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EDITORIAL

Patients' findings after COVID-19 infection and vaccinations: what to expect from [18F]FDG PET/CT

Martina Sollini[1,2] · Fabrizia Gelardi[1,2] · Matteo Biroli[1] · Arturo Chiti[1,2]

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The number of symptomatic and severe COVID-19 patients and deaths caused by COVID-19 were reduced by the large-scale vaccination campaign in 2021 [1].

Since the worldwide campaign started, vaccine-related occasional findings were described in patients performing PET/CT for other purposes. Increased tracer uptake at the injection site in the deltoid muscle and concomitant ipsilateral hypermetabolic axillary lymph nodes are the most frequently reported findings at [18F]FDG PET/CT (pooled prevalence of 30% (95% CI 20–41) and 37% (95% CI 27–47), respectively [2]). Lymph nodes can be normal or enlarged. Other ipsilateral supraclavicular and cervical lymph nodes have been more rarely observed [3]. The incidence of hypermetabolic axillary lymph nodes is higher in the first few weeks after the vaccination and decreases with time, although they may be visible even after 10 weeks [2]. After the third vaccination dose, the reported duration of hypermetabolic nodes is shorter (up to 5 days) [4]. These findings are detected more frequently in immunocompetent and young patients compared to immunocompromised and elderly [2]. Although deltoid uptake and hypermetabolic lymph nodes post-COVID-19 vaccination are typically reported with [18F]FDG, similar findings have also been described with other tracers and in patients recently vaccinated for influenza. These findings are related to the transient inflammation from immune system activation [5], and in the majority of cases, it can be easily correlated with the history of recent vaccination (Fig. 1). However, patients evaluated for certain diseases, such as lymphoma, melanoma, and breast and head and neck cancer, can be confusing and hard to interpret. Medical history should be taken into account during vaccination, and accordingly, the vaccination injection should be performed in the arm contralateral to the disease or even elsewhere (e.g. thigh). This shrewdness may reduce false-positive or inconclusive examinations.

In the last months, rare cases of autoimmune diseases that occurred or worsened after the Covid-19 vaccination were also claimed. Recently, von Tresckow et al. [6] reported the case of a patient imaged by PET/CT for an autoimmune disease possibly related to vaccination. After mRNA vaccination (Spikevax, Moderna, TX), the patient complained of cephalgia, cervicalgia, ostealgia, and pain in multiple large joints and muscles associated with increased inflammatory indices. The clinical picture was suspected for large vessel vasculitis. Images showed increased [18F]FDG uptake on vertebral and femoral arteries (associated with vessel wall thickening) and on thoracolumbar inter-spinous and pelvic bursae, findings highly suspicious for rheumatic polymyalgia [6].

Another interesting report has been recently published by Boursier et al. [7]. They presented digital-PET/CT images from two patients who experienced myocarditis a few days after the second shot of the mRNA vaccine (Spikevax and COMIRNATY, respectively). Images acquired up to 3 days from peak troponin showed increased myocardial uptake related to myocardial inflammatory cells in the infiltrate overexpressing somatostatin receptors [7].

Other reports on autoimmune disease possibly related to COVID-19 vaccination are summarized in Table 1. We also observed some anecdotal cases of autoimmune diseases after the COVID-19 vaccination (Figs. 2 and 3).

However, we must be cautious not to confound coincidental events with cause-effect relationships. Since the

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✉ Fabrizia Gelardi
fabrizia.gelardi@cancercenter.humanitas.it

1 Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090, Pieve Emanuele, Milan, Italy

2 IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089, Rozzano, Milan, Italy

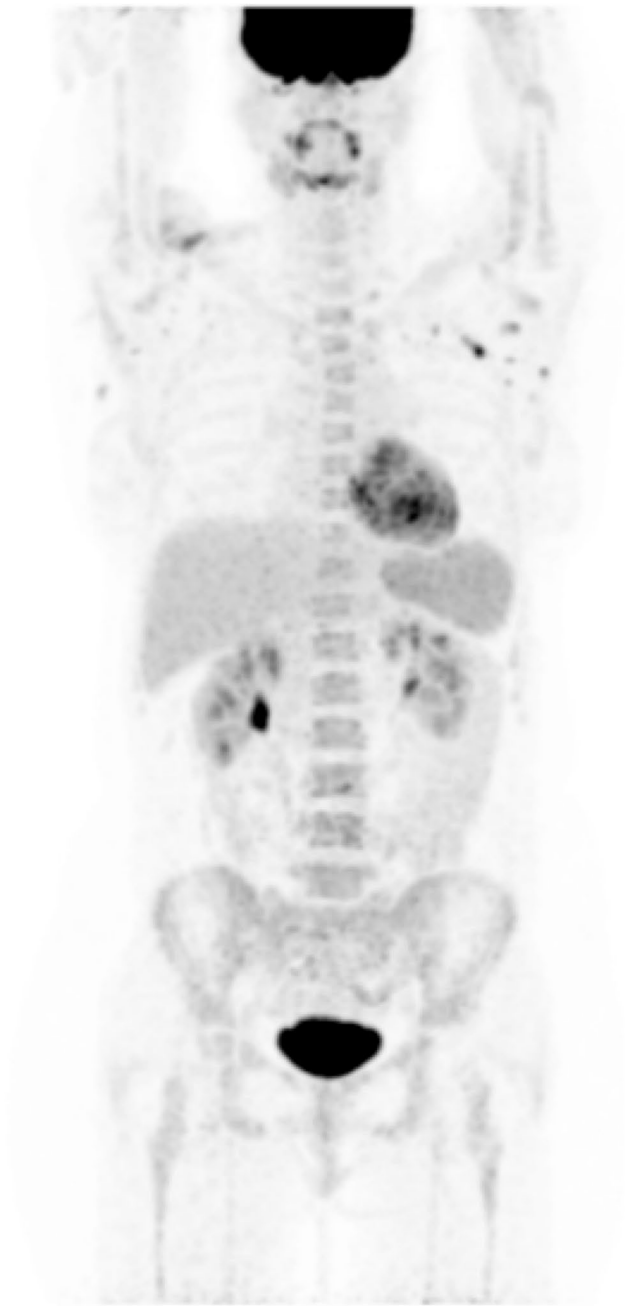

Fig. 1 Restaging [18F]FDG PET/CT after neoadjuvant chemotherapy in a patient who has right breast cancer. Six days before the examination, she received the vaccine for influenza in the right deltoid muscle and the third dose of COVID-19 vaccination on the left side. Images show hypermetabolic lymph nodes in the right and left axilla related to influenza and COVID-19 vaccinations, respectively

development of vaccines, there have been several complaints about the association with various autoimmune diseases, which were then disproved, such as between the hepatitis B vaccine and multiple sclerosis. Only in a few cases, the relationship has been scientifically proven (i.e. swine influenza vaccine and Guillain-Barré syndrome), with much lower risk than the disease itself and its related complications [12]. Also, regarding anti-COVID-19 vaccines, there is no solid scientific evidence that they may directly trigger autoimmune disorders. The above examples are predominantly rare isolated case reports. These phenomena might be explained by a genetic predisposition to develop such diseases, which probably would be precipitated equally by different factors and mechanisms. In addition, the risk of developing a severe form of COVID-19 is much higher in patients affected by autoimmune diseases than in the healthy population. Accordingly, the benefits of the vaccine are far greater than the risk of worsening the autoimmune disease. Therefore, clinical guidelines strongly recommend its administration also in patients suffering from autoimmune diseases [13].

Moreover, COVID-19 vaccination may also trigger positive effects. Indeed, the hyper-activation of innate immunity supporting the strong COVID-19-induced immune-stimulation also has potential effects on the tumour microenvironment. Cases of spontaneous regression post-COVID-19 infection have been described in lymphoma, renal carcinoma, and colorectal carcinoma patients [14–18], and the hyper-activation of innate immunity with anticancer effects generated by acute infection may be elicited similarly also by anti-COVID-19 vaccination. A case of disease spontaneous regression after BNT162b2 vaccination (COMIRNATY, BioNTech/Pfizer) has been recently described in lymphoma [19].

We recently observed a similar case in a multi-refractory diffuse large B-cell lymphoma (DLBCL) patient who experienced a spontaneous metabolic complete response after COVID-19 vaccination (Fig. 4).

After all, vaccine-induced immune system stimulation for anti-tumour purposes is currently used in daily clinical practice. Bacillus Calmette-Guérin (BCG) is an attenuated vaccine from *Mycobacterium bovis* developed as an anti-tuberculosis vaccine. BCG is the standard of therapy as intravesical adjuvant treatment for non-invasive high- and medium-risk muscle bladder cancer. BCG induces a local immune response resulting in an anti-tumour effect called trained immunity [20, 21].

We can conclude that the COVID-19 vaccine and the acute COVID-19 disease cause a strong activation of the immune system that may result in several phenomena that can be observed at PET/CT images. These “incidental”

Table 1 Reports on autoimmune disease possibly related to COVID-19 vaccination

Reference	Sex, age	Tracer	Vaccination	Days between vaccination and examination	Main findings at PET/CT	Injection site uptake	Hypermetabolic lymph nodes
[8]	F, 35 yr	[18F]FDG	1st administration of mRNA-1273	10	Thymic hyperplasia	nr	Yes
[9]	M, 67 yr	[18F]FDG	2nd administration of mRNA-1273	4	Radiation recall pneumonitis	nr	nr
[10]	F, 46 yr	[18F]FDG	nr	7	Splenic and bone marrow uptake	nr	Yes
[11]	F, 65 yr	[18F]FDG	1st administration of mRNA-1273	5	Splenic uptake	Yes	Yes
[7]	M, 18 yr	[^{68}Ga]Ga-DOTATOC	2nd administration of mRNA-1273	2	Myocarditis	nr	nr
	M, 21 yr		2nd administration of BNT162b2	3		nr	nr
[6]	F, 78 yr	[18F]FDG	1st administration of mRNA-1273	nr	Rheumatic polymyalgia	nr	nr

F, female; *M*, male; *nr*, not reported; *yr*, years

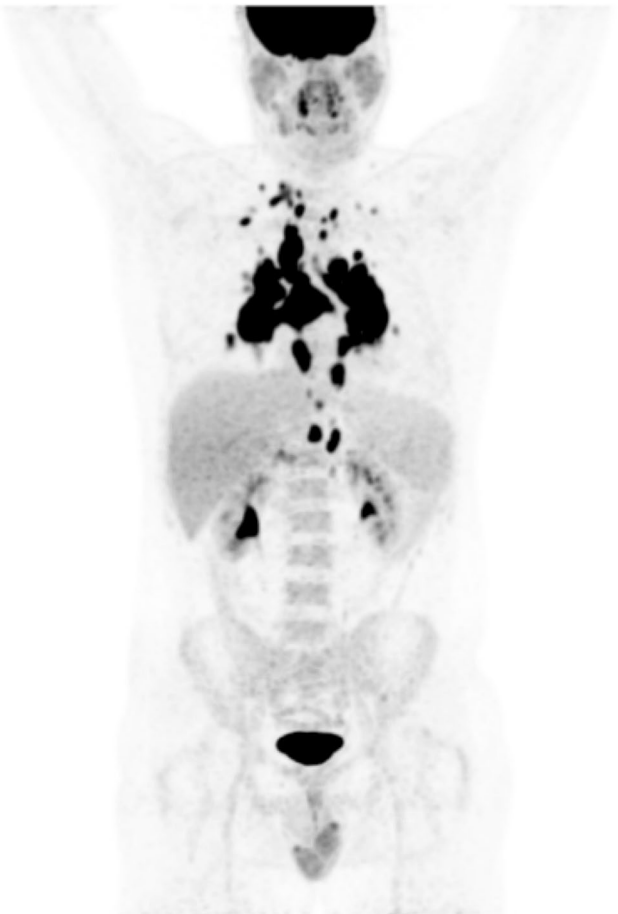

Fig. 2 [18F]FDG PET/CT in a patient with a known history of psoriatic arthritis and erythema nodosum, still under treatment with corticosteroids. He complained of the onset of indolent lateral-cervical lymphadenopathies and bilateral salivary glands swelling after COVID-19 vaccination. PET/CT shows a pattern suspicious for sarcoidosis, with symmetric lymphadenopathies with high [18F]FDG uptake in the mediastinum, lateral-cervical and pulmonary hilum bilaterally, and in sub-diaphragmatic stations. Mediastinal lymphadenopathy biopsy confirmed the diagnosis of non-necrotizing granulomatous sarcoidosis

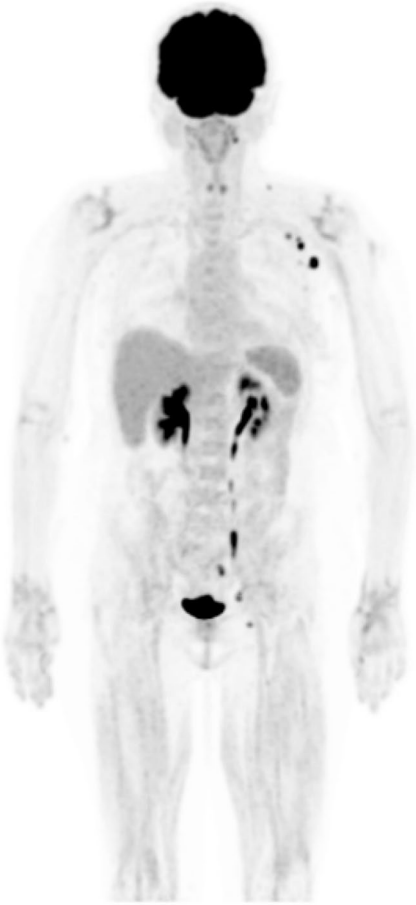

Fig. 3 [18F]FDG PET/CT images in a patient who experienced a herpes zoster–associated erythema on the left thigh with associated ipsilateral inguinal lymphadenopathies that occurred after the second dose of COVID-19 vaccination. PET/CT images show [18F]FDG-avid left external inguinal lymphadenopathies associated with known herpes zoster–related erythema. COVID-19 vaccine-related swelled lymph nodes with [18F]FDG uptake are also visible in the left supraclavicular and ipsilateral axillary region

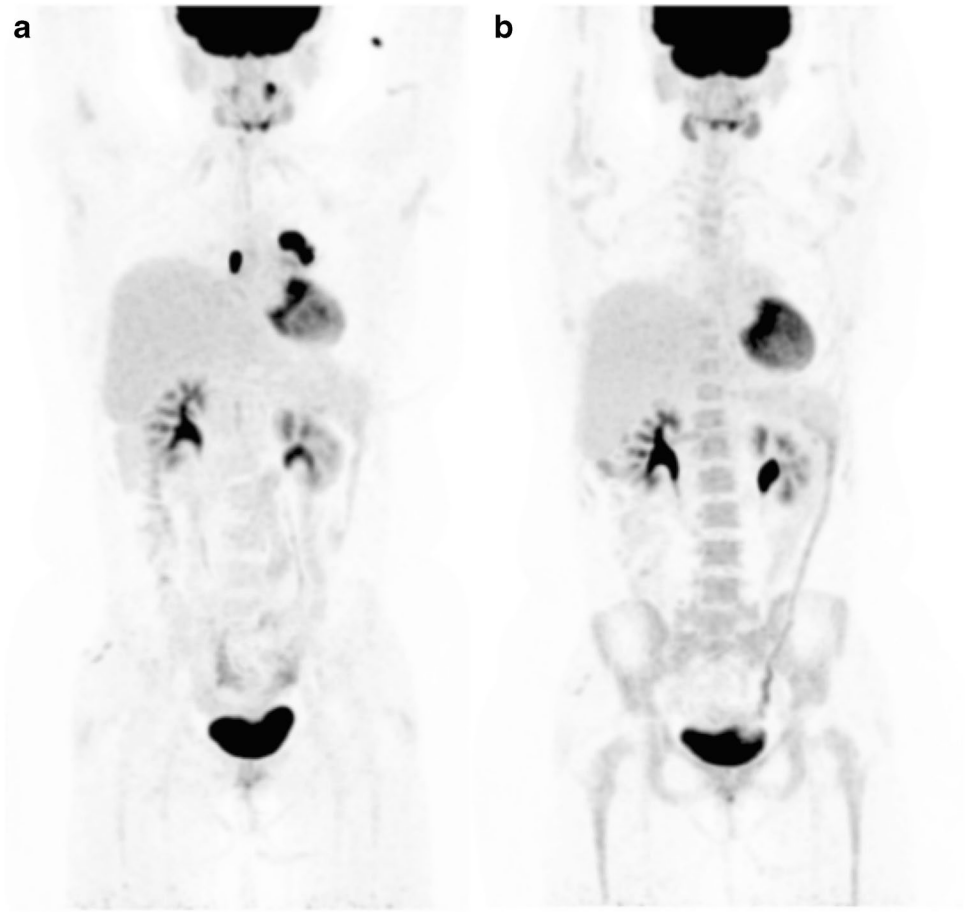

Fig. 4 [18F]FDG PET/CT images before (**A**) and after (**B**) COVID-19 vaccination in a multi-refractory diffuse large B-cell lymphoma (DLBCL) patient. She was treated with immunotherapy, and PET/CT images obtained after 5 cycles showed a disease progression (**A**). The treatment was stopped immediately, and she underwent a biopsy which confirmed DLBCL. About 1 month after, the patient underwent a new [18F]FDG PET/CT for restaging (**B**). Unexpectedly, previously reported lesions were no longer visible on either PET or CT images. Between the biopsy and the last PET/CT, the patient received the COVID-19 vaccination.

findings range from classic local inflammation signs to more unusual events that may occur in predisposed individuals, such as the triggering of autoimmune diseases or tumour regression. The cause-effect relationship of these events, being rare, cannot be demonstrated yet.

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Declarations

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