Editorial

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Regional Lymphadenopathy Following COVID-19 Vaccination in Patients with or Suspicious of Breast Cancer: A Quick Summary of Current Key Facts and Recommendations

Jung Min Chang[1, 2], Su Min Ha[1]

[1]Department of Radiology, Seoul National University Hospital, Seoul, Korea; [2]Department of Radiology, Seoul National University College of Medicine, Seoul, Korea

Take-home points

- Unilateral axillary lymphadenopathy, which lasts for a variable period, is frequently observed following COVID-19 vaccination.
- COVID-19 vaccine-associated lymphadenopathy and malignant lymphadenopathy cannot be easily distinguished based on imaging appearance or location.
- To avoid diagnostic confusion, vaccination should be performed in the contralateral arm or thigh in patients with or suspected of having breast cancer.
- Knowledge of the incidence of lymphadenopathy according to the type of vaccine and time since vaccination will help manage patients visiting breast clinics.

With the population-based large-scale vaccination campaign against coronavirus disease-2019 (COVID-19), lymphadenopathy related to the COVID-19 vaccine that mimics malignant lymphadenopathy has become an issue that radiologists should be aware of. Accordingly, *the Korean Journal of Radiology* recently published related articles [1,2] that have drawn much attention, including an interesting post-publication debate between Dr. Finsterer [3] and Dr. Ashoor et al. [4] about recommended injection sites and routine baseline imaging before vaccination. Therefore, this editorial provides a quick summary of the current key facts and recommendations regarding COVID-19 vaccine-related lymphadenopathy.

The first COVID-19 vaccine dose was administered on December 14, 2020, under emergency authorization from the U.S. Food and Drug Administration. Since then, messenger RNA (mRNA)-1273 (Moderna), BNT162b2 (Pfizer-BioNTech), ChAdOx1 nCoV-19 (AstraZeneca), and Ad26.COV2.S (Janssen/Johnson & Johnson) vaccines have been used to prevent COVID-19 infection in Korea. The first COVID-19 vaccine was administered in the Republic of Korea on February 26, 2021. The initial vaccination scheme targeted high-risk groups, which included patients aged ≥ 65 years, disabled individuals, and healthcare workers; large-scale vaccination for the general population began in May [5]. With increasing vaccine availability and wider vaccinated populations, case reports and research on axillary lymphadenopathy on imaging have increased in the past two years.

COVID-19 vaccine-associated reactive lymphadenopathy is a local adverse reaction to vaccination. Lymph node enlargement is related to the accumulation of locally activated antigens at the injection site and their

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Corresponding author: Jung Min Chang, MD, PhD, Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
• E-mail: imchangjm@gmail.com

subsequent migration to the draining nodes [6]. Previous studies have shown that conventional vaccines such as H1N1 influenza, smallpox, Bacille Calmette–Guerin, and human papillomavirus vaccines cause infrequent axillary lymphadenopathy [7-10].

In asymptomatic healthy women without risk of metastatic lymphadenopathy, imaging–detected unilateral axillary lymphadenopathy on the same side of the recent COVID-19 vaccination (i.e., within 12 weeks) should be classified as a benign finding, and no further workup should be recommended [11]. According to published articles on COVID-19 vaccine-associated lymphadenopathies, the most frequently observed morphological characteristics include enlarged lymph nodes with uniform cortical thickening > 3 mm and increased numbers of enlarged lymph nodes [12,13]. It is more commonly observed within a time interval of 4 weeks after receiving COVID-19 mRNA vaccines than after receiving vector vaccines [13]. A recent study reported that 44% of patients who received the vaccine and underwent breast imaging exhibited lymphadenopathy on at least one breast imaging modality, with 9% identified on mammography alone, 61% on ultrasound (US) alone, and 30% on both examinations [14]. In ^{18}F-fluorodeoxyglucose PET/CT scans performed for oncologic indications, axillary lymphadenopathy following COVID-19 vaccination has been reported in up to 15% and 57% of recipients of BNT162b2 and mRNA-1273 vaccines, respectively [15].

COVID-19 vaccine-associated unilateral axillary lymphadenopathy is particularly relevant in women with breast cancer who are at high risk for metastasis to the axillary lymph nodes. Incidental detection of ipsilateral enlarged lymph nodes in patients with newly diagnosed breast cancer could not only confound the accurate assessment of disease extent but may also increase patient anxiety and lead to additional and unnecessary interventions. In these patients, ipsilateral lymphadenopathy during preoperative staging would mandate a targeted US and lymph node biopsy, unless the lymphadenopathy could be confidently attributed to COVID-19 vaccination [16]. Only a limited number of studies on this topic have been published. Chung et al. [12] reported that suspicious nodal morphologic types of generalized lobulated cortical thickening, focal cortical lobulation, or totally hypoechoic nodes with no visible hilum and fewer than three suspicious lymph nodes detected on axillary US were significant predictive features of malignant lymphadenopathy [12]. When the lymph nodes show a complete or near-complete absence of fatty hilum or perilymphatic infiltration [17,18], these findings could be considered highly suspicious features for metastasis, and clinicians should proceed to tissue confirmation regardless of the COVID-19 vaccination history. When lymph nodes show 3 to 4 mm uniform cortical thickening, which is a low suspicious feature, reactive lymphadenopathy should be considered first, though the possibility of malignancy cannot be completely excluded (Fig. 1). Indeed, there is an overlap in the imaging findings between COVID-19 vaccine-associated lymphadenopathy and malignant lymphadenopathy, which cannot be easily distinguished from metastatic disease by morphology or location [19]. In the report by Ha et al. [19], the patients who exhibited cortical thickening of 3.6 and 4.8 mm without loss of fatty hilum were finally confirmed to have metastatic lymph nodes, while those patients who underwent axillary lymph node dissection owing to multiple suspicious lymphadenopathies were finally proven to have no metastasis. US-guided biopsy of suspicious lymph nodes can be considered in these diagnostic dilemmas. However, even a biopsy cannot completely provide an answer for these cases, since it is difficult to selectively perform a biopsy of the exact metastatic lymph node when multiple lymph nodes are enlarged by COVID-19 vaccination in the presence of metastasis (Fig. 2).

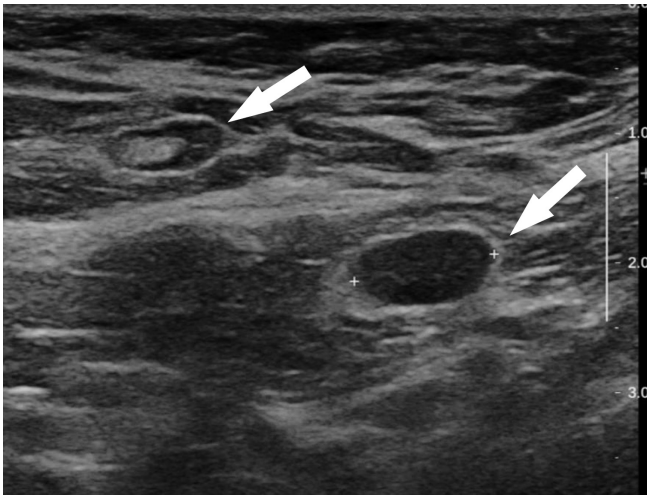

Fig. 1. A 48-year-old woman with mucinous carcinoma in the left breast. Axillary US demonstrating suspicious lymph nodes with cortical thickening (arrows) and effacement of the fatty hilum (crosses). The patient received a third dose of the BNT162b2 vaccine in the left deltoid muscle four days before the preoperative axillary US. Ultrasonography-guided fine-needle aspiration of the lymph nodes was negative for malignant cells. Left breast-conserving surgery and sentinel lymph node biopsy were performed, and final pathology revealed no axillary lymph node metastasis. US = ultrasound

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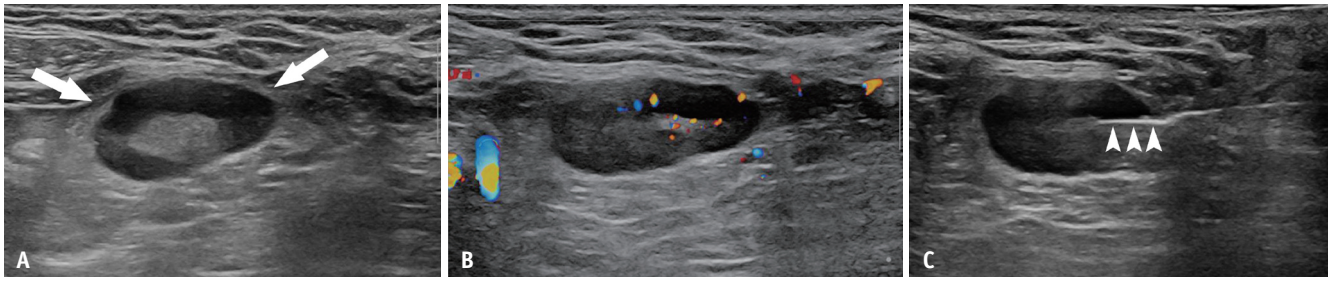

Fig. 2. A 56-year-old woman with mucinous carcinoma in the left breast.
A, B. Axillary US showing a suspicious lymph node with diffuse uniform cortical thickening (arrows) and increased vascularity. The woman received a second dose of the mRNA-1273 vaccine in the left deltoid muscle three months before undergoing preoperative axillary US.
C. Ultrasonography-guided core needle biopsy of the lymph node (arrowheads) was negative for malignant cells. However, the final axillary lymph node dissection revealed three out of 28 metastatic axillary lymph nodes. US = ultrasound

In patients with a personal history of breast cancer, enlarged lymph nodes noted in the axilla ipsilateral to the primary cancer site on surveillance examinations such as breast MRI or chest CT scan also raise concerns for axillary recurrence, which is known to be associated with poor prognosis, simultaneous local recurrence, and distant metastases [20].

COVID-19 vaccine-associated lymphadenopathy is more likely to occur within 2 weeks after vaccination and is frequently noted within 4 weeks of vaccination, supporting the idea that immediate lymphadenopathy after vaccination is more likely to be attributed to the vaccine [13,21]. However, the presentation of lymphadenopathy as late as 71 days after the second dose has also been reported [14]; thus, later presentation should not be hastily attributed to metastatic disease. Furthermore, there is considerable variability in the degree of lymphadenopathy [13] and time-to-resolution according to vaccine type [21]. The time to complete resolution is longer than 12 weeks [21] and can even reach up to 43 weeks [14]; therefore, spontaneous remission cannot be expected within a short period, which might consequently delay axillary nodal staging and proper management.

To avoid confusion between COVID-19 vaccine-associated lymphadenopathy and metastatic lymphadenopathy from breast cancer, management guidelines and recommendations should be customized for women at a higher risk of metastasis, including patients with newly diagnosed breast cancer or with a personal history of breast cancer. In these patient groups, COVID-19 vaccination should be performed in the contralateral arm or thigh [11,22], and patients should be educated about the importance of this. Despite efforts to vaccinate the arm contralateral to the breast cancer site, lymphadenopathy may develop unexpectedly at the bilateral axillae or the atypical site to the injection site [23-26]. However, this is a rare condition, and we are convinced that the majority of patients will benefit to a great extent through vaccination in the arm contralateral to the breast cancer.

Prior negative imaging followed by COVID-19 vaccination may show an antecedent relationship between vaccination and lymphadenopathy, and cautious interpretation of lymphadenopathy, considering the timeframe from vaccination and overall nodal metastatic risk, can provide clues [21]. However, it is usually not feasible to have axillary imaging obtained short time before vaccination in patients with breast cancer. Since the examinations are performed according to the typical annual or semi-annual surveillance or screening schedule for breast cancer, most prior imaging was likely performed several months to years before the post-vaccination imaging [27]. Therefore, the prior images usually do not help to establish the relationship between vaccination and lymphadenopathy.

In the COVID-19 pandemic era, imaging at breast clinics should no longer be postponed owing to prior vaccination because the number of advanced-stage breast cancer patients is projected to increase after the COVID-19 pandemic [28]. Therefore, it is of paramount importance to follow the recommended guidelines and avoid actions that can cause confusion as much as possible. In addition, understanding the different timelines for lymphadenopathy resolution according to the vaccine type will help manage patients visiting breast clinics.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

ORCID iDs

Jung Min Chang
https://orcid.org/0000-0001-5726-9797
Su Min Ha
https://orcid.org/0000-0002-1833-0919

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