

July 19, 2021

Dennis A Bloomfield

Editor-in-Chief

*World Journal of Clinical Cases*

Dear Prof. Bloomfield:

I am writing to request that you kindly consider our revised manuscript titled “**Anesthesia and perioperative management for giant adrenal Ewing’s sarcoma with inferior vena cava and right atrium tumor thrombus**” for publication in *World Journal of Clinical Cases* as a case report. We thank you and the reviewers for the helpful comments and suggestions. We have now revised the manuscript, taking into account the reviewers’ constructive comments. **The revised manuscript has been uploaded as Supplementary Material.** The revised parts in the manuscript are displayed in blue text. We have addressed all the concerns and comments from the reviewers in the following paragraphs.

For Reviewer 1:

*Thank you very much for letting me contribute to this manuscript. Congratulations for the excellent clinical achievement. This report will be a great clue for other future cases with similar characteristics. Here were my comments on this manuscript.*

*1. In Laboratory examinations of Case Presentation, the authors indicated that elevated renin secretion was a result of increased renal perfusion. But I believe renin secretion increase in accordance with decreased renal perfusion. The authors mentioned coagulopathy but the gold standard to diagnose or rule out venous thromboembolism is d-dimer, or other type of fibrin degraded products. Did the authors measured those values as well?*

**Response:** We thank the reviewer for these important comments. As the reviewer indicated, the high renin-angiotensin secretion was possibly to be attributed to decreased renal perfusion, and the manuscript has been revised in page 5. We measured D-dimer during ECMO treatment, thus the data was added in table 4 as suggested (Page 19). The blue words represent revised part in the revised manuscript.

*2. According to Multidisciplinary expert consultation of Case Presentation, the patient had the sudden history of dyspnea five days before surgery. However, the multidisciplinary conference took place seven days after that, where they decided to perform surgery.*

**Response:** We thank the reviewer for the important comment. Considering the tumor thrombus was in the right atrium and the resection surgery was extremely dangerous, the multidisciplinary team used several days to make operation design and preparation. Then, they decided to perform surgery after the multidisciplinary team meeting in the urology ward. It is several, but not seven days (Page 6 Paragraph 3).

*3. Timeline should be corrected as appropriate.*

**Response:** We thank the reviewer for the important comment. We have corrected the timeline, and for the last time, it has been changed to POM 20 (Postoperative month 20, Page 25).

*4. Does Ewing sarcoma produce any hormone? How did it affect the decision-making process in perioperative management.*

**Response:** We thank the reviewer for the important comment. Extrasosseous Ewing's sarcoma has neuroendocrine function and secretes endocrine factors, and the markers include CD56, Syn and CgA. The endocrine affects the cardiovascular stabilization and internal environment, and it could be related to the increased level of procalcitonin (PCT, 1.82 ng/ml) and the increased percentage of neutrophils (84.7%) after surgery, which has been described in the 2<sup>nd</sup> paragraph of page 13. The diagnosis of Ewing's sarcoma was made after surgery and histopathologic examination, thus, its influence on the decision-making process of surgery and anesthesia during perioperative management was relative limited.

*5. Were there any specific reasons that the authors selected dopamine and norepinephrine rather than other cardiac supporting agents? As it can be dangerous to use beta-blockers in management of pheochromocytoma, do we have to take hormonal potential risks as well in the case of Ewing sarcoma?*

**Response:** We thank the reviewer for the important comment. Before surgery, the 24-hour urine catecholamine levels were normal and pheochromocytoma was excluded. Thus, we selected norepinephrine and dopamine based on the cardiovascular variation (BP decrease) during surgery, especially the processes of tumor dissociation and heart outflow tract obstruction (Page 8 Paragraph 1).

As the tumor located within the adrenal gland, we didn't use beta blockers in the perioperative period. Extrasosseous Ewing's sarcoma has neuroendocrine function and secretes endocrine factors include CD56, Syn and CgA. It has been reported that CgA depletion could result in the reduction of adrenal chromaffin granules in number, size, and electron density, as well as disruption of transmitter secretion from the regulated pathway [1]. Thus, Ewing's sarcoma may secrete other endocrine factors and affect cardiovascular stabilization.

1. Mahapatra, N. R., O'Connor, D. T., Vaingankar, S. M., Hikim, A. P., Mahata, M., Ray, S., et al. (2005). Hypertension from targeted ablation of Chromogranin A can be rescued by the human ortholog. *J. Clin. Invest.* 7, 1942–1952.

we still use beta-blockers. About hormonal potential risks Ewing's sarcoma, we lack experience in this area, and no relevant literature has been found.

*6. In Postoperative treatments, the authors came across sudden cardiopulmonary arrest. What was the initial waveform? Electromechanical dissociation was not clearly understandable.*

**Response:** We thank the reviewer for the important comment. Prior to transport, the patient presented with normal sinus rhythm, but during the process, we suddenly noticed that the normal ECG waveform and pulse oxygen waveform disappeared, along with the carotid pulse disappearance. The initial waveform was ventricular fibrillation, and then electromechanical dissociation. CPR was performed immediately, 1mg adrenaline was injected intravenously, and the heartbeat was restored one minute later. Thus, the duration of ventricular fibrillation or electromechanical dissociation was very short, and we revised the description in latest manuscript (Page 9 Paragraph 4).

*7. The authors mentioned the necessity of IABP in Discussion. But when was this device used?*

**Response:** We thank the reviewer for the important comment. We have mentioned that the IABP could be used during perioperative period, especially for the patients with congestive heart failure and CHD. However, the IABP has not been used in the present case.

*8. In Discussion, the authors indicated the possibility of pulmonary embolism as a cause of cardiac arrest. That makes sense clinically simply because there were residual tumor thrombus in IVC and possibly in hepatic veins. But if this resulted in the cardiac arrest, I assume right heart should have been expanded because of sudden elevated afterload, rather than been shrunk. In Discussion, whereas systemic inflammatory response could be a reason for the collapse, septic shock does not seem to be the reason. Sepsis is a series of organ failure caused by systemic infection. pro-inflammatory cytokines secretion itself does not cause sepsis.*

**Response:** We thank the reviewer for the important comment. As the reviewer indicated, pulmonary embolism caused by the residual tumor could be the primary cause. Although TTE had not provided definite evidence for the embolus, the chamber of right ventricle was small with hypokinesis, which could be the result of acute pulmonary embolism. Ewing's sarcoma could promote the release of pro-inflammatory cytokines and SIRS. As the reviewer indicated,

it may not be the primary or direct reason, but it could participate the process, so we described it in that part of discussion (2<sup>nd</sup> paragraph of page 13).

For Reviewer 2:

*Ewing's sarcoma of the adrenal gland is rare and occasionally invades to IVC. Because of its rarity, surgical treatment is usually avoided due to its high risk for operation in many hospitals except some special experts of surgeons. This report is one of the best experiences of such difficult cases. Although this paper presented the case vividly, I found that further discussions were needed in some parts.*

*1. Operation for adrenal Ewing's sarcoma with IVC invasion needs a multi-disciplinary task force. On the other hand, urosurgeons might be more experienced in renal cell carcinoma (RCC) with invasion/extension to the IVC. Please compare to such cases in RCC and adrenal Ewing's sarcoma, technically or intraoperatively. Eg: the order of vessel blockage, etc.*

**Response:** We thank the reviewer for the important comment. In the present case, Firstly, the liver and duodenum of the colon were dissociated to expose the right kidney and IVC.

Secondly, the dissociation between the lower pole of the tumor and the kidney was extended, and other parts of the tumor were dissociated to expose the right renal vein, right renal artery, right ureter, and to retain the right kidney. Thirdly, the cardiac surgeon continued to make median sternotomy, and after systemic heparinization, the inferior vein cava, superior vena cava and the ascending aorta were cannulated to establish cardiopulmonary bypass. Finally, the right atrium was opened to reveal part of the tumor thrombus. The remaining tumor thrombus was pushed into the inferior vein cava, which was removed after blocking the proximal and distal ends of the IVC (Page 7 Paragraph 3 and Page 8 Paragraph 2). And according to the previous reports of RCC, there are no obviously technical or intraoperative differences between RCC and adrenal Ewing's sarcoma resection.

*2. Although there is no recurrence of metastasis for 17 months after the operation, it is necessary to follow up for a long time. This caution should be addressed in the Discussion section.*

**Response:** We thank the reviewer for this important comment, and we have addressed the caution in the revised manuscript.

"Since discharge, the patient has survived for 20 months, and we will follow up the patient for a long time." (Page 11 Paragraph 2)

*3. Please describe concretely what does it mean by stating "Since 2020, only 39 cases of Ewing's sarcoma arising from the adrenal gland have been reported since 2020" ( The second*

*sentence in the Discussion part). It seems to be a typo since the expression is vague and unclear. Please write it concretely.*

**Response:** We thank the reviewer for this important comment, and we have revised the sentence in the manuscript (Page 11 Paragraph 3).

**In Discussion:**

"Up to now, only 39 cases of Ewing's sarcoma arising from the adrenal gland have been reported." (Page 11 Paragraph 3)

*4. As the title described, the purpose of this paper is to discuss anesthesia and perioperative management. Thus, I would expect more information on the intraoperative and postoperative anesthetic care part, such as fluids management, opioids use, etc. Moreover, postoperative care details in the urology ward, such as pain management, abdominal drainage, oral intaking, return of ambulation, postoperative nausea and vomiting (PONV), etc., should be provided.*

**Response:** We thank the reviewer for this important comment, and we have added the discussion of fluids management. "The key point of anesthetic management is to maintain perioperative hemodynamic stability, and multiple monitoring including EEG, IABP, CVP, temperature, respiratory parameters and blood gas analysis was employed during the perioperative period." and "Fluid management and vasoactive drugs are also important components for perioperative hemodynamic management. It has been reported that the perioperative outcomes favored goal directed therapy rather than liberal fluid therapy [34]. Considering the infiltration of the tumor in the liver and possible bleeding, we performed volume preloading, and used norepinephrine and dopamine to prevent hypotension during the processes of dissociation. During and after the cardiopulmonary bypass, BP remained relatively stable, and the transfusion was performed according to the blood loss. The total intraoperative transfusion included 14 U of red blood cells, 3200 ml of plasma and colloid solution, and 7200 ml of crystal solution." (Page 12 Paragraph 3)

The patient was transferred to urology ward 15 days after surgery, opioids and flurbiprofen (Cyclooxygenase blocker) were used for pain management, and postoperative nausea and vomiting were not obvious for this patient. The following has been added in the revised manuscript. "Closed thoracic drainage was used for the pleural effusion, and opioids and flurbiprofen were used for pain management." (Page 12 Paragraph 3)

*5. Are there any models that have been established to predict the malignancy or recurrence of Ewing's sarcoma? If so, please describe it and apply it to this case.*

**Response:** We thank the reviewer for this important comment. There are two main prognostic factors to predict the recurrence of Ewing's sarcoma. The disease-free interval (DFI) between

diagnosis and first relapse is an important prognostic factor. The patients with DFI>2 years have an estimated 5-year overall survival of approximately 30%, but the patients with DFI<2 years have an estimated 5-year overall survival of only 7%. The site of recurrence is another prognostic factor, and the patients with combined local and distant relapse have the worst outcomes, while those with isolated local recurrences appear to fare better [1-2]. We have added these descriptions in the revised manuscript (Page 11 Paragraph 3).

1. Leavey PJ, Mascarenhas L, Marina N, et al. Prognostic factors for patients with Ewing sarcoma (EWS) at first recurrence following multi-modality therapy: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2008;51(3):334–338.

2. Stahl M, Ranft A, Paulussen M, et al. Risk of recurrence and survival after relapse in patients with Ewing sarcoma. *Pediatr Blood Cancer*. 2011; 57(4):549–553.

6. *Any intraoperative photos?*

**Response:** We thank the reviewer for this important comment. However, we are sorry that there are no suitable intraoperative photos for the present case. In the further investigation, we will prepare more relevant photos, thanks.

7. *Further language editing is needed.*

**Response:** We thank the reviewer for this important comment. In addition, we have carefully checked and revised the manuscript for the inappropriate or wrong expression. The revised parts are in blue color in the revised manuscript.

Once again, we are very grateful for the helpful and insightful comments, criticisms and suggestions from you and the Reviewers. In addressing these concerns, we feel that the manuscript has been significantly improved. Thank you very much in advance for your kind consideration of our revised manuscript for publication in *World Journal of Clinical Cases*.

Sincerely yours,  
Jilian Wang, Cheng Ni