

CASE REPORT

COVID-19 Vaccine-related Lymphadenopathy in Lung Cancer Patients: a Presentation of Three Cases with Suggestions for Management

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ABSTRACT — **Background.** Axillary lymphadenopathy after COVID-19 vaccination have been frequently reported in the medical literature. This benign reaction can be confused with metastases of thoracic malignancies. We experienced three lung cancer cases with COVID-19 vaccine-related lymphadenopathy. **Case presentations.** Three patients were included. One was a pre-operative patient, and the others were post-operative patients. All of them were patients with lung cancer and had been vaccinated for COVID-19. They were found to have swelling of the axial lymph nodes on computed to-

mography several days after undergoing vaccination for COVID-19. Two patients underwent an axial lymph node biopsy. The results of biopsies and close follow-up revealed that none of them actually had metastasis. **Conclusions.** Invasive examinations should be avoided, but inappropriate upstaging and downstaging may result in miserable outcomes. We herein report three cases with imaging and pathological characteristics.

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KEY WORDS — COVID-19, COVID-19 vaccination, Lymphadenopathy, Lung cancer

BACKGROUND

With the increasing prevalence of COVID-19 vaccination, vaccine-related lymphadenopathy has been reported with imaging examinations. The Moderna Company reported the detection of axillary swelling or tenderness in 8.4% of patients over 65 years old in a trial of mRNA-1273 vaccine, and Nishino et al. reported that the rate of lymphadenopathy identification on computed tomography (CT) was 9.0%.¹ Furthermore, it seems that 8 to 12 weeks are needed for the size of the lymphadenopathy to decrease back to the normal size. Axillary lymphadenopathy is a worrisome finding for patients with thoracic malignancies. Although some reports have found vaccine-related lymphadenopathy to be a rare but benign reaction, we cannot always distinguish this kind of vaccine-related reaction from metastases of lung cancer easily when encountering patients with progressive cancers in practical settings.

We herein report three lung cancer cases with axil-

lary lymphadenopathy after vaccination. All three patients had received the mRNA-1273 vaccine.

CASE PRESENTATION

Patient 1

A woman in her late 60s with a lung adenocarcinoma in the right upper lung lobe was referred to our hospital. She had histories of diabetes mellitus, chronic kidney disease, hypertension, and hepatic cirrhosis. Chest CT showed a solid tumor in the right upper lobe, and ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG PET)-CT showed a high FDG uptake in the tumor in the right upper lobe, lymph nodes of the hilum of the right lung, and right axial lymph nodes, with maximum standardized uptake values (SUVs) of 5.07, 2.71, and 1.92 respectively. Metastases in the right axial lymph nodes would have meant there was no chance of surgery.

However, the patient reported that she had received her second dose of the COVID-19 vaccine in her right arm 12 days before FDG PET-CT, with no symptoms af-

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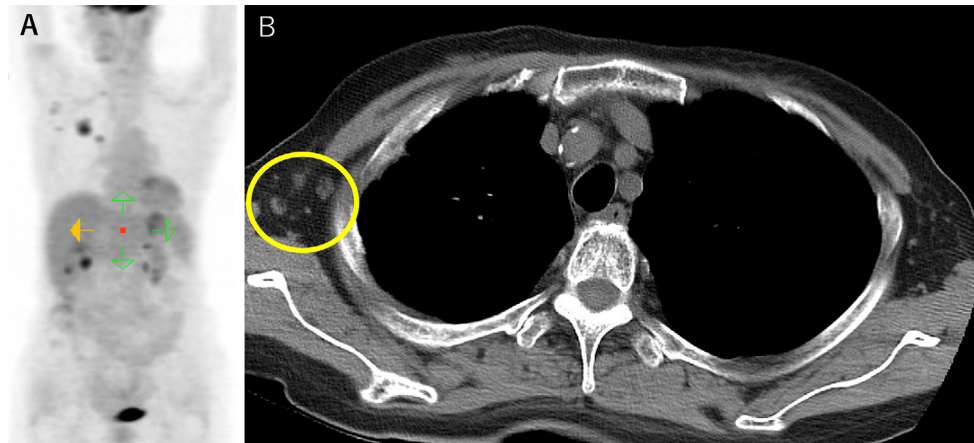


Figure 1. Images of Patient 1. (A) FDG PET-CT (maximum intensity projection image) revealed a high FDG uptake in the right upper lobe (primary tumor), right axial lymph nodes, and right hilar lymph nodes. (B) Cortical thickening of the lymph nodes in right axilla (yellow circle) was detected.

ter vaccination. The high uptake in the right axial lymph nodes was thought to possibly be a reaction due to the vaccination, but observation time was scarce because of her potentially progressive lung cancer. We therefore decided to perform a right axial lymph node biopsy. The pathology reported benign fibro fatty connective tissue. She was diagnosed with clinical T1cN1M0 stage IIB adenocarcinoma and then underwent surgery (Figure 1).

Patient 2

A man in his late 60s who had a history of left upper lobectomy for pathologically stage IIB lung adenocarcinoma three years before came to our hospital for a follow-up examination. Chest CT showed enlarged lymph nodes in his left axilla, and a blood test showed elevated levels of serum CEA (41 ng/ml). He had received his second dose of the COVID-19 vaccine in his left arm 17 days prior to CT. He had felt mild swelling in his left arm for a few days after vaccination. Upper and lower gastrointestinal endoscopy were performed, but no malignant lesions were detected. We proposed close follow-up, but he requested further examinations. Therefore, we performed a left axial lymph node biopsy. The pathological confirmation was reactive hyperplasia (Figure 2).

Patient 3

A woman in her early 70s underwent wedge partial lung resection for lung adenocarcinoma in the left upper lobe. At her one-year follow-up examination, chest CT revealed enlarged lymph nodes in her left axilla. She had

received her second dose of the COVID-19 vaccine in her left arm 14 days before the examination. She had felt only fatigue for five days after vaccination. Since she did not wish to undergo further invasive examinations, we chose close follow-up. Four months later, chest CT showed the diminution of lymph nodes in her left axilla (Figure 3).

DISCUSSION AND CONCLUSIONS

Vaccine-related lymphadenopathy is rare but has been reported with other vaccines, including those for H1N1 influenza, human papillomavirus, smallpox, Bacille Calmette-Guerin (BCG), and measles vaccines.² Therefore, we must bear in mind the possibility of lymphadenopathy after vaccination, even when the COVID-19 age has passed.

Lymphadenopathy after COVID-19 vaccination has been recognized in axillary, supraclavicular, and cervical lymph nodes on the same side as vaccination was performed, a fact that has been broadly reported.³ In lung cancer, lymphatic metastasis to the axial lymph nodes is extremely rare; indeed, Satoh et al. reported that only 0.75% of lung cancer patients had axial lymph node metastasis.⁴ We therefore don't always suspect metastasis when we detect lymphadenopathy in axial lymph nodes after vaccination. However, other examinations, such as FDG PET-CT, are often needed to confirm such findings in patients with progressive cancers.

Radiologists reported that 29-36% of patients who underwent FDG PET-CT had a positive axillary uptake 7-

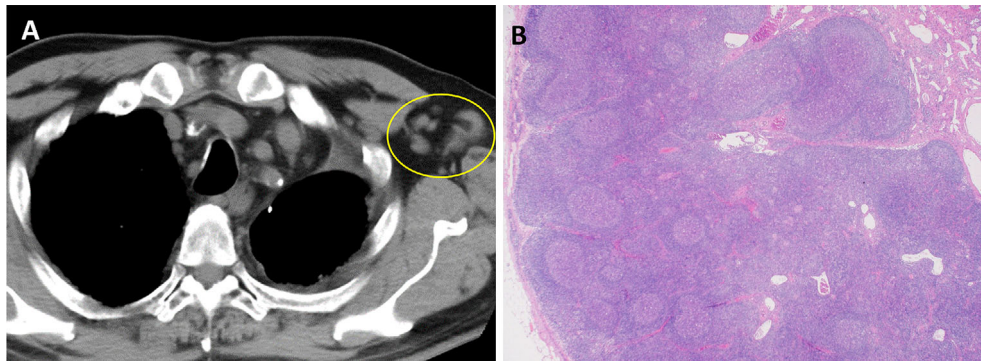


Figure 2. CT and pathological images of Patient 2. (A) Chest CT showed enlarged lymph nodes in the left axilla (yellow circle). (B) Pathological findings showed benign hyperplasia.

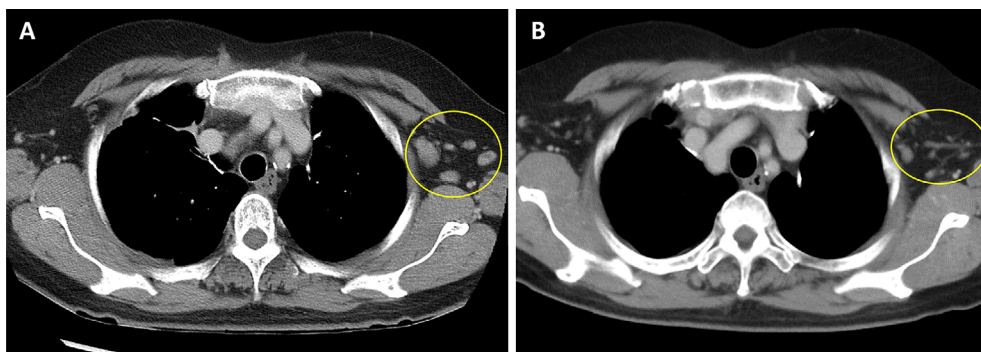


Figure 3. Images of Patient 3. (A) CT performed 14 days after the second vaccination showed enlarged lymph nodes in the left axilla (yellow circle). (B) CT performed four months after the vaccination showed that the lymph nodes had shrunk (yellow circle).

10 weeks after receiving their second COVID-19 vaccination.^{5,6} Denying the possibility of metastasis is therefore difficult, even with FDG PET-CT. The European Society of Breast Imaging recommends that close follow-up be performed when lymphadenopathy is detected after COVID-19 vaccination or else postpone imaging examinations for at least 12 weeks after the last vaccine dose.⁷ This recommendation matches well with the CT images from our third case, as it took about four months to be certain of the diminution of the lymphadenopathy. However, 12 weeks can seem like a long time in patients with progressive lung cancer, as they may lose the chance to undergo curative surgery.

In two of our cases, we performed axial lymph node biopsy to obtain definitive information. Despite the trend toward avoiding performing invasive procedures for such lymphadenopathy cases, an axial lymph node biopsy or echography-guided biopsy is a relatively easy procedure and can be performed under local anesthesia.

Furthermore, if a patient were clinically diagnosed with metastasis in the axial lymph nodes or if other metastases were found during close follow-up, the patient might lose the chance to receive proper treatments. We therefore believe that physicians should consider a quick biopsy when encountering such challenging cases and also carefully consider the indications of choosing close follow-up based on the clinical or pathological stage, CT findings, etc.

本論文内容に関連する著者の利益相反：なし

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