

Dear Editors and Reviewers:

Thanks for your letter and for the reviewers' comments concerning our manuscript entitled "Local hyperthermia combined with chemotherapy for the treatment of multiple recurrences of undifferentiated pleomorphic sarcoma: A case report" (ID:72103). Those comments are all valuable and very helpful for revising and improving our manuscript, as well as the important guiding significance. We have made correction according to the comments, revised portion are marked in blue in "Revised Manuscript with Track Changes" file. The main corrections in the paper and the responds to the reviewer's comments are as following:

Responds to the reviewer's comments:

**Reviewer #1:** Acknowledgements section is empty.

*Response:* We are very sorry for our negligence of acknowledgements, and we have added this part accordingly as following:

*"ACKNOWLEDGEMENTS*

*The authors would like to thank and acknowledge the patient and his family for taking part in this study."*

**Reviewer #2:**

*Comment 1: Chief Complain:* the sentence “that recurred 6 year after surgery and recurred 4 months after the last surgery” was obscure. I suggested the modification of “6 year after the first surgery”.

*Comment 2: Results:* The pathological pictures of UPS should be added to confirmed the diagnosis.

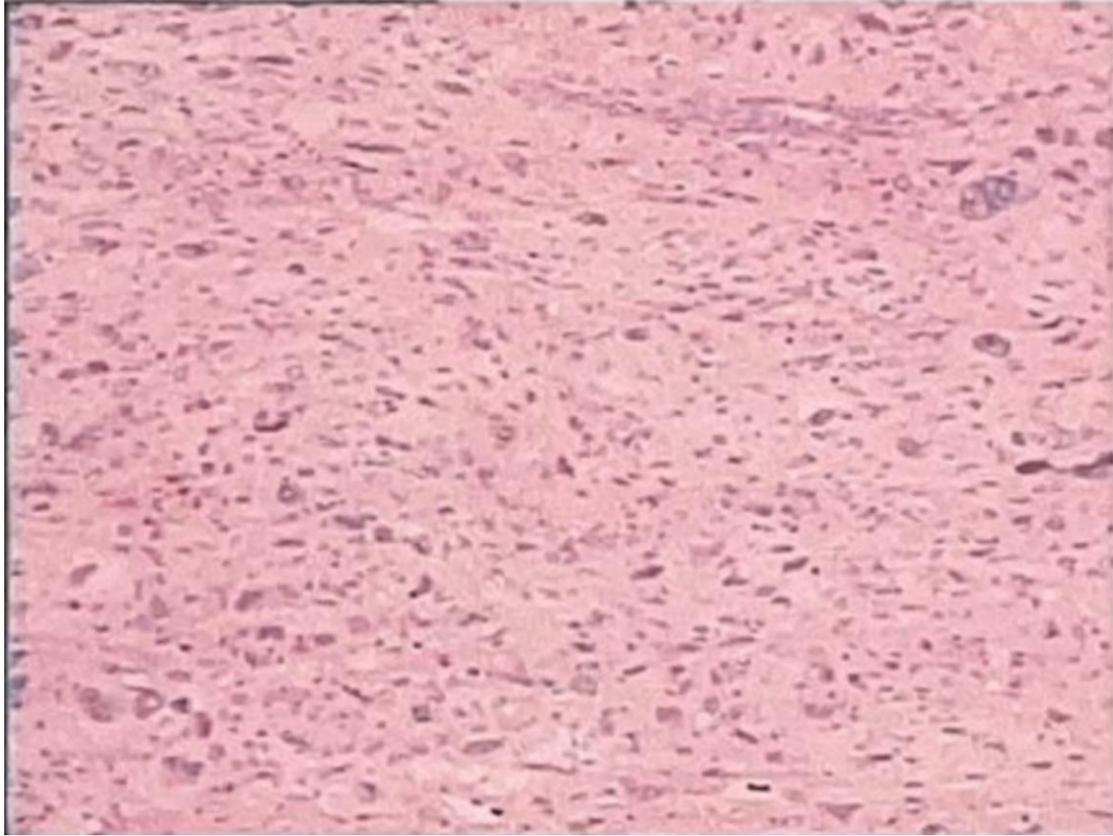
*Comment 3: Discussion:* At present, there are some gene mutations found in the pathogenesis of UPS, such as MET and PRDM10, which have some prognostic valuation. I suggested the part of content added to the manuscript. This would provide new therapeutic strategy for future recurrence.

***Response:*** Thank you very much for your constructive comments.

we have revised comment 1 as following:

*“A 65-year-old elderly male patient was admitted to the hospital 6 years after the first surgery to remove a pleomorphic sarcoma from the right side of his back, and he experienced recurrence 4 months after the last surgery.”*

We have added the pathological pictures of UPS as following:



*Figure 1 Postoperative pathological section (400×).*

As for comment 3, we have re-written this part according to the Reviewer' s suggestion, and added something about gene mutations, which found in the pathogenesis of UPS in recent years. The specific additions are as following (clean version of manuscript):

*“At the same time, this case also caused us to think more about the diagnosis, treatment and prognosis of UPS. At the 2021 Chinese Society of Clinical Oncology (CSCO) academic annual meeting, it was proposed that some types of soft tissue tumors show molecular changes, such as soft tissue tumors with PRDM10 rearrangement, which are mainly seen in low-grade UPS. The study of Pazzaglia, L and colleagues proposed that the MET gene can predict the risk of metastasis in such patients at the genetic level. When their study divided the patients into prognostic subgroups, they found that the level of MET mRNA in metastatic patients was*

significantly higher than that in nonmetastatic patients. Regarding the treatment of UPS, in addition to the local hyperthermia combined with traditional chemotherapy strategy used for this patient, molecular targeted drugs and PD-1 and PD-L1 inhibitors have also gradually received attention. Molecular targeted drugs and PD-1 and PD-L1 inhibitors are also gradually becoming valued. For example, drugs such as apatinib, olazumab, lidafromus and anlotinib have shown significant efficacy in UPS treatment. In 2021, a study on the efficacy of chidamine combined with the PD-1 inhibitor teriprizumab for the treatment of advanced soft tissue sarcoma (STS) conducted at Sun Yat-sen University found that after a follow-up of up to 40 weeks, 3 of the 7 patients with advanced STS, 3 patients experienced partial remission, and 2 patients were in stable condition. According to existing international studies, the synergistic effect of hyperthermia and immunotherapy on tumors such as pancreatic cancer and breast cancer has been confirmed. However, there are no relevant reports for UPS treatment at present, so more basic and clinical research is needed to explore the synergistic effects of hyperthermia and immunotherapy in the future."

**Reviewer #3:** The conclusions are not particularly innovative.

**Response:** Thank you for your constructive comments. We have redrawn the conclusion accordingly as following (clean version of manuscript):

"UPS has a high clinical misdiagnosis rate, and patients with locally advanced, unresectable, or metastatic disease have a poor prognosis and few treatment options. Local hyperthermia combined with chemotherapy for multiple recurrences of undifferentiated sarcoma after surgery has been rarely reported in clinical practice. By reporting this case, we hope to provide new ideas for the treatment of postoperative recurrence of advanced UPS, which could help to optimize surgical opportunities and achieve R0 resection. Along with the application of molecular-pathological diagnosis, continuous prospective research on the use of hyperthermia combined with

*radiotherapy, chemotherapy, and immunotherapy will provide more options for the comprehensive management of UPS."*

We tried our best to improve the manuscript and made some changes marked in blue in revised paper which will not influence the content and framework of the paper. We appreciate for Editors/Reviewers' warm work earnestly, and hope the correction will meet with approval. Once again, thank you very much for your comments and suggestions.

Yours sincerely,

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