

Peer Review File

Article information: <https://dx.doi.org/10.21037/gpm-24-39>

Reviewer A

Comment 1: Please discuss more about DICER 1 gene associated ERMS in the discussion section.

Reply 1: According to the reports, the developments of ERMS may be associated with the mutations of DICER 1 gene. In the discussion part, we spent a whole paragraph to discuss the pathogenetic relationship between DICER 1 gene mutation and the ERMS.

Changes in the text: To make this paper more scientific and understandable, we added the introduction of the physiological function of DICER 1 gene products, which is cited from very rigorous investigation. The DICER 1 gene product is a key component of a highly conserved cellular pathway responsible for generation of small RNAs (miRNAs and siRNAs), which could negatively regulate gene expression and appear to play critical roles in stem cell maintenance, organogenesis, cell cycle progression, and oncogenesis. Thus, decreased DICER1 expression would weaken the down-regulation of oncogenesis pathway, which results in the tumorigenesis like ERMS. We hope this paragraph in the discussion part would help the understand the relationship between DICER1 and the ERMS.

Reviewer B

Comment 1: In the abstract, please briefly summarize the findings from the literature review and have more detailed comments for the clinical implications such as how to early diagnose and reduce the likelihood of misdiagnosis. In the introduction, the authors did not analyze the rarity and uniqueness of this case. I suggest the authors to emphasize the clinical importance of this case such as diagnosis and treatment or other points.

Reply1: Thanks for the summary of Reviewer B after carefully reading our manuscript. we want to share this case because of the tricky appearance of the tumor which makes the initial diagnosis as a prolapsed cervix.

Changes in the text: According to the Reviewer B's suggestion, we briefly summarized the findings from the literature review and have more detailed comments for the clinical implications such as how to early diagnose and reduce the likelihood of misdiagnosis.

Comment 2: The authors need to briefly analyze why they simultaneously performed a literature review. In the main text, please have a separate part to review the literature.

Reply2: thanks for the Reviewer B's suggestions. After careful consideration, we decided to delete the "literature review" from the title. The emphasis of this study was to share the diagnosis and

treatment for a rare cervical ERMS case. We want to raise the vigilance of all the gynecologist for the possible tumor diagnosis for the suspicious mass in the reproductive tracts in young females.

Changes in the text: we had deleted the “literature review” from the title.

Comment 3: In the discussion, the authors need detailed comments for the clinical implications of the findings in future similar cases. Please consider to cite several related papers: 1. Mao K, Li P, Yuan Y, Yi X, Fang J, Yuan J, Cao Z, Lu Z, Lo R, Luo B. Embryonal rhabdomyosarcoma of prostate combined with prostatic abscess in an adult patient: a case report and literature review. *Transl Androl Urol* 2024;13(9):2146-2152. doi: 10.21037/tau-24-117. 2. Yang J, Gao J, Hu J, Hu W, Qiu X, Huang Q, Kong L, Lu JJ. Particle beam radiation therapy for head and neck rhabdomyosarcoma in adults. *Ann Transl Med* 2022;10(22):1191. doi: 10.21037/atm-20-8238. 3. Navid F, Biegel JA. Detection of pretreatment circulating tumor DNA as a biomarker of poor outcome in intermediate-risk rhabdomyosarcoma. *Transl Pediatr* 2024;13(5):869-872. doi: 10.21037/tp-24-7.

Reply 3: We had thoroughly learned the paper provided by Reviewer B and those paper provided some latest research on the MRS, such as the diagnosis of rare prostate EMRS, the use of carbon-ion beam RT for treatment, the detection of ctDNA as a potential biomarker for prognosis in RMS. Changes in the text: We had cited those research in our manuscript to enrich our understanding about the MRS.

Reviewer C

Comment 1: As a case report, please consider refining the title by adding the characteristic of the patient, intervention, and patient outcome. This would greatly increase its readability and highlight the unique point.

Reply 1: Thanks for the Reviewer C’s kind suggestion, we changed the title accordingly. The diagnosis was delayed because of the cervix-similar appearance and the initial ultrasound examinations. We try to emphasize that the rare case reminds us of the tumor diagnosis should always be taken into consideration for any unexpected mass.

Changes in the text: the title had changed into “Delayed Diagnosis for DICER1-associated embryonal rhabdomyosarcoma in the cervix for a 15-year-old girl: a case report and literature review”.

Comment 2: Abstract: The abstract does not provide a complete and accurate description of the article's content. (1) While the authors mentioned the rarity of cervical embryonal rhabdomyosarcoma, it might be worth highlighting more explicitly why this case is noteworthy or unique. For the authors’ reference, specify like “Here we report a case of This case is unique in terms of...”. You can find the unique point from the well-known PICO (e.g., the characteristic of the patient, fast assessment, successful treatment, no adverse events, good outcomes). (2) In

Abstract-Case Description, please report the patient's essential disease and medication history. Besides, more detailed should be added for the "Three cycle of VAC combination chemotherapy", such as the dosage, frequency and duration. In addition, consider specifying "15-year-old" instead of using "a teenage girl" in the abstract and main text.

Reply 2: Thanks for the Reviewer C's kind suggestion. We had refined our description of this case and emphasized the rarity of its cervix-similar appearance. "15-year-old" is more scientific and specific than "a teenage girl".

Changes in the text: we had made some change in the abstract to emphasized the rarity of this case and used "15-year-old girl" instead of "a teenage girl" in the manuscript.

Comment 3: Keywords: Consider adding "cervical or cervix" and "case report" as the keywords.

Reply 3: thanks for the suggestion, we had added the "cervix" and "case report" as keywords.

Changes in the text: We had added the "cervix" and "case report" as keywords.

4. Structure: Please reorganize the introduction and restructure the discussion section as per the journal's case report guidelines (template download link: <https://cdn.amegroups.cn/static/public/Case-Reports-Structure-template.docx?v=1731481383876>).

Reply 4: thanks for the suggestions, we had restructured the introduction and discussion part to make the manuscript more scientific.

Changes in the text: we had made some changes introduction and discussion part according to the template.

Comment 5. The rationale and knowledge gap for conducting this study is not clearly expressed in the introduction.

Reply 5: The initial diagnosis of a prolapsed cervix was made according to the mass's tricky appearance and then the surgical plan was to cut the mass. After reviewing this case now, the biopsy should be suggested firstly, which could be a better choice to make the right diagnosis. Thus, we want to share this case to remind all the gynecologist the likelihood of tumor for any vulval mass in teenage girl.

Changes in the text: we had made some changes and added the "importance of biopsy" in the "Rationale and Knowledge Gap" subsection in the introduction part.

Comment 6. Case Presentation

(1) Clearly mentioning the time course of the events could help readers to follow along with the progression of the patient's condition and understand the severity of the situation.

Reply: The mass prolapsed from vagina during menstrual period and then retracted for the last three month. At this visit in our hospital, the mass would not retract anymore after period. The vulval mass were detected by the patient for 4 months in total.

Changes in the text: we had added the sentence “The patient was in good condition at visit and walked into the clinic with her mother.” as a statement to show the patient was in a good condition at her visit to our hospital.

(2) Consider providing more details about menstrual period, such as, the time of menarche, the duration of menstrual, and menstrual blood volume.

Reply: The patient had normal menstrual cycle every 28 days since 13 years old and the bleeding lasted 5 days.

Changes in the text: we had added the details of the patient’s menstrual period in the case presentation part.

(3) “Based on the above examinations, the vulval mass was suspected to be a prolapsed cervix”, the statement seems to be inconsistent with the sentence “The MRI scanning supported the idea the mass was a neoplasm which originating from the cervix”.

Reply: although the MRI scanning did not support the idea of a prolapsed cervix. Combination of the physical examination and ultrasonography, a prolapsed cervix was highly considered.

Changes in the text: we had deleted the “Based on the above examinations” to make the manuscript more scientific.

(4) “Since then, ERMS was finally made due to the pathological diagnosis”, please add the histological grading.

Reply: due to the limited ability of pathological department in our hospital, there are some inadequacies of the histological grading for the pathological results. We hope in the future the pathological reports for ERMS would be more comprehensive.

(5) “Then cervical conization was implemented to remove the residue of the tumor”, consider adding the reason for this treatment, for the authors’ reference, “Considering the age and the stage, then cervical conization...”.

Reply: During the initial surgery, the tumor was resected but the margin of the resection tissue was observed with tumor cells. Then cervical conization was implemented to remove the residue of the tumor to cut all the tumor tissue in the cervix. There are no guidelines or consensus regarding the treatments for this disease. To avoid radiotherapy to the reproductive system, the gynecologist and oncologist suggested a second surgery to cut all the tumor tissue in the cervix instead of radiotherapy as a supplementary therapy. When it is possible to achieve negative microscopic margins with minimal morbidity, resection of the primary tumor is the preferred method of local control (Meza JL, Anderson J, Pappo AS, et al. Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: the Children's Oncology Group. *J Clin Oncol* 2006;24:3844-51).

Changes in the text: none.

(6) Please kindly note that all case reports should explicitly mention the presence or absence of adverse events. I suggest authors disclose no adverse and unanticipated events in the manuscript if they are none (not just in the checklist). For the authors' reference, "The postoperative course/period was uneventful".

Reply: thanks for the suggestion of mentioning the presence or absence of adverse events. No complications were observed during treatment.

Changes in the text: we added the sentence of "No complications of surgery or chemotherapy were observed during the treatments" in the case presentation part.

(7) 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 standing alone. The authors are encouraged to merge the current figures in the timeline too. Authors could find such examples from existing case reports.

Reply: thanks for the suggestion of addition of visual timeline.

Changes in the text: we had added Figure 5 to summarize the whole process of diagnosis and treatment for this patient.

7. Discussion: The discussion section appears to lack the necessary rigor, critical thinking, and comprehensiveness.

(1) What is the novelty of your work in the light of existing case reports? Please elaborate on this in your discussion based on compared with other similar case reports. In addition, to be consistent with the title "literature review", consider adding a table summarizing previously reported cases with DICER1-associated cervical embryonal rhabdomyosarcoma.

Reply: In this manuscript, we mentioned several times that tricky cervix-resembled appearance, the physical examination and ultrasonography of the mass supported the initial diagnosis of a prolapsed cervix. the diagnosis was corrected until the pathological results. The cervical ERMS is a rare, and it usually presents as a cervical polyp or multiple polyps. But it first presented as a big vulval mass in this patient, and no other symptoms were found. We admitted the lack of knowledge concerning the ERMS is one of the reasons for delayed diagnosis. We also discussed the early diagnosis in teenage girls is not easy for some reasons. Firstly, the irregular vaginal bleeding is also common in teenage girls for the immaturity of hypothalamic-pituitary-ovarian (HPO) axis. Secondly, the obsession with virginity in some areas impedes the examination or biopsy for vagina and cervix in these groups. Lastly, some girls are shamed to confide their symptoms with even intimate persons. In this case, the patient started with protruding vulval mass during menstrual period three month ago without telling others, and finally resorted to her mother when the mass continuously stuck in the vaginal opening. That's to say, she could get diagnosis as well as treatment three-month earlier once the vaginal mass appeared.

(2) “However, there was an indication of possible tumor mass according to the enhanced MRI scanning, which showed the mass was uneven enhancement”, did the authors suggest enhanced MRI scanning was performed for any suspicious mass in every single patient? The authors could consider adding the information/value of MRI for diagnosis in Abstract-Case Description and Conclusions.

Reply: MRI is good for the detection of any abnormality of soft tissues and is recommended in the cervical cancer and endometrial cancer by all the authoritative academic guidelines. For any suspicious mass in the reproductive system, the MRI scanning could help in the diagnosis and follow-ups.

Changes in the text: we added the sentence “a MRI scanning be a prior choice in front of any suspicious mass” in the discussion part.

(3) It is necessary and important to transparently discuss the strengths and limitations of the study in the discussion. A separate paragraph is highly suggested.

Reply: thanks for the suggestion of adding the strengths and limitations of the case study in the manuscript, which could be more rigorous for scientific paper. However, there existed some limitations in this study. First of all, it was a rare sporadic case. Secondly, the level of local health care varied all over the world. Thus, the diagnosis and treatment for this case could not be representative for all the cervical EMRS case. Even though, we could still learn from the this rare case that tumor diagnosis should always be taken into consideration for any unexpected mass. A multi-disciplinary team could be a good choice to avoid such pitfall of misdiagnosis.

Changes in the text: according to the suggestions, we had added the strengths and limitations of the case study in the last paragraph in the discussion part.

8. Figures are not well annotated and are not easy to read and understand. Please present the full names of abbreviations in the footnotes. Besides, “Once removal, the mass was found to be originate from the right part of the cervix, of which the left part was intact (Figure 1)”, it’s more appropriate to cite the subparts of Figure 1 (i.e., Figure 1C) instead of the whole Figure 1. Please check the cited figures in the manuscript and revise the similar problems accordingly.

Reply: thanks for the suggestion, we had made some revisions as “Figure 1C” in the manuscript. we used the full name as “internal cervical orifice” instead of “internal cervical OS” to make the manuscript clearer to readers.

Changes in the text: we had made some revisions in the figure citations and used the full name instead of abbreviations in the footnotes.

9. The statements lack appropriate parenthetical citations for support. For example, “Generally, ERMS in GU respond well to chemotherapy. Thus, surgery taken out in a small group is only for biopsy, organ preservation and avoids functional or cosmetic deformity”.

Reply: thanks for the reminding of inappropriate citations and we added the citations accordingly.
Changes in the text: we added the citations in the manuscript accordingly.

10. The authors stated informed consent was obtained, so please mark the item 13 with “yes” in the CARE checklist. Besides, please also revise the statement “This case was described according to the SCARE 2020 criteria(9)”.

Reply: thanks for the reminding.

Changes in the text: we had ticked the “yes” in the the CARE checklist. And we deleted the statement of “This case was described according to the SCARE 2020 criteria”. In the manuscript.

11. Reference list is inconsistent. Please refer to the journal guidelines.

Reply: thanks for the suggestions. We had checked and relisted the Reference.

Changes in the text: we had checked and relisted the Reference.