Malignant changes in adenomyosis in patients with endometrioid adenocarcinoma

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Summary

Objective: The aim of our retrospective study was to evaluate pathological changes in adenomyotic foci in hysterectomy specimens, and point out a possible mechanism of carcinogenesis in adenomyotic foci inside the myometrium. *Methods:* Retrospective analysis of clinical data; 219 patients were operated at our departments from 2003-2008 with the diagnosis of early endometrial cancer. Standard staging operation was used in all cases and all hysterectomy specimens were afterwards routinely analyzed. *Results:* Adenomyosis was found in 88 of a total of 219 hysterectomy specimens, while 205 of these 219 were affected by endometrioid adenocarcinoma, ten with clear cell carcinoma and four with papillary serous carcinoma. Within these subgroups adenomyosis was documented in 87 of 205 specimens with endometrioid adenocarcinoma (42.4%) and in one specimen of ten with clear cell carcinoma (2.2%), all found in the eutopic endometrium. All cases of malignant changes (n = 6) in adenomyosis were found exclusively with coexisting endometrioid adenocarcinoma: adenocarcinoma in adenomyosis was well or moderately differentiated in five cases, and poorly differentiated in just one case. Differentiation of the tumor in adenomyosis correlated with differentiation of the eutopic endometrial cancer in 50%. Hyperplastic changes like benign glandular hyperplasia, or atypical complex hyperplasia (ACH) were identified simultaneously in all cancer-positive adenomyotic foci. *Conclusion:* Malignant changes in adenomyosis were present in 6.8% of patients with endometrial cancer. All malignancy-positive cases of adenomyosis were associated with endometrioid adenocarcinoma of the eutopic endometrium. Interestingly, in all these cases, different stages of hyperplastic changes were also simultaneously identified. This observation suggests a similar pathway of carcinogenesis in adenomyosis as is known in estrogen-responsive endometrial cancer type I.

Key words: Hysterectomy; Myometrium; Adenomyosis; Endometrial cancer; Adenocarcinoma; Carcinogenesis.

Introduction

Endometrial adenocarcinoma and adenomyosis are hormone-dependent uterine lesions affecting the uterine corpus with increased frequency today [1-4]. The precise etiology of adenomyosis is still unknown while endometrial cancer shows two elucidated pathways of carcinogenesis [2, 3, 5, 6]. Case reports describe *de novo* malignant transformation inside adenomyotic foci while the eutopic endometrium was unaffected [7-11]. On the other hand, simultaneous malignant changes of the eutopic endometrium and adenomyosis have been described as well [12-15]. Adenocarcinomas involving adenomyosis are characterized by frequent preceding estrogen use, low histological grades, and excellent prognosis [15]. According to some studies coexisting adenocarcinoma arising from adenomyosis did not worsen the prognosis of the disease [6, 16], but is more often connected with deep myometrial invasion [13]. The distinction between true myoinvasion and malignant changes inside adenomyosis is very difficult, however crucial since the patient can be upstaged and inappropriately treated [17].

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Materials and Methods

A total of 219 patients were operated in our department between the years 2003 and 2008 with the diagnosis of early endometrial cancer. The average age was 61.4 years (45-85) and the average body mass index (BMI) 31.4 (17.1-57.3). Standard staging operation was used and all hysterectomy specimens were afterwards routinely analyzed in the Department of Pathology. The formalin-fixed uterus was cut in a standard manner and the whole specimen was histologically analyzed. Isolated malignant changes in adenomyosis were strictly distinguished from the secondary invasion of endometrial cancer. Adenomyosis was defined as the presence of endometrial glands and stroma in the myometrium, disconnected from the native endometrium and fulfilling the criteria of Colman and Rosenthal [18].

Results

Of the 219 patients operated for early endometrial cancer, endometrioid adenocarcinoma was confirmed in 205 cases, clear cell carcinoma in ten cases, and papillary serous carcinoma in four cases. Adenomyosis was found in 88 cases of 219 specimens (40.2%); in 87 cases it coexisted with endometrioid adenocarcinoma, in one case with clear cell carcinoma, and it was not found in the hysterectomy specimen affected by papillary serous carcinoma (Table 1).

The histopathological changes in adenomyosis in our cases were as follows: common structure - 17 patients

Table 1. — *Presence of adenomyosis in different types of endometrial cancer (n = 88).*

Endometrial cancer	Adenomyosis
Endometrioid adenocarcinoma	87 (97.8%)
Clear cell carcinoma	1 (2.2%)
Papillary serous carcinoma	0

Table 2. — *Histopathological changes of adenomyosis in patiens with endometrioid adenocarcinoma (n = 87).*

Glandular hyperplasia without atypia	25 (28.7%)
Atrophy	21 (24.1%)
Atypical complex hyperplasia (ACH)	18 (20.7%)
Malignant changes	6 (6.8%)
No pathological changes	17 (19.5%)

Table 3. — *Correlation between the final staging of endometrial cancer and malignant changes in adenomyosis (n = 6).*

Endometrial adenocarcinoma final staging	Malignant changes in adenomyosis
IcG2	moderately differentiated
IcG2	well differentiated
IcG3	poorly differentiated
IcG2	well differentiated
IcG1	well differentiated
IbG2	well differentiated

Table 4. — *Correlation between the final staging of endometrial cancer and malignant changes in adenomyosis (n = 6).*

n	Age	BMI	HRT	Myometrial invasion > 50%	Final staging	Hyperplastic changes in adenomyosis
1	76	25.2	–	+	IcG2	+
2	55	32.8	–	+	IcG2	+
3	63	25.4	+	+	IcG3	+
4	72	28.2	–	+	IcG2	+
5	54	33.4	–	+	IcG1	+
6	61	33.5	–	–	IbG2	+

(19.5 %), atrophy – 21 patients (24.1%), glandular hyperplasia without atypia – 25 patients (28.7%), ACH – 18 patients (20.7%), and malignant changes – six patients (6.8%) (Table 2). All cases of malignant changes in adenomyosis were found in patients with estrogen-dependent type I endometrioid adenocarcinoma (Table 3). The average age of this group of six patients was 63.5 (55-76) and average BMI was 29.8 (25.2-33.4). Only one patient with cancer-positive adenomyosis had a history of hormone replacement therapy (HRT). The malignant changes in adenomyosis were in four well differentiated cases, in one moderately differentiated case, and in one poorly differentiated case. No stromal invasion into the adjacent myometrium was found. In the group with malignant changes in adenomysis there were five cases where deep myometrial invasion of the tumor into the eutopic endometrium was proven (Table 4). In all cancer-positive adenomyotic lesions, other hyperplastic changes like benign glandular hyperplasia or atypical complex hyperplasia (ACH) were simultaneously identified.

Discussion

The risk factors for malignant transformation in adenomyosis are poorly defined [12, 13, 19, 20]. Systemic exogenous or endogenous hyperestrogenism, local overproduction of estrogens and other conditions, such as p53 mutation and increased activity of cyclooxygenase-2 are mostly discussed [9, 10, 20, 21]. In several studies, the usual findings are concomitant malignant changes of the endometrial epithelium located inside the myometrium and in normally located endometrium [9, 12, 15, 20]. We observed such findings in six cases (6.8%) of our study group (n = 87) (Tables 2 and 3). All patients in our study with cancer-positive adenomyosis were overweight or obese with possible endogenous hyperestrogenism as a risk factor. However one patient did have a history of increased systemic exogenous hyperestrogenism by HRT.

It is often difficult to distinguish myometrial invasion from the extension of carcinoma into adenomyosis, especially in the cornual area of the uterus [6, 9, 22, 23]. The presence of carcinoma in adenomyosis deeper than the maximum depth of the true tumor invasion does not worsen the prognosis [6]. Colman and Rosenthal proposed criteria for the diagnosis of carcinoma arising within adenomyosis [18]. These were: a) the carcinoma must be absent from the normal surrounding endometrium, b) the carcinoma must be seen to arise from the adenomyotic epithelium without invasion from another source, and c) endometrial stromal cells supporting a diagnosis of adenomyosis must be present. All our six cases of malignancy inside adenomyosis fulfilled the above-mentioned criteria. Since no myoinvasion of the tumor into the adenomyotic foci was observed, no correlation with stromal invasion of the intrauterine malignancy was proved (Table 3). In all cases of malignant findings in adenomyosis, we observed an increased stromal reaction around afflicted adenomyotic lesions. This reaction probably protects against myoinvasion into the surrounding myometrium [19].

Malignant changes of adenomyosis were confirmed only in the group with endometrioid adenocarcinoma, and they correlated with the tumor grading of the eutopic endometrium – in three cases (50%) (Table 3). In the other three cases the differentiation of the tumor located in the uterine cavity was lower than in the adenomytoic foci. Five of six tumors in adenomyosis were well or moderately differentiated and only one had poor differentiation. In our study the presence of adenocarcinoma in adenomyosis was connected with deep myometrial invasion of the tumor located inside the eutopic endometrium in five of six cases. This is almost the same result as that published by Ismiil [13].

Case reports also present adenocarcinoma arising de novo in an isolated adenomyotic lesion inside the myometrium [7-11]. These isolated ectopic changes are probably more aggressive like type II endometrial cancer [9]. In these specimens no malignancy of the normally located endometrium was observed. There was no such case in our series. In ten patients with clear cell carci-

noma of the eutopic endometrium, adenomyosis was found only in one case, and interestingly, featured an atrophic appearance.

In summary, we evaluated malignant changes in adenomyosis in patients with concomitant endometrial cancer. Adenomyosis is not a malignant disease, but it can undergo malignant changes. We observed different forms of hyperplasia in adenomyotic foci including ACH. Interestingly ACH as a premalignant lesion was confirmed in 18 hysterectomy specimens (20.7%) and it was present also in already malignant adenomyotic foci in 100%. All cancer-positive cases of adenomyosis in our study were found in the group with endometrioid adenocarcinoma, which is the same observation as published by Mittal and Barwick [15]. This fact may partially explain a better prognosis of these carcinomas. Our results also show malignant changes in adenomyosis with various differentiation (well, moderate, poor). These changes did not correlate with the tumor differentiation inside eutopic endometrium. However, there is no clear study demonstrating the natural transformation of adenomyosis to adenocarcinoma, and the mutual relationship of these two diseases is still speculative. According to published literature and our results, it can arise de novo or copy the model of carcinogenesis of type I endometrial cancer. Therefore it can also possess different biological features with different impact on the prognosis of the disease. Further studies are necessary to elucidate the clinical relevance of distinguishing the two possible pathways of malignant changes in adenomyosis.

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