

Peer Review File

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Reviewer comments

Comment 1: Please have the paper edited by native English speakers after revisions.

Reply 1: The manuscript was revised by a native English-speaker, focusing on grammar and syntax.

Changes in the text: We identified some spelling and grammatical mistakes. We have modified our text as advised.

Comment 2: In the title the authors should be cautious to use “comprehensive” because it is difficult to make a review comprehensive. As an academic paper, terms should be used strictly.

Reply 2: Following reviewer’s recommendations, we have deleted the term “comprehensive” from the manuscript title.

Changes in the text: The final title is: **“Primary epithelioid hemangioendothelioma of the penis: A case report and literature review”**

Comment 3: Abstract: Please indicate how the current case is unique and the clinical significance of this case report.

Reply 3: We have explained the contribution of this case report to the literature.

Changes in the text: We added some data (see Page 2, lines 6-7)

<<The relevance of this case report derives from the need for better clinical characterization of patients with penile EHE and the importance of defining the outcomes>>.

Comment 4: Abstract: Second, please indicate lessons learned from this case and clinical implications of findings from this case.

Reply 4: We have added information regarding lessons learned from the case report.

Changes in the text: We added some data (see Page 2, lines 19-20)

<<This case report highlights the importance of understanding of understanding the diagnosis and treatment of this type of rare non-squamous malignant tumours of the penis>>.

Comment 5: Abstract: Third, for the literature review, please present the main findings from literatures, and also have comments on their limitations.

Reply 5: We summarized in the Abstract the findings and limitations of the literature review.

Changes in the text: We added some data (see Page 2, lines 13-18)

<<According to the literature review, most of the patients were in their fifth and sixth decades of life at the time of diagnosis and lesions were usually located in the glans. The most common clinical presentation was as a painful mass. Follow-up period ranged from 2 months to 5 years. Three patients showed systemic metastases, two of which died due to cancer. The conclusions from the literature review are limited by the reduced number of cases and the short follow-up>>.

Comment 6: In the part of introduction, please have a brief review on existing knowledge on

the research topic, and indicate why the current case is needed.

Reply 6: In the Introduction section, we summarized what is already known from previous studies about EHE of the penis.

Changes in the text: We added some data (see Page 2, lines 13-18)

<<Non-squamous cell carcinoma primary malignancies represent fewer than 5% of penile cancers. Soft tissue malignancies of the penis are mainly vascular tumours, such as Kaposi sarcoma, EHE and angiosarcoma, followed by other sarcomas like rhabdomyosarcoma and leiomyosarcoma (3)>>.

<<There is a scarcity of published data on penile EHE's management and its natural history. Until 2015, 17 cases of penile EHE have been reported in the literature (3). Of these cases, two presented with metastasis and two with multifocal penile EHE lesions. Furthermore, the benign type of the spectrum, the penile epithelioid hemangioma (EH), is also a very rare vascular neoplasm. Until 2015, only 28 cases in the literature have been reported (4).

To date, reported characteristics of EHE are based on this small number of published cases. The rates of local recurrences, metastases and mortality of this tumour are 10%, 20-30% and 15%, respectively. Treatment decisions should be based on pathological findings. Treatment options include excision or multimodal therapy (1)>>.

<<This case report contributes to widen our knowledge of this rare tumour and the literature review offers an update on its management>>.

Comment 7: For the literature review, the authors should have a separate part to indicate its methodology, including literature search and how findings from previous studies were summarized.

Reply 7: We have added the sub-heading "**Literature review**".

Changes in the text: We have added the sub-heading "**Literature review**".

<<**Literature review**

We carried out a literature review in PubMed (MEDLINE) of reported cases and analysed therapeutic arsenal (surgery, antitumour drugs and radiation) used in the treatment of these unusual tumours.

The search strategy was as follows: ("Hemangioendothelioma, Epithelioid"[Mesh] OR "Hemangioendothelioma"[Title/abstract]) AND ("Penis"[Mesh] OR "penile"[title/abstract] OR "Penile Neoplasms"[Mesh]). Inclusion criteria were: histologically confirmed cases of penile EHE, and no language or temporal restrictions were applied. Two authors independently reviewed the literature and decided which case reports to include in this study. We summarized the case reports in Table 1, and we extracted the most important aspects: age, clinical presentation, size and location, management, follow-up period, local recurrence or metastases, and survival time>>.

Comment 8: In the part of discussion, please compare your findings with those from previous studies.

Reply 8: We tried to compare the results of our case report with those from previous research.

Changes in the text: We added some data:

<<We present the case of an EHE in a patient in the fifth decade of life, with a size of 13mm and debuting with painful erections>> (see Page 6, lines 21-23)

<<In our case, the patient was initially misdiagnosed with the acute phase of Peyronie's disease, as pain may occur without an erection, caused by inflammation in the area of the developing plaques>> (see Page 7, lines 11-13)

<<The mitotic rate in our case was low, that is, ≤ 2 mitoses per 10 high-power fields. Therefore, it was classified as a low-grade EHE>> (see Page 7, lines 19-21)

Comment 9: Please comment on the limitations of previous studies, and based on the current findings, please suggest some research directions for this topic.

Reply 9: We analysed the limitations of our review and the need for further research to be carried out on the management of penile EHE.

Changes in the text: We added some data (see Page 8, lines 3-8)

<<Limitations of this review are the scarcity of cases and short follow-up. These limitations prevent us from drawing strong conclusions.

This case report and the related literature review give some insights about the management of this rare tumour and may help clinicians recognize its clinical presentation. Nevertheless, it is crucial to improve future research and compile new reported cases to better establish the

characteristics of EHE>>.