

Peer Review File

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To Reviewer A

The authors reported a case of sarcomatoid bladder cancer patients with Behcet syndrome who underwent radical cystectomy and showed successful postoperative convalescence.

The reviewer considers this case report is wonderful. However, it is questionable whether this case report provides objective and scientific significance to the urological community.

The following comments may be helpful improving the present manuscript.

Comment 1: Abstract and the text: The authors mention that the case report is the world's first case of bladder cancer complicated with Behcet syndrome treated with minimally invasive radical cystectomy. The reviewer does not think so because of a potential publication bias.

Reply 1: Sorry for the misunderstanding and inconvenience that we have caused. The reason we are indicating that this case report is "the world's first case" is based on a literature search on both Pubmed (English) and CNKI (Chinses) databases. Yes, there would be a potential publication bias as there might be articles in other languages or operations that had not been reported. Thank you for pointing this out and we have revised the relating content in both the abstract and introduction sections to make it more straightforward and more objective.

Changes in the text:

Abstract: We reviewed the literature in both English and Mandarin Chinese. Currently, two published articles describe the adoption of cystectomy in treating bladder cancer patients complicated with BS, whereas not any had shared the experience of using minimally invasive surgery.

Introduction: Here, we report our initial experience of laparoscopic radical cystectomy on a BS patient with bladder cancer.

Summary: We have re-written the sections mentioned above to make our statement more objective. (see Page 2, Line 42; Page 3, Line 64).

Comment 2: The authors may want to describe pathological findings in detail for TUR specimens and those for radical cystectomy specimens including pT stage, the presence of LVI, etc.

Reply 2: Sorry for the confusing expressions we had made in the text. The second time TURBt was performed at a local hospital. Thus the pathological report might be less detailed. The final TUR findings are listed in full-length: *Sarcomatoid urothelial carcinoma, no myometrial infiltration was found in the specimens*. We have revised the expression accordingly.

In the aspect of radical cystectomy specimens' results, the final pathological report is: *The pathological result indicated that proliferative spindle cells could be seen in the full thickness of the left bladder wall, no tumor residual, lymphatic vessels invasion, or metastatic lymph node was found (0 out of 10). Immunohistochemical result: CK14 (-), CK 20 (-), CK5/6 (-), Desmin (+), GATA3 (-), Her-2(0), Ki-67 (index 5%), P53(-), AE1/AE3(+). The final TNM stage was T0N0M0.*

We discussed this report with our colleague in the Pathology Department, they suggested the presence of proliferative spindle cells could be seen as evidence of the previous existence of sarcomatoid urothelial carcinoma, whereas the tumor might be resected completely in the TURBt operation. Yet, this result is unpredictable preoperatively unless we have the entire specimens.

We also updated our follow-up results during our revision period. The updated content would be: No evidence of tumor residual or ureterocutaneostomic necrosis was found on his latest follow-up visit in December 2021 (*Figure 2*).

Changes in the text:

1: The final pathological diagnosis was sarcomatoid urothelial carcinoma, no myometrial infiltration was found in the TURBt specimen.

2: The pathological result indicated that proliferative spindle cells could be seen in the

full thickness of the left bladder wall. No tumor residual, lymphatic vessels invasion or metastatic lymph node was found (0 out of 10). Immunohistochemical result: CK14 (-), CK 20 (-), CK5/6 (-), Desmin (+), GATA3 (-), Her-2(0), Ki-67 (index 5%), P53(-), AE1/AE3(+). The final TNM stage was T0N0M0. We discussed this report with our colleague in the Department of Pathology. They suggested the presence of proliferative spindle cells could be seen as evidence of the previous existence of sarcomatoid urothelial carcinoma. In contrast, the tumor might have been entirely resected in the last TURBt operation. Yet, this result is not predictable unless we have the entire specimens. No evidence of tumor residual or ureterocutaneostomic necrosis was found on his latest follow-up visit in December 2021 (Figure 2).

Summary: We have re-written the sections as mentioned earlier to make our statement more objective. Several updates have been made as well (see Page 4, Line 74; Page 6, Line 114)

Comment 3: The authors may want to provide a cumulative dose of cyclophosphamide given in the present case because it can be associated with the risk of development of bladder cancer. Please discuss this point.

Reply 3: Dear Reviewer, thank you for pointing this out. We did a literature search on the relationship between the CTX amount and bladder cancer. It turns out that we did omit this vital issue in the case report. We have added a paragraph in the discussion section. Also, relevant information on drug consumption has been added in the paper.

Changes in the text:

Discussion

The Relationship Between Bladder Cancer and CTX

Understanding the relationship between bladder cancer and CTX is in a spiral process. Acrolein, a metabolite of CTX, was reported to be urotoxic in 1979 (9). Eight years later, a cohort of 119 patients who adopted cyclophosphamide for treating rheumatoid arthritis was introduced, the incidence rate of bladder cancer in that cohort was 5% (10). Moreover, half of the tumors were diagnosed after eleven years or later.

Similarly, in 1991, Harold et al. (11) revealed the time of initial tumor occurrence was between 15 to 180 months. Those studies also suggested bladder cancer might not be associated with the daily intake of CTX. In contrast, it was related to the cumulative dosage, that is, the greater the amount of CTX is, the higher the risk of tumor occurrence would be, and this risk could last for several years after drug withdrawal (10, 11).

As in this case, the patient started CTX treatment in 2008 (100 mg/day), and the prescription was alternated to 100 mg of CTX every other day in 2016. The drug was ceased in 2021 owing to the discovery of bladder neoplasms. Hence, the total CTX intake was estimated to be 350~383 grams. This the time of tumor occurrence and the cumulative amount of CTX intake are in line with previously published articles (10, 11).

REFERENCES

9. Brock N, Stekar J, Pohl J, Niemeyer U, Scheffler G. Acrolein, the causative factor of urotoxic side-effects of cyclophosphamide, ifosfamide, trofosfamide and sufosfamide. *Arzneimittelforschung*. 1979;29(4):659-61.
10. Baker GL, Kahl LE, Zee BC, Stolzer BL, Agarwal AK, Medsger TA, Jr. Malignancy following treatment of rheumatoid arthritis with cyclophosphamide. Long-term case-control follow-up study. *Am J Med*. 1987;83(1):1-9.
11. Sigal SH, Tomaszewski JE, Brooks JJ, Wein A, LiVolsi VA. Carcinosarcoma of bladder following long-term cyclophosphamide therapy. *Arch Pathol Lab Med*. 1991;115(10):1049-51.

Summary: We have re-written the sections as mentioned above (see Page 6, Line 132)

Comment 4: Line 149: Please spell out "BD" at its first appearance.

Reply 4: Sorry for this misspell we had made. This is a typo. We meant to write BS instead of BD. We have modified this typo in the text.

Changes in the text: Ureterocutaneostomy was preferred in the case of BS-induced postoperative intestinal anastomosis fistula.

Summary: We have revised the typo mentioned above. (see Page 10, Line 220)

To Reviewer B

Interesting report and well written.

Reply to Reviewer B: Sir, thank you for recognizing our work. Nothing could inspire us more. Thank you for your time and effort.

To Reviewer C

This case study reported patients with Behcet's syndrome treated with laparoscopic radical cystectomy.

Comment 1: This title showed initial experience on perioperative safety, but there is no description in terms of the surgical findings. Although the authors said that patient with Behcet's syndrome would be received minimum invasive surgery, there is no explanation.

Reply 1: Sir, sorry for the inconvenience we have caused. An updated manuscript with our thoughts on minimum invasive surgery has been uploaded. Also, we have added a new paragraph to discuss our intraoperative findings.

Changes in the text: Considering the large incision of traditional radical cystectomy and poor wound healing ability in patients with BS, we decided to perform the cystectomy minimal-invasively. In case of uncontrollable bleeding and midway laparotomy, we compromised with laparoscopic radical cystectomy rather than robot-assisted laparoscopic radical cystectomy. The operation of laparoscopic radical cystectomy with standard pelvic lymph node resection and bilateral ureterocutaneostomy was performed in August. Intraoperative exploration showed that the patient had thin visceral fat tissue, proliferative pelvic vessels, and enlarged parailiac lymph nodes.

Summary: We have re-written the sections as mentioned earlier to make our statement more objective. (see Page 5, Line 93)

Comment 2: In addition to this, there is no mention how to perform surgery and what is important thing to do radical surgery in the context.

Reply 2: Sir, we would like to summarize our personal experience and thoughts on performing surgery and what is essential to do radical surgery in the context.

Changes in the text: Therefore, the surgical team made three core principles accordingly: 1) In case of anastomotic necrosis, we preferred to adopt a simple, less extensive but easy-observative urinary diversion method: bilateral ureterocutaneostomy; 2) Attention should be paid to unnecessary clamping, stretching, or sharp stabbing made by dissecting forceps; 3) To avoid postoperative bleeding and reduce the amount of drainage, the coagulation feature of ultrasonic scalpel shall be used as often as possible when facing unclear vessel-like tissue, and Hem-O-Lock clamps shall also be used if necessary.

Summary: We have re-written the sections as mentioned above to make our statement more objective. (see Page 5, Line 100)

Comment 3: Furthermore, there is no description of clinical and pathological stage in patient with bladder cancer.

Reply 3: Sorry for the confusing expressions we had made in the text. The second time TURBt was performed at a local hospital. Thus the pathological report might be less detailed. The final TUR findings are listed in full-length: *Sarcomatoid urothelial carcinoma, no myometrial infiltration was found in the specimens*. We have revised the expression accordingly.

In the aspect of radical cystectomy specimens' results, the final pathological report is: *The pathological result indicated that proliferative spindle cells could be seen in the full thickness of the left bladder wall, no tumor residual, lymphatic vessels invasion, or metastatic lymph node was found (0 out of 10). Immunohistochemical result: CK14 (-), CK 20 (-), CK5/6 (-), Desmin (+), GATA3 (-), Her-2(0), Ki-67 (index 5%), P53(-), AE1/AE3(+). The final TNM stage was T0N0M0*. We discussed this report with our colleague in the Pathology Department. They suggested the presence of proliferative

spindle cells could be seen as evidence of the previous existence of sarcomatoid urothelial carcinoma, whereas the tumor might be resected completely in the TURBt operation. Yet, this result is unpredictable preoperatively unless we have the entire specimens.

We also updated our follow-up results during our revision period. The updated content would be: No evidence of tumor residual or ureterocutaneostomic necrosis was found on his latest follow-up visit in December 2021 (*Figure 2*).

Changes in the text:

1: The final pathological diagnosis was sarcomatoid urothelial carcinoma, no myometrial infiltration was found in the TURBt specimen.

2: The pathological result indicated that proliferative spindle cells could be seen in the full thickness of the left bladder wall. No tumor residual, lymphatic vessels invasion or metastatic lymph node was found (0 out of 10). Immunohistochemical result: CK14 (-), CK 20 (-), CK5/6 (-), Desmin (+), GATA3 (-), Her-2(0), Ki-67 (index 5%), P53(-), AE1/AE3(+). The final TNM stage was T0N0M0. We discussed this report with our colleague in the Department of Pathology. They suggested the presence of proliferative spindle cells could be seen as evidence of the previous existence of sarcomatoid urothelial carcinoma. In contrast, the tumor might have been entirely resected in the last TURBt operation. Yet, this result is not predictable unless we have the entire specimens. No evidence of tumor residual or ureterocutaneostomic necrosis was found on his latest follow-up visit in December 2021 (*Figure 2*).

Summary: We have re-written the sections as mentioned earlier to make our statement more objective. Several updates have been made as well (see Page 4, Line 74; Page 6, Line 114)

Comment 4: After discharging hospital, patient showed ureterocutaneostomic necrosis. Then what did you do?

Reply 4: Sir, to prevent the happening of ureterocutaneostomic necrosis, we had made a lot of effort. Including preoperative urinary diversion planning, applying wound

dressing with fibroblast growth factors solution, and postoperative daily observation.

Luckily, ureterocutaneostomic necrosis was not observed in Figure 1 except for mild subcutaneous hematoma (*Postoperative view of bilateral ureterocutaneostoma and wound healing*). This Figure was shot on postoperative day 12, when the patient was discharged. To have a better understanding of the long-term condition of the anastomosis and wound, one author made a special follow-up trip to the patient's locality. We have uploaded a new figure (*Figure 2*) to showcase the long-term status of the patient's ureterocutaneostoma and wound healing (photo taken on 22nd Dec 2021, 4 months after the surgery). This trip was tiring and hard during the COVID-19 pandemic period.

Changes in the text: We have uploaded a newly taken photo as *Figure 2* presenting the long-term status of the patient's ureterocutaneostoma and wound healing. No evidence of tumor residual or ureterocutaneostomic necrosis was found on his latest follow-up visit in December 2021 (*Figure 2*).

Summary: We have re-written the above-mentioned sections (see Page 6, Line 124).

Comment 5: There are several parts omitted citation of previous studies.

Reply 5: Sorry for the carelessness regarding the citation issue. We have made revisions accordingly.

Changes in the text: We have added the omitted citations in the revised manuscript.

Summary: We have added the omitted citations in the revised manuscript.

Comment 6: I know the care of patient with Behcet's syndrome after the surgery which you used most of the part of paragraph, but there is less information.

Reply 6: Dear reviewer, we have added extra information on postoperative care such as the withdraw of gastric tube and drainage tube, the prevention of stress ulcers, etc. We have re-written the above-mentioned part in the manuscript.

Changes in the text:

Postoperative Monitoring and Patient Education

The role of postoperative monitoring and patient education cannot be ignored. Inflammatory evidence such as ESR, hsCRP, ulcers, and wound oozing should be regularly checked. As the patient was blind and did not exercise too much, he was encouraged to start early ambulation under his wife's custody. This would promote gastrointestinal peristalsis, establish self-confidence, avoid decubitus and prevent deep venous thrombosis.

To avoid intraoperative gastrointestinal flatulence, it is necessary to indwell the gastric tube after anesthesia. The gastric tube could be withdrawn if there is not much gastric juice postoperatively. The time of drainage tube withdrawing is not different from ordinary cases. Acid suppressants are recommended in case of stress ulcers. Since the intestine was intact in this patient, oral food-intaking, including the prescription of glucocorticoids, was resumed on postoperative day three. To prevent postoperative ileus and its following flatulence and intestinal ischemia, the patient was recommended to prophylactically take 20 mL of liquid paraffin oil daily and chew gum. Paraffin oil is rarely absorbable and non-digestible, colorless and tasteless mineral oil, preventing water absorption, lubricating the intestinal wall and feces, and softening the stool (19). Chewing gum can promote gastrointestinal peristalsis and digestive enzyme secretion (20).

Summary: We have added the omitted citations in the revised manuscript. See Page 11, Line 243.

To Reviewer D

The authors reported their experience with laparoscopic radical cystectomy for bladder cancer in a patient with Behcet's disease. Behcet's disease seems to be unfamiliar to urologic surgeons, and this case report and the proposal in the discussion section may be useful. Please consider the following points.

Comment 1: The Bechet disease seems to be wide from mild to severe. In what kind of condition should we pay close attention as in this case, and should we try to make the surgery less invasive?

Reply 1: Sir, albeit several point-based evaluating forms have been introduced to assess the activity and severity of BS, specific cut-off values to define the severity of BS are not currently available. Involvement of the ocular, vascular, neurological, and gastrointestinal systems might be associated with poor prognosis. For well controlled BS, we would recommend that the surgery that should be planned according to the patient's age, gender, types of organ involvement and oncological prognosis.

Also, several surgical principles/core ideas of performing this operation have been added.

Changes in the text:

Preoperative Preparations, Examinations and the Best Time for Surgery

Several point-based evaluating forms have been introduced to assess the activity of BS (12-14). Some scales are based purely on BS symptoms per se, while others also include laboratory examination results. Observative indices that revile the activity of BS include oral and genetic ulcers, ocular symptoms, skin lesions, joint pain/arthritis, vomiting/abdominal pain, diarrhea with bloody stool, and elevation of ESR (> 20 mm) and CRP (> 8 mg/L). However, the disease severity should be assessed by experienced rheumatologists as specific cut-off values to define the stage of BS are not currently available (12, 13). In Japan, the activity of BS is determined to be active if a patient presents two or more major evaluating criteria (12). Involvement of the ocular, vascular, neurological, and gastrointestinal systems might be associated with poor prognosis (1). For well-controlled BS, we recommend that the surgery be planned according to the patient's age, gender, types of organ involvement, and oncological prognosis.

REFERENCES

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14. Kim DY, Choi MJ, Kim HY, Cho S, Cho SB, Bang D. Development and validation of an electronic medical record-based disease activity index for Behçet's disease. *Clin Exp Rheumatol*. 2014;32(4 Suppl 84):S40-4.

Summary: We have added extra content regarding the comment (see Page 7, Line 151).

Comment 2: According to past reports, there have been many complications in cases of urinary diversion using their intestine, but in the field of gastrointestinal surgery, surgery of the intestine is unavoidable. Is there anything we should be careful about?

Reply 2: Sir, owing to the rarity of BS itself, reports from the general surgery world are lacking. Hence, we consulted our colleagues from the Dept. of GI Surgery and presented their thoughts on this issue. A new paragraph regarding this comment has been added.

Changes in the text:

Our Thoughts on Urinary Diversions, Bowel Preparations, and Surgical Approaches

Previous studies indicated that BS could involve the mesenteric vessels and cause chronic ischemic inflammation on the intestinal wall. In contrast, around two-third of the patient might not have apparent symptoms of active bleeding and gastrointestinal ulcers (1, 17). Therefore, the confirmation of gastrointestinal involvement of BS is complicated (1). Owing to its rarity, experience on BS patients undergoing gastrointestinal surgery is lacking. Sevinc et al. (7). reported a spontaneous ileal ischemia case who had no gastrointestinal complaints nor any definite ulcer foci found in the gross pathology. The author concluded that notwithstanding long-term immunosuppressants or steroids prescription, chronic arteritis could gradually and ultimately cause intestinal ischemia (7, 18). We consulted our colleagues from the Department of General Surgery, who opined that whether the anastomotic leakage would happen or not majorly depended on three factors: the blood supply of the anastomosis, regional tension, and stitching techniques. For patients with BS, they

would suggest open anastomosis, when necessary, because it could provide surgeons with an intuitive feeling of the anastomotic tension and opportunity of serosal-muscle layer embedding, and reduce chances of impairing major vascular arches. Overall, urinary diversion and bowel preparation methods should be considered according to the patient's situation.

REFERENCES

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18. Iscan ZH, Vural KM, Bayazit M. Compelling nature of arterial manifestations in Behcet disease. *J Vasc Surg.* 2005;41(1):53-8.

Summary: We have added a new paragraph discussing this issue (see Page 9, line 199).

To Reviewer E

This is a rare single case report on a laparoscopic radical cystectomy on a patient suffering Behcet syndrome. From the pure surgical point of view, it does not provide any information of additional interest, but the extreme rarity of this association deserves the awareness of the community.

Reply: Sir, we appreciate your recognition of our work a lot. Yes, in surgical technique, experienced surgeons could make it without too much extra effort. This paper aims to introduce our experience to the urology community. Hopefully, the story of this patient could inspire more medical partitioners, as well as BS patients. Thank you for your

recognition and encouragement.

To Reviewer F

In the manuscript entitled "Case Report: Laparoscopic radical cystectomy on a patient with Behcet's syndrome, our initial experience on perioperative safety", the authors reported the experience of laparoscopic radical cystectomy for bladder cancer patients with BS. This is a very informative case report because of the rarity of bladder cancer with BS. There are a few comments that need to be addressed to insist on what they have claimed in their manuscript.

Comment 1: The authors should not write the exact year and month in the manuscript.

Reply 1: Sir, we have modified our manuscript accordingly to make the relevant date more implicit.

Changes in the text: Some specific date, month, and year information have been replaced in another form. The order of relevant date information has been re-written in an "xxx days later," "xxx months later" format. *However, to make the manuscript consistent and easy to read, we did not re-write all months/years.*

Summary: We have fixed this issue mentioned above accordingly.

Comment 2: Figure 2A is a little obscure. If possible, the authors should change the picture and the yellow comments should be larger.

Reply 1: Sir, we are so sorry for this inconvenience we have caused. Figure 2A (now as Figure 3A as we have added another Figure in this version) is an intraoperative picture captured by the laparoscopic camera (Full HD). The maximum resolution would be 1920*1080 (about 2 megapixels). As a result, we do not have a picture with higher resolution. We do not want to sharpen it in Photoshop. However, the yellow fronts have been changed to make a comment more straightforward.

Changes in the text: We have re-sized the in-picture captions to make Figure 2A (now as Figure 3A) clearer and more straightforward.

Summary: Changes have been made in Figure 2A (now as Figure 3A) accordingly.

1