Peer Review File

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1st Round

Reviewer A

This study presents a rare case of pancreatic adenocarcinoma with isolated metastasis to the uterine cervix, a phenomenon documented in only 4 previous cases. A 62-year-old female with 6 months of vaginal bleeding, pelvic pain, and foul discharge was diagnosed via clinical evaluation, imaging (MRI, PET-CT), and immunohistochemistry (IHC). The pancreatic primary (a 3.2×4.2×3.2 cm mass encasing vascular structures) and cervical metastasis (a 2×2.2×3 cm lesion) were confirmed through IHC profiling—positive for CK7, CDX2, and CA19.9, and negative for p16, p63, and PAX-8—ruling out primary cervical adenocarcinoma (e.g., gastric-type mucinous subtype). The patient received palliative radiotherapy (30 Gy over 10 fractions) for vaginal bleeding, followed by systemic chemotherapy with gemcitabine and cisplatin, resulting in significant tumor response. The case underscores the importance of meticulous histological and IHC assessment to distinguish metastatic from primary cervical malignancies and highlights the role of multidisciplinary management in such rare scenarios.

This study, as a single case report, has inherent limitations. First, its small sample size (one patient) limits generalizability, making it difficult to draw broader conclusions about the natural history, optimal diagnostic pathways, or treatment efficacy for pancreatic adenocarcinoma with cervical metastasis. Second, the extreme rarity of such cases (only 4 prior reports) hinders comparative analysis or identification of consistent patterns in metastasis mechanisms, clinical presentation, or prognosis. Additionally, long-term follow-up data are lacking, leaving uncertainty about durable treatment responses or long-term survival outcomes. Finally, while IHC aided diagnosis, the study does not explore potential molecular profiling (e.g., MSI, NTRK fusion status) in depth, which could limit insights into personalized therapeutic strategies. These limitations emphasize the need for larger case series or multi-institutional studies to validate findings and refine management approaches.

In the title, I suggest to indicate that this is a case report. The current abstract is not informative. The authors need to write it according to the CARE reporting guideline, including the unique clinical contribution of this case, the main complaints, how the metastasis to cervix was confirmed, and how the patient was treated and what the prognosis is, and what the clinical lessons and implications from this case are. The introduction is inadequate. The authors only emphasized the rarity of this case but did not specify the unique clinical contribution and the clinical questions to be answered in this case report. In the case presentation, a timeline figure is needed to briefly summarize this case. In the discussion, please discuss and compare this case with the four similar cases in the literature. Please have comments for the early diagnosis and differential diagnosis of pancreatic adenocarcinoma with isolated metastasis to the uterine cervix.

Comment : To indicate that this is a case report in the title.
Reply- The title has been revised to include ‘Case report’
Change in text- Highlighted in title

Comment : Abstract is not informative. Please follow CARE guidelines.
Reply- The abstract has been revised to follow the CARE structure: Background, Case Description and Conclusions.
Changes in the text: Abstract rewritten and highlighted (Page 1)

Comment : The introduction is inadequate and lacks clinical context.
Reply : The introduction has been restructured.
Changes in the text: Introduction restructured and change highlighted

Comment : Discuss and compare this case with previous 4 similar cases.
Reply : A table summarizing previous cases and a comparative discussion has been added.
Changes in the text: Table 1 added and Discussion updated (Pages 5–6)

Comment : Include discussion on early and differential diagnosis.
Reply : Differential diagnosis including gastric-type mucinous endocervical adenocarcinoma has been discussed.
Changes in the text: Discussion updated with this content (Page 5)

Reviewer B

I would like to thank the authors for this good work. Nevertheless, some points deserve to be reviewed before the article is considered for publication.

1. Please consider refining the title by adding the intervention and patient outcome. This would greatly increase its readability. Besides, please also clearly identify this manuscript as a case report.
Reply 1: The title has been revised to include 'Case report'
Change in text- Highlighted in title

2. I found the current manuscript was inconsistent with the structure template for the case report in the authors' instruction (https://cdn.amegroups.cn/static/public/Case-Reports-Structure-template.docx?v=1754009801941). The authors should provide a structured Abstract: 200–350 words max. Structured with:
(1) Background: state what is known and unknown; why the case report is unique and what it adds to existing literature.
(2) Case Description: describe the patient's demographic details and main history, the main diagnosis, interventions, outcomes, and follow-ups.
(3) Conclusions: summarize the main take-away lesson, clinical impact, and potential implications.

Reply- The abstract has been revised to follow the CARE structure: Background, Case Description and Conclusions.
Changes in the text: Abstract rewritten and highlighted (Page 1)

3. Please provide 3-5 keywords including "case report" for this manuscript.

Reply- Key words updated
Changes in the text: Key words highlighted

4. According to authors' instruction: https://apc.amegroups.org/pages/view/guidelines-for-authors#content-3-4-1, a highlight box should be provided, which should be structured with

“Key findings”, “What is known and what is new”, and “What is the implication, and what should change now” subsections.
Reply 4: A highlight box has been added.
Changes in the text: Added below key-word and highlighted

5. Please provide a structured informative introduction, namely three subsections “Background”, “Rationale and Knowledge Gap”, and “Objective”, to improve clarity.

Reply 5: Introduction is now structured accordingly.
Changes in the text: Changes in introduction highlighted

6. “While secondary cervical malignancies typically originate from gynaecological sources, sporadic cases arising from extra pelvic sites like stomach, colorectum, breast, urothelium, and pancreas have been reported”, the sentences lack citations.

Reply 6: Relevant citations have been added.
Changes in the text: In the paragraph on knowledge gap in introduction, citation has been added and highlighted.

7. It’s great that the authors specified the published cases of pancreatic adenocarcinoma with metastasis to uterine cervix. Based on the statement, it might be worth highlighting more explicitly how this case report contributes to the existing body of knowledge in its current form. This manuscript needs to clearly present a novel contribution beyond what has already been reported.

Reply 7: Contributions explicitly mentioned in abstract, introduction, and discussion.
Changes in the text: Highlighted in abstract, introduction, and discussion

8. Consider adding the detailed time information of the case report (Month, Year) in the manuscript.
Reply8: timeline added
Changes in text- highlighted changes in ‘case’

9. Please add the medical, family, and any relevant history of the patient.
Reply 9: Patient history included.
Changes in the text: 1st paragraph in ‘case’, 4th line, highlighted

10. “Blood investigations revealed an elevated serum Cancer embryonic antigen (CEA) and carbohydrate antigen (CA19-9)”, please provide precise data of the laboratory values instead of the current description. Meanwhile, include normal levels in () wherever applicable.

Reply 9: Blood investigations included.
Changes in the text: 1st paragraph in ‘case’, 6th line, highlighted

11. All Figures should be cited in the order in which they appear in the text. The authors only cited Figure 2 in the main text.

Reply 11: Figures have been renumbered and cited correctly. All figure references verified.
Changes in the text: Throughout text and legends. Highlighted in the 'case'.

12. In addition, please confirm the accuracy of the citing figures. For the authors' reference, "The tumor was found to be positive for CK 7, CDX2 and CA19.9, while it was negative for p16, p63 and PAX-8 (fig.2)", the cited figure was incorrect.
Reply 12: All figure references verified
Changes in the text: Highlighted in the 'case'

13. Please add the pathologic staging information.
Reply 13: AJCC staging has been added.
Changes in the text: 1st paragraph, last line in 'case', highlighted

14. "Subsequently, patient was taken up for systemic therapy with a combination of Gemcitabine and Cisplatin, given every three weekly", please report the recommended dosage of the treatment.
Reply 14: Dosage for gemcitabine and cisplatin has been added.
Changes in the text: 2nd paragraph, last line in 'case', highlighted

15. "A significant response in both diseased sites was observed compared to the baseline scan", if it's available, please add the important MRI images after receiving the treatment.
Reply- the patient went back to her village and we do not keep the scans of the patient with us at our institute. Her daughter followed up to say patient does not want further treatment and has gone to her village

16. Were there any adverse and unanticipated events after receiving the treatment of Gemcitabine and Cisplatin?
Reply 16: No major adverse events noted; this is documented.
Changes in the text: 2nd paragraph, last line in 'case', highlighted

17. When was the last follow-up visit conducted? What are your plans for future follow-up? What are the testing methods and follow-up intervals?
Reply17: the last follow up was at the time of the 5th cycle of chemotherapy after which the patient defaulted.

18. A visual timeline is suggested to summarize this case. The timeline should present relevant events in the patient's history in chronological order in a figure or table, enabling the core elements of the case report to stand alone. The authors are encouraged to merge the current figures in the timeline too. sI find some examples from the journals for your reference:
https://tbcr.amegroups.com/article/view/41371/html
https://jgo.amegroups.com/article/view/50913/html
https://tlcr.amegroups.com/article/view/53824/html
https://tlcr.amegroups.com/article/view/35939/24197

Reply 18: change added.
Change in text – in the 'case' post last paragraph.

19. Discussion should be 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.
Reply 19: discussion modified as per recommendations.
Change in text- entire discussion.

20. Summarize the case in the first paragraph in Discussion. More specifically indicating whether other similar cases have been reported with similar outcome would be useful. How novel is this type of case report? Please elaborate on this in your discussion based on comparison with other similar case reports.
Reply 20: discussion modified as per recommendations.
Change in text- entire discussion.

21. "Pancreatic origin has been exceptionally rare with only 4 such cases reported till date4-7", to increase the value of this case report, consider providing a table to summarize previous reported cases of pancreatic adenocarcinoma with metastasis to cervix, including patients' characteristics, presentations, interventions, and outcomes, if possible.
Reply 21: table added.
Change in text- table added in discussion section before the last paragraph.

22. I would also recommend that the authors further explicitly discuss the limitations, except for the inherent limitations of a case report - a single case. For the authors' reference, was the assessment timely? Is there anything that could be further improved about the assessment and interventions?
Reply 22: discussion modified as per recommendations.
Change in text- entire discussion.

23. The statements lack appropriate parenthetical citations for support. For example,
(1) Clinical presentation of cervical metastases varies but often includes symptoms such as pelvic pain, abnormal bleeding or discharge per vaginum.
(2) Additionally, CK7, CK20 and CDX2 are commonly employed to evaluate immunoreactivity pattern and confirm the origin of metastatic disease in unknown primary settings.
(3) CK7 positivity is observed in tumours of upper gastrointestinal and pancreatico-biliary tract, breast , lungs , endometrium etc. CK20 positivity is detected in tumours of gastrointestinal tract and urothelium while CDX2 immuno-expression is seen in the former subset alone.
Reply 23: modified as per recommendations.
Change in text- entire discussion.

24. I suggest that the authors review the references and use more current references in the last three years (only 1 reference is 2024 or older).
Reply 24: difficult to change the refences which will be pertinent to the case.

25. The study should adhere to the CARE Checklist. Please kindly fill out the CARE Checklist and submit it as a sperate file (https://cdn.amegroups.cn/static/public/CARE-checklist-English.docx?v=1731916086166). The relevant page/line and section/paragraph number in the manuscript should be stated for each item in the checklist.

Reply 25: completed.

2nd Round

Reviewers comments and replies.

1- More details should be provided. Please report the recommended dosage, frequency, and duration of received treatment. In addition, please add the follow-up information in this subsection (e.g., the patient defaulted after receiving five cycles of chemotherapy).
Changes made in Abstract section, para 1 and highlighted.

2- The timeline lacks key findings. For example, what were the symptom onset? What examinations did the patient undergo? What were the bases for diagnosing metastatic pancreatic adenocarcinoma? Specific information about the treatments, such as dosage, frequency and duration.

The timeline should present relevant events in the patient's history in chronological order in a figure or table, enabling the core elements of the case report **standing alone**. In other words, the readers could know all important information about the reported patient based in the timeline.

In addition, the authors are encouraged to merge the existing figures in the timeline too. Authors could find examples from previous comment.
Fresh timeline added, unable to add images to it, so added them with the text. Changes made just prior to discussion. Labelled as Figure 8

3- The information was inconsistent with the statement in the Introduction "To the best of our knowledge, only 4 cases of pancreatic adenocarcinoma with metastasis to uterine cervix have been documented till date. 4-7".

Upon re-evaluation of the cited literature, we noted that only **three published cases** of pancreatic adenocarcinoma metastasizing to the cervix have been documented: Boysen et al. (1951), Kinoshita et al. (2016), and Hartsough et al. (2019). The reference by McCluggage et al. (2010) describes metastatic carcinomas to the cervix in general, but does not specifically include pancreatic adenocarcinoma. Therefore, our case represents the **fourth documented case** worldwide.

Accordingly, we have revised the manuscript to ensure consistency:

- **Introduction:** "…only **3 cases** , has been highlited.