Concurrent Invasive Ductal Carcinoma and Chronic Lymphocytic Leukemia Manifesting as a Collision Tumor in Breast

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Abstract: Collision tumors are rare clinical entities in which two histologically distinct tumor types show involvement in the same site. The occurrence of these tumors in the breast is extremely rare. Here, we present a case of a patient with both invasive ductal carcinoma and chronic lymphocytic leukemia in the breast. Wide excision with sentinel lymph node biopsy revealed palpably abnormal lymph nodes negative for breast carcinoma on frozen section. Histopathological examination of these lymph nodes showed extensive involvement by lymphoma and review of the breast specimen demonstrated the same lymphoma at the periphery of the ductal carcinoma. We review the literature and discuss possible etiologies for the dual presentation of both cancers.

Key Words: breast cancer, chronic lymphocytic leukemia, collision tumor, ductal carcinoma

Coincident presentation of breast carcinoma and axillary lymphoma has been reported for a variety of lymphoma subtypes. These include, mantle cell lymphoma (1,2), follicular lymphoma (2,3), centroblastic-centrocytic lymphoma (2,4), centroblastic polymorphic lymphoma (5), Waldenstrom subtype lymphoma (6), and small lymphocytic lymphoma/chronic lymphocytic leukemia (5,7,8). In a subset of these cases, collision tumors of breast and lymphoma within a single axillary lymph node have also been reported (4,6–8).

Collision tumors consisting of both breast lymphoma and breast carcinoma appear more unusual. To date, two reports have described mucosa-associated lymphoid tissue lymphoma in breast admixed with invasive ductal carcinoma (9,10). In the first case, all axillary nodes excised were involved with lymphoma and one lymph node demonstrated metastatic carcinoma (10). Bone marrow biopsy showed involvement by lymphoma with no evidence of carcinoma. In the second case, sentinel lymph node biopsy showed lymphoma involvement without carcinoma. Bone marrow biopsy did not show involvement of either malignancy (9). In addition, Rosen described a collision tumor consisting of tubulolobular carcinoma and small lymphocytic lymphoma (11). Wiernik et al. also report a collision tumor of breast carcinoma with an unspecified low- or intermediate-grade lymphoma (12).

In contrast to all previous reports, here we describe a patient with a collision tumor in the breast consisting of invasive ductal carcinoma and chronic lymphocytic leukemia. Axillary node dissection showed extensive involvement by lymphoma and breast carcinoma micrometastasis in a sentinel lymph node. Bone marrow also demonstrated lymphoma involvement.

CASE REPORT

A 55-year-old woman with a family history of breast cancer and a history of three benign biopsies of the right breast was found to have a complex solid nodule on a 6-month screening breast sonogram. A bilateral mammogram performed at the same time showed a questionable new nodular density but no definite abnormality at the site of the complex nodule. This
density was not present in a previous study 1 year prior. There was no evidence of disease in the left breast. Ultrasound-guided core biopsy of the complex solid nodule demonstrated invasive moderately differentiated ductal carcinoma with intermediate nuclear grade and microcalcifications associated with carcinoma as well as benign ducts.

The patient was asymptomatic at time of diagnosis and denied night sweats, fever, or weight loss. Family history was notable for premenopausal breast carcinoma in her mother at age 47 and bilateral breast cancer in her maternal aunt at age 42. Her paternal aunt also had stage I breast cancer in her 60s.

The patient underwent preoperative needle localization and wide excision of the carcinoma with sentinel lymph node biopsy. Preoperative lymphoscintigraphy of the right breast did not reveal a sentinel lymph node, and methylene blue was injected intraoperatively. Three lymph nodes with subcapsular blue dye were identified; their macroscopic appearance was highly abnormal and was consistent with metastatic disease. However, no metastatic tumor was present on the intraoperative frozen section. Routine histopathologic examination demonstrated that all three nodes contained an atypical lymphoid infiltrate. One of these lymph nodes contained a 1 mm micrometastasis confirmed by cytokeratin AE1/3 immunostain (Fig. 1). No extracapsular extension of tumor was evident.

The breast specimen demonstrated a moderately differentiated infiltrating carcinoma grade 2 \[2,2,3\] measuring 19 mm in its maximum diameter associated with cribiform-type ductal carcinoma in situ occupying approximately 5% of the tumor. Immunohistochemical staining was positive for estrogen receptor (ER) (>90%), progesterone receptor (PR) (>90%), and was negative for HER-2/neu; the Ki67 labelling index was 15%. This tumor was associated with large aggregates of small lymphocytes located predominately at the periphery of the tumor (Fig. 2). Atypical lobular hyperplasia bordering on lobular carcinoma in situ was also present in the specimen (Fig. 3). The bone marrow aspirate was negative for cytokeratin-positive cells/million bone marrow cells. In light of these findings, a level I and II axillary lymph node dissection was performed. On pathology, no further breast carcinoma metastasis was identified (0 of 25 lymph nodes); an atypical lymphoid infiltrate was also present in these same lymph nodes. These findings were consistent with a diagnosis of stage II \((\text{T}1c\text{N}1\text{micN}0)\) ER+ PR+ HER-2/neu negative invasive ductal carcinoma.

![Figure 1. Concurrent CLL/SLL and breast carcinoma micrometastasis in a sentinel lymph node. A. A micrometastasis of breast cancer (T) is located beneath the capsule of the sentinel lymph node populated by monotonous small lymphocytes of CLL/SLL. B. Double immunohistochemical staining demonstrated cytokeratin-positive (brown) breast cancer cells surrounded by neoplastic CD20-positive (red) B cells. Horseradish peroxidase-labeled and alkaline phosphatase-labeled antibodies were used for cytokeratin and CD20 staining, respectively (×400). CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma.](image)

Immunophenotypic analysis of the lymphoid infiltrate demonstrated a large number of B cells admixed with a smaller number of T cells. These B cells co-expressed CD5 and CD23 were negative for BCL-1 (Fig. 4). B cells were ZAP-70 negative (data not shown). Lymphoid infiltrates were analyzed for immunoglobulin gene rearrangements by polymerase chain amplification. A monoclonal rearranged band from the immunoglobulin heavy-chain gene could not be obtained using \(V_H\) and \(J_H\) primers, mostly likely due to somatic hypermutations in the heavy-chain
sequence. However, monoclonal rearrangement was demonstrated by amplification of the light-chain gene. Sequence analysis showed usage of the O12/O2 Vκ gene and the Jκ2 gene. These findings were diagnostic of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Subsequent evaluation of the patient’s lymphoid tumor was as follows. On further questioning, the patient described a history of lymphadenopathy that began 20 years ago for which she had never received follow-up. At that time, she developed cervical lymph node enlargement after an ear infection as well as elevated lymphocyte counts. Since then she has had ruberry right cervical lymph nodes and intermittently elevated lymphocyte counts, but has been otherwise asymptomatic. On physical examination, small bilateral cervical lymphadenopathy was detected. From available past records, the patient was found to have elevated lymphocyte counts of 4,200 and 3,600 cells/mm³ with normal white blood cell counts 1 month prior to her lumpectomy. Since resection and treatment for her breast cancer, both white blood cell counts and lymphocyte counts have been within normal limits (lymphocyte counts <2,900 cells/mm³).

Computed tomography of the head, chest, abdomen, and pelvis did not identify lymphomatous disease. Examination of the bone marrow aspirate demonstrated marked lymphocytosis comprising a monotonous population of small round lymphocytes. This lymphocyte population showed a monoclonal immunoglobulin light-chain gene rearrangement, identical to that found in the lymph node populated by small lymphocytes with characteristic immunophenotypic of CLL/SLL. These studies suggested a diagnosis of indolent chronic lymphocytic leukemia.

The patient underwent accelerated partial breast irradiation via a MammoSite device placed
intraoperatively, followed by six cycles of Adriamycin, cyclophosphamide and paclitaxel. Since then she has been maintained on tamoxifen 20 mg daily. At last follow-up 1 year postoperatively, she was without evidence of disease.

**DISCUSSION**

Rates of non-Hodgkin’s lymphoma in breast cancer patients are increased after radiation and chemotherapy (13), but simultaneous presentation of both diseases in the absence of therapy is rare. In this report, we describe a patient with invasive ductal carcinoma and chronic lymphocytic leukemia manifesting as a collision tumor in the breast.

This case raises several important points. With regard to diagnosis, the presence of palpably abnormal lymph nodes negative for breast carcinoma on frozen section should raise concern for a second malignancy. Poor tracer uptake of sentinel lymph nodes in this context is also consistent with this possibility. In this patient, lymphatic infiltration in the axillary nodes most likely contributed to the absence of uptake of radioisotope.

In terms of staging, we identified a single micrometastasis in the sentinel lymph node of this patient. However, the prognostic value of micrometastasis in the sentinel lymph node in predicting metastases to nonsentinel lymph nodes has not been defined in the setting of coincident lymphoma (14). It is unclear, whether effacement of the axillary tree by lymphoma confers added or decreased risk of breast cancer metastasis. In our case, axillary lymph node dissection did not reveal further metastatic disease in nonsentinel lymph nodes.

The evidence for an association between breast carcinoma and lymphoma also warrants discussion. While the presence of both tumors may simply be due to chance, it has been suggested that among women with both diseases, lymphoma is diagnosed more frequently simultaneously with or after the diagnosis of breast cancer (12).

One possible mechanism is that an underlying etiology predisposes to both tumor types. For example, mutations of the ATM gene at 11q22-q23 (implicated in ataxia-telangiectasia) are associated with lymphoid neoplasias and breast cancer (15,16). Infection with viral agents such as mouse mammary tumor virus and Epstein–Barr virus have also been suggested as underlying causes of both lymphoma and breast tumors (17,18). The significance of these viruses in causing breast cancer, however, remains controversial (19,20).

Alternatively, breast carcinoma may enhance progression of lymphoproliferative disease. Susnik et al. postulated, that antigenic stimuli from breast carcinoma may have driven lymphomagenesis of an adjacent mucosa-associated lymphoid tissue (MALT) tumor in their patient (10), analogous to the effect of Helicobacter pylori infection on the pathogenesis of MALT lymphoma seen in stomach. In our patient, a similar mechanism is plausible for breast carcinoma and CLL. CLL express B-cell antigen receptors, which show evidence of restriction and antibody selection. Moreover, experimental evidence suggests that antigenic stimulation of B-CLL may play a functional role in leukemic tumorigenesis (21).

Early-stage CLL can sometimes show heavy infiltration of a single atypical site such as breast, lung, and prostate (22). CLL with heavy infiltration of the prostate was found to bind to prostate cells with high affinity and hybridomas from these cells could secrete prostate-specific IgM (22). In our patient, the heaviest infiltrate of CLL in the breast was located primarily at the periphery of the breast carcinoma, with only small foci of perivascular infiltrate elsewhere in the breast. The architectural distribution of these neoplastic B
lymphocytes, suggests that their growth may be reactive towards the breast carcinoma cells. Given these observations, it is conceivable that the CLL in this patient may express a B-cell receptor with affinity for an, as yet, undefined breast cancer antigen.

In summary, we describe a case of simultaneous invasive ductal carcinoma and CLL in breast. Grossly abnormal lymph nodes negative for breast carcinoma should raise suspicion for second malignancy. In cases where simultaneous breast cancer and lymphoproliferative disease is suspected, we encourage future efforts to investigate the role of tumor immunity in this process.

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