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Original Investigation

Ultrasound Features to Differentiate COVID-19 Vaccine-Induced Benign Adenopathy from Breast Cancer Related Malignant Adenopathy

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Rationale and Objective: To identify nodal features used to distinguish coronavirus disease 2019 (COVID-19) vaccine-Induced benign reactive adenopathy from malignant adenopathy.

Materials and Methods: This IRB-approved, single-institution, retrospective study compared features of 77 consecutive patients with benign adenopathy secondary to a messenger RNA COVID-19 vaccine with 76 patients with biopsy-proven malignant adenopathy from breast cancer. Patient demographics and nodal features were compared between the two groups using univariate and multivariate logistic regression models. A receiver operating characteristic analysis with the maximum value of Youden’s index was performed for the cutoff value of cortical thickness for predicting nodal status.

Results: The mean cortical thickness was 5.1 mm ± 2.8 mm among benign nodes and 8.9 mm ± 4.5 mm among malignant nodes (p < 0.001). A cortical thickness ≥3.0 mm had a sensitivity of 100% and a specificity of 21% (area under the curve [AUC] = 0.60, 95% confidence interval [CI]: 0.52-0.68). When the cutoff for cortical thickness was increased to ≥5.4 mm, the sensitivity decreased to 74%, while the specificity increased to 69% (AUC = 0.77, 95% CI: 0.70-0.84). Cortical thickness correlated with nodal morphology type (r² = 0.57). An axillary node with generalized lobulated cortical thickening had a 7.5 odds ratio and a node with focal cortical lobulation had a 123.0 odds ratio compared to one with diffuse, uniform cortical thickening only (p < 0.001).

Conclusion: Cortical thickness and morphology are predictive of malignancy. Cortical thickness cutoff of ≥5.4 mm demonstrates higher specificity and improved accuracy for detecting malignant adenopathy than a cutoff of ≥3.0 mm.

Key Words: COVID-19; vaccine; lymphadenopathy; cortical thickness, ultrasound.

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INTRODUCTION

As worldwide vaccination against the severe acute respiratory syndrome coronavirus 2virus was initiated at the end of 2020, radiologists around the world have noted a marked increase in the incidence of unilateral axillary adenopathy (1,2). The changes in lymph node features after vaccination, reported in a study of 91 volunteer employees, include an increase in the lymph node size by 5.3 mm, increase in cortical thickness by 2.1 mm, increase in the number of visible lymph nodes by 1.8, and an overall increase in the associated Doppler signal (3). Faermann et al reported that the mean cortical thickness of lymph nodes after vaccination was 5 mm ± 2 mm and that the longitudinal length of lymph nodes increased between the first and the second doses of a messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccine (4). As reports of vaccine-induced reactive adenopathy increased, management recommendations were developed and modified regarding the need for imaging and biopsy (5–8).

The differential diagnosis for unilateral axillary adenopathy is broad and ranges from benign etiologies, such as vaccine-induced reactive adenopathy to metastatic adenopathy from breast carcinoma or other malignancies (9). There is an overlap in the ultrasound appearance of benign and malignant nodes, making differentiation of benign versus malignant difficult. Objectively differentiating benign from malignant adenopathy is of clinical value and can reduce costs and
anxiety related to unnecessary biopsies and/or the need for follow-up examinations.

Normal-appearing lymph nodes have a reniform shape with an imperceptible or thin cortex and a visible central hilum, while suspicious or malignant lymph nodes demonstrate variable degrees of cortical thickening (10). Currently, a cortical thickness of $\geq 3.0$ mm is commonly accepted as the cutoff threshold for differentiating benign from malignant adenopathy (11-15). The primary aim of this retrospective study was to identify ultrasound features that may be used to differentiate COVID-19 vaccine—induced benign reactive adenopathy from malignant adenopathy secondary to breast cancer.

**MATERIALS AND METHODS**

This institutional review board—approved and Health Insurance Portability and Accountability Act—complaint retrospective study was performed at a National Cancer Institute—designated comprehensive cancer center. The need for informed consent was waived. The electronic health records were queried for all patients with an axillary ultrasound (AUS) examination describing ipsilateral adenopathy after the receipt of a mRNA COVID-19 vaccine from December 2020 to September 2021. We excluded patients $<$18 years old, patients without an AUS examination performed at our center, and patients with axillary adenopathy on the ipsilateral side of a newly diagnosed breast cancer.

Imaging studies, pathology results, and vaccine records were reviewed. Ultrasound lymph node features were collected from the AUS examinations, including the number of visible suspicious lymph nodes, the maximum longitudinal lymph node size, the nodal cortical thickness, and visibility of the hilum. A retrospective review was performed to classify the lymph nodes into one of six morphologic types: type 1, no visible cortex; type 2, thin ($<3.0$ mm) cortex; type 3, diffuse, uniform cortical thickening ($\geq 3.0$ mm); type 4, generalized lobulated cortical thickening; type 5, focal cortical lobulation; or type 6, totally hypoechoic node with no visible hilum (10). A comparable number of breast cancer patients with malignant adenopathy from the same institution who had available pre-treatment AUS examinations, percutaneous lymph node biopsy results, and subsequent axillary lymph node dissection confirmation were randomly selected as the comparison malignant cohort. No special selection criteria was used to select the malignant cases based on other factors, such as age, histology, or racial background, though we excluded patients with N3 nodal stage or distant metastatic disease. Retrospective data collection of the breast cancer cases with malignant adenopathy was performed to identify the characteristics of the malignant group according to histology, molecular subtype, tumor (T) and nodal (N) classification and is shown in Table 1. The benign cohort was independently reviewed by one breast imaging fellowship trained radiologist with 21 years of practice experience who was blinded to the AUS findings of the vaccine-induced reactive adenopathy cases. The primary reviewer for each cohort obtained consensus from two additional radiologists (GW and JL) with 23 plus years of practice experience in a small percentage of cases.

**Data Analysis**

Patient demographics and lymph node features were summarized using frequencies, percentages, means, standard deviations, medians, minima, and maxima. These findings were compared between the benign and malignant groups using the Wilcoxon Rank Sum test, Fisher’s exact test, and Pearson Chi-squared test. The distributions of cortical thickness among the nodal morphologic types were compared between benign and malignant nodes using box plots, and the associations were tested using the Kruskal-Wallis test. A receiver operating characteristics analysis with the maximum value of Youden’s index was performed to select the cutoff value for cortical thickness in predicting benign versus malignant nodal status. Univariate analyses were used to select unadjusted significant predictors, which then underwent multivariate logistic regression model analyses to assess associations, adjusted for the effects of covariates. Backward model selection by the Akaike information criterion was used to select the final model. Statistical significance was defined as $p < 0.05$. Statistical analysis was carried out using R (version 3.6.3, R Development Core Team).

**RESULTS**

**Patients**

A total of 153 patients with axillary adenopathy were identified for analysis, with 77 patients with benign reactive

| Table 1. Breast Cancers with Malignant Adenopathy |
|--------------------------------------------------|
| **Histology** | **Malignant (N = 76)** |
| Ductal | 58 (76.3) |
| Lobular | 13 (17.1) |
| Mixed ductal ad lobular | 5 (6.6) |
| **Molecular subtype** | |
| Luminal A | 6 (7.9) |
| Luminal B | 40 (52.6) |
| HER2 enriched | 12 (15.8) |
| Triple negative | 18 (23.7) |
| **Tumor (T) size** | |
| T1 ($<2$ cm) | 15 (19.7) |
| T2 ($2.1-5$ cm) | 45 (59.2) |
| T3 ($>5$ cm) | 16 (21.1) |
| **Nodal (N) stage** | |
| N1 | 67 (88.2) |
| N2 | 9 (11.8) |
adenopathy after the receipt of a mRNA COVID-19 vaccine and 76 patients with biopsy-proven malignant adenopathy from breast cancer. The median age of the benign reactive adenopathy cohort was 59 years (range, 30-84 years) while the median age for the malignant adenopathy group was 55 years (range, 28-87 years). After the final multivariate analysis, age was not a significant difference between the two groups ($p = 0.9$). With regard to race, the pairwise comparisons of the different racial backgrounds and the $p$-values adjusted using false discovery rate method showed no statistically significant racial differences ($p = 0.163$). The demographic characteristics of both groups are shown in Table 2. Of the 77 patients who developed adenopathy after receipt of a mRNA COVID-19 vaccine (mean 14.4 days and median 12.5 days between vaccination and imaging), 26 had ultrasound-guided biopsy-proven benign adenopathy and 40 had resolution of the suspicious adenopathy on follow-up ultrasound exams (range, 1 week to 6 months). The remaining 11 patients had clinical follow-up with a negative exam and review of systems for adenopathy (eight patients) or an upcoming clinical and imaging appointment scheduled in the near future (three patients). These latter 11 patients were felt to be appropriately managed based on the national and published recommendations at the time of the ultrasound examination (6-8).

### Nodal Characteristics

The number of visible suspicious lymph nodes, the lymph node size, the nodal cortical thickness, and the morphologic classification were compared between the vaccine and the breast cancer groups. Patients with fewer than three suspicious nodes detected on AUS had a higher probability of malignancy compared to patients with three or more suspicious nodes (odds ratio [OR] = 2.7, 95% confidence interval [CI]: 1.1-6.7, $p = 0.029$). For lymph node size, the mean maximum longitudinal length was 19.7 mm (standard deviation [SD], 8.0) for the benign reactive nodes and 21.1 mm (SD, 8.0) for the malignant nodes. There was no statistically significant difference in the size of the lymph nodes between the two groups ($p = 0.221$).

When the nodal cortical thickness was compared between the two groups, the mean cortical thickness was 5.1 mm (SD, 2.8) for the benign nodes and 8.9 mm (SD, 4.5) for the malignant nodes ($p < 0.001$). The commonly accepted threshold for abnormal cortical thickening is 3.0 mm. In our study, when a threshold cortical thickness $\geq 3.0$ mm was selected as abnormal or suspicious for malignancy, the sensitivity for malignant nodal involvement was 100% and the specificity was 21% (area under the curve [AUC] = 0.60, 95% CI: 0.52-0.68). When the cortical thickness threshold was increased to $\geq 5.4$ mm, the sensitivity decreased to 74% while the specificity increased to 69%.

| TABLE 2. Patient Demographics and Lymph Node Characteristics |
|-----------------|-----------------|-----------------|-----------------|
|                 | Benign ($N = 77$) | Malignant ($N = 76$) | Total ($N = 153$) |
| Age, y          |                 |                 |                 |
| Median (range)  | 59.0 (30-84)    | 55.0 (28-87)    | 56.0 (28-87)    |
| Race, no. (%)   |                 |                 |                 |
| White           | 49 (63.6)       | 56 (73.7)       | 105 (68.6)      |
| Black           | 14 (18.2)       | 8 (10.5)        | 22 (14.4)       |
| Hispanic        | 6 (7.8)         | 11 (14.5)       | 17 (11.1)       |
| Asian           | 8 (10.4)        | 1 (1.3)         | 9 (5.9)         |
| Lymph node morphology type, no. (%) |                 | $<0.001$        | $<0.001$        |
| 3               | 56 (72.7)       | 10 (13.2)       | 66 (43.1)       |
| 4               | 20 (26.0)       | 27 (35.5)       | 47 (30.7)       |
| 5               | 1 (1.3)         | 24 (31.6)       | 25 (16.3)       |
| 6               | 0 (0.0)         | 15 (19.7)       | 15 (9.8)        |
| Hilum visibility, no. (%) |                 |                 | $<0.001$        |
| Yes             | 77 (100.0)      | 61 (80.3)       | 138 (90.2)      |
| No              | 0 (0.0)         | 15 (19.7)       | 15 (9.8)        |
| Number of lymph nodes, no. (%) |                 |                 | $0.001$        |
| $<3$            | 22 (28.6)       | 42 (55.3)       | 64 (41.8)       |
| $\geq 3$        | 55 (71.4)       | 34 (44.7)       | 89 (58.2)       |
| Maximum longitudinal size (mm) |               |                 | $0.221$        |
| Mean (SD)       | 19.7 (8.0)      | 21.1 (8.0)      | 20.4 (8.0)      |
| Cortical thickness (mm) |               |                 | $<0.001$        |
| Mean (SD)       | 5.1 (2.8)       | 8.9 (4.5)       | 7.0 (4.2)       |

SD, standard deviation.

a Wilcoxon Rank Sum test
b Fisher’s exact test
(AUC = 0.77, 95% CI: 0.70–0.84, Fig 1). The degree of cortical thickening was directly correlated with the nodal morphologic type ($r^2 = 0.57$, OR = 6.2, 95% CI: 3.1–12.7, $p < 0.001$, Fig 2). When the cortical thickness was reviewed along with the nodal morphologic classification for all 153 patients, the mean cortical thickness was 4.8 mm among type 3 nodes, 7.1 mm among type 4 nodes, 10.3 mm among type 5 nodes, and 14.5 mm among type 6 nodes.

### Features Predictive of Malignant Adenopathy

Univariate analysis indicated younger age, greater cortical thickness, and the absence of a visible hilum as predictors of malignancy. After final multivariate analysis, higher nodal morphologic type classification (types 4, 5, or 6) and fewer than three suspicious lymph nodes detected on AUS remained as significant predictive features of malignant adenopathy. For example, a morphologic type 4 node with generalized lobulated cortical thickening had a 7.5 times higher probability of being malignant compared to a type 3 node with diffuse, uniform cortical thickening (OR = 7.5, 95% CI: 3.1–19.4, $p < 0.001$). A morphologic type 5 node with focal cortical lobulation had a 123.0 times higher probability of being malignant compared to a type 3 node (OR = 123.0, 95% CI: 21.7–2,340, $p < 0.001$) (Table 3). Patients with fewer than three suspicious nodes had a higher probability of malignancy, compared to patients with three or more nodes (OR = 2.7, 95% CI: 1.1–6.7, $p = 0.029$). The number of suspicious lymph nodes and the nodal morphologic type were unrelated.

### DISCUSSION

In the current environment of primary and booster COVID-19 vaccine recommendations, radiologists’ encounters with vaccine-induced, benign reactive adenopathy are expected to continue. While the current accepted threshold for abnormal cortical thickening is ≥3.0 mm, our data shows that a cortical thickness cutoff of ≥5.4 mm would allow for an improvement in AUS specificity (69% versus 21%), albeit with some loss in sensitivity (74% versus 100%). The thicker cortical cutoff threshold of 5.4 mm also demonstrates improved accuracy compared to 3.0 mm (77% versus 60%) in differentiating benign from malignant lymph nodes. In the absence of suspicious ipsilateral breast imaging findings and confirmation of vaccination on the side of adenopathy, a cortical thickness <5.4 mm may be assessed as benign, especially if the nodal morphology shows only diffuse, uniform cortical thickening.

The morphologic classification previously described by Bedi et al is not universally used in clinical practice (10). This classification allows for standardized reporting and categorization of lymph nodes. In our study population, the cortical thickness and its effect on the morphology was the single most important differentiating feature of benign versus malignant lymph nodes. While benign reactive lymph nodes were most often morphologic type 3 (Fig 3) and some type 4 (Fig 4), our results showed that morphologic type 4 and type 5 (Fig 5) nodes had significantly higher probabilities of being malignant. In fact, a morphologic type 5 node was only observed in a single case of vaccine-induced, benign reactive adenopathy (Fig 6). There were no patients with a morphologic type 6 node among the benign cohort but 15 of 76 (20%) patients in the malignant group had morphologic type 6 nodes. The effacement of the hilum of a node was only observed among the malignant nodes and not in the benign

**Table 3. Odds Ratios (OR) for Malignant Adenopathy**

| Lymph node morphology type | OR   | 95% CI          | p value |
|----------------------------|------|-----------------|---------|
| 3                          | 2.70 | 1.12–6.74       | 0.029   |
| 4                          | 7.5  | 3.11–19.4       | <0.001  |
| 5                          | 123.0| 21.7–2,340      | <0.001  |

CI, confidence interval.
Figure 3. A 62-year-old woman with benign reactive adenopathy after COVID-19 vaccination. (a) Longitudinal AUS, 17 days after COVID-19 vaccination, demonstrates a type 3 node measuring 27 mm in long axis in the axilla. Diffuse, uniform cortical thickening measures 5.3 mm (arrows) on the ipsilateral side of vaccination. (b) Longitudinal AUS, 5 months later, demonstrates a decrease in cortical thickness to 2.4 mm (arrows). AUS, axillary ultrasound; COVID-19, coronavirus disease 2019.

Figure 4. A 49-year-old woman with benign reactive adenopathy after COVID-19 vaccination. Longitudinal AUS demonstrates a node with generalized lobulated cortical thickening, with a maximum cortical thickness of 4.5 mm (solid arrows). Fine needle aspirate biopsy confirmed a benign reactive node. AUS, axillary ultrasound; COVID-19, coronavirus disease 2019.
nodes. While a lymph node with cortical thickening ≥3.0 mm has indeterminate potential for malignancy, there is a significantly higher likelihood of malignancy if the cortical thickening is great enough to cause the lymph node to develop lobulated cortical thickening (Fig 7). Our data suggests that the higher morphologic types are more likely to be seen with malignant adenopathy rather than with benign reactive adenopathy from COVID-19 vaccines.

Figure 5. A 41-year-old woman with malignant metastatic adenopathy due to breast cancer. Longitudinal AUS demonstrates a type 5 node measuring 37 mm in long axis, with focal cortical lobulation. At the focal cortical thickening, the cortex measures 15 mm (arrows) while the remainder of the node shows a thin cortex (arrowheads). Fine needle aspiration biopsy performed on the focal hypoechoic lobulation confirmed metastatic adenopathy from breast cancer.

Figure 6. A 53-year-old woman with benign reactive adenopathy after COVID-19 vaccination. (a) Longitudinal AUS, 6 days after receipt of COVID-19 vaccination, demonstrates a type 5 node measuring 29 mm in long axis, with focal cortical lobulation measuring 18 mm (solid arrows) and displacement of the hilum (dashed arrow). (b) Longitudinal AUS, 5 months later, demonstrates a decrease in the cortical thickness (arrows) from 18 mm to 7.6 mm at the thickest portion of the cortex. The cortex surrounds the now centrally located hilum (dashed arrow). AUS, axillary ultrasound; COVID-19, coronavirus disease 2019.
The observation that patients with fewer (<3) suspicious nodes had a higher probability of malignant adenopathy compared to patients with more (≥3) suspicious nodes should be interpreted with caution. The malignant group was comprised of clinical N1 and N2 breast cancer patients and excluded locally advanced and inflammatory breast cancer patients, which may account for the fewer number of suspicious lymph nodes reported among the malignant group. Since ultrasound is an operator dependent imaging modality, it is possible that not all suspicious lymph nodes were documented at the time of image acquisition. Therefore, rather than interpreting this observation to mean that fewer suspicious lymph nodes implies an association with malignancy, our findings suggest that vaccine-induced benign adenopathy may manifest with many suspicious nodes. While the precise mechanism of this manifestation is unknown at this time, it is possible that the immune response triggered by a mRNA vaccine may be more systemic, rather than localized to the injection site alone.

Potential inter-reader differences between the two radiologists who independently reviewed either the benign or malignant adenopathy group are expected, however we suspect these differences to be minimal without invalidation of our findings as cortical measurements and its effect on the hilum have been previously described in many prior publications. The AUS nodal features used in this study has previously undergone meticulous comparison of AUS findings with pathology from surgery (10).

Other limitations include the small sample size and the lack of follow-up imaging in some patients within the vaccine cohort due to the changes and evolving recommendations on the management of COVID-19 vaccine-induced axillary adenopathy. Earlier patients were more likely to receive a follow-up or biopsy recommendation, however, later during the pandemic period, publications outlined scenarios in which it may be appropriate to do less (6-8). In February 2021, Lehman et al (6) suggested that unilateral axillary adenopathy on the ipsilateral side of recent vaccination may be assessed as benign so long as there were no other imaging findings. Later in June 2021, the same group suggested that isolated unilateral axillary lymphadenopathy on the ipsilateral side of the vaccination was akin to the ACR BI-RADS recommendations for unilateral axillary adenopathy due to an inflammatory cause. In the context of a benign or negative clinical follow-up, the authors suggested that imaging follow-up was not necessary and follow-up imaging should be reserved for cases of contralateral adenopathy or persistence of adenopathy beyond 6 weeks. Should adenopathy persist at follow-up imaging, tissue sampling may then be indicated (7). Similar to these recommendations, a multidisciplinary panel of experts from three leading tertiary cancer centers proposed additional guidelines for post vaccination imaging.

Figure 7. A 61-year-old woman with malignant metastatic adenopathy due to breast cancer. Longitudinal AUS demonstrates a type 4 node measuring 36 mm in long axis with generalized lobulated cortical thickening (arrows) measuring 12 mm. Core needle biopsy of the node confirmed malignant adenopathy. AUS, axillary ultrasound.
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