Cervical lymphadenopathy following COVID-19 vaccine: Clinical characteristics and implications for head and neck cancer services

Ahmad K. Abou-Foul[1], Elizabeth Ross[1], Mahmoud Abou-Foul[2], and Ajith P George[1,3]

[1]Department of Otolaryngology-Head and Neck surgery, University Hospitals of North Midlands NHS Trust, Royal Stoke University Hospital
[2]-Radiology Department, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Trust
[3]School of Medicine, Keele University

April 16, 2021

Cervical lymphadenopathy following COVID-19 vaccine: Clinical characteristics and implications for head and neck cancer services

Running title: COVID-19 vaccine-associated lymphadenopathy

Ahmad K. Abou-Foul[1]*, Elizabeth Ross[1], Mahmoud Abou-Foul[2], Ajith P. George[1,3]

Affiliations:

1- Department of Otolaryngology-Head and Neck surgery, University Hospitals of North Midlands NHS Trust, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom.

2- Radiology Department, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Trust, Queen Victoria Road, Newcastle upon Tyne, United Kingdom.

3- School of Medicine, Keele University, Stoke-on-Trent, United Kingdom.

***Correspondent author**

Correspondent author's address: Department of Otolaryngology-Head and Neck surgery, Royal Stoke University Hospital, Newcastle Rd, Stoke-on-Trent, ST4 6QG, United Kingdom. Email: ahmadkamal.abou-foul@nhs.net

Authors' details:

1-Ahmad K. Abou-Foul: Specialist registrar, department of Otolaryngology-Head and Neck surgery, University Hospitals of North Midlands NHS Trust, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom. **ORCID ID:** 0000-0002-5321-5465

2-Elizabeth Ross: Consultant, department of Otolaryngology-Head and Neck surgery, University Hospitals of North Midlands NHS Trust, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom.**ORCID ID:** 0000-0002-6310-7046

3- Mahmoud Abou-Foul: Specialist registrar, radiology Department, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Trust, Queen Victoria Road, Newcastle upon Tyne, United Kingdom.**ORCID ID:** 0000-0002-6272-5037

4-Ajith P. George : Consultant, department of Otolaryngology-Head and Neck surgery, University Hospitals of North Midlands NHS Trust, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom; and Senior clinical lecturer, school of Medicine, Keele University, Stoke-on-Trent, United Kingdom. **ORCID ID:**0000-0002-5132-0915

Acknowledgements:

Contributors: AA-F, LR, and APG conceived and designed the study. AA-F and LR contributed to data collection and management. AA-F, MA-F contributed to the analysis and interpretation of the data, and the manuscript preparation. All authors reviewed and approved the final version of the manuscript. AA-F led the study and is the guarantor and the corresponding author. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: Nothing to declare

Acknowledgments: Nothing to acknowledge

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no external funding support. APG reports being the managing director for Endoscope-I company. No other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This was a retrospective observational study, and ethical approval was waived by our institution.

Data sharing: The data that support the findings of this study are available on request from the corresponding author.

Cervical lymphadenopathy following COVID-19 vaccine: Clinical characteristics and implications for head and neck cancer services

Abstract

Objectives: Lower neck lymphadenopathy usually harbour malignancy in around 75% of cases, and should warrant an urgent referral to the head and neck (H&N) cancer services. The presented work is the first study to report on the incidence, clinical course, and imaging features of cervical CVAL (cCVAL), with special emphasis on the implications for the H&N cancer services.

Design: Retrospective cohort study.

Setting: Leading UK NHS trust providing tertiary H&N cancer services.

Participants: Patients referred to our H&N cancer clinics with cCVAL between 16 December 2020 and 12 March 2021 (12 weeks). We defined cCVAL as any unilateral and lower cervical lymphadenopathy, noticed within two weeks of COVID-19 vaccination in the ipsilateral deltoid muscle.

Main outcome measures: The proportion of patients referred with cCVAL. Secondary outcomes included the clinical and imaging characteristics and follow-up measures.

Results: From 88 patients referred with cervical lymphadenopathy, 13 patients (14.8%) had cCVAL. Pain was only reported in six patients (46.2%), but swelling was noticed by all patients within a median of four days. The average diameter of CVALs on ultrasound scans was 5.5 $\pm$ 1.4 mm, and five patients (38.5%) had abnormally looking rounded node or increased vascularity on colour doppler. Seven patients (53.9%) reported full resolution of their lymphadenopathy within an average of 3.1 $\pm$ 2.3 weeks.

Conclusion: Reactive cervical CVAL can mimic malignant lymphadenopathy, and therefore might prove challenging to correctly diagnose and manage. Over the next few months, primary care and H&N cancer services should be prepared for a potentially significant increase in referrals.

Keywords: COVID-19 vaccine, lymphadenopathy, Head and Neck Neoplasms, neck ultrasonography, Head and neck malignancy

Key points

-Reactive cervical COVID-19 vaccine-associated lymphadenopathy (CVAL) can mimic malignant lymphadenopathy with abnormal features on imaging.

-Cervical CVAL might create a diagnostic and management dilemma for the head and neck cancer services.

-Cervical CVAL might fully resolve within a period of 3-6 weeks in more than half of the patients, and therefore referrals should be rationalised.

- Over the next few months, primary care and H&N cancer services will potentially encounter a rise in vaccine-related reactive lymphadenopathy referrals.

- COVID-19 vaccination history must be included in all referrals with head and neck lymphadenopathy.

Manuscript: (Word count: 2500)

Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 virus has resulted in millions of deaths and strained health-care systems all around the globe. Huge collaborative efforts led to the development and deployment of successful vaccinations that have shown to reduce the risk of severe infections and mortality.[1-3] In the United Kingdom (UK), following a rigorous review of safety and efficacy data, the Pfizer/BioNTech was the first COVID-19 vaccine to be approved by the Medicines and Healthcare products Regulatory Agency (MHRA), followed by the Oxford/AstraZeneca and the Moderna vaccines.[1-3] The rollout of COVID-19 vaccination in the UK, and in many other countries, prioritized those most likely to die from the disease especially older care-homes residents and immunocompromised adults, as well as protected health and social care workers.

Similar to other vaccines, local adverse drug reactions (ADRs) like shoulder pain and erythema, in addition to mild systemic symptoms like fatigue, myalgia and headache are commonly reported after COVID-19 vaccination.[3-6] However, data from recent clinical trials and early post-marketing clinical experience have suggested a higher incidence of local lymphadenopathy reactions in the axilla and neck.[3,5-7] With the widespread rollout of COVID-19 vaccination programmes, lymphadenopathy have created a diagnostic and therapeutic dilemma for cancer screening and diagnosis services.[8-10] For this reason, the United States Society of Breast Imaging, the Canadian Society of Breast Imaging, the Canadian Association of Radiologists, and a multidisciplinary team (MDT) of experts from three leading cancer centres in the United States have all recently released emergency recommendations for the management of COVID-19 vaccine-associated lymphadenopathy (CVAL).[7,10,11]

Cases of ipsilateral lymphadenopathy in the lower neck and supraclavicular region following COVID-19 vaccinations are quickly emerging in the international literature, and certainly being increasingly referred to the healthcare services for advice and management.[12-14] As lower neck lymphadenopathy usually harbours malignancy in around 75% of cases, the UK National Institute for Health and Care Excellence (NICE) recommended fast-track referral of unexplained or persistent cases through a dedicated pathway for suspected H&N cancer.[15,16] The differential diagnosis of lymphadenopathy in the lower neck is broad, but it is imperative to exclude pathologies like head and neck (H&N) malignancy, lymphoma, and metastatic lung or cutaneous cancers.[10,15] However, as vaccine deployment is still in its early stages, no data is yet available regarding the presentation, clinical course, or imaging characteristics of cervical COVID-19 vaccine-associated lymphadenopathy (CVAL) to guide the decision-making process in such patients. The presented work is the first study to report on the characteristics and clinical course of cervical lymphadenopathy following COVID-19 vaccination, with special emphasis on potential implications for the head and neck cancer services.

Methods

Study design and setting

We conducted a retrospective cohort study of individuals referred to our fast-track suspected H&N cancer clinics. Our hospital is a leading NHS trust providing tertiary H&N cancer services, with a dedicated regional MDT. The study period covered 12 weeks between 16 December 2020 to 12 March 2021. Data was collected from the fast-track clinic referral forms and the electronic records.

Study population

All patients referred to our fast-track H&N cancer clinics during the study period were initially screened for their COVID-19 vaccination status, and the reason for referral. All patients with cervical CVAL (cCVAL) were included. We defined cCVAL as any unilateral and lower cervical lymphadenopathy (level IV or V), first noticed within two weeks of COVID-19 vaccine injection in the ipsilateral deltoid muscle. All patients with bilateral, upper cervical, or known previous history of cervical lymphadenopathy were excluded. We also excluded patients if they received any other injection in the ipsilateral deltoid muscle within four weeks before the onset of lymphadenopathy.

Main outcome measures

Demographic data regarding age and gender of included patients were collected. The main outcome measure collected was the number of patients referred with cCVAL. Secondary outcomes included the clinical and imaging characteristics and follow-up measures.

Reporting guidelines and ethical considerations

Our study design and reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.[17] Due to the retrospective nature of the study, ethical approval was waived by our institution.

Statistical techniques

Continuous variables with normal distribution were summarised using the means and standard deviations (SD), otherwise we used medians and interquartile ranges (IQR). Independent samples t-test was used to evaluate association between groups, and a p -value [?] 0.05 was considered statistically significant. All analysis was performed using SPSS version 26.0 (IBM Corporation, Armonk, NY).

Results

Patients' characteristics

From 404 patients referred to our fast-track H&N clinics during the study period, 88 patients had cervical lymphadenopathy. A total of 13 patients (14.8%) had cCVAL and were consecutively included in the study (**Figure 1**). The mean age was 54.8 +- 16.1 years, and interestingly most of the patients were females (N=11, 84.6%),**Table 1.** All patients had the Pfizer/BioNTech vaccine, and the majority had the injection in the left deltoid (N=12, 92.3%). The study period mostly covered the early phases of vaccination rollout in the UK, and most patients (N=12) had only one dose by the time of presentation. All patients experienced a feeling of a lump in the ipsilateral neck, but pain was only reported in six patients (46.2%), **Table 1 and 2.** The swelling was first noticed by patients within a median of four days (IQR 2-7) from vaccination, and in seven patients (53.9%) a referral was made to the fast-track clinic within three weeks from the onset of symptoms (**Table 2**).

Lymphadenopathy features on neck ultrasound scans (USS)

All patients had USS, with median interval between the swelling onset and the scan was 25 days (IQR 10-49). **Table 3** summarises the USS characteristics of the examined lymph nodes (LNs). Targeted USS confirmed the presence of one or more LNs, all in level IV or V of the neck. The average short axis diameter (SAD) of the most prominent nodes was 5.5 +- 1.4 mm, but five patients (38.5%) had more rounded nodes with short axis: long axis ratio (S:L) > 0.5. Scans performed [?]4 weeks from swelling onset showed significantly larger nodes (6.5 +- 1.4 mm) compared to scans performed >4 weeks (4.8 +- 0.8 mm),P =0.03. The overall scan impression was recorded as benign reactive lymphadenopathy in all patients, but two cases had increased vascularity on colour doppler (**Figure 2, Table 3**). Moreover, two patients had mildly hypoechoic LNs but none had fatty hilar abnormality. Two patients had fine-needle aspiration biopsy, but cytology demonstrated features of benign reactive lymphadenopathy. Moreover, two patients had follow-up USS that showed reduction in CVAL size.

Lymphadenopathy outcomes

The outcomes of lymphadenopathy were subjectively reported by patients during virtual follow-up (**Table 2**). Seven patients (53.9%) reported full resolution (FR) of their palpable swelling within an average of 3.1 +- 2.3 weeks from the onset of their symptoms. Five patients (38.5%) reported partial reduction (PR) in the size of their palpable lumps over an average period of 8.4 +- 3.1 weeks (**Figure 1**). When compared to the FR group, the PR group interestingly presented to their general practitioner significantly later (35.6 *vs.* 9.0 days, P = **0.001**), and had significantly smaller LNs on USS (4.6 *vs.* 6.4 mm, P =**0.024**), **Table 4.**However, neither the patients' age, nor the vaccination to lymphadenopathy interval were found to be significantly Impacting the clinical outcome.

Discussion

Post-vaccination lymphadenitis is an uncommon phenomenon that can be triggered by intramuscular vaccine injections in the deltoid muscle. It has been previously reported in adults following many viral vaccinations especially for human papillomavirus (HPV)[18] and H1N1 influenza[19]. More recently, cases with CVAL have been described in reports from the United States, Spain, Israel and the UK.[8,12-14,20-22]

The available evidence has suggested that mRNA-based vaccines are likely more immunogenic than standard vaccines, and hence show higher incidence of CVAL.[7,21,22] In clinical trials on the Pfizer/BioNTech mRNA vaccine, lymphadenopathy was only reported as an unsolicited ADR, with incidence in the vaccine group as high as ten times that in the placebo group (0.3% and 0.03% respectively).[1] As a solicited ADR, axillary lymphadenopathy was the second most frequently reported reaction in the Moderna vaccine trials, with incidence of 10.2% and 14% after the first and second doses respectively.[3] Reporting lymphadenopathy in these trials was only based on physical examination, and the true incidence rate was likely much higher.[1,3,7] Interestingly, clinical trials on the Oxford/AstraZeneca adenovirus-vectored vaccine reported a lower incidence of lymphadenopathy in the vaccination group (0.3%) compared to the placebo group (0.4%).[2] Our results show that all patients referred to us with cervical CVAL (cCVAL) had the Pfizer/BioNTech vaccine, and none had the Oxford/AstraZeneca vaccine despite it accounting to almost 53% of the total UK vaccine doses given during our study period.[4] Moreover, real-life data from the MHRA (reported using the yellow card scheme for ADRs) has shown that the Pfizer/BioNTech vaccine had almost double the number of reports for lymphatic system disorders compared to the Oxford/AstraZeneca vaccine (22.4 *vs* . 11.7 per 100,000 doses given respectively).[4-6]

Most of the COVID-19 vaccinations during our study period were nationally prioritised to people [?] 65 years old. The mean age of patients with cCVAL in our study was 54.8 years, with only three patients were 65 years or older. Data from the Pfizer/BioNTech trials also demonstrated higher incidence and severity of ADRs in younger participants, with lymphadenopathy reported five times more common in the 16-55 years age group (0.5%) compared to the >55 years age group (0.1%).[1] Similarly, CVAL was more frequently reported in younger individuals (18-64 years) following the first and second doses of the Moderna vaccine

(11.6% and 16% respectively), compared to individuals aged [?]65 years (6.1% and 8.4% respectively).[3] In a case series of 20 female healthcare workers with cCVAL, Fernandez-Prada et al. [12] reported that 75% of patients (N=15) had full resolution within 16 days from symptoms onset. In our study, full clinical resolution was reported within an average of 3.1 weeks from symptoms onset in more than half of our cohort, and partial improvement within an average of 8.4 weeks in 40% of patients. Interestingly, half of our patients were directly referred to our fast-track H&N cancer clinics within three weeks of symptoms onset.

USS features of COVID-19 vaccine-associated lymphadenopathy

The role of ultrasonography in the assessment of supraclavicular (level IV/V) lymphadenopathy is well established. All our patients had USS within a median of 8 days from referral, and a median of 25 days from onset of symptoms. There was a significant inverse association between the timing of the scan and the size of the imaged nodes, possibly highlighting a time-dependant reactive nature of the nodes. While the overall impression was of benign nature, some nodes in our cohort showed abnormal features. Large nodes with increased vascularity and a high S:L ratio (more rounded) usually indicate abnormality.[23]Ying et al. recommended that the optimum cut-off value of SAD (S:L ratio) in the lower neck should be 3-5 mm (0.4-0.5), with a high specificty and moderate sensitivity.[23] Our data demonstrated that around half of our patients had nodes >5 mm and 40% had S:L ratio >0.5. These findings are in line with previous reports that demonstrated that CVALs may show abnormal morphology, and can appear enlarged, rounded, hypoechoeic and with loss of echogenic fatty hila.[8,9,13,20]

Implications for the Head and neck cancer services

The impact of CVAL on clinical services and patients should not be underestimated. In the 12-weeks period of our study, cCVAL cases accounted for around 15% of all fast-tracked lymphadenopathy referrals. With the ongoing expansion of the vaccination programme in the UK to cover younger individuals and more second dose vaccinations, as well as the upcoming rollout the Moderna mRNA vaccine, we predict that the number of referrals will increase exponentially.[14,21]

Moreover, awareness of clinical features and course of CVAL is also crucial for the radiologists involved in cancer diagnosis and follow-up, and it should nowadays be recognised in the differential diagnosis of cervical or axillary lymphadenopathy.[9,10]Lymphadenopathy detected clinically or in routine surveillance scans might create a diagnostic and management dilemma for oncology patients.[10,21] Not only that CVALs could exhibit abnormal features on ultrasound scans, but they are also shown to be metabolically active on positron emission tomographic (PET) images, with intensities similar to malignant lymphadenopathy.[8-10,21] A recent study by Cohen et al. on PET-positive supraclavicular and axillary lymphadenopathy in 728 oncology patients, following the Pfizer/BioNTech vaccine, the incidence of overall and supraclavicular CVAL was 36.5% and 8% respectively, with supraclavicular CVAL being more commonly encountered after the second dose (9.1%) compared to the first dose (5.5%).[21]

Recommendations for appropriate management of CVAL should aim to strike a balance between avoiding delayed cancer diagnoses, and minimizing patient harm by invasive biopsies, unnecessary scans, and heightened anxiety.[8,10,22,24] All requests for imaging in the H&N and breast regions, and referrals to the fast-track cancer services, should include full information about COVID-19 vaccine status, especially the dates, the site, the side, and the type of the vaccine. For patients with pre-existing history of H&N malignancy, administration of the vaccine on the contra-lateral side is recommended. Recently published recommendations from institutions in north America have advised timing H&N and breast imaging for before, or 4-6 weeks after COVID-19 vaccination, and recommended considering a follow-up scan 4-12 weeks after the second dose of the vaccine.[7,10,11,24] Moreover, evidence from our current study and previously published data demonstrated that a good proportion of cervical CVAL usually fully resolve within 3-6 weeks.[12,13,21] Therefore, it is not unreasonable for primary care physicians to rationalise referrals to specialist cancer clinics, and to prioritise cases with persistent lymphadenopathy beyond 3-6 weeks, or patients with other concerning features of malignancy.[10] Until more data becomes available, H&N cancer MDTs should carefully advise against

delaying vaccine administration, and should weigh the risks and the benefits of timing any H&N imaging to before or 4-6 weeks after the COVID-19 vaccination.

limitations and strengths of the study

Our results are limited by the inherent weakness in retrospectively collected data. We adapted a strict definition for cCVAL and excluded cases with upper or bilateral neck nodes, and cases with nodes first noticed >14 days following vaccination. We believe this definition increased our specificity and confidence in our diagnosis but possibly have reduced the sensitivity and missed some cases presented in atypical ways. In our cohort, lymphadenopathy was spatially and temporally associated with COVID-19 vaccinations, however, it was difficult to ascertain a causality link. Our results could be useful and universally generalisable to members of cancer MDTs, including surgeons, radiologists, oncologists, and haematologists, in addition to primary care physicians, vaccinators, and the general public.

Conclusion

The widespread rollout of COVID-19 vaccination has important implications for clinicians and patients. Over the next few months, primary care and H&N cancer services will potentially encounter a rise in vaccine-related reactive lymphadenopathy referrals. Therefore, COVID-19 vaccination history must be included in all referrals. Reactive cervical CVAL can mimic malignant lymphadenopathy, and therefore might become challenging to correctly diagnose and manage. Furthermore, consideration should be given for alternative strategies and referral pathways for low-risk patients presenting with lymphadenopathy which have the COVID-19 vaccination as the most likely aetiology.

References

1-Medicines and Healthcare products Regulatory Agency. Public Assessment Report. Authorisation for Temporary Supply, COVID-19 mRNA Vaccine BNT162b2 (BNT162b2 RNA) concentrate for solution for injection. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/944544/COVID-19_mRNA_Vaccine_BNT162b2__UKPAR___PFIZER_BIONTECH__15Dec2020.pdf [Accessed 12/04/2021].

2-Medicines and Healthcare products Regulatory Agency. Public Assessment Report. Authorisation for Temporary Supply, COVID-19 Vaccine AstraZeneca, solution for injection in multidose container COVID-19 Vaccine (ChAdOx1-S [recombinant]). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963928/UKPAR_COVID_19_Vaccine_AstraZeneca_23.02.2021.pdf [Accessed 12/04/2021].

3-Medicines and Healthcare products Regulatory Agency. Public Assessment Report. Authorisation for Temporary Supply, COVID-19 Vaccine Moderna, 0.20 mg/mL dispersion for injection (COVID-19 mRNA Vaccine [nucleoside modified]). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/962920/Public_Assessment_Report_for_Moderna_COVID-19_vaccine.pdf [Accessed 12/04/2021].

4-Medicines and Healthcare products Regulatory Agency. Coronavirus vaccine - weekly summary of Yellow Card reporting (09/12/2020 to 14/03/2021). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/972844/Coronavirus_vaccine_-_summary_of_Yellow_Card_reporting_14.03.21.pdf [Accessed 12/04/2021].

5-Medicines and Healthcare products Regulatory Agency. COVID-19 mRNA Pfizer-BioNTech vaccine analysis print (09/12/2020 to 14/03/2021). Available from:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_-data/file/972832/COVID-19_mRNA_Pfizer-_BioNTech_Vaccine_Analysis_Print.pdf [Accessed 28/03/2021].

6-Medicines and Healthcare products Regulatory Agency. COVID-19 vaccine AstraZeneca analysis print (04/01/2021 to 14/03/2021). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_-data/file/975786/COVID-19_AstraZeneca_Vaccine_Analysis_Print.pdf [Accessed 28/03/2021].

7-Grimm L, Destounis S, Dogan B, et al. SBI Recommendations for the Management of Axillary Adenopathy in Patients with Recent COVID-19 Vaccination: Society of Breast Imaging Patient Care and Delivery Committee;2021. Available from: https://www.sbi-online.org/Portals/0/Position%20Statements/2021/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination.pdf [Accessed 12/04/2021].

8-Ozutemiz C, Krystosek LA, Church AL, et al. Lymphadenopathy in COVID-19 Vaccine Recipients: Diagnostic Dilemma in Oncology Patients. Radiology. 2021:210275. doi: 10.1148/radiol.2021210275. PMID: 33625300.

9-McIntosh LJ, Bankier AA, Vijayaraghavan GR, Licho R, Rosen MP. COVID-19 Vaccination-Related Uptake on FDG PET/CT: An Emerging Dilemma and Suggestions for Management. AJR Am J Roentgenol. 2021 Mar 1. doi: 10.2214/AJR.21.25728. PMID: 33646823.

10-Becker AS, Perez-Johnston R, Chikarmane SA, et al. Multidisciplinary Recommendations Regarding Post-Vaccine Adenopathy and Radiologic Imaging: Radiology Scientific Expert Panel. Radiology. 2021:210436. doi: 10.1148/radiol.2021210436. PMID: 33625298.

11- Seely JM, Barry MH. The Canadian Society of Breast Imaging/ Canadian Association of Radiologists' Recommendations for the Management of Axillary Adenopathy in Patients With Recent COVID-19 Vaccination. Can Assoc Radiol J. 2021:846537121998949. doi: 10.1177/0846537121998949. PMID: 33622040.

12-Fernandez-Prada M, Rivero-Calle I, Calvache-Gonzalez A, Martinon-Torres F. Acute onset supraclavicular lymphadenopathy coinciding with intramuscular mRNA vaccination against COVID-19 may be related to vaccine injection technique, Spain, January and February 2021. Euro Surveill. 2021(10):2100193. doi: 10.2807/1560-7917.ES.2021.26.10.2100193. PMID: 33706861.

13-Hiller N, Goldberg SN, Cohen-Cymberknoh M, Vainstein V, Simanovsky N. Lymphadenopathy Associated With the COVID-19 Vaccine. Cureus. 2021;13(2):e13524. doi: 10.7759/cureus.13524. PMID: 33786231.

14-Mitchell OR, Dave R, Bekker J, Brennan PA. Supraclavicular lymphadenopathy following COVID-19 vaccination: an increasing presentation to the two-week wait neck lump clinic? Br J Oral Maxillofac Surg. 2021;59(3):384-385. doi: 10.1016/j.bjoms.2021.02.002. PMID: 33685772.

15-Cunnane M, Cheung L, Moore A, di Palma S, McCombe A, Pitkin L. Level 5 Lymphadenopathy Warrants Heightened Suspicion for Clinically Significant Pathology. Head Neck Pathol. 2016;10(4):509-12.

16-National Institute for Health and Care Excellence. Suspected cancer: recognition and referral. [London]: NICE; 2015 [updated 2021 Jan]. (NICE guideline [NG12]). Available from: https://www.nice.org.uk/guidance/ng12/ [Accessed 12/04/2021].

17-von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806-8. doi: 10.1136/bmj.39335.541782.AD. PMID: 17947786.

18-Coates EE, Costner PJ, Nason MC, et al. Lymph node activation by PET/CT following vaccination with licensed vaccines for human papilloma viruses. Clinical Nuclear Medicine. 2017;42(5):329-334. DOI: 10.1097/RLU.0000000000001603. PMID: 28288041.

19-Burger IA, Husmann L, Hany TF, Schmid DT, Schaefer NG. Incidence and intensity of F-18 FDG uptake after vaccination with H1N1 vaccine. Clin Nucl Med. 2011;36(10):848-53. DOI:

10.1097/RLU.0b013e3182177322. PMID: 21892032.

20-Mortazavi S. Coronavirus Disease (COVID-19) Vaccination Associated Axillary Adenopathy: Imaging Findings and Follow-Up Recommendations in 23 Women. AJR Am J Roentgenol. 2021. doi: 10.2214/AJR.21.25651.PMID: 33624520.

21-Cohen D, Krauthammer SH, Wolf I, Even-Sapir E. Hypermetabolic lymphadenopathy following administration of BNT162b2 mRNA Covid-19 vaccine: incidence assessed by [18F]FDG PET-CT and relevance to study interpretation. Eur J Nucl Med Mol Imaging. 2021:1–10. doi: 10.1007/s00259-021-05314-2. PMID: 33774684.

22-Mehta N, Sales RM, Babagbemi K, et al. Unilateral axillary Adenopathy in the setting of COVID-19 vaccine. Clin Imaging. 2021;75:12-15. doi: 10.1016/j.clinimag.2021.01.016. PMID: 33486146.

23-Ying M, Ahuja A. Sonography of neck lymph nodes. Part I: normal lymph nodes. Clin Radiol. 2003;58(5):351-8. doi: 10.1016/s0009-9260(02)00584-6. PMID: 12727162.

24-Lehman CD, D'Alessandro HA, Mendoza DP, Succi MD, Kambadakone A, Lamb LR. Unilateral Lymphadenopathy After COVID-19 Vaccination: A Practical Management Plan for Radiologists Across Specialties. J Am Coll Radiol. 2021:S1546-1440(21)00212-X. doi: 10.1016/j.jacr.2021.03.001. PMID: 33713605.

Clinical data	**Value (N=13)**
Age at diagnosis, mean (SD) [range] days	54.8 (16.1) [27-81]
Gender, N (%)	**Gender, N (%)**
Female	11 (84.6)
Male	2 (15.4)
Injection site, N (%)	**Injection site, N (%)**
Left deltoid	12 (92.3)
Right deltoid	1 (7.7)
First dose, N (%)	12 (92.3)
Pfizer/BioNTech vaccine, N (%)	13 (100)
Symptoms, N (%)	**Symptoms, N (%)**
Neck lump/fullness	13 (100)
Tenderness	6 (46.2)
Ultrasound scan, N (%)	13 (100)
Outcome, N (%)	**Outcome, N (%)**
Fully resolved	7 (53.9)

Clinical data	Value (N=13)
Partially reduced	5 (38.5)
Unknown	1 (7.7)
Time for clinical resolution, mean (SD) [range] weeks	**Time for clinical resolution, mean (SD) [range] weeks**
Fully resolved	3.1 (2.3) [1-8]
Partially reduced	8.4 (3.1) [5-12]

N; number, SD; standard deviation

Table 1. Characteristics of patients with COVID-19 vaccine-associated lymphadenopathy

	Age (y)	Sex	Dose order	Injection site	LN side	Symptoms	Vaccination to lymphadenopathy interval* (d)
1	54	F	1st	Left	Ipsilateral	Tenderness	11
2	27	F	1st	Left	Ipsilateral	Tenderness	5
3	60	F	1st	Left	Ipsilateral	None	3
4	40	M	1st	Left	Ipsilateral	None	1
5	76	F	1st	Left	Ipsilateral	None	4
6	41	F	1st	Left	Ipsilateral	None	7
7	73	F	1st	Left	Ipsilateral	Tenderness	7
8	55	F	1st	Left	Ipsilateral	None	14
9	57	F	1st	Left	Ipsilateral	None	2
10	56	F	2nd	Left	Ipsilateral	Tenderness	1
11	81	F	1st	Right	Ipsilateral	Tenderness	10
12	34	M	1st	Left	Ipsilateral	None	2
13	58	F	1st	Left	Ipsilateral	None	2

y; years, d; days; w; weeks, LN; lymph node, USS; ultrasound scan, ND; not documented, FR; fully resolved, PR; partially reduced

* Corresponding to subjective palpable swelling by patients.

+ Reported by patients during telephone follow-up.

Table 2. Clinical features and timeline of presentation of patients with COVID-19 vaccine-associated lymphadenopathy.

	Level of LN	**SAD* (mm)**	**S:L* Ratio**	**Vascularity**	**Fatty hilum**	Echogenicity	**Overall impression**	**FNAB**
1	IV	4.9	0.5	Normal	Preserved	Normal	Reactive LN	ND

	Level of LN	SAD* (mm)	S:L* Ratio	Vascularity	Fatty hilum	Echogenicity	Overall impression	FNAB
2	V	7.7	0.5	normal	Preserved	Normal	Reactive LN	ND
3	V	ND	ND	ND	ND	ND	Reactive LN	ND
4	V	5.2	0.6	Increased	Preserved	Normal	Reactive LN	ND
5	IV	4.7	0.7	Normal	Preserved	Slightly hypoechoic	Reactive LN	Benign reactive LN
6	V	5.2	0.7	normal	Preserved	Normal	Reactive LN	ND
7	V	6.6	0.5	normal	Preserved	Normal	Reactive LN	ND
8	IV/V	5.7	0.6	normal	Preserved	Normal	Reactive LN	ND
9	V	3.4	0.5	normal	Preserved	Normal	Reactive LN	ND
10	V	5	0.4	normal	Preserved	Normal	Reactive LN	ND
11	IV	4.2	0.5	normal	Preserved	Normal	Reactive LN	ND
12	V	8.2	0.6	Increased	Preserved	Slightly hypoechoic	Reactive LN	Benign reactive LN
13	V	7	0.5	normal	Preserved	Normal	Reactive LN	ND

LN; lymph nodes, USS; ultrasound scan, SAD; short axis diameter, S:L ratio, short axis diameter:long axis diameter ratio, ND; not done, FNAB; fine needle aspiration biopsy

* Measured in the biggest node.

Table 3. Ultrasound findings in patients with COVID-19 vaccine-associated cervical lymphadenopathy

Variable	Outcome^{+}	Mean (SD)	*P*-value
SAD	FR	6.4 (1.3)	**0.024**
	PR	4.6 (0.9)	
Vaccination to lymphadenopathy interval* (d)	FR	5.3 (3.3)	0.728
	PR	6.2 (5.6)	**0.001**
Lymphadenopathy to referral interval (d)	FR	9 (8.9)	
	PR	35.6 (10.9)	
Age	FR	49.6 (16.2)	0.106
	PR	65 (12.5)	

FR; fully resolved nodes, PR; partially reduced nodes, SAD; short axis diameter, USS; ultrasound scan, SD; standard deviation, d; days

* Corresponding to subjective palpable swelling by patients.

+ Reported by patients during telephone follow-up.

Table 4. Comparison between patients with fully resolved Vs partially reduced lymphadenopathy.

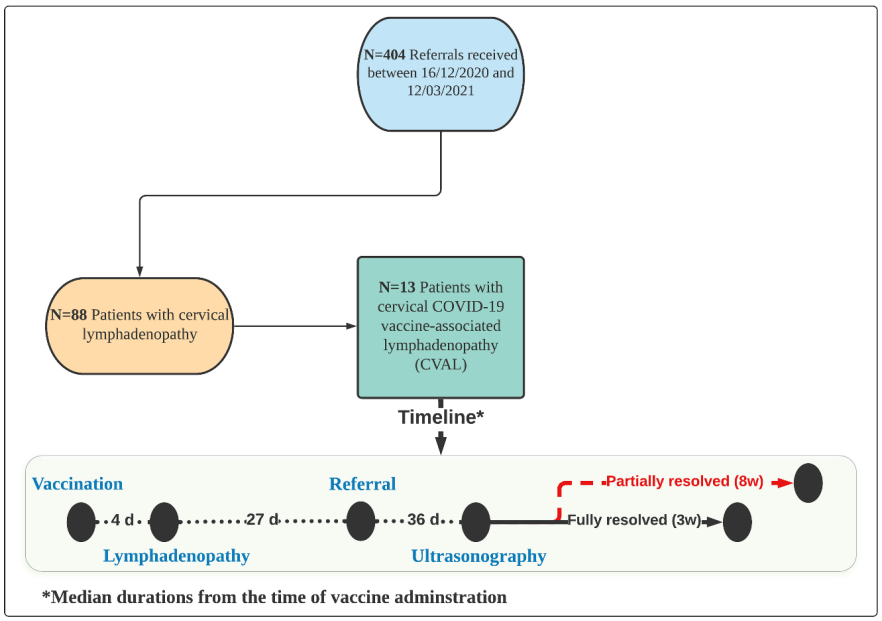

Figure 1. Diagram showing the proportion of referrals with COVID-19 vaccine-associated lymphadenopathy, and a timeline for clinical course.

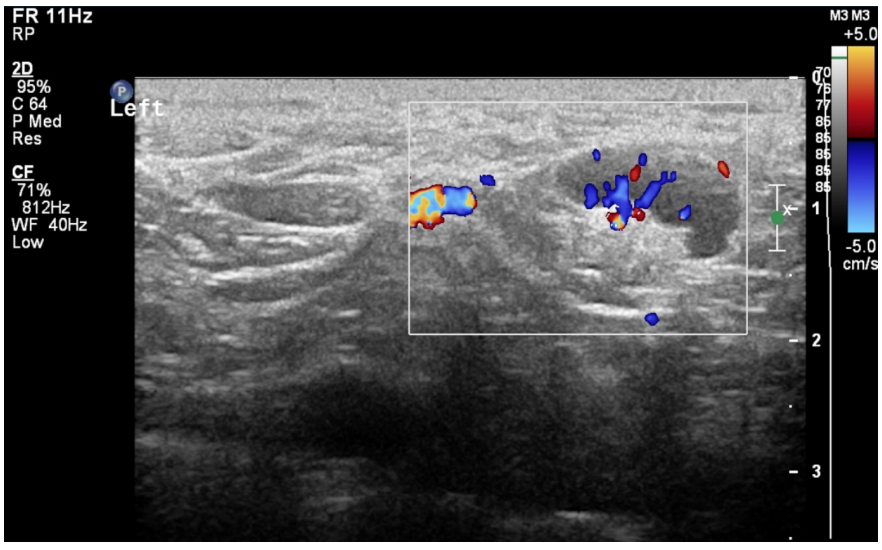

Figure 2. Ultrasound scan of patient number 12 showing an 8.2mm slightly hypoechoic lymph node in the left supraclavicular region with increased vascularity on colour doppler.