

Occurrence of chronic myeloid leukemia in two breast cancer survivors after 4 years

Meme kanseri tanısıyla izlenen iki olguda 4 yıl sonra kronik myeloid lösemi gelişimi

Ocakçı S¹ Görümlü G³ Şahin F¹ Özsan N² Zekioğlu O² Uslu R³ Saydam G¹

¹Ege Üniversitesi Tıp Fakültesi, Hematoloji Anabilim Dalı, İzmir, Türkiye

²Ege Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, İzmir, Türkiye

³Ege Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji Bilim Dalı, İzmir, Türkiye

Summary

The coexistence of two different malignancies in the same patient is a very rare entity. It is highly possible to see secondary malignancies in survivors of cancer after chemotherapy or radiotherapy, especially in breast cancer and Hodgkin lymphoma since the life expectancy in these disorders is quite long. The drugs or the radiation given during the treatment could provide the etiopathological basis for development of secondary cancers. However, the exact mechanisms underlying the coexistence of two different cancers in the same patients have not yet been clarified. In this article, we summarize two patients with simultaneous breast cancer and chronic myeloid leukemia.

Key Words: breast cancer, chronic myeloid leukemia.

Özet

Aynı hastada 2 ayrı malinitenin eş zamanlı saptanması çok nadir bir durumdur. Özellikle meme kanseri ya da Hodgkin lenfoma tanısı için kemoterapi ve/veya radyoterapi alan ve kür elde edilen insanlarda beklenen yaşam süresi yeterince uzun olduğu için, bu tedavilere bağlı ikincil kanser görme şansı fazladır. Burada etiyolojik ajan olarak verilen kemoterapi ya da radyoterapi suçlanabilir. Ama aynı hastada 2 ayrı malinitenin eş zamanlı saptanmasının mekanizması tam olarak aydınlatılamamıştır. Bu yazıda, meme kanseri ve kronik myeloid lösemi tanısı alan 2 olgu sunulmaktadır.

Anahtar Sözcükler: meme kanseri, kronik myelositer lösemi.

Introduction

Breast cancer is the most frequently diagnosed cancer among women. On January 1, 2005, in the United States there were approximately 2,477,847 women alive who had a history of cancer of the breast. Between 2001 and 2005, the age-adjusted incidence rate was 126.1 per 100,000 women per year. The age-adjusted death rate was 25.0 per 100,000 women per year. Leukemia risk is lower than breast cancer. The age-adjusted incidence rate was 12.3 per 100,000 men and women per year. The age-adjusted death rate was 7.4 per 100,000 men and women per year. Chronic myeloid leukemia constitutes 20% of adult leukemia cases. The age-adjusted incidence rate was 1.5 per 100,000 men and women per year. The age-adjusted death rate was 0.4 per 100,000 men and women per year (1).

Due to early detection of breast cancer and effective therapeutic regimens, survival is increasing. Now it is time to consider secondary malignancies in breast cancer survivors. Breast cancer survivors are at increased risk of secondary acute myeloid leukemia with a high mortality rate (2, 3). Chronic myeloid leukemia (CML) occurs as a carcinogenic effect of ionizing radiation mostly. It has been described particularly in atomic bomb survivors (4). But, in the last 2 decades, the role of Ph chromosome in the pathogenesis of CML has been clearly documented. In this chromosomal abnormality, t(9;22)(q34;q11) occurs and as a result of this reciprocal translocation, *bcr/abl* mRNA transcripts can be detected by PCR. Here we report two cases of chronic myeloid leukemia occurring 4 years after breast cancer diagnosis.

Case-1

The patient was born in 1943. She was diagnosed with breast cancer (left breast) in 2003 and a left modified

Yazışma Adresi: Güray SAYDAM

Ege Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı, Hematoloji Bilim Dalı, İzmir, Türkiye

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radical mastectomy was performed. Tumor diameter was 2.7 cm. Pathology of the tumor was invasive ductal carcinoma plus invasive micro papillary carcinoma. No lymph node metastasis was stated. Estrogen and progesterone receptors were positive, c-erbB2 was found to be ++ by immunohistochemistry. She was treated with 4 cycles of epirubicine and cyclophosphamide. After chemotherapy, tamoxifen was given for 2 years. In 2005, bone metastasis at 12th thoracic vertebra was defined and received surgery. Capecitabine with zoledronic acid was ordered for 1 year. Bone metastasis progressed. She was treated with letrozole and after 4 months, exemestane was ordered.

In May 2007, her leukocyte count was found as 194.9 10e9/L. During the follow-up period in last one year, it was noticed that the white blood cell counts have increased gradually. But no further investigation was performed until the count reached to 194.9 10e9/L. She was diagnosed with chronic myeloid leukemia in the chronic phase with the presence of Ph chromosome in cytogenetical analysis. 400 mg Imatinib was ordered as daily. Bone metastasis continued to progress. Fulvestrant followed with capecitabine were given. Grade 2 leucopenia developed. Imatinib dose was reduced to 300 mg daily. One year later after diagnosis of CML, she has been under complete molecular response and living with metastatic breast cancer. She has been treated with imatinib 300 mg/day until the present without any side effects of the imatinib.

Case-2

The patient was born in 1961. She was diagnosed with breast cancer (right breast) in 2001, a right modified radical mastectomy was performed. Tumor diameter was 2.5 cm. Pathology of the tumor was invasive ductal carcinoma (Figure-1). One lymph node metastasis was defined. Estrogen and progesterone receptors were positive; c-erbB2 was +3 by FISH. Four cycles of doxorubicin and cyclophosphamide were given. After completion of chemotherapy, radiotherapy for axillary lymph node metastasis was carried out. Tamoxifen with goserelin was ordered since she was in the premenopausal stage. In September 2003, anastrozole was ordered.

In July 2005, her leukocyte count was found to be 98 10e9/L. During the follow-up period in the last one year, it was noticed that the white blood cell counts have increased gradually. But no further investigation was performed until the count reached 98 10e9/L. Bone marrow biopsy revealed hypercellularity with myeloid proliferation. She was diagnosed with chronic myeloid leukemia in the chronic phase with Philadelphia chromosome positivity in 20 metaphases. Imatinib 400

mg daily was given. In January 2005, bone metastasis at the fifth lumbar vertebra was diagnosed and treated with palliative radiotherapy. The specimen extracted from metastatic vertebra was not analyzed for the presence of *bcr/abl*. Exemestane and zoledronic acid were given until November 2007. In November 2007, CEA levels increased and docetaxel chemotherapy was ordered. Grade 2 leucopenia developed and the imatinib dose was reduced to 300 mg daily. Four years later after diagnosis of CML, she has been under complete molecular response and living with metastatic breast cancer. She has been treated with imatinib 300 mg/day until the present without any side effects of the imatinib.

Figure 1. Invasive ductal carcinoma (HEX40).

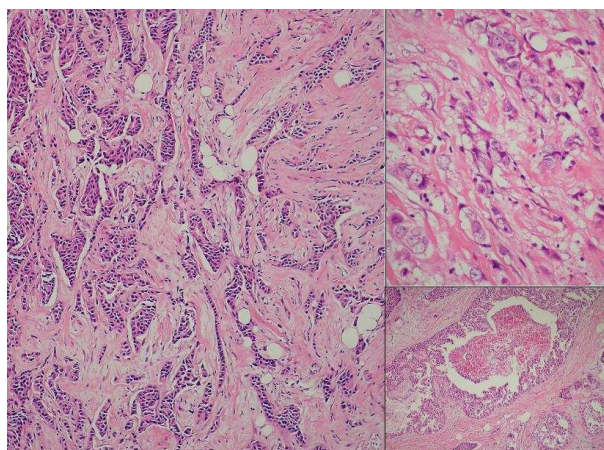
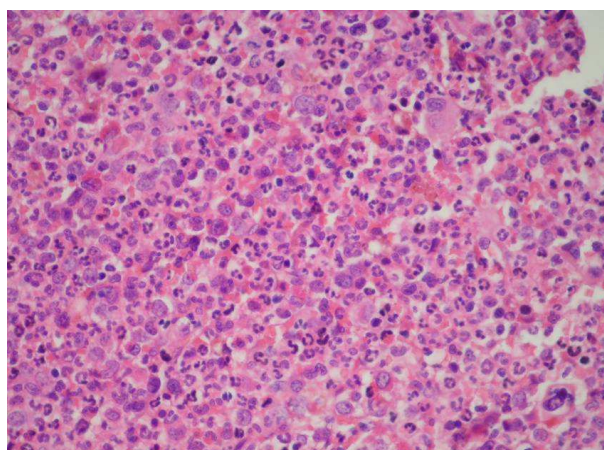


Figure 2. Hypercellular bone marrow with myeloid proliferation (HEX40).



Discussion

Breast cancer is a major health issue all around the world. Breast cancer is the most frequently diagnosed cancer among women and a leading cause of death (5). During last 30 years, survival after a diagnosis of breast

cancer has improved. In the 1970s, combination of cyclophosphamide, methotrexate, fluorouracil (CMF) regimen has been standard therapy. In the 1980s, with the addition of anthracyclines better results were obtained. In the 1990s, taxanes became available. The late 1990s and 2000s were a time of big changes. Targeted therapies changed therapy modalities. C-erbB2 testing and trastuzumab led better survival rates. Women with breast cancer now account for 20% of cancer survivors in the U.S (6). On January 1, 2005, in the United States there were approximately 2,477,847 women alive who had a history of cancer of the breast. Now it is time to consider late adverse effects of cancer therapy.

Secondary acute myeloid leukemia risk is increased in breast cancer patients. No study except Howard et al. (7) showed an increasing risk of chronic myeloid leukemia after breast cancer treatment. Howard et al. evaluated 376,825 1-year survivors of breast cancer in Sweden, Denmark, Finland, and Norway. Chronic myeloid leukemia has been most often described as a carcinogenic effect of ionizing radiation, especially in atomic bomb survivors. Howard et al. showed a significantly decreasing risk of chronic myeloid leukemia in more recent years of breast cancer diagnosis which is consistent with advances in radiation technology that permits more precise identification of target volumes and minimizing dose received by surrounding tissues, including bone marrow (8,9). However, it should not be forgotten that the individual variation and the radiation areas differ from one patient to another. The potential role of radiotherapy should be accepted cautiously.

Both of our patients were treated with alkylating agents. One of them was given adjuvant radiotherapy. Interestingly, both of them were diagnosed with chronic myeloid leukemia after 4 years of breast cancer diagnosis. Bone metastasis occurred before chronic myeloid leukemia diagnosis.

There is no current explanation of secondary chronic myeloid leukemia in a breast cancer survivor. 5-10% of breast cancers are hereditary. BRCA1 mutations are associated with families with breast and ovarian cancer.

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Families with male breast tumors are associated with mutations in the BRCA2 gene (10). There are similarities between BRCA1, BRCA2 and BCR-ABL (11). Both types of mutations are early genetic events. Both of them show sensitivity to therapy and secondary mutations in these genes result in acquired resistance to therapy (12). Both types of mutations result in increased genomic instability (13). Once the disease is established, BRCA deficiency is no longer required. BCR-ABL is essential for disease initiation and also maintenance. BRCA1 expression is down regulated in chronic myeloid leukemia cells. It becomes nearly undetectable during the chronic phase and blast crisis.

Another important point is that abl mutations has not, only in CML but also in solid tumors such as breast cancer, potential role during the initiation and progression period of the tumor. Mutant forms of the c-ABL gene are well known to be involved in hematopoietic malignancies such as chronic myeloid leukemia (CML). CML patients possess a fused BCR-ABL gene that activates the Abl tyrosine kinase domain within Bcr-Abl. In general, fusion proteins that cause oligomerization of Abl lead to activation of its tyrosine kinase activity. c-Abl tyrosine kinase, not as a fusion protein, plays an important role in malignant solid tumors of lung and breast (14).

Conclusion:

With intervention of new diagnostic and treatment options, breast cancer has become more like a chronic illness. SEER and EURO CARE-4 data show that survival for breast cancer and chronic myeloid leukemia is increasing (15). It is time to consider late adverse effects in a breast cancer patient's therapy decision. Chronic myeloid leukemia risk may be augmented especially after breast cancer radiotherapy. On the other hand, BCR-ABL based imatinib experience in chronic myeloid leukemia may bring out better response rates and survival rates with BRCA (or other molecular target) based therapy options.

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