**CLINICAL VIGNETTE**

# Axillary Lymphadenopathy after COVID-19 Vaccination

Seohyeon Im, MD[1] and David Shin, MD[2]

[1]Soonchunhyang University College of Medicine, Republic of Korea
[2]UCLA Division of Hematology-Oncology

Unilateral axillary lymphadenopathy has emerged as a local reaction following the COVID-19 vaccination. Further studies in patients with cancer are needed since this may present a diagnostic conundrum in distinguishing metastasis from benign reactions. We present a case of unilateral axillary lymphadenopathy observed after administration of the COVID-19 vaccine in a patient with a history of breast cancer and briefly discuss the epidemiology, etiology, and current recommendations.

***Case Presentation***

A 46-year-old woman with a history of triple-negative breast cancer status post mastectomy and adjuvant chemotherapy completed 2 years prior underwent surveillance computed tomography (CT), which revealed new left axillary and subpectoral lymphadenopathy, with the largest lymph node measuring 12 mm in the left axilla (Figure 1).

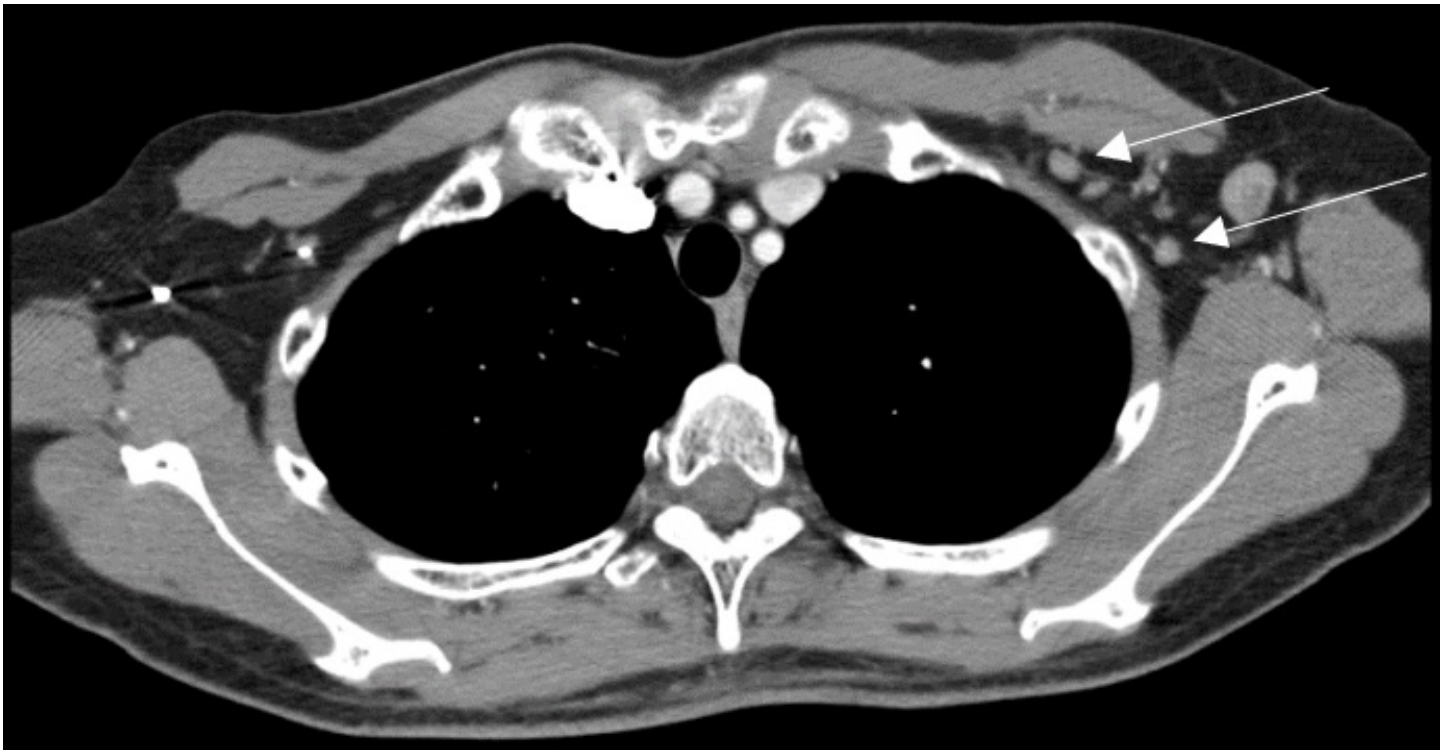

Figure 1.

Her right-sided breast cancer was detected 3 years prior during routine screening mammography. Breast magnetic resonance imaging revealed a 2.5-cm right upper-quadrant mass with prominent right axillary lymph nodes. Triple-negative breast cancer was diagnosed after biopsy results. Six-month neoadjuvant therapy with paclitaxel plus carboplatin was initiated and later switched to doxorubicin plus cyclophosphamide. Three months later, bilateral nipple-sparing mastectomy with right sentinel lymph node biopsy was performed, which revealed no residual invasive carcinoma and no metastasis to the sentinel lymph node. The patient completed adjuvant radiotherapy. Subsequently, follow-up chest, abdomen, and pelvic CT were performed every 6 months, with no recurrence noted.

She received the initial 2 doses of the Moderna COVID-19 vaccines. A month later, her surveillance chest CT scan revealed

left axillary and subpectoral lymphadenopathy. This was suspected to be reactive hyperplasia caused by the recent COVID-19 vaccination. Follow-up chest CT 3 months later revealed a reduction in the size of the previous lymphadenopathy, and no further evaluation was performed.

***Discussion***

Unilateral lymphadenopathy is a well-known but rare adverse effect of conventional vaccines, such as those for influenza and human papilloma virus.[1,2] One study reported increased fluorodeoxyglucose (FDG) uptake in the axillary lymph nodes in 13.8% of 179 FDG-positron emission tomography (PET) images after influenza vaccination. However, no significant lymph node enlargement was reported.[3]

In contrast with other vaccines, COVID-19 vaccines are associated with increased rates of axillary lymphadenopathy. The Pfizer-BioNTech and Moderna vaccines are two mRNA COVID-19 vaccines initially approved by the U.S. Food and Drug Administration for emergency use. In the Moderna trial, ipsilateral axillary swelling or tenderness was the second most frequent local reaction, occurring in 11.6% and 16.0% of recipients aged 18–64 years after the first and second dose, respectively. In terms of unsolicited adverse events due to immunological reactogenicity, lymphadenopathy was reported in 1.1% of the vaccinated group versus 0.6% of the placebo group.[4] In the Pfizer-BioNTech trial, lymphadenopathy was reported in 0.3% of the vaccinated group compared with the <0.1% in the placebo group.[5]

mRNA vaccines have recently been developed and received widespread attention for its advantages over conventional vaccines. These include safety due to lack of an infectious formula, efficacy owing to its rapid uptake and expression in the cytoplasm, and productivity based on its large-scale manufacturing using *in vitro* transcription. Exogenous mRNA is inherently immunostimulatory. It serves as an adjuvant to drive dendritic cell maturation and causes innate immune sensing.[6] Due to robust B- and T-cell responses and the production of pro-inflammatory cytokines, mRNA vaccines may contribute to more frequent systemic and local reactions, including lymphadenopathy. Vaccinations manufactured by AstraZeneca and Johnson and Johnson contain DNA delivered within non-replicating recombinant adenovirus vectors. Lymphadenopathy after AstraZeneca vaccination has also been reported.[7]

Clinicians needs to be aware of this phenomenon, as it may present a diagnostic dilemma in cancer imaging studies, especially in individuals with a history of malignancy. Suggestions and guidelines for the diagnostic approach for post-vaccination axillary adenopathy have been recently published.

The Society of Breast Imaging (SBI) proposed the first guidelines in January 2021.[8] These recommend obtaining information via questionnaires regarding vaccination timing, injection site, and patient education on possible axillary swelling to reduce patient anxiety. Short-term follow-up of 4–12 weeks after the second vaccination is recommended if axillary adenopathy occurs after the COVID-19 vaccination within the preceding 4 weeks. Lymph node biopsy may be considered to exclude malignancy if axillary adenopathy persists after follow-up. Finally, the SBI suggests scheduling screening examinations before the first dose of COVID-19 vaccination or 4–6 weeks after the second dose.

In February 2021, recommendations by a multidisciplinary panel regarding COVID-19 vaccine-related lymphadenopathy were published in *Radiology* with additional suggestions.[9] These recommend avoiding delays in COVID-19 vaccination for imaging studies in patients with a history of cancer or cancer screening. The recommendations are based on the risk of infection fatality and higher mortality rates from COVID-19 than cancer. The guidelines state that routine imaging and screening appointments should be scheduled at least 6 weeks after the final dose since some nodes remain enlarged after 4 weeks. However, imaging should not be delayed for urgent indications. In addition, to avoid diagnostic confusion in interpreting images, the guidelines advise administering the vaccine on the contralateral side to the primary cancer.

The most recent recommendations for the management of COVID-19 vaccine-related lymphadenopathy were published in the *American College of Radiology*, in June 2021.[10] These summarize the preceding recommendations and add more management plans specific to individual situations. For patients undergoing surveillance imaging after cancer treatment, no further imaging is recommended in cases of axillary lymphadenopathy ipsilateral to the injection site within 6 weeks. Follow-up imaging examination is recommended in cases of contralateral axillary lymphadenopathy or vaccination preceding > 6 weeks. In terms of assessing patients with newly diagnosed cancer or those receiving systemic chemotherapy, lymphadenopathy will likely cause diagnostic confounding. Axillary lymphadenopathy may occur in cases of breast cancer, lung cancer, or lymphoma. Cervical lymphadenopathy, particularly the supraclavicular chain, may be found in distant metastases of gastroesophageal or pancreatic cancer. In the context of staging and evaluating an appropriate oncological treatment, management decisions should be individualized based on the type of cancer, lymphatic drainage pathway, and overall risk profile. These may vary from clinical management with no further imaging, short-term follow-up, or biopsy examinations.

Given the current uncertainty and absence of definite guidelines, the management of axillary lymphadenopathy following COVID-19 vaccination remains at physicians' discretion. To prevent unnecessary imaging studies and mitigate patients' anxiety, thorough acknowledgment by the oncology care team and radiologists along with further guideline development is needed.

**REFERENCES**


1. **Studdiford J, Lamb K, Horvath K, Altshuler M, Stonehouse A**. Development of unilateral cervical and supraclavicular lymphadenopathy after human papilloma virus vaccination. *Pharmacotherapy*. 2008 Sep;28(9): 1194-7. doi: 10.1592/phco.28.9.1194. PMID: 18752390.
2. **Shirone N, Shinkai T, Yamane T, Uto F, Yoshimura H, Tamai H, Imai T, Inoue M, Kitano S, Kichikawa K, Hasegawa M**. Axillary lymph node accumulation on FDG-PET/CT after influenza vaccination. *Ann Nucl Med*. 2012 Apr;26(3):248-52. doi: 10.1007/s12149-011-0568-x. Epub 2012 Jan 21. PMID: 22271546.
3. **Park E, Graham M**. Axillary lymph node activation following Influenza vaccination on F-18 FDG PET/CT. *J Nucl Med*. 2020 May;61(supplement 1):1351.
4. Center for Disease Control and Prevention. Local Reactions. Systemic Reactions, Adverse Events, and Serious Adverse Events: Moderna COVID-19 Vaccine. 2020 Dec 20.
5. **Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group**. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020 Dec 31;383(27):2603-2615. doi: 10.1056/NEJMoa2034577. Epub 2020 Dec 10. PMID: 33301246; PMCID: PMC7745181.
6. **Pardi N, Hogan MJ, Porter FW, Weissman D.** mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov*. 2018 Apr;17(4):261-279. doi: 10.1038/nrd.2017.243. Epub 2018 Jan 12. PMID: 29326426; PMCID: PMC5906799.
7. **Nawwar AA, Searle J, Singh R, Lyburn ID**. Oxford-AstraZeneca COVID-19 vaccination induced lymphadenopathy on [18F]Choline PET/CT-not only an FDG finding. *Eur J Nucl Med Mol Imaging*. 2021 Jul;48(8):2657-2658. doi: 10.1007/s00259-021-05279-2. Epub 2021 Mar 4. PMID: 33661328; PMCID: PMC7930521.
8. Society of Breast Imaging. Recommendations for the Management of Axillary Adenopathy in Patients with Recent COVID-19 Vaccination, 2021. Available at: https://www.sbi-online.org/Portals/0/Position%20 Statements/2021/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination.pdf.
9. **Becker AS, Perez-Johnston R, Chikarmane SA, Chen MM, El Homsi M, Feigin KN, Gallagher KM, Hanna EY, Hicks M, Ilica AT, Mayer EL, Shinagare AB, Yeh R, Mayerhoefer ME, Hricak H, Vargas HA**. Multidisciplinary Recommendations Regarding Post-Vaccine Adenopathy and Radiologic Imaging: Radiology Scientific Expert Panel. *Radiology*. 2021 Aug;300(2): E323-E327. doi: 10.1148/radiol.2021210436. Epub 2021 Feb 24. PMID: 33625298; PMCID: PMC7909071.
10. **Lehman CD, D'Alessandro HA, Mendoza DP, Succi MD, Kambadakone A, Lamb LR**. Unilateral Lymphadenopathy After COVID-19 Vaccination: A Practical Management Plan for Radiologists Across Specialties. *J Am Coll Radiol*. 2021 Jun;18(6):843-852. doi: 10.1016/j.jacr.2021.03.001. Epub 2021 Mar 4. PMID: 33713605; PMCID: PMC7931722.