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Case Report

Lymphoid Neoplasms and COVID-19 Vaccination

Onochie Ikenna Obodo[1*], Sunday Ocheni[1], Odichimma Callista Obodo[2], Augustine Nwakuche Duru[1], Helen Chioma Okoye[1], Charles Emeka Nonyelu[1], Ikechukwu Okwudili Anigbogu[1], Theresa Ukamaka Nwagha[1] and Anazoeze Jude Madu[1]

[1]Department of Haematology and Immunology, University of Nigeria Teaching Hospital, Enugu, Nigeria; [2]Department of Anaesthesia, University of Nigeria Teaching Hospital, Enugu, Nigeria

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Abstract

It is established that administration of the COVID-19 vaccine may be associated with an exaggerated immune response leading to enlargement of several lymph nodes. Although most cases are benign and self-limiting, some have been reported in the literature as B-cell or T-cell lymphomas, with no reported cases of chronic lymphocytic leukaemia (CLL). We report two cases of follicular lymphoma and CLL that occurred a few weeks after COVID-19 vaccination. Case 1 is a 48-year-old woman who noticed two significantly palpable masses, one in each axilla, 48 h after receiving the first dose of the Pfizer-BioNTech BNT162b2 vaccine for COVID-19. Seven days later, she noticed another mass on the right side of her neck, which was biopsied within 48 hours. Case 2 is a 75-year-old man who presented with localized swellings in the axilla and on the neck, noted 24 h after the first dose of the Moderna messenger RNA-1273 COVID-19 vaccine. Neither patient reported any constitutional or associated symptoms. Surgical biopsy of the axillary lymph node in case 1 revealed a non-Hodgkin lymphoma, confirmed via immunohistochemistry as CD20-positive B-cell follicular lymphoma. The patient also had multiple pre- and para-aortic lymph nodes. In case 2, complete blood count showed lymphocytosis (total white blood cell – 148 × 10^9/L; lymphocyte differential – 92%), while peripheral blood film showed lymphocytosis with a predominance of small, mature-looking lymphocytes, both suggesting CLL. Although requested, immunophenotyping and molecular testing were not performed due to patient-related challenges. Although a chance occurrence is possible, lymphoid malignancies should be considered a strong differential. The vaccination history of patients presenting with clinical manifestations suggestive of a lymphoid malignancy should be thoroughly investigated, while ruling out other possible differentials such as a benign, self-limiting inflammatory process.

Introduction

The COVID-19 pandemic has led to more than seven million deaths among over 770 million recorded cases in 210 countries worldwide.[1] The introduction of the vaccine brought relief, though its acceptance varied globally. The most frequently reported haematological adverse effects of the vaccine include derangements in haemogram parameters such as thrombocytopaenia, leukocytosis, leukopaenia, neutropaenia, and eosinophilia.[2–6] Other reported haematological complications following vaccination include thromboembolic events and acquired bleeding disorders.[7–9] It is established that vaccination against COVID-19 can induce an exaggerated immune response, leading to enlargement of several lymph nodes (LNs). The most commonly enlarged sites are the axillary, supraclavicular, and cervical LNs. The majority are reactive, benign, self-limiting, and localized to the site of injection.[10–12] However, some cases of post-vaccine lymphadenopathy reported in the literature have turned out to be malignant lymphoid disorders, including lymphoma (B- and T-cell subtypes of non-Hodgkin lymphoma (NHL)) and chronic leukaemia, following further investigation. Lymphadenopathy associated with COVID-19 vaccination frequently occurs within two to four weeks after vaccination and can occur following the first, second, or booster doses.[12–15] Some cases of post-vaccine lymphadenopathy occurring within a few days (two to ten days) after vaccination have also been reported.[16,17] An extensive literature search suggests that no cases of chronic lymphocytic leukaemia (CLL) have been reported following COVID-19 vaccination.[15,18–21] This case report highlights one of the few occurrences where a low-grade lymphoma and a chronic leukaemia can be associated with COVID-19 vaccination. Here, we report two cases of FL and CLL that occurred following COVID-19 vaccination and were managed at our facility, the Uni-

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[*]**Correspondence to**: Onochie Ikenna Obodo, Department of Haematology and Immunology, University of Nigeria Teaching Hospital, Enugu, Nigeria. ORCID: https://orcid.org/0000-0003-3847-5354. Tel: +234-7036910866, E-mail: onochieobodo@unth.edu.ng
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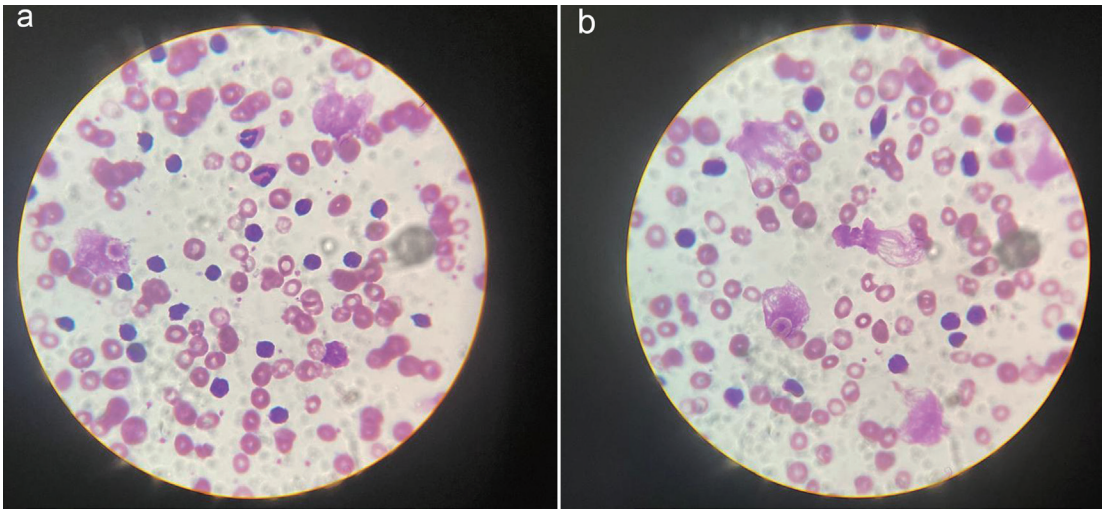

Fig. 1. Blood film (×100) showing leukocytosis with characteristic small mature-looking lymphocytes (a), and numerous smear/smudge cells, small lymphocytes, and a spindle-shaped lymphocyte (b).

versity of Nigeria Teaching Hospital, Enugu, Nigeria. This case series highlights the need for clinicians to investigate the vaccination history of patients presenting with clinical manifestations suggestive of a lymphoid malignancy and to share with the scientific community adverse events linked with the use of these novel vaccines.

Case presentation

Case 1

Patient A is a 48-year-old woman who was referred to our facility with a histologic diagnosis of FL. One month earlier, in 2022, she had received the first dose of the Pfizer-BioNTech BNT162b2 COVID-19 vaccine. She developed generalized malaise 24 h after vaccination, followed by bilateral axillary masses at 48 h and a right cervical mass by the seventh day post-vaccination. She reported no constitutional symptoms prior to or following administration of the vaccine. She presented to a tertiary facility, where a surgical biopsy of the axillary LN was performed. The histology report described macroscopic findings of multiple variably sized and shaped fragments of greyish-white tissue aggregating to 1.0 × 0.5 × 0.5 cm. Microscopy showed complete effacement of the LN architecture, with diffuse sheets of mixed populations of immature lymphocytes. Occasional cells with active mitotic figures and large cells with irregular nuclei and prominent nucleoli were seen. The overall histologic features were suggestive of NHL. Immunohistochemistry of the harvested LN showed strong and diffuse positivity for BCL2, CD20, and CD45, consistent with a diagnosis of CD20-positive B-cell FL. Abdominal ultrasound also revealed multiple enlarged, matted pre- and para-aortic LNs. Molecular and genetic testing to further characterize the disease, such as fluorescence in situ hybridization, polymerase chain reaction, and next-generation sequencing, was not available due to patient- and treatment center-related challenges. Based on the available investigations, a diagnosis of stage III NHL was made. A review of her drug, social, and occupational history revealed no exposure to any potential risk factors that could have led to the onset of FL. The results of viral screening showed that hepatitis and human immunodeficiency virus were negative. Due to diagnostic limitations, cytomegalovirus, Epstein–Barr virus, and other viruses known to increase the risk of lymphoma were not tested. There was also no family history of lymphoid or haematological malignancy. Due to patient-related challenges, further investigations such as fluorescent in situ hybridization were suggested but not performed. She was commenced on a rituximab-based chemoimmunotherapy regimen and is responding to treatment. This is the first reported case of FL occurring post-COVID-19 vaccination. Most subtypes of NHL reported in the literature are diffuse large B-cell lymphoma and cutaneous lymphomas, with no previously reported case of FL.

Case 2

Patient B is a 75-year-old man who presented to our facility with complaints of localized swellings in the axilla and neck of about three months' duration. The swellings were first noted 24 h after the first dose of the Moderna messenger RNA-1273 COVID-19 vaccine and were localized to both axillae. They began to increase in size following the second dose of the vaccine, eventually involving other sites such as the neck and submandibular region. Like the previous patient, he did not report any constitutional symptoms. On physical examination, he was found to have a moderately enlarged spleen (8 cm below the left costal margin). No other intra-abdominal organomegaly was detected. Complete blood count revealed a total white blood cell count of 148 × 10^9/L, with an absolute lymphocyte count of 136 × 10^9/L. The remainder of the haemogram parameters were within normal reference ranges. A peripheral blood smear review showed ≥90% small lymphocytes with scant agranular cytoplasm, a prolymphocyte percentage of 5%, and numerous smudge cells—findings consistent with CLL (Fig. 1a and b). Flow cytometry and cytogenetic/mutational analysis were requested but not performed due to patient-related circumstances. A review of his medication, social, and occupational history did not reveal any potential risk factors for CLL. He also reported no family history of haematological or solid malignancy. The patient was initially commenced on combination chemotherapy using steroids and alkylating agents. The initial response was good, with resolution of the enlarged LNs and normalization of the white cell count. A few weeks later, he relapsed and was started on targeted therapy with ibrutinib and venetoclax, with a partial haematological response observed. His progress is being closely monitored.

The available literature reviewed in the course of drafting this case report showed that the more common lymphoid malignancies potentially associated with COVID-19 vaccination were high grade lymphomas, with no report of chronic lymphocytic leukaemia or follicular lymphoma.[18–21]

Discussion

There have been a few cases of lymphoma diagnosed shortly after COVID-19 vaccination reported in the literature.[15,18–21] A review by Cavanna *et al*.[15] reported a total of eight patients who developed NHL post–COVID-19 vaccination. The lymphoma types identified included Epstein–Barr virus-positive diffuse large B-cell lymphoma (DLBCL), subcutaneous panniculitis-like T-cell lymphoma, extranodal marginal zone lymphoma, extranodal NK/T-cell lymphoma, and primary cutaneous anaplastic large cell lymphoma. Mizutani *et al*.[20] also reported two cases of DLBCL arising after vaccination with the Pfizer-BioNTech BNT162b2. These findings were similar to those of Zamfir *et al*.,[21] who reported two cases of DLBCL and T/NK-cell lymphoma post-Pfizer-BioNTech BNT162b2 vaccination. Of the cases reported in the literature, DLBCL appeared to be the most frequently described, with some cases of cutaneous lymphomas at the vaccine injection site being the second most common type.[15,18,19,22–24] None of the published literature reported FL or CLL as lymphoid malignancies arising post–COVID-19 vaccination. The most common presenting complaint among reported patients was the presence of lymphadenopathy, typically single and ipsilateral.[15] The time to onset of lymphadenopathy varied from as early as 24 h to as late as 110 days post-vaccination. The most commonly implicated vaccine types were the Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273, in descending order.[18] Less commonly implicated vaccines included Ad26.COV2.S (Johnson & Johnson), ChAdOx1 nCoV-19, and Novavax.[17] Both patients in our report received mRNA vaccines—Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273—and developed lymphadenopathy within 24 and 48 h in the CLL and FL cases, respectively. While symptoms leading to the diagnosis of lymphoma can occur after the first, second, third, or even booster doses, several studies reported that the majority occurred after the first and second doses.[18] Similar to some reported cases, both our patients noticed lymphadenopathy after the first dose of the COVID-19 vaccine.

Although the exact mechanism by which COVID-19 vaccines might induce the formation or progression of malignant lymphoma has not been fully elucidated, several possibilities—similar across lymphoma types—have been proposed.[13] mRNA-based vaccines are known to induce hyperstimulation of the immune system, causing the release of inflammatory cytokines such as interleukin (IL)-15, tumor necrosis factor-α, interferon-γ, C-X-C motif chemokine ligand 10, and IL-6.[13,18,20,25] This phenomenon may result from the ability of mRNA vaccines to induce a persistent and exaggerated germinal center B-cell response via activation of helper T cells, specifically T follicular helper cells.[13,21,26] Another proposed mechanism is the role of vaccine adjuvants in inducing the formation or rapid progression of lymphoid malignancies.[22,27] Adjuvants enhance both cellular and humoral immune responses via stimulation of T helper 1 and 2 cell responses, either individually or in combination.[27,28] They can also act as ligands for pattern recognition receptors in innate immunity, leading to their activation.[27,29] The resulting signaling pathways promote secretion of inflammatory cytokines such as IL-6, IL-10, IL-12, IL-1β, and IFN-α/β, ultimately improving vaccine immunogenicity.[27,29] One implicated adjuvant thought capable of inducing lymphomagenesis is the lipid nanoparticle.[18]

While it is not definitively established that COVID-19 vaccines are pro-oncogenic or capable of inducing tumor formation, they may potentiate the progression of a quiescent malignancy—including lymphoproliferative disorders—into a more overt and aggressive clinical entity. Although FL and CLL typically evolve over months to years, it is possible that both index patients had pre-existing, subclinical lymphoid disorders that became clinically apparent following the exaggerated immune response triggered by COVID-19 vaccination.

Conclusions

Although the majority of lymphadenopathy cases occurring after COVID-19 vaccination are reported to be benign with spontaneous resolution, a few have been documented in the literature as B- and T-cell lymphomas, including one of the index cases in this report, with no prior reported cases of leukaemia. Typically, the course of CLL and NHL extends over months to years; however, in the cases described here, LN enlargement and diagnosis occurred within weeks to a few months. While this does not establish a strong causal relationship between vaccination and disease onset, the fact that symptoms did not resolve spontaneously, but instead improved gradually following initiation of chemoimmunotherapy, supports the possibility of vaccine-associated lymphoid disorders in these patients. Furthermore, the small sample size and diagnostic limitations may affect the ability to draw a definitive conclusion about a direct association between vaccination and the onset of lymphoid malignancies.

The mechanisms described above warrant further investigation to better define the potential role of COVID-19 vaccination in lymphomagenesis.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Study concept and design (OIO, SO, AND), summary of the key clinical findings (OIO, OCO, IOA), drafting of the manuscript (OIO, CEN, HCO), and critical review of the manuscript for important intellectual content (SO, TUN, AJM). All authors have approved the final version and publication of the manuscript.

Ethical statement

This case report, describing two clinical cases, was a retrospective analysis of three or fewer cases and is not considered human research according to the U.S. federal policy and the institutional review board regulations of the University of Nigeria Teaching Hospital. Institutional review board approval was therefore

deemed unnecessary. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from the patients for publication of this case report and the accompanying images. In these forms, the patients gave their consent for their images and other clinical information to be reported in this journal. The patients understand that their names and initials will not be published and that due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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