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Case Report

Prolonged generalized immune response on ^{18}F-FDG PET/CT following COVID-19 vaccination ☆

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ABSTRACT

The Coronavirus disease 2019 (COVID-19) pandemic continues to be a major public health concern affecting millions of people globally. The COVID-19 vaccination has implications in medical assessment of cancer patients especially undergoing diagnostic imaging such as ^{18}F-fluoro-deoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT). The inflammatory changes following vaccination can cause false positive findings on imaging. We present a case of a patient with esophageal carcinoma who had ^{18}F-FDG PET/CT scan, 8 weeks following booster dose of Moderna COVID-19 vaccination, which showed widespread FDG avid reactive lymph nodes and intense splenic uptake for prolonged duration of approximately 8 months (34 weeks) probably representing generalized immune response. It is important from radiological/nuclear medicine perspective to recognize imaging features of such rare effect of COVID-19 vaccination, which can pose a challenge in assessing ^{18}F-FDG PET/CT scans in cancer patients. It has also opened new avenues for future research evaluating such COVID-19 vaccine-related prolonged systemic immunological response in cancer patients.

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affected more than 600 million people and more than 6 million deaths worldwide by December 2022, resulting in a major public health issue globally [1–4]. Till to date more than 13 billion doses of COVID-19 vaccines have been administered worldwide, which has played an important role in reducing the risk of infection and severity of disease from SARS-CoV-2 including more transmissible variants such as omicron (B.1.1.529) [1–3]. On a global health front approximately 20 million people have been saved during the first year of the massive COVID-19 vaccination drive [2].

A recent article from New England Journal of Medicine (NEJM), stated that as of May 6, 2022, more than 300 COVID-19 vaccines were in preclinical or clinical development as per report from World Health Organization (WHO) [2]. In the United States of America, Food and Drug Administration

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(FDA) has given either full approval or emergency use authorization to four vaccines, out of which two are messenger RNA (mRNA)- based vaccines Pfizer–BioNTech's Comirnaty (BNT162b2) and Moderna's Spikevax (mRNA-1273), the adenovirus vector-based vaccine from Johnson & Johnson's Janssen (Ad26.COV2.S), and adjuvanted protein vaccine from the Novavax's Nuvaxovid and Covovax (NVX-CoV2373) [2,5].

The mass COVID-19 vaccination has implications in medical management of patients especially cancer patients undergoing diagnostic imaging. It has been noted that following vaccination into deltoid musculature, ipsilateral regional lymphadenopathy involving axillary, supraclavicular, and cervical lymph nodes can occur [4,5]. Center for Disease Control and Prevention (CDC) of the United States has noted loco-regional reaction such as swelling, and tenderness of axillary lymph nodes as the second most common reported side effect, after pain at site of injection following Moderna COVID-19 vaccines [6,7]. In most instances there is a vaccine-induced focal uptake at the site of vaccination usually in the deltoid musculature along with hypermetabolic activity in the regional lymphadenopathy on ^{18}F-fluoro-deoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT) [4,5]. This can cause difficulty in evaluating scans for staging or assessing treatment response. FDG avid vaccine-related local muscle uptake and regional lymphadenopathy has also been seen with various other vaccination including seasonal flu/ influenza (H1N1) vaccination [8–10]. Generally, this phenomenon is transient and usually subsides by 2-6 weeks post-vaccination [4–5].

In this article, we present a case of esophageal carcinoma demonstrating FDG uptake in multi-station lymph nodes and spleen for prolonged duration of approximately 8 months (34 weeks) probably representing generalized immune response following COVID-19 vaccination.

Case presentation

A 73-year-old male was diagnosed with stage IV poorly differentiated adenocarcinoma of gastroesophageal (GE) junction metastatic to liver. Patient was started within a research protocol on FOLFOX, Regorafenib, and Nivolumab from June 2021 onwards. However, because of Nivolumab related acute interstitial nephritis, patient was continued on FOLFOX and Regorafenib only. No granulocyte-macrophage colony-stimulating factors (GM-CSF) was administered at any time in the course of therapy. Patient received 3 doses, including a booster dose, of COVID-19 Moderna vaccine in January 2021 (first dose), February 2021 (second dose), and August 2021 (third/booster dose).

Patient underwent a first ^{18}F-FDG PET/CT scan in June 2021, (Fig. 1), which showed a hypermetabolic malignant mass in distal esophagus (SUVmax 20.5), liver metastases (SUVmax up to 6.0), and a hypermetabolic nodular lesion (SUVmax 3.9), probably malignant implant, at the interface of stomach and transverse colon.

A follow up ^{18}F-FDG PET/CT scan was performed in October 2021, (Fig. 2), approximately 8 weeks following booster dose of COVID-19 vaccine. The scan showed decreased or resolved FDG uptake in distal esophageal lesion, hepatic metastases and at gastric/colonic wall while development of new FDG uptake in multi-station lymph nodes above and below the diaphragm including prominent upper abdominal lymph nodes (SUVmax up to 6.4). Furthermore, these FDG avid lymph nodes were benign appearing on CT. In addition, new diffuse increased uptake was seen in the spleen (SUVmax 4.7) without splenomegaly together with focal moderate FDG uptake in the left deltoid muscle (SUVmax 2.8), at the site of recent COVID-19 vaccine. The constellation of findings along

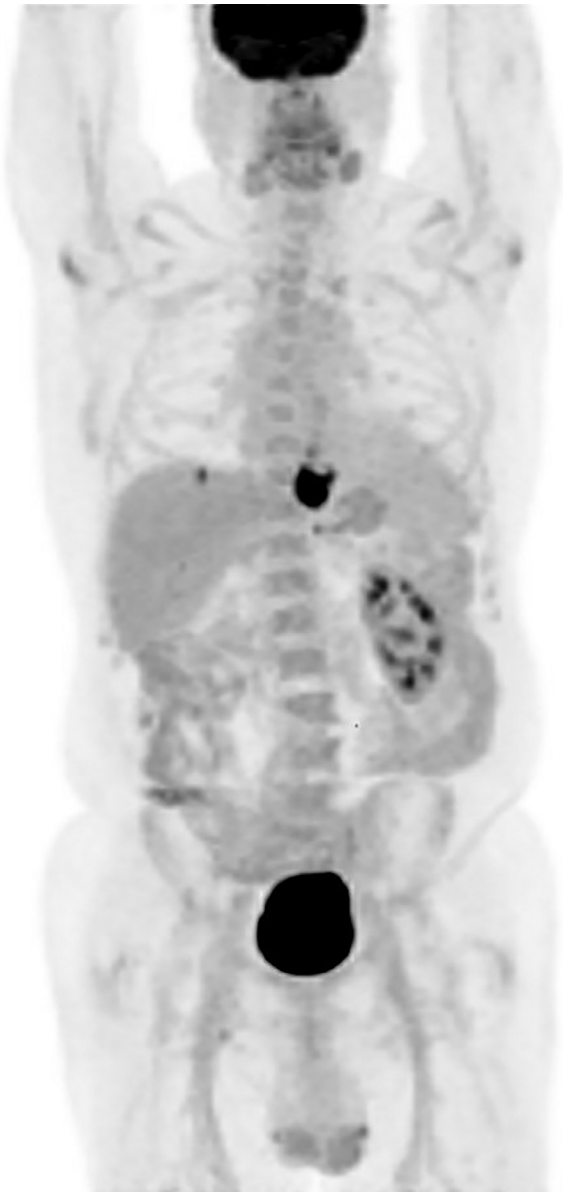

Fig. 1 – The maximum intensity projection (MIP) image from initial ^{18}F-fluoro-deoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET/CT) scan showed a hypermetabolic malignant mass in distal esophagus, liver metastases, and a hypermetabolic nodular lesion at the interface of stomach and transverse colon probably a malignant implant.

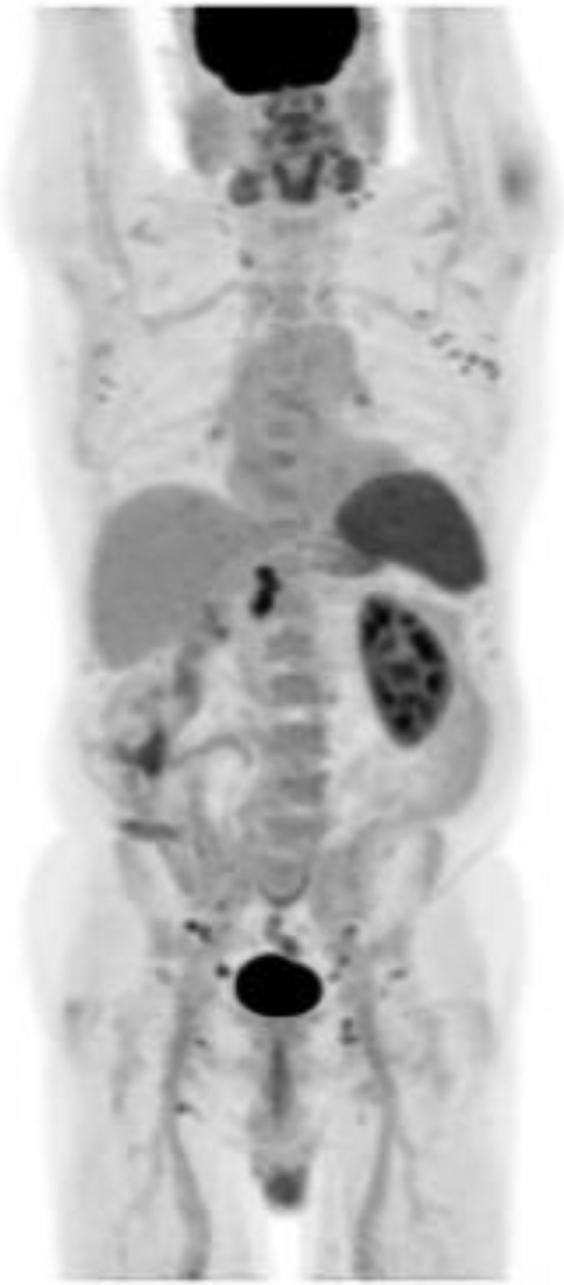

Fig. 2 – The maximum intensity projection (MIP) image from follow-up ^{18}F-fluoro-deoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET/CT) scan performed approximately 8 weeks following booster dose of Coronavirus disease 2019 (COVID-19) vaccine showed decreased or resolved fluoro-deoxyglucose (FDG) uptake in distal esophageal lesion, hepatic metastases and at gastric/colonic wall. However, there were new FDG avid cervical, thoracic, and abdominopelvic lymph nodes, diffuse splenic uptake without splenomegaly and focal moderate FDG uptake in the left deltoid muscle at the site of recent COVID-19 vaccine.

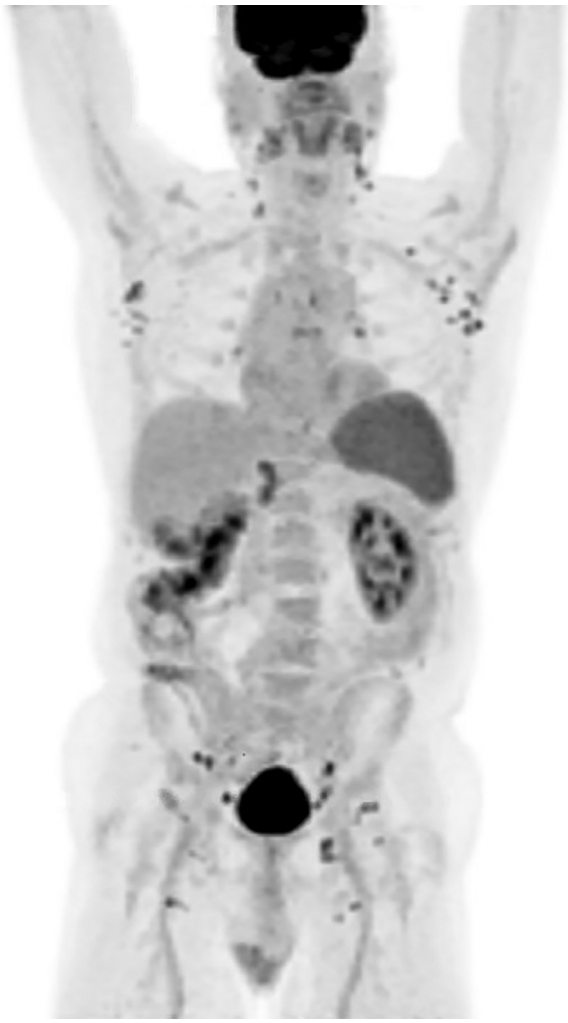

Fig. 3 – The maximum intensity projection (MIP) image from follow-up ^{18}F-fluoro-deoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET/CT) scan performed approximately 16 weeks after booster dose of Coronavirus disease 2019 (COVID-19) vaccine demonstrated persistently increased uptake in cervical, thoracic, and abdominopelvic lymph nodes, and diffuse splenic uptake.

with history of recent vaccination indicated a vaccine-related generalized immune activation.

A follow-up ^{18}F-FDG PET/CT scan in December 2021, (Fig. 3), approximately 16 weeks after booster dose of COVID-19 vaccine demonstrated persistently increased uptake in cervical (SUVmax 5.0), thoracic (SUVmax 3.5), and abdominopelvic (SUVmax 7.4) lymph nodes, as well as diffuse splenic (SUV 5.4) uptake without evidence for active malignancy.

A surveillance ^{18}F-FDG PET/CT scan obtained in February 2022, (Fig. 4), approximately 23 weeks following booster dose of COVID-19 vaccine, showed new hypermetabolic liver metastases (SUVmax 13.4), however decreased FDG uptake in mediastinal (SUVmax 2.1), and abdominopelvic (SUVmax 4.5) lymph nodes and decreased uptake in spleen (SUVmax 3.2),

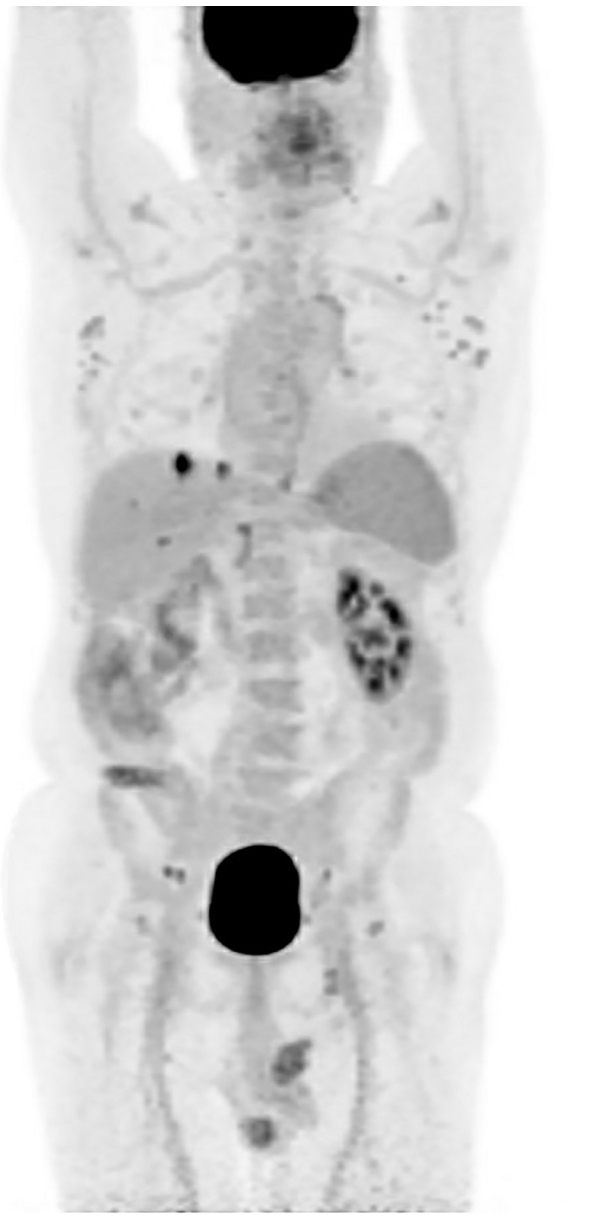

Fig. 4 – The maximum intensity projection (MIP) image from surveillance ^{18}F-fluoro-deoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET/CT) scan performed approximately 23 weeks following booster dose of Coronavirus disease 2019 (COVID-19) vaccine, showed new hypermetabolic liver metastases, however decreased fluoro-deoxyglucose (FDG) uptake in cervical, thoracic, and abdominopelvic lymph nodes and spleen.

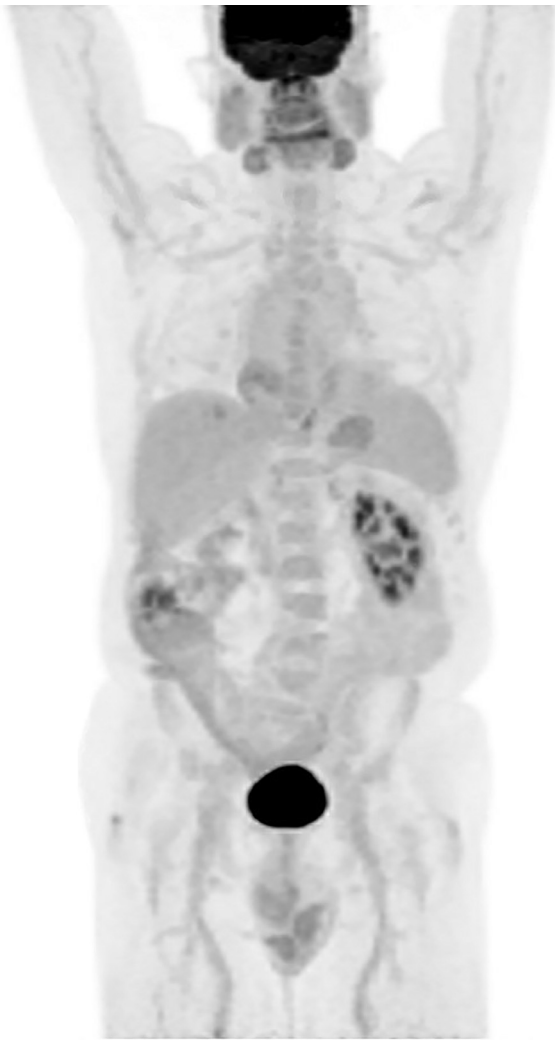

Fig. 5 – The maximum intensity projection (MIP) image from subsequent ^{18}F-fluoro-deoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET/CT) scan performed approximately 34 weeks following booster dose of Coronavirus disease 2019 (COVID-19) vaccine, showed decreased fluoro-deoxyglucose (FDG) avid hepatic metastases and resolved FDG activity in cervical, thoracic, and abdominopelvic lymph nodes and diffuse splenic uptake.

further supporting the reactive etiology while excluding lymphomatous disease process.

On a subsequent ^{18}F-FDG PET/CT scan in May 2022 after change in systemic therapy, (Fig. 5), approximately 34 weeks following booster dose of COVID-19 vaccine, decreased FDG avid hepatic (SUVmax 3.1) metastases while resolved reactive FDG activity in neck, thoracic, and abdominopelvic lymph nodes as well as diffuse splenic FDG uptake was observed.

This is a unique and interesting case of a patient with stage IV esophageal carcinoma at GE junction, who developed increase metabolic activity in spleen and benign appearing lymph nodes at several location probably indicating generalized immune response after a booster dose of Moderna COVID-19 vaccine. The sequential time course of a reactive multi-station lymph nodes with diffuse intense splenic activity are illustrated alongside oncologic disease evolution on consecutive ^{18}F-FDG PET/CT scans performed for approximately 8 months (34 weeks).

Discussion

^{18}F-FDG PET/CT as an imaging modality is an important diagnostic tool, which forms an essential part of medical management in oncologic patients [11–13]. ^{18}F-labeled glucose analogue FDG is taken up by living cells via glucose transport membrane proteins (glucose transporters/GLUT) and subsequently incorporated into the normal glycolytic pathway. FDG uptake in tissue is proportional to the metabolic activity or the amount of glucose utilization. Increased FDG uptake is seen in many malignant neoplasms, as well as benign conditions such as infection and inflammation, related to overexpression of GLUT, increased hexokinase enzyme activity along with increased blood flow and capillary permeability [11–15]. Multiple studies including case-reports have shown false-positive findings on ^{18}F-FDG PET/CT scan in cancer patients following flu / H1N1 influenza, Human Papillomavirus, and COVID-19 vaccinations, which usually ranges from local axillary, supraclavicular, and cervical lymphadenopathy to systemic diffuse splenic uptake and last for short duration of time of 10-14 days, or rarely persist for 4-6 weeks indicating that these findings were vaccine related and not cancer related or malignant metastasis [4,7,9,10,12,16,17].

The pathophysiology of loco-regional lymphadenopathy is related to immune mechanism. The antigens present in the vaccines interact with the host leading to increased immunological response, which leads to inflammatory reaction at the site of injection and surrounding lymphoid tissue. The inflammatory changes are due to release of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), prostaglandins, and interleukins (IL-1 and 6), by immune cells such as macrophages, dendritic cells, and monocytes mimicking innate and adaptive immune response to a natural infection, resulting in lymphadenopathy with swollen and occasionally painful lymph nodes [18–21].

Lymphoid tissues such as lymph nodes and spleen are important modulators of T cell immunity, therefore increased immune response to the COVID-19 vaccination could also be associated with increased metabolic activity leading to increased glucose metabolism and FDG uptake on PET/CT scan [22,23]. Multiple published articles have shown that this regional lymphadenopathy and systemic immune response with diffuse splenic uptake following the COVID-19 vaccination typically resolved within 2-6 weeks [4,7,12,22]. However, in this case an unusually prolonged FDG uptake in multi-station lymph nodes and spleen was observed after a booster (third) dose of Moderna COVID-19 vaccine lasting for approximately 34 weeks/8 months probably indicating a more prolonged and generalized systemic immune response than usual postvaccination short duration immune response lasting for 10-14 days. Moreover, these FDG avid lymph nodes were benign appearing based on CT criteria for morphological assessment differentiating metastatic versus nonmetastatic lymph nodes [24].

This prolonged generalized systemic immune response following COVID-19 vaccination has not been reported in the literature to our knowledge. This pattern of presentation is most probably of multifactorial etiology, with factors such as the new mechanism of action in mRNA based COVID-19 vaccines, exacerbating effect of a vaccine booster dose, interaction with various cancer-directed therapies, immunemodulatory effect of cancer and inherent immunity of the patient possibly playing a role in mounting such prolonged persistent global immune response. This interesting case scenario poses new questions pertaining to our understanding of immune response after COVID-19 vaccination and might trigger avenues of research elucidating the interplay between immune system and oncology. From a practical perspective, it is important for radiologists /nuclear medicine physicians to recognize imaging features of this rare effect of COVID-19 vaccination, which can pose a challenge in assessing ^{18}F-FDG PET/CT scans in cancer patients.

Conclusion

COVID-19 vaccinations can have relevant implications on ^{18}F-FDG PET/CT scan interpretation in cancer patients potentially leading to false positive findings particularly in cases of prolonged generalized immune response. This rare but important manifestation can present as multi-station hypermetabolic reactive lymph nodes and diffuse splenic uptake up to 8 months following the vaccination. Therefore, ^{18}F-FDG PET/CT scans should be interpreted with caution in patients with COVID-19 vaccines.

Patient consent

A written informed consent and permission was obtained from the patient.

REFERENCES

[1] Perico N, Cortinovis M, Suter F, Remuzzi G. Home as the new frontier for the treatment of COVID-19: the case for anti-inflammatory agents. Lancet Infect Dis 2023;23:e22–33.

[2] Barouch DH. COVID-19 Vaccines - immunity, variants, boosters. N Engl J Med 2022;387(11):1011–20.

[3] Coronavirus Resource Center, John Hopkins University & Medicine; Available from: https://coronavirus.jhu.edu/map.html [accessed December 6.12.22].

[4] Minamimoto R, Kiyomatsu T. Effects of COVID-19 vaccination on FDG-PET/CT imaging: a literature review. Glob Health Med 2021;3(3):129–33.

[5] 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;217(4):975–83.

[6] Skawran S, Gennari AG, Dittli M, Treyer V, Muehlematter UJ, Maurer A, et al. [18F]FDG uptake of axillary lymph nodes after COVID-19 vaccination in oncological PET/CT: frequency, intensity, and potential clinical impact. Eur Radiol 2022;32(1):508–16.

[7] McIntosh LJ, Rosen MP, Mittal K, Whalen GF, Bathini VG, Ali T, et al. Coordination, and optimization of FDG PET/CT and COVID-19 vaccination; lessons learned in the early stages of mass vaccination. Cancer Treat Rev 2021;98:102220.

[8] Thomassen A, Lerberg Nielsen A, Gerke O, Johansen A, Petersen H. Duration of 18F-FDG avidity in lymph nodes after pandemic H1N1v and seasonal influenza vaccination. Eur J Nucl Med Mol Imaging 2011;38(5):894–8.
[9] Panagiotidis E, Exarhos D, Housianakou Bournazos A, Datseris I. FDG uptake in axillary lymph nodes after vaccination against pandemic (H1N1). Eur Radiol 2010;20:1251–3.
[10] 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;36:848–53.
[11] Czepczyński R, Szczurek J, Mackiewicz J, Ruchała M. Interference of COVID-19 vaccination With PET/CT leads to unnecessary additional imaging in a patient with metastatic cutaneous melanoma-case report. Front Oncol. 2021;11:690443.
[12] Schapiro R, Moncayo VM, Meisel JL. Case report of lymph node activation mimicking cancer progression: a false positive F18 FDG PET CT after COVID-19 vaccination. Curr Probl Cancer Case Rep 2021;4:100092.
[13] Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumor imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015;42(2):328–54.
[14] Rahman WT, Wale DJ, Viglianti BL, Townsend DM, Manganaro MS, Gross MD, et al. The impact of infection and inflammation in oncologic 18F-FDG PET/CT imaging. Biomed Pharmacother 2019;117:109168.
[15] Schierz JH, Sarikaya I, Wollina U, Unger L, Sarikaya A. Immune checkpoint inhibitor-related adverse effects and ^{18}F-FDG PET/CT findings. J Nucl Med Technol 2021;49(4):324–9.
[16] Coates EE, Costner PJ, Nason MC, Herrin DM, Conant S, Herscovitch P, et al. Lymph node activation by PET/CT following vaccination with licensed vaccines for human papillomaviruses. Clin Nucl Med. 2017;42(5):329–34.
[17] Mingos M, Howard S, Giacalone N, Kozono D, Jacene H. Systemic immune response to vaccination on FDG-PET/CT. Nucl Med Mol Imaging 2016;50(4):358–61.
[18] Gales LN, Brotea-Mosoiu S, Trifanescu OG, Lazar AM, Gherghe M. Understanding COVID vaccination and its implication in cancer patients' imaging of lymph nodes by PET-CT. Diagnostics (Basel) 2022;12(9):2163.
[19] Megha K, Joseph X, Akhil V, Mohanan P. Cascade of immune mechanism and consequences of inflammatory disorders. Phytomedicine 2021;91:153712.
[20] Hervé C, Laupèze B, del Giudice G, Didierlaurent AM, da Silva FT. The how's and what's of vaccine reactogenicity. npj Vaccines 2019;4:39.
[21] Ren L, Zhang J, Zhang T. Immunomodulatory activities of polysaccharides from Ganoderma on immune effector cells. Food Chem 2021;340:127933.
[22] Seban RD, Champion L, Deleval N, Richard C, Provost C. Immune response visualized in vivo by [18F]-FDG PET/CT after COVID-19 vaccine. Diagnostics (Basel) 2021;11(4):676.
[23] Steinberg J, Thomas A, Iravani A. 18F-Fluorodeoxyglucose PET/CT findings in a systemic inflammatory response syndrome after COVID-19 vaccine. Lancet 2021;397(10279):e9.
[24] Mao Y, Hedgire S, Harisinghani M. Radiologic assessment of lymph nodes in oncologic patients. Curr Radiol Rep 2014;2:36.