DETECTION OF AXILLARY LYMPHADENOPATHY AFTER COVID-19 VACCINATION DURING BREAST EXAMINATION: CASE SERIES AND REVIEW OF THE LITERATURE AFTER ONE YEAR

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SUMMARY

Objectives: The aim of this study is to evaluate accidental findings of axillary lymphadenopathy during breast examination. Postvaccination axillary lymphadenopathy is a possible cause of adenopathies but these findings used to be exceedingly rare. Nowadays, after Covid-19 vaccination it is found more often. Covid-19 vaccination started at the end of December 2020 with two types of vaccine, Moderna and Pfizer-BioNTech in the Czech Republic. The aim of this article is to present a single centre experience with Covid-19 lymphadenopathy during the general vaccination in the Czech population and summarization of recommendations.

Methods: In January to February 2021 ultrasound revealed axillary lymphadenopathy in several patients during breast examination in our certified centre. In four of them it was concluded as lymphadenopathy after Covid-19 vaccination. A search (using databases PubMed and Google Scholar) of the available literature for the years 2020 and 2021 was performed.

Results: These four patients were examined during the first two months of 2021. In all of them pathological lymph nodes with typical sonographic signs were seen in the ipsilateral axilla. We searched the literature for follow-up recommendations and summarized them in our article.

Conclusion: Accidental findings of axillary lymphadenopathy during ultrasound breast examination will be more often. There will be more cases of lymphadenopathy with an increasing number of people being vaccinated against Covid-19.

Key words: Covid-19, vaccination, axilla, lymphadenopathy, lymph node, ultrasonography

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INTRODUCTION

In the course of ultrasound breast examination, it is necessary to perform routine investigation of the axillary lymph nodes. Breast cancer staging is also based on ultrasound evaluation of the axillary lymph nodes (1, 2). In the Czech Republic, the breast ultrasound is performed for instance as complementary examination after screening mammography as main examination in women with palpable mass in the age under 40 or as a preventive examination in women who are self-payers, mostly younger than 40 years. Cases of accindental axillary lymphadenopathy are rare during these breast examinations, the rate is 0.02–0.04% (3–6). Ipsilateral adenopathy is one of the possible side effects after recent vaccination and occurs two or four days after it (7). Nowadays, during Covid-19 vaccination with an US FDA-approved Covid-19 vaccine, new findings in the ipsilateral axilla are being found more often. In the Czech Republic, Covid-19 vaccination started at the end of December 2020 with two types of vaccine, Moderna and Pfizer-BioNTech. In this article the first four cases of accidental findings of axillary lymphadenopathy during breast examination are presented. With an increasing number of people being vaccinated against Covid-19, there will be more cases of axillary lymphadenopathy, both symptomatic and subclinical as random findings. The new role of radiologists constists of the exclusion of breast malignancy and thinking about recent vaccination.

MATERIALS AND METHODS

The evaluation of four cases was performed, correlations between ultrasonographic images of the nodes and clinical symptoms were evaluated. A search (using databases PubMed and Google Scholar) of the available literature for the years 2020 and 2021 was performed. Keywords for searching were lymph nodes, ultrasonography, vaccination, Covid-19, and axilla.

Case Reports

During the first two months of 2021 four women who underwent examination of their breasts with ultrasound were diagnosed with axillary lymphadenopathy.

Case Report 1

The first patient aged 34 years was examined within a preventive ultrasound investigation. She was without any symptoms of breast disease and without any palpable mass. There was no history of breast cancer. Axillary lymphadenopathy was an accidental finding. Mamary gland was without leasions and it was negative according to the breast imaging-reporting and data system (BI-RADS) classification. In her left axilla two hypoechoic lymph nodes were found. In one of them the hyperechoic hilar structure was absent (Fig. 1). Perinodal oedema was also presented. Patients confirmed recent vaccination against Covid-19 to the left arm. Ultrasound examination of the left axilla after 2–3 months after the second dose was recomended. After two months the appearance of these axillary lymph nodes was normal. Their cortices were physiological, hyperechoic hilar structures were found and perinodal oedema dissapeared.

Case Report 2

The second patient was 36 years old and she also had preventive ultrasound investigation. She was without symptoms of breast disease and without pain or palpable mass. There was no history of breast cancer. In her left axilla one lymph node with cortical thickening was found (Fig. 2), and also one lymph node with L/T ratio about 1 was seen (Fig. 3). During this examination there were no masses in patients breasts. The patient confirmed our suspicion about recent vaccination against Covid-19. Ultrasound examination of the left axilla after 2 months after the second dose was recomended. After these two months lymph nodes in the left axilla became physiological. The width of the cortex was to 3 mm, symmetrically to the lymph nodes in contralateral axilla. No lymph node with L/T ratio about 1 was seen.

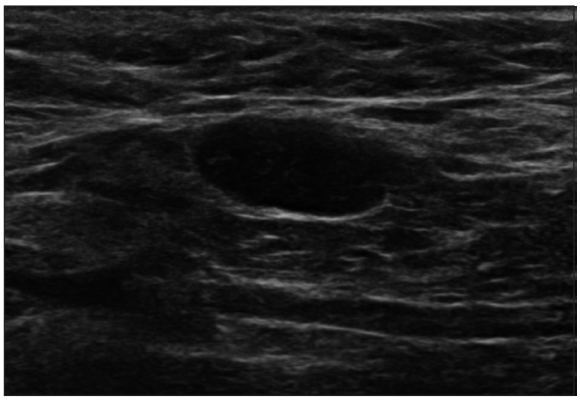

Fig. 1. *Ultrasound of the axillary lymph node with absence of hyperechoic hilum.*

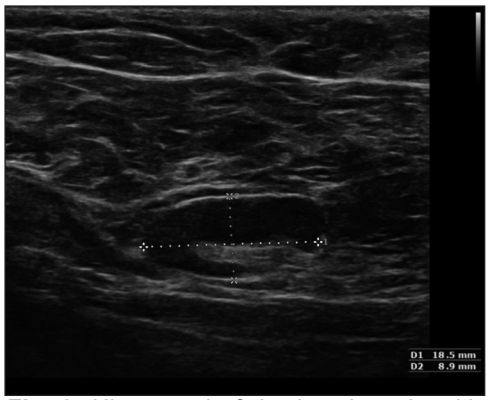

Fig. 2. *Ultrasound of the lymph node with diffuse cortical thickening.*

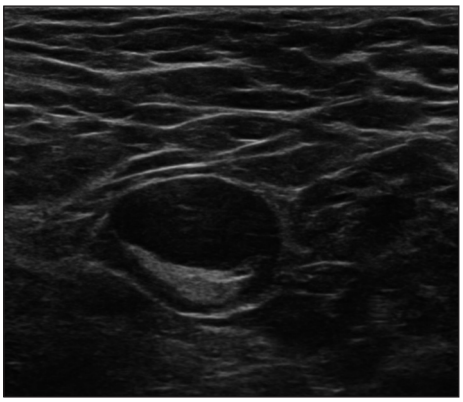

Fig. 3. *Ultrasound of the lymph node with abnormal L/T ratio.*

Case Report 3

The third patient was 75 years old and she was symptomatic. There was no history of breast cancer, but she had a palpable mass in her left armpit and felt pain in the lateral parts of the left breast. Her screening mammography before 6 months was negative. She underwent the examination six days after the first dose of vaccine against Covid-19. Lymph nodes in the left armpit had cortical thickening, one with focal cortical nodule (Fig. 4). There were inhomogeneities in the cortex of axillary lymph nodes (Fig. 5). The information about recent vaccine against Covid-19 was known after targeted query. She underwent complementary ultrasound examination of the left armit in three months after the second dose of vaccine. Pathological changes in the lymph nodes of the left armpit dissapeared, as well as palpable mass and pain. She was returned to the screening programme.

Case Report 4

The fourth patient was woman aged 28 years with control ultrasound after 6 months as a high-risk patient with the risk of breast cancer of 37%. She was asymptomatic. There was no history of

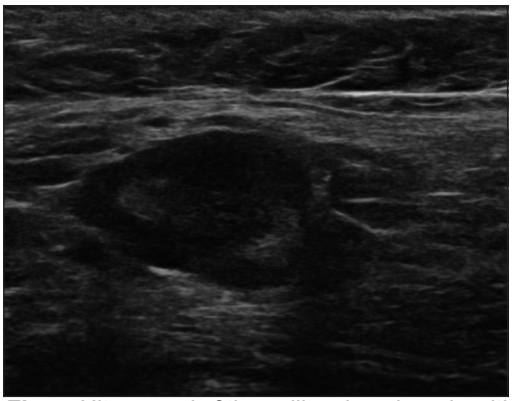

Fig. 4. *Ultrasound of the axillary lymph node with focal cortical extending.*

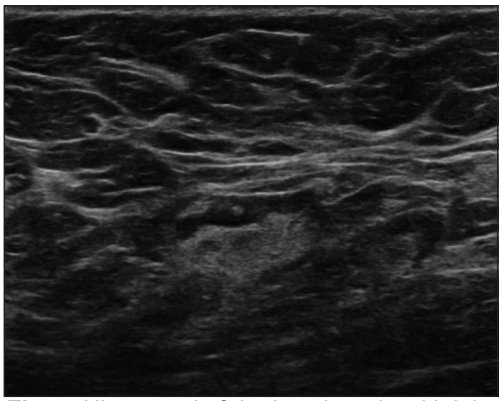

Fig. 5. *Ultrasound of the lymph node with inhomogeneities in the cortex.*

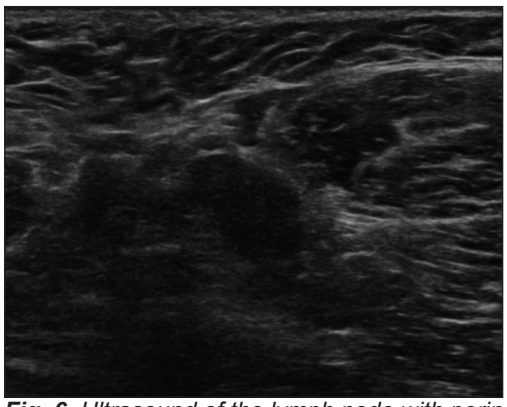

Fig. 6. *Ultrasound of the lymph node with perinodal oedema.*

breast cancer in her personal history. But there was a family history of breast cancer. There was one hypoechoic lymph node in the left armit. This lymph node was without a fatty hilum, it was hypervascularized and perinodal oedema was presented (Fig. 6). It was suspicious for metastatic involvement, but there was no lesion in the left breast, and she confirmed the information about recent vaccination against Covid-19. The patient underwent follow-up ultrasound in the short period of time because of high risk. The ultrasound of the left axilla was performed after one month and during this examination no suspicious lymph node was found.

DISCUSSION

Accidental axillary lymphadenopathies are rare during breast examinations, the rate is 0.02–0.04% (3–6). Ipsilateral lymphadenopathy is one of the usual side effects after a recent vaccination, especially after a vaccine with a strong immune response such as the Covid-19 vaccine (7–22). Nowadays, during Covid-19 vaccination with the FDA-approved vaccines, new findings in the ipsilateral axilla are occurring more often. According to the manufacturers of Moderna and Pfizer-BioNTech, these adenopathies can occur in 11% of cases after the first dose of Covid-19 vaccine and in 16% after the second dose (7, 8). During the last two years there are many articles in the literature describing this phenomenon and updating clinical guidelines (7–22, 26–31).

With the ever-increasing number of people being vaccinated against Covid-19, there will be more cases of accidental ipsilateral unilateral axillary lymphadenopathy during breast examination and also during screening mammography.

The physiological axillary lymph node is oval in shape (23–25), with a hyperechoic hilum (23–25), thin cortex to 2 mm (24), central type of vascularization, longitudinal to the transversal axis ratio about 2, without a perinodal oedema, and with no cortical focal thickening or cortical inhomogeneities (1, 24).

Postvaccination lymphadenopathy may occur in the ipsilateral axilla, and it is unilateral. Lymph nodes in the axilla after vaccination could be hypoechoic, with cortical thickening, diffuse or focal (Fig. 2–5), with or without a hyperechoic hilum, they could be oval or round in shape. Perinodal oedema may or may not be present. All of these changes in the lymph nodes could mimic metastatic lymph nodes in breast cancer disease (10, 26).

In our four cases, pathological, hypoechoic lymph nodes were found in all patients, some of them without a hyperechoic fatty hilum, some of them with the present central hyperechoic structures. Sonographic sign such as an expanded cortex was presented, with diffuse thickening more than 5 mm or focal thickening more than 10 mm. In two patients there were multiple pathological lymph nodes in the ipsilateral axilla. In one case the lymph nodes were round and with perinodal oedema. These lymph nodes were mimicking metastatic lymph nodes. Examinations of ipsilateral breast in these patients were negative. All patients had no history of breast cancer, there was no suspicious finding in the ipsilateral breast, and there was certainty of recent Covid-19 vaccination. For these reasons it was possible to avoid biopsy. All of them were recommended to follow-up ultrasound examination within 1–3 months.

Currently, during and after Covid-19 vaccination, it is necessary to consider this cause of axillary lymphadenopathy (7–22). From January 2021 to January 2022, many cases of axillary lymphadenopathy after Covid-19 vaccination were described during ultrasound breast examination or during CT or PET/CT examination. Hence the need to make recommendations for routine clinical practice.

The study about differences among various types of Covid-19 vaccines was published and no significant differences among the three anti-Covid-19 vaccines (Pfizer-BioNTech, Moderna and AstraZeneca) were observed. All types of vaccines may present lymphadenopathy with "worrisome" features regarding size, shape, morphology, cortex-hilum, superb microvascular imaging, and elastography (27). Lymphadenopathy in the ipsilateral supraclavicular region is also mentioned in the literature (28). The massive cervical lymphadenopathy post Covid-19 vaccination was also described (29).

A very rare cause of lymphadenopathy after vaccination is Kikuchi-Fujimoto disease also known as necrotizing histiocytic lymphadenitis; it was also published after anti-Covid-19 vaccine in one case (30).

According to the multidisciplinary recommendations, some routine imaging examinations, such as those for screening, should be performed before or at least 6 weeks after the final vaccination dose. However, there should be no delay of other clinically indicated imaging, for instance in the case of acute symptoms, short-interval treatment monitoring, urgent treatment planning, or complications. The vaccine should be administered on the side contralateral to the primary or suspected cancer (17).

The recommendations of the Society of Breast Imaging (SBI) are to exclude malignity, especially breast cancer, and consider other reasons for axillary lymphadenopathy. It is recommended to perform a follow-up examination of the axilla four to twelve weeks after the second dose of vaccination. It is appropriate to ask patients before screening mammography or before breast ultrasound whether they have had a recent Covid-19 vaccination. According to the SBI recommendations it is advisable to order screening examinations before vaccination or four to six weeks after the second dose (7, 8). It is recommended to use BI-RADS 3 category, if the information about recent vaccine is known (8). Some studies recommend BI-RADS 2 category. If there is no history of vaccination, it is necessary to use BI-RADS 0 category and further evaluation (22).

The recommendations of the European Society of Breast Imaging (EUSOBI) propose ten points in routine clinical practice. The first point is performing of vaccination in the contralateral arm or in the thigh if the patient has a history of breast cancer. The second point is to collect data about recent vaccination. The third point is to perform breast imaging before vaccination or at least 12 weeks after the last vaccine dose. The fourth point is to apply standard imaging protocols in patients with newly diagnosed breast cancer, regardless of vaccination status. The fifth point is to examine both breasts and contralateral axilla in patients with symptomatic or imaging-detected axillary lymphadenopathy to exclude malignancy. The sixth point is to perform standard work-up if the axillary lymphadenopathy is contralateral to the side of vaccination. The seventh point is to consider lymphadenopathy as benign or probably benign in patients without history of breast cancer, if it is ipsilateral to the side of vaccination and if it persists 12 weeks after vaccination, depending on clinical context. The eighth point is to perform standard work-up in patients without breast cancer history and with post-vaccination lymphadenopathy coupled with suspicious breast finding, including biopsy if appropriate. The ninth point is to consider the timeframe from vaccination and overall nodal metastatic risk of primary breast cancer in the patients with breast cancer history. The tenth point means to discuss complex or unclear cases by the multidisciplinary team (31).

It is important to be more careful in the cases of patients with a history of breast cancer in the ipsilateral breast and it is also necessary to think about possible occult cancer. Taking samples by core biopsy should be considered if this suspicious appearance of the lymph nodes persists.

CONCLUSIONS

With the ongoing Covid-19 vaccination, radiologists will encounter unilateral axillary lymphadenopathy more often. If the axillary lymphadenopathy is ipsilateral, it is necessary to exclude breast malignancy and to recommend the follow-up examinations of these lymph nodes, on the other hand to avoid false positivity of malignancy and unnecessary core biopsy. Radiologists should ask about a recent vaccination before screening mammography, as well as before the ultrasound examination of the axilla. In the case of accidental finding of unilateral axillary lymphadenopathy by another imaging method, the possibility of benign post-vaccination reaction should be considered. This reaction should regress within four to twelve months after the last dose of vaccination.

Conflicts of Interest
None declared

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REFERENCES

1. Dialani V, James DF, Slanetz PJ. A practical approach to imaging the axilla. Insights Imaging. 2015;6(2):217-29.
2. Da Costa Pinheiro DJP, Elias S, Pinto Nazario AC. Axillary lymph nodes in breast cancer patients: sonographic evaluation. Radiol Brasil. 2014;47(4):240-44.
3. Murray ME, Given-Wilson RM. The clinical importance of axillary lymphadenopathy detected on screening mammography. Clin Radiol. 1997;52(6):458-61.
4. Patel T, Given-Wilson RM, Thomas V. The clinical importance of axillary lymphadenopathy detected on screening mammography: revisited. Clin Radiol. 2005;60(1):64-71.
5. Lim ET, O'Doherty A, Hill AD, Quinn CM. Pathological axillary lymph nodes detected at mammographic screening. Clin Radiol. 2004;59(1):86-91.
6. Chetlen A, Nicholson B, Patrie JT, Harvey JA. Is screening detected bilateral axillary adenopathy on mammography clinically significant? Breast J. 2012;18(6):582-7.
7. Grimm L, Destounis S, Dogan B, Nicholson B, Dontchos B, Sonnenblick E, et al. SBI recommendations for the management of axillary adenopathy in patients with recent COVID-19 vaccination. Society of Breast Imaging; 2021.
8. Palmer WJ. SBI publishes management guidance for COVID-19 vaccine-related adenopathies [Internet]. Diagnostic Imaging; 2021 [cited 2023 Jun 11]. Available from: https://www.diagnosticimaging.com/view/sbi-publishes-management-guidance-for-covid-19-vaccine-related-adenopathies.
9. Mehta N, Sales RM, Babagbemi K, Levy AD, McGrath AL, Drotman M, et al. Unilateral axillary adenopathy in the setting of COVID-19 vaccine. Clin Imaging. 2021;75:12-5.
10. Palmer WJ. COVID-19 vaccine-linked adenopathies could mimic breast cancer malignancies [Internet]. Diagnostic Imaging; 2021 [cited 2023 Jun 11]. Available from: https://www.diagnosticimaging.com/view/covid-19-vaccine-linked-adenopathies-could-mimic-breast-malignancies.
11. Washington T, Bryan R, Clemow C. Adenopathy following COVID-19 vaccination. Radiology. 2021 Jun;299(3):E280-1.
12. 2. 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 Aug 1;7(8):1241-2.
13. Ahn RW, Mootz AR, Brewington CC, Abbara S. Axillary lymphadenopathy after mRNA COVID-19 vaccination. Radiol Cardiothorac Imaging. 2021 Feb 3;3(1):e210008. doi: 10.1148/ryct.2021210008.
14. Nawwar AA, Searle J, Hagan I, Lyburn ID. COVID-19 vaccination induced axillary nodal uptake on [18F]FDG PET/CT. Eur J Nucl Med Mol Imaging. 2021 Jul;48(8):2655-6.
15. Hanneman K, Iwanochko RM, Thavendiranathan P. Evolution of lymphadenopathy at PET/MRI after COVID-19 vaccination. Radiology. 2021 Jun;299(3):E282. doi: 10.1148/radiol.2021210386.
16. Keshavarz P, Yazdanpanah F, Rafiee F, Mizandari M. Lymphadenopathy following COVID-19 vaccination: imaging findings review. Acad Radiol. 2021 Aug;28(8):1058-71.
17. Becker AS, Perez-Johnston R, Chikarmane SA, Chen MM, El Homsi M, Feigin KN, et al. Multidicsiplinary recommendations regarding post-vaccine adenopathy and radiologic imaging: radiology scientific expert panel. Radiology. 2021; 300(2):E323-7.
18. Mehta N, Sales RM, Babagbemi K, Levy AD, McGrath AL, Drotman M, et al. Unilateral axillary adenopathy in the setting of COVID-19 vaccine. Clin Imaging. 2021 Jul;75:12-15.
19. Cellina M, Irmici G, Carrafiello G. Unilateral axillary lymphadenopathy after coronavirus disease (COVID-19) vaccination. AJR Am J Roentgenol. 2021 May;216(5):W27. doi: 10.2214/AJR.21.25683.
20. Dominguez JL, Eberhardt SC, Revels JW. Unilateral axillary lymphadenopathy following COVID-19 vaccination: a case report and imaging findings. Radiol Case Rep. 2021;16(7):1660-4.

21. 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(6)843-52.
22. Lim J, Lee SA, Khil EK, Byeon SJ, Kang HJ, Choi JA. COVID-19 vaccine-related axillary lymphadenopathy in breast cancer patients: case series with a review of literature. Semin Oncol. 2021;48(4-6):283-91.
23. Dudea SM, Lenghel M, Botar-Jid C, Vasilescu D, Duma M. Ultrasonography of superficial lymph nodes: benign vs. malignant. Med Ultrason. 2012;14(4):294-306.
24. Pinheiro DJPC, Elias S, Pinto Nazario AC. Axillary lymph nodes in breast cancer patients: sonographic evaluation. Radiol Bras. 2014;47(4):240-4.
25. Abe H, Schmidt RA, Kulkarni K, Sennett CA, Mueller JS, Newstead GM. Axillary lymph nodes suspicious for breast cancer metastasis: sampling with US-guided 14-gauge core-needle biopsy - clinical experience in 100 patients. Radiology. 2009;250(1):41-9.
26. Özütemiz C, Krystosek LA, Church AL, Chauhan A, Ellermann JM, Domingo-Musibay E, et al. Lymphadenopathy in COVID-19 vaccine recipients: diagnostic dilemma in oncologic patients. Radiology. 2021 Jul;300(1):E296-300.
27. Cocco G, Delli Pizzi A, Fabiani S, Cocco N, Boccatonda A, Frisone A, et al. Lymphadenopathy after the anti-COVID-19 vaccine: multiparametric ultrasound findings. Biology (Basel). 2021;10(7):652. doi: 10.3390/biology10070652.
28. Surasi DSS, Lin L, Ravizzini G, Wong F. Supraclavicular and axillary lymphadenopathy induced by COVID-19 vaccination on 18F-Fluorthanatrace, 68Ga-DOTATATE, and 18F-Fluciclovine PET/CT. Clin Nucl Med. 2022 Feb 1;47(2):195-6.
29. Ganga K, Solyar AY, Ganga R. Massive cervical lymphadenopathy post-COVID-19 vaccination. Ear Nose Throat J. 2021 Oct 2:1455613211048984. doi: 10.1177/01455613211048984.
30. Tan HM, Hue SS, Wee A, See KC. Kikuchi-Fujimoto Disease post COVID-19 vaccination: case report and review of literature. Vaccines (Basel). 2021 Oct 29;9(11):1251. doi: 10.3390/vaccines9111251.
31. Schiaffino S, Pinker K, Magni V, Cozzi A, Athanasiou A, Baltzer PAT, et al. Axillary lymphadenopathy at the time of COVID-19 vaccination: ten recommendations from the European Society of Breast Imaging (EUSOBI). Insights Imaging. 2021;12(1):119. doi: 10.1186/s13244-021-01062-x.

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