**Case Reports:**

**Extramedullary Hematopoiesis in Breast after Neoadjuvant Chemotherapy for Breast Carcinoma**

Jun Wang and Farbod Darvishian  
Department of Pathology, New York University Medical Center, New York, New York

**Abstract.** We report incidental extramedullary hematopoiesis (EMH) in breasts of 2 patients following neoadjuvant chemotherapy for locally advanced breast cancer. Neither of the patients had a history of hematologic disorders. After chemotherapy, one of the patients had a complete pathologic response and the other had residual carcinoma. In both cases, EMH was mostly seen as myelopoiesis in a background of chemotherapy-induced changes. In the patient with residual carcinoma, EMH was observed in the contralateral prophylactic mastectomy specimen. EMH should be considered a diagnostic pitfall in the differential diagnosis of unusual cellular infiltrates in breast after neoadjuvant chemotherapy. To our knowledge, the association of EMH and neoadjuvant chemotherapy has not been previously reported.

**Keywords:** extramedullary hematopoiesis, breast, neoadjuvant chemotherapy

**Introduction**

Extramedullary hematopoiesis (EMH) occurs when the normal function of the bone marrow is disrupted by primary hematologic disorders, most commonly chronic idiopathic myelofibrosis, by secondary infiltrative lesions in the bone marrow such as metastatic diseases, or by ineffective hematopoiesis such as congenital anemic disorders including thalassemia major, hereditary spherocytosis, and sickle cell disease [1,2]. EMH may also be drug-induced, most notably after administration of granulocyte colony-stimulating factor [3]. The organs of the reticulo-endothelial system, including liver, spleen, and lymph nodes, are the main hosts of EMH, although involvement of other organs, including kidney, adrenals, dura mater, gastrointestinal tract, lung, pleura, skin, and breast, has also been reported [2,4-9]. EMH in breast can present as a mass or as an incidental finding in association with cancer or benign conditions such as fibroadenoma [8-15]. We report 2 cases of incidental EMH in mastectomy specimens in patients who had been treated with neoadjuvant chemotherapy for locally advanced breast cancer and we analyze the possible underlying mechanisms and clinical significance. For the presence of EMH, we also reviewed the histology slides of all breast specimens excised at our hospital within the past 3 years with locally advanced breast cancer after neoadjuvant chemotherapy.

**Case Histories**

**Case 1.** This 43-yr-old woman presented with a palpable fullness in the upper inner quadrant of her left breast. On examination, a hard mass (5 cm in diameter) was palpated in the central portion of the left breast. A mammogram demonstrated a 2 cm mass in the central area of the breast with 2 satellite nodules at the 11-1 o'clock position. Core biopsies of both sites yielded a diagnosis of poorly differentiated invasive ductal carcinoma with lymphovascular invasion. Multiple enlarged lymph nodes were seen by computerized tomography (CT) scan of the left axilla. The patient's history was significant for hypothyroidism, which had been treated with hormone replacement. There was no history of hematologic disorders. She had a family history of breast cancer involving several members on the maternal side. Following a negative search for metastases and with a diagnosis of locally advanced breast cancer, the patient was treated with neoadjuvant chemotherapy including 4 cycles of doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan) followed by...
4 cycles of paclitaxel (Taxol). Subsequently, she was admitted to the hospital for left total mastectomy and axillary lymph node dissection.

**Case 2.** This 38-yr-old woman presented with at least 2 lesions detected by routine mammography in the upper inner and lower inner quadrants of her right breast. Core biopsies of both quadrants revealed moderately differentiated invasive ductal carcinoma. On positron emission tomography/CT scan, she was noted to have multiple lesions in the right breast and axilla. The patient’s medical history included hypothyroidism, treated with hormone replacement, and a seizure disorder. There was no history of hematologic disorders. Her history included fibroadenomas in the left breast and a meningioma, all surgically excised. She had a family history of breast cancer that involved 2 members on the maternal side. Following a negative search for metastases and with a diagnosis of locally advanced breast cancer, the patient was treated with neoadjuvant chemotherapy including doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan) followed by paclitaxel (Taxol). Subsequently, she was admitted to the hospital for bilateral mastectomy, including left prophylactic mastectomy, and right axillary lymph node dissection.

**Materials and Methods**

The 2 instances of EMH in mastectomy specimens from patients after neoadjuvant chemotherapy were encountered within a 4-mo period (September 2005 to January 2006). These findings prompted a retrospective search of our pathology archival files for EMH in breast specimens from other patients following neoadjuvant chemotherapy. This search identified 15 candidate cases within a 3-yr period (2003 to 2006). Histologic slides from the 15 cases were reviewed for possible EMH (median = 31 slides/case; range = 12-103 slides/case).

**Results**

**Case 1.** On gross examination of the mastectomy specimen, an area (8-cm diameter) of white, dense, and homogeneous tissue was present predominantly in the upper inner quadrant of the breast. Microscopically, no residual carcinoma was noted in this area or any other sections of the breast. The 8-cm area exhibited extensive fibrosis with increased number of thin-walled vessels and intralobular and perilobular fibrosis, consistent with a complete pathologic response after neoadjuvant chemotherapy. A focus of hematopoietic cellular infiltrate, arranged in single files and loosely clustered single cells, was noted within the area of fibrosis (Fig. 1). The hematopoietic cells were mostly of myeloid lineage at various stages of maturation (Fig. 2).

Tissue specimens from both of the study cases were processed according to the standard protocol for mastectomy of New York University Medical Center Department of Pathology. The tissues were fixed in 10% buffered formalin and embedded in paraffin. Four-µm-thick sections from the blocks were stained with hematoxylin-eosin. For immunohistochemistry, 5-µm-thick sections were heated for 3 min in a microwave oven at medium power and stained for myeloperoxidase (Dako Corp., Carpinteria, CA; dilution: 1:1500; antigen retrieval: CC1M; clone:A0398), using a Benchmark staining apparatus (Ventana Medical Systems, Tucson, AZ). The slides were counterstained with hematoxylin, dehydrated, and mounted with permanent medium.

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highlighted the cells, confirming their myeloid lineage (Fig. 3). The axillary lymph nodes did not show any metastatic carcinoma or EMH.

**Case 2.** On gross examination of the mastectomy specimens, a poorly-circumscribed mass was identified in the inner quadrants of the right breast. Microscopically, this area corresponded to a focus (1.7-cm diameter) of residual, moderately differentiated, invasive ductal carcinoma. Ductal carcinoma in situ was present adjacent to, and away from, the invasive component. The left prophylactic mastectomy specimen revealed areas of fibrosis consistent with chemotherapeutic effect. Foci of EMH, represented by myeloid cells at various stages of maturation, were noted within the area of fibrosis of the non-cancerous prophylactic mastectomy specimen. The myeloid cells were arranged in loose clusters and single files. Immunohistochemical staining for myeloperoxidase activity was confirmatory. One right axillary lymph node harbored metastatic carcinoma. No EMH was seen in the lymph nodes.

**Discussion**

EMH is defined as the presence of one or more of the trilineage hematopoietic series outside the bone marrow. Usually, the elements of all 3 lineages are present, especially in mass-forming EMH. However, single lineage EMH has been reported [16]. In our 2 cases, the EMH in the breast was primarily composed of myeloid cells at different stages of myelopoiesis (Figs. 2 and 3).

The underlying mechanism of EMH in breast is unknown. One hypothesis is that the stem cells differentiate into hematopoietic cells in response to changes in microenvironment [4]. Growth factors or cytokines that stimulate normal hematopoiesis may also play a role in the pathogenesis of EMH. These factors may be produced by inflammatory cells stimulated by local injury such as biopsy or surgery [2,5,7]. However, although most surgically excised breast specimens have been previously biopsied, EMH is rarely seen in routine specimens, implicating local inflammation as only one of many potential facilitating factors.

The common association between EMH and functional disruption of bone marrow, eg, myelofibrosis, raises the possibility of homing and proliferation of circulating stem cells in a favorable microenvironment outside the defected bone marrow. In such conditions, an anemic state results in the production of cytokines and growth factors that promote hematopoiesis. These chemical mediators may enter the circulation and assist in generating favorable microenvironments. Although both of our patients experienced mild anemia following completion of chemotherapy, neither had bone marrow metastases to explain a mechanism akin to EMH in myelofibrosis.

EMH has been reported in association with drug therapy, most notably granulocyte colony-stimulating factor [3]. Given the presence of EMH in breast in our 2 study patients with history of neoadjuvant chemotherapy, we postulated a possible role for chemotherapeutic agents in the pathogenesis of EMH. Among the 3 chemotherapeutic agents used in our patients, doxorubicin has been implicated in the pathogenesis of EMH in animal models [17].

To validate our observations, we reviewed the slides of 15 additional breast cancer patients, who had been treated with neoadjuvant chemotherapy for locally advanced breast cancer. We did not find EMH in any of these cases. The 2 study cases did not have antecedent breast specimens in our files, so it was not feasible to assess the presence of EMH.
prior to treatment. The pathogenesis of EMH in our cases, therefore, remains speculative.

EMH in breast usually presents as a mass in patients with history of myelofibrosis [11-14]. It can also be detected as an incidental finding associated with breast carcinoma or benign lesions [10,15]. We observed EMH as an unusual cellular infiltrate in the breast specimens of 2 patients with histories of neoadjuvant chemotherapy. These cellular infiltrates were noted in areas of fibrosis caused by prior chemotherapy. It is interesting that in our patient with bilateral mastectomy, EMH was observed in the prophylactic mastectomy specimen and was not associated with residual breast cancer.

Whatever the presentation, the significance of EMH lies in its differential diagnosis with the other more common lesions of the breast. Clinically, the presentation of EMH in the breast can mimic primary breast carcinoma because of concurrent breast mass and enlarged axillary lymph nodes. Histologically, the presence of all 3 hematopoietic lineages imparts a distinct morphology to the lesion, which helps in distinguishing EMH from breast carcinoma and other hematopoietic lesions including leukemic infiltrates. A potential pitfall, given the cellular arrangement in EMH, is misdiagnosis as invasive lobular carcinoma. However, this distinction can be correctly made by consideration of the cytologic features of the infiltrate and utilization of immunohistochemical studies. Awareness of EMH in the breast can assist pathologists to avoid misdiagnosis, especially in patients with histories of chronic myelofibrosis or neoadjuvant chemotherapy for breast carcinoma.

References