

## Case Report



# Ipsilateral Malignant Axillary Lymphadenopathy and Contralateral Reactive Lymph Nodes in a COVID-19 Vaccine Recipient With Breast Cancer

Mehmet Emin Adin <sup>1</sup>, Jennifer Wu <sup>1</sup>, Edvin Isufi <sup>1</sup>, Edison Tsui <sup>2</sup>, Darko Pucar <sup>1</sup>

<sup>1</sup>Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, USA

<sup>2</sup>Department of Oncology, University of Massachusetts, Fall River, USA

## OPEN ACCESS

Received: Dec 31, 2021

Revised: Feb 20, 2022

Accepted: Feb 22, 2022

Published online: Mar 15, 2022

### Correspondence to

Mehmet Emin Adin

Department of Radiology and Biomedical Imaging, Yale School of Medicine, 20 York St, New Haven, CT 06510, USA.

Email: Emin.adin@gmail.com

© 2022 Korean Breast Cancer Society

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ORCID iDs

Mehmet Emin Adin

<https://orcid.org/0000-0002-0070-9998>

Jennifer Wu

<https://orcid.org/0000-0001-9174-1127>

Edvin Isufi

<https://orcid.org/0000-0001-9798-9019>

Edison Tsui

<https://orcid.org/0000-0003-0629-6212>

Darko Pucar

<https://orcid.org/0000-0001-6597-5149>

### Conflict of Interest

Pucar D: Telix Pharmaceuticals (speaking fee) and Cohere Health (consulting fee). The other authors declare that they have no competing interests.

## ABSTRACT

Vaccine-related axillary nodal enlargement is a common benign condition that many mRNA vaccine receivers experience. However, a false attribution of axillary swelling to vaccination may result in delay in cancer care and potential disease progression, particularly in breast cancer patients presenting with ipsilateral axillary lymphadenopathy. We report the case of a 41-year-old pre-menopausal female who presented with suspicious axillary nodal enlargement and a right breast lump (triple-negative invasive ductal carcinoma) after recent administration of the second dose of Moderna mRNA coronavirus disease 2019 (COVID-19) vaccine. On imaging, bilateral axillary lymph nodes were detected. The ipsilateral right-sided node was proven to be metastatic, whereas contralateral nodes were related to a recent mRNA COVID-19 vaccination. Right-sided lymph node had intense uptake (maximum standardized uptake value [SUVmax] = 5), while the contralateral reactive nodes were mildly avid (SUVmax = 2.6). On magnetic resonance imaging, the right-sided node revealed asymmetric cortical thickening and marked cortical enhancement as opposed to normal-appearing left-sided nodes.

**Keywords:** Breast; COVID-19; Lymphadenopathy; Neoplasms; Vaccines

## INTRODUCTION

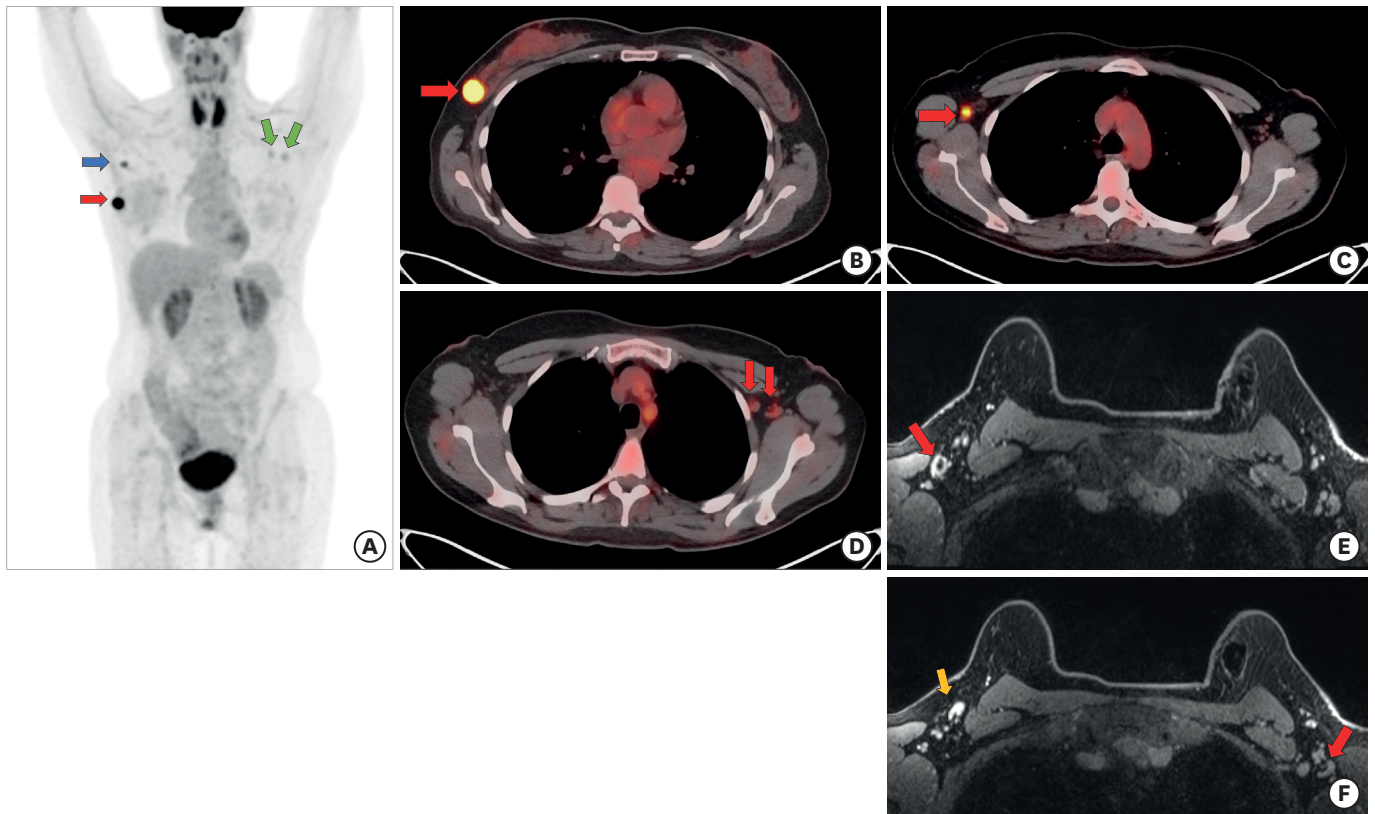
Vaccine related imaging findings including ipsilateral axillary lymphadenopathy can generate false alarms and cause patient anxiety, particularly in those with a known underlying malignancy. Occasionally this may prompt unnecessary interventions for an otherwise reactive process [1]. Conversely, false attribution of axillary lymphadenopathy to vaccination may result in delay in cancer treatment and the potential for disease progression. It has been previously reported that vaccine-related axillary nodal enlargement can occur in the setting of influenza and human papillomavirus vaccines [2,3]. Recent reports have also reported ipsilateral reactive axillary lymph node enlargement in recipients of the coronavirus disease 2019 (COVID-19) mRNA vaccines [1,4]. We report the case of a COVID-19 vaccine recipient with reactive and malignant axillary lymph node enlargement in the setting of breast cancer.

**Author Contributions**

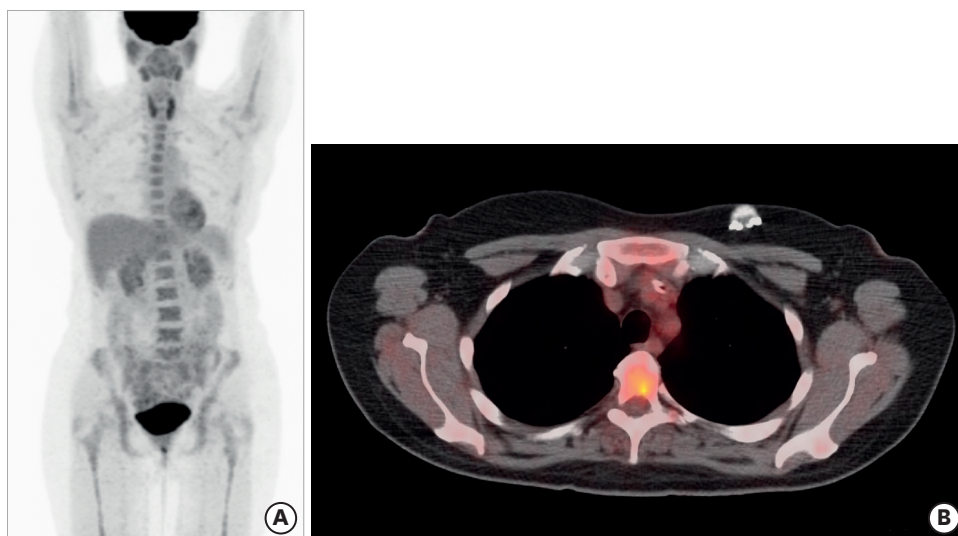
Conceptualization: Adin ME, Pucar D; Data curation: Adin ME, Wu J; Supervision: Adin ME, Pucar D; Writing - original draft: Adin ME; Writing - review & editing: Adin ME, Wu J, Isufi E, Tsui E, Pucar D.

**CASE REPORT**

A 41-year-old pre-menopausal female presented with palpable right breast lump and ipsilateral axillary nodal enlargement on physical exam. This was subsequently confirmed on dedicated breast imaging as a 1.5 cm round right breast mass with a  $0.8 \times 0.8 \times 0.7$  cm ipsilateral axillary lymph node. Core biopsies of the right breast mass revealed triple negative invasive ductal carcinoma and enlarged lymph node demonstrated findings concerning for malignant involvement. Staging  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography/computed tomography (PET/CT) (with tracer injected through an IV placed in the right antecubital fossa) showed an intensively FDG avid right axillary tail breast primary (**Figure 1**, maximum standardized uptake value [SUVmax] 19.2) and ipsilateral involved  $1.4 \times 0.8$  cm axillary node (SUVmax 5.0, [Deauville score = 5], **Figure 1**). Additionally, mildly FDG avid left axillary nodes measuring  $1.0 \times 0.8$  cm (SUVmax 2.6, which was above the activity of mediastinal blood pool of SUVmax 2.3, [Deauville score = 3], **Figure 1**) were identified. The left axillary lymph nodes were initially considered indeterminate for metastatic disease, but upon further review, they were attributed to the second dose of the Moderna mRNA



**Figure 1.** Preoperative imaging studies. (A) Whole-body,  $^{18}\text{F}$ -FDG PET/CT, 3D MIP image shows intensely hypermetabolic malignant lesion in the right breast with SUVmax 19.2 (red arrow), moderately hypermetabolic solitary lymph node in the right axilla with SUVmax 5.0 (blue arrow), and two mildly hypermetabolic lymph nodes in the left axilla with SUV max 2.6 (green arrows). (B) Whole-body  $^{18}\text{F}$ -FDG PET/CT, fused axial image shows the intense FDG avid malignant lesion in the right breast with SUVmax of 19.2 (arrow). (C) Whole-body  $^{18}\text{F}$ -FDG PET/CT, fused axial image shows a moderately hypermetabolic lymph node in the right axilla with SUVmax of 5.0 (arrow). (D) Whole-body  $^{18}\text{F}$ -FDG PET/CT, fused axial image shows two mildly avid lymph nodes in the left axilla with SUVmax of 2.6 (arrows). (E) Breast MRI (performed three weeks after whole body  $^{18}\text{F}$ -FDG PET/CT). Axial T1 weighted post-contrast image shows enhancing and enlarged lymph node with asymmetric cortical thickening and a biopsy clip in the right axilla (arrow). (F) Axial T1 weighted post-contrast image, obtained slightly below the level of image in Figure 1E, shows a cluster of reactive lymph nodes in the left axilla with no significant enhancement or asymmetric cortical thickening (red arrow). An additional right axillary node with asymmetric cortical thickening is also seen, highly suspicious for metastatic disease (yellow arrow).  $^{18}\text{F}$ -FDG PET/CT =  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/computed tomography; 3D = three-dimensional; MIP = maximum intensity projection; SUVmax = maximum standardized uptake value; MRI = magnetic resonance imaging.



**Figure 2.** Follow-up post operative whole-body 18F-FDG PET-CT images. (A) 3D MIP image shows no residual hypermetabolic activity in the right breast, no hypermetabolic activity in the right axilla, and resolution of moderately hypermetabolic left axillary lymph nodes. (B) Fused axial image shows resolution bilateral lymph nodes. 18F-FDG PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography; 3D = three-dimensional; MIP = maximum intensity projection.

COVID-19 vaccine which was administered to the left arm sixteen days previously. Contrast-enhanced breast magnetic resonance imaging (MRI; MRI study was performed before and after IV gadolinium administration) approximately 5 weeks post-vaccination and prior to any treatment revealed stable bilateral axillary nodes. However, there were differences in imaging characteristics of lymph nodes. The right axillary lymph node demonstrated eccentric cortical thickening and contrast enhancement, whereas the left axillary lymph nodes showed clear delineation of fatty hila without discernable enhancement on post contrast images (**Figure 1**). The latter is typically suggestive of a benign etiology such as inflammation/infection [5].

The patient completed neoadjuvant chemotherapy for triple negative disease, and a follow-up 18F-FDG PET/CT at approximately 6-months from her last 18F-FDG PET/CT showed complete resolution of the previously hypermetabolic bilateral lymph nodes (**Figure 2**). She underwent a right mastectomy and complete axillary node dissection, the final surgical specimen demonstrated complete histopathological response to neoadjuvant systemic therapy with treatment-related changes.

## DISCUSSION

The COVID-19 vaccines can result in reactive ipsilateral axillary and neck lymphadenopathy demonstrated on both anatomic and functional imaging that may need to be distinguished from malignancy, particularly in patients with current or a prior history of cancer [6,7]. Vaccine related nodal reactivity or adenopathy can sometimes be seen or persist up to several months after vaccination [8]. In the patient reported here, initial lymph node biopsy revealed atypical epithelial cells suspicious for malignant involvement ipsilateral to the breast mass, in line with suspicious imaging findings. PET-CT imaging following neoadjuvant systemic therapy showed complete resolution of previously hypermetabolic bilateral lymph nodes, and final surgical pathology did not reveal the viable tumor. An initial lymph node dissection and

lesion resection were not performed, as the standard of care for the management of triple-negative breast cancer continues to be with neoadjuvant systemic therapy.

Conclusive distinction between malignant or reactive lymphadenopathy remains challenging particularly in nodes with borderline activity and morphology on imaging. Imaging features such as asymmetric cortical thickening, significant enlargement, necrosis, indistinct contours, and conglomeration favor malignancy [9]. PET-CT is more sensitive, as it can detect metabolic activity in very small lymph nodes as well, regardless of its underlying condition. That said, there is no clear cut-off for a malignant or benign nodal enlargement, and the decision may be based upon multiple factors. For example, in the case we report here, the malignant node SUVmax (Deauville score = 5) value was higher than that of the reactive nodes (Deauville score = 3). On MRI, malignant nodes revealed abnormal findings such as asymmetric cortical thickening and cortical enhancement. To decrease reporting variability between PET-based imaging studies, the Deauville scoring system a globally agreed-upon approach for evaluation of treatment response in lymphoma was proposed to be used in the evaluation of vaccine-related nodal reactivity [1]. Deauville scores are more reproducible among different institutions as compared to SUV values given their individual PET protocols. In the case we report here, the reactive left-sided node had a Deauville score of 3, versus the malignant node, which had a Deauville score of 5. The Deauville activity score for the reactive node was in line with previously reported nodal activity in vaccine-related nodal enlargement [1]. Nodal reactivity with mRNA vaccines is more common after the second dose [1,10]. Moderna vaccines have shown to have slightly higher likelihood of nodal reactivity compared to Pfizer vaccine [1]. A recent retrospective study suggested that lymphopenia maybe associated with lower incidence of nodal reactivity, further supporting the link between nodal reactivity and vaccine immunogenicity [11].

In conclusion, ipsilateral axillary nodal reactivity is a common observation after administration of the second dose of COVID-19 mRNA vaccines, with the potential persistence up to several months [12]. In the case we reported here, nodal enlargement persisted beyond 6 weeks. Current expert recommendations for follow-up are ongoing and include follow-up of the affected axilla at least 6-weeks after the second dose of the vaccination, with consideration for lymph node sampling if suspicion remains. The follow-up to resolution particularly in those with known underlying malignancies should warrant careful consideration, and documentation of vaccination should be included to assist the interpreting radiologist. The timing and location of the vaccination and imaging characteristics should all be considered [7]. Management in this context is case-specific in hopes of both reducing patient anxiety, costs, and unnecessary testing with delays in diagnosis or treatment.

## REFERENCES

1. Adin ME, Isufi E, Kulon M, Pucar D. Association of COVID-19 mRNA vaccine with ipsilateral axillary lymph node reactivity on imaging. *JAMA Oncol* 2021;7:1241-2.  
[PUBMED](#) | [CROSSREF](#)
2. Coates EE, Costner PJ, Nason MC, Herrin DM, Conant S, Herscovitch P, et al. Lymph node activation by PET/CT following vaccination with licensed vaccines for human papillomaviruses. *Clin Nucl Med* 2017;42:329-34.  
[PUBMED](#) | [CROSSREF](#)
3. Shirone N, Shinkai T, Yamane T, Uto F, Yoshimura H, Tamai H, et al. Axillary lymph node accumulation on FDG-PET/CT after influenza vaccination. *Ann Nucl Med* 2012;26:248-52.  
[PUBMED](#) | [CROSSREF](#)

4. Xu G, Lu Y. COVID-19 mRNA vaccination-induced lymphadenopathy mimics lymphoma progression on FDG PET/CT. *Clin Nucl Med* 2021;46:353-4.  
[PUBMED](#) | [CROSSREF](#)
5. Marino MA, Avendano D, Zapata P, Riedl CC, Pinker K. Lymph node imaging in patients with primary breast cancer: concurrent diagnostic tools. *Oncologist* 2020;25:e231-42.  
[PUBMED](#) | [CROSSREF](#)
6. Becker AS, Perez-Johnston R, Chikarmane SA, Chen MM, El Homsy M, Feigin KN, et al. Multidisciplinary recommendations regarding post-vaccine adenopathy and radiologic imaging: *Radiology* scientific expert panel. *Radiology* 2021;300:E323-7.  
[PUBMED](#) | [CROSSREF](#)
7. 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;18:843-52.  
[PUBMED](#) | [CROSSREF](#)
8. Tu W, Gierada DS, Joe BN. COVID-19 vaccination-related lymphadenopathy: what to be aware of. *Radiol Imaging Cancer* 2021;3:e210038.  
[PUBMED](#) | [CROSSREF](#)
9. Ayati N, Jesudason S, Berlangieri SU, Scott AM. Generalized lymph node activation after Influenza vaccination on 18F FDG-PET/CT imaging, an important pitfall in PET interpretation. *Asia Ocean J Nucl Med Biol* 2017;5:148-50.  
[PUBMED](#) | [CROSSREF](#)
10. Treglia G, Cuzzocrea M, Giovanella L, Elzi L, Muoio B. Prevalence and significance of hypermetabolic lymph nodes detected by 2-[18F] FDG PET/CT after COVID-19 vaccination: a systematic review and a meta-analysis. *Pharmaceuticals (Basel)* 2021;14:762.  
[PUBMED](#) | [CROSSREF](#)
11. Seban RD, Richard C, Nascimento-Leite C, Ghidaglia J, Provost C, Gonin J, et al. Absolute lymphocyte count after COVID-19 vaccination is associated with vaccine-induced hypermetabolic lymph nodes on <sup>18</sup>F-FDG PET/CT: a focus in breast cancer care. *J Nucl Med*. Epub 2021 Dec 2. <https://doi.org/10.2967/jnumed.121.263082>.  
[CROSSREF](#)
12. Thomassen A, Lerberg Nielsen A, Gerke O, Johansen A, Petersen H. Duration of 18F-FDG avidity in lymph nodes after pandemic H1N1v and seasonal influenza vaccination. *Eur J Nucl Med Mol Imaging* 2011;38:894-8.  
[PUBMED](#) | [CROSSREF](#)