Chief Complaint

Marie is a 64-year-old woman with a history of estrogen receptor-positive breast cancer. She has been taking tamoxifen for four years, and her chief complaint is new vaginal bleeding. What are the diagnostic possibilities, and how would you work her up?

Discussion

Tamoxifen therapy in women with breast cancer clearly has been shown to reduce the development of both recurrent and new contralateral cancers. Tamoxifen acts as an antiestrogen in breast tissue by blocking the estrogen receptor and preventing cell growth. A compilation of data from published trials indicates that adjuvant tamoxifen therapy reduces the incidence of contralateral breast cancers by 40% and recurrence by 25% (“Systemic Treatment of Early Breast Cancer,” 1992). This effect was observed in women with estrogen receptor-positive tumors and was significant enough to justify trials using tamoxifen therapy to prevent breast cancer in high-risk women (Dunn & Ford, 2001). Consequently, millions of women are taking tamoxifen for either the treatment or prevention of breast cancer.

Fornander et al. (1989) provided early evidence that tamoxifen is a causal agent in the development of endometrial cancer, where it has weak estrogenic properties. This study found a 6.4-fold increase in the relative risk of developing endometrial cancer in a group of postmenopausal women with early breast cancer who were treated with adjuvant tamoxifen. The greatest risk occurred after five years in women who received 40 mg per day of tamoxifen. Fisher et al. (1994) confirmed these findings when they reported the results of the National Surgical Adjuvant Breast and Bowel Project B-14 trial involving receptor-positive, node-negative postmenopausal patients with breast cancer. Twenty-three cases of endometrial cancer were found in women who received 20 mg per day of tamoxifen, compared with two cases in placebo-treated women. Calculated rates for developing endometrial cancer were two to three times greater than those of the general population. The risk of developing endometrial cancer is dose and time dependent, with higher cumulative doses and exposures producing a greater relative risk. However, the beneficial effect of tamoxifen for breast cancer prevention far exceeded the relative risk for developing endometrial cancer.

Primary Diagnostic Possibility: Endometrial Cancer

Because the presenting sign of endometrial cancer is new vaginal bleeding and a history of tamoxifen use is considered to be a risk factor, the advanced practice nurse should consider this to be the primary possible diagnosis. Endometrial cancer is the most common gynecologic cancer in the United States. In 2004, Jemal et al. estimated 40,320 new cases of the disease and 7,090 deaths as a result of endometrial cancer. Most cases of endometrial cancer are diagnosed at an early, favorable stage when cure rates are high. Abnormal bleeding is the most common early symptom of the disease. Most endometrial cancers are associated with unopposed estrogenic stimulation of either endogenous or exogenous origin (Barakat, 1998). Obesity is a major risk factor, especially for women more than 50 pounds overweight, because obese women have chronic levels of circulating estrone produced by the aromatization of androstenedione in adipose tissue. Other estrogen-related risk factors include nulliparity, late menopause (after age 55), and unopposed oral estrogen intake. The relative risks for these factors range from 2–10 times more than in the general population. The magnitude of the tamoxifen-associated risk falls within the lower limits of these risk profiles. In standard doses, tamoxifen may be associated with endometrial proliferation, hyperplasia, polyp formation, and invasive cancer (Committee on Gynecologic Practice, the American College of Obstetricians and Gynecologists, 2001), all of which produce a thickening of the uterine lining. Lahhi et al. (1993) and Exacoustos et al. (1995) found that women who had received tamoxifen had a thicker endometrium and a higher incidence of endometrial polyps when compared with women who had not received the drug.

Which tests should be ordered for this patient?

Routine screening tests, including transvaginal ultrasound and endometrial biopsy, have been used to triage asymptomatic
women taking tamoxifen. Transvaginal ultrasound evaluates the endometrial cavity and measures the thickness of the endometrial lining. Some have used ultrasonography to determine which women would benefit from endometrial sampling based on endometrial thickening. Tabor, Watt, and Wald (2002) performed a meta-analysis of nine studies with a total of 330 women diagnosed with endometrial cancer and 3,483 women without the disease. None of the women used tamoxifen. The overall median endometrial thickness in women with endometrial cancer was 3.7 times greater than in unaffected women. However, Tabor et al. could not identify a cutoff value for endometrial thickness that did not have unacceptably high false negative or false positive rates.

Bertelli et al. (1998) examined 164 asymptomatic patients with breast cancer using transvaginal ultrasound and endometrial biopsy. One hundred and ten women treated with tamoxifen were compared to 54 women in a control group. The tamoxifen-treated women had a thinner endometrium; however, biopsies of 124 women (85 tamoxifen users, 39 controls) revealed only two cases of endometrial hyperplasia. No endometrial cancers were detected. Ultrasound findings did not correlate with significant endometrial pathology. Other studies reported similar findings (Exacoustos et al., 1995; Lahti et al., 1993). The routine use of endometrial biopsy in these studies of asymptomatic tamoxifen users failed to identify occult cancers.

In addition to stimulation of the endometrium, tamoxifen causes changes in blood flow and morphology of the subepithelial stroma. These benign proliferative effects occur at the endometrial and myometrial junction and are visible as nodular thickenings on ultrasonographic examination. These changes can be confused with those typically associated with neoplasia and provide an explanation for some of the false-positive sonographic studies (Achiron et al., 1995). Love et al. (1999) performed transvaginal ultrasounds on 357 asymptomatic patients with breast cancer who received tamoxifen. Although endometrial thickening was seen in 145 women (41%), 61 of those women had atrophic endometrium at hysteroscopy. No significant lesions were detected in any of the women.

In most clinical settings, office endometrial biopsies provide equivalent diagnostic samples to those obtained from hysteroscopy with dilatation and curettage because changes within the lining of the endometrium are uniform (Chambers & Chambers, 1992). Endometrial changes associated with tamoxifen may be heterogeneous, with focal hyperplastic lesions arising in a background of atrophy (Cohen et al., 1997). These differential effects and the presence of subepithelial stroma change make office biopsy a less accurate sampling technique.

In this setting, the visualization provided by hysteroscopy allows for a targeted biopsy and increased diagnostic accuracy.

For asymptomatic women, routine screening by endometrial biopsy, transvaginal ultrasound, or both has been ineffective in detecting endometrial cancer and therefore is not recommended (Committee on Gynecologic Practice, the American College of Obstetricians and Gynecologists, 2001; Smith et al., 2001). All women who receive tamoxifen should be educated about their increased risk for endometrial cancer and encouraged to report abnormal vaginal bleeding, spotting, or rust-colored vaginal discharge promptly. In addition, all women should be questioned about these symptoms during regular clinic visits and have an annual gynecologic examination and Papanicolaou smear. Tamoxifen-associated endometrial cancer risk is dose and time dependent. The current recommended regimen for adjuvant tamoxifen is 20 mg per day for five years. No benefit has been documented for tamoxifen use beyond five years.

Tamoxifen-associated cancers typically have the same stage, grade, and histology as those that occur in the general population (Barakat, Wong, Curtin, Vlamis, & Hoskins, 1994).

Because most women who develop endometrial cancer initially present with abnormal bleeding, most cancers are diagnosed at an early stage. For symptomatic women, histologic tissue evaluation of the endometrium is mandatory. Therefore, all women who present with any sign of abnormal vaginal bleeding or discharge should undergo an endometrial biopsy. Patients who have persistent symptoms after a negative biopsy should undergo endometrial sampling using hysteroscopic guidance. Ultimately, identification and testing of selective estrogen receptor modulators without a stimulatory effect on endometrial biopsy a less accurate sampling technique. Ultimately, identification and testing of selective estrogen receptor modulators without a stimulatory effect on endometrial biopsy a less accurate sampling technique.

What are the major teaching points for women receiving tamoxifen?

- Endometrial cancers usually are diagnosed at an early stage.
- Tamoxifen slightly increases endometrial cancer risk.
- Women who receive tamoxifen should report any episode of abnormal vaginal bleeding, spotting, or rust-colored discharge to their healthcare providers.
- Routine screening for endometrial cancer is not recommended for asymptomatic women.

- All women presenting with abnormal vaginal bleeding or discharge should have an endometrial biopsy. Endometrial sampling under hysteroscopic guidance may be required to evaluate persistent symptoms after a negative biopsy.

References


