

Manuscript number: 111835

Manuscript Type: Case Report

Title: Primary ileal squamous cell carcinoma: A case report and literature review

Dear Editors and Reviewers,

We sincerely appreciate the opportunity to revise our manuscript entitled “Primary ileal squamous cell carcinoma: A rare case report and literature review” (Manuscript Number: 111835) . We are deeply grateful for the insightful comments and constructive suggestions provided by the reviewers. All comments have been invaluable in improving the quality of our manuscript and hold important implications for our ongoing research.

We are grateful to **the Reviewer #1, Science Editor, and Executive Editor-in-Chief** for their insightful comments. We have addressed each of their suggestions point by point in the sections below. Revised portions of the manuscript have been highlighted in **yellow** for easy reference. Additionally, we have conducted a comprehensive revision of the entire manuscript to enhance its clarity and accuracy.

In this response letter, the reviewers’ comments are reproduced in *italics*, and our responses are shown in **red font**. All corresponding changes in the manuscript have been indicated with **yellow highlighting**.

We have made every effort to thoughtfully incorporate the feedback and hope that the revised manuscript now meets the journal’s standards for publication.

Thank you for your time and consideration.

Reviewer #1:

Comment 1:

In the “Introduction” section, it would be possible to add a little bit by defining the diagnostic problem more clearly. Although a rare case is mentioned, the emphasis

on the absence of native scaly tissue in the ileum and, as a result, the need to exclude metastases will immediately attract the reader's attention and emphasize the importance of the article.

Response 1:

We sincerely thank the reviewer for this insightful comment and excellent suggestion. We agree that providing a clearer definition of the diagnostic dilemma at the beginning will better highlight the clinical significance of our case.

As suggested, we have revised the Introduction to more explicitly emphasize the absence of native squamous epithelium in the ileum under physiological conditions, which fundamentally underscores the diagnostic challenge of primary ileal squamous cell carcinoma (PISCC).

Specifically, we have added the following sentence to the second paragraph (Line 4) of the Introduction:

“Development of PISCC is clinically uncommon, as the ileal mucosa consists of simple columnar epithelium and typically lacks squamous epithelium under physiological conditions. Diagnosis relies on exclusion of metastatic squamous cell carcinoma. Essential steps include obtaining a detailed clinical history, performing a whole-body PET-CT scan to detect extraintestinal primary tumors, and conducting a histopathologic evaluation of the tumor's growth architecture.”

We believe this addition has significantly strengthened the Introduction and immediately engages the reader by outlining the diagnostic problem, exactly as the reviewer recommended.

Comment 2:

The “Discussion” section is comprehensive, but it can be somewhat confusing in places. Splitting the Pathogenesis section into numbered subsections corresponding to the four hypotheses would improve readability.

Response 2:

We sincerely thank the reviewer for this excellent suggestion to improve the clarity and organization of our Discussion section. We agree that structuring the pathogenesis hypotheses into distinct subsections will significantly enhance readability.

The original text:

The pathogenesis of PISCC remains unclear, although four principal hypotheses are under active scientific scrutiny: (1) malignant transformation of ectopic squamous epithelium originating from embryonic remnants, as demonstrated by Adair et al. through histopathological analyses of intestinal duplication^[7]; (2) clonal evolution of adenocarcinoma to acquire secondary squamous differentiation, as substantiated by 11.6% (n=5) of reported cases displaying hybrid adenosquamous histology^[14,17,18,28,50]; (3) dysregulated differentiation of pluripotent stem cells, as supported by immunohistochemical evidence from Barnhill et al. of multiphenotypic tumor differentiation^[58]; and (4) chronic inflammation-mediated carcinogenesis *via* the metaplasia–dysplasia–carcinoma continuum, as conceptualized in Friedman’s model of multistep oncogenesis^[25].

As recommended, we have restructured the Pathogenesis segment in the Discussion by dividing it into four clearly numbered subsections, each corresponding to one of the principal hypotheses:

These changes have been made in the third paragraph (Line 2) of the Discussion.

“The pathogenesis of PISCC remains unclear. Four principal hypotheses are under active investigation: **hypothesis 1** malignant transformation of ectopic squamous epithelium arising from embryonic remnants, as demonstrated by Adair *et al*^[7] through histopathological analyses of intestinal duplication; **hypothesis 2**: clonal evolution of adenocarcinoma with secondary squamous differentiation, substantiated by 11.6% (n=5) of reported cases

displaying hybrid adenosquamous histology^[14,17,18,28,50]; **hypothesis 3:** dysregulated differentiation of pluripotent stem cells, supported by immunohistochemical evidence from Barnhill *et al*^[58], of multiphenotypic tumor differentiation; and **hypothesis 4** chronic inflammation-mediated carcinogenesis *via* the metaplasia–dysplasia–carcinoma continuum, as conceptualized in Friedman’s model of multistep oncogenesis^[25]. ”

We believe this new format provides a much clearer and more logical flow for the reader, and we are grateful for this constructive feedback.

Comment 3:

The “Treatment” section could be expanded. Although it correctly states that surgery is primary and that there are no recommendations, it could briefly discuss the specific treatment regimens used in the literature (from table 1) in this case as well. It would be useful to explain why specific chemotherapeutic drugs were chosen.

Response 3:

We are grateful to the reviewer for this insightful suggestion. We agree that expanding the “Treatment” section to include a synthesis of therapeutic approaches from the literature and their underlying rationale would significantly enhance the value of our manuscript.

The original text:

therefore, therapeutic strategies are often extrapolated from regimens established for esophageal squamous cell carcinoma (e.g., the TPF regimen or modified FOLFOX6 regimens)^[63].

As recommended, we have substantially revised the “Treatment” section in the Seventh paragraph (Line 19) of the Discussion to incorporate a discussion of the specific chemotherapeutic regimens identified in our literature review (Table 1) and the clinical rationale for their selection.

“Consequently, clinical management often adopts established regimens used for squamous cell carcinomas at other sites, such as the esophagus or head and neck. The most frequently employed regimen consists of

platinum-based agents combined with either 5-fluorouracil (5-FU) or a taxane. This combination is standard for head and neck as well as esophageal squamous cell carcinomas, owing to the synergy by which platinum agents, together with 5-FU or taxanes, disrupt DNA synthesis and impair cell division. In cases with high tumor burden or more aggressive disease, intensified regimens such as TPF (docetaxel + cisplatin + 5-FU) may be considered. The modified FOLFOX6 regimen (oxaliplatin + leucovorin + 5-FU) may also be selected because of potential suitability for the intestinal tumor microenvironment and a generally more manageable toxicity profile of oxaliplatin in some patients. The final treatment strategy should be determined through a comprehensive evaluation of tumor biology, patient performance status, and treatment goals^[63].”

We believe this addition provides a concise yet comprehensive overview of empirical treatment practices and the rationale for chemotherapeutic choice, directly addressing the reviewer’s comment. Thank you for this suggestion, which has certainly improved our manuscript.

Comment 4:

The “Conclusion” correctly points out a gap in the understanding of molecular biology. This point could have been carefully raised earlier in the Discussion to more clearly indicate the need for future research.

Response 4:

We sincerely thank the reviewer for this insightful and constructive suggestion. We agree that introducing the gap in molecular understanding earlier in the Discussion would more effectively highlight the significance of our study and better delineate directions for future research.

Accordingly, we have revised the Discussion section by adding the following sentence in the fifth paragraph (Line 4) to foreground this key point:

“ Notably, molecular mechanisms involved in PISCC remain incompletely

defined. There is an urgent need for additional molecular studies to elucidate the etiology of this rare condition and to guide the development of preventive measures and targeted therapeutic interventions.”

This addition now provides a foundation for the concluding statement regarding the need for future molecular studies, thereby strengthening the logical flow throughout the Discussion.

We believe this revision has significantly improved the manuscript by better framing the research problem and its implications, as suggested by the reviewer. We are once again grateful for this valuable comment.

Comment 5:

In table 1: It is recommended to carefully check the table to make sure that all the data from the cited sources have been accurately deciphered (for example, the sequence in the designation of stages, treatment details, results).

Response 5:

We sincerely thank the reviewer for this critical comment, which underscores the importance of data accuracy in Table 1. We fully agree with the need for meticulous verification and have thoroughly rechecked every data entry in the table against the original references.

The revisions we have made are as follows:

Staging Designations: All cancer staging entries have been standardized according to the AJCC 8th Edition guidelines to ensure consistency across all reported cases. **Treatment Details:** Descriptions of surgical procedures (e.g., “right hemicolectomy” instead of “colectomy”) and chemoradiotherapy regimens have been verified and clarified. Agent names and cycle numbers were added wherever this information was available in the original sources. **Follow-up Results:** Outcomes have been uniformly expressed (e.g., “Alive without disease at 24 months” or “Succumbed to disease at 18 months”). All numerical data, including survival duration, have been cross-verified against the original publications.

These corrections have been meticulously incorporated into the revised version of Table 1. We believe these efforts have greatly improved the accuracy and reliability of the table, and we are grateful to the reviewer for prompting this essential improvement.

Comment 6:

Page 5, Introduction: The phrase "Most of them are metastases of squamous cell carcinoma..." it can be a little misleading. This could be rephrased as follows: "Although small intestine metastases from squamous cell carcinoma of other locations do occur, primary squamous cell carcinoma of the small intestine (PISCC) is extremely rare.

Response 6:

We thank the reviewer for this insightful comment. We agree that the original phrasing could be misinterpreted and that the suggested revision more accurately frames the clinical context while highlighting the rarity of PISCC. We have therefore adopted the reviewer's exact recommendation to ensure clarity.

The original text:

The majority of these are metastases of squamous cell carcinomas; primary squamous cell carcinoma of the small intestine (PISCC) is exceptionally rare^[6].

This change has been made in the second paragraph (Line 2) of the Introduction.

" Although metastases to the small intestine from squamous cell carcinoma at other sites occur, primary squamous cell carcinoma of the small intestine (PISCC) is extremely rare^[6]. "

We believe this revision provides a more precise and balanced statement, and we are grateful to the reviewer for this valuable suggestion.

Science Editor :

Comment 1:

Country/Territory of origin: China.

Response 1:

We confirm that the country of origin for this case report is China.

We thank the reviewer for this comment.

We confirm that this case report originates from China. All clinical data and procedures were obtained at the Department of Pathology, Hebei General Hospital (No. 348 Heping West Road, Shijiazhuang 050051, Hebei Province, China; email: hbghbinglike@126.com), a tertiary care center in Hebei Province.

Comment 2:

The language classification is Grade A. Please provide the latest language certificate after Return the Manuscript to Author for Revision. Please visit the following website for the professional English language editing companies that we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

Response 2:

We thank the editor for this note. We have carefully reviewed the language editing requirements and the list of recommended professional editing companies.

We confirm that we will employ the services of one of the recommended professional English editing companies to polish the manuscript thoroughly.

A valid language editing certificate will be provided upon submission of the revised manuscript.

Comment 3:

Manuscript Title: Except for capitalization of the first word, all other words are represented in lowercase.

Response 3:

We thank the reviewer for highlighting this important formatting requirement. We have now revised the manuscript title to adhere to the journal's style, with only the first word capitalized as instructed.

The title has been changed from:

"Primary Ileal Squamous Cell Carcinoma: A Case Report and Literature Review"

to:

"Primary ileal squamous cell carcinoma: A case report and literature review"

This correction has been made in the title page and throughout the manuscript as needed.

Comment 4:

Author list. Author names (unabbreviated) should be given as first name, middle name initial (with no period) and family (sur)name, and typed in bold with the first letter of each capitalized.

Response 4:

We sincerely thank the reviewer for pointing out this important formatting requirement. We have now carefully revised the author list to fully comply with the journal's style guide.

The authors' names have been reformatted as follows:

From: Qian-qian Li, Jie Wei, Lu-yao Fang, Jia-lv Zhou, and Huan-fen Zhao

To: Qian-Qian Li, Jie Wei, Lu-Yao Fang, Jia-Lv Zhou, and Huan-Fen Zhao

Specifically, we have ensured that: Names are presented as first name, middle name initial (without a period), and surname. The first letter of each name part is capitalized. The entire author list is now typed in bold, as

required.

This correction has been consistently applied throughout the manuscript.

Comment 5:

Authors and institution(s): Author names should be written out first (as first name, middle name initial (with no period) and family (sur)name; with a hyphen included between the syllables of Chinese names) and typed in bold, followed by a comma and the complete name of the affiliated institution, city, province/state, postcode and country typed in non-bold. Examples for authors name and institutions are: Yi-Fan Chang, Tao Liu, Chong-Qing Wei, Wei-Long Chang, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Response 5:

We sincerely thank the reviewer for this important clarification regarding author and institutional formatting. We have carefully revised the author list and institutional affiliations to fully comply with the journal's specified format.

The authorship and institutional information have been revised as follows:

From:

Qian-Qian Li, Lu-Yao Fang, Huan-Fen Zhao, Department of Pathology, Hebei General Hospital, Shijiazhuang 050051, Hebei Province, China

Jie Wei, Jia-Lv Zhou, Graduate School of North China University of Science and Technology, Tangshan 063210, China

To:

Qian-Qian Li, Lu-Yao Fang, Huan-Fen Zhao, Department of Pathology, Hebei General Hospital, Shijiazhuang 050051, Hebei Province, China

Jie Wei, Jia-Lv Zhou, Graduate School of North China University of Science and Technology, Tangshan 063210, Hebei Province, China

We have ensured that: All author names are presented in bold typeface;

Chinese names include hyphens between syllables; Institutional affiliations are presented in non-bold format; Complete address information including postcode and country is provided, including the title page and any other relevant sections.

Comment 6:

Author contributions: The 'Author contributions' passage describes the specific contribution(s) made by each author. The author's names will be listed in the following format: full family (sur)name, followed by abbreviated first and middle names. For example, Bryan L Copple should be revised as Copple BL. A full multi-author example is: Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research study; Wang CL, Zou CC, Hong F and Wu XM performed the research.

Response 6:

We thank the reviewer for this important clarification regarding the format of the 'Author contributions' section. We have revised the section to strictly adhere to the specified format, wherein each author is listed by their full surname followed by abbreviated first and middle names.

The "Author contributions" section has been revised as follows and is located on the first page of the manuscript:

Author contributions: Li QQ and Wei J contributed to manuscript writing, editing, and data collection; Fang LY and Zhou JL contributed to data analysis; and Zhao HF contributed to conceptualization and supervision. All authors read and approved the final version of the manuscript.

Comment 7:

Audio Core Tip. In order to attract readers to read the full-text article, we request that the first author make an audio file describing the final core tip. This audio file will be published online, along with the article. The author can invite English language editing company to assist in resolving the language issues of Audio Core

Tip.

Response 7:

We thank the editor for this valuable suggestion to create an Audio Core Tip. We agree that this will be an excellent way to highlight the key findings of our study and attract readers' interest.

We confirm that we will comply with this request. The first author (Qian-Qian Li) will prepare the script for the Audio Core Tip summarizing the final core message of our manuscript. To ensure the highest language quality and pronunciation clarity, we will engage one of the professional English language editing companies recommended by the journal to assist in polishing the script and/or providing pronunciation guidance for the recording.

The completed audio file will be submitted along with the revised manuscript.

Comment 8:

Reference numbers in the main text. The name of the author(s) of a reference is listed in the sentence, the reference number should be placed immediately after the author(s) of the reference. Example: Mandal et al[8] proposed that retractor aponeurosis disinsertion is the most likely cause of congenital low lid entropion.

Response 8:

We thank the reviewer for pointing out the required format for reference numbering when authors' names are mentioned in the text. We have now carefully reviewed the entire manuscript and corrected all instances where the reference number did not immediately follow the author(s)' name.

The corrections have been applied throughout the manuscript, including but not limited to the following examples in the Discussion section:

Original: ...by Adair *et al.* in 1981^[7].

Revised: ...by Adair *et al*^[7]. in 1981.

Original: ...by Adair *et al.* through histopathological analyses^[7];

Revised: ...by Adair *et al*^[7] through histopathological analyses;

Original: ...from Barnhill *et al.* of multiphenotypic tumor differentiation^[58].

Revised: ...from Barnhill *et al*^[58] of multiphenotypic tumor differentiation.

We confirm that all similar occurrences have been corrected to ensure consistency with the journal's style.

Comment 9:

There are issues with the references: To ensure the accuracy of the references, please use "Edit References by Auto-Analyser" (<https://www.f6publishing.com/Forms/main/ArticleReferenceTool.aspx>) to edit the references of the manuscript.

Response 9:

We thank the editor for providing clear instructions regarding reference formatting. We have carefully reviewed the provided link and will strictly follow the journal's requirement.

We confirm that we will use the "Edit References by Auto-Analyser" tool at <https://www.f6publishing.com/Forms/main/ArticleReferenceTool.aspx> to thoroughly check and reformat all references in our manuscript to ensure they comply with the journal's style guide.

We appreciate this guidance, which will help ensure the accuracy and consistency of our reference list.

Comment 10:

Figures. Original figure documents. In the meantime, authors should provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor, and upload it to the file destination of "Image File" in the F6Publishing system.

Response 10:

We thank the editor for this instruction regarding figure preparation and submission. We will strictly comply with this requirement.

We confirm that we have prepared the original, high-resolution figure files using Microsoft PowerPoint, as specified. All graphs, arrows, labels, and text portions within the figures are editable and can be fully reprocessed by the editorial team. These original figure files have been uploaded to the “Image File” destination in the F6Publishing system, in addition to the figures embedded in the manuscript document.

We appreciate this guidance to ensure the highest quality for figure publication.

Comment 11:

The main text contains (1) INTRODUCTION; (2) CASE PRESENTATION [Chief complaints; History of present illness; History of past illness; Personal and family history; Physical examination upon admission; Laboratory examinations; and Imaging examinations]; (3) MULTIDISCIPLINARY EXPERT CONSULTATION (if relevant); (4) FINAL DIAGNOSIS; (5) TREATMENT; (6) OUTCOME AND FOLLOW-UP; (7) DISCUSSION; and (8) CONCLUSION.

Response 11:

We sincerely thank the editor for providing this clear and detailed template for case report structure. We have carefully reviewed the required sections and have now reorganized our manuscript to comply fully with this format.

The manuscript now contains the following sections, as specified:

INTRODUCTION

CASE PRESENTATION

Chief complaints

History of present illness

History of past illness

Personal and family history

Original: Physical examination Revised: Physical examination upon admission

Laboratory examinations

Imaging examinations

Pathological examination

FINAL DIAGNOSIS

TREATMENT

OUTCOME AND FOLLOW-UP

DISCUSSION

CONCLUSION

We have ensured that all content from the previous version has been accurately redistributed into these new sections. We believe this revised structure significantly enhances the clarity and readability of our case report.

We are grateful for this guidance, which has helped us improve the organization of our manuscript.