Management of Unilateral Axillary Lymphadenopathy Detected on Breast MRI in the Era of COVID-19 Vaccination

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Early clinical experience with COVID-19 vaccination suggests that approved COVID-19 vaccines cause a notably higher incidence of axillary lymphadenopathy on breast MRI compared with other vaccines. Guidelines are needed to appropriately manage unilateral axillary lymphadenopathy detected by MRI in the era of COVID-19 vaccination and to avoid biopsies of benign reactive nodes. This article examines the available data on vaccine-related lymphadenopathy and offers a basic strategy for assessing axillary lymphadenopathy on MRI and guiding management. At our institution, we are adding questions regarding the date(s) and laterality of administration of COVID-19 vaccination to the intake form given to patients before all breast imaging examinations. We consider MRI-detected isolated unilateral axillary lymphadenopathy ipsilateral to the vaccination arm to most likely be related to the COVID-19 vaccine if it develops within 4 weeks of administration of either dose. In these cases, we assess the lymphadenopathy as BI-RADS 3 and recommend that follow-up ultrasound be performed within 6–8 weeks after administration of the second dose. These guidelines may be refined as we acquire further data on the expected time course of axillary lymphadenopathy after COVID-19 vaccination. Until that time, this management pathway will help avoid unnecessary biopsies of benign vaccine-related reactive lymphadenopathy.

Consider the following clinical scenario: A 48-year-old woman who is a carrier of the *BRCA1* mutation and has a strong family history of breast cancer presents for baseline breast MRI for high-risk screening. She has heterogeneously dense breast tissue and marked background parenchymal enhancement but has no suspicious findings in either breast. However, she has unilateral left axillary lymphadenopathy with left level I nodes that are asymmetric in size and similar in number compared with right level I nodes. The enlarged lymph nodes retain fatty hila but have cortical thickening that measures up to 6 mm. What would be your assessment and recommendation? Would your impression change if you knew the patient had recently undergone COVID-19 vaccination?

The aforementioned case (Fig. 1) is from our high-risk breast imaging clinic at the Hospital of the University of Pennsylvania. On further review of the medical records, we learned that the patient received the first of two COVID-19 vaccine doses 13 days before undergoing breast MRI. We contacted the patient to clarify that she received her vaccine in her left arm, ipsilateral to her axillary lymphadenopathy. This is just one of multiple cases of unilateral axillary lymphadenopathy on breast MRI that we have encountered in the weeks after approval of the COVID-19 vaccines.

On the basis of review of multiple online breast imaging forums, including the Society of Breast Imaging's open forum for member radiologists (SBI Connect), breast radiologists around the country are also increasingly observing cases of unilateral axillary lymphadenopathy and are postulating that such cases are likely related to recent COVID-19 vaccinations. Numerous posts seen on SBI Connect during month of January 2021 provided details about cases of unilateral axillary lymphadenopathy in recently vaccinated patients. Some radiologists described patients who presented for diagnostic ultrasound with painful and/or enlarged axillary nodes, whereas others noted incidental lymphadenopathy on screening mammography or breast MRI. The management recommendations vary widely. Although some radiologists maintain that, in the setting of a recent ipsilateral vaccination, lymphadenopathy may be assessed as BI-RADS 2 (benign), others suggest that such cases warrant a BI-RADS 3 assessment (probably benign) and short-term follow-up ultrasound.

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The timing of recommended follow-up is also subject to debate, with recommendations ranging from several weeks to 3 months. Other radiologists are assessing lymphadenopathy as BI-RADS 4 (suspicious for malignancy) and are performing nodal biopsies. This heterogeneity in management highlights the importance of the need for data-driven guidelines for managing unilateral lymphadenopathy in the era of widespread COVID-19 vaccination.

The differential diagnosis for unilateral axillary lymphadenopathy is broad and includes benign and malignant causes. Most of the data on unilateral axillary lymphadenopathy on imaging is from screening mammography studies. Of the cases with malignant causes, most are due to lymphoma or metastatic breast cancer [1–3]. Although it is critical to exclude malignancy, most cases of isolated axillary lymphadenopathy (e.g., lymphadenopathy without concurrent abnormality within the breast parenchyma and with no known diagnosis to explain the lymphadenopathy) are due to benign causes [1–3]. After biopsy, common benign diagnoses include benign reactive hyperplasia, inflammatory arthritides, and conditions with infectious causes [2, 3].

Before implementation of COVID-19 vaccination, immunizations were considered a rare cause of benign reactive axillary lymphadenopathy. Influenza, measles, smallpox, anthrax, and bacille Calmette-Guérin vaccines all elicit occasional axillary lymphadenopathy [4, 5]. However, data from COVID-19 vaccine clinical trials suggest that the first two FDA-approved COVID-19 vaccines are highly immunogenic, with greater percentages of patients noting both local and systemic reactions after receiving COVID-19 vaccines compared with other routine vaccines. In addition, the early clinical experience of breast radiologists around the country suggests that the two COVID-19 vaccines (mRNA-1273 [Moderna] and BNT162b2 [Pfizer]) approved for emergency use by the FDA at the time of the writing of this article have caused numerous cases of unilateral axillary lymphadenopathy on breast imaging, including breast MRI.

The phase III randomized placebo-controlled clinical trials of the two COVID-19 vaccines approved by the FDA for emergency use offered early data on vaccination-related reactions specific to mRNA COVID-19 vaccines. The Moderna mRNA COVID-19 vaccine (mRNA-1273) trial, in particular, offered robust data on rates of vaccine-related axillary lymphadenopathy. Safety assessments in the Moderna trial included soliciting local and systemic adverse events for 7 days after the first and second injections. Results showed that 10.2% of vaccine recipients had localized axillary swelling or tenderness ipsilateral to the vaccination arm develop within 7 days of the first dose (compared with 4.8% of placebo recipients). Of the vaccine recipients, 14.2% had axillary swelling or tenderness develop within 7 days of the second vaccine dose, compared with 3.9% of placebo recipients [6]. Rates of axillary lymphadenopathy were even higher in the younger of the two age cohorts, with 16.0% of those who were 18–64 years old having axillary symptoms develop after receiving the second vaccine dose [7].

HIGHLIGHT

- *Vaccination is an established but uncommon cause of unilateral axillary lymphadenopathy.*

Although the comparable phase III randomized placebo-controlled clinical trial of the Pfizer mRNA vaccine (BNT162b2) noted a lower rate of postvaccination lymphadenopathy than the Moderna vaccine trial, only unsolicited axillary symptoms were collected [8]. Thus, data from the Pfizer trial likely underestimate the true incidence of vaccine-induced axillary lymphadenopathy. However, the Pfizer trial does offer limited data on the time course of symptomatic lymphadenopathy, which included combined data for axillary and cervical lymphadenopathy. Unsolicited cases of lymphadenopathy were all reported between 2 and 4 days after vaccination, and the mean duration of lymphadenopathy was 10 days [9].

The Society of Breast Imaging recently released recommendations for the management of axillary lymphadenopathy detected on screening mammography examinations of patients who have recently undergone COVID-19 vaccination [10]. In the setting of the limited data available to date, this provides breast imagers with much-needed guidance. However, the question of how to manage unilateral axillary lymphadenopathy detected on breast MRI remains a unique challenge. Unilateral axillary lymphadenopathy on MRI must be treated with caution, given the elevated lifetime risk of breast cancer in this patient population. In our breast imaging clinic, we have more frequently encountered new axillary lymphadenopathy that may be attributed to recent COVID-19 vaccination on breast MRI compared with screening mammography. This may at least in part be due to the more complete visualization of the axillary nodal basin on breast MRI compared with mammography; although level I, II, and III axillary nodes are visualized on MRI, only a portion of the level I nodes may be visualized on mammography. We know from our limited experience thus far that postvaccine lymphadenopathy is not limited to level I (Fig. 2).

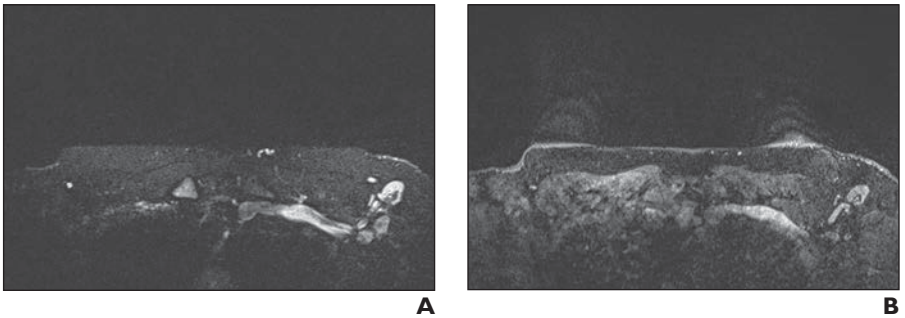

Fig. 1—48-year-old woman with *BRCA1* mutation and family history of breast cancer who underwent baseline screening mammography 13 days after receiving first dose of COVID-19 vaccine.
A and **B,** Axial fat-saturated T2-weighted (**A**) and axial fat-saturated contrast-enhanced T1-weighted (**B**) MR images show unilateral left level I axillary lymphadenopathy.

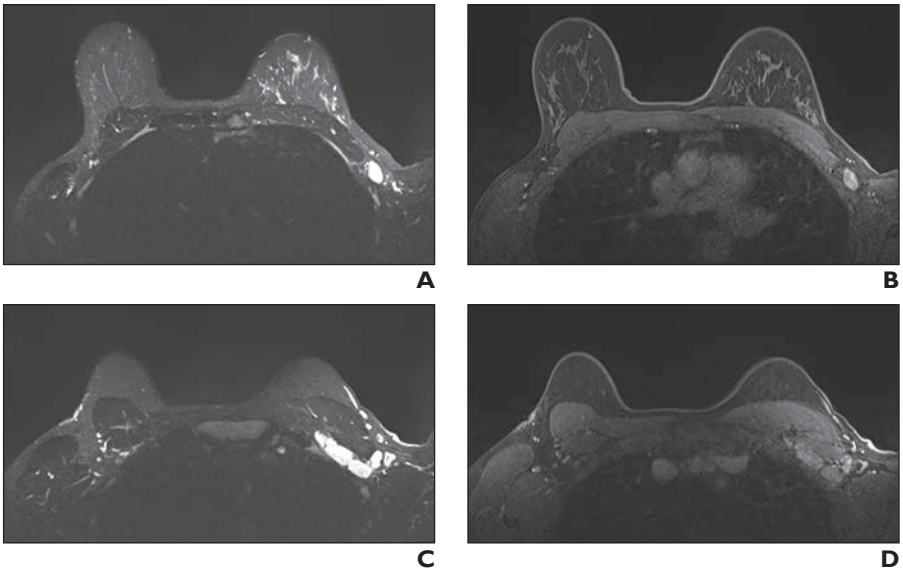

Fig. 2—33-year-old woman who underwent diagnostic follow-up breast MRI 16 days after COVID-19 vaccination.
A–**D,** Axial fat-saturated T2-weighted (**A** and **C**) and axial fat-saturated contrast-enhanced T1-weighted (**B** and **D**) MR images show unilateral left level I (**A** and **B**) and level II (**C** and **D**) axillary lymphadenopathy.

In our quest to appropriately manage axillary lymphadenopathy detected on MRI in the era of COVID-19 vaccination, we must clarify the expected time course of vaccine-related lymphadenopathy on MRI. There are few published data on the time course of visible axillary lymphadenopathy on MRI after administration of any human vaccines. However, we might extrapolate from relevant FDG PET/CT studies that investigated the effects of recent influenza vaccination on axillary nodal assessment by FDG PET/CT. For example, one study of 58 patients who underwent FDG PET/CT within 4 weeks of receiving their H1N1 influenza A vaccine recorded the site of vaccination (right or left deltoid) and the time (in days) between vaccination and the PET scan. Results showed that the influenza vaccine could cause false-positive findings on FDG PET/CT when administered within 14 days before the scan [5]. Of the 58 patients, 15 (25.9%) had axillary lymph nodes with increased FDG uptake as measured by the SUV ipsilateral to the injection arm compared with the contralateral axillary nodes. In addition, axillary nodal SUVs were notably higher in patients who had undergone vaccination within 1 week of scanning compared with patients who had undergone vaccination 2 or more weeks before scanning. No axillary nodes were found to be FDG avid more than 14 days after vaccination. Axillary nodes were also found to be significantly larger in those who had increased SUV values [5]. This finding suggests that the time frame during which radiologists may expect to see postvaccination reactive axillary lymphadenopathy on anatomic imaging such as breast MRI may mirror the time frame of increased SUV on FDG PET/CT.

Several additional studies of FDG PET/CT have shown a similar time frame for increased axillary nodal FDG uptake after H1N1 influenza vaccination. A small retrospective study found that patients vaccinated 5–12 days before the scan was obtained showed the highest uptake of FDG [11]. Another study found that 80% (4/5) of patients who underwent PET/CT within 7 days of influenza vaccination had increased FDG uptake in the ipsilateral axillary nodes, compared with zero of 78 patients who underwent vaccination more than 7 days before PET/CT [12].

Further clinical data are warranted to optimize the assessment and management of suspected COVID-19 vaccine–related axillary lymphadenopathy on breast MRI. It will take at least several more months to obtain the requisite data. However, in the meantime, we can use available data from phase III mRNA vaccine trials combined with prior imaging studies of influenza vaccine–related axillary lymphadenopathy on FDG PET/CT to inform management. We should expect that axillary lymphadenopathy may develop on MRI as early as 1 or 2 days after vaccination and may persist for at least 2 weeks. Therefore, if isolated unilateral axillary lymphadenopathy is noted ipsilateral to the vaccination arm within several weeks of vaccination, it is likely to be secondary to COVID-19 vaccination. Critical to making this determination, however, is having documentation in the medical records regarding the date(s) of administration of the COVID-19 vaccination doses as well as the laterality of each vaccine injection. We are adding these questions to our intake form that each patient completes before undergoing breast imaging, including breast MRI.

At our institution, we currently consider MRI-detected isolated unilateral axillary lymphadenopathy ipsilateral to the vaccination arm to most likely be COVID-19 vaccine related if it is observed within 4 weeks of administration of either vaccine dose. In these cases, we assess the lymphadenopathy as BI-RADS category 3 and recommend that follow-up ultrasound be performed within 6–8 weeks after the second vaccine dose. In addition, when clinically appropriate, screening MRI may be scheduled 6–8 weeks after the second vaccine dose to minimize the likelihood of detecting reactive lymphadenopathy that necessitates follow-up imaging. As we gain further data on the expected time course of axillary lymphadenopathy after COVID-19 vaccination, we may refine these guidelines. However, in the meantime, this management pathway will allow us to avoid many unnecessary biopsies of benign vaccine-related reactive lymphadenopathy.

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