Primary ALK-positive Anaplastic Large Cell Lymphoma of the Breast: A Case Report and Review of the Literature

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Background: Non-Hodgkin lymphomas of the breast are uncommon, which represent less than 1% of all breast malignancies and predominantly are of B-cell origin.

Observation: In this report, a rare case of anaplastic lymphoma kinase (ALK)-positive anaplastic large T-cell lymphoma in the breast of a 16-year-old female without breast implant is described. The patient presented with a 3-month history of progressive right breast swelling and erythema. Clinically, inflammatory breast carcinoma was highly suspected. A tru-cut needle biopsy of the right breast demonstrated infiltration of tumoral cells around the breast lobules and soft tissue and also in angiolymphatic spaces. The immunohistochemical profile showed positivity for CD30 and ALK and confirmed the diagnosis of ALK-positive anaplastic large T-cell lymphoma of the breast.

Conclusion: Anaplastic large T-cell lymphoma of the breast is rare, and can clinically mimic inflammatory breast carcinoma in adolescence.

Key Words: anaplastic lymphoma kinase (ALK), anaplastic large cell lymphoma, breast

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Anaplastic large cell lymphoma (ALCL) is a T-cell lymphoma typically seen in children and young adults, which accounts for 10% to 15% of all childhood lymphomas and less than 5% of adult non-Hodgkin lymphomas.1 Non-Hodgkin lymphomas of the breast are very rare events, which comprise less than 1% of all breast malignancies.2,3 Clinically, most lymphomas of the breast present as a solid mass with or without mammographic findings,4 although diffuse firm infiltrating anechoic mastitis-like processes have also been described.4

The breast is one of the least common involved locations by ALCL.1,5 It seems that the most of ALCL in the breast have been reported as a primary lymphoma.5 It is interesting to note that most of the primary ALCL have developed as a consequence of breast implants.6–12 There is only one earlier report describing an anaplastic lymphoma kinase (ALK)-positive ALCL mimicking inflammatory breast carcinoma.13 In the present report, a case of ALK-positive ALCL inside the breast parenchyma without prior breast implant is described, which clinically mimicked inflammatory breast carcinoma.

CASE REPORT

A 16-year-old girl presented with a 3-month history of progressive symptoms of swelling, tenderness, heaviness, and pain with erythematous changes in the right breast (Fig. 1) followed by right axillary and supravacular lymphadenopathy. There was no history of B symptom at presentation. An excisional biopsy of right supravacular lymph node and tru-cut needle biopsy of the breast were done. A diagnosis of ALK-positive ALCL was made. On histopathologic examination of the lymph node, the cells were large, pleomorphic with vesicular nuclei, and prominent single or multiple nucleoli. Immunohistochemistry was carried out using standard avidin-biotin-peroxidase technique with primary monoclonal antibodies against CD30, ALK, LCA, CK, EMA, S100, HMB45, Desmin, CD31, Epstein-Barr Virus, CD20, CD15, CD5, CD79a, TdT, and CD3. Appropriate positive and negative controls were included. The neoplastic cells were positive for the CD30, EMA, and ALK. All other markers were negative in the tumor cells. Interestingly, the ALK-positive ALCL cells were arranged predominantly perivascularly and in the subcapsular vessel and sinuses of the right supravacular lymph node (Fig. 2). On the basis of routine histopathology and immunohistochemistry investigations, the diagnosis of the ALK-positive ALCL was reached. The tru-cut needle biopsy of the right breast confirmed the breast

![FIGURE 1. Inflammation, edema, and erythema of the right breast at presentation.](image-url)
as the primary site. Histologic sections show epidermis, dermis and breast tissue. High-power examination shows large, highly atypical cells with perinuclear halo, irregular nuclear contours, and occasional prominent nucleoli close to breast acini (Fig. 3). The dermis shows perivascular chronic inflammatory cell infiltration together with tumoral cells in the angiolymphatic spaces. Immunohistochemical marker of CD30 and ALK were positive in lymphoid tumoral cells and cells localized within angiolymphatic spaces. Further imaging studies by ultrasonography and computed tomography scan revealed abdominal lymph node involvement. The patient was treated with the induction of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen chemotherapy. Three weeks after receiving chemotherapy, the breast swelling with significant desquamation and exfoliation that indicated extensive breast skin involvement subsided. Despite initial good response to chemotherapy, a few months later, she developed disseminated disease and died owing to extensive lung involvement.

DISCUSSION

Non-Hodgkin lymphomas of the breast are very rare events, which comprise less than 1% of all breast malignancies.2,3 Most lymphomas of the breast are large cell lymphoma. Patients who have lymphomas in the breast range from teenagers to those in their ninth decade.4 Generally, the peak incidence for lymphomas of the breast seems to be around the sixth decade of life, although some cases usually occur in the third decade.2 Associations of the autoimmune diseases have been described as the reason for this occurrence.5 Only about 2% of the extranodal non-Hodgkin lymphomas are located in the breast.6 Most of them are B-cell phenotype6 and are more common in the right side with only rare cases showing a T-cell phenotype.16 In the reported implant-associated lymphomas of the breast, the T-cell lymphoma predominate.8 ALC, as defined in the Revised European-American Classification of Lymphoid Neoplasms and World Health Organization Classification of Hematopoietic and Lymphoid Neoplasms, is a T-cell or null-cell lineage lymphoma that consistently expresses the activation marker CD30,17,18 T-cell-type ALC is most frequent. Null cell type ALC (lacking both T-cell and B-cell markers) accounts for about 10% of the cases. The frequency of the null cell type depends on the number of T-cell antigens investigated in a given study. By using more extensive cytologic molecular markers, such as perforin, granzyme B, and TIA-1, most null cell cases have been found to belong to the T-cell type.19

Two clinical forms of this type of lymphoma have been described. The most common systemic form accounts for 3% of all adult non-Hodgkin lymphomas and 10% to 30% of childhood lymphomas.17 The less common cutaneous form accounts for about 25% of all primary cutaneous T-cell lymphomas.1,20 Although both types express CD30, systemic ALC is the only one that often expresses ALK-1 positivity.1,20 Similarly, although ALK-positive systemic ALCs are more often seen in younger male patients, ALK-negative ones are associated with advanced age and show no sexual predominance. ALK-negative ALCs are found somewhat less frequently outside of the lymph nodes. In three-fourths of the cases, the patient presents with B symptoms, which was not the case in the present patient.17

Microscopically, the most striking feature of hematoxylin and eosin-stained sections of the present patient was the presence of pleomorphic, highly atypical cells with abundant eosinophilic cytoplasm. The nuclei were vesicular and seemed variably round, oval, irregular, or lobulated with coarse granular chromatin and 1 or more prominent nucleoli. CD30 (Ki-1) and ALK were positive in the tumor cells of the present patient.

A review of the literature searching for the ALC of the breast revealed a total of 21 reports. Fifteen papers report single cases,1,5–11,13,21–26 3 reports include 2 cases each,12,27,28 and in 3 recent studies, 4,29 6,30 and 11 reports patients with ALC with breast involvement have been reported. There are a total of 27 primary1,5–12,22–25,28–30,31 and 15 secondary ALC of the breast.13,21,26,27,30,31 Twenty-three of these cases occurred in proximity to the breast implants.5–12,25,28–31 It seems that the primary ALC of the breast without implant is rare and only 7 cases of the primary ALC of the breast without implant are available in the literature, including 6 females1,2,21,23,31 and 1 male.24 In the present case, no implant was presented in breast or any other organ. Clinical information of the ALC of the
<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Age</th>
<th>Stage</th>
<th>CD30</th>
<th>ALK</th>
<th>P/S</th>
<th>Side</th>
<th>Other Sites</th>
<th>Breast Implant</th>
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<tbody>
<tr>
<td>Tan and Sng</td>
<td>1996</td>
<td>67/F</td>
<td>II</td>
<td>+</td>
<td>NA</td>
<td>S</td>
<td>Right</td>
<td>Right axillary LN</td>
<td>NA</td>
</tr>
<tr>
<td>Lin et al</td>
<td>1997</td>
<td>58/M</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>S</td>
<td>Left</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Keech and Croick</td>
<td>1997</td>
<td>34/F</td>
<td>III</td>
<td>+</td>
<td>NA</td>
<td>S</td>
<td>Right</td>
<td>Inguinal and axillary LNs</td>
<td>NA</td>
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<tr>
<td>Pillay and Chetty</td>
<td>1999</td>
<td>41/F</td>
<td>II</td>
<td>+</td>
<td>NA</td>
<td>P</td>
<td>Right</td>
<td>Enlarged right axillary LN</td>
<td>Yes</td>
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<tr>
<td>Aguilera et al</td>
<td>2000</td>
<td>19/M</td>
<td>I</td>
<td>+</td>
<td>NA</td>
<td>P</td>
<td>Left</td>
<td>Pleural effusion without malignant cells</td>
<td>No</td>
</tr>
<tr>
<td>Gaudet et al</td>
<td>2002</td>
<td>87/F</td>
<td>I</td>
<td>NA</td>
<td>–</td>
<td>P</td>
<td>Right</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Pereira et al</td>
<td>2002</td>
<td>50/F</td>
<td>II</td>
<td>+</td>
<td>–</td>
<td>P</td>
<td>Right</td>
<td>None</td>
<td>Yes</td>
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<tr>
<td>Sahoo et al</td>
<td>2003</td>
<td>36/F</td>
<td>I</td>
<td>+</td>
<td>–</td>
<td>P</td>
<td>Left</td>
<td>No systemic disease</td>
<td>Yes</td>
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<tr>
<td>Iyengar et al</td>
<td>2005</td>
<td>72/F</td>
<td>I</td>
<td>+</td>
<td>–</td>
<td>P</td>
<td>Left</td>
<td>Left axillary lymphadenopathy</td>
<td>No</td>
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<td>Fritzth et al</td>
<td>2006</td>
<td>56/F</td>
<td>I</td>
<td>+</td>
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<td>P</td>
<td>Left</td>
<td>None</td>
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<tr>
<td>Olack et al</td>
<td>2007</td>
<td>34-59/F</td>
<td>I</td>
<td>+</td>
<td>–</td>
<td>P (4)</td>
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<td>No lymphadenopathy or signs of systemic disease</td>
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<tr>
<td>Wong et al</td>
<td>2008</td>
<td>40/F</td>
<td>I</td>
<td>–</td>
<td>–</td>
<td>P</td>
<td>Right</td>
<td>Without lymphadenopathy</td>
<td>Yes</td>
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<tr>
<td>Newman et al</td>
<td>2008</td>
<td>52/F</td>
<td>I</td>
<td>NA</td>
<td>NA</td>
<td>P</td>
<td>Right</td>
<td>No palpable lymphadenopathy</td>
<td>Yes</td>
</tr>
<tr>
<td>de Jong et al</td>
<td>2008</td>
<td>24-68/F</td>
<td>I</td>
<td>–</td>
<td>–</td>
<td>P (6)</td>
<td>Right (5)</td>
<td>Left subcapsular, left axillary, and supravacular, bilateral inguinal, right infracavicular, right axillary, mediastinal and, upper abdominal LNs, lung, and right skull base</td>
<td>5 (Yes)</td>
</tr>
<tr>
<td>Miranda et al</td>
<td>2009</td>
<td>21-65/F</td>
<td>I</td>
<td>(1)</td>
<td>+</td>
<td>(4)</td>
<td>P (1)</td>
<td>Axillary and pleural mass, inguinal, mediastinal, lung and skin</td>
<td>3 (Yes)</td>
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<tr>
<td>Kelten et al</td>
<td>2009</td>
<td>35/F</td>
<td>IV</td>
<td>+</td>
<td>–</td>
<td>S</td>
<td>Left</td>
<td>Left and right axillary region, parasternal, and hilar LN</td>
<td>No</td>
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<tr>
<td>Alobeid et al</td>
<td>2009</td>
<td>68/F</td>
<td>II</td>
<td>+</td>
<td>–</td>
<td>P</td>
<td>Right</td>
<td>Bilateral axillary</td>
<td>Yes</td>
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<tr>
<td>Gualco et al</td>
<td>2009</td>
<td>65/M</td>
<td>I</td>
<td>+</td>
<td>P</td>
<td>Left</td>
<td>No extramammary disease</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Bishara et al</td>
<td>2009</td>
<td>66/F</td>
<td>I</td>
<td>+</td>
<td>–</td>
<td>P</td>
<td>Right</td>
<td>No extramammary disease</td>
<td>No</td>
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<tr>
<td>Krishnan et al</td>
<td>2009</td>
<td>33/F</td>
<td>III</td>
<td>+</td>
<td>–</td>
<td>S</td>
<td>Right</td>
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<td>Yes</td>
</tr>
<tr>
<td>This study</td>
<td>2009</td>
<td>16/F</td>
<td>III</td>
<td>+</td>
<td>–</td>
<td>P</td>
<td>Right</td>
<td>Mediastinal, supravacular, abdominal LNs</td>
<td>No</td>
</tr>
</tbody>
</table>

*After breast involvement.
†Sarcomatoid variant.
‡Intravascular ALCL/subcutaneous nodule.
§Breast involvement years after skin and LN involvement.
LN indicates lymph node; NA, not available; P, primary; S, secondary.

breast in the literature plus this report is summarized in Table 1. This information represents that all patients of the ALCL with breast involvement are CD30-positive in which only 6 cases were ALK-positive, 13 were ALK-negative, and in the remaining 6 cases, the result of ALK was not known (not declared). In our case, the ALCL was located in the right breast. The right breast is often reported to be more commonly involved than the left.

The criteria that have to be fulfilled for the diagnosis of primary lymphoma of the breast are defined by Wiseman and Liao (1972), including an adequate pathological specimen, close proximity of mammary tissue, and lymphomatous infiltrate with no prior diagnosis of extra-mammary lymphoma and no concurrent widespread lymphoma. Secondary breast lymphoma is a systemic lymphoma that invades the breast tissue. According to these standards, the tumor in our patient is considered as primary ALCL of the breast.

In addition, the presence of numerous tumor cells in the angiolymphatic vessels of the breast could be another indication for the widespread tumor involvement. In our case, the tumoral cells in the right supravacular lymph node showed a strong cytoplasmatic expression of CD30, EMA, and ALK protein, and negativity for CD3, CD5, CD15, CD79a, Epstein-Barr Virus, Tdt, HMB-45, and S100. In conclusion, the diagnosis of the ALCL in the breast represents a diagnostic challenge. On the basis of the review...
of the literature, helpful studies in making the diagnosis of breast ALCL include MRI, aspiration cytology, and possible percutaneous or open biopsy together with confirmatory immunohistochemical markers, such as CD30 and ALK.

REFERENCES