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THE RISK OF LATE BREAST CANCER SCREENING VERSUS AXILLARY LYMPHADENOPATHY ASSOCIATED WITH COVID-19 VACCINATION

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic has significantly impacted morbidity and mortality worldwide. Unilateral axillary lymphadenopathy induced by the COVID-19 vaccine is particularly relevant in women with breast cancer, with a predilection for metastasis to the axillary lymph nodes. Clinicians, radiologists, and patients may be concerned about COVID-19 vaccine-induced unilateral axillary lymphadenopathy because it may be a sign of breast cancer metastasis, leading to a diagnostic conundrum over whether to recommend a biopsy or short-term follow-up. This literature review aims to assess the best available evidence of axillary lymphadenopathy after COVID-19 vaccination. Recognizing COVID-19 vaccine-induced unilateral axillary lymphadenopathy as a potential differential diagnosis and making efforts to investigate the patient's vaccination history are crucial to avoid overestimating the burden of axillary disease and making appropriate therapeutic recommendations.

Keywords: Vaccine, Lymphadenopathy, Covid-19.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has significantly impacted morbidity and mortality worldwide. The first dose of the COVID-19 vaccine was administered on December 14, 2020, under Emergency Use Authorization from the US Food and Drug Administration. Since then, Moderna, Pfizer/BioNTech, Oxford-AstraZeneca and Janssen Pharmaceuticals vaccines have been used to prevent COVID-19 infection in Korea. Local and systemic reactions have been observed in relation to the administration of COVID-19 vaccines, with the most commonly reported adverse event being unilateral "axillary swelling or tenderness" in women who received Moderna (occurring in 11.6% and

16.0% of recipients). after the first and second doses, respectively) and Pfizer-BioNTech vaccines (RIAD et al. 2021). A recent article reported ipsilateral axillary nodal reactivity on positron emission tomography/computed tomography of fluor-18 2-deoxy-2-fluoro-D-glucose, occurring in up to 57.0% (4 of 7) of patients after the second dose of Moderna vaccine and 15.0% (3 of 20) of patients after the second dose of Pfizer-BioNTech vaccine; these proportions are higher than those reported in clinical trials (ADIN et al. 2021). Unilateral lymphadenopathy develops in the ipsilateral axilla and supraclavicular regions because COVID-19 vaccine is usually injected into the deltoid muscle (YOUN et al. 2019; MEHTA et al. 2021). Moderna vaccine induces clinically detected lymphadenopathy within 2 to 4 days after vaccination and lasts an average of 1 to 2 days. The Pfizer/BioNTech vaccine also induces clinically detected lymphadenopathy within 2 to 4 days after vaccination and lasts an average of 10 days (RIAD et al. 2021; ADIN et al. 2021).

Unilateral axillary lymphadenopathy induced by the COVID-19 vaccine is particularly relevant in women with breast cancer, with a predilection for metastasis to the axillary lymph nodes. Clinicians, radiologists, and patients may be concerned about COVID-19 vaccine-induced unilateral axillary lymphadenopathy because it may be a sign of breast cancer metastasis, leading to a diagnostic conundrum over whether to recommend a biopsy or short-term follow-up. A radiology scientific panel recommended an "expectant management strategy with no standard follow-up imaging" for patients in whom lymphadenopathy is more likely due to COVID-19 vaccination rather than malignancy. However, in high-risk situations, short-term follow-up imaging or tissue biopsy must be considered (BEKER et al. 2021). The Journal of the American College of Radiology summarized practical management plans regarding COVID-19 vaccine-induced unilateral axillary lymphadenopathy and recommended that, for patients newly diagnosed with cancer or those in pre- or peri-treatment, immediate imaging, regardless of vaccination status and vaccination in the contralateral arm or at the site furthest from the cancer must be encouraged.

COVID-19 vaccines are commonly given intramuscularly in the arm. Axillary lymphadenopathy has been reported as an adverse event after vaccination against COVID-19. Enlarged axillary lymph node, in addition to being symptomatic in some patients, in breast cancer patients who have received the COVID-19 vaccination, the presence of ipsilateral (or contralateral) lymphadenopathy poses a diagnostic dilemma - clinicians must decide whether or not to proceed with more lymph node biopsy. Fine needle aspiration (FNA), which is commonly performed in newly diagnosed breast cancer patients with axillary lymphadenopathy, may be associated with a huge increase in public health burden. This literature review aims to assess the best available evidence of axillary lymphadenopathy after COVID-19 vaccination.

MATERIAL AND METHODS

A non-systematic literature review was performed. The PubMed and EMBASE databases were searched for relevant articles in English until March 24, 2022. The search terms used were "Vaccine" OR "Vaccination" AND "Lymphadenopathy" OR "Lymph node" AND "Covid-19". Abstracts were independently selected by 2 reviewers for relevance and level of evidence. Articles from selected abstracts were retrieved. Review articles, congress abstracts, non-research articles (such as comments, opinions and guidelines) were excluded. However, the references of review

articles were checked for cross-referencing. Identical articles and abstracts were identified to avoid duplication. Studies published by the same institution were reviewed, only the most recent study or the study with the most complete report of outcomes of interest were included to avoid duplication of data. Data extraction was performed independently by 2 investigators and the results were pooled for analysis.

RESULTS

31 studies or reports were identified using the predefined keywords from the systematic review protocol. After excluding irrelevant articles (such as guidelines, reviews, opinions and comments), 10 studies or reports were included in the review.

INCIDENCE OF CLINICAL AXILLARY LYMPADENOPATHY AFTER COVID-19 VACCINATION

Two large studies evaluated the adverse effect with axillary lymphadenopathy after COVID-19 vaccination. In a large international study by Polack, et al. evaluating 21,729 subjects. Axillary swelling or pain occurred in 11% and 16% after the 1st and 2nd dose of COVID-19 vaccine, respectively. Clinically detectable axillary lymphadenopathy was reported in 64 people (0.3%) after administration of the Moderna/BNT162b2 COVID-19 vaccines (Pfizer-BioNTech) (POLACK et al. 2020). Another study from the United States found a much higher incidence of clinically detectable lymphadenopathy after vaccination withCOVID-19 - 27 (3,3%) patients had clinically detected axillary lymphadenopathy after vaccination with BNT162b2 (Pfizer-BioNTech) (KADALI et al. 2021). The combined incidence of clinically detectable lymphadenopathy following COVID-19 vaccination was 91/22,532 (0.4%).

INCIDENCE OF PET-CT AXILLARY LYMPHADENOPATHY AFTER COVID-19 VACCINATION

Two studies evaluated the incidence of vaccine-associated hypermetabolic lymphadenopathy (VAHL) after vaccination against COVID-19. A retrospective review in Israel on 951 patients with FDG PET-CT performed after vaccination found that 332 (45.6%) patients had VAHL. 36.4% received a single dose of the vaccine while 53.9% received two doses. 17 (5.1%) patients who had hypermetabolic lymphadenopathy after PET-CT subsequently confirmed malignant nodal disease (KADALI et al. 2021). Differentiation between malignant lymphadenopathy and VAHL could not be made in 49 patients, and the nature of the hypermetabolic lymphadenopathy was considered inconclusive (KADALI et al. 2021). Most patients resolved axillary hypermetabolic lymphadenopathy within 20 days of vaccine administration.

Another retrospective study in 140 patients with Moderna/BNT162b2 vaccination (Pfizer-BioNTech) revealed that up to 75 (54%) patients had HAVLA. Of these, VAHL was most frequently observed after the Moderna vaccine - 36/50 (72%) compared to the Pfizer-BioNTech vaccine - 39/90 (43%). Similar to the Israel study, most patients resolved axillary hypermetabolic lymphadenopathy after 3 weeks of vaccine administration. The combined incidence of VAHL from the two studies was 407/1091 (37.3%).

CHARACTERISTICS OF AXILLARY LYMPHADENOPATHY AFTER COVID-19 VACCINATION

6 case series/studies reported 148 cases of enlarged axillary lymphadenopathy after administration of the COVID-19 vaccine (FAERMANN et al. 2021; ÖZÜTEMIZ et al. 2021; ; ; ; ;). Two studies were from Israel

(119 and 1 case respectively), two studies were from Italy (11 and 8 cases respectively) and two studies were from the United States (5 and 4 cases respectively).

Patients received BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), or AstraZeneca ChAdOx1 before axillary lymphadenopathy occurred. The mean size of axillary lymphadenopathy was 18.2 mm (range 16 – 21 mm). The median duration of vaccination until the occurrence of axillary lymphadenopathy was 6.9 days (range 2 – 18 days). In Faermann's study of 119 patients, enlarged axillary lymphadenopathy resolves in 4 to 5 weeks.

DISCUSSION

Since the COVID-19 vaccination program was launched worldwide in late 2020, vaccine-associated axillary and supraclavicular lymphadenopathy has become an emerging clinical problem. The current study focuses on axillary lymphadenopathy after vaccination. The reported rate of clinically detectable axillary lymphadenopathy was up to 0.4%, while the rate of incidentally detected lymph nodes on imaging was even more common. However, only up to 5% of HAVL have been proven malignant (6). Several clinical guidelines on the management of this condition have been published, but consensus has not yet been reached.

The decision-making process requires multidisciplinary communication and collaboration between radiologists, surgeons, medical oncologists and radiation oncologists. Thus, to avoid confusion, vaccination in the contralateral arm or at the site furthest from the index cancer must be encouraged; however, in patients who have already received COVID-19 vaccine in the arm ipsilateral to the site of the diagnosed breast cancer, management must be determined with caution, considering the index tumor information and risk assessment with the involvement of a multidisciplinary team. In patients who receive initial surgery treatment without neoadjuvant chemotherapy, changes occur in the cortical thickness range from the date of vaccination. and the location of the axillary lymphadenopathy on the image. may reflect COVID-19 vaccine-induced unilateral axillary lymphadenopathy rather than metastasis. However, this is not always the case; thus, tissue biopsy must be considered. At the same time, surgeons must be more precise and try to avoid unnecessary axillary lymph node dissection rather than sentinel node biopsy because of the diagnostic challenges posed by COVID-19 vaccination. In particular, in the presence of extensive level II and III nodal involvement, caution is required in the decision to perform axillary lymph node dissection, as shown in 2 of our cases. Currently, there are insufficient data on the duration of radiologically evident lymphadenopathy or adequate follow-up intervals. More research is needed to provide optimal management of COVID-19 vaccine-induced lymphadenopathy in breast cancer patients.

In addition to the probabilities, we have to consider the magnitude of the impact of a specific risk of delayed screening versus delayed vaccination. The impact of having COVID for a woman over 70 years of age with multiple medical morbidities would be much greater than for a 40 year old woman with no underlying health conditions. We must also better understand each person's individual risk profile – what risk capacity do they have and what is their individual risk tolerance? For one woman, having a follow-up exam for possible abnormal lymph nodes would be a minor event, but for another woman, it can cause extreme anxiety, compounded by the prospect of waiting 3 months for a follow-up ultrasound to confirm the diagnosis. resolution of lymphadenopathy.

Four classic strategies for managing risk include prevention, mitigation, transfer to third parties (insurance), and acceptance. When risks like getting COVID or breast cancer cannot be completely avoided, other strategies must be employed to mitigate the damage. Since 1990, the death rate from breast cancer in the United States has decreased by 41%, which has been attributed to advances in screening, treatment, and early detection. Pfizer-BioNTech and Moderna COVID-19 vaccines are more than 90% effective in preventing symptomatic disease. Women and their healthcare providers need to be educated with the latest information available to better manage these competing risks. Fortunately, in the US and Israel, an increasing percentage of women of screening age are now vaccinated for COVID 19, eliminating the need to delay the known benefit of breast cancer screening.

Vaccination against COVID-19 induces ipsilateral axillary lymphadenopathy that may lead to unnecessary lymph node biopsy with suspected breast cancer metastasis, which may be falsely assumed to be caused by reactive changes due to recent vaccination rather than cancer, based on results imaging or biopsy, delaying the diagnosis of cancer and therefore potentially having a detrimental effect on patient management. For patients with a high suspicion of breast cancer, it is important to educate the clinician and patients to receive the COVID-19 vaccination in the contralateral arm or at the site furthest from the cancer. Recognizing COVID-19 vaccine-induced unilateral axillary lymphadenopathy as a potential differential diagnosis and making efforts to investigate the patient's vaccination history are crucial to avoid overestimating the burden of axillary disease and making appropriate therapeutic recommendations.

FINAL CONSIDERATIONS

We suggest that the management of COVID-19 vaccine-associated lymphadenopathy be based on multidisciplinary decision, taking into account patient demographics, vaccination history, and radiological findings. Additional imaging and biopsies can lead to unnecessary health burdens. Proper arrangement of vaccination and imaging with respect to timing and laterality must be advocated to avoid patient confusion and anxiety.

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