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Profiles of Axillary Lymphadenopathy without Breast Lesions: An Analysis of 62 Patients Who Underwent Axillary Lymph Nodes Biopsies

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Abstract

Background: Although axillary lymph node metastasis from breast cancer is a common disease that breast surgeons encounter, clinical and pathological characteristics of axillary lymphadenopathy without breast pathology are not fully clarified.

Methods: We conducted an analysis of 62 patients who had no breast lesions radiologically and underwent axillary lymph node biopsy in our institutes between 2002 to 2015.

Results: Of the 62 patients, 21 (34%) patients had benign lymph nodes including non-specific reactive lymphadenopathy, Epstein - Barr virus infection (3 patients), ectopic breast fibro adenoma (3 patients), and tuberculosis (1 patient). Of 62 patients, 41 (66%) had malignant lymphadenopathy including 24 patients of metastasis with metastasis from other organs and 17 patients with lymphomas. Of the 24 patients with metastasis, 10 patients had occult breast cancer. Lymph node diameters in lymphoma were greater than in the other disease. We should take account of lymphoma when lymph nodes are greater than 30 mm in diameter.

Conclusion: Since 66% of patients with axillary lymphadenopathy had general malignant disease, biopsy for axillary lymphadenopathy should be needed to establish pathological diagnosis and to initiate treatment for malignant disease without delay.

Keywords: Axillary lymph node; Lymphadenopathy; Biopsy

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Introduction

Since in almost all breast cancer patients (98%), lymphoscintigraphy following radio-labeled colloid injection to the breast reveals initial distribution to the axillary Lymph Nodes (LNs) [1], which are also called the Sentinel Lymph Nodes (SLNs), it is reasonable to suppose that the most breast cancers first metastasize to the axillary LNs. However, there is room for reconsidering whether the most common cause of axillary lymphadenopathy may be metastasis from breast cancer. Based on some reports so far [2,3], the causes of axillary lymphadenopathy have been classified as reactive lymphadenopathy caused by inflammatory disorders: lymph nodes metastasis from other organs' malignant lesions, including the breast: and LN malignancy itself, namely lymphomas. Although radiographic evaluation of axillary lymph nodes abnormalities has reported [4], details on prevalence, therapeutics and outcomes of these diseases remain unclear. Since axillary LN dissection accompanied with mastectomy for breast cancer is routinely performed by breast surgeons and surgeons are well versed in axillary surgery, in general hospitals, most cases of axillary biopsies are tend to be referred to breast surgeons. To evaluate axillary pathology, Fine-Needle Aspiration (FNA) is widely utilized especially in breast cancer patients [5,6]. National Comprehensive Cancer Network (NCCN) guidelines for breast cancer management recommended SLN biopsy for node-negative cases for FNA or Core Needle Biopsy (CNB) [7].

However in the present series, LN samplings were performed by CNB or incisional biopsies for the reasons as follows:

1. CNB appears to have a greater sensitivity than FNA [8]. It is reported that diagnostic accuracy is not higher with sensitivity of 65% to 99% and specificity of 80% to 100%, and percentage involvement by carcinoma for true positive FNAs averaged 69% while false negative averaged 25%

Table 1: Clinical characteristics of patients who underwent axillary lymph node biopsy.

Clinical characteristics		Lymph node pathology		
	Benign	Malignant		Total
		Metastasis	Lymphoma	
No. of cases	21	24	17	62
Age, mean (range)	55 (21–79)	57 (35–74)	64(42–85)	59 (21–85)
Female/Male	17/4	20/4	12/5	49/13
Subjective symptoms				
Yes	8	13	8	29
No	13	11	9	34
Mean lymph node length (mm)	23.4 ± 2.5	23.3 ± 2.6	34.2 ± 3.1*	27.6 ± 1.8
Additional treatment				
Systemic chemotherapy	0	20	17	37
RT	0	15	15	30
Surgery	0	15	0	17
Outcomes				
Alive	21	19	15	55
Disease-free	21	18	14	53
Mortality	0	6 (25%)	2 (12%)	8 (13%)

RT: Radiotherapy; * p<0.05: benign *vs.* metastasis group

[9].

2. When lymphomas are suspected, it is necessary to remove enough volume of tissue samples to diagnose.

3. To diagnose occult breast cancer, immunohistochemical studies are needed.

In the present series, 62 patients were referred to undergo axillary LN biopsies within the last 10 years in our two institutes, Dokkyo Medical University Saitama Medical Center and Tokyo University Hospital, and we retrospectively studied the pathogenesis of the biopsied axillary LNs in these patients. Here we report the patients' backgrounds and outcomes, and the pathogenesis of the biopsied axillary LNs.

Patients and Methods

This was a historical series of 62 patients with axillary lymphadenopathy who underwent CNB or excisional LN biopsy between September 2002 and March 2015 in our institution. Patients with breast lesions detected using mammography and ultrasound were considered to have node-positive breast cancer, and were excluded from the study. Subjects with a history of breast cancer treatment in the opposite site and malignant disease in another organs were included. CNBs were done by 16-G core needle biopsy kit. When LNs were adjacent to main vessels including axillary vein, open biopsy operations were performed with general or local anesthesia and the largest single LNs were resected. Resected specimens were measured and underwent pathological examination. Pathological findings, laboratory data, radiological records, treatment, and clinical course were examined, referring to the medical records. The value of LN size measured by ultrasound are expressed as mean ± SEM. Comparisons between benign, metastasis and lymphoma groups was performed by one-way Analysis of Variance (ANOVA) with Scheffe's correction for multiple comparisons, and P values <0.05 was considered to be significant.

Table 2: Methods by which enlarged axillary lymph nodes were detected.

	Benign	Metastasis	Lymphoma	Total
CT	7	6	5	18
MMG	2	4	0	6
PET	0	2	4	6
US	3	0	0	3
Incidental	12	12	9	33

CT: Computed Tomography; MMG: Mammography; PET: 18F-fluorodeoxyglucose Positron Emission Tomography; US: Ultrasonography

Table 3: Classification of axillary malignant lymphadenopathy.

Metastasis	Occult breast cancer	10
	Breast cancer	3
	Esophageal cancer	2
	Thyroid papillary cancer	2
	Ovarian cancer	2
	Melanoma	2
	Breast phyllodes tumor	1
	Lung cancer	1
	Unknown origin	1
	Total	24
Lymphoma	Follicular	8
	Chronic lymphocytic	3
	T-cell prolymphocytic	3
	Anaplastic large cell	2
	Classical Hodgkin	1
	Lymphoma total	17
	Total	41

Results

LN sampling was performed by US guided CNBs in 42 patients.

Table 4: Characteristics of 10 occult breast cancer patients.

case	age	AxLN size	surgery	NO. of LN	breast pathology	receptor status	chemoterapy	radition	outcome	
1	43	30 mm	Ax	1/24		ER- PgR- HER2-	FEC paclitaxel	50 Gy	2009.5.30-	d/f alive
2	72	35	Bt Ax	1/3	no lesion	ER+ PgR+ HER2+++	FEC,antiHER2	-	2007.11.8-	d/f alive
3	42	50	Ax	1/15		ER- PgR- HER2-	FEC6	50 Gy	2006.10.19	d/f alive
4	63	20	Bt Ax	1/24	no lesion	ER+ PgR- HER2-	FEC 4, LET	-	2005.6.23	d/f alive
5	46	40	Bp Ax	2/5	3 mm carcinoma	ER+ PgR- HER2-	FEC 4, LET	50 Gy	2007.7.22	d/f alive
6	63	43	Ax	2/2		ER+ PgR+ HER2++	FEC,antiHER2	50 Gy	2008.7.1	rec.alive
7	58	35	Ax	1/4		ER+ PgR- HER2-	AC 4, paclitaxel, ANZ	50 Gy	2008.12.12	d/f alive
8	64	20	Bp Ax	1/12	no lesion	ER+ PgR+ HER2-	AC, docetaxel	50 Gy	2009.7.30	d/f alive
9	48	23	Ax	12/24		ER+ PgR+ HER2+++	AC, docetaxel,antiHER2,ANZ	50Gy	2012.8.28	d/f alive
10	72	22	Bt Ax	5/10	no lesion	ER+ PgR- HER2-	EC, docetaxel	_	2014.12.12	d/f alive

AxLN: Axillary Lymph Node; Ax: Axillary Lymph Node Dissection; Bt: Mastectomy; Bp: Partial Mastectomy; FEC: 5-FU+epirubicin+cyclophosphamide; LET: Letrozole; AC: Adriamycin+cyclophosphamide; ANZ: Anastrozole; d/f: Disease Free

Twenty patients underwent axillary lymph nodes removal as biopsies through axillary incision. In all patients, the largest LN was removed. Forty-nine of the 62 patients were women and 13 were men (mean age: 59 years). Of the 62 patients, 29 (46.8%) had clinical symptoms as a palpable nodule in the axilla. Of the 33 (53.2%) patients who had no clinical symptoms, 18 patients (54.5%) were detected using Computed Tomography (CT), 6 patients using mammography, 6 using 18F-fluorodeoxyglucose Positron Emission Tomography (PET), and 3 using Ultra Sound (US) (Table 1,2). Of the 62 patients, 21 (34%) patients had benign LNs, and 41 (66%) had malignant, of which 24 were metastatic LNs, 17 were lymphomas. The mean maximal length of the removed LN in the benign patients was 23.4 ± 2.5 mm, 23.3 ± 2.6 mm in the metastasis patients, and 34.2 ± 3.2 mm in the lymphoma patients ($P<0.05$, benign *vs.* metastasis). Based on the results of pathologic diagnosis, additional treatments were performed. Systemic chemotherapy was administered in 20 of the 24 metastatic LN patients and in all 17 lymphoma patients. Additional radio-therapy was done in 15 patients of 24 metastatic LN patients and in 15 patients of 17 lymphoma patients. Surgical treatment including axillary LN dissection was performed in 15 patients of 24 metastatic LN patients. The outcome of all patients was described in (Table 1): the mortality rate was 25% in LN metastasis patients and 12% in lymphoma patients. The causes of malignant lymphadenopathy are summarized in (Table 3). The most frequent malignant disease metastasized in axillary LNs was breast cancer (54%), including occult breast cancer. Other primary sites included the esophagus (2 patients), the thyroid gland (2 patients), the ovarium (2 patients), and skin melanoma (2 patients). Characteristics of occult breast cancer patients are shown in (Table 4). The median age was 57 years old (range 42-72). Median length of follow-up was 115 months (range, 54-155). Median length (maximum size) of axillary LN was 32 mm (range, 20-50 mm). Eight patients had N1 LN metastasis, and 2 patients had N2 (5 to 12 LN metastasis) disease. Eight patients had estrogen receptor-positive lymph nodes, 2 had triple-negative tumors and 3 had HER2 positive tumors. All patients underwent axillary LN dissection. Five patients had ALND without breast surgery, 3 patients underwent mastectomy with ALND, and 2 had lumpectomy with ALND. Seven patients received adjuvant radio-therapy (total 50 Gy) to the breast and chest wall. All patients received chemotherapy, including anti-HER2 therapy in 2 patients. Four patients received endocrine therapy including letrozole and anastrozole. Nine patients are alive without any evidence of recurrent or metastatic disease, one patient had bone lesions. The second category of malignant disease was lymphoma (41%). This category contained eight patients with B cell-derived follicular lymphoma, three patients with chronic lymphocytic leukemia, three patients with T-cell prolymphocytic lymphoma, two patients with anaplastic large cell lymphoma and one patient with Hodgkin lymphoma. All patients were treated with chemotherapy and 15 of 17 patients were treated with radiotherapy. Two of 17 patients died (12%). Details of axillar lymphadenopathy from benign disease are indicated in (Table 5). The most frequent pathology is reactive lymphadenopathy (67%). Of the 21 benign diseases other than lymphadenopathy, 3 patients had Epstein-Barr virus infection-associated lymphadenopathy, 3 had breast fibro adenoma, and one patient had tuberculosis.

Discussion

Although axillary lymphadenopathy is by no means a rare disease, little knowledge has been reported concerning the cause of axillary LN pathology so far. It is worthwhile to note that few reports have addressed mammographic axillary abnormalities by radiologists [4-6]. In the mammographic axillary disorders, both palpable and non-palpable LNs can be detected. However, the final diagnosis can be made with CNB or incisional LN biopsy and pathological examinations for resected LN. Since in our institution, axillary LN biopsy has been usually performed by breast surgeons who are generally familiar with axillary anatomy, breast lesions have been carefully examined using radiological and ultrasound modalities. As a result, several cases of LN metastasis from occult breast cancers have been found and diagnoses were confirmed. In the present series, the most frequent axillary LN malignancy was occult breast cancer, which is histologically consistent with breast cancer presenting as axillary LN metastasis without clinical and radiological evidence of primary breast tumors. The disease is reported to be rare with an incidence rate of 0.1% to 0.8% [12-14]. In our institution, of 1685 breast cancer patients, 10 patients with occult breast cancers (0.65%) have been treated in the last 13 years, and the incidence rate is consistent with the results by several investigators as quoted earlier. Since occult primary breast cancer is a rare disease, evidence-based standard treatment has not been established. A Meta-analysis study of 92 patients in a total of 15 studies reported by Fayanju et al. [15] revealed that Asian patients were more likely to undergo breast surgery, but not receive chemotherapy; in contrast, American patients were more likely to receive chemotherapy, and more

Table 5: Classification of benign axillary lymphadenopathy.

Pathology	n (%)	Age (mean)	Female / male
Reactive lymph adenopathy	14 (67)	57	11 / 3
EBV infection	3 (14)	52	2 / 1
Fibroadenoma (breast)	3 (14)	51	3 / 0
Tuberculosis	1 (5)	31	1 / 0
Total	21 (100)	55	17 / 4

EBV: Epstein-Barr Virus

patients with positive Magnetic Resonance Imaging (MRI) findings received chemotherapy than patients with negative MRI findings. They recommended establishing an international standard occult breast cancer treatment. In the present series, we encountered 10 occult breast cancer patients: all patients received chemotherapy, including anti-human epidermal growth factor receptor 2 (HER2) therapies; 5 patients underwent total or partial mastectomy; and 6 patients received radiotherapy. Considering that all patients have survived, it appears to be clear that chemotherapy including anti-HER2 therapy, as well as mastectomy or radiotherapy for the breast is strongly recommended for occult breast cancer. The second-most frequent malignant disease was lymphoma, which accounted for 27.4% of axillary LN pathology. The clinical feature of axillary lymphadenopathy from lymphomas was larger size of LNs than from other disease (34.2 mm *vs.* 27.6 mm). Walsh and colleagues reported that when bilateral marked enlarged LNs were present, the most likely cause was chronic lymphocytic lymphoma, or small well-differentiated lymphocytic lymphoma [4]. They also pointed out that the mean length of malignant lymphadenopathy included lymphomas that were greater or equal to 45 mm. It should also be added that the important clinical feature of lymphadenopathy from lymphomas is rapidly growing LNs. Thus, from previous discussions, it should be noted that bilaterally rapidly growing LNs greater than 45 mm are likely to be lymphomas and immediate pathological diagnosis using biopsy is needed to introduce chemotherapy promptly. The present study revealed that the prevalence of benign disease was 33% of axillary lymphadenopathy. Of the benign disease, the most common pathology was non-specific reactive lymphadenopathy (67%). The remainder of the benign axillary lymphadenopathies included three cases of Epstein -Barr virus-associated lymphadenopathy, three cases of fibro adenoma of the breast, and one case of tuberculosis infection. The mean length of benign lymphadenopathy was 23 mm, which was smaller than the length from lymphoma. However, the length of LNs in our one case of Epstein-Barr virus -associated lymphadenopathy was 45 mm. Since it has been shown that some types of lymphoma are involved in Epstein-Barr virus infection [16], it seems necessary to follow up clinically in patients with large-sized lymphoadenopaty. Breast axillary nodes, which are not LNs, usually remain asymptomatic, but appear clinically to be symptomatic during menstruation, pregnancy and after puberty [17,18]. Rarely do tumors including benign adenoma and carcinoma arises in the ectopic axillary mammary glands [19,20]. Since in extra pulmonary type of tuberculosis, the most commonly affected LNs are cervical, supraclavicular, and inguinal LNs [21], tuberculosis involving axillary LNs is also rare event [22]. Because radiological images of this disease are not specific, open LN biopsy is needed for pathological diagnosis. With respect to the prevalence of tubercular lymphadenitis, there are one more things to be added. The causes of lymphadenopathy are depending on the geographical conditions. Malhota et al. [23] reported that tubercular lymphadenitis is the single most common cause of lymphadenopathy (44%) in North India. In conclusion, our analysis of 62 patients who underwent axillary LN biopsy revealed that the most frequent pathology of axillary lymphadenopathy was malignant disease (41 cases, 66%) including LN metastasis (24 cases) and lymphomas (17 cases), and the other was benign disease (21 cases, 34%). Clinical characteristics of malignant axillary lymphadenopathy included large-sized LNs (larger than 35 mm in diameter), concomitant malignant disease or history of malignant disease, and suspected breast cancer. It should be noted that of the 24 cases of malignant lymphadenopathy, 10 cases were from occult breast cancer. It is for this reason that prompt biopsy for axillary lymphadenopathy is suggested for pathological diagnosis.

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