Late onset of distant metastases from breast cancer

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Breast cancer is the most frequently diagnosed cancer in females and characterized by long duration and heterogeneity among patients. Even in early stage breast cancer, probability of local recurrence and metastasis in long period should be considered. A 65 year old female patient presented with growing mass in left side of neck, loss of appetite and weight loss. Past medical history revealed a right breast cancer treated by right modified radical mastectomy and adjuvant chemotherapy consisting of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) 15 years ago. This patient's presentation was late-onset of lymph node, pleura and lung metastases. Metastases 15 years after diagnosis of the primary tumor is uncommon. Late recurrence is thought to be due to cancer cells being in a 'dormant' state. [Turk J Cancer 2001;31(3):125-130]

Key words: Breast cancer, metastasis, adjuvant treatment, tumor dormancy

Breast cancer is the most common malignant neoplasm in women worldwide (1). The natural history of breast cancer is characterized by long duration and heterogeneity among patients. Most women after primary treatment are not cured and are still carriers of occult disease, that refers to the requirement for long term follow up (2).

We present here a node positive breast cancer patient who received adjuvant chemotherapy but no radiotherapy or hormonotherapy at the time of diagnosis and had distant metastases 15 years later.

Case Report

A 65 year old female patient presented with growing mass in left side of neck, loss of appetite and weight loss (10 kg in one year). Physical examination showed lymphadenopathy in left cervical (3x2 cm), right cervical (0.5x0.5 cm) and left supraclavicular region (1x1 cm), dullness in percussion and decrement in breath sounds in left hemithorax. Past medical history revealed right breast cancer (information available: invasive ductal carcinoma, pT2N1M0, stage IIB) treated by right modified radical mastectomy and adjuvant chemotherapy consisting of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) 15 years
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ago. Laboratory examination showed hemoglobin 10 g/dl, leucocytes 4100/mm³, platelets 355000/mm³, erythrocyte sedimentation rate 130 mm/hour, kidney and liver function tests in normal limits. Posteroanterior chest film and computerized tomography revealed pleural effusion from apex to basal part in left hemithorax, discoid atelectasias in central side, 1.5 cm nodular image in apicoposterior segment of left lung, increased linear density and fibrotic bands at the apex of right lung. Group of tumor cells were detected in cytologic analysis of pleural fluid (Figure 1). Excisional biopsy of the left supraclavicular lymphadenopathy showed invasive ductal carcinoma metastasis invading the surrounding tissue (Figure 2). Immunocytochemistry showed positivity for estrogen and negativity for progesterone receptors. The serum CA15-3 level was 68.73 U/ml (normal range 0-35 U/ml). Mammography and breast ultrasound examination showed neither left breast tumor nor axillary lymph node recurrences. Abdominal ultrasonography was negative for metastases. Cardiologic examination including echocardiography was normal.

Fig 1. Group of tumor cells in cytologic analysis of pleural fluid (May-Grünwald-Giemsa, original magnification X200)

This patient's presentation was late-onset lymph node, pleura and lung metastases from breast carcinoma treated 15 years previously. Chemotherapy consisting of cyclophosphamide, epirubicine, 5-fluorouracil and sequential tamoxifen as hormonotherapy were planned to be administered, but unfortunately 10 days after the second cycle of chemotherapy she had acute myocardial infarction and died.
Discussion

Breast cancer is the most frequently diagnosed cancer in females and a major medical problem with significant public health and social ramifications. Despite major advances made in the past 25 years in understanding the biologic and clinical nature of the disease, and notwithstanding dramatic changes in its treatment, the problem continues to persist and has become more complex (3).

In early stage breast cancer, because of the higher incidence of recurrence in patients having surgery or radiotherapy alone, the probability of the presence of micrometastases with systemic dissemination of the disease raised the concept of adjuvant treatment which aims to increase the disease free and overall survival by eliminating micrometastases and delaying recurrences (4-6). Irradiation clearly reduces the risk of locoregional failure for patients with invasive breast cancer treated with mastectomy (7-9). The first sites of failure were as follows: isolated locoregional failure (LRF) 13%; LRF with simultaneous distant failure 8%; and distant only 34% after mastectomy in breast cancer patients with histologically involved axillary nodes treated with chemotherapy with or without tamoxifen without irradiation (9). The Danish and British Columbia trials furnish strong support for the general principle that attaining maximal initial locoregional tumor control is necessary to achieve the best possible outcome in patients with positive axillary nodes treated with
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mastectomy and chemotherapy (10,11). Demicheli et al. (12) analysed the risk of recurrence at given times after surgery for breast cancer patients receiving or not receiving adjuvant CMF in 1452 node positive patients. The recurrence risk of CMF treated patients is lower than the corresponding risk of patients undergoing surgery only. However the difference is highly evident for early recurrences, while it declined and disappeared afterwards. As late relapsing patients seem to have at most marginal benefits from adjuvant CMF, ways to recognise patients doomed to have late recurrence and new ways for treating micrometastases resulting in late recurrences are required (13). For this reason, after completion of combined-modality therapy for primary breast cancer, patients are followed at regular intervals even more than twenty years after breast cancer diagnosis to detect recurrent disease, second primary tumors or complications of therapy.

In this case lymph node, pleura and lung metastases were detected simultaneously as the first indication of recurrent disseminated disease. Late onset of metastasis is often associated with better prognosis than early recurrences (14). However visceral metastases do worst and the number of involvement is an important marker of prognosis (15). Cancers that are positive for estrogen or progesterone receptors tend to be more indolent and have a better response to both hormonal therapy and chemotherapy than cancers that are negative for hormone receptors. Tamoxifen adds to the benefits of chemotherapy in the treatment of postmenopausal patients with receptor positive disease. Addition of tamoxifen to polychemotherapy results in a further 28% reduction in the odds of recurrence compared with polychemotherapy alone (16). In this patient receptor status was not known at time of diagnosis and adjuvant hormonotherapy was not considered at that time. However if patient had had adjuvant hormonotherapy, it could be useful from point of metastases, because it has been shown that tamoxifen addition to adjuvant therapy in case of unknown hormonal receptor status is beneficial (17).

Metastases 15 years after diagnosis of the primary tumor is uncommon, but has been previously described as well as local relapse (18-20). Late recurrence is thought to be due to cancer cells being in a ‘dormant’ state, in which little or no de novo DNA transcription occurs and only enough RNA is translated into proteins to maintain the vegetative functions that sustain cell viability (21). Some genetic factors, humoral factors or local conditions may repress mitosis for extended periods (22). This suggests that one may be ‘clinically cured’ but never ‘biologically free’ of cancer. As Fisher (23) proposed, breast cancer is accepted as a systemic disease rather than a local disease. A new general outline of metastatic development of breast cancer incorporating tumor dormancy in specific micrometastatic phases, stochastic transitions between them, and start signals from surgery for micrometastatic growth is designed. The proposed model suggests new views concerning scheduling of current chemotherapy, new treatment approaches aimed at keeping micrometastases in a dormant state for the patient’s entire life (24). Our case presented here illustrates the necessity of long term follow-up in breast carcinoma.

Treatment of metastatic breast cancer needs to be individualised because breast cancer is heterogenous in its biology and clinical course. Hormonal therapy is generally less toxic than chemotherapy and best candidates for
hormonal therapy are those patients with a long disease free interval and nonvisceral disease. Long time is required to properly monitor hormone response if only hormonal therapy was started as first line treatment for metastatic disease. Chemotherapy is used as first treatment of metastatic disease if the patient has extensive visceral involvement or if the tumor is growing rapidly, especially in visceral sites (25). Combination chemotherapy consisting of cyclophosphamide, epirubicine, 5-fluorouracil and sequential tamoxifen as hormonotherapy were planned because she had estrogen receptor positive distant metastases with multiple sites of involvement. Unfortunately she had acute myocardial infarction 10 days after the second cycle of chemotherapy. From point of cardiac toxicity of chemotherapeutic agents, epirubicin is associated with both acute and chronic cardiac toxicity although it is less than other anthracyclines and a syndrome of chest pain, cardiac enzyme elevations, electrocardiographic changes consistent with myocardial ischemia may be seen in temporal association with 5-fluorouracil administration (26). However it is doubtful to correlate this myocardial infarction with chemotherapy.

References


