

Case Report

Running Title: Dual Bone Marrow Pathology: Breast Cancer and ALL

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Simultaneous Bone Marrow Involvement by Breast Carcinoma Metastasis and Acute Lymphoblastic Leukemia: A Case Report

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Abstract

Breast cancer is among the most common malignancies in women and frequently metastasizes to the bone marrow, where it may be clinically silent or present with hematologic abnormalities. Although secondary hematologic malignancies, particularly therapy-related acute leukemias, can arise following cytotoxic chemotherapy, the simultaneous presence of metastatic breast carcinoma and acute lymphoblastic leukemia (ALL) within the bone marrow is exceptionally rare. In this study, we report a unique case of a 41-year-old woman with high-grade invasive ductal carcinoma of the breast who later developed B-cell ALL during follow-up. Initial pathology revealed extensive locally advanced breast carcinoma with dermal invasion. Approximately two years after treatment initiation, the patient developed progressive cytopenia, prompting bone marrow evaluation. Bone marrow aspiration demonstrated marked hypercellularity with over 80% blasts along with small clusters of metastatic epithelial cells. Flow cytometry confirmed a B-ALL immunophenotype, while immunohistochemistry identified breast-origin metastatic cells positive for GATA-3 and cytogenetic study on bone marrow specimen revealed t(4;11). This dual pathology highlights the diagnostic challenges of differentiating leukemic infiltration from metastatic carcinoma in bone marrow specimens and underscores the need for integrated morphologic, immunophenotypic, and immunohistochemical assessment. Recognizing such rare coexistence is essential for accurate diagnosis and appropriate clinical decision-making.

Keywords: Secondary neoplasm, Flow cytometry, Immunohistochemistry

Introduction

Breast cancer remains one of the most prevalent malignancies among women

worldwide, accounting for over two million new cases in 2020.¹ The most frequent sites of distant metastasis include the bone, lungs,

liver, and brain.² Bone marrow involvement occurs in a considerable proportion of patients and may either be clinically silent or manifest through hematologic abnormalities such as anemia, thrombocytopenia, or leukopenia. In certain instances, bone marrow infiltration is detected only microscopically as isolated disseminated tumor cells identifiable through immunohistochemical analysis.³⁻⁵

A subset of breast cancer patients may subsequently develop hematologic malignancies, including acute leukemia—most notably acute lymphoblastic leukemia (ALL). Such secondary leukemias are frequently associated with prior exposure to cytotoxic agents, particularly topoisomerase II inhibitors and alkylating agents.⁶⁻⁸

The coexistence of metastatic breast carcinoma and ALL within the bone marrow is exceptionally rare. In this paper, we present a unique case demonstrating this concurrent pathology.

Case Presentation

A 41-year-old woman attended Saadi Hospital in Shiraz for evaluation of cytopenia. Two years earlier, she had presented with a large left-sided breast mass measuring 21 × 15 × 5 cm accompanied by extensive ulceration on the overlying skin. The tumor was staged as pT4bN2Mx, corresponding to at least stage IIIB disease. Microscopic examination of the firm area revealed invasive ductal carcinoma, showing a Nottingham histologic grade II/III. Six lymph nodes were dissected from the specimen, all of which were involved by tumor (macrometastasis) (Figure 1).

The patient had been under regular medical treatment and surveillance for the underlying primary condition. Throughout this period, therapeutic management was carried out according to established clinical guidelines. Routine laboratory evaluations and clinical assessments during the first months of follow-up showed relative stability, with no

major hematologic abnormalities. However, approximately two years into treatment, subtle changes began to appear in serial blood counts, eventually progressing to marked thrombocytopenia and leukopenia, prompting further diagnostic investigation. Bone marrow aspiration and biopsy were performed, revealing a hypercellular marrow with more than 80% blasts and small foci of duct forming non-hematopoietic cells, suggestive of metastatic involvement. Myeloid and erythroid maturation were markedly arrested (Figure 1, 2).

Flow cytometric immunophenotyping was performed on the aspirate using a leukemia-oriented antibody panel. A blast population (54% of total cells) was identified on SSC/CD45 and SSC/FSC scattergrams, showing an ALL-B phenotype, positive for CD10, CD19, HLA-DR, and CD45 and negative for CD33, CD13, CD14, CD117, and CD7. Remaining cellular events appeared within normal limits. Negative controls were assessed using IgG1-FITC, IgG1-PE, and IgG-PerCP.

Immunohistochemistry (IHC) on the formalin-fixed paraffin-embedded bone marrow biopsy showed that the blast cells were positive for CD19, CD79, PAX-5, and TdT, confirming a B-cell lineage. Additionally, GATA-3 was positive in the metastatic cells, supporting the breast origin of these cells (Figure 2).

Cytogenetic study with G-banding method was performed on bone marrow specimen which revealed a mosaic karyotypic pattern characterized as 47,XX,+X,t(4;11)(q21;q23)[9]/46,XX[9].

Ethical consideration

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1404.490).

Discussion

Bone marrow involvement by metastatic breast carcinoma is a well-documented event, particularly in advanced stages of disease.

However, the simultaneous occurrence of metastatic breast cancer and ALL within the bone marrow is exceedingly rare. The coexistence of these two distinct malignancies poses significant diagnostic and therapeutic challenges, as well as intriguing questions regarding their potential pathogenetic relationship.

Several hypotheses have been proposed to explain the concurrent development of solid tumors and hematologic malignancies. One possibility is that the two neoplasms arise independently, coincidentally affecting the same organ. However, in patients with a history of breast cancer, the emergence of acute leukemia may be therapy-related where development of ALL is less common than AML. Exposure to cytotoxic agents, particularly topoisomerase II inhibitors and alkylating agents, has been associated with secondary leukemias, often manifesting several years after chemotherapy. Genetic alterations, including rearrangements involving the KMT2A gene at chromosome 11q23, have been implicated in the pathogenesis of therapy-related ALL. In our case, the patient had previously been treated with doxorubicin, a topoisomerase II inhibitor. Therefore, the presence of an 11q23 rearrangement and the subsequent development of ALL may be attributable to this therapeutic exposure. Similar findings have been reported in other studies. For example, Shim et al. conducted a study in South Korea evaluating post-treatment acute leukemia in patients with breast cancer. Among 9,228 patients, 12 developed acute leukemia; all had received topoisomerase II inhibitors, including nine cases of AML and three cases of ALL.^{7, 9, 10}

From a diagnostic perspective, distinguishing between bone marrow metastasis and leukemic infiltration can be challenging, particularly when both entities coexist. Morphologic evaluation, immunophenotyping, and IHC are essential

to accurately identify each component. The presence of cytokeratin-positive epithelial cells alongside lymphoblasts expressing lineage-specific markers (such as CD19, CD10, and TdT) confirms the dual pathology.

Therapeutically, the management of patients harboring both ALL and metastatic breast carcinoma is complex and must be individualized. The coexistence of two aggressive malignancies limits therapeutic options and often worsens prognosis. In most reported cases, supportive and palliative care are prioritized due to poor performance status and overlapping toxicities of chemotherapy regimens.

In summary, the concurrent presentation of metastatic breast carcinoma and ALL within the bone marrow is an exceptionally uncommon phenomenon. Recognition of this coexistence is crucial for appropriate diagnosis and management. Further studies and accumulated case reports are needed to elucidate the underlying mechanisms linking these malignancies and to optimize therapeutic strategies.

Conclusion

By reporting a rare case of simultaneous B-ALL and bone marrow metastasis from aggressive invasive ductal carcinoma, we suggest that comprehensive morphologic, immunophenotypic, and immunohistochemical evaluation is essential to correctly diagnose coexisting malignancies. Awareness of such dual pathology is crucial for guiding appropriate therapeutic strategies and anticipating complex clinical outcome.

Consent to Publish

The participant has consented to the submission of the case report to the journal.

Consent to Participate

Written informed consent was obtained from the patient.

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Authors' Contributions

Conceptualization: M.M; Data collection and writing – original draft preparation: K.N; Writing – reviewing and editing: M.M, M.S, K.N; Supervision: M.M, M.S, A.D, N.O.

All authors read and approved the final manuscript version and agree with all parts of the work in ensuring that any queries about the accuracy or integrity of any component of the work are appropriately investigated and handled.

Conflict of Interest

None declared.

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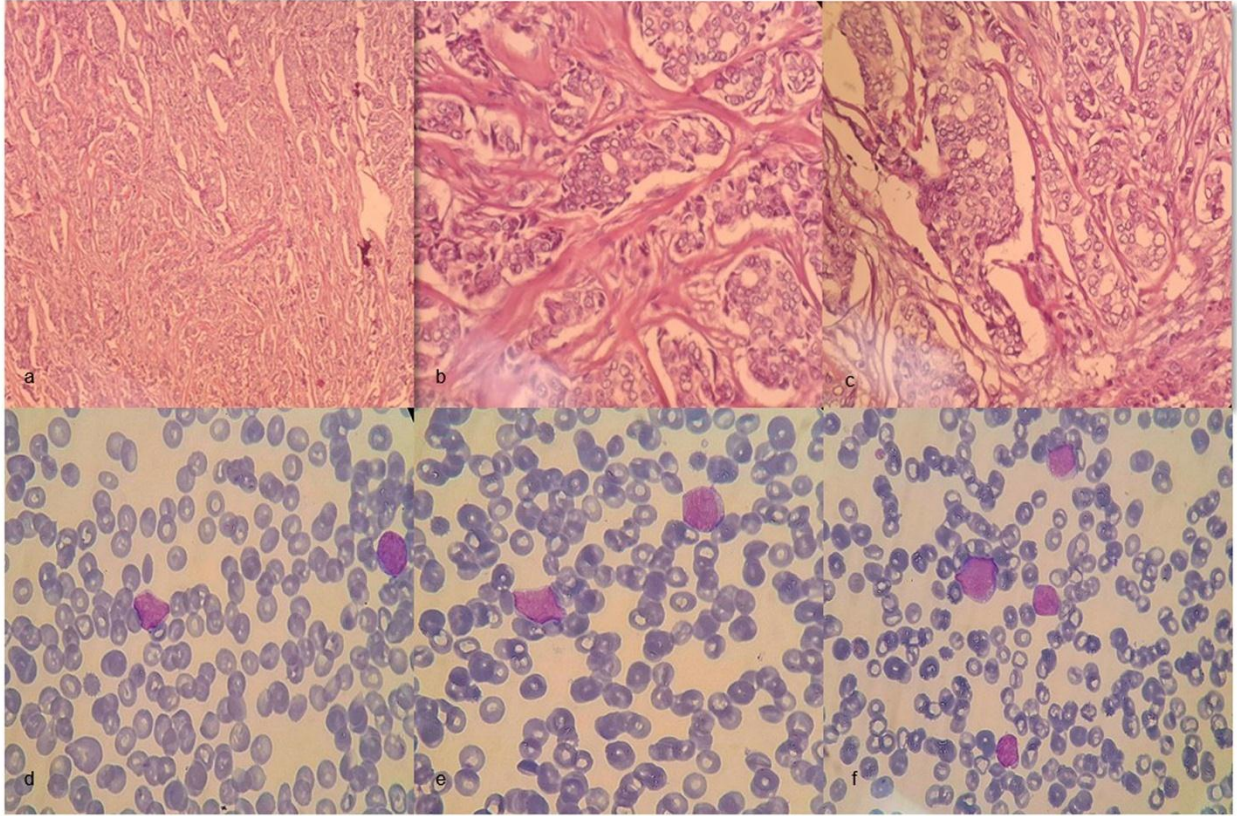


Figure 1. This figure shows the invasive ductal carcinoma of breast and acute lymphoblastic leukemia in bone marrow aspiration: (a-c) Hematoxylin-eosin staining of left breast specimen. Nests of tumoral cells are seen; a: 100× magnification. b and c: 400× magnification. (d-f) Wright stain for bone marrow aspiration. Blast cells are seen; 1000× magnification.

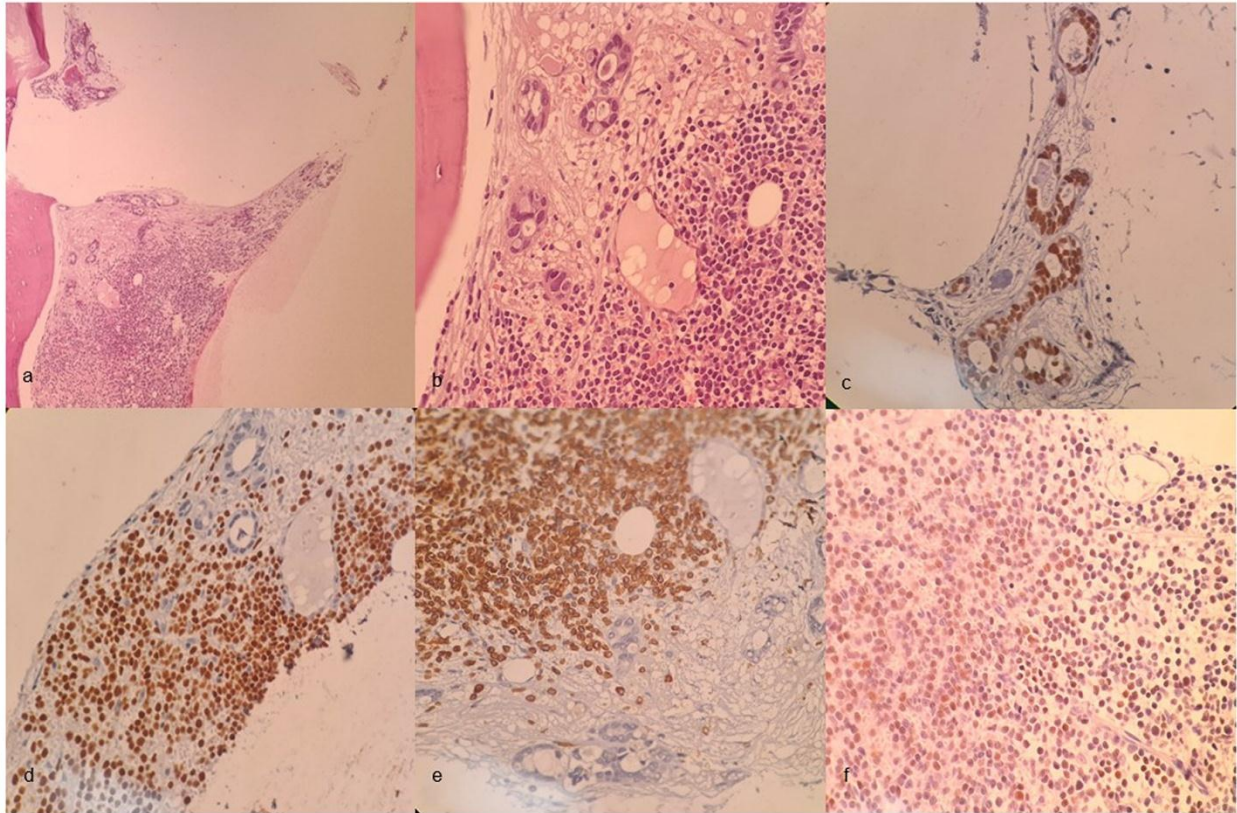


Figure 2. This figure shows the bone marrow biopsy and Immunohistochemistry study: (a-b) Hematoxylin-eosin staining of bone marrow biopsy specimen. Nest of breast's tumor cells infiltrate the bone marrow; a: 100× magnification. b: 400× magnification. (c-f) IHC staining; c: GATA-3, positive in tumoral cells of breast origin, d: Pax5, positive in blast cells, e: CD79a, positive in blast cells and f: TDT, positive in blast cells.