Author's response to reviews

Title: Small primary adenocarcinoma in adenomyosis with nodal metastasis: a case report

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Author's response to reviews: see over
To the editor of BMC Cancer

We read with interest the attached referees’ report.
We respond to the various remarks, one by one.

Reviewer 1 p.1

In Background, in references and discussion
The authors should be considered other cases of endometrial carcinoma arising in adenomyosis i.e.:
-Mittal KR, Barwick KW. Endometrial adenocarcinoma involving adenomyosis without true myometrial invasion is characterized by frequent preceding estrogen therapy, low histologic grades, and excellent prognosis. Gynecol Oncol. 1993 May;49(2):197-201.
The sentence: “only about 30 cases of adenocarcinoma arising from adenomyosis have been reported in English literature” is not correct. The above cited papers are not considered by authors.

And Reviewer 2 p. 1

1) include a couple of paragraphs describing the importance of using strict criteria when diagnosing adenocarcinoma arising in adenomyosis versus surface invasive adenocarcinoma involving adenomyosis, and methods to differentiate between these two conditions (see Nascimento et al. Mod Pathol 2003;16:22-27.)

We carefully sought in literature cases of malignant transformation of adenomyosis not associated with endometrial adenocarcinoma.
We know that the simultaneous occurrence of adenocarcinoma both in the endometrium and adenomyosis is a frequent finding with an important differential diagnosis between adenocarcinoma arising in adenomyosis vs. endometrial invasive adenocarcinoma involving adenomyosis. Since in some instances this distinction may be difficult, an immunohistochemical panel including CD10 is helpful as showed by Nascimento et al.
But, as described in the Pathological Findings section of our paper, the endometrium in our case was totally examined and was tumor free.
In this regard, in the article by Nascimento et. al 39 cases of adenocarcinoma in adenomyosis were associated with endometrial adenocarcinomas, at clinical presentation.
Likewise, the series presented by Taskin included 84 cases with endometrial carcinoma and 10 cases of benign adenomyosis as a control group.
Again, all the 164 cases described by Mittal showed adenocarcinoma involving the endometrium. For these reasons the three above mentioned references were not considered pertinent for our paper. However, we acknowledge our inadvertent omission of the case report by Takeuchi, so we add this case to the reference list. The negative staining for estrogen receptors of the neoplasm reported by Takeuchi confirms the peculiarity of the case we are again submitting for publication.
(Reviewer 1 p.1)
The authors do not report the symptoms of the patient which can motivate the gynaecological examination and ultrasound scan which reveal enlarged uterus. In result of ultrasound scan a leiomyoma is not reported. Why? This lesion, instead, is described in pathological findings. Moreover, in postmenopausal women, because endogenous systemic hyperestrogenism can be related with obesity the authors should state precisely if the patient is obese, in clinical summary.

As requested, we added the important clinical details in the Clinical Summary section, that were omitted.

In the Material and methods, Pathological findings
Although the authors performed C-erb B2 immunostaining, they do not mention the results in pathological findings and discussion.

We added the c-erb B2 staining status and comments.

Fig 1 C is not adequate to demonstrate the metastasis of endometrial carcinoma into a lymph node. More adequate is a photo of histological section showing both neoplasm and lymphonodal tissue, at low magnification

The enlarged lymph nodes was not removed, but only biopsied by fine-needle aspiration, as described in Pathological findings: Figure 1 C is Cell block cytology, that unfortunately does not contain lymphoid cells

Ca-125 represents more adequate marker than Cytokeratins AE1/AE3 to identify endometrial metastasis in the lymph node.
The diagnosis of lymph nodal metastatic adenocarcinoma was firstly clinical: the tumor developed in the uterine fundus, from which the lymphatics run to the external iliac nodes where the metastatic deposits were discovered. Based on the second-look surgical inspection and the extensive clinical work-up, as described in our paper, primaries, other than adenomyotic adenocarcinoma, were excluded. We presently performed immunohistochemical analysis for steroid receptors and COX-2 on the cell block cytology of the lymph nodal metastasis, as suggested by the reviewer: ER, PR and COX-2 positive staining, similarly to the primary tumor were observed.

In discussion
1) For major clarity, a brief mention about the role of aromates and the 17 ?-hydroxysteroid dehydrogenase should be made, because the endometriosis is considered an estradiol-dependent disorder, a consequence of aberrant aromates expression and 17 ? hydroxysteroid dehydrogenase deficiency.

A mention about the role of COX-2 and 17beta-hydroxysteroid dehydrogenase in endometriosis has been added in the Discussion.
2) Since the authors observe strong expression of ER/PR and weak aromatase expression in the leiomyoma, they suggest that this tissue could represent a hyperestrogenic microenvironment able to promote growth and neoplastic transformation of adenomyotic foci.

Since ER represents only a promotor for neoplastic transformation of adenomyotic foci, to clarify the mechanisms of carcinogenesis in adenomyosis, the authors should evaluate the expression of other markers such as cyclooxygenase-2 (COX-2) and P53.

I think these markers can have an important role in neoplastic transformation of adenomyotic tissue. In fact, (COX-2) is an enzyme responsible for prostaglandin synthesis, onset and progression of many malignant tumors.


Giordano G et al Postmenopausal status hypertension and obesity as risk factors for malignant transformation in endometrial polyps Maturitas 2007; 56: 190-197

Moreover, (COX-2) overexpression has been already documented in ovarian cancer concomitant with ovarian endometriosis


The authors should consider overexpression of P53 because this tumor suppressor gene is thought to play an important role in the neoplastic transformation and progression of endometrial adenocarcinoma and in other cases of endometrial carcinoma arising from adenomyosis.


We added COX-2 to the immunohistochemical panel. Unfortunately p53 staining didn’t work, due to the use of Bouin solution as fixative.

Anyway, we think that further widening tumor markers’ assessment, as suggested by a reviewer would change the aim of the present study, based primarily on the clinico-pathological case presentation and the analysis of the possible hormonal role in the development of cancer in adenomyosis.
The article should be revised for many typographic errors ie:
In clinical Summary at the age of 33 (years)
Progeston corrected with progesterone
Metastases should be metastasis.
In references delete [] (reference 11)
In Reference 2 3rd author is de Oliveira C.
Journal of reference 12 is Arch Surg 1925; 10:172
The title of paper should be modified as: Small primary adenocarcinoma in adenomyosis with nodal metastasis……
English language should be revised in clarity particularly in discussion, where the last sentences are long

We adjusted the ms according to all the above-mentioned instructions.