

# SECRETORY ENDOMETRIAL ADENOCARCINOMA IN A TAMOXIFEN USER WITH BREAST CANCER AFTER MENOPAUSE

Chia-Jen Wu, Yi-Jen Peng<sup>1</sup>, Mu-Hsien Yu, Chi-Huang Chen\*

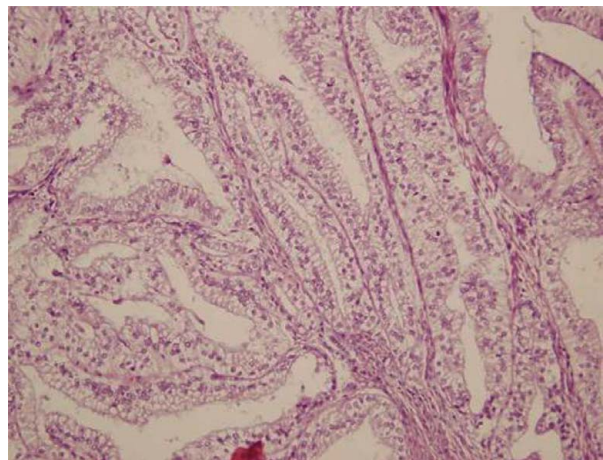
Department of Obstetrics and Gynecology, and <sup>1</sup>Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Tamoxifen has been used to treat patients in all stages of breast cancer. However, the drawback of its estrogen-mimicking effects on endometrium raises the risk of endometrial cancer for chronic users as it has been shown to stimulate growth of some endometrial adenocarcinoma cell lines by estrogen receptor-independent mechanisms *in vitro* [3]. For long-term Tamoxifen use for breast cancer patients, development of secretory endometrial adenocarcinoma without estrogen receptors occurs rarely. According to the keyword searches for “secretory endometrial adenocarcinoma,” “Tamoxifen,” and “breast cancer” on MEDLINE of the reports in English language between 1970s and the end of 2005, our case is the second one to describe secretory endometrial adenocarcinoma associated with Tamoxifen use for breast cancer.

A 71-year-old woman, multigravida, complained of postmenopausal vaginal bleeding for 2 to 3 months. She had undergone right mastectomy for stage II breast cancer 15 years prior to this admission. Thereafter, she had received chemotherapy and had been taking oral 10 mg Tamoxifen twice a day for 10 years. Current medical diseases include hypertension and diabetes mellitus for 10 years and 2 months, respectively. She denied any history of estrogen replacement therapy after menopause at the age of 50 years.

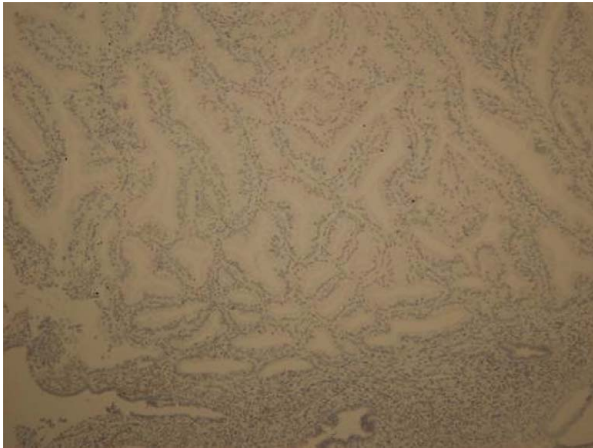
Under vaginal echography, unusual endometrial contour was detected as thick as 21 mm. Her pelvic examination results revealed no senile changes but a large uterus as if in 3-months' gestation. Coupled with atypical glandular cells on her Papanicolaou smear, fractional

endometrial dilatation and curettage (D&C) revealed endometrial carcinoma with secretory changes. She underwent staging laparotomy including total hysterectomy, bilateral salpingoophorectomy, partial omentectomy, sampling of pelvic and paraaortic lymph nodes, and peritoneal cytology. Grossly, the uterus showed no apparent myometrial invasion or generalized thickness of endometrium with multiple polypoid lesions. On paraffin sections, the tumor measured 1 cm at the greatest dimension and was estimated at only 5 mm downward invasion into the 3-cm thick myometrium. The histological morphology revealed a well-differentiated adenocarcinoma with dominant papillary and glandular patterns, consisting of columnar epithelial cells and containing intracytoplasmic basal vacuoles (Figure 1), which was similar to secretory endometrium arising from atypical complex secretory hyperplasia. Using immunohistochemical stains, we found exclusively strong positive results for progesterone receptors,

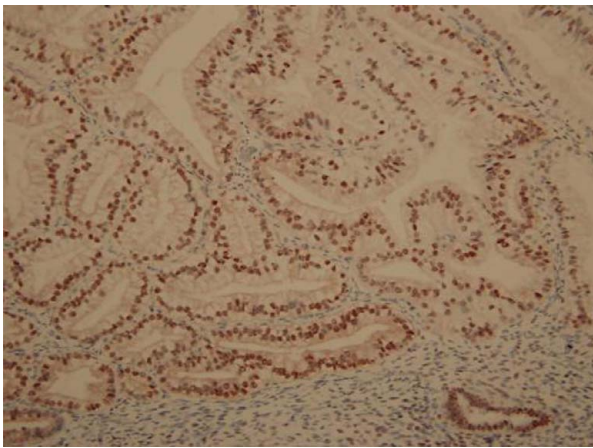


**Figure 1.** Secretory endometrial adenocarcinoma showing a well-differentiated papillary pattern, comprising columnar epithelial cells with intracytoplasmic basal vacuoles, similar to the secretory phase of endometrium (hematoxylin and eosin, 100×).

\*Correspondence to: Dr Chi-Huang Chen, Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, 325, Cheng-Kung Road, Section 2, Neihu, Taipei 114, Taiwan.  
E-mail: baloh.tw@yahoo.com.tw  
Accepted: December 6, 2006



**Figure 2.** Immunohistochemical stain for estrogen receptor: negative nuclear staining for tumor and normal glands (40 $\times$ ).



**Figure 3.** Immunohistochemical stain for progesterone receptor: positive nuclear staining for tumor cells, normal glands, and some endometrial stromal cells (40 $\times$ ).

but the results were negative for estrogen receptors (Figures 2 and 3).

Secretory adenocarcinoma is an uncommon variant of endometrioid adenocarcinoma which usually presents as a well-differentiated tumor with progesterone changes and it is difficult to differentiate it from secretory endometrium [1]. The histological pattern comprises well-differentiated glands resembling those of early or midsecretory endometrium. Subnuclear and/or supranuclear vacuolation is also commonly seen. There is minimal cellular atypia, stratification, and pleomorphism. The intracellular secretions are not mucin but glycogen. The glands are positive with periodic acid-Schiff (whether predigested or not); they are partly positive using alcian blue and negative using Best Carmine. The cellular features of secretory carcinoma differentiate it from clear-cell carcinoma, which is more papillary with more pleomorphic nuclei. Because of its lack of mucin,

it may be differentiated from mucinous carcinoma [2]. Confused identification may occur in patients with history of recent ovulation or progestin use before tissue sampling in what would have otherwise been atypical hyperplasia or well-differentiated endometrioid carcinoma. A thorough clinical history should be provided to the pathologist to avoid confusion even though the prognosis is good for patients with secretory adenocarcinoma.

As a well-known risk factor of endometrial cancer for Tamoxifen users, a median Tamoxifen cumulative dose of 29 g has been suggested as a threshold for the development of endometrial carcinoma. The risk of endometrial cancer increases two- to three-fold after an exposure of up to 5 years. In our case, the total cumulative dose was 73 g and the use was up to 10 years in addition to other risk factors such as hypertension and diabetes mellitus.

Tamoxifen is the most widely prescribed antineoplastic drug for the treatment of both localized and metastatic breast cancer. It is the prototype for a class of drugs that are referred to as selective estrogen receptor modifiers, most of which have both estrogenic and antiestrogenic effects on the female genital tract, depending on the ambient estradiol concentration and the menopausal status of the patient. It has been proposed that Tamoxifen has an estrogen agonistic effect on the vaginal epithelium, the uterine myometrium, and the endometrium in postmenopausal women. This may induce benign cystic hyperplasia of the endometrial stroma and cause an increased polyp formation [3]. The proposed estrogenic effects of Tamoxifen include prognostically favorable, highly differentiated, endometrioid carcinomas, compatible with Bochman Type I.

The genetic predisposition toward endometrial carcinoma and endometrial carcinogenesis by Tamoxifen users is not well known. In recent years, the molecular genetic alterations associated with Type I endometrial carcinomas, including mutations in PTEN, K-ras, and the presence of microsatellite instability, have been elucidated. These distinct mutations segregated by histological subtypes rather than Tamoxifen exposure, and Tamoxifen may only act as initiators of tumorigenesis via estrogen agonistic activity in the endometrium [4]. However, it is interesting that the endometrial carcinoma was negative for estrogen receptors and exclusively positive for progesterone receptors in this described case. The results of a few studies have suggested that Tamoxifen caused a net increase in the progesterone receptors and sex hormones-binding globulin, and a significant decrease in the estrogen receptors [5]. Therefore, it is possible that the progestational changes

are related to the use of Tamoxifen, which prompts us to postulate that the mechanisms of Tamoxifen activity that promote endometrial carcinogenesis are independent of its action as an estrogen agonistic. So a more complete understanding of the steroid receptor status, somatic alterations in oncogenes, and tumor suppressor genes and inherited susceptibility in endometrial carcinomas associated with Tamoxifen use is required.

Although the pathogenesis of the striking progestational changes in the secretory endometrial adenocarcinoma encountered in this patient remains unclear, this unusual case was added to the spectrum of Tamoxifen-associated endometrial carcinomas. It is necessary to evaluate the stage of pathological changes on the myometrium and endometrium, both before and during the period of administration of Tamoxifen. In asymptomatic Tamoxifen users, gynecologic surveillance may not be recommended but transvaginal ultrasonography

and fractional D&C are indicated in cases of postmenopausal vaginal bleeding.

## References

1. Folk JJ, Mazur MT, Eddy GL, Musa AG. Secretory endometrial adenocarcinoma in a patient on tamoxifen for breast cancer: a report of a case. *Gynecol Oncol* 1995;58:133–5.
2. Tobon H, Watkins GJ. Secretory adenocarcinoma of the endometrium. *Int J Gynecol Pathol* 1985;4:328–35.
3. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. *Gynecol Oncol* 2004;94:256–66.
4. Prasad M, Wang H, Douglas W, Barakat RR, Ellenson LH. Molecular genetic characterization of tamoxifen-associated endometrial cancer. *Gynecol Oncol* 2005;96:25–31.
5. Nola M, Jukic S, Ilic-Forko J, et al. Effects of tamoxifen on steroid hormone receptors and hormone concentration and the results of DNA analysis by flow cytometry in endometrial carcinoma. *Gynecol Oncol* 1999;72:331–6.