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SPOTLIGHT

PET findings after COVID-19 vaccination: "Keep Calm and Carry On"

Giorgio Treglia[1,2,3,4,5] · Marco Cuzzocrea[1] · Barbara Muoio[6] · Luigia Elzi[6,7]

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Large-scale worldwide vaccination programs against the 2019 coronavirus diseases (COVID-19) are being rapidly deployed. As this vaccination is becoming more widespread, we are observing an increase of patients with previous vaccination against COVID-19 who underwent ^{18}F-FDG PET/CT for different indications (i.e., cancer staging or restaging or evaluation of inflammatory diseases). Knowledge of vaccination-related effects is important to prevent wrong interpretations and alleviate patient concern during diagnostic imaging procedures. The earliest publications on this topic occurred in the field of breast imaging, where COVID-19 vaccine-induced lymphadenopathy was cited as a cause of unilateral axillary lymphadenopathy [1].

Taking into account recent literature data, we are also observing a rapid increase of published scientific articles reporting PET findings with different radiotracers in patients with previous vaccination against COVID-19 [2–21, 27, 28].

Overall, these articles are mainly case reports or small case series recently published by research groups from different countries worldwide reporting PET findings in COVID-19 vaccine recipients who underwent PET/CT or PET/MRI with different radiotracers for several indications [2–21] (Table 1). Most of the described patients underwent vaccination against COVID-19 from 1 day to 3 weeks before ^{18}F-FDG PET/CT. About the ^{18}F-FDG PET findings after COVID-19 vaccination, most of the published articles reported increased radiophamaceutical uptake in axillary and subpectoral lymph nodes at the same side of the vaccine inoculation. Increased uptake in deltoid muscle corresponding to the vaccine inoculation site was also frequently described. Beyond the axilla, increased radiopharmaceutical uptake in supraclavicular and lower cervical lymph nodes was also illustrated in some reports. The hypermetabolic lymph nodes were normal-sized or enlarged. Less frequently, diffuse splenic ^{18}F-FDG-uptake was also described. All these described sites of increased radiopharmaceutical uptake were interpreted as reactive due to immune response after recent vaccination against COVID-19 [2–10, 12–15, 17–21].

Radiopharmaceutical uptake in axillary lymph nodes was also described after PET/CT with radiolabelled choline or somatostatin analogues in COVID-19 vaccination recipients [11, 16].

We would like to underline that the main advantages of these case reports and small case series is to inform the nuclear medicine community about the increasing appearance of these PET findings following COVID-19 vaccination.

On the other hand, these findings are not surprising for the nuclear medicine physicians for several reasons [22, 23]. First of all, it is well known that inflammatory cells may take up ^{18}F-FDG due to their increased glucose uptake and glycolytic activity. Therefore, ^{18}F-FDG is not a specific tracer for cancer cells and reactive lymph nodes may take up ^{18}F-FDG mimicking neoplastic lesions at PET. For these reason, ^{18}F-FDG PET/CT may also be used to evaluate inflammatory and infectious diseases with good diagnostic accuracy as demonstrated by several evidence-based manuscripts [24].

It is also not surprising that reactive lymph nodes may show increased ^{18}F-FDG uptake and normal size in some

Barbara Muoio and Luigia Elzi share the last authorship.

✉ Giorgio Treglia
giorgio.treglia@eoc.ch

1 Clinic of Nuclear Medicine, Imaging Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

2 Department of Nuclear Medicine and Molecular Imaging, Lausanne University Hospital, Lausanne, Switzerland

3 Health Technology Assessment Unit, Academic Education, Research and Innovation Area, General Directorate, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

4 Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

5 Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland

6 Department of Medicine, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

7 Faculty of Medicine, University of Basel, Basel, Switzerland

Table 1 Case reports and small case series on PET findings in patients with recent vaccination against COVID-19 (source: PubMed/MEDLINE; last search date: 22 April 2021)

First author	Year	Country	Age/sex of patients	Vaccine manufacturer	Inoculation site	Time from vaccine to PET scan	PET indication	PET tomograph	PET tracer	PET findings
Ahmed [2]	2021	UK/Kuwait	86/F	Pfizer	Left deltoid muscle	6 days**	Melanoma (restaging)	PET/CT	^{18}F-FDG	Uptake in left deltoid muscle and in normal-sized left subpectoral LN
Avner [3]	2021	Israel	57/F	Pfizer	Left arm	6 days**	Melanoma (restaging)	PET/CT	^{18}F-FDG	Uptake in left proximal arm, enlarged left axillary and subpectoral LN
Bauckneht [4]	2021	Italy	44/M	Pfizer	Left arm	1 day**	Target for LN biopsy	PET/CT	^{18}F-FDG	Uptake in left proximal arm and in enlarged left axillary LN
Brown [5]	2021	UK	67/F	NR	Left arm	2 weeks	Breast cancer (restaging)	PET/CT	^{18}F-FDG	Uptake in normal-sized left axillary and subpectoral LN
			48/F	NR	Right arm	3 weeks	Breast cancer (restaging)	PET/CT	^{18}F-FDG	Uptake in right proximal arm and in normal-sized right axillary LN
			83/F	NR	Left arm	2 weeks	Breast cancer (restaging)	PET/CT	^{18}F-FDG	Uptake in normal-sized left axillary and subpectoral LN
			66/F	NR	Left arm	< 3 weeks	Breast cancer (restaging)	PET/CT	^{18}F-FDG	Uptake in a normal-sized left subpectoral LN
Doss [6]	2021	USA	70/F	Pfizer	Left arm	2 days**	Lymphoma (restaging)	PET/CT	^{18}F-FDG	Uptake in left deltoid muscle and in normal-sized left axillary LN
Eifer [7]	2021	Israel	72/F	Pfizer	Right deltoid muscle	10 days	Breast cancer (restaging)	PET/CT	^{18}F-FDG	Uptake in right deltoid muscle and in normal-sized right axillary LN
Finnegan [8]	2021	Ireland	50/M	Pfizer	Left arm	10 days**	NR (staging)	PET/CT	^{18}F-FDG	Uptake in left axillary LN
Hanneman [9]	2021	Canada	56/F	Pfizer	Left deltoid muscle	1 day**	Cardiac diseases (research)	PET/MRI	^{18}F-FDG	Uptake in enlarged left axillary LN

Table 1 (continued)

First author	Year	Country	Age/sex of patients	Vaccine manufacturer	Inoculation site	Time from vaccine to PET scan	PET indication	PET tomograph	PET tracer	PET findings
Johnson [10]	2021	USA	NR/F	Moderna	Left deltoid muscle	10 days*	Parotid cancer (staging)	PET/CT	^{18}F-FDG	Uptake in left axillary and supraclavicular LN
			NR/F	NR	Left deltoid muscle	2 weeks*	Oropharyngeal cancer (restaging)	PET/CT	^{18}F-FDG	Uptake in left axillary and supraclavicular LN
Lu [11]	2021	USA	64/F	Pfizer	Both arms	6 weeks* and 3 weeks**	Carcinoid (restaging)	PET/CT	^{68}Ga-DOTATATE	Uptake in bilateral axillary and subpectoral LN
McIntosh [12]	2021	USA	40/F	Moderna	Left deltoid muscle	3 days	Breast cancer (staging)	PET/CT	^{18}F-FDG	Uptake in left axillary, supraclavicular and lower cervical LN
			72/F	Pfizer	Right deltoid muscle	11 days*	Breast cancer (restaging)	PET/CT	^{18}F-FDG	Uptake in normal-sized right axillary LN
			72/F	NR	NR	4 days**	Lung nodule (characterization)	PET/CT	^{18}F-FDG	Uptake in right axillary LN
			40/F	Moderna	NR	3 days	NR	PET/CT	^{18}F-FDG	Uptake in enlarged left axillary LN
			59/M	NR	NR	14 days	Lung cancer (staging)	PET/CT	^{18}F-FDG	Uptake in enlarged left axillary, supraclavicular and lower cervical LN
			68/F	Moderna	Left deltoid muscle	9 days	Cervical cancer (restaging)	PET/CT	^{18}F-FDG	Uptake in left axillary LN
Moghimi [13]	2021	Canada	71/M	NR	Left deltoid muscle	6 days	Melanoma (staging)	PET/CT	^{18}F-FDG	Uptake in left deltoid muscle and left axillary and lower cervical LN
Nawwar [14]	2021	UK/Egypt	76/F	AstraZeneca	Left arm	14 days	Myeloma (restaging)	PET/CT	^{18}F-FDG	Uptake in left deltoid muscle and left axillary LN
Nawwar [15]	2021	UK/Egypt	70/M	AstraZeneca	Left arm	7 days	Lung cancer (staging)	PET/CT	^{18}F-FDG	Uptake in left axillary LN
Nawwar [16]	2021	UK/Egypt	75/M	AstraZeneca	Left arm	3 days	Prostate cancer (restaging)	PET/CT	^{18}F-choline	Uptake in left deltoid muscle and left axillary LN

Table 1 (continued)

First author	Year	Country	Age/sex of patients	Vaccine manufacturer	Inoculation site	Time from vaccine to PET scan	PET indication	PET tomograph	PET tracer	PET findings
Özütemiz [17]	2021	Turkey	32/F	Pfizer	Left arm	6 days**	Melanoma (restaging)	PET/CT	^{18}F-FDG	Uptake in left arm and enlarged left axillary LN
			46/F	Pfizer	Left deltoid muscle	7 days**	Breast cancer (restaging)	PET/CT	^{18}F-FDG	Uptake in left deltoid muscle and enlarged left axillary and supraclavicular LN
Smith [18]	2021	USA	40/F	Pfizer	Left arm	1 day**	Osteosarcoma (restaging)	PET/CT	^{18}F-FDG	Uptake in left deltoid muscle and in normal-sized left axillary and supraclavicular LN
Steinberg [19]	2021	USA	65/F	Moderna	Right deltoid muscle	5 days*	Lung nodules (characterization)	PET/CT	^{18}F-FDG	Uptake in right deltoid muscle, right axillary LN and diffuse splenic uptake
Ulaner [20]	2021	USA	68/M	Moderna	Left arm	3 weeks*	Melanoma (restaging)	PET/CT	^{18}F-FDG	Uptake in left axillary LN
Xu [21]	2021	USA	72/M	Pfizer	Left arm	2 days	Lymphoma (restaging)	PET/CT	^{18}F-FDG	Uptake in left deltoid muscle and left axillary LN

CT computed tomography, *F* female, *^{18}F-FDG* ^{18}F-fluorodeoxyglucose, *LN* lymph nodes, *M* male, *MRI* magnetic resonance imaging, *NR* not reporte, *PET* positron emission tomography

* After the first dose of vaccine

** After the second dose of vaccine

Table 2 Recent studies about the prevalence of COVID-19 vaccine-related lymphadenopathies on ^{18}F-FDG PET/CT (source: PubMed/MEDLINE; last search date: 22 April 2021)

First author	Year	Country	No. of COVID-19 vaccine recipients	mean age/male percentage	Vaccine manufacturer	Overall prevalence of HALN after COVID-19 vaccination	Prevalence of HALN after first dose of COVID-19 vaccine	Prevalence of HALN after second dose of COVID-19 vaccine
Bernstine [27]	2021	Israel	650	68.9 y/46%	Pfizer	25.8%	14.5%	43.3%
Cohen [28]	2021	Israel	728	69.2 y/43%	Pfizer	45.6%	36.4%	53.9%

HALN hypermetabolic axillary lymph nodes at ^{18}F-FDG PET

cases, because functional abnormalities as revealed by ^{18}F-FDG PET may precede morphological alterations detected by CT or MRI [24]. Similar to ^{18}F-FDG, radiopharmaceutical uptake in reactive lymph nodes has been already widely described with PET using radiolabelled choline [25] or somatostatin analogues [26].

Moreover, increased ^{18}F-FDG uptake in hypermetabolic lymph nodes due to vaccine-related immune response has been already described in several patients who underwent different types of vaccinations beyond those against COVID-19 [22], therefore this is not a significant novelty.

Furthermore, we should also take into account that a clear information about the prevalence of these PET findings in COVID-19 vaccine recipients cannot be obtained by using these case reports and small case series only, because these manuscripts are strongly affected by publication bias; in other words, positive results (presence of increased radiopharmaceutical uptake at PET with different radiotracers after vaccination) are more likely to be published compared to negative findings (absence of increased radiopharmaceutical uptake at PET with different radiotracers after vaccination).

Conversely, two interesting cohort studies from Israel demonstrated that the detection of hypermetabolic axillary lymph nodes at ^{18}F-FDG PET/CT is quite common after vaccination against COVID-19, mainly after the inoculation of the second dose of COVID-19 vaccine (Table 2) [27, 28]. However, accurate data reporting the time required after COVID-19 vaccination to allow for resolution of ^{18}F-FDG uptake in sites of vaccine-related immune response are currently lacking.

Notably, taking into account all the evidence-based data available so far, we cannot state that PET with ^{18}F-FDG or other radiopharmaceuticals are really able or may be used to detect COVID-19 vaccination sequelae as well as for COVID-19 [29, 30]. It could be interesting to perform a trial in the future for evaluating if the increased ^{18}F-FDG uptake associated with the vaccination could give some useful information on the immune response for vaccinated individuals (as example: duration of immunity) or showing different behaviours when using different types of vaccine.

To date, we can only state that, in a still unclear percentage of COVID-19 vaccine recipients, some radiopharmaceutical uptake patterns as those described in the available articles may be found and these may be due to vaccine-related immune response. These PET findings will likely increase in number in the next months due to the parallel increase of global immunization against COVID-19.

Nuclear medicine physicians should be (already) able to recognize the possible PET findings due to COVID-19 vaccination, in particular both hypermetabolic lymph nodes (mainly axillary) and ipsilateral increased radiopharmaceutical uptake in the deltoid muscle at ^{18}F-FDG PET. Documenting vaccination history and vaccine injection location at the time of PET scan is (already) extremely useful for PET reporters to avoid false interpretation, useless further diagnostic examinations, unnecessary changes in management and additional patient anxiety and this should be valid for all (COVID-19 and beyond) vaccine recipients.

Declarations

Conflict of interest The authors declare that they have no financial or non-financial competing interests.

Ethical approval This article does not contain any studies with human participants or animals.

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