

Vaccine-associated axillary lymphadenopathy with a focus on COVID-19 vaccines

Impfassozierte axilläre Lymphadenopathie mit Fokus auf COVID-19-Impfstoffe

Authors

Caroline Wilpert¹, Evelyn Wenkel^{2, 3}, Pascal Andreas Thomas Baltzer⁴, Eva Maria Fallenberg⁵, Heike Preibsch⁶, Stephanie Tina Sauer⁷, Katja Siegmann-Luz⁸, Stefanie Weigel⁹, Petra Wunderlich¹⁰, Daniel Wessling¹¹

Affiliations

- 1 Department of Diagnostic and Interventional Radiology, University Medical Center Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
- 2 Radiology, Radiologie München, Munich, Germany
- 3 Medical Faculty, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
- 4 Unit of General Radiology and Paediatric Radiology, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria
- 5 Diagnostic and Interventional Radiology, TUM, Munich, Germany
- 6 Diagnostic and Interventional Radiology, University Hospital Tuebingen, Tuebingen, Germany
- 7 Department of Diagnostic and Interventional Radiology, University Hospital Wuerzburg, Wuerzburg, Germany
- 8 Reference Centre Mammography, Berlin, Germany
- 9 Department of Clinical Radiology and Reference Center for Mammography, University Hospital Muenster, Muenster, Germany
- 10 Radiological practice, Radebeul, Germany
- 11 Department of Diagnostic and Interventional Neuroradiology, University Hospital Heidelberg, Heidelberg, Germany

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Correspondence

Dr. Caroline Wilpert

Department of Diagnostic and Interventional Radiology, University Medical Center Freiburg, Faculty of Medicine, University of Freiburg, Hugstetterstraße 55, 79106 Freiburg, Germany

Caroline.wilpert@uniklinik-freiburg.de



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ABSTRACT

Objective Axillary lymphadenopathy (LA) after COVID-19 vaccination is now known to be a common side effect. In these cases, malignancy cannot always be excluded on the basis of morphological imaging criteria.

Method Narrative review for decision-making regarding control and follow-up intervals for axillary LA according to currently published research. This article provides a practical overview of the management of vaccine-associated LA using image examples and a flowchart and provides recommendations for follow-up intervals. A particular focus is on patients presenting for diagnostic breast imaging. The diagnostic criteria for pathological lymph nodes (LN) are explained.

Results Axillary LA is a common adverse effect after COVID-19 vaccination (0.3–53%). The average duration of LA is more than 100 days. LA is also known to occur after other vaccinations, such as the seasonal influenza vaccine. Systematic studies on this topic are missing. Other causes of LA after vaccination (infections, autoimmune diseases, malignancies) should be considered for the differential diagnosis. If the LA persists for more than 3 months after COVID-19 vaccination, a primarily sonographic follow-up examination is recommended after another 3 months. A minimally invasive biopsy of the LA is recommended if a clinically suspicious LN persists or progresses. In the case of histologically confirmed breast cancer, a core biopsy without a follow-up interval is recommended regardless of the vaccination, as treatment appropriate to the stage should not be influenced by follow-up intervals. For follow-up after breast cancer, the procedure depends on the duration of the LA and the woman's individual risk of recurrence.

Conclusion Vaccination history should be well documented and taken into account when evaluating suspicious LN. Biopsy of abnormal, persistent, or progressive LNs is recommended. Preoperative staging of breast cancer should not be delayed by follow-up. The risk of false-positive findings is accepted, and the suspicious LNs are histologically examined in a minimally invasive procedure.

Key Points

- The vaccination history must be documented (vaccine, date, place of application).
- If axillary LA persists for more than 3 months after vaccination, a sonographic follow-up examination is recommended after 3 months.
- Enlarged LNs that are persistent, progressive in size, or are suspicious on control sonography should be biopsied.
- Suspicious LNs should be clarified before starting oncological therapy, irrespective of the vaccination status, according to the guidelines and without delaying therapy.

Citation Format

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ZUSAMMENFASSUNG

Ziel Die axilläre Lymphadenopathie (LA) nach COVID-19-Impfung ist inzwischen als häufige Nebenwirkung bekannt. Maligne Ursachen können in solchen Fällen anhand der bildmorphologischen Kriterien nicht immer ausgeschlossen werden.

Methode Narratives Review zur Entscheidungsfindung von Kontroll- und Nachsorgeintervallen der axillären LA nach aktuell publiziertem Kenntnisstand. Die Arbeit bietet anhand von Bildbeispielen und einem Flussdiagramm eine praxisorientierte Übersicht zum Umgang mit impfasoziierte LA und Empfehlungen für Kontrollintervalle. Ein Fokus wurde dabei auf die Anforderungen im Bereich der Mammadiagnostik gelegt. Die Befundungskriterien für pathologische Lymphknoten (LK) werden erläutert.

Ergebnisse Die axilläre LA ist eine häufige Nebenwirkung nach COVID-19-Impfung (0.3–53 %). Die Dauer der impfasoziierten LA beträgt im Mittel über 100 Tage. Auch nach anderen Impfungen wie z. B. der saisonalen Grippeimpfung ist das Auftreten einer LA bekannt. Systematische Untersuchungen dazu fehlen. Andere Ursachen für eine LA (Infektionen, Autoimmunerkrankungen, Malignome) müssen differenzialdiagnostisch bedacht werden. Wenn die LA nach COVID-19-Impfung länger als 3 Monate andauert, wird eine primär sonografische Kontrolluntersuchung nach weiteren 3 Monaten empfohlen. Eine minimal-invasive Abklärung der LA wird empfohlen, wenn ein klinisch suspekter LK persistiert oder progredient ist. Im Rahmen eines histologisch gesicherten Mammakarzinoms wird unabhängig von der Impfung eine Stanzbiopsie ohne Kontrollintervall empfohlen, da eine stadiengerechte Therapie nicht durch Verlaufskontrollen beeinflusst werden sollte. In der Nachsorge des Mammakarzinoms hängt das Procedere von der Dauer der LA und dem individuellen Rezidivrisiko ab.

Schlussfolgerung Die Impfanamnese sollte dokumentiert und bei der Abklärung suspekter axillärer LK berücksichtigt werden. Es wird empfohlen, morphologisch auffällige, persistierende oder progrediente LK im Verlauf zu biopsieren. Das präoperative Staging bei Mammakarzinom darf durch Verlaufskontrollen nicht verzögert werden. Das Risiko falsch positiver Befunde wird akzeptiert und die auffälligen LK werden minimal invasiv histologisch abgeklärt.

Kernaussagen

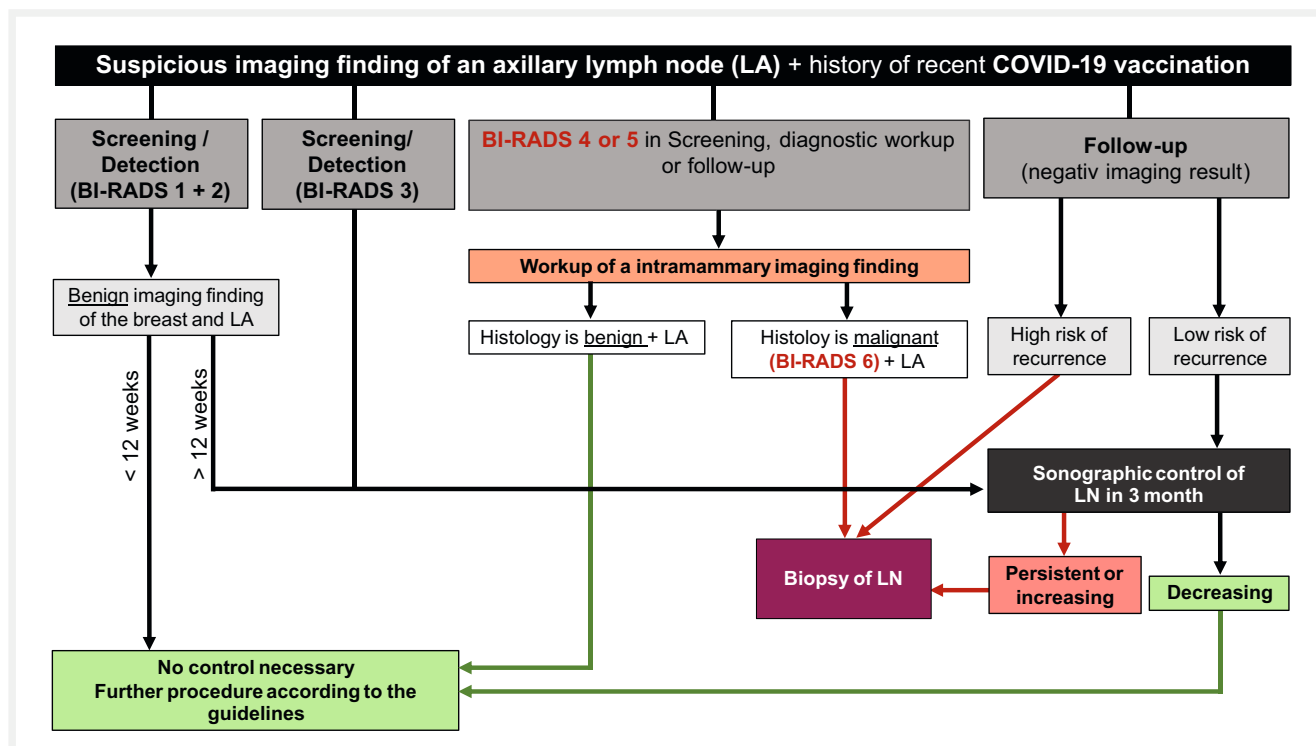
- Der Impfstatus ist zu dokumentieren (Impfstoff, Datum, Applikationsort).
- Sollte die axilläre LA länger als 3 Monate nach Impfung andauern, wird eine sonografische Kontrolle nach weiteren 3 Monaten empfohlen.
- In der Kontrollsonografie persistierend vergrößerte, größenprogrediente oder malignomsuspekte LK sollten biopsiert werden.
- Suspekte LK werden vor einer onkologischen Therapie unabhängig vom Impfstatus leitliniengerecht und ohne Verzögerung der Therapie abgeklärt.

Abbreviations

BI-RADS	Breast Imaging Reporting and Data System
CT	Computed tomography
EUSOBI	European Society of Breast Imaging
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography
HIV	Human immunodeficiency virus
LA	Lymphadenopathy
LN	Lymph nodes
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NST	No special type

Introduction

The evaluation of axillary lymph nodes (LNs) is particularly important for early detection, diagnostic workup, and follow-up in breast diagnosis. Suspicious LNs can indicate a previously undetected malignancy or metastasis or can be a reaction to numerous other causes [1, 2]. As a result of the vaccines that have been available since the end of 2020 for the prevention of severe COVID-19 disease, an increase in usually ipsilateral axillary lymphadenopathy (LA) has been seen. Even if the relationship often seemed clear from the patient history, there was uncertainty regarding how to handle such findings. A reliable conclusion about vaccine-induced LA caused by other vaccines like the SARS-CoV-2 vaccine cannot be made due to a lack of data. The SARS-CoV-2



► **Fig. 1** Flowchart summarizing the procedure for LA in the context of diagnostic breast imaging after COVID-19 vaccination. BI-RADS = Breast Imaging and Reporting Data System, LA = lymph adenopathy, “>” and “<” means time interval to vaccination, LN = lymph node.

and flu vaccines, which are typically administered in the fall/winter months, as well as combined flu/COVID-19 vaccines, which may be available in the future, could result in a renewed increase in axillary LA in the total population [3]. Therefore, it would be helpful to examine the influences and procedure in the case of vaccine-associated axillary LA.

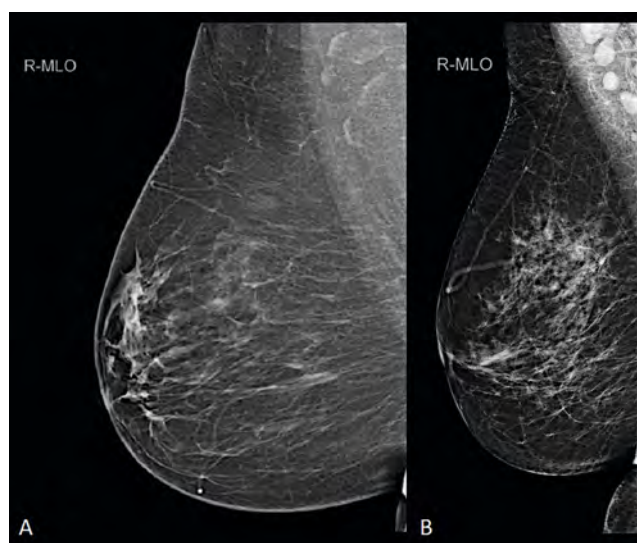
The article provides an overview of the current data and illustrates this based on the available evidence with examples. Based on the EUSOBI recommendations [4, 5] initially published in 2021 and updated in 2023, a flowchart summarizing the recommended procedure is provided (► **Fig. 1**).

Diagnosing axillary lymph nodes

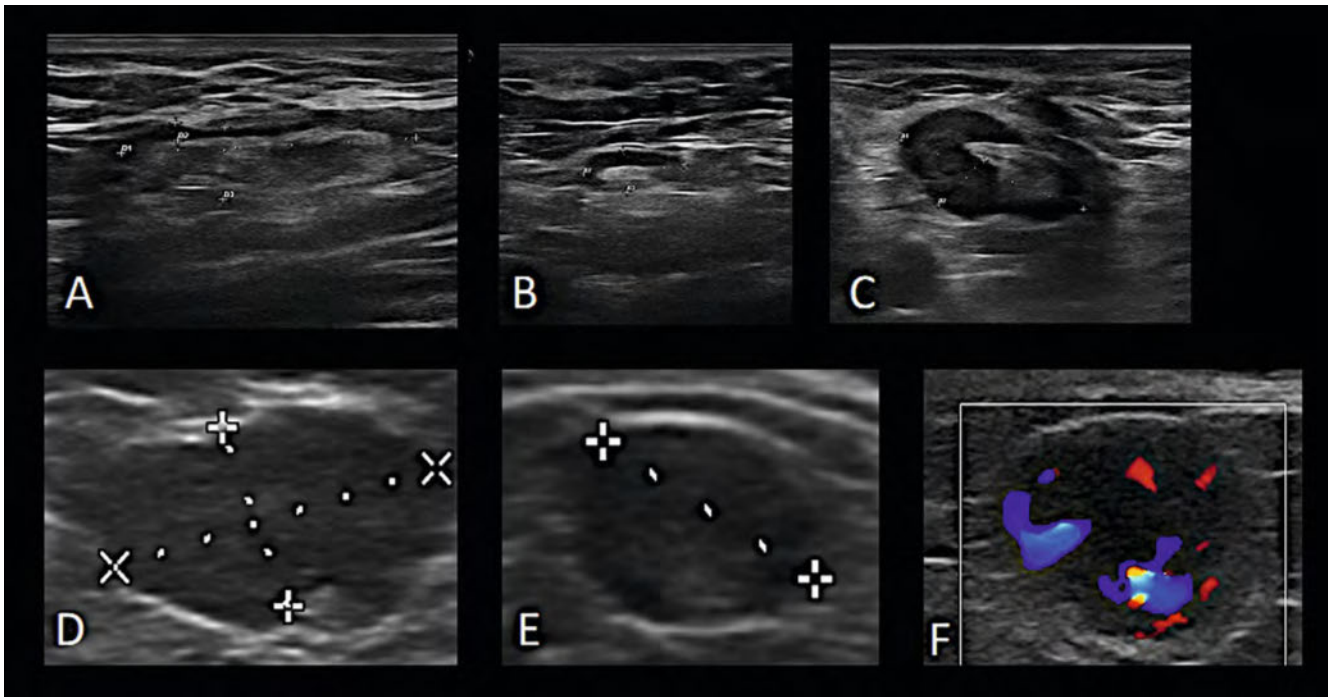
Mammography is suitable on a limited basis for evaluating the status of axillary LNs (► **Fig. 2**). In the case of suspicious axillary LNs, supplementary ultrasound and possibly a biopsy are recommended according to the proposed algorithm for the diagnostic workup of clinically suspicious LNs (► **Fig. 1**).

On FDG-PET-CT, reactive LNs can exhibit tracer uptake after a COVID-19 vaccine [6, 7]. Treatment-relevant PET-CT should not be delayed by a COVID-19 vaccine. If possible, there should be a time delay between FDG-PET examination and vaccination: more than 2 weeks after vaccination in the case of malignancies, and 4–6 weeks after vaccination in the case of all other diseases [7].

Ultrasound is considered the modality of choice when evaluating axillary LNs [8] and has better diagnostic accuracy compared



► **Fig. 2** A–B Mammograms in MLO projection. **A** Screening mammogram of a 53-year-old woman with normal axillary lymph nodes (LNs). **B** Screening mammogram of a 73-year-old female patient. Several round and oval, dense LNs can be seen in the right axilla. The last COVID-19 vaccination was more than 8 months ago. Sonography revealed several LNs without fatty hilus. The sonographic follow-up after 3 months revealed unchanged findings. One of the LNs was biopsied on a representative basis and showed histologically inflammatory, benign changes.



► **Fig. 3** Differences in the morphologic presentation of benign and malignant lymph nodes (LNs) on sonography of the axillary region. **A** and **B** Benign LN with a size of A: 27 × 7 mm, cortex < 2 mm and B: 12 × 6 mm, cortex up to 2 mm. The fatty hilum is preserved in each case and the cortex < 3 mm. **C** Suspicious LN with asymmetrically enlarged cortex up to 8 mm and preservation of the fatty hilum. Note that the cortex width is more decisive for the approach to lymph node diagnosis than the total diameter of the lymph node of 25 × 12 mm; the histology result revealed reactive changes. **D** Suspicious LN with destruction of the fatty hilum in a patient who presented for screening. It was a reactive LN after a COVID vaccination. **E + F** Sonography (**E**) and Doppler (**F**) in a patient who presented as part of the previously unremarkable follow-up of a breast carcinoma. Increased vascular perfusion of the cortex was noted, leading to the suspicion of malignant findings. Histology revealed chronic lymphocytic leukemia.

to mammography [9]. An unremarkable LN has an oval shape with a hyperechoic, fatty hilum and a hypoechoic, thin cortex with a width of ≤ 3 mm (► **Fig. 3**).

The metastatic involvement of a LN occurs from peripheral to central resulting in a corresponding change in the cortico-medullary structure. The criteria for suspicious axillary LNs are partial or complete thickening of the cortex > 3 mm, lobulated asymmetric configuration of the cortex, and loss of the cortico-medullary structure with a displaced fatty hilum or partial or complete loss of the fatty hilum [10, 11]. Malignant LNs can have increased vascularization including peripheral and subcapsular portions (► **Fig. 3**, ► **Fig. 4**, ► **Fig. 5**).

Causes of axillary lymphadenopathy

LA can have numerous causes (► **Table 1**). Reactive LA is seen in 13–24% of cases [12]. In addition to infection, autoimmune or more rarely malignant diseases can cause axillary LA (8). Vaccine-associated axillary LA was rarely observed prior to the introduction of the COVID-19 vaccines. LA after administration of a flu, measles, varicella, or anthrax vaccine is known [13]. A further reason for the frequency of axillary LA observed following COVID-19 vaccination could be due to the immunogenic effect of mRNA vaccines [14]. With respect to determining the cause of axillary LA, it is essential to record the patient’s medical history. Whether LA occurs on a unilateral or bilateral basis can also indicate the ori-

gin. While a unilateral axillary LA indicates lymphatic metastasis or local infection, bilateral axillary LA can indicate systemic inflammatory disease, lymphoma, or leukemia.

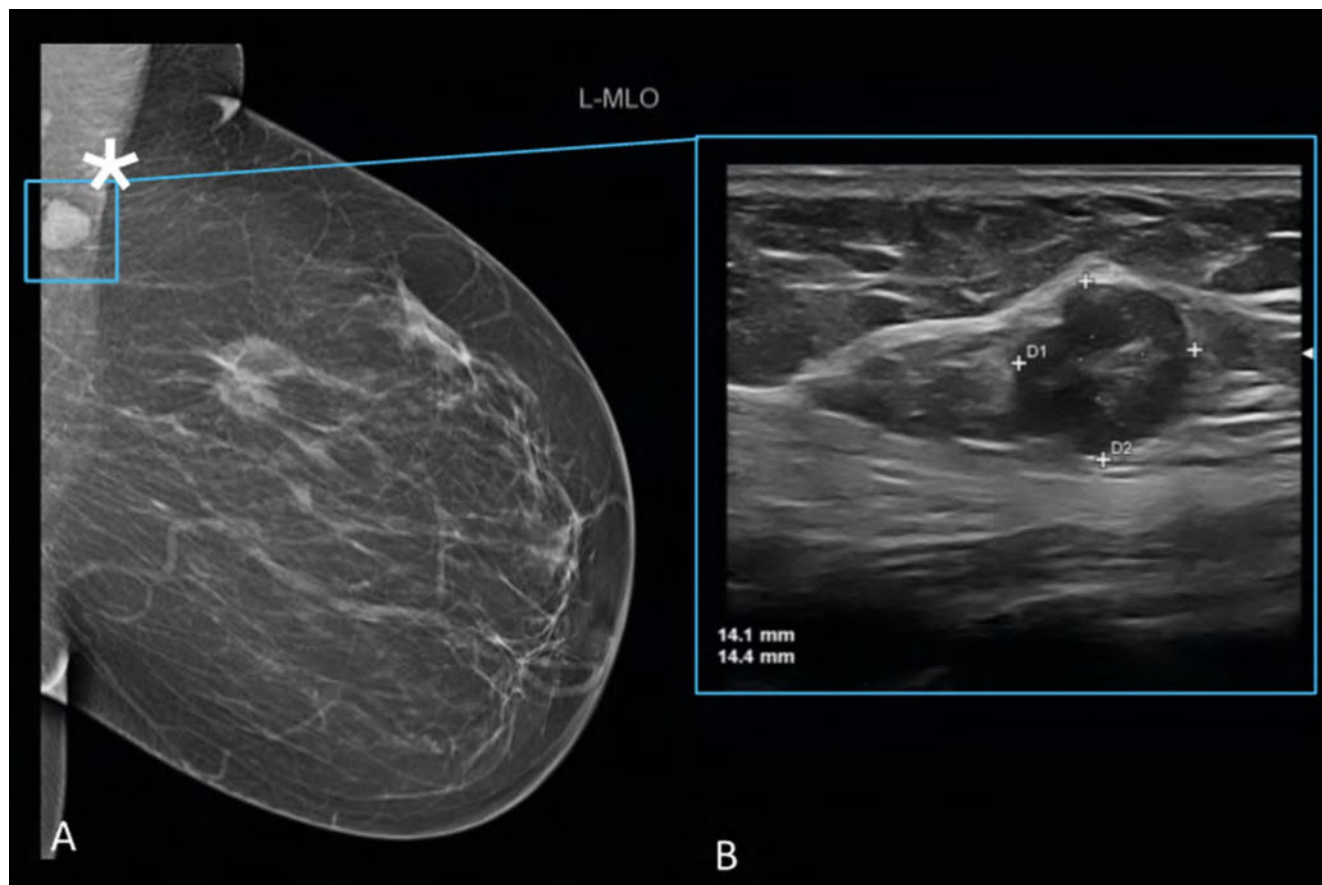
An overview of the causes of axillary LA is provided in ► **Table 1**.

Studies on lymphadenopathy with a focus on the COVID-19 vaccine

Axillary LA after vaccination in the muscles of the upper arm is a known side effect of several vaccines and is the result of a local immune response. In contrast to the COVID-19 vaccines, the data regarding other vaccines is insufficient to make precise statements about the frequency and duration of axillary LA (► **Table 2**).

An immune response in the form of axillary LA after vaccination has been described in PET-CT studies on various vaccines [15, 21]. In a cohort study in 2021, increased tracer uptake in the axillary lymph nodes was seen on PET-CT in 4 of 78 patients (5%) after recent flu vaccination [15]. In a direct comparison study between the COVID-19 vaccine and the flu vaccine, axillary LA was significantly more common after a COVID-19 vaccine (45%) than after the flu vaccine (19%) [16].

After the introduction of the COVID-19 vaccines, many vaccinated people, especially younger people [22], complained of swelling of the axillary lymph nodes that was often painful in the



► **Fig. 4** Mammography (A) and ultrasound (B) of a 40-year-old female patient with histologically confirmed breast cancer in the left breast (G2, moderately diff. NST, ER: 95 %, PR: 5 %, HER2: 1 +, Ki-67: 10 %) and a histologically confirmed lymph node (LN) metastasis. A Mammography of the left breast (MLO). The breast carcinoma corresponds to the spiculated mass. The LN metastasis corresponds to the enlarged LN without fatty hilus (star). B Sonographically, the LN shows an enlarged, irregularly shaped cortex and a destroyed fatty hilus.

days following vaccination. The pain regressed on average 7 days after vaccination [23, 24, 25]. Primarily case reports were published [13, 26, 27]. The duration of axillary LA after COVID vaccination was on average 97–129 days after primary immunization and 102 ± 56 days after administration of the booster vaccine [28, 29]. It has since been shown that LA after COVID-19 vaccination occurs later and lasts longer than assumed in 2021.

Varying recommendations regarding follow-up after 4–12 weeks in the case of LA after COVID-19 vaccination have been published [4, 28, 30]. Enlarged axillary LNs after COVID-19 vaccination regressed on average after 4.3 months [31].

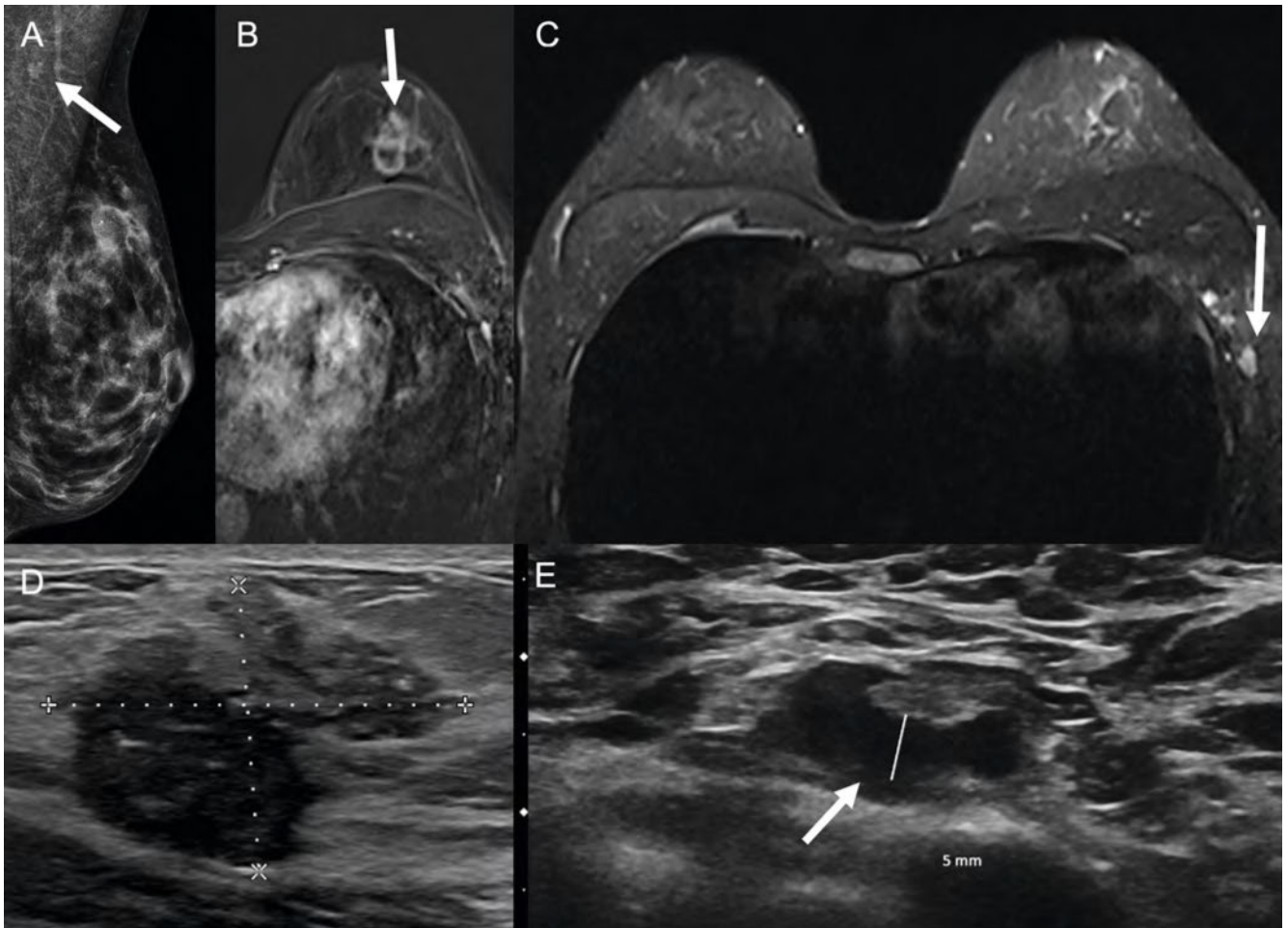
Axillary lymphadenopathy usually goes unnoticed by those affected. This is shown by comparing two large cohort studies. Among the 16,471 people vaccinated with the Spikevax (Moderna) vaccine, the maximum incidence of axillary LA after 27 days documented by physicians in the medical history was 0.7 % in a retrospective study [17]. If those vaccinated were asked specifically about axillary LA, they stated feeling axillary pain and swelling that was classified as LA. Based on this focused question, an incidence of 23.8 % was seen in a cohort of 15 181 vaccinated people [18]. Interestingly, not only the frequency of axillary LA among the different vaccines but also the morphology of the LNs varied. While a higher number of enlarged LNs was seen after the admin-

istration of Comirnaty (BioNTech/Pfizer), the participants vaccinated with Spikevax (Moderna) had a larger average diameter and a greater cortical thickness than those previously vaccinated with the Comirnaty vaccine (BioNTech/Pfizer) [17, 19].

The studies on the duration of axillary LA after booster vaccination showed a slightly shorter duration of LA [20] compared to primary vaccination. Due to the different vaccine combinations, these studies are difficult to compare.

Most studies relate to primary immunization with COVID-19 vaccines. An overview of the average rate of LA after COVID vaccination is provided in ► **Table 3**. In addition, it must be taken into consideration that the data on the different vaccines also varies. Due to the more frequent use of the mRNA-based vaccines, many studies have focused on axillary LA after vaccination with mRNA vaccines, while the remaining vaccines were only mentioned in case reports or smaller studies. One study on the simultaneous administration of the COVID-19 vaccine and the seasonal flu vaccine did not show an increase in side effects but did show an adequate antibody response to both vaccines [3]. There are currently not yet any results regarding the combined COVID-19 and flu vaccines that recently entered phase 2 and 3 trials.

In summary, axillary LA after COVID-19 vaccination is a common side effect that must be taken into consideration in senology.



► **Fig. 5** 34-year old female patient with biopsy-confirmed, invasive ductal breast carcinoma in the left breast (no special type (NST), triple negative, G3, Ki-67: 30%). **A** Mammography of the left breast in MLO projection. The inhomogeneous, dense breast tissue masks the breast cancer. A lymph node (LN) can be delineated (arrow). No diagnosis can be made regarding malignancy. **B** Breast MRI: T1-weighted subtraction image shows inhomogeneous contrast enhancement with central necrosis of breast cancer 2 cm in diameter (arrow). **C** Breast MRI: The T2-weighted sequence shows an increased number of LNs in the left axilla, but no clear malignant changes are identified (arrow). **D** Ultrasound of the breast carcinoma shows an inhomogeneous, hypoechoic mass lesion. **E** Sonography of the left axilla: All LNs had a preserved fatty hilus and an oval shape on sonography. One of these LNs had asymmetrical enlargement of the cortex up to 5 mm (arrow). This LN was a lymph node metastasis.

Procedure in the case of suspicion of vaccine-associated LA during breast diagnosis

The patient's vaccination status should first be determined. This includes documentation of the vaccine, vaccination date, number of vaccines, and location in which the vaccine was administered [4]. The time between vaccination and the onset LA should be determined in order to determine the plan for follow-up. If the vaccine was administered more than 3 months ago and LA is still present, follow-up is recommended [31]. Follow-up can also be useful when a reliable connection between axillary LA and a vaccine cannot be established, e. g., due to a lack of medical history data or unclear data regarding the side or date on which the vaccine was administered. Based on the EUSOBI recommendations [4, 5], the flowchart shows the procedure depending on the duration of LA, the clinical finding, and the medical history (► **Fig. 1**). The 5th edition of the Breast Imaging Reporting and Data System (BI-RADS) was used in the flowchart.

With respect to follow-up, vaccines should be administered on the contralateral side of a treated breast carcinoma and with a time delay if possible, ideally after a planned follow-up appointment [4]. Mammography screening should not be delayed because of vaccination status. Therefore, extending the screening interval by postponing a screening mammography appointment is not recommended [5, 32]. This is in line with an update by the EUSOBI on the management of axillary LA after COVID-19 vaccination since a negative effect on breast cancer morbidity and mortality in the USA has been observed [33, 34, 35].

A. LA in early detection and in the workup of symptomatic patients without suspicion of malignancy on diagnostic breast imaging (BI-RADS 1 and 2)

In the case of axillary LA in previously healthy patients with unremarkable breast findings on imaging (BI-RADS 1 or BI-RADS 2) the following procedure is recommended (references): [4, 36, 37].

► **Table 1** Causes of axillary masses: Lymphadenopathy (LA) and differential diagnoses.

Type	Disease or pathogen
Reactive without detection of pathogens	Lymph node abscess, skin damage, abscesses on the arm and hand, dermatitis, phlegmon, nonspecific after infection, endocarditis, after surgery
Reactive as a result of foreign objects	Silicone implants, foreign body granuloma, reaction to suture material, reaction to a tattoo
Vaccine-associated reaction	COVID-19, flu, measles, varicella, anthrax
Reactive with detection of pathogens	Viral: Epstein-Barr virus, cytomegalovirus, infectious hepatitis, postviral lymphadenitis, adenoviruses, herpes viruses, human immunodeficiency virus (HIV), Kaposi sarcoma Bacterial: Local cutaneous infections with staphylococcus or streptococcus. Cat scratch disease (<i>Bartonella henselae</i>), tuberculosis, atypical mycobacteria, syphilis, chlamydia, toxoplasmosis, borreliosis, rickettsia, helminths (filariasis), salmonella Mycotic: Histoplasmosis, cryptococcosis
Malignant	Locoregional metastases of breast cancer and malignant melanoma, distant metastases of all other malignancies, lymphoma, acute and chronic leukemia
Autoimmune	Rheumatoid arthritis, systemic lupus erythematosus, psoriasis, dermatomyositis, Sjögren's syndrome
Atypical lymphoproliferative diseases	Angiofollicular lymph node hyperplasia (Castleman disease), angioimmunoblastic LA with dysproteinemia, angiocentric immunoproliferative diseases
Granulomatous diseases	Sarcoidosis (Boeck's disease), tuberculosis, granulomatosis with polyangiitis, berylliosis, silicosis, lymphomatoid granulomatosis
Hypersensitivity syndromes	Medication-associated: Diphenylhydantoin, carbamazepine, primidone, gold, allopurinol, indomethacin, sulfonamide, silicone reaction, serum disease, graft-versus-host disease
Lymphatic and lymphoproliferative	Lymphangioma, amyloidosis, storage diseases, vasculitis, systemic mastocytosis, Waldenström's macroglobulinemia
Other rare causes of LA	Inflammatory pseudotumor of the lymph nodes, histiocytic necrotizing lymphadenitis (Kikuchi LA), Rosai-Dorfmann disease
Axillary masses imitating lymph nodes without connection to lymphatic tissue	Neurogenic: Perineurium tumors, schwannoma/neurofibroma Lipomatous: Lipoma, liposarcoma Vascular: Hemangioma Muscular: Rhabdomyoma, rhabdomyosarcoma Chondrogenic: Osteochondroma, chondroma, chondrosarcoma Fibrous: Fibroma, malignant fibrous histiocytoma

HIV = human immune deficiency virus, LA = lymphadenopathy, LN = lymph node

► **Table 2** Vaccines with frequency and duration of lymphadenopathy.

Vaccine	Frequency	Duration
Influenza	5.13–19% [15, 16, 17]	Min. 5–7 days
Measles (attenuated live vaccine)	Case report [18]	Not specified
Tetanus	Case report [19]	Not specified
Varicella	61.8% [20]	Min. 10 days

- In the case of axillary LA with a corresponding vaccination history (COVID-19 vaccine administered on the symptomatic side a few days to weeks before the onset of LA) and regression of LA within 3 months, further follow-up is not necessary if there are no suspicious breast imaging findings [5].

- If axillary LA has been present for longer than 3 months and there is a positive history of vaccination, one-time follow-up is recommended after an additional 3 months. If follow-up shows persistent, progressive, or morphologically suspicious LNs a biopsy should be performed.

B. LA and an intramammary finding in early detection, diagnostic workup, and follow-up (BI-RADS 3–5)

BI-RADS 3 findings in the breast can present a challenge. In such cases, special attention should be paid to the morphology of the LNs and to the risk profile. Follow-up of intramammary BI-RADS 3 findings with axillary LA should be performed after 3 months. A minimally invasive diagnostic workup of intramammary BI-RADS 4 or 5 findings is performed. In the case of BI-RADS 5 findings, the minimally invasive workup of the breast and LA can be performed simultaneously.

If a biopsy of an intramammary finding shows a malignancy (BI-RADS 6), a core needle biopsy of the suspicious LN is performed under ultrasound guidance.

► **Table 3** Overview of the frequency of axillary LA according to vaccine.

Vaccine	Frequency of LA (range in %)	Number of vaccinated subjects per study
Comirnaty (BioNTech/Pfizer)	0.3–53 [32, 33, 34, 35, 36, 37]	19 [32], 91 [33], 728 [34, 36], 390 [35], 51795 [37]
Spikevax (Moderna)	0.7–40 [32, 33, 35, 37, 38, 39]	14 [32], 55 [33], 43 [35], 15181 [38, 39], 16471 [37]
Jcovden (Johnson&Johnson)	Insufficient data	
Vaxzevria (AstraZeneca)	63.6 [33]	77 [33]
Birmervax (Hipra)	Insufficient data	
Nuvaxovid (Novavax)	Insufficient data	
VidPrevtyn Beta (Sanofi Pasteur)	Insufficient data	

C. LA when diagnosing a malignancy in early detection, diagnostic workup, and follow-up (BI-RADS 6)

A newly diagnosed carcinoma is classified as BI-RADS 6 [4, 36, 38, 39]:

Suspicious axillary LNs should be confirmed histologically even in the case of a history of vaccination. The further diagnostic workup and treatment should be initiated in a timely manner (see example, ► **Fig. 5**).

D. LA in follow-up and intramammary findings in BI-RADS category 1, 2, or 3

An individualized approach based on the risk profile for recurrence should be used for follow-up. However, the following generally applies [4, 6, 36]:

- In the case of a low risk of recurrence with a corresponding vaccination history (COVID-19 vaccine administered on the symptomatic side a few days to weeks before the onset of LA) and regression of LA within 3 months, further follow-up is not necessary if the diagnostic workup of the breast is otherwise unremarkable [5]. The follow-up intervals remain unchanged.
- In the case of a low risk of recurrence and a corresponding history of vaccination and LA lasting longer than 3 months, a one-time follow-up is recommended after another 3 months. If the follow-up shows persistent, progressive or morphologically suspicious LNs, a biopsy should be performed.
- In the case of a high risk of recurrence, a biopsy is recommended regardless of the vaccination date.

E. LA in complex situations and rare diseases

If the situation is complex, e. g., in the case of puerperal and non-puerperal mastitis or changes resulting from treatment, an individualized approach is needed. LA can be caused in these cases by the underlying disease. Follow-up of the LN status after 3 months or after resolution of the mastitis is recommended.

The flowchart in ► **Fig. 1**, which is based on the EUSOBI recommendations [4], provides an overview of the procedure for LA occurring after COVID-19 vaccination.

Clinical relevance

- LA, particularly after COVID-19 vaccination, is a common finding. The condition should resolve completely within 6 months at the latest.
- If a malignancy cannot be ruled out based on the constellation of findings, either short-term ultrasound follow-up is performed after 3 months or a biopsy is performed depending on the risk profile.
- If the follow-up situation shows regression of the findings, the normal early detection or follow-up schedule can be resumed.

Conflict of Interest

The authors declare that they have no conflict of interest.

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