confusion caused by ambiguous expression. We cannot agree more that such vague and unclear expressions will hinder understanding. we have revised the context of the manuscript to draw a clearer description as follows:

Page6, Line164-182: Ultrasound is generally used for the initial diagnosis and screening of abdominal masses. Radiography, especially computed tomography (CT) scan and magnetic resonance imaging (MRI), are crucial diagnostic tools for further evaluation of retroperitoneal tumours. The characteristics of adipose tissues are consistent on CT and MRI, but they differ on ultrasonography depending on the physical properties and histologic types. The fatty content is the fundamental feature to identify fat-containing retroperitoneal tumours during imaging examinations. Typical lipomas appear as extensive hyperechoic lesions on ultrasound, while they appear as homogeneous fat-containing masses with thin septa on CT and MRI. Retroperitoneal lipomas are difficult to identify preoperatively since they mimic liposarcomas, which is the majority of fat-containing retroperitoneal tumors. Liposarcomas present heterogeneous signal intensity and variable appearances on MRI and CT due to the varying subtypes, which included well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid/round cell liposarcoma (MLPS), pleomorphic liposarcoma (PLPS) and mixed liposarcoma. The increased vascularity in Liposarcomas that present as low-intensity signals on T1-weighted images can be used for differentiation. However, both lipomas and well-differentiated liposarcoma (WDLPS) are accompanied by a large amount of fat and minimal soft tissue and have identical appearances on CT and MRI scans, making it hard to

distinguish lipomas from well-differentiated liposarcomas preoperatively.

Comment 6: How will IHC detect molecular patterns like '12q13–15'? Some unremarkable details are there in the case report. Kindly put only relevant information in the text.

Answer 6: Thank you a lot for your work in this manuscript and your valuable comments, which are very helpful for improving our paper. We want to express a sincere apology for the inconvenience for our careless mistake. and we have attentively revised this part of the manuscript as following:

Page7, Line208-215: Postoperative histopathology remains the gold standard for diagnosis. Histologic characteristics for WDLPS include mature adipocytes punctuated with big atypical hyperchromatic cells. However, WDLPS are likely to be misdiagnosed, because atypia may be localized, especially in deep lesions with tiny samples. Murine double minute (MDM2, located at 12q14-15) and cyclin-dependent kinase (CDK4) gene are regularly amplified in WDLPS, which cannot be observed in benign lipomas. Hence, fluorescence in situ hybridization (FISH) has emerged as a promising method for differential diagnosis.

Comment 7:

Authors have not mentioned the figure legends in the case report.

Answer 7:

We are grateful to the reviewers for their time and effort. In response to the reviewer's question, the figure legends were not mentioned in the manuscript. we have made corresponding supplements, as shown below. We sincerely apologize for the confusion and difficulty given to reviewers as a result of our negligence and carelessness. During the revision process, we have found many deficiencies in our writing, which may make the readers confused, including but not limited to the introduction and discussion sections. Therefore, we have checked and polished the whole manuscript and put some relevant information in the text to draw the principal findings to convey a more comprehensive portrait of retroperitoneal lipoma.

Page 4, Line 92-93: Minimal blood signals were detected by colour Doppler ultrasound (Figure 1).

Page 4, Line 94-96: It measured 16.6 cm × 28.6 cm in volume and pushed the peritoneal contents, such as the bowel loops and uterus, to the right part of the abdomen (Figure 2).

Page 4, Line 110-111: The total weight of the mass was 7.126 kg (Figure 3).

Page 4-5, Line 115-126: The final paraffin pathology showed that the tumour was composed of mature adipose tissues and hematopoietic cells, without cytologic atypia and confirmed the diagnosis of multiple lipomas and multiple myelolipomas (Figure 4).

Page 5, Line 133-136: Retroperitoneal lipomas are rare mesenchymal-originated tumours. It was first reported in 1947 [22], and since then, a total of 22 cases have been reported in adults sporadically (Table 1).