

Reviewer A

The authors reported a disseminated intravascular coagulation (DIC) case after cryoablation of pancreatic cancer bone metastasis. While the presented case has raised an alert that DIC might occur after cryoablation as a rare complication, the case is not adequately presented or investigated in the manuscript. Therefore, I have several suggestions to make the case report meaningful.

Major comments:

1. It should be clarified whether the laboratory data of "procedure day" shown in Table 1 was obtained before or after the cryoablation. If it was before the procedure, it means that the parameters of DIC, such as platelet count, fibrinogen level, and PT-INR were worst before the procedure and might lead to the thought that these parameters were mainly due to the patient's underlying condition and not caused by cryoablation. On the other hand, if it was after the procedure, this case report lacks the patient's baseline data.

Response: The laboratory data of "procedure day" shown in Table 1 were obtained on arrival to the recovery area after the cryoablation procedure. The patient had a complete blood count and coagulation tests 4 days earlier which revealed a hemoglobin of 7.4 g/dL, platelets of 70,000/ μ L, and INR of 1.61. This information has been added to the revised manuscript and Table 1 has been updated. There was no fibrinogen or D-dimer level available pre-procedure. There was one D-dimer level obtained 3 days post-cryoablation and this information was added to Table 1.

2. The manuscript should present the patient's baseline condition and the post-procedural change more precisely to distinguish between the effects of cancer and cryoablation on DIC.

Response: Besides the pancreatic cancer, the patient did not have any other pre-existing medical condition. As described in the manuscript, she presented to the hospital from home for the second cryoablation procedure because of ongoing persistent pain despite the initial cryoablation and requiring high doses of narcotics. The patient had a complete blood count and coagulation tests 4 days earlier which revealed a hemoglobin of 7.4 g, platelets of 70,000, and INR of 1.61. The moderate anemia and thrombocytopenia were attributed to her progressive and metastatic pancreatic cancer. Her worsening thrombocytopenia and coagulopathy as well as hypofibrinogenemia consistent with DIC occurred following the cryoablation.

3. The laboratory findings should include D-dimer.

Response: There was only one D-dimer level obtained 3 days post-cryoablation and this was added to Table 1.

4. The term "Cryoshock" was used for the first time in the conclusion paragraph. If "cryoshock" is suspected of having caused life-threatening DIC in this patient, the entire manuscript should be presented from this standpoint.

Response: We have clarified that conclusion statement and replaced life-threatening "cryoshock" with life-threatening DIC. Our patient only developed severe coagulopathy and DIC but not cryoshock.

5. The patient developed deep venous thrombosis and was treated with rivaroxaban before the second cryoablation, which involved life-threatening complications. Did the patient undergo screening for thrombotic predisposition other than cancer, such as protein C/S deficiency?

Response: Other than the pancreatic cancer, our patient had no family history of venous thromboembolism (VTE) nor any previous episode of VTE before her pancreatic cancer diagnosis to necessitate screening for thrombotic predisposition.

6. Was rivaroxaban stopped before the procedure?

Response: Yes, the rivaroxaban was stopped 4 days before procedure and never restarted.

Reviewer B

1. In the title, "Case Report" should be revised to "A Case Report".

Response: Done

2. In the Abstract-Background, a brief background information about pancreatic cancer is required.

Response: Done

3. In the Abstract-Case Description, the history information "no significant past medical history" also should be specified.

Response: Done

4. In the Abstract-Case Description, "followed by chemotherapy with gemcitabine and paclitaxel. She developed a painful right femoral bone metastasis and underwent surgical tumor excision and local radiation therapy", the case description should follow the chronological order of events. It's better to revised to "Due to the abdominal lymph nodes, peritoneum, right femur, and surrounding soft tissue metastases. She received systemic palliative chemotherapy with gemcitabine and

paclitaxel and underwent right femur tumor excision, open reduction and internal fixation, followed by radiation therapy.”

Response: Done

5. In the Abstract-Conclusion, the authors need to be careful about claims. In this case report, the authors reported a disseminated intravascular coagulation (DIC) case after cryoablation of pancreatic cancer bone metastasis (i.e., DIC occurred after cryoablation). The conclusion “DIC can be exacerbated by large volume tumor cryoablation” isn’t supported by the reported case report. Similar statement in “Highlight Box” and “Conclusion” also should be considered.

Response: Done. The phrase “..can be exacerbated by large volume tumor cryoablation” has been deleted in the Abstract conclusion and Highlight Box section.

6. In the Introduction, please kindly reorganize the content to provide a more informative Introduction according to the “Author Instruction” (<https://cdn.amegroups.cn/static/public/2.5-Structure%20of%20Case%20Reports-template-V2022.11.4.docx>). In brief, Introduction should be structured in three parts: a) Background, b) Rationale and knowledge gap, c) Objective.

Response: Done, the first 3 paragraphs provide the background information on pancreatic cancer and cryoablation including mechanisms of injury. The rationale/knowledge gap is stated in the sentence, “To our knowledge, the occurrence of DIC after cryoablation is rare.” The Objective is now stated separately in the last sentence of the Introduction.

7. In the Introduction, the authors also should give a summary about the vascular events or complication of advanced pancreatic cancer, especially DIC.

Response: Done.

8. “A few studies have reported safe and successful palliative use of cryoablation in patients with locally advanced and unresectable pancreatic cancer with no adverse reactions (4, 5)”. The included references seem less cutting-edged. Please consider using the literature in recent years, such as PMID 34279799.

Response: Thank you. We have added the suggested reference (ref #11).

9. Please specify the detailed information of rivaroxaban, gemcitabine and paclitaxel therapy, such as dosage, frequency and duration

Response: Done

10. “Immediately post procedure, she developed bleeding at the ablation site”. Is it possible to be

more specific in the description of blood loss? Ex: Do you have the volume amount, or any further description.

Response: Done

11. For the readers' convenience, we suggest the authors add the normal range for the fibrinogen level, such as "markedly low fibrinogen level of 36 mg/dL (range 200–400)". Besides, please provide the corresponding literature for the diagnostic criterion for DIC.

Response: Done. The reference for the diagnostic criteria for DIC was added (ref #14).

12. Similarly, Discussion is structured in five parts: a) Key Findings, b) Strengths and limitations, c) Comparison with similar researches, d) Explanations of findings, e) Implications and actions needed.

Response: Done. The key findings are now stated in the first paragraph of the Discussion.

13. Lots of references missing in the text - each claim and reference to previous work should be cited, such as, lines 88-90, lines 156-160 and so on.

Response: Done. New references added include refs 11-14 and 16, as requested.