Case Report

Pre-B acute lymphoblastic leukemia masquerading as breast carcinoma: A rare case report

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ABSTRACT

Leukemic involvement of the breast is very rare and more commonly seen in acute myeloid leukemia. Involvement of the breast in acute lymphoblastic leukemia (ALL) at diagnosis is very rarely reported and is often confused with primary breast tumors. We present a case of young female presenting with breast mass and axillary lymphadenopathy, thus masquerading as breast carcinoma. Breast biopsy and bone marrow examination revealed leukemic infiltration of pre-B cell ALL. Cerebrospinal fluid showed involvement with leukemic cells. The patient was treated with MCP-841 protocol and therapeutic cranial irradiation, followed by maintenance oral chemotherapy leading to complete resolution of breast mass. Thus, ALL should be considered in the list of differential diagnosis of breast masses, especially in young females.

Key words: Acute lymphoblastic leukemia, breast mass, chemotherapy, cytopenia, young female

INTRODUCTION

Breast involvement in hematological malignancies is uncommon. It is more commonly seen in non-Hodgkin's lymphoma (NHL) and acute myeloid leukemia (AML) and rarely multiple myeloma and chronic lymphoid leukemia.[1-3] Breast involvement in acute lymphoblastic leukemia (ALL) is very rare and occurs more commonly at the time of leukemic relapse or after stem cell transplantation. Breast involvement in ALL at presentation has been very rarely reported. We report a case of pre-B ALL presenting as breast lump and axillary lymphadenopathy. The purpose of this report is to highlight the atypical presentation of ALL and importance of prompt biopsy and immunohistochemistry (IHC) in the diagnosis.

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CASE REPORT

A 30-year-old female presented with a palpable lump in the right breast for the last 2 months. It was clinically diagnosed as fibroadenoma and was advised further investigations for diagnosis; however, she neglected it. One month later, the patient again presented with progressive increase in the size of right breast mass and new development of right axillary swelling. This was associated with generalized weakness and weight loss of 3 kg over the last 1 month. There was no history of fever, night sweats, vomiting, and abdominal pain. Family history, personal history, obstetric history, and menstrual history were not significant.

Clinical examination revealed 5.5 cm × 3 cm firm, mobile, and nontender lump in the upper outer quadrant of right breast. Right axillary lymph nodes were also palpable. At this stage, a clinical diagnosis of right breast carcinoma (cT3N1) was

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made. Mammosonography revealed 49 mm × 29 mm size ill-defined speculated hypoechoic lesion in the right breast in outer central region, with few microcalcifications with adjacent parenchymal distortion with multiple hypoechoic nodes with the loss of hila in the right axilla (breast imaging reporting and data system [BIRADS]-V). Left breast also showed 12 mm × 20 mm sized ill-defined hypoechoic lesion in the upper outer quadrant (BIRADS-IV) [Figure 1a and b]. Complete blood count revealed pancytopenia with hemoglobin - 9.0 g/dL, total leukocyte count - 1.8 × 10^9/L, and platelet count - 97 × 10^9/L. Rest of the blood investigations were within normal limits. In view of pancytopenia, bone marrow infiltration by breast carcinoma was suspected. However, trucut biopsy from the right breast mass revealed infiltration with atypical lymphoid cells possibly NHL [Figure 2a]. Fine needle aspiration from the left breast mass also showed atypical lymphoid cell aggregates. Patient was economically very poor, and in view of likely curative malignancy, it was decided to support the entire treatment of patient in patient assistance program at our institute. Hence, in view of resource-limited settings, basic IHC panel on breast biopsy showed AE1-negative, CD20 (Pan B)-positive, CD 79a-positive (pre-B cell marker), CD2-negative, myeloperoxidase (MPO)-negative, MIB1-positive (70%–80%) (<95%, not favoring Burkitt's lymphoma) [Figure 2b-e]. Terminal deoxynucleotidyl transferase marker was not done in view of nonavailability. Thus, combined morphological and IHC diagnosis of pre-B cell lymphoblastic lymphoma was made. Bone marrow aspiration revealed 88% malignant lymphoid cells, medium to large with scanty cytoplasm and high nuclear: cytoplasmic ratio and open chromatin [Figure 3a]. Hence, in view of breast biopsy suggestive of pre-B cell lymphoblastic lymphoma and bone marrow infiltration with 88% typical malignant lymphoid cells (lymphoblasts), further special stains were not performed on bone marrow aspiration and a final diagnosis of pre-B lymphoblastic leukemia was made. Fluorescence *in situ* hybridization for t (9;22) was negative. Conventional cytogenetics was normal. Cerebrospinal fluid (CSF) cytology was done as a part of workup and was found to be positive for malignant cells [Figure 3b]. Patient was started on MCP-841 protocol with biweekly triple intrathecal therapy (methotrexate, hydrocortisone, cytarabine). After completion of induction chemotherapy, bone marrow showed morphological remission, CSF was negative for malignant cells, and mammosonography revealed complete resolution of both right and left breast masses [Figure 1c and d]. The patient completed the second phase of induction with therapeutic cranial irradiation, followed by reinduction and consolidation as per the MCP-841 protocol. Treatment course was complicated by recurrent febrile neutropenia, hepatotoxicity, and vincristine-induced severe peripheral neuropathy. In view of poor tolerance to vincristine and daunorubicin, the patient was given daily 6 mercaptopurine and weekly methotrexate as maintenance and is currently on follow-up.

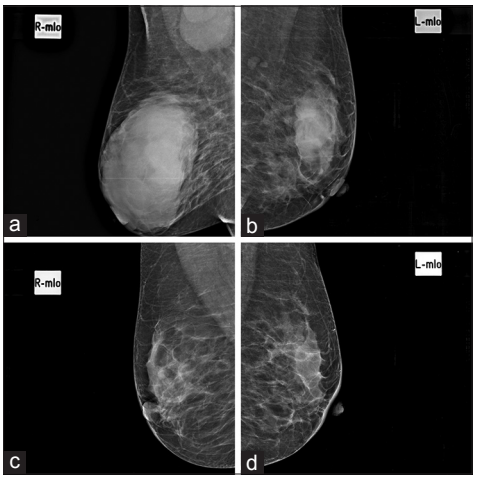

Figure 1: (a and b) Mammography showing breast mass with axillary lymphadenopathy in the right breast and similar small mass in the left breast. (c and d) Complete resolution of both breast masses and lymphadenopathy after induction chemotherapy

DISCUSSION

Leukemic and lymphomatous breast involvement is very rare and constitutes approximately 0.25% of all breast tumors.[1] Furthermore, leukemic involvement of breast is more commonly seen in AML than in ALL. Breast involvement in ALL was first reported by Williams in 1912.[4] It is more commonly seen in patients already diagnosed with acute leukemia or sometimes as a site of relapse and after bone marrow transplantation.[5] Very rarely, breast

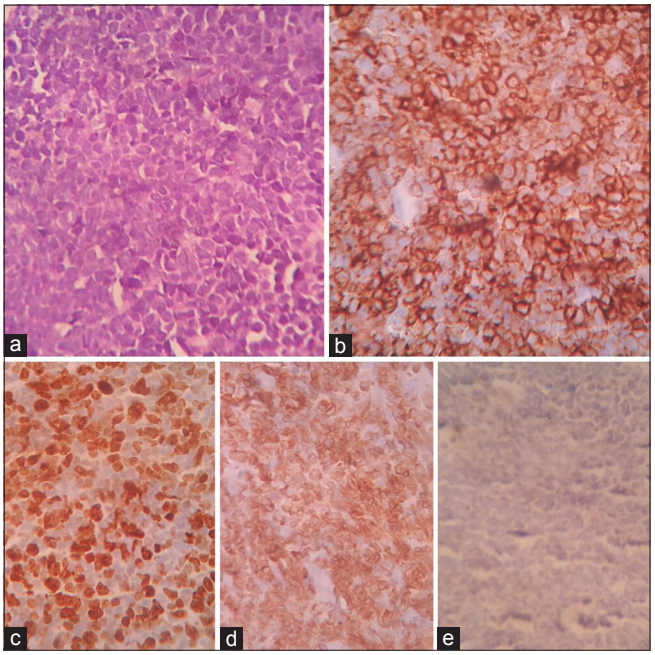

Figure 2: (a) Breast biopsy showing atypical lymphoid cell infiltrate. (b) Immunohistochemistry showing CD20-positive. (c) Immunohistochemistry showing CD79a-positive (d) MiBi index 70%–80% (e) CD2-negative

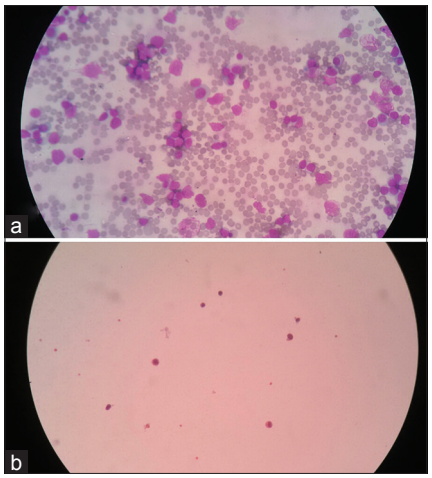

Figure 3: (a) Bone marrow aspiration (×40) showing 88% lymphoblasts. (b) Cerebrospinal fluid showing leukemic cell involvement

involvement is seen as primary manifestation of an ALL.[6] In such cases, it is often confused with primary breast tumor as in our case.

It generally occurs in young patients with unilateral or bilateral breast involvement presenting as a single or multiple palpable masses or with diffuse enlargement of breast resembling a fibroadenoma.[7] The lesion is generally well-circumscribed and rapidly enlarging. In a systematic update of breast leukemia (BL) by Surov *et al.*,[8] palpable breast mass was the most common presentation, and axillary lymphadenopathy was seen in 17.3% of the cases, thus making the clinical presentation similar to breast carcinoma.

Mammography findings are nonspecific and variable. They can be unremarkable or may show an enlarged breast with diffusely coarse parenchyma, an ill-defined mass with irregular borders, or solitary nodule simulating primary breast carcinoma.[1] Microcalcifications are very rarely reported. On ultrasonography, most masses are homogeneously hypoechoic with microlobulated or indistinct margins.[8] In contrast, primary carcinoma of the breast usually shows microcalcifications on mammography.

The differential diagnosis on morphology includes primary breast carcinoma (especially lobular carcinoma), chloroma, and NHL involving the breast.[4] Bone marrow carcinomatosis is a rare manifestation of metastatic breast cancer and is reported in only 0.17% breast cancer cases and commonly presents with anemia and thrombocytopenia similar to our case.[9]

The diagnosis can be established by fine needle aspiration biopsy of the breast mass which shows atypical lymphoid cell infiltrate. Typical IHC profile revealed tumor cells are positive for CD 19, CD79a, and CD22 and variably may express CD20, CD34, CD45, and CD99 and are negative for MPO, CD2, and CD3. Presence of more than 25% lymphoblasts in bone marrow or peripheral blood confirms the diagnosis of acute leukemia.[10]

Cunningham[11] also reviewed all acute leukemia cases with breast involvement reported in literature between 1969 and 2005 and found that only 13 cases of ALL presented with breast mass at the time of diagnosis. Most common age group for breast involvement at the time of diagnosis was 20–29 years. Twelve patients were treated with chemotherapy and two patients with combination of chemotherapy and radiotherapy. Eight patients achieved remission, but four cases later relapsed in 4–10 months.

The exact pathophysiology of extramedullary involvement in ALL is uncertain. Proposed mechanisms include chemokine receptor CXCR4 signaling, stromal-derived factor-1 mediated chemotaxis, and transendothelial migration of pre-B cells to extramedullary tissues. CXCR4 antagonists have shown to inhibit "extramedullary homing" by mobilizing leukemic blasts to the peripheral blood. Another proposed theory is that vascular endothelial growth factor receptor-1 (VEGFR-1 or FLT-1) regulates the localization of ALL cells to the bone marrow and their survival and exodus to systemic circulation and FLT-1 neutralization impedes the mobilization of leukemic cells and results in apoptosis.[10]

It is important to differentiate leukemic infiltration in the breast from primary breast lymphoma as local therapy alone has resulted in long disease-free survival in primary breast lymphoma. The median age in breast lymphoma is typically above 50 years,[12] whereas breast involvement at diagnosis in ALL is more commonly seen in young females (median age 20 years).[13] Association with recent pregnancy has also been reported and considered as a poor prognostic sign.[14] Leukemic involvement of the breast after treatment of ALL and after stem cell transplantation is most commonly reported within 24 months of completion of treatment.

Multiagent chemotherapy protocols used in treatment of ALL with central nervous system prophylaxis form the backbone of treatment of ALL with breast involvement. Local radiotherapy and surgery do not have a definite role as patients treated with only radiotherapy or surgery almost invariably have relapsed. Exact role of local radiotherapy in addition to intensive systemic therapy is also not clear as long disease-free survival has been reported both with and without radiation. In view of high risk for local and contralateral relapse, regular follow-up of patients on chemotherapy and after transplant, with regular mammograms, is advocated.[11]

BL does not have specific radiological or clinical features and can be misdiagnosed as primary breast carcinoma or even as fibroadenoma. In addition, BL can also occur in patients with known primary breast carcinoma as a collision malignancy.[15] Therefore, the diagnosis of BL can be confirmed only histopathologically and by IHC. Thus, ALL should be considered in the differential diagnosis of breast masses, especially in young females with bilateral involvement and with cytopenias, and prompt biopsy should be considered even if clinically and radiologically appearing benign lesions and with or without signs of acute leukemia. High index of suspicion, rapid diagnosis and confirmation by IHC, and prompt institution of multiagent chemotherapy can help in achieving complete remission and long-term cure.

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Conflicts of interest
There are no conflicts of interest.

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