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Imaging of axillary lymph nodes in the COVID-19 era: A lesson to be learned

Invited commentary

Since the last months of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and the related coronavirus disease 2019 (COVID-19) pandemic has aroused great amazement in the public opinion and the medical and scientific community. This is certainly due to its epidemiological relevance and global spread: up to June 27, 2022, a total of over 543.5 million cases, 6.3 million deaths, and 11.6 billion administered vaccine doses are reported by the Johns Hopkins University website [1]. This pandemic has focused our attention on limitations and potential of contemporary biomedicine. The former regarding the unpreparedness of health systems for such a disease (also in high-income countries), the latter regarding the capacity to obtain effective vaccines in an incredibly short time.

Pandemics are far from being a novel story, as David Quammen had definitively shown in his masterful book significantly titled *Spillover*, published in 2013 [2], where the current pandemic is predicted with a daunting level of detail, also resting on the SARS-CoV-1 story. Infectious diseases, in particular viral, are an integral part of the humankind history, even before humans began to organize themselves from small groups to larger societies. The growth of the global population and the spread of contagious diseases has radically influenced the course of history, as happened for the plague of Justinian (541–542 E.V.) or the smallpox up until 1979, and, recently, for the human immunodeficiency virus (HIV), from 1981 onward. Notably, HIV therapies enable a certain disease control but – over 40 years after the epidemic onset – no vaccine is available. Thus, we cannot think pandemics be confined in time and space, possibly not involving our backyard. Notwithstanding clear evidence, we thought that, at least in high-income countries, infectious diseases were something related to the old past times and that degenerative chronic disease (cancer, cardiovascular, and dementia) were the challenges to be worried about. COVID-19 forced us to come to reality.

Currently, we are coping a pandemic virus, we hope only endemic in the next future, probably needing cycles of vaccinations, with (yearly?) re-inoculations of vaccines, possibly modified according new viral variants, as currently happens with influenza virus. Therefore, we are facing (and so it will be for a long time) problems of differential diagnosis between effects of COVID-19 vaccinations and other pathologies. In particular, authors focused on the importance in the discrimination of axillary lymphadenopathies following COVID-19 vaccination from breast cancer nodal metastasis [3,4].

In the context of a virtual special issue of *European Journal of Radiology*, dedicated to "New trends in Breast Imaging", T.J.A. van Nijnatten, M.S. Jochelson, and M.B.I. Lobbes published an interesting review about axillary lymph node characteristics after COVID-19 vaccination as compared to those of lymph node metastatic disease from breast cancer [5]. They highlighted that the reported frequency of lymphadenopathy after COVID-19 vaccination is from 49 % to 85 % for ultrasound studies, 29 % for breast magnetic resonance imaging (MRI), and from 15 % to 54 % for ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) studies.

Regarding ultrasound studies, the following issues were noted: abnormal lymph node can be detected also at the axilla contralateral to the vaccination side; diffuse cortical thickness is mostly related to previous COVID-19 vaccination while focal cortical thickness and fatty hilum effacement are mostly due to metastasis; lymphadenopathy post-COVID-19 seems to be more frequent after mRNA vaccination than after vector vaccination; normalization of axillary lymph nodes is expected within 12–16 weeks vaccination (no cases reported after week 16). Regarding MRI, the authors highlighted the inversion of the lymph node levels involved: mostly level II and III after vaccination; mostly level I and II in metastatic involvement. Finally, at ^{18}F-FDG PET/CT studies, hypermetabolic nodes, more frequent after the second dose of mRNA COVID-19 vaccination, can persist at least 70 days after vaccination.

While differences in reported frequencies of lymphadenopathies after COVID-19 vaccination can be related to variable study settings, the following key points are clinically relevant:

1. preferential ultrasound-detected diffuse cortical thickness after vaccination;
2. expected normalization at ultrasound within 16 weeks;
3. possibility of normal level I and abnormal level II/III at MRI;
4. long persistence of hypermetabolic nodes after vaccination at PET/CT (at least 70 days).

Notably, abnormal lymph nodes after COVID-19 vaccination can be also encountered at mammography (mainly on medio-lateral oblique views), particularly in women who received COVID-19 vaccine within 8 weeks. In this setting, different approaches are proposed. For example, while Wolfson et al. [6] suggest not to delay the screening mammograms and to interpret the investigation considering the patients risk factors and the presence of other mammographic findings in the ipsilateral breast, Raj et al. [7] advise to consider to anticipate or postpone the vaccination by 8 weeks in order to avoid unnecessary and bothersome follow-up examinations.

In this context, the ten rules recommended by the European Society of Breast Imaging (EUSOBI) in 2021 [3] keep their validity:

1. in patients with previous history of breast cancer, vaccination should be performed in the contralateral arm or in the thigh;

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2. collect vaccination data for all patients referred to breast imaging services;
3. perform breast imaging examinations preferentially before vaccination or at least 12 weeks after;
4. in patients with newly diagnosed breast cancer, apply standard imaging protocols regardless of vaccination status;
5. in case of symptomatic or imaging-detected axillary lymphadenopathy before vaccination or at least 12 weeks after, examine with appropriate imaging the contralateral axilla and both breasts to exclude malignancy;
6. in case of axillary lymphadenopathy contralateral to the vaccination side, perform standard work-up;
7. in patients without breast cancer history and no suspicious breast findings, lymphadenopathy only ipsilateral to the vaccination within 12 weeks after vaccination can be considered benign or probably-benign;
8. in patients without breast cancer history, post-vaccination lymphadenopathy coupled with suspicious breast finding requires standard work-up, including biopsy when appropriate;
9. in patients with breast cancer history, interpret post-vaccination lymphadenopathy considering the timeframe from vaccination and overall metastatic risk;
10. complex or unclear cases should be managed by the multidisciplinary team.

In conclusion, this topic goes beyond the narrow implication of having good skills for differential diagnosis of lymphadenopathies. Indeed, it opens a relevant window on the need of general knowledge that breast radiologists must have, also in the context of the multisciplinary team when discussing breast cancer, metastatic breast cancer, and comorbidities.

The general population aging is a challenge for the whole medicine for clinicians and researchers. Many of the cutoffs between normal and pathological findings have been fixed on normal populations much younger than that we now encounter in our hospitals. Comorbidities, often multiple, affect treatment options and outcomes for many diseases, including breast cancer and COVID-19. To practice evidence-based medicine for this aged population is more and more difficult. Vaccinations are a variable that further complicates the breast imaging picture. Breast radiologists must first and foremost be physicians, doctors. This is the lesson to be learned.

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