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Secondary ALK-Positive Anaplastic Large Cell Lymphoma Masquerading as Inflammatory Breast Cancer

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ABSTRACT

Background: Secondary breast lymphoma accounts for 0.12% of breast malignancies. Anaplastic large cell lymphoma (ALCL) metastases to the breast are rare, considering the fact that lymphoid tissue is a minor component of the breast. We describe a case of secondary ALK-positive ALCL identified during the workup of inflammatory breast cancer in the setting of diffuse erythema, induration, and pitting lymphedema of the right breast with weeping serous fluid in a septic patient.

Case Presentation: A 28-year-old female presented with septic shock and 2 weeks of right breast pain, erythema, swelling, and fever. Imaging demonstrated a mass in the right axillary/subpectoral region and bilateral axillary, mediastinal, supraclavicular, and retroperitoneal lymphadenopathy. Physical examination demonstrated tenderness, diffuse erythema, induration, pitting lymphedema of the right breast with palpable lymphadenopathy, which are symptoms of inflammatory breast cancer. Punch biopsy was performed. Immunohistochemical analysis revealed CD30 and CD45 positivity. Reflex fluorescent in situ hybridization testing demonstrated ALK (2p23). Subsequent nodal biopsies revealed hallmark cells. The cumulative findings were indicative of ALK-positive ALCL.

Conclusion: This study underscores the importance of including lymphoma within the differential during the workup of suspected inflammatory breast cancer.

INTRODUCTION

The breast is composed of a small amount of lymphoid tissue and is consequently a rare site for extranodal involvement by lymphoma. Secondary lymphoma is differentiated from primary by the presence of involvement outside of the breast and axillary lymph nodes at the time of diagnosis. Secondary breast lymphoma accounts for 0.12% of breast malignancies by biopsy.[1] Anaplastic large cell lymphoma (ALCL) is a non-Hodgkin lymphoma and the most common type of peripheral T-cell lymphoma. ALCL is classified as primary systemic ALCL: anaplastic lymphoma kinase (ALK) positive, primary systemic ALCL: ALK negative, primary cutaneous ALCL (PC-ALCL), and breast implant-associated ALCL (BIA-ALCL): ALK negative, CD30 positive.[2] The t(2;5) translocation is the most common rearrangement with subsequent fusion of nucleophosmin (NPM1) and ALK genes, which leads to a constitutively active oncogenic tyrosine kinase that stimulates signaling involved in growth and inhibition of apoptosis.[3] ALK-positive ALCL has a favorable prognosis compared to ALK-negative ALCL (5-year overall survival 70% vs 49%; P=0.032,

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respectively),[4] and patients older than 40 receive prognostic benefit from ALK status.[5]

CASE PRESENTATION

A 28-year-old female presented with septic shock, lactic acidosis, hypoxic respiratory failure, and encephalopathy. The symptoms included 2 weeks of right breast pain, erythema, swelling, fever, nausea, and vomiting. A CT of the chest, abdomen, and pelvis with intravenous contrast demonstrated a 5.7x8.2cm mass in the right axillary/subpectoral region, a lobulated 2.5×3.2×5.3 cm mass in the right atrium, 2 nodular densities in the left lung, and lymphadenopathy involving bilateral axillary, mediastinal, hilar, and supraclavicular nodes, and diffuse involvement through the retroperitoneal cavity. Physical examination revealed tenderness, diffuse erythema, induration, pitting lymphedema of the right breast with sparing of the upper inner quadrant (Figure 1). Weeping serous fluid extending into the right axilla and upper arm as along with palpable lymphadenopathy, was observed. There were no discrete areas of fluctuance, purulent drainage, gross tissue necrosis, or crepitus. Ultrasound revealed no drainable collections in the breast or axilla. Lactate dehydrogenase was 557 U/L.

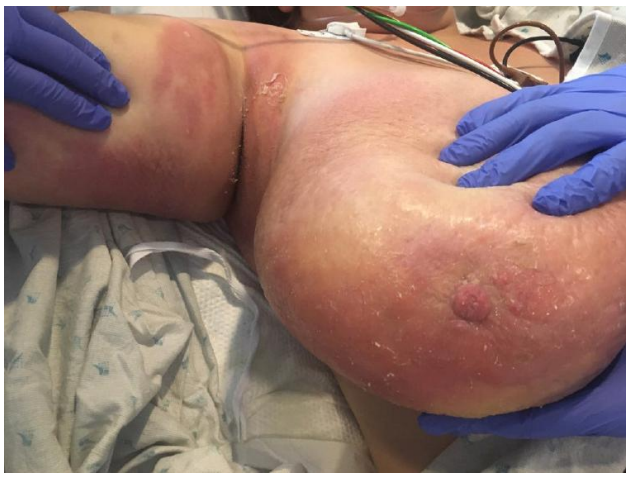

Figure 1. Right Breast and Axilla. The right breast and axilla demonstrated diffuse erythema, induration, and pitting lymphedema with sparing of the upper inner quadrant. This raised concern for inflammatory breast cancer.

Breast punch biopsy and core-needle biopsies of the right axillary/subpectoral and enlarged left axillary and left inguinal lymph nodes were performed for tissue sampling to evaluate possible synchronous metastatic breast carcinoma and lymphoma. Due to the absence of a defined breast mass available for core biopsy, a punch biopsy was performed for convenience while the patient was intubated and sedated in the intensive care unit. Punch biopsy pathology demonstrated pleomorphic malignant cells arranged in bands in the dermis with CD30 and CD45 positivity consistent with a malignant lymphoma. Hematoxylin and eosin staining on the core biopsies demonstrated pleomorphic cells with round to occasionally eccentric, horseshoe-shaped nuclei, and abundant eosinophilic cytoplasm, which were characteristic of hallmark cells (Figure 2).

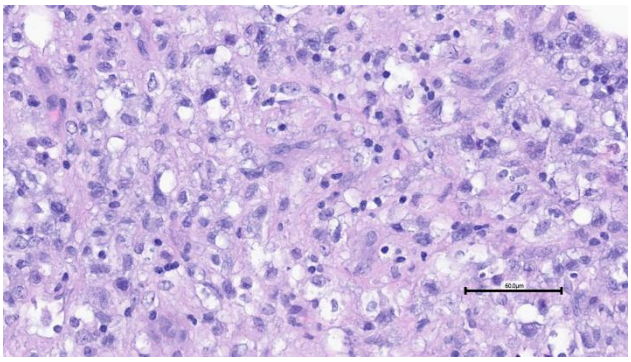

Figure 2. Hematoxylin and Eosin Staining of Nodal Tissue at 40× Magnification**.** The lymph node shows a diffuse infiltrate of large, pleomorphic cells. These cells exhibit round to occasionally eccentric, horseshoe-shaped nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm.

Reflex fluorescent in-situ hybridization (FISH) testing on the punch biopsy revealed ALK (2p23). Immunostaining on the core biopsies demonstrated positivity for CD45 (weak), CD4, CD5 (partial), CD30 and alk-1, and negativity for CD3, CD2, CD7, CD8, PAX5, CD20, CD138, pancytokeratin (AE1/AE3), S100 and myeloperoxidase (Figure 3 A–D). The corresponding nomenclature was determined to be nuc ish(ALKx2)(5′ALK sep 3′ALKx1)[44/200]. The overall findings were consistent with ALCL. The patient was initiated on A+CHP: brentuximab vedotin, cyclophosphamide, doxorubicin, mesna, and filgrastim. After recovery, she was lost to follow-up due to moving out of state.

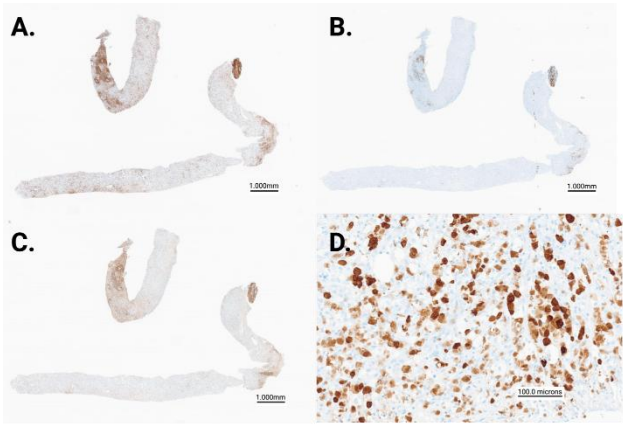

Figure 3. Immunohistochemistry of Lymph Node Core Biopsies**.** A, CD3 is negative in neoplastic cells but shows positivity in normal T cells. B, CD20 is negative in the neoplastic cells. It stains some scattered B cells in the

normal lymph node at the periphery. C, CD45 is weakly positive in the neoplastic cells and strongly stains normal T and B cells. D, ALK1 at 20× magnification demonstrates nuclear positivity in the neoplastic cells.

DISCUSSION

Non-mammary metastases to the breast represent 2% of all breast malignancies.[6] ALCL metastases to the breast are exceedingly rare, as lymphoid tissue constitutes only a minor component of breast volume. Our report describes a case of secondary ALK-positive ALCL identified during the workup of suspected inflammatory breast cancer.

ALCL is a rare and generally aggressive cancer of T cells, often presenting at a late stage. ALK-positive ALCL is often diagnosed in young adults and usually presents in the lymph nodes with metastases, with a 5-year overall survival of 70%.[4] T-cell lymphomas can occasionally mimic the clinical presentation of inflammatory breast carcinoma or other infectious disorders of the breast, such as infectious mastitis, abscesses, or idiopathic granulomatous lobular mastitis.[7] Inflammatory breast cancer is a clinical diagnosis pertaining to the rapid onset of breast erythema, occupying at least one-third of the breast, edema, and/or peau d'orange in less than 6 months, with pathologic confirmation of invasive breast cancer. In this patient's clinical context, pathologic confirmation was essential in differentiating ALCL from inflammatory breast cancer. A case of ALK-positive ALCL mimicking inflammatory breast cancer has been reported; however, the location of the malignancy was intravascular.[8]

Primary and secondary lymphomas of the breast have been described elsewhere but are limited to case series or case reports.[9-10] Radiological features of secondary breast lymphoma are non-pathognomonic and can mimic invasive forms of primary breast cancer, but in the right clinical setting, imaging provides appropriate foundational grounds for staging and surgical planning. CT or mammographic findings of skin thickening or lymphadenopathy could suggest inflammatory breast cancer, but are nonspecific. Distant lymph node involvement was attributed to diffuse metastatic disease with consideration of the patient's breast clinical presentation, but her generalized distant lymph node involvement was suggestive of lymphoma. PET/CT can help identify the extent of disease and guide diagnosis in stable patients. Lymphoma can demonstrate high uptake in lymphoid tissues; however, PET was not used in this patient's case due to limitations at the inpatient facility. Instead, bedside biopsies provided a diagnosis, bypassing the need for imaging, which would still have been necessary to guide proper treatment.

CONCLUSION

Although rare, this presentation underscores the importance of including lymphoma within the differential during the workup of suspected inflammatory breast cancer.

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None.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, or publication of this article.

ETHICAL CONSIDERATIONS

The patient was fully informed about the presentation of the details of her medical information in this medical journal. Informed consent was obtained.

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DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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