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Regional lymphadenopathy following COVID-19 vaccination:

considerations for primary care management

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Regional lymphadenopathy has been rarely reported following the administration of vaccinations for tuberculosis, influenza, and human papillomavirus (≤1–2/100 000 vaccines).[1,2] In the first months of 2021, there seems to have been an increase in the number of women being referred to breast units from primary care and other specialties with clinically enlarged axillary/supraclavicular nodes or with image-detected lymphadenopathy. This has been reported anecdotally across the UK as well as in other European countries and in the US. Recent radiology reports, mainly from the US, have identified a probable link between such lymphadenopathies and COVID-19 vaccination administered up to a few weeks earlier.[3–5] As the national vaccine programme progresses, this article considers the implications of this still little-known side effect on vaccine delivery and management of such patients, particularly those with previous history of cancer.

WHAT IS THE CURRENT EVIDENCE?

There are currently three different COVID-19 vaccines approved for emergency use in the UK: the Pfizer-BioNTech, the AstraZeneca, and the Moderna vaccine. Adverse events reported in the randomised controlled trials of these vaccines include data on lymphadenopathy.[6–8] For the Moderna vaccine, whose first doses will be available in the UK during the spring, the reported rate of ipsilateral axillary lymphadenopathy or tenderness (symptoms were not reported separately) was up to 11.6% and 16.0% after the first and second dose, respectively. A small number of cases of neck lymphadenopathy were also reported.[6] For the other two vaccines, the incidence of ipsilateral axillary lymphadenopathy is reported to be lower (<1%).[7,8] However, it is worth noting that in these trials, unlike the Moderna one, lymphadenopathy was only reported as an unsolicited adverse event and hence the true incidence rate is likely to be higher.

The recipients of both the Pfizer-BioNTech and Moderna COVID-19 vaccine reported the onset of lymphadenopathy within 2–4 days after vaccination; however, the average duration of adenopathy was approximately 10 days in those vaccinated with the Pfizer-BioNTech vaccine, compared with an average duration of 1–2 days with the Moderna COVID-19 vaccine.[6,7] These data from the trials, however, do not seem to correlate with the real-world data from the current authors' clinical experience and that of others, where patients with persistent lymphadenopathy have been seen as long as 3–5 weeks after vaccination.[3,4,9] At present, no data are available on how long such lymphadenopathy will persist on imaging or about appropriate follow-up intervals, with some authors recommending a targeted ultrasound scan 4–12 weeks after the patient's scheduled second vaccination dose to ensure resolution.[3,10]

CONSIDERATIONS FOR PRIMARY CARE MANAGEMENT

Lymphadenopathy, defined as an abnormality in the size or consistency of lymph nodes, is a common finding in primary care practice and can be typically explained by an identifiable regional injury or infection. Among the serious illnesses that can present with lymphadenopathy, perhaps the most concerning to the patient and physician alike is the possibility of underlying malignancy. The prevalence of malignancy between primary care patients presenting with lymphadenopathy has been estimated to be around 1.1%, but this percentage increases with advancing age and can be as high as 4.0% in patients aged >40 years.[11]

Most axillary lymphadenopathy is of non-specific or reactive aetiology, in relation with infections or injuries of the upper extremities. Malignancy can be diagnosed in ≤20% of patients with persistent, unexplained axillary lymphadenopathy and, of those, the cancer originates from the breast in >50% of cases.[12] Hodgkin's and non-Hodgkin's lymphomas can also be initially discovered by the patient as axillary adenopathy.[11] Supraclavicular lymphadenopathy is more frequently associated with malignancy as it can also

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be associated with intra-abdominal and thoracic neoplasms. Overall, the prevalence of malignancy in this presentation is unknown, but rates of 34–50% have been reported and hence a prompt evaluation is recommended.[11]

With an increasing proportion of the population being vaccinated against COVID-19, it is anticipated that a growing number of patients will present with vaccine-related unilateral axillary and/or supraclavicular lymphadenopathy (palpable or image detected). The current National Institute for Health and Care Excellence suspected-cancer guidelines recommend a suspected-cancer 2-week referral for *unexplained* axillary lymphadenopathy in those aged >30 years.[13] For patients with no history of breast cancer and a normal breast examination who have ipsilateral lymphadenopathy occurring within the first week after COVID-19 vaccination, a 'watchful wait' approach may be appropriate with further examination up to 2 weeks later and referral to secondary care for those with non-resolving lymphadenopathy.

However, for patients with current or previous history of breast cancer, where a new regional adenopathy may represent the first sign of recurrence, an urgent referral to the breast clinic would be advisable. To prevent any unnecessary anxiety to those patients, and potentially reduce the number of diagnostic investigations and specialist referrals, it may be preferable to administer the vaccination to the arm opposite to the cancer site. Should those patients develop lymphadenopathy after vaccination, this could be managed with the same 'watchful wait' approach used in non-cancer patients, as contralateral axillary metastasis is an infrequent clinical condition with a reported incidence of between 1.9% and 6.0%.[14] The same approach could be reasonably applied to patients with history of arm/upper trunk melanoma or head and neck malignancy. The information leaflet currently provided to patients before vaccination should be updated to include this advice.

SECONDARY CARE MANAGEMENT PATHWAY

Patients referred to the breast clinic with palpable regional lymphadenopathy will receive a breast examination and an ultrasound scan. A mammogram is also routinely performed in women aged ≥40 years and can also be offered to those aged 35–39 years, at the radiologist's discretion. Axillary metastatic carcinoma without detection of a primary breast lesion is rare, reported as occurring in only 0.3–1.0% of all breast cancer patients.[12] So, in patients with axillary/supraclavicular lymphadenopathy, normal breast imaging, and a history of recent COVID-19 vaccination in the ipsilateral arm, short-term follow-up is generally preferred to a potentially unnecessary and costly axillary lymph node biopsy. In patients with family history of breast cancer or when another malignant cause (that is, lymphoma) is suspected, lymph node biopsy would still be preferable.

The current recommendation of repeating imaging after 4–12 weeks from the second vaccine dose,[10] which has been adopted in the US and many EU countries, may not be appropriate for UK clinical practice because of the UK government strategy of delaying the second vaccine dose to 12 weeks. This leaves clinicians with a dilemma: on the one hand, such a long follow-up interval could lead to a significant diagnostic delay but, on the other hand, a shorter follow-up appointment may fall just after the second vaccine dose administration, potentially misleading the clinician by reversing any improvement of the lymphadenopathy. The appropriate management strategy (that is, early biopsy versus follow-up) will have to be determined on a case-by-case basis, according to the degree of clinical concern. Box 1 presents an example of one patient who was managed in the current authors' unit.

Box 1. Case description

A 38-year-old woman, with no personal or family history of breast cancer, presented with a 4 weeks' history of a palpable lump inferior to the left clavicle, which was first noticed approximately 1 week after receiving the first dose of the Pfizer-BioNTech COVID-19 vaccine in the left arm. Ultrasound of the left axilla and supraclavicular fossa revealed normal appearing axillary lymph nodes and a couple of lymph nodes up to 8 m in size in the area of interest (see Supplementary Figure S1), with appearances of benign reactive nodes. A bilateral mammogram showed no abnormalities. As the patient was due to have her second vaccine dose in 5 weeks' time, she was advised to return for a 10 weeks' follow-up ultrasound scan and clinical examination to ensure resolution.

Provenance

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Patient consent

The patient gave consent for publication of this article.

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