

Peer Review File

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Reviewer A

In the presented case report, Casarin and co-investigators gently described an unusual case of the 59-years old woman who developed primary endometrioid adenocarcinoma from the vaginal endometriosis. Although the case is truly uncommon, the report is well-presented and documented. Treatment options were also reviewed, and all similar clinical case studies were presented at Table 1. I feel this case study is worth publishing, only minor comments are outlined below hoping they enhanced the strength of the report.

Comment 1: I wonder why pelvic and para-aortic lymphadenectomy has not been performed as surgery?

Reply 1: At the time of the surgery, the evidence supporting lymphadenectomy in primary vaginal cancer was not well-established due to the rarity of this disease and the lack of randomized controlled trials specifically addressing this issue.

The decision to perform lymphadenectomy in primary vaginal cancer should be individualized, taking into account the patient's overall health, the stage and extent of the disease, and the potential risks and benefits of the procedure.

Changes in the text: We better explained this in the Results, Case report section (see Page 5, line 116-118).

Comment 2: Although English language is acceptable, there are some mis-leading for example ... In the present study, we present....

Reply 2: We appreciate the reviewer's comment and have made some edits to improve the flow of the text.

Changes in the text: See page 3, line 72-73; Page 4, line 103-104; Page 6, line 143-144.

Comment 3: I recommend to use the title ... Primary endometrioid adenocarcinoma arising on vaginal endometriosis..... Also it will be better to use the vaginal endometrioid adenocarcinoma throughout the text.

Reply 3: We would like to thank the reviewer for this comment.

Changes in the text: The title and text have been revised as recommended. (see Page 1, line 1-2; Page 3, line 57 the Highlight box text).

Comment 4: Did endometriotic foci were documented in other sites during surgical intervention?

Reply 4: During the surgical procedure we did not individuate any other endometriotic foci.

Changes in the text: We better defined this in the Results, Case Report section (see Page 5, line 115-116).

Comment 5: What was the potential cause of the development of vaginal cancer originated from endometriosis in a 32-years old woman? Please give a short explanation.

Reply 5: The process of developing endometriosis-associated carcinomas remains unclear. Inflammation associated with endometriosis and the presence of reactive oxygen species may represent the initial step in DNA damage and

cancer initiation. Furthermore, mutations in genes such as K-RAS, PTEN, and ARID1A may increase the risk of endometriosis-associated cancers in young women.

Changes in the text: We better explained this in the Discussion section (see Page 6, line 153-163).

Reviewer B

Comment 1: Well written review of the literature on a rare disease.

Could the authors discuss the risk of hormonal treatment in patients with known endometriosis.

Reply 1: We would like to thank the reviewer for this comment. Hormonal treatment may represent a potential risk factor for the causal pathway of cancer in endometriosis. When comparing the effects of risk factors for ovarian cancer in women with and without endometriosis, long-term menopausal estrogen-only therapy use showed an increased risk of ovarian cancer. Furthermore, the risk appeared to be greater for women with endometriosis than for those without. Unfortunately, there is not enough data available on the variation of cancer risk when hormonal treatments are initiated during perimenopause.

Changes in the text: We better explained the possible pathogenesis of endometriosis related cancer and the risk associated with hormonal treatment in the Discussion section (see Page 6, line 152-163).