Micro-metastases into the uterine leiomyoma from invasive ductal breast cancer under adjuvant tamoxifen therapy: case report

A. Dirican[1], Y. Kucukzeybek[1], I. Somali[1], C. Erten[1], L. Demir[1], A. Can[1], I.V. Bayoglu[1], S.C. Yigit[2], F.C. Unay[2], M.H. Yetimalar[3], M.O. Tarhan[1]

[1]Medical Oncology Clinic, [2]Pathology Clinic, [3]Obstetrics and Gynecology Clinic
Izmir Atatürk Training and Research Hospital, Izmir (Turkey)

Summary

Metastasis of breast cancer to the uterus is extremely rare. However, breast cancer is the leading tumor metastasizing from extragenital organs to the uterus. The most common signs of uterine metastasis are bleeding and mass effect. Tamoxifen use is known to increase risk of endometrial cancer. Immunohistochemical staining with GCDFP can be useful in differentiating primary uterine tumors from breast cancer metastasis. Metastasis to the uterus has been reported to worsen the prognosis. Although hysterectomy has been effective on survival, treatment modality to be used in the presence of other systemic metastases is not clear. Locoregional treatments can be used in oligometastatic cases. In addition, removal of solitary organ metastasis together with bone metastasis provides improvement in survival.

Key words: Uterine leiomyoma; Micrometastasis; Breast cancer.

Introduction

More than one million women are diagnosed with breast cancer annually [1]. Less than 10% of women diagnosed with breast cancer have Stage IV disease. Despite the absence of data obtained from prospective randomized studies, removal of the primary tumor or isolated metastatic lesions can be an attractive treatment strategy to improve survival in these patient subgroups [2]. Risk of endometrial cancer is increased in breast cancer patients receiving premenopausal and postmenopausal tamoxifen treatment. Therefore, regular gynecologic follow-up is recommended in women using tamoxifen. This is the presentation of a case diagnosed with breast cancer which metastasized into uterine leiomyoma while using tamoxifen.

Case Report

A 47-year-old premenopausal female patient underwent mammography and fine needle aspiration biopsy following breast ultrasonography (US) because of a breast mass. Partial mastectomy and axillary dissection were performed with the diagnosis of breast cancer. Surgical material was diagnosed to be invasive ductal carcinoma following histopathologic examination. Following immunohistochemical examination, progesterone receptor (PR) was 30% (++), estrogen receptor (ER) and Cerb B-2 were negative (Figure 1 A/a). Metastasis was not found in systemic screening and the patient was staged as T2N0M0. A chemotherapy regimen consisting of cyclophosphamide 500 mg/m², epirubicin 100 mg/m², 5-fluorouracil 500 mg/m² was administered for a total of six sessions in 21 days. Following this, adjuvant radiotherapy was applied. Tamoxifen was started for adjuvant hormone therapy. Gynecologic examination and pelvic US revealed a larger than normal cervix and uterus, and probe curettage which was performed twice, and cervical smear yielded benign findings. In the 46th month of follow-up and and 38th month of tamoxifen treatment, whole body bone scintigraphy carried out because of elevated serum CA 15-3 levels in routine work up together with back pain was suspicious of bone metastases and lumbar magnetic resonance imaging (MRI) revealed diffuse infiltrative vertebral bone metastases (Figure 2). Palliative radiotherapy was applied to the painful lumbar vertebral region. Abdominal computed tomography (CT) revealed a solid mass measuring 8-8.5 mm in the long axis with heterogeneous density and suggesting uterine myomatosis extending to the adnexa and Douglas pouch in the right side and with borders not separated from the uterus-cervix borders. Although our patient underwent probe curettage for the third time and cervical smear, no malignancy was found. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Histopathologic examination of the surgical material revealed carcinoma metastasis in the form of microscopic foci originating from the breast within the leiomyoma (Figure 1 B/b). For example, immunohistochemical staining was positive for GCDFP-15 (Figure 1 C), 30% positive for pancytokeratin (Figure 1 D) and negative for smooth muscle actin, CerbB2 and ER. These findings led to the conclusion that metastatic foci within the uterine leimyoma belonged to breast carcinoma. It was planned to administer a chemotherapy regimen with docetaxel 100 mg/m² every 21 days and zoledronic acid 4 mg treatment every 21 days with the diagnosis of metastatic breast cancer. At the time of case presentation, CA 15-3 levels of the patient who underwent a third session of chemotherapy and biphosphonate treatment decreased by 50%. For two months, follow-up without progression has been ongoing.

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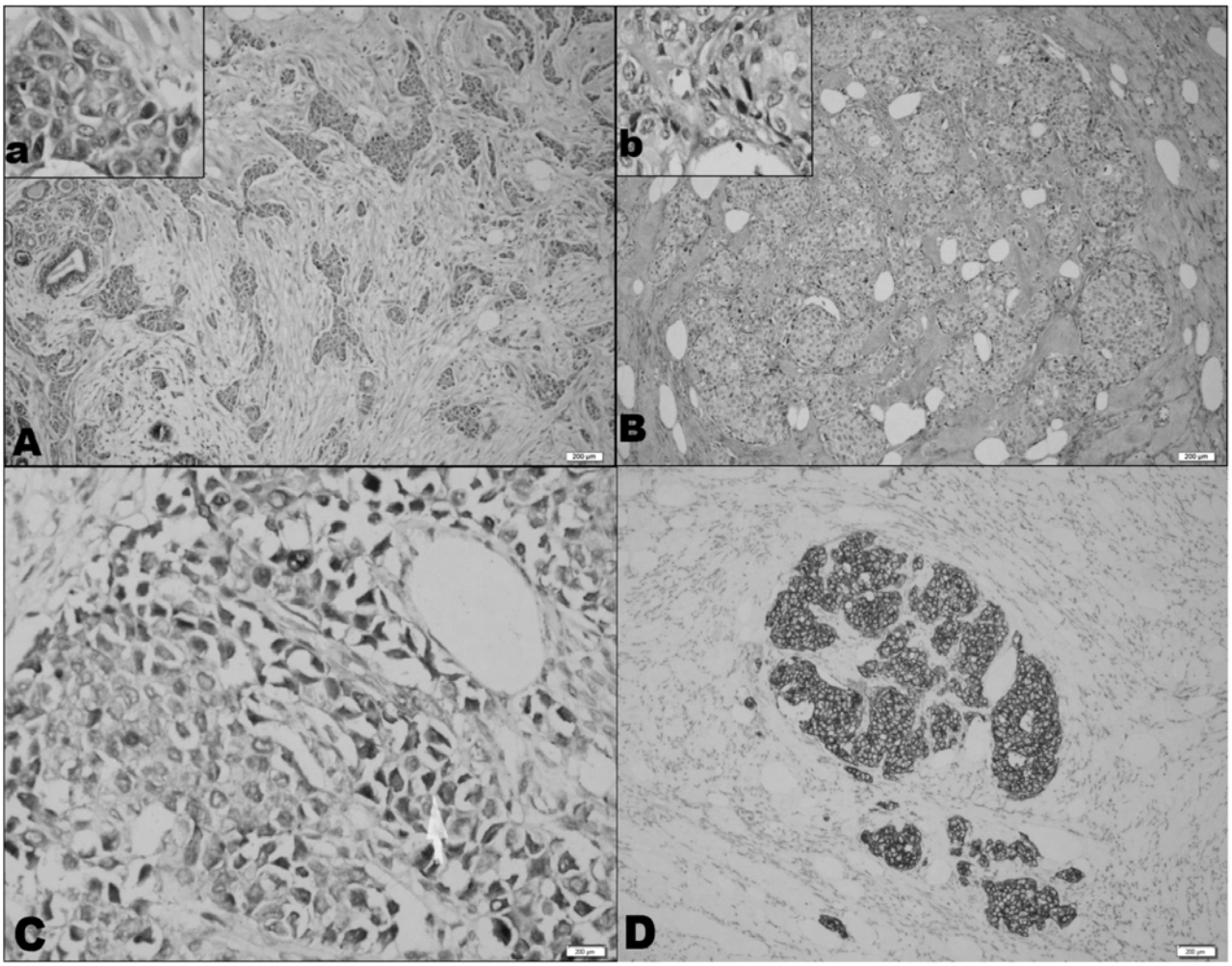

Figure 1. — A) Microscopic appearance of the invasive ductal carcinoma of the breast (HE x 44); a) Cellular details of the carcinoma of the breast (HE x 440). B) Microscopic image of breast cancer cells infiltrating into the uterine leiomyoma (HE x 44); b) Cellular details of the metastatic tumor which has a similar appearance to the primary breast carcinoma (HE x 440). C) Positive staining for GCDFP-15 by immunohistochemistry (IHC) (DAB x 220). D) Strong positivity for pan CK by IHC (DABX 44).

Discussion

Breast cancer most commonly metastasizes to the liver, bones and lungs. Among tumors which metastasize from extragenital organs to the uterus are the breast, colon, stomach, pancreas, gallbladder, lung, cutaneous melanoma, urinary bladder, and thyroid tumors. Breast cancer is among the leading cancers. In three separate studies, breast cancer rates of tumors metastasizing from extragenital organs to the uterus were 56%, 60% and 42.9% [3-5]. When the literature is searched, metastasis of breast cancer to the uterus is frequently seen to be in the histological subtype of invasive lobular carcinoma [3, 6-8]. On the other hand, Kondo *et al*. reported that in 11 cases of breast cancer metastasizing to the uterus nine had the histological subtype of invasive ductal carcinoma (breast cancer) [9]. Mean survival in metastatic breast cancer has been reported to be 18-24 months [10]. Case reports have shown uterine metastasis of breast cancer to be an indicator of poor prognosis. Again in these reports, hysterectomy was reported to provide improvement in survival but oophorectomy did not affect survival. It show be kept in mind that these studies are case reports and not prospective studies. In cases of metastases such as bone metastases which are not visceral metastases, the effect of hysterectomy is not known. According to multivariable analyses, it has been reported that in breast cancer with solitary metastasis local treatments (only surgery or radiotherapy combined with surgery) lead to improvement in survival or disease-free survival [2, 11]. When resection of liver metastasis associated with bone metastasis is performed in breast cancer patients, long-term results have not shown a difference with the long-term results of metastasectomy in patients with only solitary liver metastases [12, 13]. However, the effect of surgical resection of metastatic regions outside the liver with bone metastasis on survival is not known.

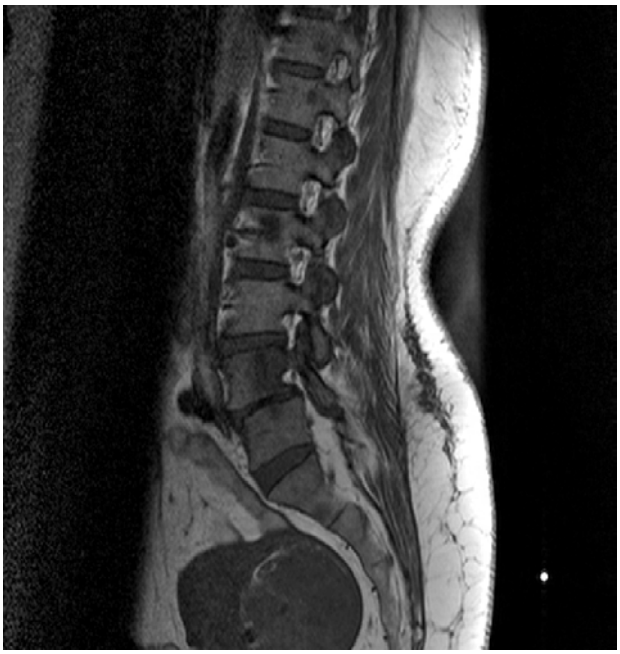

Figure 2. — Bone metastases in lumbar and sacral vertebrae, particularly in L4.

Tamoxifen use increases the risk of endometrial carcinoma due to its partially agonistic effect on endometrium [14, 15] and most commonly presents with vaginal bleeding [16]. When case reports are analyzed, uterine metastases present most commonly with vaginal bleeding. The second most common presentation is with a uterine mass. Our case presented with a uterine mass. In breast cancer, GCDFP IHC stain is positive at a rate of 65%-80% and is relatively specific for breast cancer [17-19]. GCDFP can be used in distinguishing a primary uterine malignancy from a breast cancer metastasis particularly detected during tamoxifen use. General survival in five cases administered chemotherapy following hysterectomy has been reported between four months and four years. Axillary lymph node metastasis has been found in two patients, visceral metastases such as brain and liver metastases in two patients and bone metastases in two patients [20-24]. The number of cases are too small to allow an evaluation of the effect of chemotherapy on survival.

One case had a diagnosis of invasive lobular carcinoma metastasizing to the bone and into a uterine leiomyoma during tamoxifen treatment. The patient presented with pain due to the bone metastasis and a uterine mass. Due to the absence of visceral metastases in abdominal and thoracic CT screening and presence of only bone metastases, diagnostic total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Micrometastases within the leiomyoma were positive for GCDFP which is relatively specific for breast cancer. In patients with metastases limited to the bone with no life risk, surgical removal of other solitary metastatic areas is important to increase quality of life, and to improve symptoms and survival. Furthermore, total abdominal hysterectomy with bilateral salpingo-oophorectomy may be useful in distinguishing primary uterine cancer from metastasis of breast cancer to the uterus in cases with abnormal vaginal bleeding or uterine masses particularly during tamoxifen treatment. Even in cases with diffuse metastatic disease, hysterectomy can be performed to alleviate symptoms. In this case, there are no sufficient data on the effect of chemotherapy in addition to surgery on survival.

It should be kept in mind that in breast cancer patients receiving adjuvant tamoxifen, in addition to the possibility of endometrial cancer, uterine metastases can also occur. Larger series are needed to evaluate the contribution of hysterectomy on survival.

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Address reprint requests to:
M.O. TARHAN, M.D.
Izmir Atatürk Training and Research Hospital
Medical Oncology Clinic
35360 Izmir (Turkey)
e-mail: motarhan@yahoo.com