Anaplastic Large Cell Lymphoma Involving the Breast
A Clinicopathologic Study of 6 Cases and Review of the Literature

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Context.—Lymphomas involving the breast are rare, and most cases are of B-cell lineage; T-cell neoplasms represent less than 10% of all breast lymphomas.

Objective.—To define the clinicopathologic spectrum of anaplastic large cell lymphomas (ALCLs) involving the breast.

Design.—Six cases of ALCL involving the breast were identified at a single institution during 21 years. The clinicopathologic and immunophenotypic features are presented, and the literature is reviewed.

Results.—All patients were women, with a median age of 52 years. There were 4 anaplastic lymphoma kinase–negative (ALK−) ALCL cases; 3 of these neoplasms developed around breast implants. Two patients with ALK− ALCL had a history of cutaneous ALCL. There were 2 ALK+ ALCLs; both patients had stage IV disease. Histologically, all neoplasms were composed of large anaplastic cells that were uniformly CD30+ and expressed markers of T-cell lineage. Four patients with adequate follow-up are alive, with a mean of 4.1 years (range, 1.5–9 years) after diagnosis of the breast tumor. Included in this group are 2 patients with ALK− ALCL associated with breast implants who were alive 4 years and 9 years after diagnosis.

Conclusions.—Including the 6 cases we describe, a total of 21 cases of ALCL involving the breast are reported. Fifteen cases, all ALK−, were associated with breast implants, suggesting a possible pathogenetic relationship, and associated with an excellent prognosis. Patients with cutaneous ALCL can subsequently develop ALK− ALCL involving the breast, and these tumors can be associated with breast implants.

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Nonepithelial neoplasms involving the breast are uncommon. The most common nonepithelial breast neoplasms are of hematologic origin, with non-Hodgkin lymphomas being most frequent. Non-Hodgkin lymphomas involving the breast account for 1.7% to 2.2% of extranodal lymphomas, and 0.38% to 0.7% of all non-Hodgkin lymphomas. Similar to non-Hodgkin lymphomas in general, lymphomas involving the breast are mainly of B-cell lineage; T-cell neoplasms represent less than 10% of neoplasms, most of which are unspecified peripheral T-cell lymphomas. Anaplastic large cell lymphoma (ALCL) of the breast is rare; only a subset of these neoplasms have been further specified as systemic versus cutaneous with dissemination, or as anaplastic lymphoma kinase positive (ALK+) versus ALK−. Fifteen cases of ALCL involving the breast and associated with breast implants have been reported.

In this study, we describe 6 cases of ALCL involving the breast identified during 21 years at our institution. We show that all types of ALCL as defined in the World Health Organization classification can occur in the breast and report 3 additional cases of ALCL associated with breast implants, including 1 patient with a history of cutaneous ALCL who subsequently developed ALK− ALCL surrounding a breast implant.

MATERIALS AND METHODS

Clinical Information

The files of The University of Texas M. D. Anderson Cancer Center (Houston) were searched for patients with lymphoid neoplasms involving the breast that were biopsied or excised during the course of their disease. Among all patients with breast lymphoma identified from January 1986 to the time of writing, 6 cases of ALCL involving the breast were identified. These patients were either referred to our institution for treatment, or their slides were submitted for consultation. All cases were reviewed and classified using the criteria of the World Health Organization classification. Clinical data, which included age, sex, side, of involvement, clinical stage, treatment, and clinical follow-up were available for all patients, although follow-up was very short for one recently diagnosed patient. The criteria for breast involvement by lymphoma were described previously.

Histologic and Immunohistochemical Techniques

Hematoxylin-eosin–stained slides and unstained slides for immunohistochemical analysis were prepared from fixed, paraffin-embedded tissue blocks. Immunohistochemical stains were performed using heat-induced epitope retrieval, an avidin-biotin complex method, and an automated immunostainer (Ventana Medical Systems, Tucson, Arizona) as described previously. The antibody panel used to assess these cases included the following antibodies (and dilutions): CD3 (1:150), CD20 (1:700), CD45 (1:300), CD45RO (1:100), and ALK1 (1:30); all from DAKO, Carpinteria, California; CD43 (1:120; Becton-Dickinson Biosciences, San Jose, California); and CD30 (1:20; Signet, Dedham, Massachusetts).
Molecular Analysis

T-cell receptor γ-chain gene rearrangement studies were performed using polymerase chain reaction–based methods on DNA extracted from fixed, paraffin-embedded tissue. A mixture of 4 family-specific, multicolored, fluorescently labeled variable region primers and 4 unlabeled joining primers was used in a multiplex assay as has been described.8

RESULTS

Clinical Features

The clinical features are summarized in Table 1. All patients were women, with a median age of 52 years (range, 21–65 years). Complete blood counts at the time of breast tumor diagnosis were available for 4 patients (cases 1–3 and 6). All patients had normal white blood cell and differential counts. Hemoglobin and platelet counts were within normal range, except for one patient (case 3) who had mild anemia and one patient (case 6) who had mild thrombocytosis. All patients had a palpable breast mass. The left breast was involved in 3 patients and the right in 3 patients; no patients had bilateral involvement. The surgical procedures that patients underwent included 3 excisional biopsies, 2 needle-core biopsies, and 1 capsulectomy.

Four patients had ALK− neoplasms (cases 1–4) involving the breast, and 2 patients had ALK+ neoplasms (cases 5 and 6) with breast involvement as a part of clinical stage IV disease. The ALK− neoplasms can be further divided into 2 subgroups. Two patients had a history of cutaneous ALCL 1 year and 4 years, respectively, before the diagnosis of ALCL in the breast. One patient (case 1), who also had a history of breast carcinoma 8 years earlier, had cutaneous ALCL involving the wrist, hip, and vagina. The ALCL involving the breast was associated with a breast implant that had been inserted 8 years earlier. This patient did not have a history of cutaneous ALCL. Both tumors were associated with breast implants. In one patient (case 3), the implant was placed 9 years earlier, and the ALCL was not associated with a seroma. In the other patient (case 4), the length of time the patient had implants is not known, and the neoplasm was associated with 80 mL of seroma-like fluid. One patient (case 3) had a history of focal involvement of an axillary lymph node by a lymphoid tumor that expressed CD15 and CD30 and was initially interpreted as classic nodular sclerosis Hodgkin lymphoma. This tumor was diagnosed 2.5 years before breast ALCL. The patient had clinical stage II disease and was treated with doxorubicin, bleomycin, vincristine, and dacarbazine chemotherapy. Subsequently, 0.5 years before breast ALCL, the patient had cervical and supraclavicular lymph nodes involved by ALK− ALCL. In retrospect, the initial axillary lymph node was probably also involved by ALK− ALCL, because these tumors can express CD15 in a subset of cases.

Two patients had ALK+ ALCL (cases 5 and 6). In both, breast involvement occurred as a part of clinical stage IV disease. Neither patient had breast implants.

Clinical Follow-up

Clinical follow-up (Tables 2 and 3) after diagnosis of the breast ALCL was available for all patients, but one patient (case 4) was diagnosed recently. The follow-up interval for 5 patients ranged from 1.2 to 9 years (mean, 3.5 years). Four patients are alive. One patient (case 1) with a history of cutaneous ALCL and subsequent ALK− ALCL in breast was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and is disease free 10 years after diagnosis of skin lesions and 9 years after diagnosis of breast ALCL. The other patient (case 2) with a history of cutaneous ALCL and subsequent ALK− ALCL involving the breast was treated with rituximab (R)-CHOP and subsequently anti-CD30 antibody, and she went into partial remission. R-CHOP was employed because a biopsy specimen of a skin lesion showed T-cell lineage with aberrant expression of CD20. This patient is alive with disease 5.5 years after diagnosis of skin disease and 2 years

Table 1. Anaplastic Large Cell Lymphoma (ALCL) Involving the Breast: Clinical Features

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, y</th>
<th>Clinical Presentation</th>
<th>History</th>
<th>Breast Presentation</th>
<th>Tumor Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>Skin lesions in hip, wrist, and vagina</td>
<td>Breast cancer T1N1M0. Chemotherapy and mastectomy. Implant after surgery. Smoker × 10 y.</td>
<td>Mass effect. Fluid around implant.</td>
<td>1 cm</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>Supraclavicular and neck</td>
<td>ALK− ALCL 2 y before. Chemotherapy and radiation. Implanted, cosmetic, 9 y before.</td>
<td>Pain and swelling. Scar; no fluid.</td>
<td>1.5 cm</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>Breast swollen</td>
<td>NA</td>
<td>Swelling. Fluid around implant.</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>Nodal inguinal, mediastinal, and lung</td>
<td>NA</td>
<td>Mass effect.</td>
<td>1.5 cm</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>Shoulder soft tissue, axillary and pleural mass</td>
<td>ALCL 8 y before. Astrocytoma 16 y before. Seizures.</td>
<td>Swelling.</td>
<td>4 cm</td>
</tr>
</tbody>
</table>

Abbreviations: ALK, anaplastic lymphoma kinase; AWD, alive with disease; DFS, disease-free survival; DOD, dead of disease; NA, not available.

a TNM staging for cutaneous lymphomas; Ann Arbor staging for nodal or extranodal lymphomas.

b Here, y indicates years after diagnosis of breast tumor.
Table 1. Extended

<table>
<thead>
<tr>
<th>Side</th>
<th>Specimen</th>
<th>Implant</th>
<th>Stage</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>Excision</td>
<td>Yes</td>
<td>T1a</td>
<td>Chemotherapy</td>
<td>DFS 9 y</td>
</tr>
<tr>
<td>Left</td>
<td>Core</td>
<td>No</td>
<td>T3b</td>
<td>Chemotherapy</td>
<td>AWD 2 y, Breast cancer 2 y later.</td>
</tr>
<tr>
<td>Left</td>
<td>Excision</td>
<td>Yes</td>
<td>IIIE</td>
<td>Chemotherapy, radiation</td>
<td>DFS 4 y</td>
</tr>
<tr>
<td>Left</td>
<td>Capsule</td>
<td>Yes</td>
<td>NA</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Right</td>
<td>Excision</td>
<td>No</td>
<td>IV</td>
<td>Chemotherapy</td>
<td>DOD 1.2 y</td>
</tr>
<tr>
<td>Right</td>
<td>Core</td>
<td>No</td>
<td>IV</td>
<td>Chemotherapy, radiation</td>
<td>AWD 1.5 y</td>
</tr>
</tbody>
</table>

Figure 1. Anaplastic lymphoma kinase–negative anaplastic large cell lymphoma (ALCL) disseminated from cutaneous ALCL (case 2). Tumor cells are monotonous, some with prominent nucleoli (hematoxylin-eosin, original magnification ×400).

Figure 2. Anaplastic lymphoma kinase–negative anaplastic large cell lymphoma (case 3). Scattered large pleomorphic cells are identified (hematoxylin-eosin, original magnification ×400).

after diagnosis of breast ALCL, but she developed contralateral breast carcinoma. For the 2 patients with ALK-ALCL without a history of cutaneous ALCL, one patient (case 3) was treated with a number of chemotherapy regimens and is disease free at 4 years. The recently diagnosed patient (case 4) has had only 1 month of follow-up at time of writing, and details of the chemotherapy plan are unknown.

For the 2 patients with ALK+ ALCL, one patient (case 5) died with disease 1.2 years after diagnosis, despite being treated with various chemotherapeutic regimens. The other patient (case 6) is alive with disease 9.5 years after initial diagnosis of ALK+ ALCL and 1.5 years after biopsy showed breast involvement. She has been treated with local radiation and multiple chemotherapy regimens.

Histologic and Immunohistochemical Features

Cases 1 and 2 occurred in patients with a history of cutaneous ALCL who subsequently developed ALK-ALCL of the breast. In case 1, the breast neoplasm was a 1-cm mass around the breast implant that was associated with fluid. Aspiration and cytologic examination of the fluid revealed neoplastic cells. The biopsy specimen showed a monotonous infiltrate of pleomorphic cells with rare hallmark cells admixed with neutrophils, eosinophils, and a background of sclerosis and necrosis. In case 2, the neoplasm was a 1.2-cm mass composed of a monotonous, diffuse infiltrate of large cells with prominent central nucleoli (immunoblastic morphology) and a background of sclerosis (Figure 1). Both cases were positive for CD3 and CD30 and were negative for ALK. Case 1 was granzyme B+. Previous skin lesions but not the breast ALCL of case 2 coexpressed CD20. Molecular studies showed monoclonal T-cell receptor γ-chain gene rearrangements in both neoplasms.

Cases 3 and 4 were de novo ALK- ALCL. Case 3 was a 1.5-cm mass around a breast implant that was composed of a monotonous infiltrate of pleomorphic cells with frequent hallmark cells and sclerosis. Necrosis as well as neutrophils and eosinophils were present (Figure 2). In case 4, no distinct tumor was identified grossly. Histologically, the neoplasm appeared to lie within a fibrinous exudate and penetrate or become trapped in a thick fibrous capsule (Figure 3, A). The neoplastic cells were large and

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pleomorphic with vesicular nuclei, prominent nucleoli, and numerous mitoses. The neoplastic cells were focally admixed with abundant neutrophils when surrounded by the fibrinous exudate (Figure 3, B), or they were distributed in large clusters when immersed in the fibrous capsule (Figure 3, C). Chronic inflammation was present at the periphery of the fibrous capsule. In both cases, the neoplastic cells were positive for CD30 (Figure 3, D) and negative for CD20 and ALK. In case 3, the neoplastic cells were also positive for CD4, CD43, EMA, and granzyme B.

Cases 5 and 6 were ALK<sup>+</sup> ALCL. Case 5 was a 1.5-cm tumor that infiltrated breast parenchyma, and the neoplastic cells were monotonous with centroblast-like nuclei. No hallmark cells were identified (Figure 5). Case 6 was a 4.0-cm mass. A needle-core biopsy showed neoplastic cells arranged in a nested pattern, and the cells were large and pleomorphic, including hallmark cells (Figure 6, A). Mitotic figures were numerous. Both tumors were positive for CD30, granzyme B, and ALK (Figure 6, B), and were negative for CD3. Both neoplasms had a nuclear and cytoplasmic pattern of ALK expression, consistent with the t(2;5)(p23;q35). Case 5 was CD43<sup>+</sup>, and case 6 was EMA<sup>+</sup>.

**COMMENT**

We report 6 cases of ALCL involving the breast. Four cases were ALK<sup>+</sup>, including 2 patients who had a history of cutaneous ALCL, and 2 cases were ALK<sup>+</sup>. Three patients, all with ALK<sup>-</sup> ALCL, including one patient with a history of cutaneous ALCL, had tumors associated with breast implants. Two implant-associated tumors had fluid accumulation or “seromas.”

ALCL rarely involves the breast (Tables 2 and 3). Including the 6 cases of breast ALCL we report, 21 cases have been reported in the literature, and these cases are heterogeneous. Seventeen cases were ALK<sup>-</sup>, or ALK status was not reported, including 4 cases occurring in patients with a history of cutaneous ALCL. A review of several case series of breast lymphomas published within the past 10 years did not disclose additional cases of ALCL.

A total of 15 cases of ALCL associated with breast implants are now reported in the literature, of which 10 had seromas or concomitant fluid accumulation. The association between breast implants and lymphoma involving the breast has been reported rarely, not only associated with ALCL, but rarely with other lymphomas, such as follicular lymphoma and lymphoplasmacytic lymphoma. However, it is intriguing that ALCL, a relatively uncommon type of lymphoma representing approximately 2% of all non-Hodgkin lymphomas in North America, seems to be particularly associated with breast implants. If chance alone were the explanation, one would expect to observe more cases of common lymphoma types, such as diffuse large B-cell lymphoma or follicular lymphoma, to be associated with implants. The frequency of ALK<sup>-</sup> ALCL in this clinical setting suggests a pathogenetic relationship with implants, as has been suggested by others.

Clinically, reported cases of ALCL associated with a breast implant have arisen from 3 to 19 years (median, 8 years) after implant, placed for either cosmetic or reconstructive surgery reasons in 7 cases each. The reason for implant is unknown for one patient. Seroma or fluid accumulation is commonly but not invariably associated with these neoplasms. The amount of fluid has ranged from 80 to 720 mL. Fluid obtained via fine-needle aspiration was analyzed in 7 cases; 6 were diagnosed as positive for malignant cells, and 1 was diagnosed as suspicious for malignancy. Thirteen patients had clinical stage I and 2 had clinical stage II disease. Ten patients received therapy: 6 patients received local radiation and chemotherapy (most often the CHOP regimen), 3 patients received chemotherapy alone, and 1 patient received local radiation only. Two patients did not receive therapy, and the status is unknown in 3 patients. Adequate clinical follow-up was reported for 9 patients and ranged from 0.8 to 9 years (median, 1 year). No lymphadenopathy or systemic disease developed during the follow-up interval.

Grossly, a tumor mass was identified in only 6 cases and ranged from 1 to 3 cm. In the remaining 9 cases, the tumors were contained in fibrous tissue, not identified grossly, and presented as thickening or nodularity in the capsule around the breast implant. In these cases, the tumor was only identified by histologic examination of extracted fibrous capsule. Seven implants were filled with saline, which is also reported in breast implants. Intraoperative ultrasound examination of the implant also revealed fluid (seroma), but this was not confirmed histologically.
Table 2. Extended

<table>
<thead>
<tr>
<th>Time implant to ALCL, y</th>
<th>Stage</th>
<th>Type of Specimen</th>
<th>Cytology</th>
<th>Immunophenotype</th>
<th>PCR</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>T1a/IE</td>
<td>Excision</td>
<td>Positive</td>
<td>T-cell</td>
<td>Clonal</td>
<td>Chemotherapy</td>
<td>DFS 9 y</td>
</tr>
<tr>
<td>NA</td>
<td>T3b/IE</td>
<td>Core</td>
<td>NA</td>
<td>T-cell</td>
<td>Clonal</td>
<td>Chemotherapy</td>
<td>AWD 2 y Breast</td>
</tr>
<tr>
<td>9</td>
<td>IE</td>
<td>NA</td>
<td>NA</td>
<td>T-cell</td>
<td>NA</td>
<td>Chemotherapy</td>
<td>AWD 1 y</td>
</tr>
<tr>
<td>16</td>
<td>T1a</td>
<td>Incision</td>
<td>NA</td>
<td>T-cell</td>
<td>NA</td>
<td>Chemotherapy</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>IIIE</td>
<td>Excision</td>
<td>NA</td>
<td>T-cell</td>
<td>NA</td>
<td>Chemotherapy, radiation</td>
<td>DFS 4 y</td>
</tr>
<tr>
<td>NA</td>
<td>IIIE</td>
<td>Excision</td>
<td>NA</td>
<td>T-cell</td>
<td>NA</td>
<td>Chemotherapy</td>
<td>DOD 0.3 y</td>
</tr>
<tr>
<td>5</td>
<td>IIIE</td>
<td>Excision</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Chemotherapy, radiation</td>
<td>DFS, unknown</td>
</tr>
<tr>
<td>19</td>
<td>IE</td>
<td>Capsule</td>
<td>NA</td>
<td>T-cell</td>
<td>Clonal</td>
<td>Chemotherapy, radiation</td>
<td>NA</td>
</tr>
</tbody>
</table>

Figure 3. Anaplastic lymphoma kinase–negative anaplastic large cell lymphoma associated with effusion (case 4). A, Capsule was associated with fluid accumulation displaying fibrinoid exudate on the inner surface (hematoxylin-eosin, original magnification ×20). B, Individual and small clusters of neoplastic cells within fibrinoid exudate (hematoxylin-eosin, original magnification ×100). C, Large clusters of neoplastic cells immersed in a sclerotic stroma (hematoxylin-eosin, original magnification ×100). D, Immunohistochemistry demonstrates that large neoplastic cells are positive for CD30 (original magnification ×400).
ALCL of the Breast

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Table 3. Breast Implant Associated with Anaplastic Large Cell Lymphoma (ALCL) and Anaplastic Lymphoma Kinase–Positive (ALK+) ALCL Involving the Breast: Clinicopathologic Features and Review of the Literature

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age, y</th>
<th>Breast Presentation</th>
<th>Tumor Size</th>
<th>Side</th>
<th>Implant</th>
<th>Reason for Implant</th>
<th>Material</th>
<th>Time Implant to ALCL, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast implant and “seroma”-associated ALCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>65</td>
<td>Seroma 720 mL</td>
<td>Not detected</td>
<td>Left</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Roden et al, 2008</td>
<td>45</td>
<td>Seroma</td>
<td>Not detected</td>
<td>Right</td>
<td>Yes</td>
<td>CA</td>
<td>Saline</td>
<td>7</td>
</tr>
<tr>
<td>Roden et al, 2008</td>
<td>59</td>
<td>Seroma</td>
<td>NA</td>
<td>Left</td>
<td>Yes</td>
<td>CA</td>
<td>Silicone</td>
<td>3</td>
</tr>
<tr>
<td>Roden et al, 2008</td>
<td>34</td>
<td>Seroma 700 mL</td>
<td>NA</td>
<td>Left</td>
<td>Yes</td>
<td>Cosmetic</td>
<td>Saline</td>
<td>4</td>
</tr>
<tr>
<td>Roden et al, 2008</td>
<td>44</td>
<td>Seroma</td>
<td>NA</td>
<td>Left</td>
<td>Yes</td>
<td>Cosmetic</td>
<td>Saline</td>
<td>NA</td>
</tr>
<tr>
<td>Sahoo et al, 2003</td>
<td>33</td>
<td>Seroma</td>
<td>1 mm</td>
<td>Left</td>
<td>Yes</td>
<td>CA</td>
<td>Siliccone</td>
<td>9</td>
</tr>
<tr>
<td>Gaudet et al, 2002</td>
<td>87</td>
<td>Seroma</td>
<td>NA</td>
<td>Right</td>
<td>Yes</td>
<td>CA</td>
<td>Saline</td>
<td>8</td>
</tr>
<tr>
<td>Newman et al, 2008</td>
<td>52</td>
<td>Seroma 200 mL</td>
<td>3 cm</td>
<td>Right</td>
<td>Yes</td>
<td>Cosmetic</td>
<td>Siliccone</td>
<td>14</td>
</tr>
<tr>
<td>Olack et al, 2007</td>
<td>64</td>
<td>Seroma</td>
<td>NA</td>
<td>Right</td>
<td>Yes</td>
<td>CA</td>
<td>Saline</td>
<td>7</td>
</tr>
<tr>
<td>ALK+ ALCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 5</td>
<td>21</td>
<td>Mass effect</td>
<td>1.5 cm</td>
<td>Right</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Case 6</td>
<td>35</td>
<td>Swelling</td>
<td>4 cm</td>
<td>Right</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Aguilera et al, 2000</td>
<td>13</td>
<td>Fungating mass</td>
<td>6 cm</td>
<td>Left</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Iyengar et al, 2006</td>
<td>36</td>
<td>Mass cystic</td>
<td>3.5 cm</td>
<td>Left</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AWD, alive with disease; DFS, disease-free survival; DOD, dead of disease; CA, breast cancer; NA, not applicable or not available.

1. PCR indicates polymerase chain reaction for T-cell receptor γ-chain gene rearrangement.
2. None indicates no therapy in addition to surgery.
3. Here, y indicates years of follow-up after diagnosis.

and 7 were filled with silicone; the type of implant is unknown in one case. In all cases, these tumors have been composed of large and pleomorphic cells. Twelve cases had a T-cell immunophenotype, and 3 had a null-cell immunophenotype. When performed, monoclonal T-cell receptor gene rearrangements have been identified. In aggregate, these clinical and pathologic findings suggest that ALCL associated with breast implants is a distinctive entity, associated with clinically indolent behavior and a good prognosis, as has been suggested previously by others.

Including 2 cases we report, there are 4 cases of cutaneous ALCL with secondary involvement of the breast parenchyma (Table 2) reported in the literature. All patients were women, with an age range of 13 to 36 years (mean, 26 years). In the 2 cases we report, the skin biopsies specimens were initially interpreted as cutaneous CD30+ T-cell lymphoproliferative disorder, to be correlated with clinical data. In retrospect, the skin lesions were involved by cutaneous ALCL that disseminated to the breast after 1 and 4 years, respectively. Three patients reported receiving chemotherapy; the one patient who did not receive chemotherapy was lost to follow-up. A 63-year-old patient with breast mass and fluid accumulation is alive and is disease free 9 years after diagnosis of the breast tumor; the other 2 patients were alive with disease at 1 and 2 years of follow-up (Table 2). Cutaneous ALCLs are ALK+, and many affected patients have a protracted course or even spontaneous regression. It is reported that cutaneous ALCLs may occasionally progress and rarely affect viscera, but cutaneous ALCL cases disseminating to breast have been described rarely in the literature. The 63-year-old patient associated with breast implant and fluid accumulation we report is alive 10 years after initial diagnosis of cutaneous ALCL. This case is similar to the other cases with breast implants, and ALCL associated with fluid accumulation in that the tumor mass was small, ALK+, and was associated with an excellent outcome. Roden and colleagues have suggested that ALK+ ALCL associated with breast implants, which they term as seroma-associated ALCL, may be closely related to cutaneous ALCL based on its clinicopathologic features. The 2 patients with a history of cutaneous ALCL we report, as well as the other 2 cases reported in the literature, provide support for the suggestion of Roden and colleagues. ALK+ ALCL results from cytogenetic abnormalities involving ALK, of which the t(2;5)(p23;q35) is most common. The t(2;5) fuses the ALK gene on 2p23 to the nucleophosmin (NPM) gene on 5q35, resulting in the constitutive activation of ALK kinase. Including the 2 cases we report, 4 cases of ALK+ ALCL involving breast (Table 3) are reported in the literature. All patients were women, with an age range of 13 to 36 years (mean, 26 years). All presented with a breast mass ranging from 1.5 to 6 cm (mean, 3.5 cm); one tumor was partially cystic. All had localized disease involving breast and regional lymph nodes (stage IIE). The 2 patients we report received chemotherapy (Table 3). Therapy is not reported for the other 2 cases in the literature. In 3 cases with follow-up, 2 died of disease at 0.5 and 1.2 years; one is alive with disease 9.5 years after initial diagnosis of ALCL and 1.5 years after diagnosis of breast ALCL. Thus, it is apparent that ALK+ ALCL involving the breast usually occurs as a part of disseminated disease and with a variable outcome, similar to what is described for patients affected by ALK+ ALCL involving other anatomic sites.

In summary, we describe 6 cases of ALCL involving the breast. Our cases, in addition to 15 cases described in the literature, highlight the clinical and pathologic spectrum of ALCL affecting the breast. This study also highlights 3 distinct groups. The first group includes patients with a history of cutaneous ALCL who subsequently develop ALK+ ALCL of the breast. Although we have not sequenced the neoplasms in the skin and breast, presumably the cutaneous and breast lesions are related. The second group includes cases of ALK+ ALCL associated with breast implants. The first and second groups are not mutually exclusive, because patients with a history of cutaneous ALCL can subsequently develop implant-associated ALCL of the breast. The association of ALK+ ALCL, an
Table 3. Extended

| Stage | Specimen | Cytology | Immunophenotype | PCR | Therapy | Outcome  
|-------|----------|----------|-----------------|-----|---------|---------
| IE    | Capsule  | Positive | T-cell          | NA  | None    | NA      
| IE    | Capsule  | Positive | T-cell          | Clonal | Radiation | DFS 1.7 y  
| IE    | Capsule  | Positive | T-cell          | Clonal | Chemotherapy, radiation | DOD 1.2 y  
| IE    | Capsule  | NA       | T-cell          | Clonal | NA      | NA      
| IE    | Capsule  | NA       | T-cell          | Clonal | Chemotherapy, radiation | DFS 1 y  
| IE    | Core     | Suspicious | NA       | NA | Chemotherapy | DFS 1.5 y  
| IE    | Capsule  | Positive | T-cell          | NA | Chemotherapy, radiation | AWD 1.5 y  
| IV    | Excision | NA       | T-cell          | NA | Chemotherapy | DOD 1.2 y  
| IV    | Core     | NA       | Null-cell       | NA | Chemotherapy, radiation | DOD 0.5 y  
| IV    | Excision | NA       | T-cell          | Clonal | NA | NA      
| IIE   | Core     | Positive | T-cell          | NA | NA      | NA      

Figure 4. Anaplastic lymphoma kinase–negative anaplastic large cell lymphoma (case 3). Immunohistochemistry demonstrates that some large neoplastic cells are positive for CD43 (original magnification ×1000).

Figure 5. Anaplastic lymphoma kinase–positive anaplastic large cell lymphoma (case 5) infiltrating breast parenchyma. Neoplastic cells show a centroblast-like nuclei (hematoxylin-eosin, original magnification ×400).

Figure 6. Anaplastic lymphoma kinase–positive anaplastic large cell lymphoma (case 6). A, Large cells, including occasional hallmark cells, arranged in a nested pattern (hematoxylin-eosin, original magnification ×400). B, Immunohistochemistry positive for ALK-1 with nuclear and cytoplasmic reactivity (original magnification ×400).
uncommon lymphoma type, with breast implants suggests an etiologic relationship. These lesions are commonly but not invariably associated with seromas. The third and last group includes patients with ALK⁺ ALCL involving the breast. Patients with ALK⁺ ALCL usually have widespread systemic disease, of which breast involvement is only one site of dissemination.

References