in vivo *36*: 1977-1981 (2022)
doi:10.21873/invivo.12921

Axillary Lymph Node Swelling After COVID-19 Booster Vaccination: Japanese Case Report and Literature Review

NOBUYASU YOSHIMOTO[1,2], AKEMI YANAGI[3], SATORU TAKAYAMA[4], MASAKI SAKAMOTO[4], KEISUKE TOMODA[4], KEN ISHIKAWA[4], AKIFUMI KAWATE[4], SHORYU TAKAYAMA[4], MASAKATSU YAMASHITA[4], SHINYA YAMAMOTO[4], KIOTO YOKOYAMA[4], HIROTO SUZUKI[4] and HISANORI KANI[4]

[1]*Department of Breast Surgery, Nagoya Tokushukai General Hospital, Kasugai, Japan;*
[2]*Clinical Research Center, Nagoya Tokushukai General Hospital, Kasugai, Japan;*
[3]*Department of Radiology, Nagoya Tokushukai General Hospital, Kasugai, Japan;*
[4]*Department of Surgery, Nagoya Tokushukai General Hospital, Kasugai, Japan*

Abstract. *Background/Aim: COVID-19 has been a global pandemic for more than 2 years, and vaccination against COVID-19 using an mRNA vaccine is widespread. The COVID-19 vaccination can cause specific side-effects, such as axillary lymph node swelling; therefore, breast oncologists should pay attention to such occurrences. Initially, only two COVID-19 vaccinations were planned; however, in some countries third or fourth vaccines have been administered. Here, we present a female case who developed axillary lymph node swelling after her third vaccination. We have also reviewed the literature regarding this side-effect after a third or fourth COVID-19 vaccination. Case Report: A 64-year-old woman who came to our clinic regarding a mammography abnormality in her left breast. She had no palpable mass, but a left breast mass was shown by mammography, and ultrasonography and magnetic resonance imaging indicated a hamartoma. At 2 months after her second COVID-19 vaccination when she underwent these tests, she had no axillary lymph node swelling. We planned a follow-up after 6 months. At her next visit, by chance, she underwent ultrasonography 14 days after she received a third COVID-19 vaccination, and a swollen axillary lymph node was observed. Conclusion: Axillary lymph node swelling can occur after a third COVID-19 vaccination. Therefore, breast oncologists will have to consider this side-effect of COVID-19 vaccination when diagnosing breast tumors.*

Correspondence to: Nobuyasu Yoshimoto, MD, Ph.D., Department of Breast Surgery, Nagoya Tokushukai General Hospital, 2-52, Kozojicho-Kita, Kasugai-Shi, Aichi, 487-0016, Japan. Tel: +81 568518711, Fax: +81 568517115, e-mail: paris@s4.dion.ne.jp

Key Words: COVID-19 booster vaccine, axillary lymph node swelling, side-effect.

Pneumonia caused by the novel coronavirus, called Coronavirus Disease 2019 (COVID-19), was first reported in Wuhan, China in December 2019 (1). Two years later and the pandemic has become global. During this pandemic, COVID-19 vaccines, such as the BNT162b2 vaccine (Pfizer) (2) and mRNA-1273 vaccine (Moderna) (3), have been developed rapidly, and in many countries, including Japan, vaccination with these vaccines has been performed. BNT162b2 and mRNA-1273 are mRNA vaccines and this is the first time this type of vaccine has been used in a clinical setting.

When these vaccinations were started, clinical trials of BNT162b2 and mRNA-1273 (2, 3) were designed to administer two doses. However, this pandemic has continued for 2 years, and therefore booster vaccinations have been required to prevent COVID-19 infection because antibody levels to the virus decrease within several months. In Japan, the third vaccination started in December 2021 (4). Currently, a third vaccination is indicated for those who received a second vaccination more than 6 months previously, and further vaccination might be needed. Indeed, Japan is planning to administer a fourth COVID-19 vaccination (5).

These vaccines have characteristic side-effects including fever, general fatigue, injection-site pain, and swelling (2). In addition, local lymph node swelling can also occur after these vaccinations (3). In cases of axillary lymph node swelling, breast oncologists should consider whether these swellings are metastases of breast cancer or a side-effect of the vaccine. Here, we present a case with axillary lymph node swelling, observed by ultrasonography (US), which was thought to be related to a third COVID-19 vaccination. We

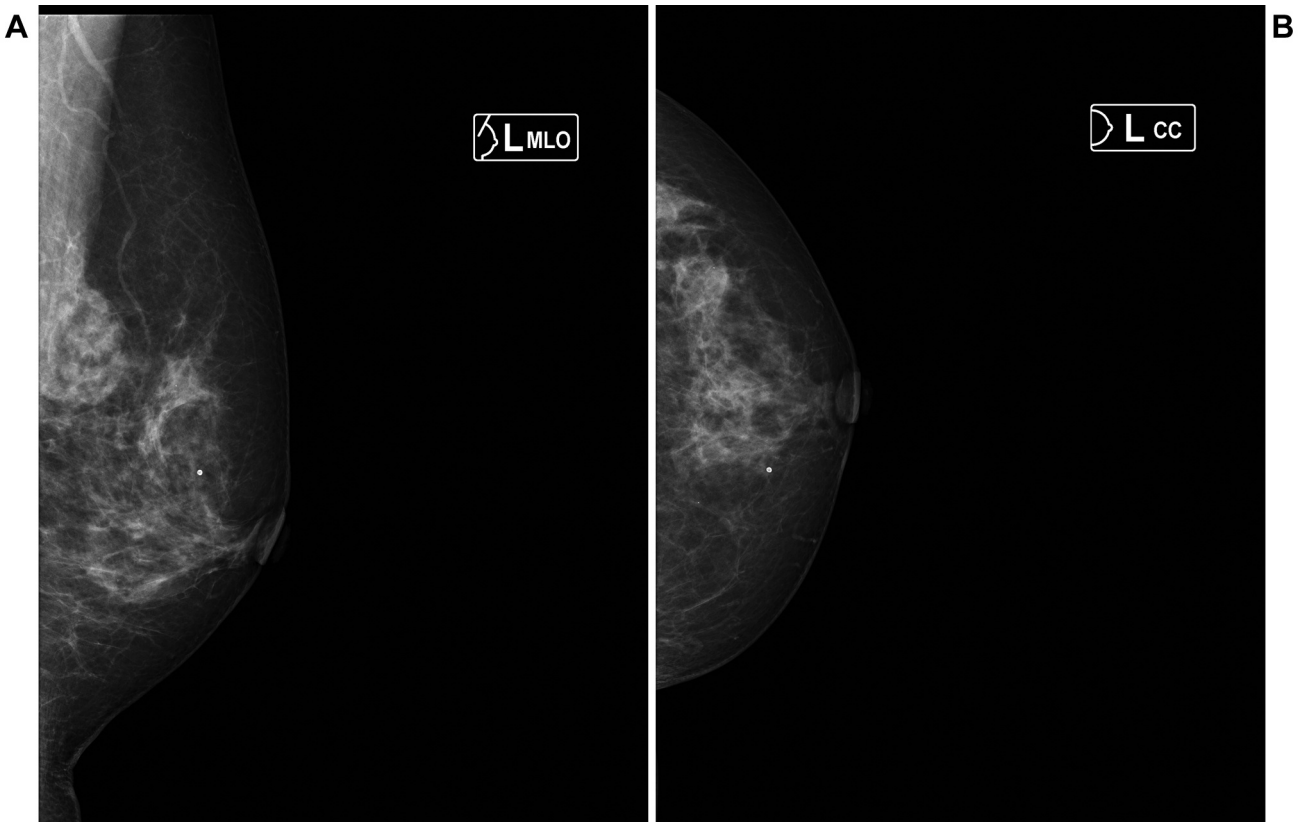

Figure 1. *Mammography in July 2021, showing a round, circumscribed mass in the upper left breast in mediolateral oblique (MLO) (A) and ipsilateral craniocaudal (CC) (B) views.*

also present a literature review of studies of cases receiving a third or fourth COVID-19 vaccination.

Case Report

A 64-year-old woman came to our breast surgery clinic after a screening mammography abnormality in July 2021. She had undergone resection of an ascending colon carcinoma 6 years previously, partial liver resection due to metastatic colon cancer 3 years previously, and partial resection of the right lung assisted with a thoracoscope due to metastatic colon cancer 2 years previously. There was no palpable abnormality in either breast or axilla. A mass, which seemed to be a hamartoma, was present in her left upper area on mammography (Figure 1); a mass was present in the left superolateral quadrant, which also seemed to be a hamartoma on US (Figure 2). We also performed magnetic resonance imaging (Figure 3), which was also compatible with a hamartoma. Both US and magnetic resonance imaging indicated no swollen axillary lymph nodes. These imaging studies had been performed 2 months after the second COVID-19 vaccination with Pfizer BNT162b2 in her left arm. We decided to continue follow-up without aspiration biopsy cytology. At the 6-month follow up, no palpable abnormality was observed, and almost the same left breast mass as before was present. In addition, an axillary lymph node with a thickened cortex was observed on US (Figure 4). This was 14 days after her third COVID-19 vaccination in her left arm. It was thought that the swelling was related to the third COVID-19 vaccination. We decided to follow-up 3 months later. In May 2022, she came to our clinic and underwent US again; and she had no swelling of the axillary lymph node was found.

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. This was a case report and therefore we did not require additional permission from our review board.

Discussion

When BNT162b2 and mRNA-1273 were developed, they were designed for two vaccinations. Davit *et al*. reported the need for an additional vaccination for immunocompromised individuals and seniors in Israel (6). Werbel *et al*. reported the efficacy of increased antibody levels by the third

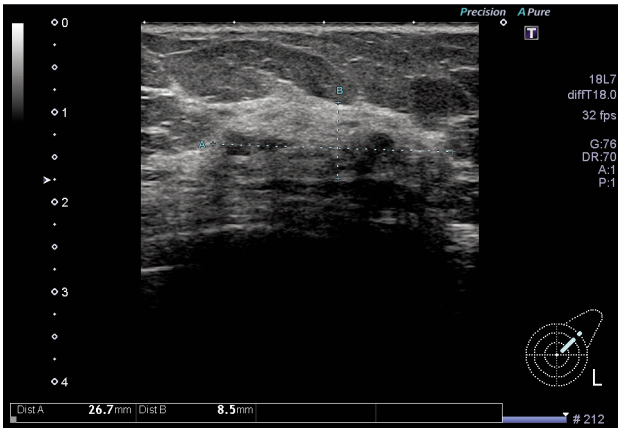

Figure 2. *Ultrasonography in August 2021, 2 months, and 2 weeks after the second COVID-19 vaccination. A mass in the left superolateral quadrant (suspected hamartoma) is shown and there were no swollen lymph nodes in the axilla.*

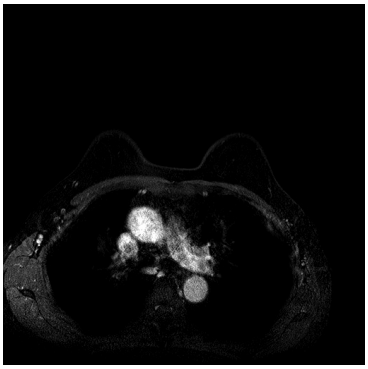

Figure 3. *Magnetic resonance imaging in August 2021, 2 months, and 3 weeks after a second COVID-19 vaccination. There were no swollen lymph nodes in the axilla.*

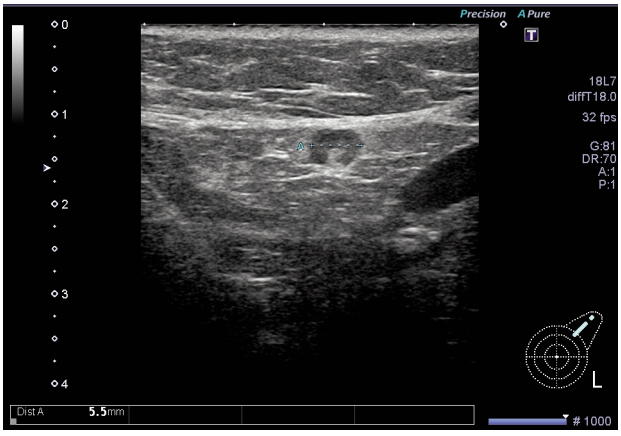

Figure 4. *Ultrasonography in February 2022, 14 days after the third COVID-19 vaccination. A lymph node with a thick cortex in the patient's left axilla is shown.*

vaccination in solid-organ transplant recipients (7). Albach *et al*. reported a case with higher antibody levels achieved by a third vaccination with immunosuppressive medication for rheumatoid arthritis (8). Therefore, it was reported that insufficient efficacy was achieved after two doses of the vaccines for particular immunological cases, such as those with specific immunological conditions.

Because the COVID-19 pandemic remains globally, a third vaccination for the general public was discussed. Flaxman *et al*. reported that in 18- to 55-year-olds, antibody levels increased after a third vaccination (9). Bar-On *et al*. reported the efficacy of a third vaccination to protect people aged ≥60 years against COVID-19 (10). Spitzer *et al*. reported the efficacy of a third vaccination in people aged ≥18 years (11). A third vaccination has become popular, and similar to other countries, a third vaccination was offered in December 2021 in Japan.

There are some reports about two dose COVID-19 vaccine-induced axillary lymph node swelling (12-14). Raj *et al*. reported this side-effect on screening mammography (15), and Romeo *et al*. reported it in a prospective study (16). However, there have been few reports about the side-effects of a third COVID-19 vaccination. Dicks *et al*. reported a rare case of leukocytoclastic vasculitis after a third BNT162b2 COVID-19 vaccination (17). Aviram *et al*. reported four cases of myocarditis after a third dose of the BNT162b2 COVID-19 vaccine (18). David *et al*. reported side-effects caused by a third BNT162b2 vaccination in a relatively large cohort, and these included fatigue, myalgia, fever, and lymphadenopathy, similar to that reported after the second vaccination (6). In our case, axillary lymph node swelling was observed 14 days after the third COVID-19 vaccination. Therefore, axillary lymph node swelling might be induced after the first, second, or third COVID-19 vaccination. In our case, although there seemed to be no axillary lymph node swelling after the second vaccination (imaging was conducted 2 months after the second vaccination), swelling was observed after the third. We previously reported axillary lymph node swelling as a side-effect of the first or second COVID-19 vaccination (19); therefore, this side-effect observed after the third vaccination can be considered similar to that after the first or second COVID-19 vaccinations.

Axillary lymph node swelling as a side-effect of COVID-19 vaccination can influence breast cancer screening. The Japan Association of Breast Cancer Screening presented guidelines on the effects of COVID-19 on breast cancer screening (20). It suggested that breast cancer screening

should be conducted before vaccination or 6-10 weeks after the second COVID-19 vaccination in case reactive axillary lymph node swelling occurs.

A major limitation of this report was that only one case was presented, and some of the image analyses were conducted 2 months after the second vaccination. Axillary lymph node swelling due to COVID-19 vaccination might occur after the first or second vaccination, or after the third vaccination. Therefore, further case studies are needed.

Conclusion

Axillary lymph node status is very important in breast oncology. It was thought that after two doses of COVID-19 vaccination were administered, axillary lymph node swelling would have reduced some months after the second vaccination. However, under the present situation, third and possibly fourth vaccinations might be required. Therefore, breast oncologists should continue to be aware of axillary lymph node swelling related to COVID-19 vaccinations when diagnosing a breast tumor. Further research on the side-effects of COVID-19 vaccinations, especially axillary lymph node swelling, is required.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Author's Contributions

Research design: N. Yoshimoto; collection and analysis of data: N. Yoshimoto and A Yanagi; all Authors contributed to reviewing the article. All Authors approved the final article.

Acknowledgements

The Authors express their appreciation to Ms. Haruna Hashio for her preparation of the reference papers.

References

1 Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W and China Novel Coronavirus Investigating and Research Team: A novel Coronavirus from patients with pneumonia in China, 2019. N Engl J Med *382(8)*: 727-733, 2020. PMID: 31978945. DOI: 10.1056/NEJMoa2001017

2 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 and C4591001 Clinical Trial Group: Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med *383(27)*: 2603-2615, 2020. PMID: 33301246. DOI: 10.1056/NEJMoa2034577

3 Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T and COVE Study Group: Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med *384(5)*: 403-416, 2021. PMID: 33378609. DOI: 10.1056/NEJMoa2035389

4 Notice about booster vaccination (third vaccination). Ministry of Health, Labour and Welfare. Available at https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/vaccine_booster.html [Last accessed on May 20, 2022]

5 Ministry of Health, Labour and Welfare. Available at https://www.mhlw.go.jp/content/000936229.pdf [Last accessed on May 20, 2022]

6 Shapiro Ben David S, Shamir-Stein N, Baruch Gez S, Lerner U, Rahamim-Cohen D and Ekka Zohar A: Reactogenicity of a third BNT162b2 mRNA COVID-19 vaccine among immunocompromised individuals and seniors - A nationwide survey. Clin Immunol *232*: 108860, 2021. PMID: 34571262. DOI: 10.1016/j.clim.2021.108860

7 Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM and Segev DL: Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. Ann Intern Med *174(9)*: 1330-1332, 2021. PMID: 34125572. DOI: 10.7326/L21-0282

8 Albach FN, Burmester GR and Biesen R: Successful BNT162b2 booster vaccinations in a patient with rheumatoid arthritis and initially negative antibody response. Ann Rheum Dis *80(10)*: 1361-1362, 2021. PMID: 34167947. DOI: 10.1136/annrheumdis-2021-220834

9 Flaxman A, Marchevsky NG, Jenkin D, Aboagye J, Aley PK, Angus B, Belij-Rammerstorfer S, Bibi S, Bittaye M, Cappuccini F, Cicconi P, Clutterbuck EA, Davies S, Dejnirattisai W, Dold C, Ewer KJ, Folegatti PM, Fowler J, Hill AVS, Kerridge S, Minassian AM, Mongkolsapaya J, Mujadidi YF, Plested E, Ramasamy MN, Robinson H, Sanders H, Sheehan E, Smith H, Snape MD, Song R, Woods D, Screaton G, Gilbert SC, Voysey M, Pollard AJ, Lambe T and Oxford COVID Vaccine Trial group: Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). Lancet *398(10304)*: 981-990, 2021. PMID: 34480858. DOI: 10.1016/S0140-6736(21)01699-8

10 Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, Mizrahi B, Alroy-Preis S, Ash N, Milo R and Huppert A: Protection of BNT162b2 vaccine booster against Covid-19 in Israel. N Engl J Med *385(15)*: 1393-1400, 2021. PMID: 34525275. DOI: 10.1056/NEJMoa2114255

11 Spitzer A, Angel Y, Marudi O, Zeltser D, Saiag E, Goldshmidt H, Goldiner I, Stark M, Halutz O, Gamzu R, Slobodkin M, Amrami N, Feigin E, Elbaz M, Furman M, Bronstein Y, Chikly A, Eshkol A, Furer V, Mayer T, Meijer S, Melloul A, Mizrahi M, Yakubovsky M, Rosenberg D, Safir A, Spitzer L, Taleb E, Elkayam O, Silberman A, Eviatar T, Elalouf O, Levinson T, Pozyuchenko K, Itzhaki-Alfia A, Sprecher E, Ben-Ami R and Henig O: Association of a third dose of BNT162b2 vaccine with incidence of SARS-CoV-2 infection among health care workers in Israel. JAMA *327(4)*: 341-349, 2022. PMID: 35006256. DOI: 10.1001/jama.2021.23641

12 Co M, Wong PCP and Kwong A: COVID-19 vaccine associated axillary lymphadenopathy – A systematic review. Cancer Treat Res Commun *31*: 100546, 2022. PMID: 35334408. DOI: 10.1016/j.ctarc.2022.100546

13 Özütemiz C, Krystosek LA, Church AL, Chauhan A, Ellermann JM, Domingo-Musibay E and Steinberger D: Lymphadenopathy in COVID-19 vaccine recipients: Diagnostic dilemma in oncologic patients. Radiology *300(1)*: E296-E300, 2021. PMID: 33625300. DOI: 10.1148/radiol.2021210275

14 Faermann R, Nissan N, Halshtok-Neiman O, Shalmon A, Gotlieb M, Yagil Y, Samoocha D, Friedman E and Sklair-Levy M: COVID-19 vaccination induced lymphadenopathy in a specialized breast imaging clinic in Israel: Analysis of 163 cases. Acad Radiol *28(9)*: 1191-1197, 2021. PMID: 34257025. DOI: 10.1016/j.acra.2021.06.003

15 Raj S, Ogola G and Han J: COVID-19 vaccine-associated subclinical axillary lymphadenopathy on screening mammogram. Acad Radiol *29(4)*: 501-507, 2022. PMID: 34906409. DOI: 10.1016/j.acra.2021.11.010

16 Romeo V, Stanzione A, D'Auria D, Fulgione L, Giusto F, Maurea S and Brunetti A: COVID-19 vaccine-induced lymphadenopathies: incidence, course and imaging features from an ultrasound prospective study. J Ultrasound: 1-7, 2022. PMID: 35507248. DOI: 10.1007/s40477-022-00674-3

17 Dicks AB and Gray BH: Images in Vascular Medicine: Leukocytoclastic vasculitis after COVID-19 vaccine booster. Vasc Med *27(1)*: 100-101, 2022. PMID: 34720009. DOI: 10.1177/1358863X211055507

18 Aviram G, Viskin D, Topilsky Y, Sadon S, Shalmon T, Taieb P, Ghantous E, Flint N, Banai S and Havakuk O: Myocarditis associated with COVID-19 booster vaccination. Circ Cardiovasc Imaging *15(2)*: e013771, 2022. PMID: 35100809. DOI: 10.1161/CIRCIMAGING.121.013771

19 Yoshimoto N, Takura K, Yanagi A, Takayama S, Sakamoto M, Ishikawa K, Katada T, Kawate A, Takayama S, Yamashita M, Yamamoto S, Yokoyama K and Kani H: Axillary lymph node swelling mimicking breast cancer metastasis after COVID-19 vaccination: A Japanese case report and literature review. In Vivo *36(2)*: 1041-1046, 2022. DOI: 10.21873/invivo.12800

20 Japan Association of Breast Cancer Screening. Available at http://www.jabcs.jp/images/covid-guide202107.pdf [Last accessed on March 31, 2022]

Received April 19, 2022
Revised May 21, 2022
Accepted May 24, 2022