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BRIEF REPORT

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COVID-19 post-vaccination lymphadenopathy: Report of cytological findings from fine needle aspiration biopsy

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Abstract

The coronavirus COVID-19 pandemic has spurred the rapid development of vaccines, with vaccination programmes already underway in many countries. Regional lymphadenopathy is one of the documented side effects of vaccination. We document the fine needle aspiration cytological findings of an enlarged supraclavicular lymph node in a 34-year-old Asian female following the first dose of the Pfizer-BioNTech COVID-19 mRNA vaccine, which appears to be the first such report in a premorbidly well patient with no known history of malignancy. The cytological findings featured a reactive pattern in keeping with follicular hyperplasia, with prominent germinal centre elements including lymphohistiocytic aggregates and tingible-body macrophages. Despite an increased proportion of larger lymphocytes, the overall pattern was in keeping with a reactive pattern, bearing in mind the temporal and geographic relation to the vaccination injection. In instances of localised lymphadenopathy, particularly in supraclavicular or axillary locations, pathologists should be cognizant of the possibility of post-vaccination reactive lymphadenopathy, and seek clinical and radiological hints favouring a benign process, whilst recognising potential morphological overlaps with lymphoproliferative disorders. Awareness of this diagnostic pitfall is especially important as COVID-19 vaccination coverage is ramped up worldwide, leading to an expected increase in incidence of post-vaccination reactive lymphadenopathy.

KEYWORDS
COVID-19, cytology, FNA, lymphadenopathy, post-vaccination

1 | INTRODUCTION

The COVID-19 pandemic has spurred the rapid development of several vaccines over the last year. In Singapore, vaccination using the Pfizer-BioNTech COVID-19 mRNA vaccine is currently underway. One of the documented side effects of the Pfizer-BioNTech COVID-19 vaccine is post-vaccination lymphadenopathy.[1]

2 | CASE REPORT

We report findings of a lymph node aspirate from a 34-year-old Asian female patient who experienced left supraclavicular lymphadenopathy 1 day after her first dose of Pfizer-BioNTech COVID-19 mRNA vaccine. She sought medical advice 16 days after the vaccine when the lymphadenopathy persisted. In addition to lymphadenopathy, the patient experienced mild soreness over the left deltoid region where the vaccine had been administered. She was otherwise well, with no accompanying fever or systemic symptoms. There was no clinical suspicion of infection, autoimmune disease or any other cause of lymphadenopathy at the time of presentation.

On palpation, there was a slightly tender, ovoid left supraclavicular lymph node measuring 10 mm in maximal dimension. Examination of the ear, nose and throat, including nasopharyngeal endoscopy, was unremarkable. At a follow-up visit 8 days later (24 days post-vaccination), the lymphadenopathy persisted but was

no longer tender. Bedside ultrasound revealed a well-circumscribed lymph node measuring 10.9 × 9.9 × 7.1 mm with minimal internal vascularity and no calcification. The hilum was not clearly visualised, however, no sonographically suspicious features were noted.

In view of persistent supraclavicular lymphadenopathy in the context of an otherwise unremarkable head and neck examination, a fine needle aspiration (FNA) biopsy was performed to exclude an occult metastatic malignancy from thoracic and abdominal sites. Direct air-dried and alcohol-fixed smears of the aspirate were stained with Hemacolor and Pap stains respectively. The smears revealed a mixed lymphoid population comprising a range of small to large lymphocytes. There was an increased proportion of large, activated lymphocytes in some areas (Figure 1A). The larger lymphoid cells featured a thin rim of bluish cytoplasm, and small, sometimes peripheral nucleoli. Germinal centre components including lymphohistiocytic aggregates with follicular dendritic cells, tingible body macrophages and centroblasts were also present (Figure 1B). Tingible-body macrophages were particularly prominent and many contained abundant karyorrhectic debris (Figure 1C, D). Plasma cells and eosinophils were not prominent. No necrosis or granulomas were seen. The overall findings favoured a reactive process that was suggestive of reactive follicular hyperplasia. No cellblock was processed and no ancillary studies were performed.

Upon review a further 2 weeks later, the lymph node was observed to have reduced in size to 8.0 mm in maximal dimension. The patient subsequently proceeded with the second dose of vaccination. Four weeks following the second dose of vaccination (2 weeks after the first vaccination dose), she was seen in clinic where the lymph node was neither palpable nor readily appreciable on ultrasound.

3 | DISCUSSION

Post-vaccination lymphadenopathy refers to reactive changes occurring within lymph nodes following vaccination, and it has been documented in multiple vaccine types.[2,3] Recently, several case reports and series of COVID-19 post-vaccination lymphadenopathy, mostly focusing on the imaging aspects of the enlarged nodes, have been published.[4–12] The finding of lymphadenopathy on sonography or magnetic resonance imaging, and/or increased fluorodeoxyglucose uptake in lymph nodes seen on positron emission tomography/computed tomography scans may prompt suspicion for a neoplastic process, especially if recent history of vaccination is not elicited.[4–7,10,11] Awareness of this is particularly pertinent in female patients who may have post-vaccination axillary lymphadenopathy at the time of breast cancer screening. Some authors regard ipsilateral axillary lymphadenopathy within 4–6 weeks of any dose of COVID-19 vaccine to be most likely vaccination-related, with current proposed guidelines advocating cancer surveillance, screening or staging imaging to be performed either prior to vaccination or at least 4–6 weeks after the second dose.[6,12–14] Additionally, the sonographic finding of a preserved fatty hilum favours a benign process.[12]

In nanoparticle encapsulated mRNA vaccines, nanoparticle uptake and production of antigen occurs primarily at the site of injection and within the draining lymph node, followed by activation of antigen-presenting cells and priming of robust CD4+ T-cell responses, formation of germinal centres and production of antigen-specific antibodies.[15,16] At the time of writing, the histological features of COVID-19 mRNA post-vaccination lymphadenopathy have only been described in two publications, in which three patients with either a

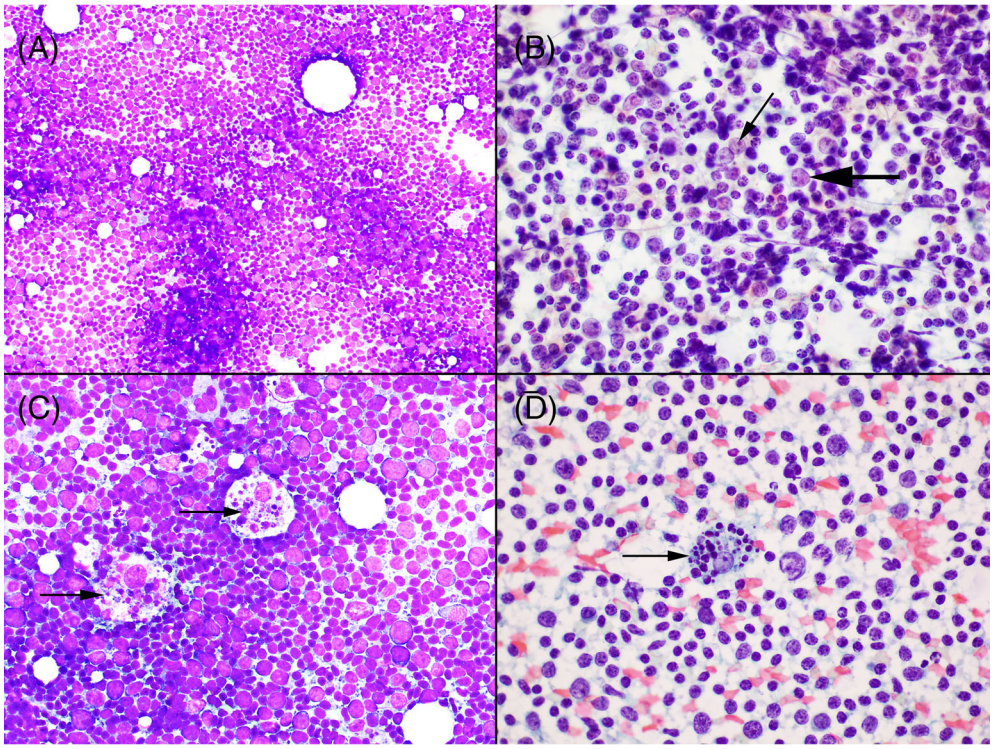

FIGURE 1 Cytological findings. (A) A mixed lymphoid population with increased numbers of larger lymphocytes. Hemacolor, ×200. (B) Lymphohistiocytic aggregate from germinal centre, with occasional follicular dendritic cells (thin arrow) and centroblasts (thick arrow). Papanicolaou, ×600. (C) Tingible-body macrophages (arrows) and increased numbers of large lymphocytes. Hemacolor, ×400. (D) Tingible-body macrophage (arrow) containing abundant apoptotic debris. Papanicolaou, ×600

personal or family history of breast cancer had biopsies of enlarged axillary lymph nodes showing follicular hyperplasia and interfollicular expansion of small lymphocytes, consistent with post-vaccination reactive lymphadenopathy.[4,14]

To our knowledge, this is the first report of FNA cytology of COVID-19 post-vaccination lymphadenopathy in a patient without a prior history of malignancy, and the second documentation in the literature illustrating the cytomorphological features. Aalberg et al. have documented cytological findings in an axillary lymph node in a 73-year-old patient with renal cell carcinoma, showing a polymorphous lymphoid population with no evidence of metastatic disease.[17] In the current tissue sample, we observed prominent germinal centre elements in the smears such as conspicuous tingible-body macrophages admixed with lymphohistiocytic aggregates and follicular dendritic cells, on a polymorphic lymphocytic background. Despite an increased proportion of larger lymphocytes, the overall mixed lymphoid population reflects a "milieu" typical of reactive lymph nodes, and suggests a pattern of reactive follicular hyperplasia that is congruent with the previously described histological findings.

As post-vaccination lymphadenopathy typically occurs in readily accessible sites for example, cervical, axillary and supraclavicular lymph nodes, direct or image-guided FNA cytology may be employed as a first-line investigation, considering its ease, cost-effectiveness and minimally invasive nature. That said, FNA cytology should be interpreted in the context of relevant epidemiological, clinical and radiological findings. In view of the global and widespread administration of the COVID-19 vaccine, a history of recent vaccination, vaccine type and the site of vaccination should routinely be sought in patients of vaccine-eligible ages. Sonographic findings of a preserved fatty hilum are also somewhat reassuring and may prompt a more conservative, wait-and-see approach. However, even with a history of recent vaccination, certain circumstances should prompt a more cautious approach to labelling these cases as reactive. Possible clinical red flags include the presence of rounded or matted lymph nodes, persistent or prolonged lymphadenopathy, particularly in elderly patients, generalised lymphadenopathy and/or constitutional symptoms (e.g., weight loss). In these situations, smears which show increased numbers of large lymphoid cells/immunoblasts must be reviewed carefully and may invoke consideration of lymphoma. Moreover, tingible-body macrophages can be numerous in some high-grade non-Hodgkin lymphomas and should be evaluated in conjunction with the usual morphological features of predominant lymphoid cell size, cell makeup and cytomorphology.

In the absence of accompanying worrisome clinical and radiological features, a mixed lymphoid population with increased numbers of activated lymphoid cells can still be in keeping with post-vaccination reactive lymphadenopathy and it may be appropriate to simply continue clinical or radiological follow-up. A carefully worded cytopathology report suggesting follow-up, and further investigations if lymphadenopathy persists (e.g., excision, core biopsy, flow cytometry), may be prudent.

As many countries ramp up COVID-19 vaccination coverage, we can only expect the clinical presentation of post-vaccination lymphadenopathy to increase in frequency. Thus, pathologists should be cognizant of the spectrum of cytological findings of COVID-19 post-vaccination lymphadenopathy, which may pose a potential diagnostic pitfall for false positive diagnosis of lymphoproliferative disease owing to the enriched population of larger activated lymphoid cells. Likewise, documentation of temporal relation to COVID-19 vaccination would also be helpful in clinical notes, when encountering lymphadenopathy in the usual locations for example, supraclavicular, cervical and axillary lymph nodes, as well as mention of the site of vaccination injection. Finally, further studies to document different cytological patterns of reactive lymphadenopathy may also be relevant, in view of the variety of vaccines that are available in the market.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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