

Dear Editors for *World Journal of Clinical Cases*

I wish to submit a case report for publication in *World Journal of Clinical Cases* titled **“Recurrent Atypical Leiomyoma in Bladder Trigone, Confused with Uterine Fibroids: A Case Report and Review of the Literature.”** The paper was coauthored by Jeonghwa Song and Heekyoung Song.

Mesenchymal tumors represent 5% of all urinary bladder tumors. Leiomyomas of the urinary bladder are very rare neoplasms, with an incidence of <0.5% of all bladder tumors. We reported a case of a 29-year-old woman with recurrent bladder myoma resected surgically and reviewed the relevant literature. We believe that our study makes a significant contribution to the literature because the diagnosis of a tumor originating from the posterior bladder wall is challenging, and our case report highlighting the features of such tumors can help minimize injury to the adjacent organ during resection. Based on our experience in this case, as well as a detailed review of the literature, we suggest that bladder leiomyoma on trigone is very rare and can be easily mistaken for uterine fibroid. In such cases, surgical excision is mandatory to confirm pathology.

Further, we believe that this paper will be of interest to the readership of your journal because our findings are of educational value and might likely aid clinicians in the treatment and management of patients with a presentation similar to that of our patient. The widespread availability and high impact of your reputed journal provide an ideal platform to disseminate the findings of this study.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. The patient provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal’s policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Reviewer #1:

The authors presented a case of recurrent trigonal leiomyoma in a 29-year-old woman. The preoperative diagnosis was mainly based on the findings of MRI examination. Treatment was by surgical excision in the first time and recurrence of the tumor. The major concerns are the ignoring the roles of cystoscopy and transurethral resection biopsy in diagnosis (especially in the first time) and improper presentation of the information relative to the subheadings designed in Case presentation section. The criticism is detailed in the following points that need to be addressed and fulfilled:

1) Overall, there are a few writing and language mishaps need editing. For example, in the Treatment section, the word (resulting) in the sentence (Both ureteral orifices were deviated due to mass effect, resulting in double-J catheterizations.) is not correct. You should replace it by another one such as warranting, indicating, etc. Also, double-J is better written as (... bilateral Double-J stent placement).

2) Abstract: Case Summary: This section should present the most important findings of the case in a concise form. Provide a clinical complaint (if possible) or describe clearly an accidental discovery of the mass. The patient presented with a mass with which symptoms? In other words, what was the indication of ultrasonography by which the mass was discovered? 3) Case Presentation: -Chief complaints: Also, provide a complaint or tell whether the mass was accidentally discovered during gynecological examination. - Laboratory examinations: Beside the urine analysis, Provide the values of the basic tests (hemoglobin level, blood sugar, serum creatinine, etc.), even when they were normal. - Describe the MRI findings that supported the diagnosis of leiomyoma and to how much the confusion between leiomyoma of the bladder and uterine myoma (fibroids) was significant (especially, you designed the title of this case based on this point mainly). - Why did not you do a diagnostic cystoscopy before surgery? Clarify the role, benefits, contraindications, or what was the reason for not doing it. 4) Final diagnosis: - How could you diagnose focal atypia in bladder leiomyoma before taking a biopsy and doing histopathological examination? You did not mention this in the previous part of case presentation. 5) Treatment: -Mention the surgical approach of laparotomy: Transvesical or combined transvesical and extravesical. -It is not clear why did not you perform a

transurethral resectional biopsy. In the first time, the mass may be not amenable due to its uncertainty as a bladder mass. However, in the recurrence time, was it possible to be biopsied transurethrally before laparotomy? -You should include the treatment of the recurrence here under the heading of Treatment similar to the first time. Also, the second time or recurrence was a definite part of the treatment of this case. 6) Outcome and follow up: - Transfer the part of the resection of the recurrence to the Treatment section, as described above. Here, mention only the final follow up (including follow up cystoscopy) and final outcomes. - Again, why did not you perform a transurethral resectional biopsy before exploration for this recurrent mass? MRI alone should not be an alternative to biopsy, when the latter was possible. 7) Discussion: - Discuss the difficulties encountered during surgery of this case. 8) Images: - An intraoperative surgical or cystoscopic view can be more representative if available. - The magnification of the pathological images is not sufficient. 9) The Checklist: - The patient did not give a consent. I think that this is a must to publish this work. Clarify.

Thank you so much for your precise comments on the manuscript. I think the point you pointed out is a very important part that we missed in this study. In this revision, we have improved the paper by addressing the remaining issues raised by the review team. We sincerely thank you for giving us another opportunity to revise the paper. **The revised sentences were highlighted blue color**, and **the added sentences were highlighted yellow color**. We proofread all manuscript again to improve readability. We hope that we have addressed the review team's concerns adequately.

1) Overall, there are a few writing and language mishaps need editing. For example, in the Treatment section, the word (resulting) in the sentence (Both ureteral orifices were deviated due to mass effect, resulting in double-J catheterizations.) is not correct. You should replace it by another one such as warranting, indicating, etc. Also, double-J is better written as (... bilateral Double-J stent placement).

**Response:** Thanks for pointing out our mistakes. Like your opinion, we think the sentence was wrong. Also, we thought that the sentence might be misinterpreted to the reader because the sentence was ambiguous, so we revised it to make the meaning clear. We changed those sentences in treatment section to:

“Both ureteral orifices were deviated due to mass effect. To avoid damage to the ureteral orifices, we performed bilateral Double J-stent placement before tumor resection.”,

“The bilateral Double-J catheters were removed two weeks after surgery.”

2) Abstract: Case Summary: This section should present the most important findings of the case in a concise form. Provide a clinical complaint (if possible) or describe clearly an accidental discovery of the mass. The patient presented with a mass with which symptoms? In other words, what was the indication of ultrasonography by which the mass was discovered?

**Response:** There were no specific symptoms complained by the patient before the examination. Many Korean women have regular checkup ultrasonography and pap smear at a lower price compared to other countries even if they have no symptoms. We revised some sentences in abstract and case presentation as follows:

“A 29-year-old woman with a uterine fibroid incidentally found at a regular checkup was referred to our hospital.” in abstract of case summary.

We also wrote about these factors in case presentation as follows:

“A 29-year-old woman was diagnosed with a uterine fibroid on ultrasonography at a regular checkup and was referred to our hospital for surgical treatment.”

3) Case Presentation: -Chief complaints: Also, provide a complaint or tell whether the mass was accidentally discovered during gynecological examination. -Laboratory examinations: Beside the urine analysis, Provide the values of the basic tests (hemoglobin level, blood sugar, serum creatinine, etc.), even when they were normal. -Describe the MRI findings that supported the diagnosis of leiomyoma and to how much the confusion between leiomyoma of the bladder and uterine myoma (fibroids) was significant (especially, you designed the title of this case based on this point mainly). - Why did not you do a diagnostic cystoscopy before surgery? Clarify the role, benefits, contraindications, or what was the reason for not doing it.

- Chief complaints: Also, provide a complaint or tell whether the mass was accidentally discovered during gynecological examination.

**Response:** We revised chief complaints and present illness as follows:

“The patient was incidentally diagnosed with a uterine fibroid at a clinic.”,

“A 29-year-old woman was diagnosed with a uterine fibroid on ultrasonography at a regular checkup and was referred to our hospital for surgical treatment.”

- Laboratory examinations: Beside the urine analysis, Provide the values of the basic tests (hemoglobin level, blood sugar, serum creatinine, etc.), even when they were normal.

**Response:** We inserted following sentences in Physical examination and laboratory examinations:

“Laboratory findings were non-specific except for micro-hematuria (red blood cell: 5-9/high power field (HPF) in urine sediment examination), and no abnormalities were found on physical examination. The laboratory findings were as follows: hemoglobin (14.3 g/dL), white blood cell (WBC) count (8,810/mm<sup>3</sup>), platelet count (311,000/mm<sup>3</sup>), sodium (139 mmol/L), potassium (3.8 mmol/L), fasting blood glucose (97 mg/dL), creatinine (0.6 mg/dL), aspartate aminotransferase (AST) (28 U/L), and alanine aminotransferase (ALT) (37 U/L).

”

-Describe the MRI findings that supported the diagnosis of leiomyoma and to how much the confusion between leiomyoma of the bladder and uterine myoma (fibroids) was significant (especially, you designed the title of this case based on this point mainly).

**Response:** We revised Imaging examinations section as follows:

“We considered the tumor a uterine fibroid, and a pelvis MRI was performed to determine the exact anatomical location. Based on MRI findings, the mass was suspected leiomyoma (6 x 4.6 cm) between the cervix and urinary bladder. The mass protruded into the urinary bladder with relatively increased signal intensity on T2-weighted image suggesting high cellularity and ruling in either bladder leiomyoma or pedunculated cervical fibroid (Figure 1A).”

We also added the following sentences in the Treatment section.

“Magnetic resonance imaging was performed before surgery, but considering the incidence,

we focused on pedunculated uterine fibroid rather than bladder leiomyoma. Therefore, instead of cystoscopy, laparotomy was performed.”

- Why did not you do a diagnostic cystoscopy before surgery? Clarify the role, benefits, contraindications, or what was the reason for not doing it.

**Response:** Thanks for the good comments. Preoperative cystoscopy would have helped diagnose. Before the first operation, we did not perform cystoscopy because we thought the tumor was pedunculated uterine fibroid on ultrasonography and MRI. Although the possibility of bladder leiomyoma after MRI was considered, we focused on pedunculated uterine fibroid rather than bladder leiomyoma and performed laparotomy because bladder fibroids are very rare.

In second operation, we referred to urologist for preoperative cystoscopy. They checked cystoscopy as Figure 3A, however, they did not biopsy before surgery. They also thought that recurrent mass would be atypical bladder leiomyoma. Therefore, we decided to surgical excision except preoperative biopsy.

We inserted following sentences in treatment section:

“Magnetic resonance imaging was performed before surgery, but considering the incidence, we focused on pedunculated uterine fibroid rather than bladder leiomyoma. Therefore, instead of cystoscopy, laparotomy was performed. No mass was found in the pelvic cavity when the abdominal wall was incised. Therefore, we made an incision on the bladder and found a submucoal tumor.”

“Transvesical laparotomy was performed considering recurrence of the previous pathology, atypical leiomyoma.”

Added We inserted following sentences in discussion section:

“Before the first surgery, since bladder leiomyomas are very rare, we thought that uterine fibroids were more likely and did not perform preoperative cystoscopy. At the time of recurrence, cystoscopy was performed, but a biopsy was not performed because it was assumed that the recurrent mass would be the same atypical bladder leiomyoma as before. Unlike our expectations, the final diagnosis was leiomyoma without atypia. Although we did not perform cystoscopy and biopsy, the procedures would have been helpful in determining preoperative diagnosis. If fibroids protruding from the cervix to the bladder are

found on imaging tests, though rare, there is a possibility of bladder fibroids, so a cystoscopy is recommended.”

4) Final diagnosis: - How could you diagnose focal atypia in bladder leiomyoma before taking a biopsy and doing histopathological examination? You did not mention this in the previous part of case presentation.

**Response:** As your review, histopathology was the definite method to find atypical myoma. We also totally agree with you. In our case, hypercellular in MRI findings was related focal atypia in bladder myoma, but this was not definite findings. We inserted these related sentences in introduction as follows:

“Imaging studies such as ultrasonography or Magnetic resonance imaging (MRI) are effective methods to predict histopathology. In ultrasonography, atypical leiomyoma demonstrated irregular cauliflower shape and homogenous enhancement<sup>[5]</sup>. In the MRI view, atypical myoma is similar to bladder malignancy rather than bladder leiomyoma, showing an isointense signal on T1- and T2-weighted images and an uneven surface with a cauliflower-like appearance<sup>[5]</sup>. However, there is no definitive imaging finding that could diagnose atypical bladder leiomyoma.”

Also, we revised the following sentences in Preoperative imaging examinations:

“We considered the tumor a uterine fibroid, and a pelvis MRI was performed to determine the exact anatomical location. Based on MRI findings, the mass was suspected leiomyoma (6 x 4.6 cm) between the cervix and urinary bladder. The mass protruded into the urinary bladder with relatively increased signal intensity on T2-weighted image suggesting high cellularity and ruling in either bladder leiomyoma or pedunculated cervical fibroid (Figure 1A).”

We revised and added the following sentences in Discussion:

“Magnetic resonance imaging is considered to be superior to computed tomography (CT) or ultrasonography for assessing bladder leiomyoma<sup>[1, 8, 13]</sup>. Leiomyoma shows intermediate signal intensity on T1-weighted MR images and low signal intensity on T2-weighted MR images<sup>[1, 14]</sup>. In our case, atypical bladder leiomyoma showed hypercellularity on MRI. However, imaging findings could not accurately diagnose atypical bladder leiomyoma. Therefore, pathological confirmation was the best option to diagnose atypical bladder leiomyoma.”

5) Treatment: -Mention the surgical approach of laparotomy: Transvesical or combined transvesical and extravesical. -It is not clear why did not you perform a transurethral resectional biopsy. In the first time, the mass may be not amenable due to its uncertainty as a bladder mass. However, in the recurrence time, was it possible to be biopsied transurethrally before laparotomy? -You should include the treatment of the recurrence here under the heading of Treatment similar to the first time. Also, the second time or recurrence was a definite part of the treatment of this case.

**Response:** We described detailed initial and recurrent surgical procedures in treatment section as follows:

“Magnetic resonance imaging was performed before surgery, but considering the incidence, we focused on pedunculated uterine fibroid rather than bladder leiomyoma. Therefore, instead of cystoscopy, laparotomy was performed. No mass was found in the pelvic cavity when the abdominal wall was incised. Therefore, we made an incision on the bladder and found a submucosal tumor. The tumor was resected by visually complete excision.”

“Cystoscopy revealed a protruding mass in the posterior bladder wall (Figure 3A). For further evaluation, a preoperative MRI revealed a 3.8 cm × 3 cm-sized homogeneous mass on the posterior wall of the bladder (Figure 1B). Transvesical laparotomy was performed considering recurrence of the previous pathology, atypical leiomyoma. A round solid mass was found in the bladder trigone during surgery (Figures 3B and 4A), and it was resected without injuring either ureteric orifice. This well-encapsulated tumor was found to be leiomyoma without atypia on permanent pathology (Figure 4B).”

In response to your third question, the reason for not having a biopsy was described and inserted into the manuscript. The limitations of our case have also been inserted into the discussion as follows:

“Before the first surgery, since bladder leiomyomas are very rare, we thought that uterine fibroids were more likely and did not perform preoperative cystoscopy. At the time of recurrence, cystoscopy was performed, but a biopsy was not performed because it was assumed that the recurrent mass would be the same atypical bladder leiomyoma as before. Unlike our expectations, the final diagnosis was leiomyoma without atypia. Although we did not perform cystoscopy and biopsy, the procedures would have been helpful in

determining preoperative diagnosis. If fibroids protruding from the cervix to the bladder are found on imaging tests, though rare, there is a possibility of bladder fibroids, so a cystoscopy is recommended.”

We also moved the treatment of the recurrence under “the heading of Treatment” from “outcome and follow-up”.

“ At both six months and one year after surgery, no recurrence was found on ultrasonography. However, tumor recurrence was detected by ultrasonography without specific symptoms when the patient visited our hospital for a third checkup, four years after surgery. Cystoscopy revealed a protruding mass in the posterior bladder wall (Figure 3A). For further evaluation, a preoperative MRI revealed a 3.8 cm × 3 cm-sized homogeneous mass on the posterior wall of the bladder (Figure 1B). Transvesical laparotomy was performed considering recurrence of the previous pathology, atypical leiomyoma. A round solid mass was found in the bladder trigone during surgery (Figures 3B and 4A), and it was resected without injuring either ureteric orifice. This well-encapsulated tumor was found to be leiomyoma without atypia on permanent pathology (Figure 4B).”

6) Outcome and follow up: - Transfer the part of the resection of the recurrence to the Treatment section, as described above. Here, mention only the final follow up (including follow up cystoscopy) and final outcomes. - Again, why did not you perform a transurethral resectional biopsy before exploration for this recurrent mass? MRI alone should not be an alternative to biopsy, when the latter was possible.

**Response:** We transferred the treatment of the recurrence under Treatment section from Outcome and follow-up section we mentioned in number 5 question.

The follow-up course until recurrence was added to the Treatment section as follows:

“At both six months and one year after surgery, no recurrence was found on ultrasonography. However, tumor recurrence was detected by ultrasonography without specific symptoms when the patient visited our hospital for a third checkup, four years after surgery.”

We followed up with gynecological ultrasonography, which can simultaneously perform gynecological examinations and can be easily performed in a gynecological outpatient clinic. We planned to refer to the urologist if abnormal findings were found in ultrasonography. After reading your excellent comments, we realized that cystoscopy is important for early diagnosis of tumor. Korean women are reluctant to go to urologists and it is difficult to perform cystoscopy on a regular basis. We hope for your understanding and thank you very much for the good comments.

We have inserted the following into the discussion:

“At the time of recurrence, cystoscopy was performed, but a biopsy was not performed because it was assumed that the recurrent mass would be the same atypical bladder leiomyoma as before. Unlike our expectations, the final diagnosis was leiomyoma without atypia. Although we did not perform cystoscopy and biopsy, the procedures would have been helpful in determining preoperative diagnosis.”

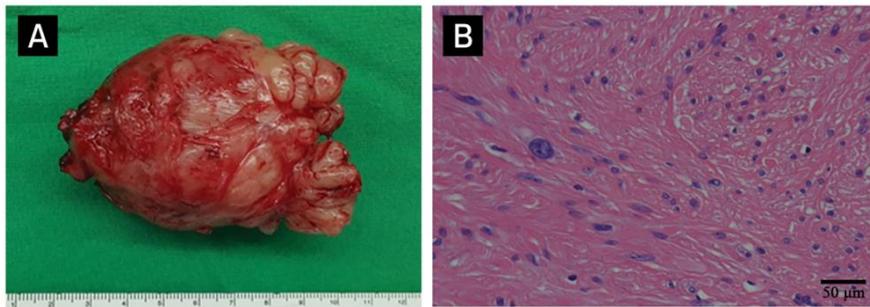
7) Discussion: - Discuss the difficulties encountered during surgery of this case.

**Response:** We inserted the following sentences related difficulties during surgery of this case in discussion:

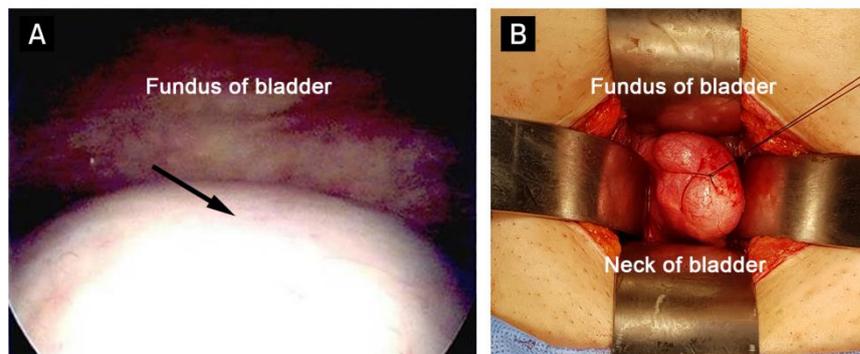
“In the first surgery of this case, the tumor was completely removed visually. However, given the recurrence of leiomyoma, it appears that the tumor has not been removed with a sufficiently wide and deep margin because there were ureteral orifices right next to the tumor and the cervix behind it.”

8) Images: - An intraoperative surgical or cystoscopic view can be more representative if available. - The magnification of the pathological images is not sufficient.

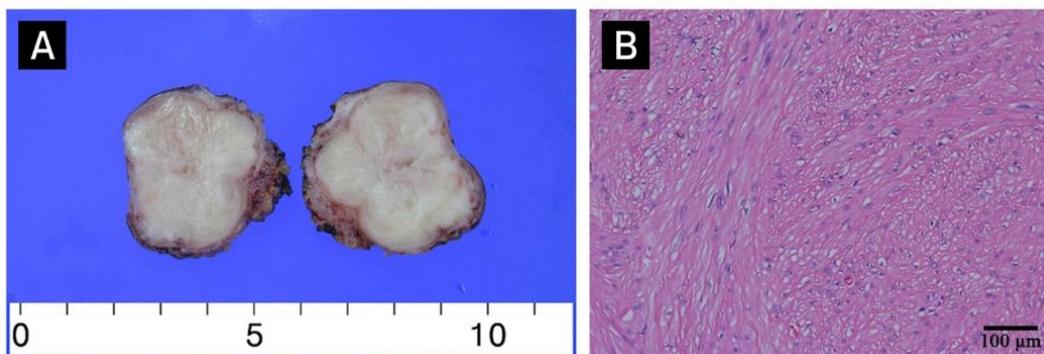
**Response:** Thank you for precise review. We inserted the cystoscopic image as Figure 3A and the scale bars in Figure 2B and 4B.



**Figure 2 Initial pathological findings. A: Gross image; B: Leiomyoma with bizarre nuclei and moderate cytologic atypia cells (hematoxylin-eosin stain, scale bar = 50 µm).**



**Figure 3 Cystoscopic and intraoperative findings after recurrence. A: Cystoscopic image (arrow: protruding mass); B: Intraoperative finding (protruding mass in bladder).**



**Figure 4 Pathological findings after recurrence. A: Gross image; B: Leiomyoma without atypia (hematoxylin-eosin stain, scale bar = 100 µm).**

9) The Checklist: - The patient did not give a consent. I think that this is a must to publish this work. Clarify.

**Response:** We are sorry that we didn't go through the CARE checklist carefully. We revised the CARE checklist from the 2013 version to the 2016 version. At the time of preparing submission, we thought that informed consent was not required and we were going to submit the results of our university's IRB because this study was single case report. As our university only accepts IRB-approved clinical papers, all papers must undergo our university's IRB review at the time of writing. Therefore, we applied for our university's IRB and our study was approved as an IRB review exemption because it was a case report. Also, our university hospital basically receives informed consent for research and thesis submission from all patients undergoing surgery on admission. And, for example, when we conduct clinical trials, such as administering a new drug, we get additional consent. At the time of surgery, we had already obtained informed consent from the patient in this case for the study and submission of the thesis. When submitting this manuscript, we found that as a final step we needed to upload an informed consent form. Therefore, we found and uploaded the informed consent we had received at the time of surgery. However, the CARE checklist was uploaded without correction by mistake. We will re-upload the corrected CARE checklist (the 2016 version), informed consent, and university IRB-approved documents for review exemption. Added we inserted this sentence in Informed consent statement.

"This was a retrospective case report study also approved by the institutional review board for IRB review exemption."

Reviewer #2:

Nicely written manuscript. What was the follow up protocol for this patient? This would give the readers an idea about how fast the recurrent mass developed. Magnification of the histopathological slide in figure 2 and 3 are mentioned as 100x but both do not appear to be at same magnification.

Thank you so much for your positive and encouraging comments on the manuscript. In this revision, we have improved the paper by addressing the remaining issues raised by the review team. We sincerely thank you for giving us another opportunity to revise the paper. The revised sentences were highlighted blue color, and the added sentences were highlighted yellow color. We proofread all manuscript again to improve readability. We hope that we have addressed the review team's concerns adequately.

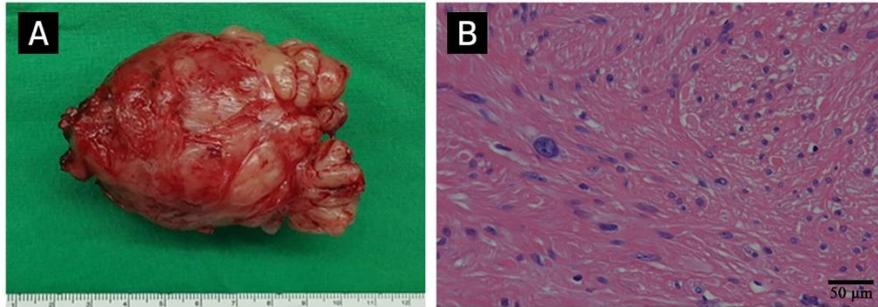
1. What was the follow up protocol for this patient? This would give the readers an idea about how fast the recurrent mass developed.

**Response:** We follow up with ultrasonography every 6 months. The patient became lost to follow-up one year after surgery. When the patient visited our hospital 4 years after surgery, tumor recurrence was detected by ultrasonography. We added these sentence in Treatment section:

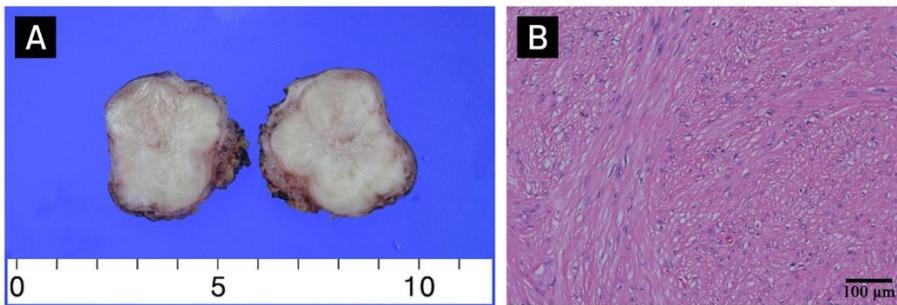
“At both six months and one year after surgery, no recurrence was found on ultrasonography. However, tumor recurrence was detected by ultrasonography without specific symptoms when the patient visited our hospital for a third checkup, four years after surgery.”

2. Magnification of the histopathological slide in figure 2 and 3 are mentioned as 100x but both do not appear to be at same magnification.

**Response:** We are sorry to confuse for understanding Figures. We revised Figure 2B and 4B as your comments. Scare bars were inserted in the lower right corners.



**Figure 2 Initial pathological findings.** A: Gross image; B: Leiomyoma with bizarre nuclei and moderate cytologic atypia cells (hematoxylin-eosin stain, scale bar = 50 µm).



**Figure 4 Pathological findings after recurrence.** A: Gross image; B: Leiomyoma without atypia (hematoxylin-eosin stain, scale bar = 100 µm).

Reviewer #3:

Dear Authors, an interesting case report on atypical leiomyoma in bladder trigone. The paper presentation is provided with attention to detail, thank you for that.

I have only minor comments: (1) On page 3, I think you can delete all commas in this part "Submucosal, i.e., endovesical, leiomyomas are the most common". Plethora of commas are already in the rest part of this sentence (2) You can add space on page 6 in part "to computed tomography(CT) or ultrasonography", before brackets. (3) Consider adding scale bar in Figure 2B and 3B.

I am also unsure whether CARE checklist was filled in correctly. Only check marks (✓) are added with no report on which line the specific item can be found. Moreover, in the last question "Did the patient give informed consent? Please provide if requested" you marked no, while the Signed Consent for Treatment Form is provided in the system.

Additionally, do you have any advice on how to avoid tumor recurrence and how to not mislead this atypical leiomyoma with e.g. fibroids in MRI scans?

Thank you so much for your detailed and important comments on the manuscript. We appreciate that. In this revision, we have improved the paper by addressing the remaining issues raised by the review team. We sincerely thank you for giving us another opportunity to revise the paper. **The revised sentences were highlighted blue color**, and **the added sentences were highlighted yellow color**. We proofread all manuscript again to improve readability. We hope that we have addressed the review team's concerns adequately.

1. On page 3, I think you can delete all commas in this part "Submucosal, i.e., endovesical, leiomyomas are the most common". Plethora of commas are already in the rest part of this sentence.

**Response:** Thanks for the good point. We have removed the corresponding commas from the text to make it easy to understand as follows:

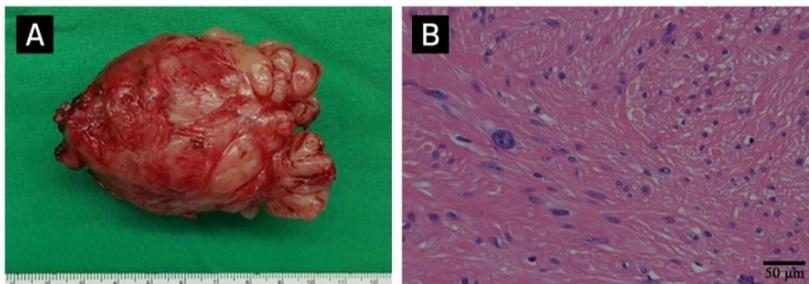
“Submucosal (i.e. endovesical) leiomyomas are the most common, corresponding to 63–86% of all cases, while intramural and extravesical leiomyomas represent 3–7% and 11–30% of cases, respectively. “

2. You can add space on page 6 in part "to computed tomography(CT) or ultrasonography", before brackets.

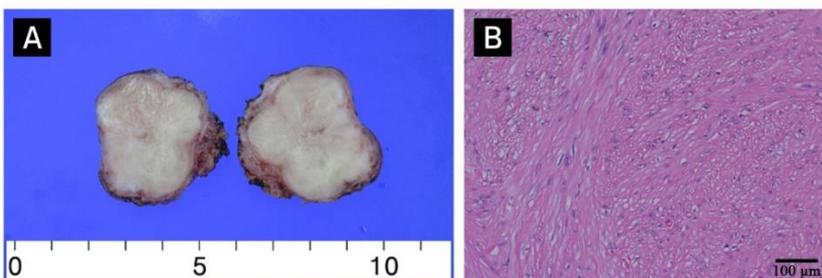
**Response:** We revised the sentence as your recommendation, “Magnetic resonance imaging is considered to be superior to computed tomography (CT) or ultrasonography for assessing bladder leiomyoma.”

3. Consider adding scale bar in Figure 2B and 3B.

**Response:** We made a mistake. We to inserted scale bar in Figure 2B and 3B. Thank you for your attentive review for our manuscript. All revised point were highlighted yellow color in manuscript.



**Figure 2 Initial pathological findings.** A: Gross image; B: Leiomyoma with bizarre nuclei and moderate cytologic atypia cells (hematoxylin-eosin stain, scale bar = 50 µm).



**Figure 4 Pathological findings after recurrence.** A: Gross image; B: Leiomyoma without atypia (hematoxylin-eosin stain, scale bar = 100 µm).

4. I am also unsure whether CARE checklist was filled in correctly. Only check marks (✓) are added with no report on which line the specific item can be found. Moreover, in the last question "Did the patient give informed consent? Please provide if requested" you marked no, while the Signed Consent for Treatment Form is provided in the system.

**Response:** We are sorry that we didn't go through the CARE checklist carefully. We revised the CARE checklist from the 2013 version to the 2016 version. We have checked the lines where you can find the items. At the time of preparing submission, we thought that informed consent was not required and we were going to submit the results of our university's IRB because this study was single case report. As our university only accepts IRB-approved clinical papers, all papers must undergo our university's IRB review at the time of writing. Therefore, we applied for our university's IRB and our study was approved as an IRB review exemption because it was a case report. Also, our university hospital basically receives informed consent for research and thesis submission from all patients undergoing surgery on admission. And, for example, when we conduct clinical trials, such as administering a new drug, we get additional consent. At the time of surgery, we had already obtained informed consent from the patient in this case for the study and submission of the thesis. When submitting this manuscript, we found that as a final step we needed to upload an informed consent form. Therefore, we found and uploaded the informed consent we had received at the time of surgery. However, the CARE checklist was uploaded without correction by mistake. We will re-upload the corrected CARE checklist (the 2016 version), informed consent, and university IRB-approved documents for review exemption. Added we inserted this sentence in Informed consent statement.

"This was a retrospective case report study also approved by the institutional review board for IRB review exemption."

5. Additionally, do you have any advice on how to avoid tumor recurrence and how to not mislead this atypical leiomyoma with e.g. fibroids in MRI scans?

**Response:** Thank you for your great comment. Avoiding tumor recurrence and the typical MRI findings are the most important points in this manuscript. The contents related to avoidance of recurrent mass were added to the discussion as follows:

“Recurrent cases are very rare in atypical or benign bladder leiomyoma. Khater N. et al., who reviewed 36 reports for bladder leiomyoma, reported no recurrent cases [13]. Conversely, 2 recurrent bladder leiomyomas in all 9 cases were reported, and no recurrent disease was noted after the complete resection of bladder leiomyoma [14]. To avoid recurrent disease, complete resection was effective and important method [13]. In large-sized bladder leiomyoma, partial cystectomy was considered to obtain complete resection with a clear surgical margin [21]. In the first surgery of this case, the tumor was completely removed visually. However, given the recurrence of leiomyoma, it appears that the tumor has not been removed with a sufficiently wide and deep margin because there were ureteral orifices right next to the tumor and the cervix behind it.”

We inserted MRI findings in introduction as follows:

“Imaging studies such as ultrasonography or Magnetic resonance imaging (MRI) are effective methods to predict histopathology. In ultrasonography, atypical leiomyoma demonstrated irregular cauliflower shape and homogenous enhancement[5]. In the MRI view, atypical myoma is similar to bladder malignancy rather than bladder leiomyoma, showing an isointense signal on T1- and T2-weighted images and an uneven surface with a cauliflower-like appearance[5]. However, there is no definitive imaging finding that could diagnose atypical bladder leiomyoma.” “

Reviewer #4:

Reviewer #4:

Atypical leiomyoma in bladder trigone is very rare. This article gives us a lot of inspiration.

- 1 What were the pathological findings of the mass removed during the first operation?
- 2 What are the possible causes of recurrence after the first operation? How to avoid recurrence ?
- 3 What are the main points of differentiation between this disease and uterine myoma?
- 4 About MRI features of rare atypical leiomyoma in bladder trigone, Could you give the readers some advice?

We greatly appreciate your constructive comments and suggestions. In this revision, we have improved the paper by addressing the remaining issues raised by the review team. We sincerely thank you for giving us another opportunity to revise the paper. **The revised sentences were highlighted blue color**, and **the added sentences were highlighted yellow color**. We proofread all manuscript again to improve readability. We hope that we have addressed the review team's concerns adequately.

1. What were the pathological findings of the mass removed during the first operation?

**Response:** The pathological findings was described in the Final diagnosis section. The result were highlighted blue color in manuscript:

**"The final diagnosis of the initial case was bladder leiomyoma with focal atypia (mitotic count: 1/10 HPF). In the recurrent case, bladder leiomyoma without atypia was diagnosed.**

"

2. What are the possible causes of recurrence after the first operation? How to avoid recurrence?

**Response:** Thank you for your great comment. Avoid for tumor recurrence is the most important points in this manuscript. We added the followings in discussion:

“Recurrent cases are very rare in atypical or benign bladder leiomyoma. Khater N. et al., who reviewed 36 reports for bladder leiomyoma, reported no recurrent cases [13]. Conversely, 2 recurrent bladder leiomyomas in all 9 cases were reported, and no recurrent disease was noted after the complete recurrent lesion of bladder leiomyoma [14]. To avoid recurrent disease, complete resection was effective and important method [13]. In large-sized bladder leiomyoma, partial cystectomy was considered to obtain complete resection with a clear surgical margin [21]. In the first surgery of this case, the tumor was completely removed visually. However, given the recurrence of leiomyoma, it appears that the tumor has not been removed with a sufficiently wide and deep margin because there were ureteral orifices right next to the tumor and the cervix behind it.”

3. What are the main points of differentiation between this disease and uterine myoma?

**Response:** I am very grateful for your sharp point of view. Tissue within bladder fibroids is indistinguishable from tissue within uterine fibroids. If the fibroid had been a uterine fibroid protruding from the uterus, it would be covered by the serosa of the uterus and all layers of the bladder wall would have covered the fibroid or the bladder wall would have been compressed by the uterine fibroid. To avoid confusion, we corrected the sentences in the Treatment section and changed from "endovesical tumor" to "submucosal tumor".

Before: During surgery, a mass inside the bladder and an intact uterine wall was noted. The bladder wall was incised, and the endovesical tumor was resected by visually complete excision.

Revised: “No mass was found in the pelvic cavity when the abdominal wall was incised. Therefore, we made an incision on the bladder and found a submucosal tumor.”

If the MRI is read accurately, I think that accurate discrimination will be possible even before surgery. Since bladder fibroids are so rare, I think that the MRI reading at our hospital also suspected the possibility of uterine fibroids. **Methods that can be helpful in preoperative diagnosis such as MRI and cystoscopy were described in more detail.** Therefore, we added and revised several sentences in the introduction and discussion as follows:

“Imaging studies such as ultrasonography or Magnetic resonance imaging (MRI) are capable methods to predict histopathology. Atypical leiomyoma demonstrated irregular cauliflower shape and homogenous enhancement in ultrasonography<sup>[5]</sup>. In MRI view, atypical myoma was more resemble with bladder malignancy rather than bladder leiomyoma, showing iso-intense signal on T1- and T2-weighted images and uneven surface with cauliflower like appearance<sup>[5]</sup>. However, there is no definitive imaging finding that could diagnose atypical bladder leiomyoma.”

“Magnetic resonance imaging is considered to be superior to computed tomography (CT) or ultrasonography for assessing bladder leiomyoma<sup>[1, 8, 13]</sup>. Leiomyoma shows intermediate signal intensity on T1-weighted MR images and low signal intensity on T2-weighted MR images<sup>[1, 14]</sup>. In our case, atypical bladder leiomyoma showed hypercellularity on MRI. However, imaging findings could not accurately diagnose atypical bladder leiomyoma. Therefore, pathological confirmation was the best option to diagnose atypical bladder leiomyoma.”

“Cystoscopy is a high-value diagnostic tool that can show the leiomyoma’s morphology and anatomical location<sup>[12]</sup>. Moreover, cystoscopy can be used to confirm the histopathology of bladder mass. However, cystoscopy, an invasive procedure, is usually performed when abnormalities in the urethra or bladder are detected on imaging tests<sup>[15, 16]</sup>.”

4. About MRI features of rare atypical leiomyoma in bladder trigone, Could you give the readers some advice?

**Response:** We discussed it in the introduction and discussion as follows:

“Imaging studies such as ultrasonography or Magnetic resonance imaging (MRI) are capable methods to predict histopathology. Atypical leiomyoma demonstrated irregular cauliflower shape and homogenous enhancement in ultrasonography<sup>[5]</sup>. In MRI view, atypical myoma was more resemble with bladder malignancy rather than bladder leiomyoma, showing iso-intense signal on T1- and T2-weighted images and uneven surface with cauliflower like appearance<sup>[5]</sup>. However, there is no definitive imaging finding that could diagnose atypical bladder leiomyoma.”

“Magnetic resonance imaging is considered to be superior to computed tomography (CT) or ultrasonography for assessing bladder leiomyoma<sup>[1, 8, 13]</sup>. Leiomyoma shows intermediate

signal intensity on T1-weighted MR images and low signal intensity on T2-weighted MR images<sup>[1, 14]</sup>. In our case, atypical bladder leiomyoma showed hypercellularity on MRI. However, imaging findings could not accurately diagnose atypical bladder leiomyoma. Therefore, pathological confirmation was the best option to diagnose atypical bladder leiomyoma.”

Deleted sentences

### **Abstract-case summary**

Ultrasonography revealed a 6 cm-sized solid mass in the bladder trigone.

Cystoscopy revealed a lesion in the bladder trigone, suspected to be a leiomyoma.

### **Introduction**

Recognizing this lesion can help minimize injury to the adjacent organs during resection.

### **Treatment**

Exploratory laparotomy was recommended. During a mass inside the bladder and an intact uterine wall was noted. Both ureteral orifices were deviated due to mass effect, resulting in Double -J catheterizations.