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COVID-19 vaccine associated axillary lymphadenopathy – A systematic review

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ABSTRACT

Introduction: COVID-19 vaccines are commonly administered intramuscularly to the arm. Axillary lymphadenopathy has been reported as an adverse event after COVID-19 vaccination. In patients with breast cancers who received COVID-19 vaccination, presence of ipsilateral (or contralateral) lymphadenopathy poses diagnostic dilemma. This systematic review aims to evaluate the incidence and clinical characteristics of vaccine associated axillary lymphadenopathy.

Methods: The systematic review was conducted with accordance to the PRISMA statement. The search terms used were “Vaccine” OR “Vaccination” AND “Lymphadenopathy” OR “Lymph node” AND “Covid-19”.

Results: 31 studies or reports were identified using the predefined keywords from the systematic review protocol. After excluding irrelevant papers (such as guidelines, reviews, opinions and commentaries), 10 studies or reports were included in the review. Pooled incidence of clinically detectable lymphadenopathy after COVID-19 vaccination was 91/22,532 (0.4%). Mean size of the vaccine associated axillary lymphadenopathy was 18.2 mm (Range 16 – 21 mm). Mean duration from vaccination to occurrence of axillary lymphadenopathy was 6.9 days (Range 2 – 18 days). In a study on 119 patients, enlarged axillary lymphadenopathy resolves in 4 to 5 weeks.

Conclusion: Vaccine associated axillary lymphadenopathy is not uncommon. Management of it is based on multidisciplinary decision with patient demographics, vaccination history and radiological finding being taken into account. Additional imaging and biopsy may lead to unnecessary healthcare burden. Proper arrangement of vaccination and imaging regarding timing and laterality should be advocated to avoid confusion and patient anxiety.

Main text

Introduction

COVID-19 pandemic has resulted in more than 5.7 million deaths worldwide after the initial outbreak in Wuhan China in December 2019 [1, 2]. In December 2020, United Kingdom was amongst the first nations to roll out a COVID-19 vaccination programme [3]. Soon afterwards, COVID-19 vaccination programme was then implemented in many other countries. COVID-19 vaccination was associated with significant reduction in symptomatic covid-19 in older adults, and with further protection against severe disease [4].

COVID-19 vaccines are commonly administered intramuscularly to the arm. Axillary lymphadenopathy has been reported as an adverse event after COVID-19 vaccination. The enlarged axillary lymph node, apart from being symptomatic in some patients, in patients with breast cancers who received COVID-19 vaccination, presence of ipsilateral (or contralateral) lymphadenopathy poses diagnostic dilemma – clinicians were to decide whether or not to proceed with further lymph node biopsy. Fine needle aspiration (FNAC), which is commonly performed in newly diagnosed breast cancer patients with axillary lymphadenopathy, can be associated in enormous increase in public healthcare burden.

This systematic review aims to evaluate the best available evidence of axillary lymphadenopathy after COVID-19 vaccination.

Material and methods

The systematic review was conducted with accordance to the PRISMA statement and current methodological literature. As this was a systematic review / meta-analysis, institutional review board approval was not required. Please refer to Fig. 1 for PRISMA flowchart.

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Data sources and eligibility

PubMed, Cochrane and EMBASE databases were searched for relevant English language articles up till 12th September 2021.

Search terms

The search terms used were “Vaccine” OR “Vaccination” AND “Lymphadenopathy” OR “Lymph node” AND “Covid-19”. Abstracts were screened by 2 reviewers independently for relevance and level of evidence. Articles from selected abstracts were retrieved.

Study selection

Review articles, conference abstracts, non-research articles (such as commentaries, opinions and guidelines) were excluded. However, references from review articles were checked for cross-reference. 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 most complete reporting of outcomes of interest were included to avoid data duplication. Data extraction was performed independently by 2 investigators and results were combined for analysis.

Results

31 studies or reports were identified using the predefined keywords from the systematic review protocol. After excluding irrelevant papers (such as guidelines, reviews, opinions and commentaries), 10 studies or reports were included in the review [5, 6, 7, 8, 9, 10, 11, 12, 13, 14].

Incidence of clinical axillary lymphadenopathy after COVID-19 vaccination (Table 1)

Two large studies evaluated adverse effect with axillary lymphadenopathy after COVID-19 vaccination. In a large international trial by Polack, et al. evaluating 21,729 subjects. Axillary swelling or pain occurred in 11% and 16% after 1st and 2nd dose of COVID-19 vaccine respectively. Clinically detectable axillary lymphadenopathy was reported in 64 people (0.3%) after administration of Moderna / BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines [5]. Another study from the United States found much higher incidence of clinically detectable lymphadenopathy after COVID-19 vaccination - 27 (3.3%) patients presented with clinically detected axillary lymphadenopathy after BNT162b2 (Pfizer-BioNTech) vaccination [6]. Pooled incidence of clinically detectable lymphadenopathy after COVID-19 vaccination was 91/22,532 (0.4%).

Records included in review
N = 10

Fig. 1. PRISMA flow diagram.
Incidence of PET-CT axillary lymphadenopathy after COVID-19 vaccination (Table 2)

Two studies evaluated the incidence of vaccine associated hypermetabolic lymphadenopathy (VAHL) after COVID-19 vaccination. A retrospective review in Israel on 951 patients with FDG PET-CT done after vaccination, found that 332 (45.6%) patients had VAHL. 36.4% received single dose of vaccine while 53.9% received two doses. 17 (5.1%) patients who had hypermetabolic lymphadenopathy after PET-CT later confirmed malignant nodal disease [6]. Differentiation between malignant lymphadenopathy and VAHL could not be made in 49 patients, and the nature of the hypermetabolic lymphadenopathy was considered nonconclusive [6]. Most patients had resolved axillary hypermetabolic lymphadenopathy after 20 days of vaccine administration.

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

Characteristics of axillary lymphadenopathy after COVID-19 vaccination (Table 2)

6 studies / case series reported 148 cases of enlarged axillary lymphadenopathy after administration of COVID-19 vaccine [9-14]. Two studies were from Israel (119 and 1 cases 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 either BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna) or AstraZeneca ChAdOx1 prior to the occurrence of axillary lymphadenopathy. Mean size of the axillary lymphadenopathy was 18.2 mm (Range 16 – 21 mm). Mean duration from vaccination to occurrence of axillary lymphadenopathy was 6.9 days (Range 2 – 18 days). In Faermann’s study on 119 patients, enlarged axillary lymphadenopathy resolves in 4 to 5 weeks time.

Discussion

Since the COVID-19 vaccination programme being 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 VAHL were proven malignant [6]. Various clinical guidelines regarding management of this condition were published but consensus was yet to be reached.

To define vaccine-related lymphadenopathy, temporal correlation was the key determining factor. Two retrospective studies reported majority of VAHL resolved in 3-weeks time with 29–38% of remaining study population having VAHL at 4th week after vaccination. Faermann et al. demonstrated the cortical thickness of enlarged lymph nodes resolved upon reassessment scan at 4-5 weeks later. In concordance with the results from these observational studies, a cut-off duration of 6 weeks was adopted in several clinical guidelines. National Institute for Health and Care Excellence (NICE) guideline advocated a “watch and wait” approach for enlarged axillary nodes with referral to specialist if persistent at 6 weeks. The Society of Breast Imaging (SBI) and the Canadian Society of Breast Imaging also endorsed the recommendation by suggesting screening imagings to be rescheduled prior to first COVID-19 vaccination or 4-6 weeks after the second dose.

Laterality was another important factor when vaccine-related effect was considered. As more than 90% of VAHL occurred at ipsilateral axillary region [7], while only up to 10% of VAHL occurred at contralateral axilla; A standard patient intake form regarding timing and side of vaccination should be obtained upon radiological examinations as recommended by the SBI. In case vaccination history could not be retrieved, synchronous finding of hypermetabolic ipsilateral deltoid muscle is an important supportive evidence of recent vaccination. In order to avoid confusion in patient with history of breast cancer, the American College of Radiology encouraged vaccination in the contralateral arm or thigh.

VAHL poses diagnostic dilemma in patients with breast cancers. Interpretation of axillary lymphadenopathy after vaccination required individualized decision regarding patient’s overall risk profile for breast cancer. In asymptomatic population with isolated unilateral axillary lymphadenopathy found on surveillance imaging after recent vaccination (within 6 weeks), both the American College of Radiology and the Canadian group suggested no further imaging is indicated for this benign finding (BI-RADS category 2). Further diagnostic work-up is only indicated if clinical concern persists for 6 weeks after final vaccination dose.

Ultrasoundographic morphology of the enlarged axillary lymph node should also be taken into account. Isolated enlarged avascular axillary lymphadenopathy with preserved fatty hilum and normal cortex thickness can be considered non-suspicious.

However, the SBI recommendation was slightly different as a short-term follow-up examination was suggested in 4–12 weeks following the second vaccine dose (BI-RADS category 3). In the setting of suspicious finding on breast examination (BI-RADS category 4 or 5), biopsy should be performed without delay regardless of vaccination status. On the other hand, in patients with staging imaging performed for peri-treatment assessment, management is at the discretion of the attending breast surgeon, oncologist and radiologist. In newly diagnosed breast cancer patients who have not been vaccinated, they should be advised against vaccination prior to PETCT scan. The same applies to breast cancer patients on post-treatment surveillance.

Based on the best available evidence from the literature and recommendations from SBI, five clinic-radiological factors were identified to be crucial in differentiating suspicious from non-suspicious lymphadenopathy – namely (i) Time from vaccination (ii) Laterality in relation to site of vaccination (iii) Indication for the imaging (iv) Associated radiological findings and (v) BI-RADS grading. (Table 3).

Conclusion

We suggested that management of COVID-19 vaccine associated lymphadenopathy is based on multidisciplinary decision with patient demographics, vaccination history and radiological finding being taken into account. Additional imaging and biopsy may lead to unnecessary healthcare burden. Proper arrangement of vaccination and imaging regarding timing and laterality should be advocated to avoid confusion and patient anxiety.

Author contribution statement

Dr. Michael Co, the first author, is responsible for data collection, statistical analysis, manuscript preparation and editing. Dr. Patrick Wong, the co-author, is responsible for data collection and manuscript preparation. Prof. Ava Kwong, corresponding author is responsible for the conceptual design and final editing of the manuscript.

Declaration of Competing Interest

Dr. Michael Co, the first author, serves as an unpaid International Review Board Advisor of the journal. He is not involved in the editorial or peer-review process of this article.
Recommendation of management of lymphadenopathy after COVID-19 vaccination.

| Author                  | Publication year | Study origin | Sample size | Incidence | Vaccine                                      | Detection modality |
|-------------------------|------------------|--------------|-------------|-----------|----------------------------------------------|-------------------|
| Poladi RAJ              | 2021             | International | 21,729      | 64 (0.3%) | BNT162b2 (Pfizer-BioNTech)                   | Clinical          |
| Cohen D                 | 2021             | Israel       | 803         | 27 (3.4%) | BNT162b2 (Pfizer-BioNTech)                   | Clinical          |
| Skawran S               | 2021             | Switzerland  | 2,232       | 91 (40.4%)| BNT162b2 (Pfizer-BioNTech)                   | PETCT             |
|                         |                  |              | 951         | 332       | BNT162b2 (Pfizer-BioNTech)                   | PETCT             |
|                         |                  |              | 140         | 75 (53.6%)| BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) | PETCT             |

Overall 148 Mean 18.2

Recommendation Clinical follow-up Repeat focused axillary USG

Radiological finding Isolated lymphadenopathy

Collaborative uptake

Normal morphology

Conclusion BIRADS-2

Recommendation Clinical follow-up Repeat focused axillary USG 6 weeks after 2nd dose FNAC if persistent lymphadenopathy (BIRADS-4)

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2022.100546.