Published in final edited form as:
Appl Immunohistochem Mol Morphol. 2009 July ; 17(4): 301–306. doi:10.1097/PAI.0b013e318195286d.

Primary and Secondary T-cell Lymphomas of the Breast: *Clinico-pathologic Features of 11 Cases*

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Abstract

Breast involvement by non-Hodgkin lymphomas is rare, and exceptional for T-cell lymphomas; we studied the morphologic, immunophenotypic, and clinical features of 11 patients with T-cell non-Hodgkin lymphomas involving the breast. Four cases fulfilled the definition criteria for primary breast lymphomas, 3 females and 1 male, with a median age of 51 years. One primary breast lymphomas was T-cell lymphoma unspecified, other was subcutaneous panniculitis-like T-cell lymphoma, and 2 cases were anaplastic large cell lymphomas. One of the anaplastic large cell lymphoma cases was found surrounding a silicone breast implant and presented as clinically as mastitis; whereas the other case occurred in a man. T-cell lymphoma secondarily involved the breast in 7 patients, all women and 1 bilateral, with a median age of 29 years. These secondary breast lymphomas occurred as part of widespread nodal or leukemic disease. Three patients had adult T-cell leukemia/lymphoma, including the patient with bilateral lesions, 3 others had precursor T-lymphoblastic lymphoma/leukemia, and the other presented with a peripheral-T-cell lymphoma nonotherwise specified type. Breast T-cell lymphomas are very infrequent and are morphologically and clinically heterogeneous.

Keywords

malignant lymphoma; breast T-cell lymphoma; extranodal; non-Hodgkin lymphoma; immunohistochemistry

T-cell lymphomas are uncommon, accounting for only about 12% to 15% of all non-Hodgkin lymphomas (NHLs) in Western countries.[1–3] Malignant lymphomas of the breast are rare, and may present as a primary or secondary tumor. They comprise less than 0.5% of all breast malignancies and 0.7% of all NHLs[4,5] and 1.7% to 2.2% of extranodal lymphomas.[6] Most lymphomas involving the breast are of B-cell lineage, with only rare cases showing T-cell phenotype, even in the largest series of breast hematolymphoid lesions involving the breast.[4–9] In the English medical literature, most of the papers referring to breast T-cell lymphomas consist of case reports or rare cases included in a general series of lymphomas of the breast. In those reports, almost all the histopathologic subtypes of T-cell lymphomas have been

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Disclosure/Conflict of Interest: No conflict of interest to declare.

described to involve the breast parenchyma, including both precursor and mature cell types.[7,9–15]

In this study, we have analyzed the clinical presentation and morphologic and immunohistochemical features of 11 patients with T-cell lymphoma involving the breast parenchyma.

MATERIALS AND METHODS

From the files of Consultoria em Patologia, a large consultation service in anatomic pathology in Brazil, we retrieved all cases diagnosed as lymphomas of the breast from June 1997 to December 2007. Clinical data including sex, age at diagnosis, and anatomic location were available for all the cases. Size information was based on clinical findings. Follow-up was obtained from the referring pathologists/oncologists for a subset of patients. The patients were divided in 2 groups: primary breast lymphomas (PBLs) (localized) and secondary breast lymphomas (SBL) (disseminated lymphomas with primary extramammary site involvement and/or leukemia presentation). PBLs were defined according to the Wiseman and Liao criteria.[5]

Routine Light Microscopy and Immunohistochemistry

Tissues from all cases were formalin fixed and paraffin embedded. The hematoxylin and eosin-stained slides were reviewed for routine morphology. Immunohistochemistry was performed using the following panel of antibodies: CD20 (L26, 1:1200); CD30 (BerH2, 1:300); terminal deoxynucleotidyl transferase (polyclonal 1:1600); epithelial membrane antigen (E29, 1:800); Ki-67 (MIB-1, 1:4800); anaplastic lymphoma kinase (ALK) (ALK-1, 1:200); cytokeratins 40, 48, 50, and 50.6KDa (AE1/AE3, 1:500) (DAKO, Carpinteria, CA); CD3 (SP3, 1:300) (Lab-Vision, Fremont, CA); CD2 (271, 1:200), CD4 (1F6, 1:100), CD5 (4C7, 1:150), CD8 (SP16, 1:300), and CD25 (4C9, 1:200) (Novocastra, Newcastle upon Tyne, UK). Novolink polymer (Novocastra, Newcastle upon Tyne, UK) was the detection system, and diaminobenzidine was the chromogen.

The cases were classified or reclassified according to the criteria proposed by the World Health Organization classification of tumors of hematopoietic and lymphoid tissue.[3]

The Ki-67 proliferation index was calculated using the mean percentage of 500 positive nuclei in 10 high power fields (400 ×).

Molecular Study

DNA was isolated from both formalin-fixed, paraffin-embedded lymph nodes with PK1 buffer as described previously.[16] Clonality studies for T-cell receptor (TCR) γ and TCRβ were performed by polymerase chain reaction amplification using multiplex polymerase chain reaction according to the BIOMED-2 protocol.[17]

RESULTS

Clinical Findings

From a total of 66 cases of breast NHLs belonging to 64 patients, we identified 12 specimens with T-cell lymphomas from 11 patients (17.2%). Fifty-one of these 64 patients were part of a previous study.[8] Four of the T-cell lymphoma cases were PBLs and the other 7 were SBLs. One PBL case occurred in a male patient. The clinical features of the cases are summarized in Table 1. The age ranged from 21 to 70 years old, with a median age of 34 years. For PBL, the mean age was 51 years and for SBL was 29 years. Two cases presented as edema and swelling,

1 of these had a periprosthetic lesion. The other cases presented with a mass lesion, 7 cases as a painless palpable mass (63.6%) and 2 as painful poorly defined masses (18.1%); 1 of the latter patients had bilateral similar lesions. The clinical tumor size reported in 10 patients ranged from 1.5 to 6 cm. The right breast was involved in 7 cases (63%), the left in 3 (27%), and 1 patient (9%) had bilateral breast lesions.

Histologic and Immunohistochemical Findings

The histopathologic analysis of the 4 cases of PBL revealed 2 patients with anaplastic large cell lymphomas (ALCLs); 1 T-cell lymphoma, nonotherwise specified (NOS); and 1 subcutaneous panniculitis-like T-cell lymphoma. One of the $CD30^+$ ALCL occurred in a male patient and was ALK positive. Other $CD30^+$ ALCL occurred in a young female who developed the lymphoma in her breast adjacent to a silicone breast implant 6 years after elective breast augmentation. ALCL morphology was classic in both cases, including the presence of horseshoe hallmark cells of large and medium size infiltrating between ductolobular breast parenchyma. It is worth mentioning that there was evidence of refractile material in close association with lymphoma cells, which could indicate leakage of silicone. This case showed expression of CD30 and CD2; CD3 and ALK were negative (Fig. 1). None of ALCLs had skin compromise. Other case was a subcutaneous panniculitis-like T-cell lymphoma, characterized by necrosis and rimming of fat cells by large, irregular malignant T cells infiltrating the breast parenchyma. No skin compromise was noted. The last case of PBL was a peripheral T-cell lymphoma (PTCL) NOS, composed of medium size, polymorphic clear cells in a background rich in eosinophils and histiocytes. The lymphoma cells seemed to follow the lobular breast architecture, with a nodular pattern and showed many lymphoepithelial lesions (Fig. 2). All PBL except 1 case of ALCL were $CD3^+$.

The secondary breast T-cell lymphomas included 3 cases of the human T-cell leukaemia virus-1–associated lymphoma (adult T-cell leukemia/lymphoma), 1 bilateral, containing highly atypical large and intermediate size cells and a high proliferation score. All of these cases had expression of CD25. Three other cases were precursor T- lymphoblastic lymphoma/leukemias and 1 was a PTCL- NOS. All cases had a high proliferation index (>50%, range between 50% and 95%).

Molecular Study

TCR study was performed in 7 cases, all PBL, including the ALCL associated with silicone implant and 3 SBL (cases 5, 6, and 7). All cases showed clonal TCRγ rearrangement; 2 cases also revealed TCRβ rearrangement (cases 3 and 7). The other 4 were inconclusive because the DNA quality and/or quantity were insufficient for analysis.

Follow-up was available in 10 cases. Five patients died owing to disease, between 2 and 12 months after diagnosis, and 5 other are still alive with a follow-up range between 5 and 40 months. The treatment protocols were applied variably, but all patients received stage- adapted chemotherapy and 2 cases (cases 3 and 4) also received radiation therapy.

DISCUSSION

T-cell lymphomas comprise less than 15% of all NHLs.[3] Breast T-cell lymphomas are extremely infrequent, reported mainly as isolated cases, but almost all currently recognized subtypes have been described.[7–14,18–20] Our cases showed a slightly higher frequency of SBL than PBL, as was also observed in the largest general study of breast lymphomas of Talwalkar et al.[9] Lymphomas with secondary breast involvement occur mostly in the context of widespread preexisting nodal or, less frequent, extranodal extramammary primary disease. The frequency of T-cell lymphoma involving the breast varies from 3.4% to 15%.[6,9,14,21] The

present series of T-cell breast lymphoma is larger than previously reported, accounting to 17.1% of all our breast lymphoma cases.[8] The pathogenesis of T-cell lymphoma in the breast is poorly understood, mainly because of its rarity. PBL is reported mostly in postmenopausal women but may appear at any age. These lesions are exceedingly rare in men, and, to the best of our knowledge, our case is the first T-cell PBL reported in a man. Unexplained right side predominance is reported for breast lymphoma in general[6,21]; in our patients, 63% of the cases presented on the right side. The typical clinical presentation is as one or multiple painless mass, similar to breast B-cell lymphoma and breast carcinoma; 9 of 11 (81%) of our cases had this presentation. Enlarged ipsilateral axillary lymph node is reported in 13% to 50% of PBL cases[9]; we found no cases with this presentation. There are no pathognomonic mammographic features for breast lymphoma in general and sometimes these lesions are only detected by ultrasound.[22]

ALCL has been reported previously in the breast, more frequently as PBL.[6,10,18–20] One of our patients presented an ALCL in her breast adjacent to a silicone breast implant, 6 years after elective breast augmentation. Review of the literature revealed several cases of PBL associated with a breast implant.[10,23–27] None of these reported cases presented with clinical features of mastitis as ours. The most common T-cell lymphoma type in close proximity to a breast implant is ALCL. Roden et al[24] have proposed a pathogenic mechanism for these cases involving hyperstimulation of T lymphocytes by the silicone, eventually resulting in clonal expansion. Other types of T and B-cell breast lymphoma have been described in association with breast implants, most of them SBL[13,28–30]; thus, the causality in the development of breast T-cell lymphoma in association with silicone breast implants is purely speculative.

PTCLs, unspecified, are mainly nodal lymphomas, accounting for more than 50% of all T-cell lymphomas in adults. The breast cases reported have included both PBL and SBL. The clinical outcome of these patients is variable, most of them having aggressive course, but there are reports with very good clinical evolution, applying similar therapeutics regimens.[18–20] Our primary PTCL-NOS case showed lymphoepithelial lesion, a rare event that has been previously reported.[31]

Breast involvement is very rarely seen in precursor T-lymphoblastic lymphoma, particularly as the presenting manifestation.[14] When observed, it usually occurs in the context of other systemic disease.[4,6,7,18] Involvement of the breast by precursor T-lymphoblastic lymphoma/leukemia presents as a mass or frequently as bilateral diffuse involvement. All our cases showed a well-defined mass, and 2 of them occurred in a setting of leukemic disease.

Adult T-cell leukemia/lymphoma affects adults and it is considered an aggressive disease. Involvement of the breast usually occurs in the course of widespread disease, frequently as bilateral lesions as occurred in 1 of our patients.[32] Human T-cell leukaemia virus-I/II infection is present in all regions of Brazil, but its prevalence varies according to the geographical area, being higher in the Northeastern and North regions,[33] where 2 of our patients came from.

Extranodal, extracutaneous T-cell lymphomas are very rare; the gastrointestinal tract and nasopharyngeal topographies are the most frequent sites of involvement.[1,2] This is the largest series of T-cell lymphomas involving the breast and shows the clinical and histologic heterogeneity of the disease.

Acknowledgments

The authors thank the outstanding service of Consultoria em Patologia staff for skillful technical assistance.

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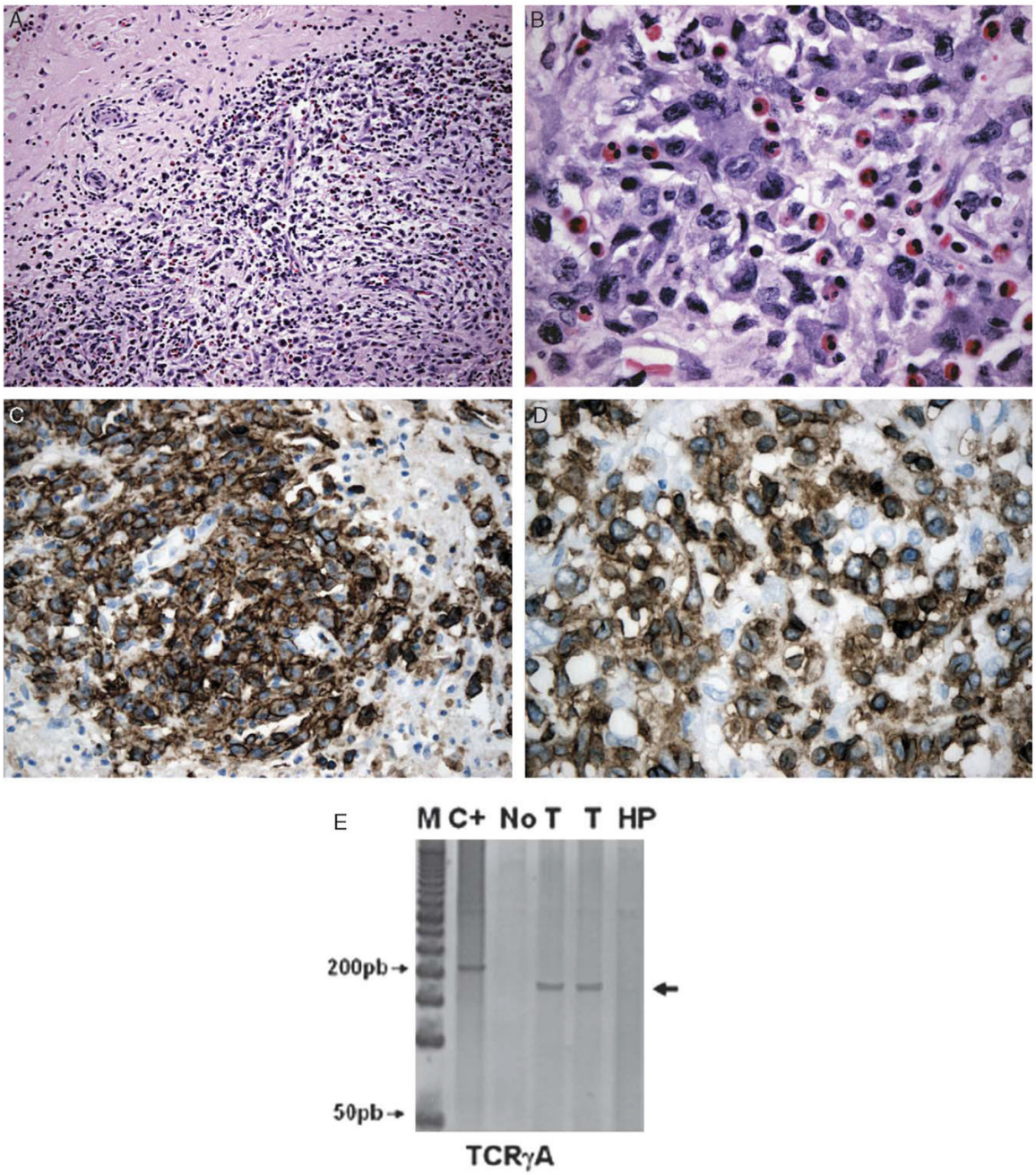

FIGURE 1.

Breast primary anaplastic large cell lymphoma in a patient with a local silicone implant (case 2). A, Lymphoma cells involve breast parenchyma and the sclerotic pseudocapsule of the implant, HE 100×. B, Neoplastic cells displayed a varied morphology with some typical horseshoe nuclei, surrounded by a polymorphic infiltrate that include eosinophils, HE 400×. C, Most of the large cells express CD30, 400×. D, Coexpression with CD3 was observed, 400×. E, Polymerase chain reaction analysis of TCRγ gene rearrangement. Heteroduplex analysis showing monoclonality in the TCR multiplex. C+ indicates T lymphoma; HP indicates case of lymphoid hyperplasia; M, DNA molecular weight marker; No, DNA absence; T, breast lymphoma in duplicate. HE indicates hematoxylin and eosin; TCR, T-cell receptor.

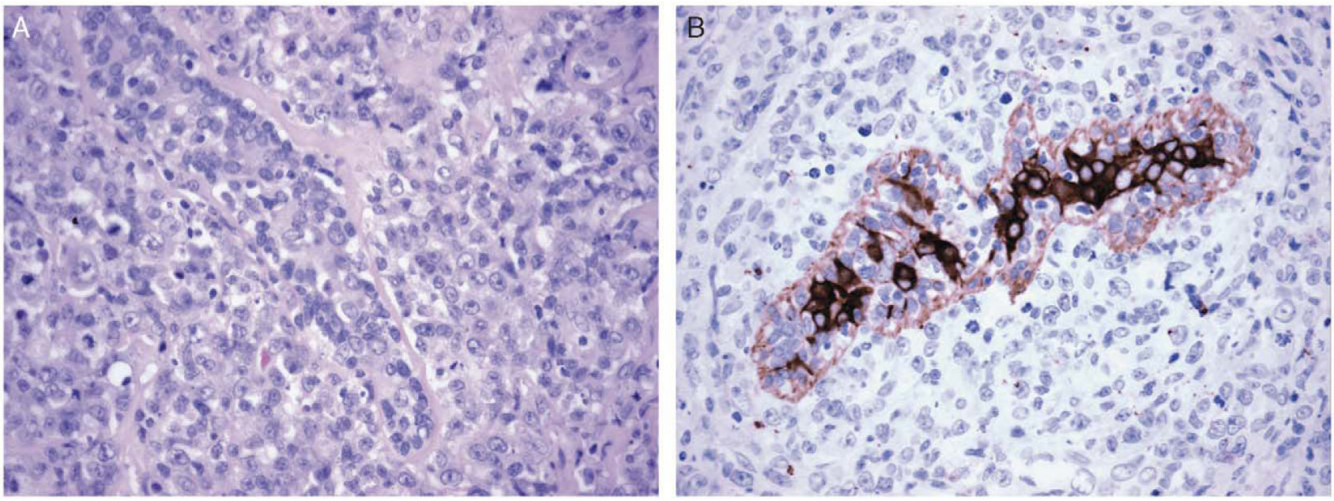

FIGURE 2.

Breast primary peripheral T-cell lymphoma, nonotherwise specified (case 3). A, Lymphomatous cells infiltrating the ductolobular units, with extensive lymphoepithelial lesions, HE 200×. B, Cytokeratin stain highlights the lymphoepithelial lesions, CK, 200×. HE indicates hematoxylin and eosin.

TABLE 1

Clinical Information and Histopathologic Distribution of all the T-cell Breast Lymphoma Cases

Cases	Age (y)	Sex	Size (cm)	Anatomic Site and Clinical Presentation	Extramammary Disease	Follow-up (mo)	Histologic Subtypes	Gene Rearrangement
1	43	F	NA	Left, skin rush, edema	No	Dead	PLTCL	+ (TCR γ)
2	28	F	NA	Left mastitis*	No	Alive (40)	ALCL	+ (TCR γ)
3	70	F	1.5	Right	No	Alive (5)	PTCL-U	+ (TCR γ and β)
4	65	M	3	Right	No	Alive (18)	ALCL	+ (TCR γ)
5	31	F	NA	Right	Yes (C, A)	Alive (29)	PTCL-U	+ (TCR γ)
6	29	F	5	Right	Yes (C, A, I, L, S)	Dead	ATLL	+(TCR γ)
7R †	35	F	6	Right, local pain	Yes (L, S, PE)	Dead	ATLL	+ (TCR γ and β)
7L †	35	F	2	Left, local pain	Yes	Dead	ATLL	ND
8	37	F	4	Right	Yes (A, BM, R, S)	NA	ATLL	ND
9	26	F	4	Right	Yes (MD)	Dead	LLB-T	ND
10	38	F	2.5	Right	Yes (BM, R)	Alive (25)	LLB-T	ND
11	21	F	3	Left	Yes (C, MD, R, BM)	Dead	LLB-T	ND

*Patient with silicone breast prosthesis.

†Case 7 had bilateral tumors.

A indicates axillary lymph node; ALCL, anaplastic large cell lymphoma; ATLL, T-cell leukemia/lymphoma associated to HTLV-1; BM, bone marrow; C, cervical lymph node; F, female; I, inguinal lymph node; L, liver; LLB-T, lymphoblastic T-cell lymphoma/lymphoblastic T-cell leukemia; M, male; MD, mediastinal; NA, not available; ND, not done; PE, pleural effusion; PLTCL, panniculitis-like T-cell lymphoma; PTCL-U, peripheral T-cell lymphoma unspecified; R, retroperitoneal lymph node; S, spleen; TCR, T-cell receptor.