ORIGINAL ARTICLE

Axillary Lymph Nodes in Breast Cancer Patients After COVID-19 Vaccine

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Abstract

One of the side effects of vaccines used to end the COVID-19 epidemic is non-specifically enlarged axillary lymph nodes. Such lymphadenopathy detected during clinical examination of breast cancer patients may require additional imaging or interventional procedures that should not normally be performed. This study has been designed to estimate the incidence of palpable enlarged axillary lymph node in breast cancer patients who had received COVID-19 vaccination in the past 3 months in the same arm as compared to those without vaccination. Breast cancer patients admitted to M.U. Medical Faculty Breast polyclinic between January 2021 and March 2022 were screened, and clinical staging was performed after thorough clinical examination. Among these patients with suspected enlarged axillary lymph node and those undergoing sentinel lymph node biopsy (SLNB), they were divided into two groups as vaccinated and unvaccinated. Age, menopausal status, tumor size, tumor location, surgery, pathology results, hormonal receptor status, and SLNB results were statistically compared with groups. There was no significant difference between groups in terms of age, menopause, tumor size, tumor location, surgery, pathological results, and hormone receptor status. The SLNB being reported as reactive only was 89.1% in the vaccinated group and 73.2% in the non-vaccinated group which was statistically significant different. Reactive lymph nodes were commonly found with an excess of 16% in patients who had received COVID-19 vaccination in the past 3 months. This required caution and additional examination of the axillary lymph nodes in this period.

Keywords Breast cancer · Tumor staging · COVID-19 vaccines · Sentinal lymph node · Axillary lymphadenopathy

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Introduction

The staging system is a standard way for the cancer treatment team to summarize information on the extent of cancer spread. As with all other cancers, staging of breast cancer is an essential element for estimating prognosis and planning treatment. There are two types of breast cancer staging: clinical and pathological. Clinical staging is based on the findings of physical examination and imaging techniques, including the breast and axilla [1, 2]. On the other hand, pathological staging is carried out by pathological examination of the removed breast tissue and axillary lymph nodes (ALNs) in addition to clinical staging. ALN status is the most important prognostic factor in breast cancer.

The coronavirus disease (COVID-19) has confronted the world with a substantial challenge affecting many other dimensions besides health. After the implementation of various measures to fight against the devastating impact of the virus, the vaccines developed have widely used [3, 4]. Side effects that may develop in the early stage with COVID-19

vaccines are somewhat similar to illness itself regardless of the type of vaccine administered. Recent studies have stated that it is common to see swollen lymph nodes, also known as lymphadenopathy, following COVID-19 vaccination, which is a short-term and harmless sign that the vaccine is working [5–7].

Vaccine-induced axillary lymphadenopathy has been shown to cause similar problems in the staging for planning treatment and estimating prognosis of breast cancer, which we also observed in our practice. This issue hasn't been sufficiently addressed in the literature, and such lymphadenopathy detected in clinical staging may require additional imaging or interventional procedures that should not normally be performed. This study aimed to investigate the possible misleading effects of COVID-19 vaccination on axillary staging in practice in patients who have presented to our clinic with a diagnosis of breast cancer since the beginning of vaccination in and country.

Patients and Methods

As Turkey launched its vaccination program against COVID-19 on January 13, 2021, patients with breast cancer who presented to the MU Faculty of Medicine Hospital Breast Clinic between January 2021 and March 2022 were screened. Clinical staging of patients with histopathological confirmed breast cancer was performed with physical examination and imaging techniques (breast ultrasound (US), mammography (MG), if necessary, breast magnetic resonance imaging (MRI)). Patients' age, gender, menopausal status, tumor laterality, tumor size, hormone receptor status, and pathological features were recorded. Patients with no evidence of axillary metastasis in line with both clinical and imaging findings were excluded from the study. Positron emission tomography-computed tomography (PET/CT) was used in suspected patients to identify distant metastases. Patients with distant metastases on PET/CT, confirmed pathological axillary involvement, or a positive result of fine-needle aspiration (FNAB) biopsy performed upon an indication were excluded from the study. Moreover, patients who received neoadjuvant chemotherapy for locally advanced breast cancer or hormone receptor status (triple negative, HER2 +) were also excluded from the study. The study included patients with suspected axillary lymphadenopathy on PET/CT or negative fine-needle aspiration biopsy results. These patients were then evaluated for COVID-19 vaccination, time of vaccination, type of vaccine, and arm of injection. Accordingly, patients who received a vaccination in the arm ipsilateral to tumors in the past 3 months constituted group 1 (vaccinated group), while patients who didn't have COVID-19 vaccination in the past 3 months or received a vaccination shot from the non-tumor

side formed group 2 (non-vaccinated group). Both groups underwent lymphoscintigraphy-guided sentinel lymph node biopsy (SLNB) using the dual technique, which was performed by the same team, and completed their local surgical treatment. Age, menopausal status, tumor laterality, tumor size, hormone receptor status, pathological diagnosis, and sentinel lymph node pathology results of these two groups of patients were recorded, and statistical analysis was conducted to compare both groups. Considering the SLNB positivity rates of both groups in the statistical analysis results, it was aimed to investigate whether the vaccination had a misleading effect on staging.

Statistical Methods

The Shapiro-Wilk test was used to check if the age variable followed a normal distribution. Descriptive statistics were presented with mean, standard deviation, and minimum-maximum values. The mean age was compared between the vaccinated and unvaccinated groups using the parametric Student's t test. Categorical variables were summarized by numbers (n) and percentages (%). Correlations between categorical variables were examined using chi-square analysis. The level of statistical significance was set at (p) ≤ 0.05.

Results

A total of 246 patients with a first time diagnosed with breast cancer between January 2021 and March 2022 were screened in the study. Thirty-eight patients with no suspected axillary involvement on physical examination and imaging study and no indication for PET CT were not included in the study. Six patients for whom surgical treatment was recommended and who were treated in another center were excluded. PET/CT was performed on 202 patients who required distant metastasis screening. Of these patients, 16 with distant metastases were excluded from the study. Moreover, 84 patients with axillary pathological involvement on PET/CT (metastatic conglomerated lymph nodes with infraclavicular, supraclavicular, internal mammary involvement), indications for fine-needle aspiration biopsy of ALN as a result of which metastasis is noted, and indications for neoadjuvant chemotherapy for locally advanced breast cancer or hormone receptor status (triple negative, HER2+) were excluded from the study. The study enrolled 102 patients with suspected axillary lymphadenopathy on PET/CT or negative fine-needle aspiration biopsy results. Based on the questioning of the COVID-19 vaccination status of these 102 patients, 46 patients who received a vaccination shot in the arm ipsilateral to tumors in the past 3 months constituted group 1 (vaccinated group), while the remaining 56 patients who didn't have COVID-19 vaccination in the past 3 months or received a vaccination

shot from the non-tumor side formed group 2 (non-vaccinated group). In the first group, 32 (69.5%) of 46 patients were Pfizer- BioNTech vaccine, and 14 (30.5%) of them were Sinovac vaccine. In addition to local cancer surgery, SLNB was performed using the dual technique in both groups of patients who underwent surgical treatment in our center.

Age, menopausal status, tumor laterality, tumor size, hormone receptor status, pathological diagnosis, and sentinel lymph node pathology results of these two groups of patients were recorded and statistically analyzed. The mean age was 50 (range, 29–72) years in group 1 and 50 (range, 34–73) years in group 2, with no statistical difference between the two groups in terms of mean age ($p>0.05$). In group 1, the number of postmenopausal patients was 26 (56.5%), while the number of premenopausal patients was 20 (43.5%). In group 2, the number of postmenopausal patients was 32 (57.1%), while the number of premenopausal patients was 24 (42.9%). There was no significant difference between the two groups in terms of menopausal status ($p>0.05$). In group 1, the tumor was located in the left breast in 32 (69.6%) patients and in the right breast in 14 (30.4%) patients. In group 2, the tumor was located in the left breast in 32 (57.1%) patients and in the right breast in 24 (42.9%) patients. There was no statistically significant correlation between both groups in terms of tumor laterality ($p>0.05$). In terms of tumor size, 28 (60.9%) in group 1 had T1 tumors, while 18 (39.1%) patients had T2 tumors. There was no significant difference between the two groups in terms of tumor size ($p>0.05$). The pathological results of the patients in group 1 were invasive ductal carcinoma in 31 (67.4%) patients, lobular carcinoma in 6 (13%) patients, papillary carcinoma in 4 (8.7%) patients, mucinous carcinoma in 3 (6.5%) patients, and mixed type in 2 (4.3%) patients. The pathological results of the patients in group 2 were invasive ductal carcinoma in 41 (73.2%) patients, lobular carcinoma in 6 (10.7%) patients, papillary carcinoma in 5 (8.9%) patients, mucinous carcinoma in 3 (5.4%) patients, and mixed type in 1 (1.8%) patient. There was no significant difference between the two groups in terms of pathological features ($p>0.05$). Both groups were also compared in terms of hormone receptors. In group 1, there were 31 (67.4%) patients with luminal A breast cancer, 7 (15.2%) patients with luminal B breast cancer, 7 (15.2%) patients with TRIPLE (−) breast cancer, and 1 (2.2%) patient with HER 2 (+) breast cancer. In group 2, there were 36 (64.3%) patients with luminal A breast cancer, 6 (10.7%) patients with luminal B breast cancer, 11 (19.6%) patients with TRIPLE (−) breast cancer, and 3 (5.4%) patients with HER 2 (+) breast cancer. There was no significant difference between the two groups in terms of hormone receptor status ($p>0.05$). Both groups were compared in terms of local surgical techniques. In group 1, 25 patients underwent BCS (breast-conserving surgery), 15 patients underwent a mastectomy, and 6 patients underwent a mastectomy with

simultaneous implant reconstruction. In group 2, 29 patients underwent BCS, 22 patients underwent a mastectomy, and 5 patients underwent a mastectomy with simultaneous implant reconstruction. There was no difference between the groups in terms of the surgical technique used ($p>0.05$).

The analysis of the groups for pathological examination results of SLNB materials revealed reactive lymph nodes in 41 (89.1%) patients and metastasis in 5 (10.9%) patients in group 1. Of these 5 patients with metastasis, 4 underwent axillary dissection in the same session, while the other patient didn't undergo axillary dissection because the tumor was hormone positive and BCS was performed on the patient. In group 2, 41 (73.2%) patients had reactive lymph nodes, while 15 (26.8) patients had metastasis. Of these 15 patients with metastasis, 3 also didn't undergo axillary dissection because the tumor was hormone positive and BCS was performed on the patients. A statistically significant correlation was found between the groups in terms of SLNB results ($p<0.05$). Accordingly, the frequency of reactive lymph nodes was 15.9% higher in the vaccinated group than in the unvaccinated group, with a significant difference. The results are shown in Table 1.

Discussion

Vaccines are the strongest weapon that protects the individual and society against fatal and poorly understood viral diseases. Since the beginning of the COVID-19 vaccination in our country as well as all over the world, many people have noted swollen lymph nodes following vaccination, presenting to breast clinics [8–10]. However, it is common for lymph nodes to swell, also known as lymphadenopathy, following COVID-19 vaccination, which has been reported by experts to be a short-term and harmless sign that the vaccine is working [7]. Although it is relatively easier to manage this condition in a patient with only lymphadenopathy, such a condition that may develop after vaccination in a patient with newly diagnosed breast cancer can cause confusion in axillary staging, which is very important in breast cancer management, when the tumor is located in the same axilla as the breast tumor. ALN involvement in breast cancer patients negatively affects the prognosis of the disease and is an important factor that determines the clinical and surgical approach [11, 12]. Assessment of ALN involvement in all newly diagnosed breast cancer patients is requisite. Physical examination and mammography (MG) can easily detect superficial pathological lymph nodes, but cannot adequately evaluate the entire ALN spread. Axillary assessment with US is more successful than MG [13, 14]. Although it is difficult to assess level II and level III ALNs with US, level I nodes and level II–III lymph nodes with abnormally enlarged thick cortex can be easily detected by US examination in most patients. Dynamic breast MRI is a technique used for the

Table 1 Statistical analysis comparison of two groups

	Group 1 (vaccinated) $n=46$ n (%)	Group 2 (non-vaccinated) $n=56$ n (%)	p^*
Age, years (mean ± SD)	50 ± SD	50 ± SD	0.844
Menopausal status			
Postmenopausal	26 (56.5%)	32 (57.1%)	0.95
Premenopausal	20 (43.5%)	24 (42.9%)	
Tumor laterality			
Left breast cancer	32 (69.6%)	32 (57.1%)	0.19
Right breast cancer	14 (30.4%)	24 (42.9%)	
Tumor size			
T1	28 (60.9%)	33 (58.9%)	0.84
T2	18 (39.1%)	23 (41.1%)	
Pathological result			
Invasive ductal carcinoma	31 (67.4%)	41 (73.2%)	0.95
Lobular carcinoma	6 (13%)	6 (10.7%)	
Papillary carcinoma	4 (8.7%)	5 (8.9%)	
Mucinous carcinoma	3 (6.5%)	3 (5.4%)	
Mix type	2 (4.3%)	1 (1.8%)	
Hormone receptors			
Luminal A	31 (67.4%)	36 (64.3%)	0.72
Luminal B	7 (15.2%)	6 (10.7%)	
TRIPLE (−)	7 (15.2%)	11 (19.6%)	
HER2 +	1 (2.2%)	3 (5.4%)	
Surgical technique			
BCS	25 (54.3%)	29 (51.8%)	0.68
Mastectomy	15 (32.6%)	22 (39.3%)	
Implant	6 (13%)	5 (8.9%)	
Sentinel lymph node			
*Sentinel reactive**	*41 (89.1%)**	*41 (73.2%)*	0.04
Sentinel metastasis	5 (10.9%)	15 (26.8%)	

*The level of statistical significance was set at (p) ≤ 0.05

preoperative local staging of breast cancer, but its role in the assessment of ALN spread is still under investigation. A study estimated the sensitivity, specificity, and accuracy of the examination as 51.3%, 92.2%, and 80.9%, respectively [15]. In our own practice, we also perform staging for the management of the newly diagnosed patients and primarily include ultrasound in the axillary staging. We order breast MRI for patients we deem necessary to obtain diagnostic MG preoperatively. PET/CT is another non-invasive imaging technique used for the assessment of axillary nodal involvement in early-stage breast cancer. A large meta-analysis of studies investigating the sensitivity of PET/CT and MRI for detecting axillary nodal involvement found the sensitivity of MRI to be higher than that of PET/CT [16]. Another study comparing PET/CT and MRI examinations estimated the sensitivity of 18F-FGD PET/CT examination for detecting

axillary nodal involvement as 67% [17]. Therefore, the routine use of PET/CT only for the assessment of ALN status seems controversial. We also use PET/CT for staging in our clinic with limited indications. In terms of ALN status in breast cancer staging, not every patient is included in the black zone with the presence of axillary metastasis or in the white zone without metastasis. A large group of patients may be in the gray zone. The present study was planned, considering that lymphadenopathy secondary to COVID-19 vaccination may cause a patient who should be in the white zone to be included in the gray zone. As a matter of fact, patients with no clinical or imaging suspicion of axillary metastasis were not included in the study since they didn't undergo PET/CT. Furthermore, patients with axillary metastasis clearly demonstrated by biopsy or imaging were also not included. Only patients in the gray zone were evaluated in the study.

While investigating effect of the COVID-19 vaccine on the assessment of lymphatic status in this study, the groups were compared in many aspects to investigate whether this effect was only caused by the vaccine. Mean age, menopausal status, and tumor laterality tumor size of the patients in the study are consistent with the literature [18–21]. In this context, age and menopausal status were analyzed between the groups, which showed homogeneity across the groups. Patients were also evaluated in terms of. In fact, vaccines are predominantly injected into the left arm in the general population.

Primary invasive tumors and hormonal receptor status may also have an effect on axillary staging [22–26]. In this context, the comparison of groups in terms of hormone receptor status and primary invasive tumors in our study revealed no significant difference.

Local surgical management of breast cancer is unlikely to affect axillary involvement. However, the comparison of the two groups in terms of local surgical techniques also showed no significant difference.

Accurate assessment of axillary involvement is of great importance in the staging of the disease and in the selection of the surgical technique for breast cancer patients whose axillary involvement isn't detected clinically. SLNB is still known as the most sensitive method in cases where the metastatic spread is more limited or in the detection of micrometastases [27, 28]. All patients included in our study underwent SLNB with the dual technique. Frozen section analysis was performed in all SLNB procedures. Axilla was considered positive when macrometastasis was detected, but reactive if no metastasis was noted. The comparison of the results showed a significantly lower frequency of axillary metastasis in the vaccinated group. A difference of approximately 15.9% was found between the two groups. As all the factors that may increase the probability of axillary metastasis mentioned above were similar in both groups according to the study plan, we speculate

that this difference is secondary to vaccination. As a matter of fact, our practice showed a significant difference in the macroscopic appearance of sentinel lymph nodes in the vaccinated group compared to the normal. It wasn't objectively possible to pathologically demonstrate this as a limitation of the study. However, as a strength of our study, patient inclusion criteria were clearly stated and homogeneity was achieved in all factors except for being vaccinated or not. While the rate of the patients in the vaccine group who had the BioNTech vaccine was 69.5%, the rate of those who had the Sinovac vaccine was 30.5%. However, we didn't examine which one is more axillary lymph node enlargement as it isn't the subject of our study.

Another issue here is that the PET/CT indications are also controversial, considering the retrospective analysis of 15.9% of patients in axillary staging. In the literature, there are studies evaluating the incidence of COVID-19 vaccine-associated hypermetabolic axillary lymph nodes on F18-fluorodeoxyglucose (FDG) PET/CT and the factors affecting hypermetabolic axillary lymph nodes in oncology patients [29, 30]. A cluster pattern of hypermetabolic ipsilateral small axillary lymph nodes has been commonly detected after COVID-19 vaccination, especially after the second injection. However, most of these studies have evaluated various cancer patients.

There aren't many studies in the literature on the effects of COVIDd-19 vaccines on axillary lymphadenopathy in breast cancer. There is also no study evaluating SLNB, which was conceptualized in our study. We also observe increasing biopsy for suspicious lymphadenopathy in our own practice. Three patients who weren't included in the study because they didn't meet the study criteria had breast cancer on the unvaccinated side, and we had to perform a fine-needle aspiration biopsy because of suspicious involvement in the contralateral axilla. The axillary pathology of these patients was clean. In some publications, it has been declared that mammography scans may be postponed due to vaccine-induced axillary lymphadenopathy [9, 31, 32]. However, considering such effect of vaccination on breast cancer patients, we believe that mammography shouldn't be delayed. Different expert consensus statements have been published on the management of axillary adenopathy in patients who have recently received a COVID-19 vaccine and are undergoing imaging. However, there is a need for guidelines on the management of COVID-19 vaccine-associated lymphadenopathies in staging breast cancer patients. We are of the opinion that this study will be a guide for establishing guidelines.

Conclusions

The COVID-19 vaccine is associated with the development of painless axillary lymphadenopathy which may be reactionary developing in the same axilla in the arm in which intra-muscular vaccine is given. If these patients present to a breast clinic with suspected breast cancer on the same side of the breast, the clinical examination of axilla may be misleading and upstaged the axillary nodal N stage clinical workup. Additional investigation to assess the enlarged axillary nodes like ultrasound or PET CT may be required. Reactive lymph nodes were commonly found with an excess of 16% in patients who had received COVID-19 vaccination in the past 3 months and had undergone sentinel lymph node biopsy for breast cancer treatment. This required caution and additional examination of the axillary lymph nodes in this period prior to taking final decision for treatment.

Declarations

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