Radiology

Follow-up of COVID-19 Vaccine–related Axillary Lymphadenopathy before 12 Weeks Is Unnecessary

Linda Moy, MD • *Eric Kim, MD*

Dr Moy is a professor of radiology at New York University. She is the senior deputy editor for *Radiology* and the deputy editor of breast imaging for *Radiology*. Her research focuses on diagnostic oncologic imaging, with an emphasis on breast cancer. She is a National Institutes of Health–funded investigator with applications in multiparametric breast MRI and artificial intelligence. She collaborates with the New York University (NYU) Center for Data Science to investigate deep learning tools for multitask learning across modalities.

Dr Kim is a clinical assistant professor in the breast imaging section of the Department of Radiology at the NYU Grossman School of Medicine. He currently serves as a senior deputy editor of the *Radiology* In Training editorial board and as a deputy editor of Images in *Radiology*. His research interests include artificial imaging in breast imaging and, more recently, the impact of COVID-19 on breast imaging.

At the time of writing, there have been almost 1 million COVID-19–related deaths in the United States (1) and over 6 million globally (2). To reduce the risk of severe COVID-19 infection, developers created vaccines effective against SARS-CoV-2 infection at an unprecedented pace. In December 2020, the U.S. Food and Drug Administration first issued emergency use authorization for the messenger RNA (mRNA) vaccines BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), only 1 year after the first reported cases of COVID-19 (3). Currently, three COVID-19 vaccines are approved for use in the United States and other vaccines are in use around the world, including the vector ChAdOx1 nCoV-19 vaccine (AstraZeneca). Because of widespread vaccination efforts and increasing availability worldwide, 65% of the world population has received at least one dose of a COVID-19 vaccine, with more than 11 billion doses administered (4).

Aided by unprecedented media coverage, adverse effects of the COVID-19 vaccines have become well recognized. Different vaccines elicit different immune responses, but one of the more common findings after vaccination is reactive lymphadenopathy. It is often seen in the axilla ipsilateral to the side of vaccine administration, may also extend beyond the axilla, and can be seen with different imaging modalities (5). Radiologists realized that vaccine-related axillary lymphadenopathy may be a diagnostic dilemma. Although bilateral axillary lymphadenopathy is often benign due to reactive, infectious, or systemic causes, unilateral axillary lymphadenopathy is concerning due to the possibility of metastatic disease from underlying breast cancer. Up to 1% of all breast cancers initially manifest as isolated lymph node metastasis even in the absence of other suspicious breast findings at conventional imaging (6). Therefore, radiologists do not want to miss a potential sign of breast cancer and have struggled with confidently stating that unilateral axillary lymphadenopathy in the setting of recent COVID-19 vaccination is benign. Instead, short-term follow-up imaging and/or biopsy of the suspicious lymphadenopathy are performed.

Various societies created guidelines to standardize the management of axillary adenopathy after COVID-19 vaccination. These guidelines were based on small retrospective studies in which the timing of the vaccination dose, arm administered, and the type of vaccine given was not verified. Furthermore, the documentation of the sonographic features of the axillary adenopathy was not performed in a consistent way. Given these limitations and the inexperience with the effects of COVID-19 vaccinations, the initial guidelines were relatively conservative. In the United States, the Society of Breast Imaging recommended bringing patients back for dedicated diagnostic evaluation (Breast Imaging Reporting and Data System [BI-RADS] category 0 assessment: needs additional imaging) for unilateral axillary adenopathy seen on screening mammograms. If patients had presumed vaccine-induced adenopathy at diagnostic work-up, then follow-up imaging in 4–12 weeks was recommended, with biopsy to be considered for any persistent axillary adenopathy at a follow-up imaging examination (7). The European guidelines varied based on patient history, clinical presentation, history of breast cancer, vaccination delivery, and imaging findings (8). The management of axillary adenopathy, presumably secondary to COVID-19 vaccinations, is still being debated. It has evolved as more data and evidence on the incidence and duration of vaccine-related adenopathy became available.

In this issue of *Radiology*, Ha and colleagues (9) describe the temporal changes of axillary lymphadenopathy after COVID-19 vaccination in 88 healthy women who underwent serial US. This study is the first prospective study to evaluate COVID-19 vaccine–related axillary lymphadenopathy. The

From the Department of Radiology, Center for Biomedical Imaging, Center for Advanced Imaging Innovation and Research, New York University Grossman School of Medicine, Laura and Isaac Perlmutter Cancer Center, 160 E 34th St, 3rd Floor, New York, NY 10016. Received April 18, 2022; revision requested and received April 19; accepted April 20. **Address correspondence to** L.M. (email: *Linda.Moy@nyulangone.org*).

Conflicts of interest are listed at the end of this article.

See also the article by Ha et al in this issue.

Radiology 2022; 305:54–55 • https://doi.org/10.1148/radiol.220962 • Content codes: BR US

prospective design reduces potential bias and confounding, which may be seen in retrospective studies. The authors recruited asymptomatic women without breast cancer who underwent axillary US after COVID-19 vaccination at a single academic institution in South Korea. Patients received either one of the mRNA vaccines, BNT162b2 or mRNA-1273, or the ChAdOx1 nCoV-19 (recombinant) vaccine. All participants had a negative or benign screening examination within 6 months of recruitment. Participants who demonstrated axillary lymphadenopathy on images, defined as focal or diffuse cortical thickening greater than 3 mm with partial or complete loss of fatty hilum or rounded nodes with nonhilar or diffuse flow, were included for analysis. Follow-up US examinations were recommended at 4–6-week intervals for persistent lymphadenopathy.

Among the 88 women who exhibited axillary lymphadenopathy at US and underwent subsequent follow-up US examinations, only 26% (n = 23) had complete resolution of axillary lymphadenopathy within 6 weeks of vaccination (9). Of the 49 women who underwent follow-up US 10–12 weeks after vaccination, 51% (n = 25) had persistent lymphadenopathy. Interestingly, patients who received the mRNA vaccines had higher cortical thickness values and more suspicious-appearing lymph nodes than those who received the vector vaccine. Of note, no patients were diagnosed with malignancy during the study period. Based on their results, the authors concluded that follow-up US in 12 or more weeks may be appropriate for cases of COVID-19 vaccine–associated axillary lymphadenopathy.

It is important to recognize the limitations of this study. This is a single-center study with a small sample size. Unfortunately, only three patients underwent follow-up US more than 12 weeks after vaccination. Considering that a large percentage of patients with follow-up US at 10–12 weeks demonstrated persistent lymphadenopathy, even longer follow-up would be helpful to get a better understanding of the duration of lymphadenopathy in this population. Finally, the reported 70% incidence of lymphadenopathy within 1 week of vaccination (in 35 of 50 women who volunteered for screening purposes) was higher than that in prior studies. One reason for this higher incidence was because the study sample was enriched with patients in whom lymphadenopathy had been detected.

The results of this study are consistent with the results of a single-institution retrospective study published in *Radiology* earlier this year by Wolfson et al (10), who analyzed 1217 patients who received the COVID-19 vaccination and underwent breast imaging. That study was notable because it contained long-term follow-up data that demonstrated persistent lymphadenopathy in patients up to 43 weeks after COVID-19 vaccination. Wolfson and colleagues also found that 537 (44%) of the 1217 patients who received the COVID-19 vaccination had axillary lymphadenopathy identified with either mammography or breast US. Neither study found a single malignancy in asymptomatic patients with neither a concurrent suspicious mammographic finding nor a recent breast cancer diagnosis. Therefore, the high incidence of adenopathy in both studies and the persistence of the adenopathy suggest that follow-up imaging examinations may be unnecessary.

As more studies with long-term data are being published and radiologists continue to gain more clinical experience, it is becoming clear that both the incidence and duration of vaccine-related adenopathy are greater than initially expected. With this in mind, the Society of Breast Imaging recently published revised recommendations on the management of axillary adenopathy in patients with recent COVID-19 vaccination. They recommend that patients with unilateral axillary lymphadenopathy at screening without other suspicious findings be given a benign (BI-RADS category 2) assessment. For those undergoing short-term follow-up imaging for probably benign (BI-RADS category 3) assessment, a follow-up interval of 12 or more weeks is recommended rather than the shorter follow-up time previously recommended (7). This recommendation is likely conservative because the mean doubling time of breast cancers is 212 days and a 3-month delay in diagnosis is unlikely to impact prognosis.

In conclusion, this is the first prospective study to look at temporal changes in axillary lymphadenopathy after COVID-19 vaccination. The high incidence of adenopathy and the fact that no breast cancers were found suggest that adenopathy is a widespread and benign adverse effect of COVID-19 vaccinations. Therefore, the recommendation by Ha and colleagues to increase the follow-up imaging interval from 4–12 weeks to more than 12 weeks seems reasonable to reduce the number of follow-up examinations.

Disclosures of conflicts of interest: L.M. Senior Deputy Editor for *Radiology;* part of advisory board for iCAD; stock/stock options in Lunit; compensation to institution from Siemens for expert testimony. **E.K.** Senior Deputy Editor of the *Radiology* In Training editorial board and Deputy Editor of Images in *Radiology*.

References

1. Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC. https://covid.cdc.gov/covid-data-tracker. Updated April 14, 2022. Accessed April 15, 2022.
2. World Health Organization. COVID-19 Dashboard. Geneva: World Health Organization. https://covid19.who.int. Updated April 14, 2022. Accessed April 15, 2022.
3. FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine. U.S. Food and Drug Administration website. https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19. Published December 11, 2020. Accessed April 15, 2022.
4. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus (COVID-19) Vaccinations. Our World in Data website. https://ourworldindata.org/covid-vaccinations. Updated April 15, 2022. Accessed April 15, 2022.
5. Özütemiz C, Krystosek LA, Church AL, et al. Lymphadenopathy in COVID-19 Vaccine Recipients: Diagnostic Dilemma in Oncologic Patients. Radiology 2021;300(1):E296–E300.
6. Görkem SB, O'Connell AM. Abnormal axillary lymph nodes on negative mammograms: causes other than breast cancer. Diagn Interv Radiol 2012;18(5):473–479.
7. Grimm L, Srini A, Dontchos B, et al. Revised SBI Recommendations for the Management of Axillary Adenopathy in Patients with Recent COVID-19 Vaccination. Society of Breast Imaging website. https://www.sbi-online.org/Portals/0/Position%20Statements/2022/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination_updatedFeb2022.pdf. Updated February 2022. Accessed April 15, 2022.
8. Schiaffino S, Pinker K, Magni V, et al. Axillary lymphadenopathy at the time of COVID-19 vaccination: ten recommendations from the European Society of Breast Imaging (EUSOBI). Insights Imaging 2021;12(1):119.
9. Ha SM, Chu AJ, Lee JB, et al. US Evaluation of Axillary Lymphadenopathy Following COVID-19 Vaccination: A Prospective Longitudinal Study. Radiology 2022;305(1):46–53.
10. Wolfson S, Kim E, Plaunova A, et al. Axillary Adenopathy after COVID-19 Vaccine: No Reason to Delay Screening Mammogram. Radiology 2022;303(2):297–299.