Case 7

Atypical polypoid adenomyoma with coexistent well-differentiated endometroid adenocarcinoma

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Clinical History

A 28-year old nulliparous patient with a clinical diagnosis of prolonged abnormal uterine bleeding underwent dilatation and explorative curettage procedure. Subsequently, a month after the initial diagnosis there were no abnormal findings on ultrasonography, while in the endometrial biopsy material taken during hysteroscopy only a few fragments of disordered endometrium were found. Due to the patient`s age the fertility preservation and reproduction was an issue; therefore, a conservative treatment (6-month high-dose gestagen therapy) and a close follow-up with repeated ultrasound and hysteroscopic monitoring were recommended. In addition, a cone biopsy was done three months after the first dilatation and curettage (D&C) procedure and subsequent biopsy. For 11 years, the patient was carefully followed up with semi-annual ultrasonography and cytological examinations. She is well and disease-free, being treated for infertility in the last 8 years with one unsuccessful pregnancy three years ago.

Pathological Findings

The material obtained by explorative curettage was abundant. Microscopical examination revealed several larger fragments of tissue measuring 0.3-1.2 cm in largest diameter containing numerous groups of tightly packed atypical endometrial glands intersected by septa of myofibromatous stroma. The glands exhibited severe architectural complexity with focal cribriform pattern and squamous metaplasia with central necrosis. Glandular cells showed varying degrees of nuclear atypia (from mild to severe) and prominent nucleoli. Mitosis were easily found. The microscopic appearance resembled atypical (complex) hyperplasia and in one focus measuring 3 mm in diameter, well-differentiated endometroid adenocarcinoma. By immunohistochemistry, most of the stromal cells showed strong immunostaining for alpha-smooth muscle actin, and vimentin, while some cells were desmin or CD34 positive. The tumor was hormone responsive, whereas Ki-67 proliferative index was 20-25% in the foci of atypical hyperplasia with severe atypia and well-differentiated endometroid adenocarcinoma. The majority fragments of uninvolved endometrium showed a disordered proliferative pattern with small areas of non-atypical or more frequently atypical hyperplasia with mild, moderate to severe cytological atypia. In addition, two small fragments of squamous epithelium of the uterine cervix having a morphology of high-grade squamous intraepithelial lesion (CIN2) were identified.

Diagnosis: ***Atypical polypoid adenomyoma (APA) with coexistent well-differentiated endometroid adenocarcinoma***

Discussion

Atypical polypoid adenomyoma (APA) is a polypoid lesion belonging to the mixed epithelial and mesenchymal tumors of the uterus. This unusual biphasic Müllerian uterine tumor was initially reported by Mazur in 1981. Most of these tumors occur in women in reproductive age (mean, 40 years; range 23-73), yet occasional tumors may occur in postmenopausal women. It may be associated with obesity, infertility, and nulliparity. Rare cases are associated with long-term unopposed estrogen therapy. Thus, Clement et al. reported three cases of atypical polypoid adenomyoma associated with Turner syndrome who have been prescribed unopposed estrogens. Some recent studies report that these tumors may be associated with MLH-1 promoter hypermethylation (approximately 40%) and microsatellite instability, as seen in complex atypical hyperplasia and endometroid adenocarcinoma.

The patients typically present with abnormal vaginal bleeding. Pelvic examination is usually negative, and in some cases, a polypoid mass may protrude from the external os of the uterine cervix.

These tumors frequently involve the uterine corpus or the lower uterine segment, and may also arise in the cervix. In most cases, the lesion has an obvious polypoid gross appearance, in a form of either solitary or rarely multiple, well circumscribed, pedunculated or broad-based polyp, ranging in size from 0.1 to 6 cm, with a mean diameter of 2 cm in greatest dimension. The sectioned surfaces are yellow-tan to grey and white, solid and firm or rubbery.

Microscopically, on low power view, most lesions have vaguely lobulated growth pattern, while the margin between the APA and the surrounding myometrium is rounded and well delineated in most cases, although in some occasions may show extensions into the superficial myometrium. The epithelial component has endometrioid glands with varying degrees of architectural and cytological atypia separated by myofibromatous stroma. The glands may be closely packed or widely spaced. There is often prominent squamous metaplasia in a form of squamous morules, which may show areas of central necrosis. Rare findings include cribriform pattern and ciliated and mucinous metaplasia. Most APAs show mild to moderate cytological atypia of the glandular component. Rarely severe atypia, or even foci with complex glandular architecture and severe cytological atypia resembling well-differentiated adenocarcinoma, may be seen. Some APAs are contiguous to or appear to be the origin of a well-differentiated adenocarcinoma. The stromal component contains in most cases interlacing bundles of cellular smooth muscle, proliferating myofibroblasts, or both. The study of Longacre et al. has shown that some APAs may contain areas of sclerotic or cellular fibrous tissue, but no case contains pure smooth muscle or fibrous tissue only. The stromal cells exhibit mild to moderate atypicality in a minority of cases. Occasional mitotic figures are usually seen, but they do not exceed 2-3 per 10 high-power fields as an average count and no atypical mitosis are found. The stroma does not condensate around the glands. There may be stromal calcification, chronic inflammatory cells and foreign body giant cell reaction to keratin. According to Longacre et al. APAs are typically noninvasive, with a well-circumscribed border in hysterectomy specimens, although rarely some of these tumors associated with foci resembling well-differentiated adenocarcinoma superficially invaded the myometrium.

By immunohistochemistry, the mesenchymal cells typically stain for smooth muscle actin, and frequently for desmin and other smooth muscle markers. They also may show some degree of positivity for CD34. The epithelial component is positive for cytokeratin (AE1/AE3 and CAM5.2), as well as hormone (estrogen and progesterone) receptor positive. The cells in squamous morular areas show strongly positive membranous CD10 and also nuclear beta-catenin staining.

The histological differential diagnosis includes endometrial adenocarcinoma, typical adenomyoma of the endometroid type, Müllerian adenosarcoma, and carcinosarcoma. Distinction from endometrial adenocarcinoma may be particularly difficult on dilatation and curettage (D&C) material when the whole lesion is not available. Nevertheless, it is unusual for the endometrial adenocarcinoma invading in the myometrium to be demonstrated in the D&C material. Furthermore, the orderly pattern of the smooth muscle or myofibromatous component of APA contrasts with the finding of desmoplastic stroma characteristically associated with endometrial adenocarcinoma. In addition, the young age of most the patients and the typical lower uterine segment location of APA often suggest the correct diagnosis. A typical adenomyoma of the endometroid type is more frequently encountered in the uterine corpus. In contrast to the APA these tumors have a rim of endometrial stroma between the glands and the smooth muscle, the glandular component is less abundant and it does not show cytological atypia or architectural complexity. Mülerian adenosarcoma may show prominent smooth muscle metaplasia; however it is characterized by the phyllodes-type architecture and neoplastic endometrial-type stroma frequently cuffing the glands. Carcinosarcoma is usually diagnosed in postmenopausal women and is composed of high-grade malignant epithelial and mesenchymal component.

Most of these tumors have an excellent prognosis. The treatment may consist of curettage or excision, with follow-up, or simple hysterectomy. In the study of Longacre et al. there was a recurrence index of 45% in patients treated conservatively and those treated in this manner rarely may progress to adenocarcinoma. APAs with foci resembling well-differentiated adenocarcinomas have higher recurrence rate (60% versus 33%), and for that reason, they have been designated by Longacre et al. as "atypical polypoid adenomyoma of low malignant potential". Nevertheless, nowadays this term is not recommended, and these foci which are virtually indistinguishable from should be best regarded as well-differentiated endometroid adenocarcinoma. These lesions may have locally aggressive, but not malignant behavior. If the lesion has only been curetted, it is important to search for endometrial hyperplasia in areas not involved by APA, which is not infrequent finding. In addition, there is about 10% risk of endometrial adenocarcinoma in women with APA, which is considerably higher than the overall risk of less than 1% in women with endometrial polyps.

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