A clinicopathological study of the relationship between adenomyosis and other hormone-dependent uterine lesions

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Summary

Aim: The aim of this study was to investigate the relationship between adenomyosis, endometrial adenocarcinoma, hyperplasia and uterine leiomyomas.

Material and Methods: 135 consecutive hysterectomy specimens showing adenomyosis and 82 consecutive cases of endometrial adenocarcinoma were studied in our laboratory in the last 5-year period. The histological sections of all cases were reviewed and in the cases with adenocarcinoma, the type of cancer, the degree of differentiation and the depth of myometrial invasion were recorded. In the adenomyosis group the presence of any other lesions, the extension of adenomyosis and the morphology of the adenomyotic glands were recorded. In ten random cases of adenomyosis, the presence of estrogens and progesterone receptors was investigated by an immunohistochemical method of peroxidase-antiperoxidase and DAB chromogen. In ten cases of this group the expression of E-cadherin was studied immunohistochemocally by an avidin-viotin method and DAB chromogen.

Results: In 47/135 cases of adenomyosis adenomatous hyperplasia coexisted (34.8%) and in 86/135 cases of leiomyomas (63.7%). In 31/82 cases of adenocarcinoma there was adenomyosis as well (37.8%), in 4/82 cases malignant changes in foci of adenomyosis were observed and in 1/82 cases the malignancy arose in a focus of adenomyosis. Immunohistochemical studies showed the presence of progesterone receptors in the glandular cells of adenomyosis in 9/10 cases and of estrogen receptors in 2/10 cases. In all study cases (10/10) a positive membrane immunoreaction was observed; focal (6/10) and extensive (4/10).

Conclusion: The high frequency of coexistence between adenomyosis and other hormone-dependent uterine lesions is indicative of the presence of a hormonal factor in the pathogenesis of adenomyosis.

Key words: Adenomyosis; Uterine adenocarcinoma; Uterine hyperplasia; Leiomyoma.

Introduction

Adenomyosis is a disease of late reproductive and perimenopausal age, observed usually in women about 40 years of age, with fertility problems, dysmenorrhea and metrorrhagia [1]. The pathogenesis of this lesion remains obscure although many theories have been proposed [2-4].

The incidence of adenomyosis varies according to the criteria used for the diagnosis. The most reliable pathologic feature diagnostic of endometriosis is the presence of ectopic foci in endometrial glands and stroma, lying at least one optical plane under high magnification (x100) underneath the endometrial-myometrial junction [2, 3]. Ectopic endometrial foci should not connected with the overlying endometrial mucosa. Some authors consider that the presence of hypertrophic myometrial bundles around the endometriotic foci is necessary for the diagnosis [3].

Greenwood [5] reported that the incidence of adenomyosis in selected hysterectomy specimens is 16%. Bird and *et al.* [4] reported that the incidence of adenomyosis varies according to the number of histological sections the pathologist studies, and it may be found in 30-60% of the studied specimens. In other non-selected series adenomyosis was found in 8-27% of the examined specimens [4-6].

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The morphology of glands in the foci of adenomyosis is that the glands in the basal portion of the endometrium and usually the ectopic glands do not show cyclical endometrial changes, in contrast to endometriosis, although it is known that they respond to progestin therapy [2, 3]. There are few reports about the coexistence of adenomyosis with other endometrial lesions such as hyperplasia or adenocarcinoma [5-10]. Gianmarko *et al.* [6] reported that the coexistence of adenomyosis and adenocarcinoma is elevated in comparison to control cases, and have suggested a common underlying pathogenetic hormonial factor.

Our aim was to study the relationship of adenomyosis with adenocarcinoma as well as with other pathological lesions such as leiomyomas, endometrial hyperplasia and polyps.

Material and Methods

The material of this study comprises 217 hysterectomy specimens selected as follows: 82 specimens were consecutive cases showing endometrial carcinoma and 135 were consecutive cases with adenomyosis. All specimens were examined in our laboratory over a 5-year period. The criteria used for the diagnosis of adenomyosis are those described in the introduction. The histological sections of all cases were reviewed and in the cases with adenocarcinoma, the type of cancer, the degree of differentiation and the depth of myometrial invasion were recorded. Cases with concomitant adenomyosis were especially

studied, and the extension of the adenocarcinoma in some of the adenomyotic foci was recorded as well as the stage of the disease.

In the adenomyosis group of cases, we recorded the presence of any other lesions, the extension of adenomyosis and the morphology of the adenomyotic glands. In ten random cases of adenomyosis, the presence of estrogens and progesterone receptors was investigated by an immunohistochemical method of peroxidase-antiperoxidase and DAB chromogen, using an Abbot Diagnostics Kit on paraffin sections of formalin-fixed tissues, previously treated with Biogenex Antigen Retrieval. In ten cases of this group the expression of E-cadherin was studied immunohistochemically by an avidin-viotin method (Monoclonal ab, Santa Cruz CA, Biotechnology, 1:100 solution) and DAB chromogen.

Results

The hysterectomy specimens with endometrial adenocarcinoma showed foci of adenomyosis in 31 cases (37.8%). In 30/31 cases, the overlying adenocarcinoma was well differentiated, endometrioid (Stage I) and in one case it was poorly differentiated adenocarcinoma (Stage II). In 3/82 cases (3.6%), in addition to the superficial mucosal neoplasms, there were malignant changes in the foci of adenomyosis as well. The differential diagnosis from a malignant extension from the overlying adenocarcinoma was established by the synchronous presence of benign ectopic glands in the same focus, surrounded by hypertrophic myometrial bundles. In 1/82 cases (1.2%) the adenocarcinoma developed in a focus of adenomyosis while the overlying endometrial mucosa was benign and showed hyperplastic changes. In these cases uterine mucosa was totally examined in multiple sections .

In the second group of hysterectomy specimens containing adenomyosis there were 47 cases (34.8%) showing hyperplasia of the endometrium of various degrees and in two cases (1.5%) hyperplastic endometrial polyps were observed. Eighty-six cases in this group (63.7%) presented with uterine leiomyomas, measuring more than 2 cm and in 56 cases multiple leiomyomas were observed.

The glands of adenomyosis showed the typical morphology of basal endometrial glands, except in four cases where they presented secretory activity in accordance to the overlying endometrium, out of 27 cases in all being in the luteal phase of the cycle.

Immunohistochemical studies showed the presence of progesterone receptors in the glandular cells of adenomyosis in 9/10 cases and of estrogen receptors in 2/10 cases. In all study cases (10/10) a positive membrane immunoreaction was observed, focal (6/10) and extensive (4/10).

Discussion

The etiology and pathogenesis of endometriosis and adenomyosis defined as the ectopic location of endometrioid glandular epithelium and stroma, have been poorly understood. Implantation (retrograde menstruation) and the metaplastic theory have been proposed to explain the development of these entities [11].

A recent theory implicating invasive mechanisms has been advanced, and the loss of E-cadherin expression in the epithelial cells is considered as the crucial mechanism [12, 13]. Clinical features and in vitro experiments have suggested that endometriotic cells are able to "metastasize" and cell adhesion molecules are central for the invasion and metastasis of these cells [12, 13]. The phenotypic similarities of ectopic endometrium to those of malignant tumor cells raised a possibility of common underlying molecular mechanisms, but the results are still controversial [12, 14].

The immunohistochemical investigation of E-cadherin expression in five of our cases was positive and although the number of cases investigated is small, it is in accordance with the view that the "invasive theory" concerns the development of endometriosis and not of adenomyosis [12, 14].

In our material, the incidence of adenomyosis in uteri harboring endometrial adenocarcinoma was 37.8% of the cases and this is higher than the reported 8-15% in the literature [5-7]. Our observations are in accordance with the study by Greenwood [5].

The development of adenocarcinoma in the foci of adenomyosis without involvement of the superficial uterine mucosa is considered a rare event and only a few documented cases have been reported. Takai *et al.* [10] presented two such cases, and suggested that prior frequent estrogen use may have been implicated. They reviewed the effects of chemotherapy and radiotherapy as a possible carcinogenetic factors in the uterus. Use of tamoxifen has been implicated in the development of proliferative and malignant changes in ectopic endometrial glands [15], but according to the clinical data our patient had not used any hormonal preparations.

No case of adenomyosis showed hyperplastic changes of the ectopic glandular epithelium, not even in the cases with hyperplasia of the overlying mucosa. Hyperplastic changes of the endometrium were observed in 34.8% of the examined cases with adenomyosis and this is in accordance with the literature [5-7]. The adenomyotic glands were of basal type in all the cases.

The coexistence of adenomyosis and leiomyomas in our material is even higher (63.7%) with the development of adenomyomas in 17 cases. In 39 cases showing adenomyosis, both hyperplastic changes of endometrial mucosa and leiomyomas were observed.

The presence of a common pathogenetic mechanism, probably hormonal, in the development of leiomyomas, endometrial adenocarcinoma and hyperplasia or hyperplastic polyps is strongly suggested by clinical and experimental observations [5, 7, 16]. Recent studies indicate that there is a relationship between unopposed estrogen use and tamoxifen use and development of adenomyosis and uterine carcinogenesis [16].

Finally, in our study the presence of progesterone receptors in the glandular cells of the adenomyosis foci is in accordance with the clinicopathological observations concerning the response of adenomyosis and endometriosis to progestin treatment.

In conclusion, the high incidence of adenomyosis in uteri harboring other hormone-dependent lesions suggests that this lesion shares a common pathogenetic factor with the above-mentioned lesions.

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