Letters

RESEARCH LETTER

Association of COVID-19 mRNA Vaccine With Ipsilateral Axillary Lymph Node Reactivity on Imaging

Intramuscular coronavirus 2019 (COVID-19) vaccinations could induce ipsilateral axillary lymph node reactivity that may be falsely attributed to malignant abnormality, prompting unwarranted interventions, or it may be falsely attributed to vaccination rather than cancer, potentially delaying cancer care. We aimed to investigate Moderna and Pfizer COVID-19 vaccine-related nodal reactivity on ^{18}F-flurodeoxyglocose (FDG) positron emission tomographic (PET)/computed tomographic (CT) scans.

Supplemental content

Methods | All patients (n = 1290) who underwent FDG-PET/CT scans between December 11, 2020 and March 1, 2021 at the Yale New Haven Hospital were screened (eMethods in the Supplement) for COVID-19 vaccination. Sixty-eight patients who received at least 1 dose of COVID-19 vaccine were analyzed. Sixty-seven of 68 patients had PET/CT for oncologic indications, none of which was adenopathy ipsilateral to the vaccination site. Intensity of lymph node activity was graded by Deauville criteria[1]; activity more intense than mediastinal blood pool was considered reactive.

Results | Reactive ipsilateral axillary lymph nodes developed in 9 of these 68 patients (13%), 7 women and 2 men. After the first vaccine dose, in 2 of 41 patients (5%) and after the second vaccine dose, in 7 of 27 patients (26%) (Fisher exact $P = .02$; odds ratio [OR], 0.15; CI, 0.01-0.89), 3 (15%) for the Pfizer vaccine and 4 (57%) for the Moderna vaccine (**Table 1**). Median time from the second vaccine dose to the FDG-PET/CT scan was 10 days in patients with nodal reactivity and 12 days in those without nodal reactivity (**Table 2**). On CT scan, axillary lymph nodes were enlarged (≥10 mm short axis) in 1 of 59 patients (2%) with nonreactive nodes and in 5 of 9 patients (56%) with reactive nodes (Fisher exact $P < .001$; OR, 0.02; 95% CI, 0.01-0.19). Overall, FDG-activity was seen at the injection site in 6 of 51 patients (12%) for Pfizer and 2 of 17 patients (12%) for Moderna vaccines.

Discussion | Axillary lymphadenopathy following intramuscular vaccine has been observed with influenza and human papilloma virus vaccines, and recently with COVID-19 mRNA vaccines.[2-4] We found that ipsilateral axillary nodal reactivity occurred after the first vaccine dose in 2 patients (5%) and after the second vaccine dose in 7 (26%); 4 patients (57%) after the second dose of the Moderna vaccine and 3 (15%) after the second dose of the Pfizer vaccine. In the Moderna trial, axillary swelling and tenderness on patient survey was reported in 1322 (11.6%) patients after the first dose (567 [5%] placebo) and in 1654 (16%) after the second dose (444 [4.3%] placebo) of vaccine; in the Pfizer trial, only unsolicited reactions were recorded.[5]

^{18}F-Flurodeoxyglocose-PET/CT is highly sensitive for detection of reactivity in nonenlarged or enlarged lymph nodes, explaining higher frequency of nodal reactivity in this study relative to the Moderna trial after the second dose. In the present study, only 5 patients (56%) with nodal reactivity on PET had nodal enlargement on CT findings. Increased nodal FDG uptake, presumably from an inflammatory immune response to the vaccine, was observed up to 32 days after vaccination in this cohort, harboring the potential risk of mimicking or masking malignant disease. Patients with cancer with a propensity for spread to ipsilateral axillary lymph nodes—breast cancer, melanoma, lymphomas—should have the COVID-19 vaccine in the axilla contralateral to the previously or potentially involved site. Nuclear medicine technologists should document vaccine site, date, type, and first vs second dose. In this cohort, ipsilateral axillary nodal activity was much

Table 1. Patient Characteristics Grouped According to Ipsilateral-to-Injection-Site Axillary Nodal Reactivity[a]

Parameter	No. (%)	
	Nonreactive	Reactive
Patients	59 (87)	9 (13)
Age, y		
Mean (SD) [range]	76 (8) [53-89]	69 (12) [46-83]
<80	40 (68)	7 (78)
≥80	19 (32)	2 (22)
Sex (% women)	29 (49)	7 (78)
Vaccine to PET scan time, median (range), d	12 (1-47)	10 (3-20)
Vaccine type		
Pfizer	47 (92)	4 (8)
Moderna	12 (71)	5 (29)
Vaccine dose		
1st Dose, total	39 (95)	2 (5)
2nd Dose total	20 (74)	7 (26)
1st Dose, Moderna	9 (90)	1 (10)
1st Dose, Pfizer	30 (97)	1 (3)
2nd Dose, Moderna	3 (43)	4 (57)
2nd Dose, Pfizer	17 (85)	3 (15)
Absolute neutrophil count, ×1000/μL[b]		
Normal	31	9
Abnormal (low)	5	0
Abnormal (high)	3	0
Not available	17	3

Abbreviation: PET, positron emission tomography.

[a] Nodes with activity greater than the mediastinal blood pool are classified as reactive.

[b] Normal range, 1.0-11.0 × 1000/μL

Table 2. Distribution of Deauville Scores for First and Second Dose of Moderna and Pfizer Vaccines

Activity scale	Moderna 1	Moderna 2	Pfizer 1	Pfizer 2
Deauville 1	6	1	22	13
Deauville 2	3	2	8	4
Deauville 3	0	2	0	0
Deauville 4	0	1	0	0
Deauville 5	1	1	1	3

less common after the first vaccine dose, and women were more likely to develop reactive nodes, an important implication for breast cancer imaging concordant with the statement issued by the Society of Breast Imaging.[6]

Limitations. This was a single institutional study with limited sample size and follow-up, comparing 2 COVID-19 vaccines available at Yale School of Medicine in early vaccination stage. However, the study was conducted by strict and reproducible PET and CT criteria, and provides a framework for the future studies in this field.

Conclusions | Ipsilateral axillary nodal reactivity is commonly seen after the intramuscular administration of the COVID-19 mRNA vaccines, more so after the second dose than after the first, and more commonly with the Moderna than the Pfizer vaccine.

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