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# Fine needle aspiration in COVID-19 vaccine-associated lymphadenopathy

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## Summary

AIMS: With ongoing intensive vaccination programme against COVID-19, numerous cases of adverse reactions occur, some of which represent rare events. Enlargement of the injection site's draining lymph nodes is increasingly reported, but is not yet widely recognised as being possibly associated with recent vaccination. As patients at risk of a severe course of COVID-19, indicated by their medical history such as a previous diagnosis of malignancy, receive priority vaccination, newly palpable lymph nodes raise concerns of disease progression. In this case series, we report on five patients who presented with enlarged lymph nodes after COVID-19 vaccination.

METHODS: Sonography guided fine needle aspiration (FNA) was performed in five patients presenting with PET-positive and/or enlarged lymph nodes after COVID-19 vaccination with either the Pfizer-BioNTech or Moderna vaccine.

RESULTS: COVID-19 vaccination had been carried out in all cases, with an interval of between 3 and 33 days prior to FNA. Three of five patients had a history of neoplasms. The vaccine was administered into the deltoid muscle, with subsequent enlargement of either the cervical, supra-, infra- or retroclavicular, or axillary lymph nodes, in four out of five cases ipsilaterally. In all cases, cytology and additional analyses showed a reactive lymphadenopathy without any sign of malignancy.

CONCLUSIONS: Evidence of newly enlarged lymph nodes after recent COVID-19 vaccination should be considered reactive in the first instance, occurring owing to stimulation of the immune system. A clinical follow-up according to the patient's risk profile without further diagnostic measures is justified. In the case of preexisting unilateral cancer, vaccination should be given contralaterally whenever possible. Persistently enlarged lymph nodes should be re-evaluated (2 to) 6 weeks after the second dose, with additional diagnostic tests tailored to the clinical context. Fine needle aspiration is a well established, safe, rapid and cost-effective method to investigate an underlying malignancy, especially metastasis. Recording vaccination history, including date of injection, site and vaccine type, as well as communicating this information to treating physicians of different specialties is paramount for properly handling COVID-19 vaccine-associated lymphadenopathy.

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## Introduction

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first registered in China in the end of 2019 from where it rapidly spread all over the globe. The first person in Switzerland was tested positive on 25 February 2020, and the World Health Organization (WHO) declared the disease a pandemic on 11 March 2020 [1]. One year later, more than 170 million cases have been reported to the WHO, with over 3.8 million fatal outcomes [2]. Battling the spread of the virus is dominating public as well as private life, with healthcare institutions constantly challenged by the high workload and management of a novel disease [3]. Researchers have been fervently pursuing the development not only of treatment options, but also of vaccines to provide protection against COVID-19 and eventually end the pandemic [4–6].

Various vaccines are being evaluated, with currently 322 vaccine candidates and 18 in use worldwide [7–10]. So far, three have been approved in Switzerland (Comirnaty® by Pfizer-BioNTech on 19 December 2020, COVID-19 Vaccine Moderna® by Moderna on 12 January 2021 and COVID-19 Vaccine Janssen by Johnson&Johnson on 22 March 2021). Over 2500 million doses have been administered globally, with more than 6.7 million in Switzerland alone [11–14]. As the demand for vaccine delivery is immediate and high, the population was vaccinated in a stratified approach. It is known that COVID-19 infections affect more severely people with certain medical conditions, such as cardiovascular, respiratory, metabolic or immune disorders [15]. Patients with malignancy also carry a considerably higher risk of infection and complications [16], making it a priority to vaccinate this group. Besides vaccination efficiency, possible adverse events are of concern. Most adverse events following immunisation (AEFI) occur locally and are mild and self-limiting (tenderness at the injection site, reddening, swelling). Systemic AEFI range from fatigue, headache and myalgia to rarely observed severe cases such as anaphylactic shock [17, 18]. Lym-

phadenopathy may also occur following COVID-19 vaccination and affects mostly ipsilateral cervical, supraclavicular or axillary lymph nodes corresponding to the drainage route after injection into the deltoid muscle. Evaluation of the Moderna COVID-19 vaccine found axillary swelling or tenderness in 11.6% of vaccinated individuals after the first and 16% after the second dose, in 1.1% with clinically detected lymphadenopathy [19]. The Pfizer-BioNTech COVID-19 vaccine trial registered lymphadenopathy in 0.3% of the study participants [20, 21]. This AEFI is most likely underdiagnosed and underreported, leading to potential clinical pitfalls in managing patients who present with a newly palpable mass.

The aforementioned prioritised vaccination of persons with previous or ongoing malignancies represents a further challenge during this COVID-19 pandemic. Newly developed enlargement of lymph nodes raises the question of metastatic disease and elicits diagnostic workup such as imaging or excisional biopsies. Here we describe a case series of five patients referred to the cytology department for a fine needle aspiration (FNA) of enlarged lymph nodes to investigate the presence of neoplastic cells. Our aim is to enhance awareness of COVID-19 vaccine-associated lymphadenopathy and reduce the risk of over-diagnosis as well as overtreatment in suspicious cases. We subsequently propose a set of recommendations on how to approach lymphadenopathy after COVID-19 vaccination.

## Material and methods

Between 16 February and 3 March 2021, five patients who had recently been vaccinated against COVID-19 with the vaccine by either Pfizer-BioNTech (Comirnaty®) or Moderna (COVID-19 Vaccine Moderna®) were referred for FNA at our institution to evaluate positron emission tomography (PET)-positive or palpably enlarged lymph nodes. Informed consent was obtained for anonymous publishing of diagnostic data in this work. Sonography guided FNA was performed by two experienced cytopathologists (MN, FS). The material was processed and triaged according to standard protocols [22]. Where indicated, additional analysis was initiated. Flow cytometry was performed as described before [23]. Clonality analysis followed standardised guidelines [24].

## Results

Patients were referred to our outpatient clinic for FNA of enlarged painless lymph nodes. Two patients (numbers 1 and 5) underwent a PET / computed tomography (CT) scan for follow-up after small cell and adenocarcinoma of the lung. One patient (number 4) was suspected of relapse after incidental diagnosis of a neuroendocrine tumour of the appendix 6 years previously. Two patients (numbers 2 and 3) were female healthcare professionals worried about having metastatic cancer, namely breast cancer, after detecting palpably enlarged lymph nodes on the lower neck, and infraclavicular and axillary sites.

All patients presented with palpable or easily detectable superficial lymph nodes on ultrasound in different locations, either in cervical level IV, supra-, infra-, or retroclavicular regions, and in the axilla. Sonographic imaging revealed partially hypo- and partially isoechogenic lymph nodes (fig. 1A). The width ranged from 1.0 to 2.4 cm in size, with ovoid to rounded shapes, sharp borders and only partially detectable hilum. Some lymph nodes presented with suspicious sonographic findings (spherical shape with loss of hilum) [25] (see also supplementary fig. S2 in the appendix).

In the detailed anamnesis in our outpatient clinic, all patients reported that they had been vaccinated against COVID-19 between 3 and 33 days prior to FNA with either Comirnaty® from Pfizer-BioNTech or COVID-19 Vaccine Moderna® from Moderna. With the exception of Patient 5, the vaccine had been administered into the left deltoid muscle. In four of five patients, the enlargement of lymph nodes was ipsilateral. In Patient 1, PET/CT scan showed enlarged and very highly $^{18}$F-2-fluorodesoxyglucose (FDG)-active axillary lymph nodes ipsilateral to the vaccination site and the radiologist already suspected vaccine-associated reactive lymphadenopathy when requesting further workup. Patient 5 presented with a contralateral retroclavicular lymph node suspicious for metastasis in a PET/CT scan with moderate FDG activity, which lead to referral for a cytopathological evaluation. In the same patient, axillary lymph nodes ipsilateral to the vaccination site showed very high FDG-activity (fig. 1B), but were assumed to be vaccine-associated by the attending radiologist and not further analysed. Simultaneously detected mediastinal lymph nodes, which were later diagnosed as metastases by endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA), showed identically high FDG-activity levels. The detailed patient information is summarised in table 1.

Microscopically, carcinoma metastases could be ruled out both morphologically and immunohistochemically. The smears showed a florid reactive lymphadenopathy pattern, characterised by a mixed lymphoid population with lymphocytes at different stages of maturation including many centroblasts admixed with numerous tingible body macrophages (fig. 1C) [26]. Immunohistochemistry in Patient 5 revealed a reactive pattern with predominant CD3- and CD5-positive T cells, admixed with CD20-positive B cells without co-expression of CyclinD1, CD5, CD10 or CD23. CD21 marked dendritic cells. Flow cytometry was performed in three samples (patients 2–4) and revealed a T-cell predominant population with 72% CD3-positive T cells over 23% CD19-positive B cells (fig. 1D), and 79% CD3-postitve T cells over 19% CD19-positive B cells, respectively, for Patients 3 and 4 (see supplementary fig. S1 in the appendix). One case (Patient 2) showed a predominance of B cells with 55% CD19-positive B cells over 37% CD3-positive T cells. IgH rearrangement polymerase chain-reaction testing revealed a polyclonal B-cell population, consistent with follicular hyperplasia. After 2 months, the lymphadenopathy had clinically regressed in all patients.

## Discussion

In this case series, we present the cytological findings of five patients with reactive lymphadenopathy following COVID-19 vaccination. Vaccine-associated lymphadenopathy is a known AEFI of various vaccines [27] such as influenza [28], human papilloma virus [29, 30], hepatitis B virus [31], measles-mumps-rubella [32–35],

**Figure 1:** A: Sonography of the axilla in Patient 1 revealed an enlarged lymph node. B: Corresponding PET-CT scan in Patient 1 shows axillar lymph nodes ipsilateral to vaccination site with high FDG activity. D: Flow cytometry in Patient 3 showing a T-cell predominant population with 72% CD3-positive T cells over 23% CD19-positive B cells. C: Smear of fine needle aspiration (FNA) (Papanicolaou staining) showing a mixed lymphoid population with lymphocytes at different stages of maturation and numerous tingible body macrophages (arrows).

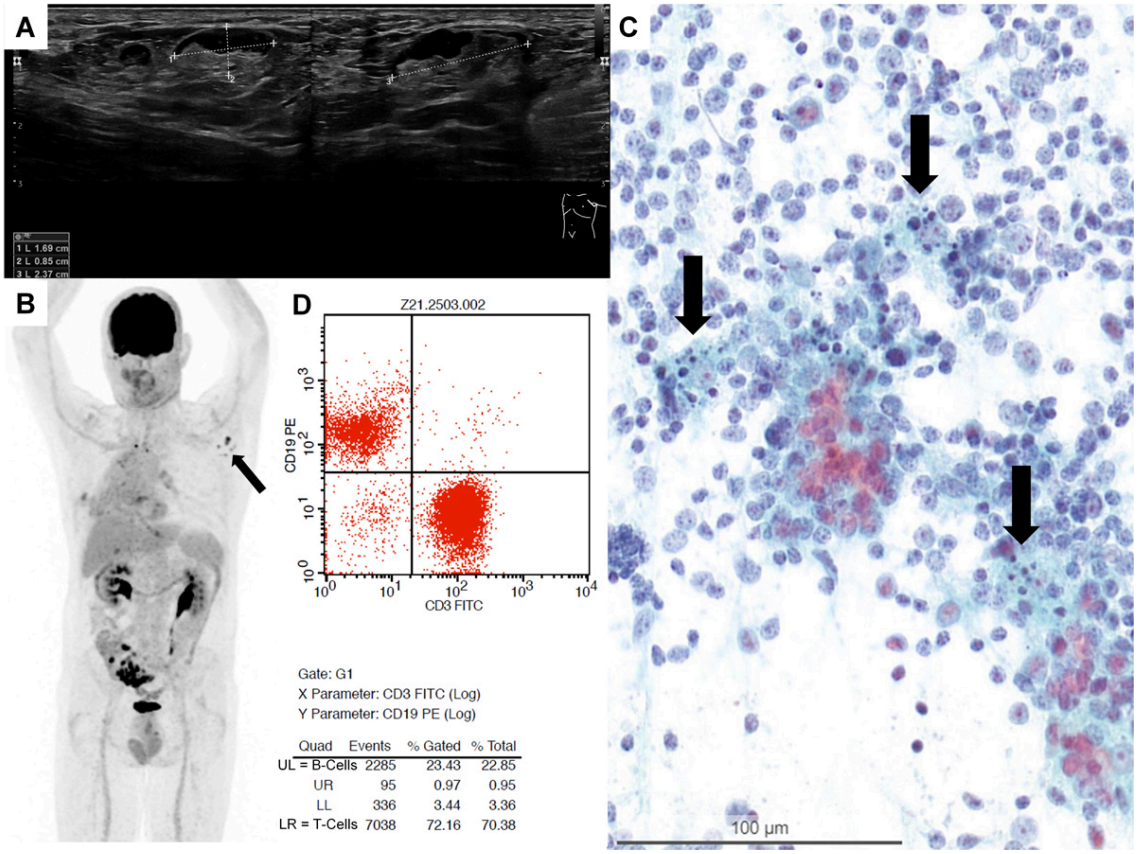


**Table 1:** Summary of patient details.

| Number | Age (years) | Sex | Medical history | Indication for FNA | Vaccination site | Type of vaccine | Interval vaccination–FNA (days) | Site of FNA | Cytological diagnosis | Sydney classification | Follow-up (2 months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 66 | M | Lung cancer | Clinical suspicion of metastasis | L | Moderna (fully vaccinated) | 22 | Left axillary LN | Reactive LA. No evidence of metastasis | 1st level: Benign 2nd level: Post COVID-19 vaccination associated LA | Lymph nodes completely regressed |
| 2 | 41 | F | None | Palpable mass | L | Moderna (1st dose) | 3 | Left infraclavicular LN | Reactive LA. No evidence of malignancy | 1st level: Benign 2nd level: Post COVID-19 vaccination associated LA | Lymph nodes completely regressed |
| 3 | 47 | F | None | Palpable mass | L | Pfizer-BioNTech (1st dose) | 19 | Left supraclavicular LN | Reactive LA. No evidence of malignancy | 1st level: Benign 2nd level: Post COVID-19 vaccination associated LA | Lymph nodes completely regressed |
| 4 | 47 | F | Appendix NET | Clinical suspicion of metastasis | L | Moderna (1st dose) | 8 | Left cervical level IV LN | Reactive LA. No evidence of metastasis | 1st level: Benign 2nd level: Post COVID-19 vaccination associated LA | Lymph nodes completely regressed |
| 5 | 52 | M | Lung cancer | Clinical suspicion of metastasis | R | Pfizer-BioNTech (fully vaccinated) | 12 | Left retroclavicular LN | No evidence of metastasis. No evidence of lymphoma | 1st level: Benign 2nd level: Post COVID-19 vaccination associated LA | Lymph nodes completely regressed |

FNA = fine needle aspiration; LA = lymphadenopathy; LN = lymph node; NET = neuroendocrine tumour

tetanus toxoid [36], smallpox [37], and bacille Calmette-Guérin [38–40], and has also been found for both the Pfizer-BioNTech and Moderna COVID-19 vaccines [41–48]. Reactive lymphadenopathy has even been suggested to be a potential indicator for successful immunisation overall, as it implies activation of the immune system [43, 49, 50]. In radiology and nuclear medicine, enhanced tracer uptake in reactive lymph nodes after any vaccination is a potential differential diagnosis in PET/CT scans [51–58] and is also emerging for COVID-19 vaccines [59–66]. However, there is little information on cytopathological findings.

Lymphadenopathy occurs in various contexts, summarised by the MIAMI acronym: malignancies, infections, autoimmune disorders, miscellaneous and unusual conditions, and iatrogenic causes [67]. FNA represents a safe, quick and cost-efficient tool in the evaluation of cervical lymphadenopathy [26]. In a systematic review and meta-analysis of 30 studies, FNA of cervical lymph nodes (total of 782 aspirates) showed a sensitivity of 94.2% and specificity of 96.9% [68]. However, it must be kept in mind that subclassification of lymphoma and inaccurate diagnosis of low grade lymphoma are well known limitations of FNA. A systematic review of 42 studies reported a median rate of 66–74% at which FNA and core needle biopsies yielded a subtype-specific diagnosis of lymphoma [69].

The recently proposed Sydney System for lymph node FNA cytology provides information on how to approach lymphadenopathy to ensure results of the best attainable quality. It provides clear reporting categories with possible differential diagnosis, and recommends further procedures depending on the context of presentation [70]. Detailed clinical information (medical history and physical examination), as well as results from further diagnostic tests such as imaging or serology, are crucial in the evaluation of cytological smears from lymph nodes. Overall, the prevalence of malignancy for incidental lymphadenopathy only amounts to 1.1% [71]. However, as cancer patients are preferentially vaccinated against COVID-19 because of the risk of severe course of the disease, vaccine-associated reactive lymphadenopathy might be misinterpreted as cancer progression. Thus, FNA can contribute to a rapid and cost-effective workup of lymphadenopathy.

The currently administered COVID-19 vaccines by Pfizer-BioNTech and Moderna both use a novel technique in which messenger RNA (mRNA) encoding the full-length viral spike protein is encapsulated in lipid nanoparticles to stimulate the production of the viral protein in the recipient's own cells, thereby provoking an immune response [72]. mRNA itself is highly immunogenic, but components of the lipid nanoparticles such as polyethylene glycol might also cause the observed reactive lymphadenopathy [73–76]. Due to the postulated strong immune response after mRNA COVID-19 vaccination, time spans of lymph node enlargement have been longer than in previous cases of vaccine-associated lymphadenopathy [77], where reactions occurred shortly after vaccination and disappeared rapidly within 14 days [54]. Indeed, we observed intervals between vaccination and FNA of up to 33 days, which calls for a longer observation period. Interestingly, other reports of vaccine-associated lymphadenopathy described mainly enlarged axillary lymph nodes, which was explained by the drainage pattern after injection into the deltoid muscle. In contrast, the enlarged lymph nodes in our patients occurred at various superficial sites of the upper body. This might be a result of varying injection techniques, slight deviation of injection site, or individual variables such as lymph draining routes and immune responses [78]. Fernández-Prada and colleagues described a series of cases of supraclavicular lymphadenopathy after COVID-19 vaccination and attributed these to higher than usual injection into the deltoid muscle [79], expanding the usual expected sites of vaccine-associated lymphadenopathy in patients with a recent COVID-19 vaccination.

In conclusion, we expect an increase of cases of COVID-19 vaccine-associated lymphadenopathy as a result of the ongoing intensive vaccination programme. The risk of overdiagnosis and overtreatment is especially high in cancer patients (e.g., head and neck carcinomas, lung, breast, skin cancer, or lymphoproliferative disease). In this patient group not only the treating physician but also the patients themselves are sensitised to palpable masses and might demand further workup. In this context, we recommend that patients be actively asked about recent COVID-19 vaccination [80]. It has been shown that the currently applied COVID-19 vaccines are safe and likewise evoke an immune response in oncological patients [81–83]. Therefore, whenever possible, vaccination should be administered contralaterally to the site of malignancy to avoid confusion regarding lymph node enlargement. In agreement with our findings and previous data from imaging studies of COVID-19 vaccine-associated lymphadenopathy [84–89], we recommend: (1) documentation of vaccination history, including date, site and type of vaccine given; (2) a low threshold for diagnostic procedures (e.g., ultrasound, FNA) in patients with a known cancer history; (3) a cautious watch-and-wait approach with follow-up physical examination in otherwise healthy patients; and (4) further diagnostic tests (e.g., ultrasound) if the lymph nodes enlarge or persist (2 to) 6 weeks after the second vaccination dose. In this context, FNA represents a fast and accurate tool to guide further management.

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## Appendix: Supplementary data

**Figure S1:** Flow cytometry in Patients 2–4 compared with a control case (48-year-old, unvaccinated female with nonspecific lymphadenopathy).

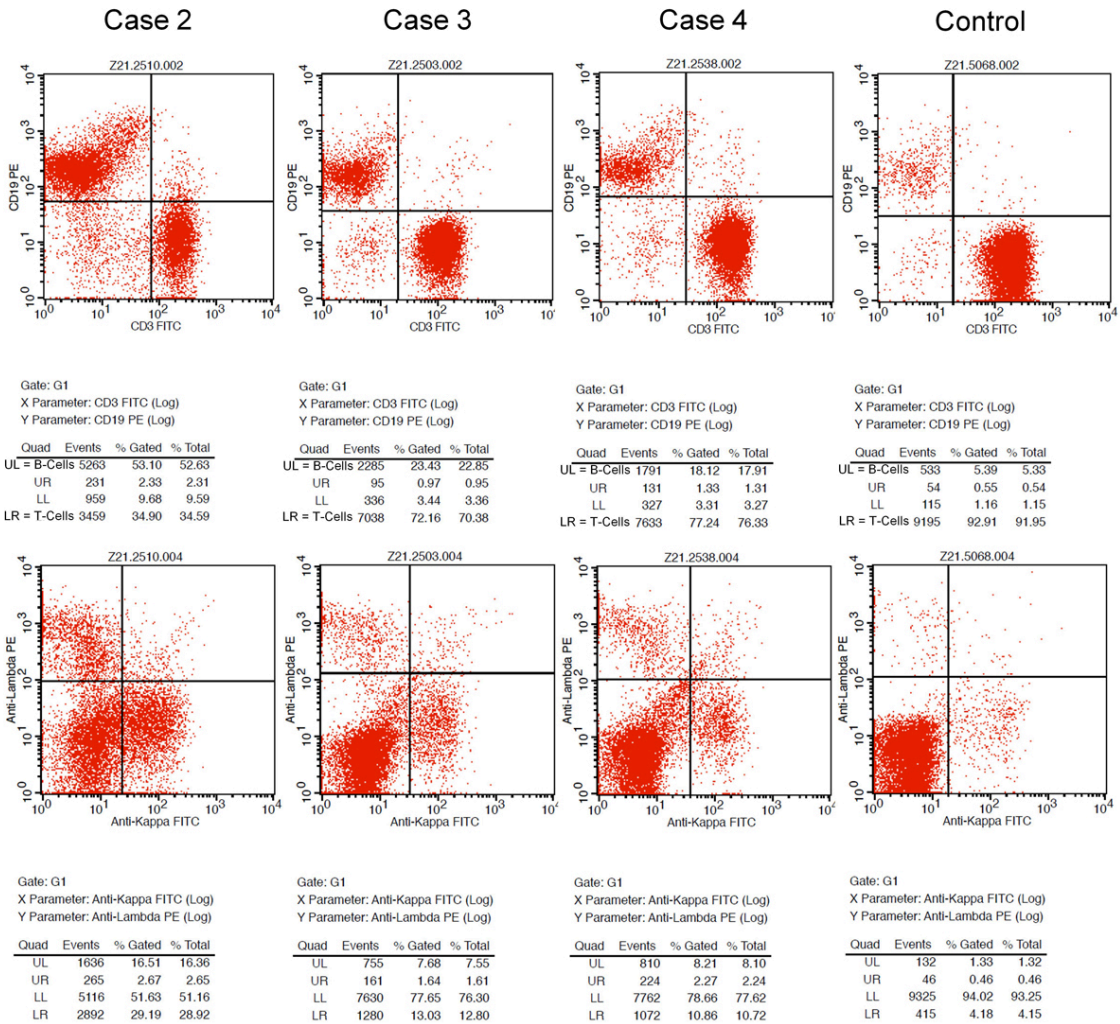

**Figure S2:** Ultrasound findings of Patients 2–4 showing enlarged ovoid to spherical lymph nodes with loss of hilum.