ORIGINAL ARTICLE

Royal Australasian College of Surgeons

COVID-19 vaccine associated cervical lymphadenopathy: a case series

Chelsea L. Heaven,* Lucy Barber,* Omid Ahmadi,†‡ Kumanan Selvarajah‡ and Subhaschandra Shetty*

*Department of Otolaryngology, Head & Neck Surgery, Whangarei Hospital, Whangarei, New Zealand
†Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand and
‡Department of Otolaryngology and Head & Neck Surgery, Waikato Hospital, Hamilton, New Zealand

Key words
cervical lymphadenopathy, COVID-19 vaccine.

Correspondence
Dr Chelsea L. Heaven, ORL Department, Whangarei Hospital, Private Bag 9742, Whangarei 0148, New Zealand.
Email: chelsea.heaven@gmail.com

C. L. Heaven MBChB; **L. Barber** MBChB; **O. Ahmadi** MBChB, PhD; **K. Selvarajah** MBChB, FRACS; **S. Shetty** MD, FRACS.

Accepted for publication 6 May 2022.

doi: 10.1111/ans.17808

Abstract

Background: COVID-19 is an evolving worldwide pandemic causing significant morbidity and mortality. COVID-19 vaccinations have been developed to increase immunity against the virus. In New Zealand, the Pfizer BioNTech mRNA vaccine has been provisionally approved for use. Axillary lymphadenopathy is a recognized side effect of the mRNA vaccine, however cervical lymphadenopathy has also been reported. Due to a wide range of differential diagnoses, the finding of cervical lymphadenopathy requires thorough investigation which can include imaging and invasive diagnostic procedures.

Methods: Five patients were identified by otorhinolaryngology (ORL) consultants at Whangarei Base Hospital and Waikato Hospital between 15/7/2021 and 21/12/2021 after being investigated through high suspicion of cancer triage pathways set by the New Zealand Ministry of Health. Inclusion criteria were adult patients with cervical lymphadenopathy following vaccination. Exclusion criteria were no history of vaccination or lymphadenopathy present before vaccination.

Results: All patients were identified to have cervical lymphadenopathy on radiological imaging and a recent history of COVID-19 vaccination with the Pfizer BioNTech vaccine. Interval vaccination to fine needle aspiration time ranged between 41 and 76 days. All patients had cytological or histological diagnosis showing reactive findings or interval imaging showing resolution of lymphadenopathy.

Conclusion: With increasing levels of COVID-19 vaccination and booster vaccinations we will continue to see cases of COVID-19 vaccine associated cervical lymphadenopathy. We highlight the importance of taking a COVID-19 vaccination history and including COVID-19 associated cervical lymphadenopathy in the differential diagnosis of presentation with a neck lump.

Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was first detected in China in 2019. It has spread across the world and was officially announced as a pandemic by the World Health Organization (WHO) in March 2020.[1] Various strains of the COVID-19 virus have spread including Delta and more recently Omicron. Vaccinations have been developed globally to reduce the overall severity and mortality of COVID-19 and limit the burden on healthcare systems. Provisionally approved COVID-19 vaccines have been assessed to be safe and effective and can reduce the risk of contracting and spreading the virus as well as reducing the severity of symptoms of COVID-19.[2] More than four and a half billion people across the world have been double vaccinated against COVID-19.[3] Pfizer BioNtech, Janssen, AstraZeneca and Novax are some of the vaccinations have been used globally. In New Zealand, the Pfizer BioNTech BNT162b2 mRNA vaccine (Comirnaty) has been provisionally approved for use and has been almost exclusively used.[2] In New Zealand, >94% of eligible population has been double vaccinated while >70% have had their booster dose.[4] The vaccine is usually administered by intramuscular injection into the deltoid muscle. Listed side effects include pain and swelling at the injection site, tiredness, fatigue, headache, myalgia, chills, arthralgia, fever, erythema at injection site, nausea, feeling unwell, insomnia, unilateral facial droop, myocarditis and anaphylaxis as well as lymphadenopathy.[5,6] Lymphadenopathy is an uncommon side effect of other vaccinations and is rarely reported in human

papillomavirus, tuberculosis and influenza vaccination.[1,6,7] A safety study of the BNT162b2 mRNA vaccine identified lymphadenopathy in 0.3% of participants.[8] Regional axillary lymphadenopathy has been reported as an immunogenic reaction to intramuscular administration in the deltoid.[7] The usual lymphatic drainage of the upper limb is via superficial lymphatic vessels which drain to the axillary lymph nodes and the subclavian lymphatic trunk.[9] However, a number of cases of cervical lymphadenopathy post COVID-19 mRNA vaccination have been reported.[1,6,7,9,10] The differential diagnoses for cervical lymphadenopathy include infection, malignancy, medications, autoimmune disease, trauma and metabolic disease.[1,10] Diagnostic investigations include imaging and invasive procedures such as fine needle aspiration (FNA) and biopsy to exclude malignancy. We present a series of five cases of cervical lymphadenopathy arising after Pfizer BioNTech COVID-19 vaccination.

Material and methods

Study population

Between 15/7/21 and 21/12/2021 respective hospital database was analysed for patients referred to the local Otorhinolaryngology (ORL) Head and Neck service. Inclusion criteria were adult patients with cervical lymphadenopathy following vaccination. Exclusion criteria were no history of vaccination, or lymphadenopathy present before vaccination. During the study period four patients within Northland District Health Board and one patient within Waikato District Health Board were identified as having cervical lymphadenopathy presumed secondary to COVID-19 vaccination with the Pfizer BioNTech COVID vaccine. Cervical lymphadenopathy referrals are triaged as 'high suspicion of cancer' and are seen urgently as per the faster cancer treatment targets set by the Ministry of Health. They are followed by a departmental cancer tracking team and are easily identified by clinicians to add to this study. Relevant clinical information was obtained from charts and electronic records including patient demographics, presenting history, investigations, and procedures. Patient demographics include age, gender and ethnicity. History includes site and side of lymphadenopathy, duration of lymphadenopathy, relevant past medical history, vaccination status, site and side of vaccination and timing of vaccination prior to onset of lymphadenopathy. Investigations and procedures include radiological imaging, FNA and excisional biopsy. This study was deemed out of scope by the New Zealand Health and Disability Ethics Committees on 9 April 2022.

Results

Case 1: 42-year-old, fit and well man with 2 weeks of an enlarged left sided supraclavicular lymph node. Recent history of an enlarged left posterior triangle lymph node a few weeks prior which had since resolved. The first Pfizer BioNTech COVID-19 vaccination was administered 42 prior and second dose 7 days prior to ORL clinical review. Ultrasound (USS) guided FNA was performed the same day which showed a polyclonal lymphoid population of both B cells and T cells, suggestive of a reactive lymphoid population on flow cytometry and no evidence of malignant cells on cytology. Due to persistent lymphadenopathy and clinical concern, patient proceeded to excision biopsy. Histology showed reactive follicular hyperplasia with no evidence of atypia or malignancy (Fig. 1).

Case 2: 70-year-old woman with a six-week history of left supraclavicular lymphadenopathy. The first and second doses of Pfizer BioNTech COVID-19 vaccination were administered 76 and 55 days prior to review, respectively. Past medical history includes psoriatic arthritis, osteoarthritis, hypothyroidism and chronic colitis. In clinic USS guided FNA was performed of a 1x1cm palpable

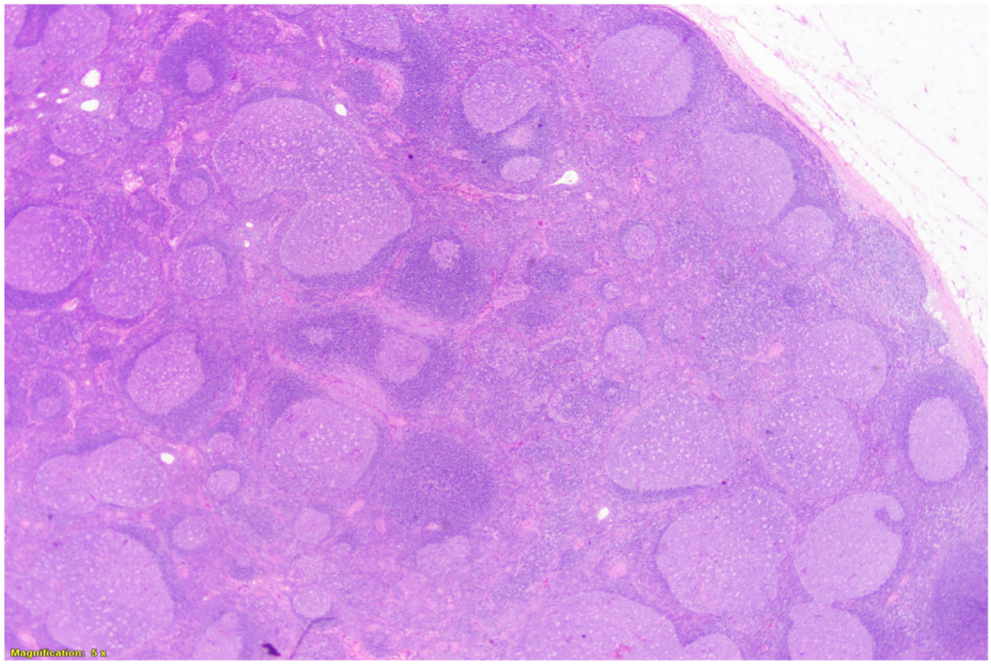

Fig. 1. Case one photomicrograph showing supraclavicular lymph node with reactive follicular hyperplasia. Secondary follicles are variable in size and shape with well-defined germinal centres.

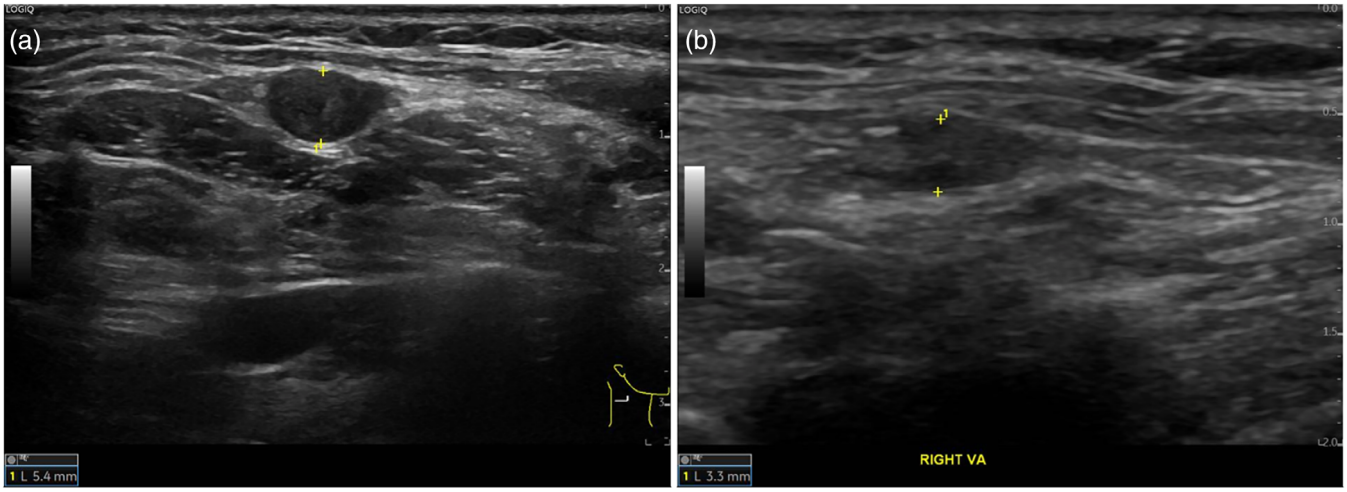

Fig. 2. (a) Case 3 USS showing right level Va node with loss of hilar pattern and short axis of 5.4 mm. (b) case 3 USS 33 days later showing normal size and morphology. Short axis of 3.3 mm.

mass posterior to the middle third of the left clavicle. This showed a reactive lymphoid population with scattered large, atypical cells of uncertain significance. At clinical follow up the patient's lymphadenopathy had regressed in size. Repeat USS at 3 months showed non-pathological left supraclavicular lymph nodes.

Case 3: 58-year-old woman with enlarged bilateral posterior triangle lymph nodes. History includes metastatic tall cell papillary thyroid carcinoma with total thyroidectomy and radioiodine in 2001 and a bilateral selective neck dissection in 2012 for cancer recurrence. History also includes a recent resolving left level Ib lymphadenopathy currently under serial USS follow-up. The patient received two doses of the Pfizer BioNTech COVID-19 vaccination 22 days prior to and 7 days following a surveillance USS. This showed a normal appearing thyroid bed and resolution of the left level Ib abnormality previously described. A new hypoechoic level Va node was identified on the right. This appeared avascular with a loss of the normal hilar pattern and a short axis of 5.4 mm. An oval avascular hypoechoic structure was also identified in level Va on the left. After multidisciplinary team review, the patient was booked for FNA. However, during the repeat USS guided FNA it was noted that the bilateral level Va lymph nodes were within normal size and morphological limits therefore no FNA was performed (Fig. 2).

Case 4: 45-year-old, usually fit and well man developed left submandibular tender lymphadenopathy 1 week following his first COVID-19 vaccination in the left deltoid. Lymphadenopathy in the left submandibular and submental regions was confirmed on USS 3 weeks following vaccination. The patient was reviewed in the ORL clinic, 8 weeks post vaccination, with FNA performed in clinic. Results were of atypical lymphocytes suggestive of a lymphoproliferative disorder. Patient proceeded to excision biopsy of the left submandibular lymph node with flow cytometry and histology revealing a benign reactive lymph node (Fig. 3).

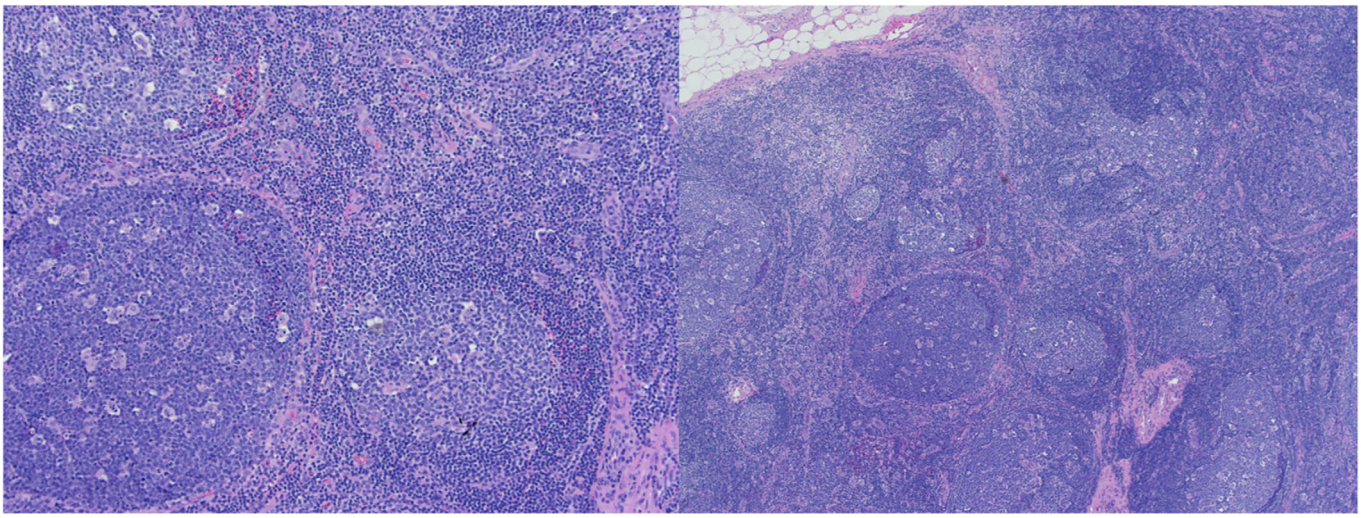

Fig. 3. (a) High power photomicrograph and (b) low power micrograph of left level Ib lymph node showing a benign reactive lymph node.

Table 1 Summary of cases

Number	Age	Sex	Ethnicity	Medical Hx	Vaccination site	Interval vaccination—FNA (days)	Site of FNA	Cytological Diagnosis (FNA)	Histological diagnosis (Excision)	Follow up
1	42	M	European	Nil	Left deltoid	41	Left supraclavicular	Reactive LA. No evidence of metastasis	Reactive LA. No evidence of metastasis	Discharged after excision biopsy
2	70	F	NZ European	Psoriatic arthritis, osteoarthritis, hypothyroidism, chronic colitis	Left deltoid	76	Left supraclavicular	Reactive LA. Large atypical cells of uncertain significance.	x	Repeat USS at 3 months
3	58	F	NZ European	Metastatic tall cell papillary thyroid carcinoma	Left deltoid	x (22 days until USS)	x	x	x	Resolved by the time of second USS (55 days)
4	45	M	NZ European	Nil	Left deltoid	63	Left submandibular	Atypical lymphocytes suggestive of lympho-proliferative disorder	Benign reactive lymph node	Discharged to GP after left submandibular lymph node excision
5	34	F	NZ European	Intellectual impairment	Left deltoid	42	Left level Ib	-	Reactive LA.	Discharged after clinical review.

Case 5: 34-year-old woman presented to the ORL clinic 7 days following her second Pfizer BioNTech COVID-19 vaccination with left level Ib lymphadenopathy. No FNA was performed due to patient anxiety and intellectual impairment. Patient had a history of atypical cell on histology after left lymphadenopathy requiring level Ib super selective neck dissection 3 years ago. Due to the history of previous neck dissection patient proceeded to a computed tomography (CT) scan. CT revealed bilateral level II cervical lymphadenopathy measuring up to 11 mm. Patient underwent excision biopsy of a left submandibular lymph node under general anaesthetic 35 days after clinical review. Histology revealed reactive lymphadenopathy and the patient was booked for further clinical follow up (Table 1).

Discussion

We present a case series of five patients presenting with cervical lymphadenopathy between seven and 34 days after vaccination with the Pfizer BioNTech COVID-19 vaccine. Three of these patients proceeded to lymph node excision biopsy showing no evidence of malignancy. The remaining two patients were followed with repeat ultrasonography showing resolution of lymphadenopathy. This case series highlights the rare but important side effect of cervical lymphadenopathy following Pfizer COVID-19 vaccination, as cervical lymphadenopathy is not in the usual regional distribution for the deltoid vaccine injection.[9] As most people are unlikely to seek medical help for cervical lymphadenopathy following COVID-19 vaccination, it is difficult to make any definite conclusion as to its incidence.

The Pfizer BioNTech vaccine given to the patients in this case series overall has a good safety profile.[8,11] As with any vaccination, clinical trials have identified several adverse effects to be aware of. A safety and efficacy study of the BNT162b2 mRNA COVID-19 vaccine by Polack *et al*. found that 64 of 43 252 (0.3%) Pfizer BioNTech vaccine recipients reported lymphadenopathy.[8] In the phase III Moderna vaccine tiral, lymphadenopathy was reported as an unsolicited event in 1.1% of recipients.[12] Separate reporting of axillary swelling and tenderness was identified in 16% of recipients aged 18–64.[12] Several studies have reported on regional axillary lymphadenopathy after COVID-19 vaccination corresponding to lymphatic drainage from the deltoid.[6,13–15] Less commonly, as shown in this study, lymphadenopathy can affect the cervical lymph nodes, which lie outside the regional lymphatic basin.[1,7,9,16] Clinical trials suggest that the mRNA COVID-19 vaccinations are highly immunogenic accounting for the relatively high rates of lymphadenopathy compared to other vaccines.[7,14,17,18]

The SARS-CoV-2 virus binds to host cells via the viral spike protein, eliciting a cascade of inflammatory events and a significant inflammatory response.[19,20] The adaptive immune system produces neutralizing antibodies which eliminate infected host cells and interfere with viral binding to host cell receptors to obstruct virus uptake into host cells.[19,20] The Pfizer BioNTech vaccine is a novel mRNA vaccine which targets this physiological process. The mRNA vaccine carries the gene that encodes the SARS-CoV-2 viral spike protein. This stimulates the production of IgA, IgM and IgG antibodies against the spike protein antigen, neutralizing

antibodies, and a long-lasting memory B and T cell response to SARS-CoV-19 to increase immunity against the disease.[11] Antigens migrate from the injection site to the regional lymph node basin, causing the resulting lymphadenopathy.[13]

It is important to note that even though lymphadenopathy in the axilla is the most common location post vaccination, palpable lymphadenopathy is most commonly detected in the supraclavicular region.[15] A literature review of 15 studies including 737 patients with vaccine-related lymphadenopathy has found that 86.5% of palpable lymphadenopathy is detected in supraclavicular region while only 10.8% of palpable lymphadenopathy is detected in the axillary region.[15] Research has also noted the lymphadenopathy can persist up to 6 weeks.[6,15] Cervical lymphadenopathy could result from a high injection site in the deltoid, individual variations in lymphatic drainage pathways and immune system characteristics.[10]

Unexplained cervical lymphadenopathy is clinically concerning as it could indicate underlying malignancy. Diagnostic work up includes imaging studies, FNA and or excisional lymph node biopsy. A 2021 study published in Swiss Medical Weekly by Hagen *et al*. reported five cases of reactive cervical and axillary lymphadenopathy following mRNA COVID-19 vaccination with either the Moderna or Pfizer BioNTech vaccines.[1] All cases underwent FNA showing reactive lymphadenopathy with no evidence of malignancy, and all were followed up at 2 months with complete clinical regression of lymphadenopathy.[1] A 2021 study in Spain by Fernandez-Prada *et al*. described 20 cases of ipsilateral supraclavicular lymphadenopathy in healthcare workers receiving intramuscular injection of an mRNA COVID-19 vaccination, either Pfizer BioNTech or Moderna.[10] Most cases reported a high vaccination site at the deltoid. On clinical follow up 15 cases had completely resolved between five and 16 days since onset and a further five were awaiting ongoing follow up.[10] These findings are in keeping with our case series that describes five cases with investigations showing reactive lymphadenopathy in the three who underwent tissue diagnosis and radiological resolution of lymphadenopathy on repeat ultrasound within 3 months in the remaining cases.

It is important for clinicians to be aware of COVID-19 vaccine associated lymphadenopathy as a differential diagnosis of cervical lymphadenopathy. This is relevant to clinicians of all disciplines as patients present to their general physician or the emergency department before they are referred for specialist assessment by ORL. Due to the concern for malignancy, it is important for patients to receive clinical tests to appropriately investigate a potential cancer while simultaneously avoiding harm associated with extensive investigations. Documentation of vaccine type, dose, date, and site of administration are necessary so that records can be reviewed for association with lymphadenopathy.[1,17] There should be a low threshold for investigations in a patient with a history of a head or neck cancer. However, invasive investigations and resulting patient anxiety can be avoided by following a conservative approach in otherwise well patients. Vaccination site contralateral to oncological site should be considered where possible to avoid confusion and unnecessary investigations.[6,17,18] Pre-vaccination imaging can be considered in high-risk oncological patients.[18] As lymphadenopathy can persist up to 6 weeks, any invasive procedure can be delayed till after 6 weeks to avoid unnecessary investigations.[1] Patients should be observed with close clinical follow up and further tests if lymphadenopathy persists beyond 6 weeks.

Conclusion

In conclusion, lymphadenopathy has been recognized as a side effect of mRNA vaccines both in the axilla and cervical basins. Due to increasing levels of COVID-19 vaccination as well as the initiation of the vaccine booster vaccine program, we will continue to see cases of COVID-19 vaccine induced cervical lymphadenopathy. This case series highlights the importance of taking a COVID-19 vaccination history and to include vaccine associated lymphadenopathy in the differential diagnosis in the presentation of a neck lump.

Acknowledgement

We would like to acknowledge our patients who are included in this case series and who have provided consent to be included.

Author contributions

Chelsea L. Heaven: Conceptualization; data curation; formal analysis; methodology; project administration; resources; validation; writing – original draft; writing – review and editing. **Lucy Barber:** Conceptualization; data curation; formal analysis; methodology; resources; writing – original draft; writing – review and editing. **Omid Ahmadi:** Data curation; resources; writing – review and editing. **Kumanan Selvarajah:** Conceptualization; data curation; resources; supervision; writing – review and editing. **Subhaschandra Shetty:** Conceptualization; data curation; methodology; project administration; resources; supervision; writing – review and editing.

Conflict of interest

None declared. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written or verbal informed consent was obtained from the patients for publication of this case report and accompanying images.

References

1. Hagen C, Nowack M, Messerli M, Saro F, Mangold F, Bode PK. Fine needle aspiration in COVID-19 vaccine-associated lymphadenopathy. *Swiss Med. Wkly.* 2021; **151**: w20557.
2. Ministry of Health. COVID-19: Assessing and approving the vaccines. Wellington: New Zealand. [Updated 9 March 2022; Cited 10 Feb 2022.] Available from URL: https://www.health.govt.nz/our-work/

diseases-and-conditions/covid-19-novel-coronavirus/covid-19-vaccines/covid-19-assessing-and-approving-vaccines

3. Ritchie, H, Mathieu, E, Rodés-Guirao, L et al. Coronavirus Pandemic (COVID-19). [Updated 9 April 2022; Cited 2 April 2022.] Available from URL: https://ourworldindata.org/covid-vaccinations
4. Ministry of Health. MOH website vaccination data. Wellington: New Zealand. [Updated 7 April; Cited 9 April 2022.] Available from URL: https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-vaccine-data
5. Ministry of Health. COVID 19: Vaccine side effects and reactions. Wellington: New Zealand. [Updated 17 March 2022, cited 9 April 2022.] Available from URL: https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-vaccines/covid-19-vaccine-side-effects-and-reactions
6. Garreffa E, York J, Turnbull A, Kendrick D. Regional lymphadenopathy following COVID-19 vaccination: considerations for primary care management. *Br. J. Gen. Pract.* 2021; **71**: 284–5.
7. Cardoso F, Reis A, Osório C, Scigliano H, Nora M. A case of cervical lymphadenopathy after vaccination against COVID-19. *Cureus* 2021; **13**.
8. Polack FP, Thomas SJ, Kitchin N *et al*. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N. Engl. J. Med.* 2020; **383**: 2603–15.
9. Mitchell OR, Couzins M, Dave R, Bekker J, Brennan PA. COVID-19 vaccination and low cervical lymphadenopathy in the two week neck lump clinic - a follow up audit. *Br. J. Oral Maxillofac. Surg.* 2021; **59**: 720–1.
10. Fernández-Prada M, Rivero-Calle I, Calvache-González A, Martinón-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; **26**: 2100193.
11. Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna vaccines. *Eur. Rev. Med. Pharmacol. Sci.* 2021; **25**: 1663–9.
12. Becker AS, Perez-Johnston R, Chikarmane SA *et al*. Multidisciplinary recommendations regarding post-vaccine adenopathy and radiologic imaging: radiology scientific expert panel. *Radiology* 2021; **300**: E323–7.
13. Lane DL, Neelapu SS, Xu G, Weaver O. COVID-19 vaccine-related axillary and cervical lymphadenopathy in patients with current or prior breast cancer and other malignancies: cross-sectional imaging findings on MRI, CT, and PET-CT. *Korean J. Radiol.* 2021; **22**: 1938–45.
14. Igual-Rouilleault AC, Soriano I, Quan PL, Fernández-Montero A, Elizalde A, Pina L. Unilateral axillary adenopathy induced by COVID-19 vaccine: US follow-up evaluation. *Eur. Radiol.* 2021; **1-8**: 3199–206.
15. Garreffa E, Hamad A, O'Sullivan CC *et al*. Regional lymphadenopathy following COVID-19 vaccination: literature review and considerations for patient management in breast cancer care. *Eur. J. Cancer* 2021; **159**: 38–51.
16. Ganga K, Solyar AY, Ganga R. Massive cervical lymphadenopathy post-COVID-19 vaccination. *Ear Nose Throat J.* 2021; **2**: 14556132110489.
17. Abou-Foul AK, Ross E, Abou-Foul M, George AP. Cervical lymphadenopathy following coronavirus disease 2019 vaccine: clinical characteristics and implications for head and neck cancer services. *J. Laryngol. Otol.* 2021; **135**: 1025–30.
18. Tu W, Gierada DS, Joe BN. COVID-19 vaccination–related lymphadenopathy: what to be aware of. *Radiol. Imaging Cancer.* 2021; **3**: e210038.
19. Hasan A, Al-Ozairi E, Al-Baqsumi Z, Ahmad R, Al-Mulla F. Cellular and humoral immune responses in Covid-19 and immunotherapeutic approaches. *Immunotargets Ther.* 2021; **10**: 63–85.
20. National Centre for Immunization and Respiratory Diseases (NCIRD), Division of viral diseases. Science brief: SARS-CoV-2 Infection-induced and vaccine-induced Immunity. Atlanta: USA. [Updated 29 October 2021, Cited 9 April 2022.] Available from URL: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/vaccine-induced-immunity.html