Estrogen receptor expression in an endometrial stromal sarcoma after tamoxifen therapy

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Summary

Introduction: Several cases of low-grade endometrial stromal sarcomas in women with breast cancer have been reported to be associated with tamoxifen therapy. Estrogen receptor expression has been used to characterize the partial estrogenic action of tamoxifen on the endometrium and has been found in tamoxifen-associated endometrial pathologies.

Case: A low-grade endometrial stromal sarcoma in a woman with a history of breast cancer treated with adjuvant tamoxifen is presented. Steroid receptor studies performed on the tumor were negative for estrogen and positive for progesterone.

Conclusion: The absence of estrogen receptor expression suggests that endometrial stromal sarcomas are not necessarily caused by the estrogenic properties of tamoxifen.

Key words: Endometrial stromal sarcoma; Tamoxifen; Estrogen receptor.

Introduction

Tamoxifen is one of the most widely prescribed treatments for breast cancers which have positive steroid receptors. Studies of women with breast cancer using tamoxifen have suggested increased risks of uterine malignancy. Investigation into the effects of tamoxifen on the endometrial glands and stroma have focused on the expression of estrogen receptors (ER) and progesterone receptors (PR) based on the belief that tamoxifen exerts a partial estrogenic effect on endometrial cells [1-4]. Endometrial adenocarcinomas are the most common uterine malignancy associated with tamoxifen therapy [5], but an increasing number of case reports and case series have emerged in the literature linking endometrial stromal sarcomas as well [6-11]. This report details a case of low-grade endometrial stromal sarcoma that demonstrated negative estrogen receptor expression in a woman who had been receiving tamoxifen therapy for breast cancer.

Case Report

A 40-year-old, G0P0, African-American woman was evaluated for menometrorrhagia. She had a history of a segmental mastectomy and axillary lymphadenectomy for a T1N0M0 breast carcinoma five years previously. Her breast tumor was positive for both estrogen and progesterone receptors and she received cyclophosphamide-methotrexate-5fluorouracil chemotherapy for six cycles. She was subsequently treated with tamoxifen, 10 mg twice a day, for the next five years.

While on tamoxifen the patient was not seen by a gynecologist. She had had a pelvic ultrasound 18 months prior to evaluation which demonstrated an enlarged and irregularly-shaped uterus measuring 14.8 x 9.0 x 8.0 cm suggestive of leiomyomata with normal adnexae and an unremarkable endometrial stripe. One month prior to evaluation the patient completed her final dose of tamoxifen. She then experienced a three-week menses with very heavy flow followed by a second episode of bleeding one week later. Except for a moderate degree of dysmenorrhea, the patient was otherwise asymptomatic. She did not have any other significant medical history and did not have any other family members with cancer.

Physical examination revealed a normal cervix with an enlarged uterus extending cephalad to the level of the umbilicus. A Papanicolau smear and an endometrial biopsy were performed and the uterus was sounded to 10 cm.

Histologic examination of the biopsy from the endometrium demonstrated endometrial polyps and tubal metaplastic changes of the endometrium. As the patient continued to experience menometrorrhagia, she elected to undergo an abdominal hysterectomy and bilateral salpingo-oophorectomy. Intraoperatively, the patient was noted to have grossly normal appearing ovaries and fallopian tubes and an enlarged, irregularly-shaped uterus. She had an unremarkable postoperative course and was discharged home after three days.

The uterus was enlarged, measuring 14.5x15x11.5 cm and weighing 800 g. The endometrial cavity contained multiple polyps and areas of simple hyperplasia without nuclear atypia. There were several lesions with increased cellularity within the endometrial stroma that were mildly atypical as well. These lesions superficially invaded portions of the myometrium and had infrequent mitotic figures, one per ten high power fields, and were consistent with a low-grade endometrial stromal sarcoma with extensive smooth muscle metaplasia. The areas involved by the endometrial stromal sarcoma were analyzed for estrogen and progesterone receptors using immunohistochemical staining of paraffin sections for the presence of receptors using monoclonal antibodies. Measurement of these receptor studies done in our laboratory is reported in a semi-quantitative fashion, with a negative report defined as weakly staining less than five percent of the specimen. These studies were negative for ER and positive for PR. Studies on the adjacent benign endometrial glands and stroma were positive for both receptors.

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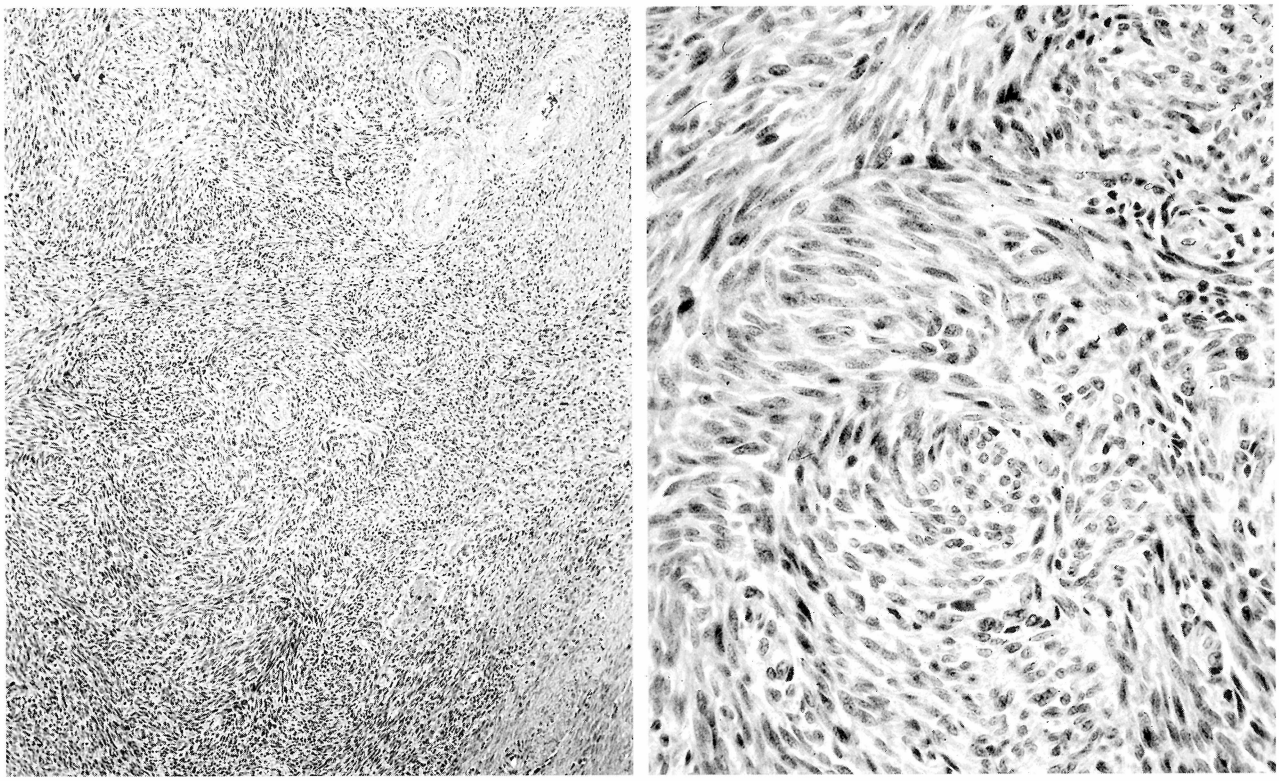

Figure 1. — Low-grade endometrial stromal sarcoma viewed under 120x and 300x magnification.

Discussion

The measurement of estrogen receptor content in endometrial stromal sarcomas has been characterized using immunohistochemical techniques. Tosi and colleagues reported seven cases of endometrial stromal sarcomas characterized in this way [12]. In that case series, five of the seven cases contained estrogen receptors. The two negative cases were high-grade and contained a very high number of mitotic figures per high-power field. This led the authors to postulate that estrogen receptors are undetectable only in highly proliferative neoplasms of this type.

There have been six prior reported cases of endometrial stromal sarcoma associated with tamoxifen therapy in both postmenopausal and premenopausal women [6-10]. None of these cases have reported the results of receptor studies for either estrogen or progesterone. Estrogen and progesterone receptors were recently analyzed by Bergman and colleagues in a nationwide case control study of a group that included malignant mixed mesodermal tumors and sarcomas after tamoxifen therapy [11]. That study concluded that-long term tamoxifen use increases the risk of developing both these types of tumors and also increases the risk of developing estrogen-receptor negative tumors overall. And perhaps as a consequence of this, tumors that were negative for estrogen receptors were more often malignant mixed mesodermal tumors or endometrial sarcomas. The authors did not specifically address the receptor status of individual tumor types or the tumor grade of the sarcomas [11].

Tamoxifen is believed to have a partial estrogenic effect on endometrial cells, which may explain its association with increased risk of developing endometrial carcinomas [3], although the exact mechanism is not completely understood. This effect has been measured in a number of studies through the use of immunohistochemical staining characterization of estrogen and progesterone receptor expression in endometrium treated with tamoxifen [1-4]. All four cases of endometrial adenocarcinomas described by Kommoss exhibited positive receptor expression of both ER and PR. Examination of endometria from tamoxifen-treated premenopausal and postmenopausal breast cancer patients have demonstrated expression of both ER and PR in both the glands and stroma, which is consistent with our findings in this case in the areas of benign endometrial glands and stroma [2]. Hachisuga's studies of PR and ER expression levels in the normal endometrial stroma did not demonstrate any significant differences with tamoxifen therapy over the untreated groups.

A significantly decreased level of ER expression has been reported in the stroma of endometrial polyps in the presence of tamoxifen therapy [4]. Schwartz has postulated that this down-regulation of stromal cell estrogen receptors may represent a unique effect of tamoxifen on the stroma [4]. The absence of estrogen-receptor expression in the low-grade tumor described in this case report supports this notion of a unique effect of tamoxifen on the stroma. In light of our current understanding of the mechanism of tamoxifen action on the endometrium, our

findings suggest that tamoxifen may not necessarily cause the development of low-grade endometrial stromal sarcomas through its partial estrogenic effect.

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