Radiology: Imaging Cancer

COVID-19 Vaccination-Related Lymphadenopathy: What To Be Aware Of

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Essentials

- With the rollout of mass COVID-19 vaccination across the world, vaccine-induced lymphadenopathy is an important side effect for clinicians, patients, and cancer researchers to be aware of.
- Vaccine-induced lymphadenopathy can present as a diagnostic dilemma for radiologists.
- Evolving imaging guidelines are needed to address management strategies of vaccine-induced lymphadenopathy in both the general population and high-risk oncology patients.
- Documentation of vaccination status is critical to decrease unnecessary biopsies and alleviate patient anxiety.

Introduction

The COVID-19 pandemic has changed the landscape of society since February of 2020 with a significant and tragic impact on morbidity and mortality with 2.77 million deaths across the world and 548,087 deaths in the United States as of March 26, 2021. Leading scientific minds have brought us a glimmer of hope with the development of multiple vaccines that are currently being distributed throughout the world. With the mass rollout of vaccination, both prevention of COVID-19 infection and reduction in morbidity and mortality can be achieved with hopes of ending the pandemic. Since

February 27, 2021, three COVID-19 vaccines have been authorized by the U.S. Food and Drug Administration for emergency use; the two-dose Pfizer and Moderna mRNA vaccines and the most recently authorized single dose Johnson and Johnson/Janssen adenovirus vector vaccine. Several other vaccines are in development or being distributed in other countries including those developed by Oxford-AstraZeneca (ChAdOx1 nCoV-19 or AZD1222), Gamaleya Research Institute of Epidemiology and Microbiology (Sputnik V), and the CanSinoBIO-Beijing Institute of Biotechnology (Convidicea or Ad5-nCoV). Through March 26, 2021, 526 million doses of vaccines have been distributed across the world.

With mass vaccination rollout, lymphadenopathy ipsilateral to the injected deltoid muscle has become an important manifestation of an immune response to be aware of as it may present as a diagnostic dilemma on cancer imaging studies. We write this editorial as a public service message at a time where other countries are starting mass vaccination programs with the goal of preventing unnecessary nodal biopsies and alleviating patient concern.

What are the side effects of COVID-19 vaccination?

The most common COVID-19 vaccine side effects include local injection site pain, fever, chills, myalgias, headache and fatigue, with resolution usually in a few days [1, 2]. However, palpable lymphadenopathy commonly involving the axilla as an immune response to vaccination may present a clinical diagnostic dilemma especially in persons with a history of malignancy. Patients may be concerned regarding lymphadenopathy as a sign of malignancy, especially persons with a prior oncologic history. This anxiety will only increase in patients with lymphadenopathy as widespread rollouts of vaccination continue. In addition, lymphadenopathy may be found incidentally on imaging examinations, such as routine screening or oncologic surveillance examinations, presenting a diagnostic dilemma for radiologists.

How common is vaccine-induced axillary lymphadenopathy?

Although unilateral lymphadenopathy is a known side effect of vaccines, it is rarely reported with vaccines such as the Bacillus Calmette–Guérin, influenza, and human papillomavirus vaccines [3-5]. In a larger series examining 83 recipients of the influenza vaccine, four patients had unexpected fluorodeoxyglucose axillary node accumulations on imaging [5]. In addition, lymph node uptake on nuclear medicine studies after vaccination has been shown by multiple studies.

This is in contrast with the two-dose approved COVID-19 vaccines in the United States, Pfizer-BioNTech and Moderna, which both have higher reported rates of axillary swelling compared to prior vaccines. This may be due to a higher immunogenic response to these mRNA vaccines, a type of vaccine that has not previously been approved for use. As a solicited adverse event in the Moderna clinical trials, axillary swelling or tenderness was reported in 11.6% of patients (5.0% placebo) after Dose 1 and 16.0% (4.3% placebo) after Dose 2 [1]. While not solicited as an adverse event in the Pfizer trials, reports of lymphadenopathy from Dose 1 through 30 days after Dose 2 were imbalanced with notably more cases in the Pfizer-BioNTech COVID-19 vaccine group (64) versus the placebo group (6), which is plausibly related to vaccination [2]. The true incidence of post-vaccination lymphadenopathy may be higher given

axillary swelling was only reported as an unsolicited adverse event. Incidence of axillary lymphadenopathy visible at imaging is likely higher as not all patients have clinical symptoms.

What has been reported in the literature so far regarding COVID-19 vaccine-related lymphadenopathy?

As of March 2021, at least 20 articles have been published illustrating or discussing COVID-19 vaccine-related lymphadenopathy, with 18 of these articles published in imaging journals. The earliest publications occurred in the field of breast imaging, where vaccine-induced lymphadenopathy was cited as a cause of unilateral axillary lymphadenopathy. Other imaging subspecialities citing this side effect included nine articles in nuclear medicine, and one article in cardiothoracic imaging. In most publications so far, there has only been one or a very small number of patients reported on; one of the largest groups of patients reported on is 23 patients with axillary adenopathy who had undergone breast imaging [6]. Journals which have published on this subject include *Radiology*, *American Journal of Roentgenology*, *European Journal Nuclear Medicine and Molecular Imaging, Clinical Nuclear Medicine* and *Journal of the American College of Radiology (JACR)*. The majority of these articles reported lymphadenopathy as a side effect after the two-dose COVID-19 Pfizer or Moderna vaccines with two recent articles citing vaccine-induced lymphadenopathy with the Oxford-AstraZeneca vaccine, currently only given as one-dose in the United Kingdom, with the second dose planned for delayed administration. The location of the lymphadenopathy was primarily axillary with four articles reporting cervical lymphadenopathy. The lymphadenopathy can be visualized on multiple modalities with most published cases demonstrated on US, followed by PET, MRI, mammography, and CT.

What are the current imaging guidelines related to vaccine-induced axillary lymphadenopathy?

The Society of Breast Imaging (SBI) was the first imaging society to propose guidelines addressing axillary lymphadenopathy seen on imaging [7], with the Canadian Society of Breast Imaging (CSBI) endorsing the SBI recommendations. There have now been multiple publications suggesting guidelines for unilateral axillary lymphadenopathy with focus on different modalities or oncologic subspecialities. We summarize these below divided in terms of different phases of care.

Clinical history:

Vaccination dates, injection site/laterality and vaccine type should be documented on patient intake forms or electronic medical record [7].

Scheduling exams:

To mitigate the diagnostic dilemma of vaccine-induced lymphadenopathy, the SBI recommends that patients should “consider scheduling screening exams prior to the first dose of a COVID-19 vaccination or 4-6 weeks following the second dose of a COVID-19 vaccination” [7]. This recommendation has been followed by a similar guideline published in *Radiology* from a multi-disciplinary panel from oncologic centers, recommending for non-urgent indications such as routine

surveillance, screening, or staging imaging to be scheduled prior to vaccination or to postpone imaging "at least 6 weeks after final vaccination dose" [8]. McIntosh et al also [9] suggested performing PET/CT "at least two weeks after vaccination in patients with a cancer for which interpretation is anticipated to be potentially impacted by the vaccination, though optimally 4-6 weeks after vaccination". However, like other imaging exams, if there is an urgent clinical indication such as treatment planning, active treatment monitoring, or assessment of new symptoms or potential complications, imaging should not be delayed, regardless of vaccination status.

An additional strategy to mitigate confounding findings would be to administer COVID-19 vaccinations "on the side contralateral to the primary cancer" [8].

Incidentally detected unilateral lymphadenopathy on imaging:

For subclinical unilateral lymphadenopathy detected on imaging, vaccination history including injection site and date is now a key piece of clinical information to obtain. In cases of unilateral axillary lymphadenopathy on screening mammography, the SBI recommends a BI-RADS 0 designation to bring the patient back for assessment of the ipsilateral breast and additional documentation of medical and vaccination history [7]. After an otherwise negative diagnostic workup, and if a COVID-19 vaccine was given on the ipsilateral side in the past 4 weeks, a BI-RADS 3 (Probably Benign) assessment is then assigned with consideration for a short term follow up in 4-12 weeks after the second vaccination dose. If lymphadenopathy persists at follow up, then consider a BI-RADS 4 (Suspicious) assessment with biopsy to exclude malignancy. As these recommendations were first announced in January 2021 based on very early experience with COVID-19 vaccinations, they are necessarily meant to be conservative. In an update (March 9, 2021), the SBI notes that individual practices may wish to establish their own guidelines based on local expertise and resources.

A different approach was suggested by a recent publication in *JACR* proposing use of "BI-RADS 2 Benign" assessment with clinical follow-up for isolated unilateral lymphadenopathy after recent COVID-19 vaccination in the ipsilateral arm [10]. This is consistent with the American College of Radiology BI-RADS recommendations for unilateral lymphadenopathy in the setting of a known inflammatory cause [10]. In comparison with the more conservative SBI recommendations, this "pragmatic" approach would result in fewer follow-up examinations.

In terms of management of clinically evident post-vaccination lymphadenopathy, the multi-disciplinary panel recommended "observing for at least 6 weeks until resolution before referring for diagnostic imaging evaluation or biopsy of the nodes" [8]. The multidisciplinary panel also recommended "expectant management strategy without default follow-up imaging" in patients whom pre-test probability of adenopathy is much more likely to due to vaccination rather than malignancy. In higher-risk situations, either a short-term imaging follow up with ultrasound and/or tissue diagnosis can be considered, especially in patients with a high-risk oncologic history (e.g. ipsilateral breast or head/neck cancer, melanoma or lymphoma) [8]. The expected duration of post-vaccination lymphadenopathy is not yet determined.

What are the implications for patients?

Widespread patient education regarding vaccine-induced lymphadenopathy is needed, especially as this may be mistaken as a sign of malignancy. Imaging societies, clinicians, and news media outlets should spread awareness to educate the public regarding this side effect to minimize patient anxiety. When vaccines are administered, side effects such as axillary swelling should be highlighted and normalized as an immune response initiated by the vaccine. Patients should be aware of the best times to schedule routine imaging exams with more infographics such as the SBI mammography recommendations for women receiving the COVID-19 vaccine being widely distributed. In patients with palpable lymphadenopathy after vaccination, another suggestion may be to proceed with clinical follow-up by a clinician or the patient themselves rather than imaging, resulting in cost-savings to the system. Care should also be taken to ensure clinical and/or imaging follow-up for those with lymphadenopathy that does not resolve, those with potentially causative malignancies (such as breast or head/neck cancer, lymphoma, or melanoma), and those with additional sites of lymphadenopathy.

References

1. Centers for Disease Control and Prevention, *Local Reactions, Systemic Reactions, Adverse Events, and Serious Adverse Events: Moderna COVID-19 Vaccine.*
2. Centers for Disease Control and Prevention, *Local Reactions, Systemic Reactions, Adverse Events, and Serious Adverse Events: Pfizer-BioNTech COVID-19 Vaccine.*
3. Newfield, L., J.E. Naschitz, and D. Yeshurun, *[BCG-induced axillary lymph-adenitis in the adult].* Harefuah, 1990. **119**(7-8): p. 199-200.
4. Studdiford, J., et al., *Development of unilateral cervical and supraclavicular lymphadenopathy after human papilloma virus vaccination.* Pharmacotherapy, 2008. **28**(9): p. 1194-7.
5. Shirone, N., et al., *Axillary lymph node accumulation on FDG-PET/CT after influenza vaccination.* Ann Nucl Med, 2012. **26**(3): p. 248-52.
6. Mortazavi, S., *Coronavirus Disease (COVID-19) Vaccination Associated Axillary Adenopathy: Imaging Findings and Follow-Up Recommendations in 23 Women.* AJR Am J Roentgenol, 2021.
7. Society of Breast Imaging, *SBI Recommendations for the Management of Axillary Adenopathy in Patients with Recent COVID-19 Vaccination*. 2021.
8. Becker, A.S., et al., *Multidisciplinary Recommendations Regarding Post-Vaccine Adenopathy and Radiologic Imaging:.* Radiology, 2021: p. 210436.
9. McIntosh, L.J., et al., *COVID-19 Vaccination-Related Uptake on FDG PET/CT: An Emerging Dilemma and Suggestions for Management.* AJR Am J Roentgenol, 2021.
10. Lehman, C.D., et al., *Unilateral Lymphadenopathy Post COVID-19 Vaccination: A Practical Management Plan for Radiologists Across Specialties.* Journal of the American College of Radiology, 2021.

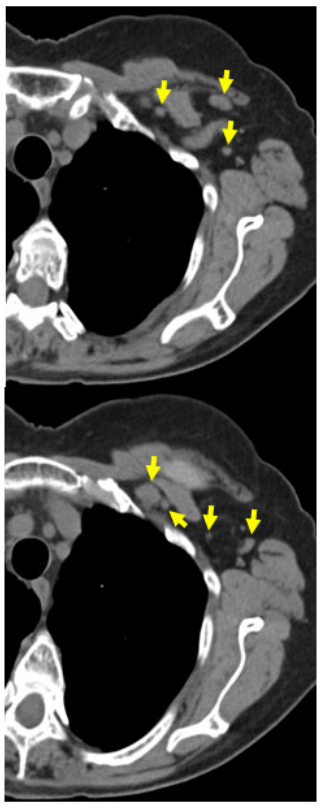

Figure 1, A

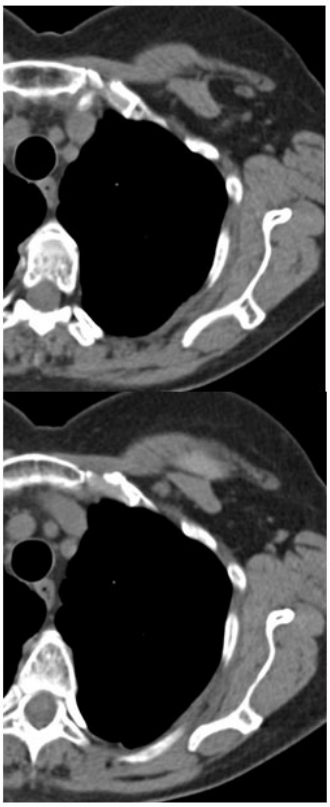

Figure 1, B

Figure 1. 69-year-old female with a history of lung adenocarcinoma and recent left arm COVID-19 vaccination three days prior (first dose). (A) Axial images from chest CT show left axillary and subpectoral lymphadenopathy (arrows) (B) Comparison chest CT images from one-year prior show normal left axillary lymph nodes.