

Breast Cancer Screening and Axillary Adenopathy in the Era of COVID-19 Vaccination

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Authors:

Stacey Wolfson, MD¹

Eric Kim, MD¹

Affiliation:

1 Department of Radiology, New York University Grossman School of Medicine, New York, New York, USA.

Institution address:

New York University Grossman School of Medicine
New York University Langone Health
Laura and Isaac Perlmutter Cancer Center
160 East 34th St, 3rd Floor
New York, NY 10016

Corresponding Author Information:

Stacey Wolfson

Stacey.wolfson@nyulangone.org

160 East 34th St, 3rd Floor
New York, NY 10016

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Summary:

As evidence continues to emerge about axillary lymphadenopathy following COVID-19 vaccination, up-to-date guidelines regarding breast cancer screening and management of axillary lymphadenopathy should be followed to reduce the need for follow-up imaging or biopsy.

Teaching Points:

- Screening mammography should not be delayed following COVID-19 vaccination (page 5).
- Reactive axillary lymphadenopathy after COVID-19 vaccination is estimated to occur in 2.4-35% of women and may persist as long as 43 weeks (pages 5-6), with higher incidence of lymphadenopathy seen in mRNA vaccines versus vector vaccines.
- Isolated unilateral axillary lymphadenopathy ipsilateral to the side of vaccination without other suspicious imaging findings may be considered benign (page 7).
- More cautious management, including possible biopsy, should be taken for patients with concurrent suspicious imaging findings and those at high risk or with a personal history of breast cancer (page 8).

Abbreviations:

COVID-19: Coronavirus 2019, SARS-CoV-2, BI-RADS: Breast Imaging Reporting and Data System,

SBI: Society of Breast Imaging, EUSOBI: European Society of Breast Imaging

Abstract

A 50-year-old woman with persistent axillary lymphadenopathy 17 weeks following COVID-19 vaccination was ultimately diagnosed with biopsy-proven benign reactive lymphadenopathy. In contrast, a 60-year-old woman with axillary lymphadenopathy and concurrent suspicious breast findings 9 weeks following COVID-19 vaccination was ultimately diagnosed with biopsy-proven metastatic breast carcinoma. This article reviews the current guidelines regarding breast cancer screening and management of axillary lymphadenopathy in the setting of COVID-19 vaccination.

Case Presentation (Dr. Stacey Wolfson)

Case 1:

A 50-year-old woman with no personal or family history of breast cancer presented for routine screening mammography and ultrasound. She had received the first dose of the mRNA-1273 (Moderna) COVID-19 vaccination in her left arm 10 days prior to her breast imaging. Screening ultrasound demonstrated two prominent lymph nodes within the left axilla with a thickened cortex measuring 6 mm (Figure 1A and B) which were mammographically occult. No other suspicious findings were seen on either mammogram or ultrasound. The new left axillary lymphadenopathy was thought to be reactive to the recent COVID-19 vaccination. Therefore, the patient's screening ultrasound examination was given a Breast Imaging Reporting and Data System (BI-RADS) category 3 (probably benign) assessment with recommendation for follow-up targeted ultrasound in three months.

The patient returned for follow-up targeted ultrasound 17 weeks after the second dose of the mRNA-1273 vaccination in the left arm. Ultrasound demonstrated persistent axillary lymphadenopathy with continued thickened cortex of 6 mm (Figure 1C). Given the persistent lymphadenopathy, the findings were thought to be suspicious (BI-RADS category 4) and an ultrasound guided core biopsy was performed (Figure 1D). Pathology yielded a benign reactive lymph node without evidence of malignancy.

Case 2:

A 60-year-old woman with no personal or family history of breast cancer presented for routine screening mammography. The patient had received the second dose of the mRNA-1273 (Moderna) COVID-19 vaccination in the left arm 9 weeks ago. There was a new spiculated mass with associated architectural distortion in the left breast. Additionally, a new dense lymph node was incompletely visualized in the left axilla (Figure 2A and B). This screening mammogram was given a BI-RADS category 0 (needs additional imaging) assessment and the patient was recalled for further imaging.

Five days later, the patient presented for a diagnostic mammogram and targeted ultrasound. Diagnostic evaluation confirmed an irregular mass in the left breast suspicious for malignancy. On ultrasound, there was an enlarged lymph node in the left axilla with focal cortical thickening measuring up to 6 mm (Figure 2C). Therefore, these findings were highly suggestive of malignancy (BI-RADS category 5) and biopsy was performed for both the breast mass and left axillary lymph node (Figure 2D). Pathology of the breast mass yielded invasive ductal carcinoma with lobular and micropapillary features. Pathology for the lymph node

yielded metastatic adenocarcinoma. The patient subsequently underwent neoadjuvant chemotherapy followed by breast conserving surgery and radiation.

Case Discussion (Dr. Eric Kim)

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the coronavirus SARS-CoV-2. The World Health Organization officially declared the COVID-19 global outbreak as a pandemic in March 2020 [2]. Since then, there have been over 90 million cases in the United States [3] and over 500 million cases globally [4] at the time of this writing.

The COVID-19 Vaccines

In order to decrease the risk of severe COVID-19 infection and COVID-19 related mortality, developers created vaccines effective against SARS-CoV-2 infection at an unprecedented pace. The U.S. Food and Drug Administration issued emergency use authorization for the BNT162b2 (Pfizer BioNTech) mRNA vaccine and the mRNA-1273 (Moderna) vaccine in December 2020 [7], just one year after the first cases of COVID-19 were reported. There are now three COVID-19 vaccines approved for use in the United States, with the JNJ-78436735 (Johnson and Johnson/Janssen) vector vaccine approved in February 2021 [8]. Multiple additional vaccines are in use around the world, including the ChAdOx1 nCoV-19 (AstraZeneca) vector vaccine.

Currently, 67% of the world population has received at least one dose of a COVID-19 vaccine with over 12 billion doses administered globally [9]. Given widespread vaccination, side effects of the COVID-19 vaccines have become well recognized and publicized in mainstream

media. The most common side effects are transient and mild, including fatigue, myalgia, headache, chills, injection site swelling or erythema, joint pain, and fever. In contrast, serious adverse effects such as anaphylaxis are rare [10].

Vaccination-Related vs. Breast Cancer-Related Axillary Lymphadenopathy

In radiology, one of the more well-known side effects is vaccination-related axillary lymphadenopathy, the result of a local immune response to the COVID-19 vaccination. When it occurs, it is usually seen in the axilla ipsilateral to the side of vaccine administration. Upon initiation of population vaccine programs, physicians have quickly realized that the vaccine dose administration may cause diagnostic dilemmas, especially in patients receiving breast imaging [11].

Unilateral axillary lymphadenopathy is a suspicious finding due to the possibility of metastatic disease from an underlying breast cancer. In fact, up to 1% of all breast cancers initially present as isolated axillary lymph node metastasis even in the absence of other suspicious breast findings on conventional imaging [12]. In contrast, bilateral axillary lymphadenopathy is usually benign, due to reactive, infectious, or systemic etiologies. Understandably, radiologists did not want to miss a possible breast cancer and were uncertain whether unilateral axillary lymphadenopathy in the setting of COVID-19 vaccination could be assessed safely as benign, especially when the incidence and duration of this lymphadenopathy was still unclear.

Several retrospective and prospective studies have now been published, with results suggesting that the incidence and duration of axillary lymphadenopathy following COVID-19

vaccination are greater than originally anticipated. In retrospective studies, the incidence of axillary lymphadenopathy has been reported to range from 2.4-35% for women undergoing screening mammogram and/or ultrasound [13, 14]. This is in stark contrast to the reported 0.02-0.04% incidence of axillary lymphadenopathy on screening mammography prior to the COVID-19 vaccine era [15]. In a retrospective study featuring long term follow-up in 1217 patients who received the COVID-19 vaccination and had breast imaging, axillary lymphadenopathy was seen as early as one day following vaccination and persisted up to 43 weeks following vaccination [13]. A recently published prospective study analyzed the temporal changes of axillary lymphadenopathy following COVID-19 vaccination in 88 otherwise healthy women who underwent serial ultrasound. They found that 51% of women who had follow-up at 10-12 weeks had persistent lymphadenopathy [16]. In both studies, no malignancy was found in asymptomatic patients without suspicious mammographic findings or history of breast cancer. Interestingly, one study demonstrated increased lymphadenopathy and cortical thickness in patients who had received a mRNA vaccine in comparison with those who received the vector-based ChAdOx1 vaccination [17].

Current Breast Cancer Screening Guidelines

Various societies have created guidelines regarding breast cancer screening in patients with recent COVID-19 vaccination. Most agree that in patients with a personal history of breast cancer, vaccination should be performed in the arm contralateral to the side of cancer. For all patients, data including date of administration, dose, injection site, laterality, and type of vaccine should be recorded and available to the interpreting radiologist [15, 18-19].

Initial guidelines were relatively conservative, aiming to reduce unnecessary diagnostic work-up and biopsies. For instance, the Society of Breast Imaging (SBI) released recommendations in early 2021 to consider scheduling screening mammography prior to the first dose of vaccination or 4-6 weeks following the last dose of vaccination [20]. The European Society of Breast Imaging (EUSOBI) guidelines recommended postponing screening for at least 12 weeks after the last vaccination dose [18].

However, updated position statements and studies including the two previously mentioned have now been published. There have also been concerns that the initial delays in breast cancer screening during the pandemic would result in delays in diagnosis and treatment with a possible negative impact on breast cancer mortality [21]. The SBI released revised guidelines in February 2022 based on this new information, no longer recommending delaying screening mammograms around the COVID-19 vaccinations [15]. This is similar to the approach recommended by Lehman et al. which encouraged screening for all patients regardless of vaccination status [22].

Management of Vaccine-Related Axillary Lymphadenopathy

Guidelines for the management of vaccine-related axillary lymphadenopathy have similarly evolved after it had become evident that vaccine-related axillary lymphadenopathy was more common and the duration was longer than originally predicted. The SBI initially recommended BI-RADS category 0 (needs additional imaging) assessment for patients presenting with unilateral axillary lymphadenopathy on screening mammography following COVID-19 vaccination. Follow-up imaging in 4-12 weeks was recommended for cases of

presumed vaccine-related lymphadenopathy with biopsy to be considered for any persistent lymphadenopathy on follow-up [20]. These initial guidelines were followed for our patient in Case 1, who had an ultrasound-guided core biopsy for persistent axillary lymphadenopathy on follow-up imaging 17 weeks following vaccination which yielded benign results.

The revised SBI guidelines now state that it may be appropriate to give a BI-RADS category 2 (benign) assessment without the need for follow-up imaging in patients with recent COVID-19 vaccination and isolated unilateral axillary adenopathy on screening without other suspicious mammographic findings. These guidelines are in line with the EUSOBI guidelines and *Radiology* scientific expert panel guidelines that do not recommend default follow-up imaging for low-risk patients without breast cancer history and without suspicious breast imaging findings [18, 19]. Biopsy may have been avoided in our patient in Case 1 if these revised guidelines were available at that time.

For patients who receive short term follow-up (BI-RADS category 3) for likely vaccine-related adenopathy, a longer follow-up interval of at least 12 weeks is recommended [15, 18] rather than the 4-12 weeks previously recommended. On follow-up, benign assessment is recommended if the axillary adenopathy is noted to improve. If the adenopathy appears unchanged, an additional follow-up in six months may be performed. If the adenopathy has increased, then biopsy should be considered to exclude malignancy [15].

Special considerations should be made in specific situations. For patients who have axillary adenopathy with suspicious findings in the ipsilateral breast, management should be based on the degree of suspicion of the breast lesion and appearance of adenopathy, with biopsy as possibly appropriate. This scenario was seen in Case 2, in which the patient

concurrently had a suspicious mass in the ipsilateral breast and was diagnosed with breast cancer metastatic to the axilla. In patients with axillary adenopathy contralateral to the site of vaccination, standard work-up including possible biopsy is recommended [18]. In high-risk patients such as those with a personal history of breast cancer, management should depend on the risk of axillary nodal metastasis with possible biopsy in higher risk patients.

Conclusion

In conclusion, we presented two cases of patients who demonstrated axillary lymphadenopathy following recent COVID-19 vaccination. In the first case, the patient had no concurrent suspicious mammographic findings, relevant cancer history, or risk factors. The patient had persistent lymphadenopathy on follow-up imaging 17 weeks after vaccination, and ultrasound-guided core biopsy of her lymph node yielded benign histology. In the second case, the patient concurrently had a suspicious breast mass. Biopsy was performed of both the suspicious breast mass and suspicious lymph node, both yielding malignancy.

Current guidelines reflect the emerging evidence that axillary lymphadenopathy is seen at higher incidence and of longer duration than originally anticipated (Table). Consequently, the revised guidelines now state that screening mammograms should not be delayed after COVID-19 vaccination. Patients with isolated unilateral axillary lymphadenopathy following COVID-19 vaccination without other suspicious mammographic findings may be given BI-RADS category 2 (benign) assessment without need for follow-up. However, more cautious management is appropriate for patients with suspicious findings in the breast or with a high risk or personal history of breast cancer.

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Dr. Eric Kim is a clinical assistant professor in the breast imaging section of the Department of Radiology at the NYU Grossman School of Medicine. He completed both his diagnostic radiology residency and fellowship in breast imaging at NYU. His current research interests include artificial imaging and the impact of COVID-19 on breast imaging.



Dr. Stacey Wolfson is a current 4th year and chief resident in the Department of Radiology at the New York University Grossman School of Medicine. Next year, she will be staying at New York University to pursue her breast imaging fellowship.

Table. Current Recommendations on Breast Cancer Screening and Management of Axillary Adenopathy in the COVID-19 Vaccinated Population¹

- Screening mammography should not be delayed because of vaccination [15]. This represents a revision of the previous recommendations [20].
- The following information should be collected and made available to the interpreting radiologist: vaccine administration date, type, dose, and injection site laterality [15, 18-19].
- For isolated ipsilateral adenopathy in recently vaccinated patients with average risk for breast cancer, assessments that may be appropriate are:
 - BI-RADS category 2 (benign) without follow-up imaging [18, 19]
 - BI-RADS category 3 (probably benign) with follow-up imaging in ≥ 12 weeks if increased clinical concern [15, 18]
- Closer interval follow-up imaging and/or biopsy should be considered in patients with:
 - Suspicious findings in the ipsilateral breast [18]
 - Adenopathy contralateral to the site of vaccination [18]
 - High risk, such as personal history of breast cancer [18]

Footnote

¹These recommendations are current at the time of writing but may continue to evolve as more information emerges.

Figures

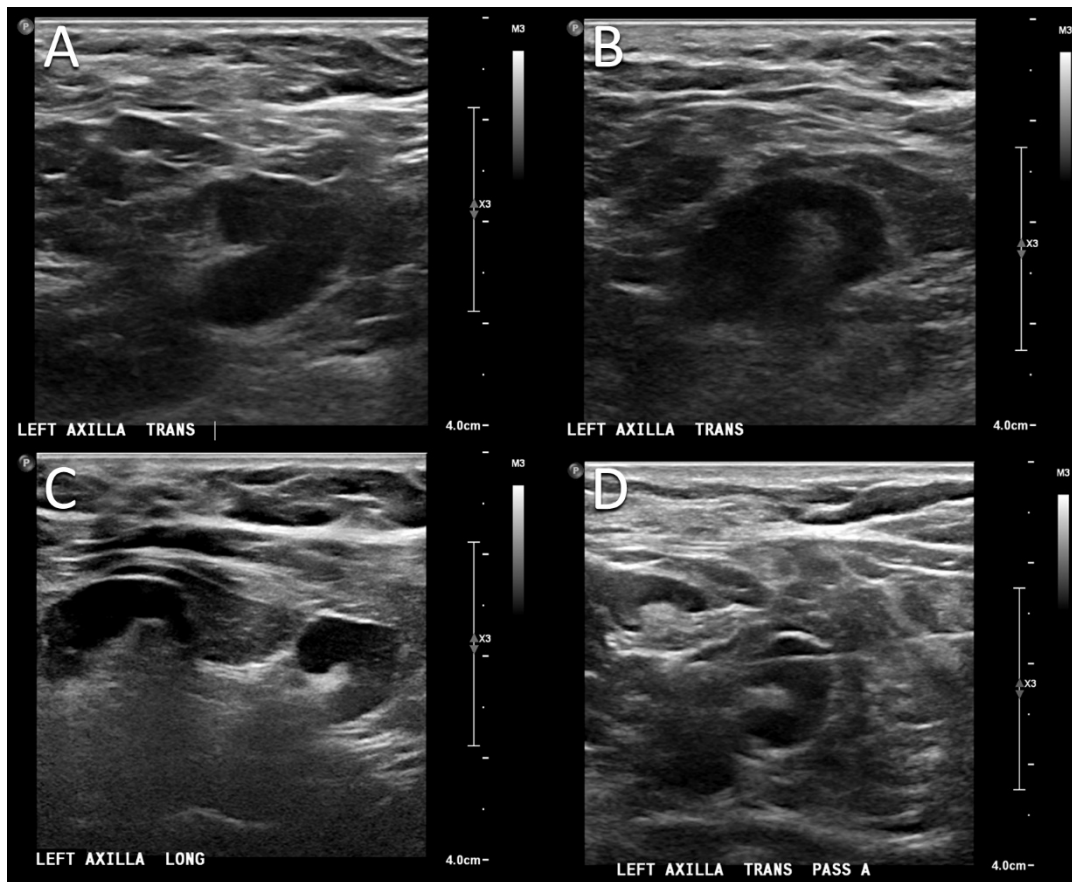


Figure 1: A 50-year-old woman presented for routine screening mammogram and ultrasound 10 days following the COVID-19 vaccination in her left arm. **(A and B)** Screening ultrasound demonstrated two prominent lymph nodes in the left axilla with cortical thickening measuring up to 6 mm. **(C)** Three month follow-up targeted ultrasound demonstrated persistent lymphadenopathy. **(D)** Ultrasound-guided core biopsy was performed and pathology yielded a benign reactive lymph node without evidence of malignancy.

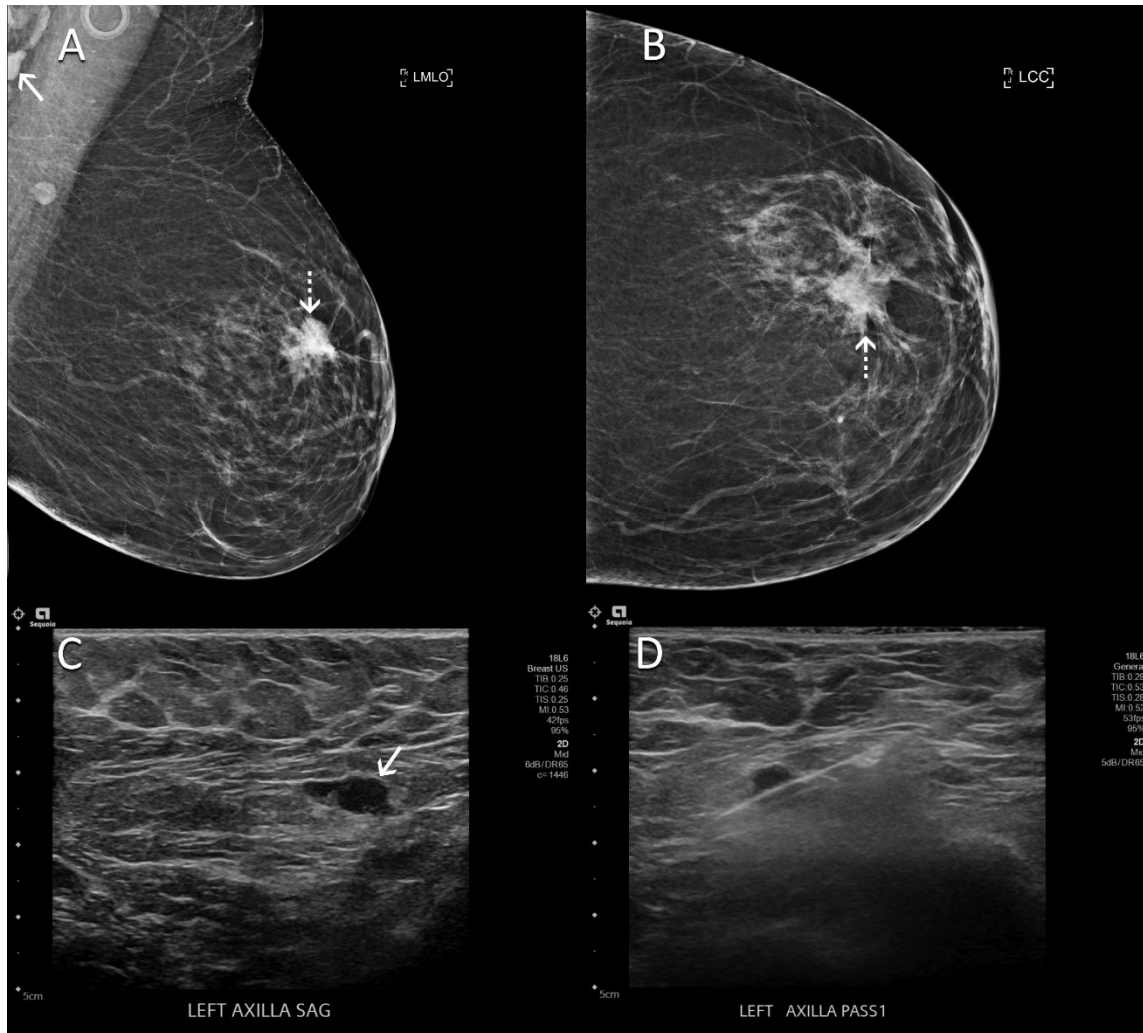


Figure 2: A 60-year-old woman with no personal or family history of breast cancer presented for routine screening mammogram 9 weeks following the COVID-19 vaccination in her left arm. Mediolateral oblique **(A)** and craniocaudal **(B)** mammographic views of the left breast demonstrated a new spiculated mass in the left breast (dotted arrows). In addition, a left axillary lymph node had increased in prominence and density in comparison with her prior mammogram (arrow). On ultrasound, a lymph node with eccentric cortical thickening measuring 6 mm (arrow) was visualized in the left axilla **(C)**. Ultrasound-guided core biopsy of lymph node yielded metastatic carcinoma **(D)**.