Case Reports

Simultaneous diagnosis and treatment of bilateral breast carcinoma and endometrial adenocarcinoma. Implications for screening

I. Dedes[1], *M.D., DFFP*; **V. Ziogas**[2], *M.D., Ph.D.*

[1]*Consultant Obstetrician and Gynaecologist, "Iaso" Women's Hospital, Marousi;*
[2]*Consultant Obstetrician and Gynaecologist, "Iaso" Women's Hospital, Marousi (Greece), and Lecturer at Zurich University (Switzerland)*

Summary

The association of breast and endometrial carcinoma has been demonstrated by many studies. Most of the cases are related to the previous use of tamoxifen for the treatment of breast carcinoma. However, triple primary malignancies on the same individual are very rare. This is an unusual case regarding simultaneous diagnosis and treatment of bilateral breast carcinoma and endometrial adenocarcinoma. The clinical aspects and treatment of this unique case are presented.

Key words: Endometrial carcinoma; Breast carcinoma; Triple primary malignancies.

Introduction

The mean age of patients with endometrial cancer is 61 years, with 75%-80% of women being postmenopausal and 3-5% being less than 40 years old [1]. The incidence of endometrial cancer varies widely, the lowest rates being in Asian populations and the highest among the North American whites. It is noteworthy, however, that when Asian populations migrate to the USA the rates rise very markedly to approach those seen in the local white population [2]. The aetiology of endometrial cancer is unknown but several factors are known to increase or decrease the likelihood of its development. The main risk factors identified for endometrial cancer relate to hormonal status and reproductive history. Obesity, nulliparity, late menopause, polycystic ovary syndrome, unopposed oestrogen therapy, functioning ovarian tumors, personal or family history of breast or colon carcinoma and also tamoxifen therapy for breast cancer increase the incidence for endometrial cancer [3]. In contrast, a decrease in risk for endometrial cancer has been observed both for cigarette smokers and for users of the combined oral contraceptive pill [1].

Breast cancer is the most common malignancy affecting women in North America and in most European countries. It is the commonest single cause of all deaths in women aged 35-55 years, but is most commonly seen in women between 55 and 85. There is no single identifiable factor or group of factors which can identify the majority of women who will develop breast cancer [4]. The practitioner must recognise that only 12% of breast cancer patients have an identifiable risk factor. In 88% of female patients no risk factor can be pointed out, indicating that all women should be considered at risk, which will enhance the thoroughness of the examination and the history. The most recognisable epidemiologic risk factors are breast cancer in a first degree relative or cancer in the opposite breast, or women who have undergone prolonged exposure to endogenous oestrogens such us early menarche, late menopause, nulliparity, and obesity. The incidence of breast malignancy in the controlateral breast is approximately 1% annually. If there is a family history of breast cancer, the risk is increased by two or three times and can be as high as nine times when there has been bilateral pre-menopausal breast cancer in the relatives [5]. Women with endometrial cancer are at higher risk of developing breast cancer. They should be offered mammography and taught self-palpation [1].

Occurrence of multiple primary cancers is a rare phenomenon. We describe an unusual case regarding simultaneous diagnosis and treatment of three primary malignancies on the same individual that, to our knowledge, has never been reported.

Case Report

A 68-year-old female patient presented at the gynaecology clinic complaining of postmenopausal bleeding. Her medical history was unremarkable. She was a non smoker and had a body mass index within the normal range. She had been postmenopausal since the age of 50. She had delivered vaginally two daughters, unfortunately one died at a young age because of leukaemia. Transvaginal ultrasound examination revealed atrophic ovaries and uterus, and a thick 11 mm endometrium. On the left breast, a suspicious mass was palpated on the upper inner segment and the right breast appeared normal. The patient was fully informed about the need to investigate the bleeding and the clinical breast findings. Therefore dilatation and curettage of the uterus and mammography of the breasts were carried out urgently. Two weeks later, histology of the sharp curettage of the uterus revealed a moderately differentiated endometroid adenocarcinoma (grade 2) expanding from the base of a hyperplastic endometrial polyp. On mammography, a mass with

Revised manuscript accepted for publication December 3, 2007

microcalifications appeared on the inner upper quadrant of the left breast and also a suspicious mass on the outer upper right breast. The patient was fully counselled and consented to proceed to total abdominal hysterectomy and bilateral salpingo-oophorectomy including pelvic lymph node sampling, and also bilateral breast lump excision and bilateral axilla lymph node sampling contemporaneously. The patient opted for radiotherapy if it was possible to keep her breasts.

Admission followed one week later. Preoperative assessment tests were all normal, including a full blood count, urea, glucose, blood group and crossmatch, clotting screen, hepatitis B status, CA 15-3, urinalysis, electrocardiogram and cardiology examination, chest X ray, technetium bone scan, and finally upper and lower abdominal computed tomography scan. Total abdominal hysterectomy and bilateral salpingo-oophorectomy, including peritoneal washings, right-sided external and common iliac as well as left external iliac lymph node sampling were uneventful. The operation then continued with wide excision of the bilateral tumors of the breasts, which were both positive for malignancy at urgent biopsy. Therefore, lymph node sampling of both axillae was carried out. The operation lasted for more than four hours. All specimens were sent for histological and histochemical examination. The histology of the left breast tumor was a poorly differentiated ductal invasive adenocarcinoma, with the margins free of disease and metastasis in two axillary lymph nodes out of the 21 excised. The hormonal receptors of the left-sided tumor were negative for oestrogen receptors (ER), negative for progesterone receptors (PR), p53 positive, EGFR positive, Ki67: 90%, HercepTest: +1 (negative). The tumor on the right breast was a moderately differentiated ductal invasive adenocarcinoma with margins free of disease. The 12 right-sided axillary lymph nodes excised were normal. The hormonal receptors of the right-sided tumor were positive for ER, positive for PR, p53 positive, EGFR negative, Ki67: 35%, HercepTest: +1 (negative). At histology the uterus appeared to have no further neoplastic disease and apparently the curettage contributed to that. Both ovaries, iliac lymph node biopsies and peritoneal washing cytology were also normal.

The patient received six cycles of adjuvant chemotherapy with epirubicin (100 mg), cyclophosphamide (800 mg) and 5 flurouracil (800 mg) and subsequently she would undergo radiotherapy.

Discussion

The occurrence of uterine carcinoma and breast carcinoma in the same patient is a very rare incidence. The following described studies include patients with breast carcinoma who subsequently developed endometrial carcinoma. Ewertz *et al.* [6] reported that among 51,638 women diagnosed with primary breast cancer in Denmark between 1943-1977, 115 cases of endometrial cancer were identified after more than three months and confirmed histologically. The study indicates that breast and endometrial cancer share several common aetiologic factors and that studies of second primary cancers have the potential to provide information on the risk factors other than those associated with therapy.

The association between cancers of the breast, endometrium and ovary was reviewed by Ewertz and Storm [7] in another study. Breast cancer patients had an approximately three-fold increased risk of developing a cancer in the controlateral breast. The risk of breast cancer was also elevated following cancers of the uterine corpus and ovary, with relative risk (RR) estimates of about 1.5 from one to four years after the diagnosis of the first primary cancer. An increased risk of cancer of the uterine corpus subsequent to breast cancer was also found. After an ovarian cancer, the risk of cancer of the uterine corpus was elevated (RR = 1.6-2.3). An increased risk of ovarian cancer was observed subsequent to breast cancer (RR = 1.3-1.7), whereas ovarian cancer risk decreased with time after the diagnosis of cancer of the uterine corpus, probably reflecting treatment involving oophorectomy.

A survey by Shunemann and Jourdain [8] included 1,503 endometrial carcinomas and concluded that 163 cases were multiple tumors (10.8%). Double malignancies that occurred within six months were termed simultaneous and all others were termed successive cases. Of these 100 (6.6%) occurred together with breast cancer and 63 (4.2%) with other primary malignancies. The average latency period from the first to the second malignancy was 4.5 years. Patients with endometrial carcinoma run higher risks of secondary tumors. One out of ten develops a double and one out of 100 a triple malignancy. The combination of endometrial and breast cancer occurs in 60% of cases and the combination of genital and breast cancer in nearly 80% of cases. Aftercare of endometrial carcinoma must also include early detection of potential double and triple malignancies.

In our case the diagnosis and treatment of the carcinoma of the uterus and bilateral breasts were synchronous. The patient was affected with the three most common gynaecological malignancies. The worse tumor was the invasive bilateral breast carcinoma.

Endometrial carcinoma with Stage pIa and grade 2, according to FIGO, is curable. Total abdominal hysterectomy and bilateral salpingo-oophorectomy, including peritoneal washings, right-sided external and common iliac as well as left external iliac lymph node sampling is a sufficient operative procedure.

Carcinoma of the left breast was poorly differentiated (grade 3), Stage pT1a/b N1pos M0 (IIA) and the right breast was a moderately differentiated (gradeII) stage pT1a/b N1neg M0(I) by the TNM system based on the UICC criteria. Histological and histochemical examinations of the breast tumors as well as lymphadenectomy were important in carrying out the treatment plan. The receptors of the left sided breast tumor were negative to ER, negative to PR and in contrast with the hormonal receptors of the right-sided breast tumor which were positive to ER, and also positive to PR, indicating that the tumors were possibly different from an aetiology point of view.

To the best of our knowledge, this is a unique case to be reported in the literature, because the diagnosis and treatment of bilateral breast carcinoma and endometrial adenocarcinoma were synchronous. Therefore, the patient did not have to go through three different operations. At the same time, she was entitled to prompt initiation of chemotherapy and radiotherapy for the breast cancers, which were apparently of different type as described.

Based on the case presented, we realise the importance of screening women with endometrial cancer with mammography. Also, women diagnosed with breast cancer should be examined with transvaginal ultrasonography for endometrial or ovarian carcinoma (a good clinical practice point).

References

[1] Quinn M., Jones B., Dina R., Soutter P.: "Malignant disease of the uterus". In: Shaw R., Soutter W., & Stanton S. (eds.), Gynaecology, 3rd edition, London, Churchill-Livingstone, 2003, 631.

[2] Sasieni P., Cuzick J.: "Epidemiology of gynaecological cancer". In: Shaw R., Soutter W., & Stanton S. (eds.), Gynaecology, 3rd edition, London, Churchill-Livingstone, 2003, 513.

[3] Saadat M., Truong P.T., Kader H.A., Speers C.H., Berthelet E., McMurtrie E., Olivotto I.A.: "Outcomes in patients with primary breast cancer and a subsequent diagnosis of endometrial cancer: comparison of cohorts treated with and without tamoxifen". *Cancer*, 2007, *110*, 31.

[4] Evans A.A., Skene A.I.: "Malignant disease of the breast". In: Shaw R., Soutter W., & Stanton S. (eds.), Gynaecology, 3rd edition, London, Churchill-Livingstone, 2003, 711.

[5] Fiorica J.: "Prevention and treatment of breast cancer". *Obstet. Gynecol. Clin. North. Am.,* 2001, *28*, 711.

[6] Ewertz M., Machado S.G., Boice J.D. Jr., Jensen O.M.: "Endometrial cancer following treatment for breast cancer: a case-control study in Denmark". *Br. J. Cancer*, 1984, *50*, 687.

[7] Ewertz M., Storm H.H.: "Multiple primary cancers of the breast, endometrium and ovary". *Eur. J. Cancer Clin. Oncol.,* 1989, *25*, 1927.

[8] Schünemann H., Jourdain M.: "Double and triple neoplasms in endometrial carcinoma". *Zentralbl. Gynakol.,* 1994, *116*, 522.

Address reprint requests to:
I. DEDES, M.D., DFFP
Consultant Obstetrician and Gynaecologist
Obstetrics and Gynaecology Surgery
34 Kifisias Avenue
11526 Athens (Greece)
e-mail: i_dedes@otenet.gr