Asymptomatic *versus* symptomatic patients: [18F]FDG-PET/CT patterns and evolutionary track of COVID-19 associated vasculitis

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Abstract

Several patients experience unexplained persistent symptoms after recovering from severe acute respiratory syndrome-related coronavirus disease 2 (SARS-CoV-2) [the so-called long coronavirus disease (COVID)], with a negative impact on their quality of life. We report the evolutionary track of fluorine-18-fluorodeoxyglucose positron emission tomography-computed tomography ([18F]FDG-PET/CT) in two patients incidentally diagnosed with SARS-CoV-2 infection. In both cases, baseline PET/CT showed bilateral pneumonia associated with [18F]FDG vascular uptake. Vascular uptake was more evident in the baseline scan of the asymptomatic patient. Vice versa, it was more marked in the follow-up examinations of the patient who developed long COVID. These findings suggested that vascular inflammation and its duration are responsible for the clinical course of the disease and the development of long COVID.

Introduction

The severe acute respiratory syndrome-related coronavirus disease 2 (SARS-CoV-2) infection is showing a new surge in the number of cases, with a sharp decline in the average age of the infected individuals. Although the number of deaths is still lower compared to the past,[1] there is growing evidence of delayed recovery after SARS-CoV-2 infection [the so-called long coronavirus disease (COVID)[2]].[3-5] Dyspnea and fatigue are the most frequent persistent symptoms reported.[3-5] The cause for these persistent symptoms is still unknown. In a preliminary analysis of a case-control study on long COVID patients, we suggested vascular inflammation as the cause for such prolonged illness. We compared fluorine-18-fluorodeoxyglucose positron emission tomography-computed tomography ([18F]FDG-PET/CT) images of ten prospectively enrolled patients with persisting symptoms (cases) with those of negative [18F]FDG-PET/CT of cancer patients matched for age and sex (controls). We observed an increased [18F]FDG uptake in blood vessels in 6/10 cases, and the semi-quantitative analysis showed higher values in long COVID patients than in controls in 13 out of 14 assessed arteries.[6] Here, we report the clinical course of SARS-CoV-2 infection in two cancer patients incidentally diagnosed using [18F]FDG-PET/CT during the lockdown. Images showed bilateral pneumonia in both patients, but the clinical course of SARS-CoV-2 differed. One patient was completely asymptomatic, while the other complained of persistent dyspnea for a month after recovering from SARS-CoV-2.
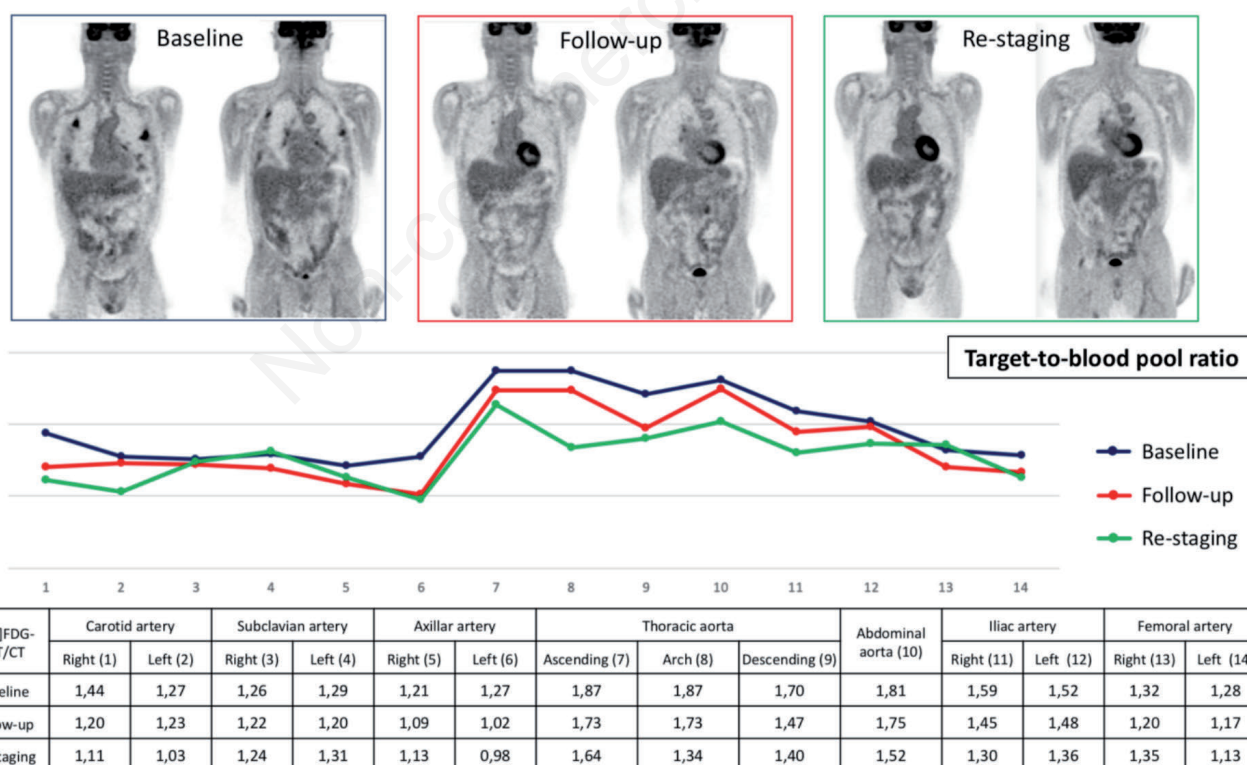
Case #1

A 62-year-old male non-Hodgkin lymphoma patient was re-staged after chemotherapy by [18F]FDG-PET/CT. Unfortunately, the treatment did not enable the patient to achieve a complete metabolic response. The images confirmed the persistence of recurrent swollen abdominal lymph nodes and, unexpectedly revealed a bi-

lateral [18F]FDG uptake potentially due to COVID-19 pneumonia. Additionally, PET/CT images showed a moderate [18F]FDG vascular uptake, especially at the level of the aorta (Figure 1). Accordingly, he was referred to the Emergency Department. The nasal swab confirmed SARS-CoV-2 infection. A non-contrast enhanced CT scan confirmed a bilateral pneumonia with a ground-glass pattern. He was completely asymptomatic, and none among his relatives was diagnosed with the infection, nor had suggestive symptoms. He had a transient ischemic attack four years earlier (on treatment with aspirin and enalapril). He was not obese [body mass index (BMI)=24.1 kg/m^2, body surface area =1.86 m^2], and he had no other co-morbidity. During his hospital stay, he was treated with hydroxychloroquine, piperacillin and tazobactam, low-molecular weight heparin, and lopinavir/ritonavir. Laboratory tests at the peak are shown in Table 1. He was discharged nine days after admission to hospital, and about three weeks after the diagnosis. At that time, he was considered *recovered* (2 negative viral nucleic acid test results from respiratory specimen). According to his medical history, continuing aspirin and enalapril was recommended after discharge. The follow-up non-contrast-enhanced CT scan showed modest interstitial lung parenchymal oedema. About two months after recovering from the infection, he underwent a follow-up [18F]FDG-PET/CT (approximately three months after the first scan). Images showed progressive disease, since the abdominal lymphoma lesions were bigger and more [18F]FDG-avid compared to the previous scan. The total vascular score calculated in seven different vascular regions (carotid arteries, subclavian arteries, axillary arteries, thoracic and abdominal aorta, iliac arteries, and femoral arteries)[7] was stable (8 *versus* 8),

but the target-to-blood pool ratio (calculated as previously reported[6] as the average $SUV_{max\ artery}$/average SUV_{mean} inferior cava vein for the same vascular regions - twice for bilateral arteries and distinguishing the three parts of the thoracic aorta) were lower compared to the baseline scan in almost all vascular regions (average decrease of 9%, plot in Figure 1). The patient underwent a CT-guided biopsy of the abdominal [18F]FDG-avid lesion which revealed a potential inflammation. Based on mismatch between imaging and biopsy findings (positivity of both [18F]FDG-PET/CT and enhanced CT

Table 1. Laboratory tests at peak.

Laboratory test, normal range	Case#1	Case#2
Highest value		
C-reactive protein (≤0.5 mg/dL)	3.93	6.64
Lactate dehydrogenase (<248 U/L)	357	198
Creatine phosphokinase (<172 U/L)	70	10
D-dimer (200-350 ng/mL)	1324	400
Troponin (<19.8 ng/L)	3.3	4.3
Pro-BNP (<100 pg/mL)	21	28
IL-6 (<6.4 pg/mL)	17	27
Lowest value		
Platelet count (150-400 ×10^3/mm^3)	169	200
Lymphocyte count (4-10 ×10^3/mm^3)	0.7	0.8

[18F]FDG-PET/CT	Carotid artery		Subclavian artery		Axillar artery		Thoracic aorta			Abdominal aorta (10)	Iliac artery		Femoral artery	
	Right (1)	Left (2)	Right (3)	Left (4)	Right (5)	Left (6)	Ascending (7)	Arch (8)	Descending (9)		Right (11)	Left (12)	Right (13)	Left (14)
Baseline	1,44	1,27	1,26	1,29	1,21	1,27	1,87	1,87	1,70	1,81	1,59	1,52	1,32	1,28
Follow-up	1,20	1,23	1,22	1,20	1,09	1,02	1,73	1,73	1,47	1,75	1,45	1,48	1,20	1,17
Re-staging	1,11	1,03	1,24	1,31	1,13	0,98	1,64	1,34	1,40	1,52	1,30	1,36	1,35	1,13

Figure 1. Baseline, follow-up and re-staging [18F]FDG-PET/CT image analyses of the asymptomatic COVID-19 patient (#1) (title). Visual assessment moderate scores (comparable to liver), the [18F]FDG thoracic aorta uptake at baseline, follow-up, and re-staging coronal PET images. Semi-quantitative analysis (graph) shows lower target-to-blood pool ratios in the follow-up scan (red line) compared to the baseline (blue line) in all vascular regions (caption). The downward trend of the target-to-blood pool ratios is less evident in the re-staging examination (green line) compared to the follow-up scan (red line).

scan, and negative biopsy), hematologists requested a second CT-guided biopsy which confirmed the previous finding (no malignancy), and supported a watchful waiting strategy. About 3 months later, he repeated both [18F]FDG-PET/CT and enhanced CT imaging. The abdominal lesion had shrunk, and did not show any [18F]FDG uptake. Accordingly, active surveillance was planned. Vascular [18F]FDG uptake was slightly decreased (average decrease of 4%) compared to the previous scan (Figure 1).

Case #2

SARS-CoV-2 pneumonia was suspected based on [18F]FDG-PET/CT findings in a 57-year-old overweight (BMI=27 kg/m^2, body surface area =1.95 m^2) male patient. He was affected by rheumatoid arthritis (previously treated with methotrexate) and esophageal cancer. PET/CT was performed for tumor re-staging after neoadjuvant chemoradiotherapy. During neo-adjuvant treatment, he developed bilateral pulmonary embolism without direct signs of deep vein thrombosis. Re-staging PET/CT showed an intense [18F]FDG uptake in the primary tumor, and unexpectedly in the lung parenchyma (Figure 2). Lung findings were suggestive of SARS-CoV-2 pneumonia. Accordingly, he was referred to the Emergency Department. The day before the examination, he started to have a fever, cough, and mild dyspnea. His wife had fever, anosmia and ageusia some days earlier.

Nasal swabs were negative for both SARS-CoV-2 and H1N1 infection, but non-contrast-enhanced CT scan confirmed bilateral pneumonia with a *crazy-paving* pattern and a significant suspicion of COVID-19 infection. Therefore, he was hospitalized, and un-derwent a bronchoalveolar lavage, which confirmed the infection. Laboratory tests at the peak are shown in Table 1. He improved rapidly on hydroxychloroquine, ceftriaxone, low-molecular weight heparin, and low-flow oxygen and he was discharged five days after admission to hospital. Low-molecular weight heparin was recommended after discharge until full recovery from the infection. About three weeks after the diagnosis, he was considered *recovered* (2 negative viral nucleic acid results from respiratory specimen). The patient kept complaining of dyspnea for over a month after recovery from SARS-CoV-2. The follow-up non-contrast-enhanced CT scan showed mild lung fibrosis, as typically observed in recovered SARS-CoV-2 pneumonia. About 50 days after recovery from SARS-CoV-2, he was re-staged with [18F]FDG-PET/CT (approximately three months after the first scan). At the time of PET/CT, he complained of mild dyspnea mainly during exercise. Images showed primary tumor progression.

Additionally, PET/CT showed a moderate [18F]FDG vascular uptake. The total visual score[7] increased from 9 at baseline to 11 in the follow-up scan, where [18F]FDG vascular uptake was especially evident at the level of the thoracic aorta (Figure 2). The semi-quantitative analyses supported visual analysis data. The target-to-blood pool ratio was higher compared to the baseline scan in almost all vascular regions (average increase of 16%, Figure 2). About 15 days after PET/CT, he was hospitalized and successfully operated for the esophageal tumor (ypT3 N0 R0). Dyspnea disappeared. About 3 months later, he had a pathological fracture of the right humerus. The re-staging PET/CT showed the appearance of [18F]FDG-avid lung and bone metastases, while vascular uptake

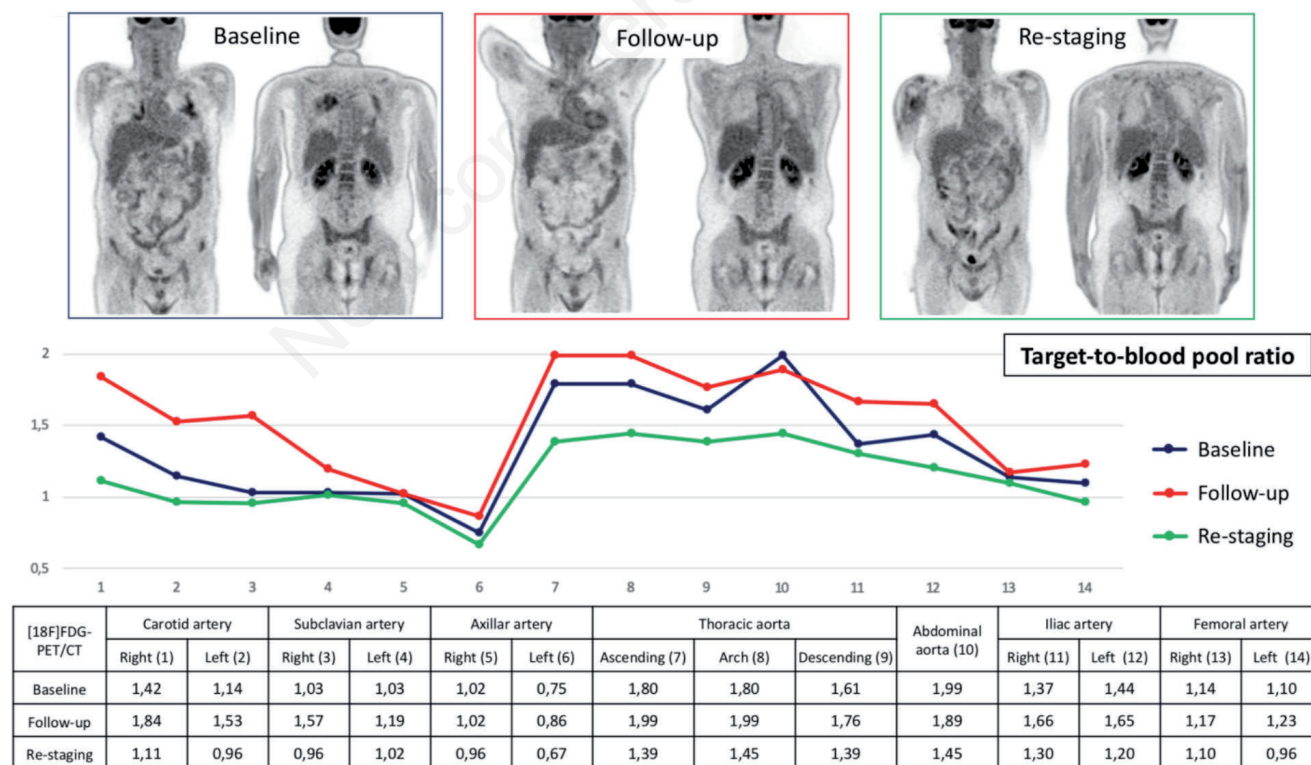| [18F]FDG-PET/CT	Carotid artery		Subclavian artery		Axillar artery		Thoracic aorta			Abdominal aorta (10)	Iliac artery		Femoral artery	
	Right (1)	Left (2)	Right (3)	Left (4)	Right (5)	Left (6)	Ascending (7)	Arch (8)	Descending (9)		Right (11)	Left (12)	Right (13)	Left (14)
Baseline	1,42	1,14	1,03	1,03	1,02	0,75	1,80	1,80	1,61	1,99	1,37	1,44	1,14	1,10
Follow-up	1,84	1,53	1,57	1,19	1,02	0,86	1,99	1,99	1,76	1,89	1,66	1,65	1,17	1,23
Re-staging	1,11	0,96	0,96	1,02	0,96	0,67	1,39	1,45	1,39	1,45	1,30	1,20	1,10	0,96

Figure 2. Baseline, follow-up, and re-staging [18F]FDG-PET/CT image analysis of the symptomatic COVID-19 patient (#2). [18F]FDG vascular uptake is higher in the follow-up PET images (red line) compared to baseline (blue line) in both visual and semi-quantitative analyses (graph) in almost all vascular regions (caption). Re-staging (green line) versus follow-up (red line) images show a markedly decreased [18F]FDG vascular uptake, as confirmed by semi-quantitative parameters (graph).

decreased (average decrease of 24%) compared to the previous scan (Figure 2). Platinum-based chemotherapy associated to palliative radiotherapy were scheduled.

Discussion and Conclusions

We describe two cases of SARS-CoV-2 infection - one with unexplained persistent dyspnea - incidentally detected by [18F]FDG-PET/CT during the first outbreak phase. Both patients developed COVID-19 pneumonia, but while one experienced common symptoms (fever, cough, and dyspnea), the other was - and remained - completely asymptomatic until recovery, and after. The clinical course of SARS-CoV-2 infection is extremely variable. Hyperinflammation magnifies the clinical manifestations of COVID-19 infection,[8] but the pathophysiological mechanisms under this nasty infection are still unknown. Becker[9,10] and Libby and Lüscher[11] have recently proposed the theory according to which COVID-19 would be an endothelial disease. Moreover, Leisman et al.[12] questioned the pathogenetic mechanisms causing organ failure in COVID-19 infection, suggesting - among others - endovasculitis. In both presented cases, PET/CT showed moderate [18F]FDG vascular uptake suggestive of vascular inflammation. In particular, in the asymptomatic case, the [18F]FDG vascular uptake was more evident in the baseline scan and fell from the acute phase to the late phase of COVID-19 (Figure 1). Vice versa, vascular uptake was more marked in the follow-up examination in the patient with persisting symptoms after recovering from COVID-19 infection (Figure 2). Data on our preliminary analysis of long COVID suggested vascular inflammation as the cause for persisting symtoms.[6] These data suggested that vascular inflammation and its duration is responsible for the clinical course of the disease and the development of long COVID. Nonetheless, a number of paraneoplastic syndromes, including vasculitis, were reported in patients with solid and hematological malignancies. Specifically, cutaneous leukocytoclastic vasculitis is the most commonly described vasculitis which is cancer-associated.[13,14] None of our patients had purpura or other signs of cutaneous vasculitis, and vascular uptake decreased over time - especially in the patient with recurrence. Overall, these findings no longer supported the hypothesis of a paraneoplastic vasculitis. However, a number of similarities between cancer and infection (being both essentially exogenous *attacks*) have been described,[15] and recent evidence suggested an interplay between tumor biology and COVID-19 infection.[16] The humoral or cellular immune response against the tumor has been claimed as the pathogenetic mechanism underlying paraneoplastic vasculitis.[13,14] Similarly, the cytokine storm is regarded as a typical feature of COVID-19 infection. Therefore, the pathogenetic mechanism underlying paraneoplastic vasculitis and SARS-CoV-2 infection, which are potentially similar, could hypothetically represent an additional analogy. The time interval between the diagnosis of COVID-19 pneumonia and the follow-up assessment was comparable in the two cases. Long COVID was reported until up to 110 days after discharge,[5] badly impacting the quality of life in 44% of cases.[4] It should be acknowledged that the medical history of patients and concomitant medications may have affected the clinical course of COVID-19 infection and outcome. Clinical and laboratory features of hospitalized COVID-19 patients [e.g., age, co-morbidities, lymphocytopenia, thrombocytopenia, high levels of D-dimer, N-terminal pro-brain natriuretic peptide, and C-reactive protein (CRP)] have been reported to be associated to severe clinical manifestations and fatal outcome.[17-19] Our patients were both males with underlying oncological diseases, both had been recently treated with chemotherapy, and both had a history of a cardiovascular event (pulmonary embolism and transient ischemic attack, respectively); one of them was overweight (the esophageal cancer patient). Laboratory tests showed higher CRP and interleukin (IL)-6 levels in patient#2 than in patient#1, on the contrary lactate dehydrogenase and D-dimer were lower in patient#2 compared to patient#1.

A recent meta-analysis concluded that a high D-dimer value and disseminated coagulopathy might be typical in patients with severe forms of COVID-19 similarly to other infections such as Ebola, Zica, and HIV, suggesting a possible helpful role of adjunctive antithrombotic therapies (e.g., anticoagulants, antithrombin or thrombomodulin) in severe COVID-19 infection.[19] IL-6 plays a crucial role in the COVID-19 *cytokine storm*, and a level over 25 pg/mL was reported to independently predict severe/critical illness or fatal outcome.[17] The lymphoma patient took aspirin which has been reported to have a potential beneficial effect on the clinical course of the infection, reducing the immune-inflammatory crisis and shifting the disease from being a severe/critical disease to a mild illness.[20] Similar effects have also been reported for methotrexate,[21,22] but patient#2 discontinued it in February 2020 during hospitalization for pulmonary embolism. Moreover, methotrexate has been reported to be useful also for vascular inflammation, being listed among the non-glucocorticoid immunosuppressive therapies for large vessels vasculitis, while aspirin is recommended only for Kawasaki disease. The acute illness was quite similar in our cases except for the presence of symptoms. However, aspirin could have had a beneficial effect on symptoms (analgesic/antipyretic effect).[20]

Finally, the SARS-CoV-2 pandemic has caused a number of detriments affecting several aspects of everyday life. Many people perished, as they were unable to fight their personal fight against the virus, but many other will have to deal with virus-related sequalae for a long time. In this regard, one of main concern of caregivers is the impact of COVID-19 on cancer-related morbidity and mortality. Delays in timely diagnosis and curative treatments will affect patient outcomes. Surgery in patient#2 was postponed until the recovery from COVID-19 infection, and about 3 months after surgery he experienced distant metastases. It is not possible to predict whether he would still develop metastasis, if he had not COVID-19, and to date data are still lacking on how the infection can impact tumor biology or the effects of antiviral therapies in the cancer population,[16,23] thus making further speculations impossible.

In conclusion, in our patients, the onset of PET incidentally detected COVID-19 pneumonia, and the recovery from the infection evolved with a different clinical course, as only one patient suffered from persistent symptoms. These data suggested that vascular inflammation and its duration are responsible for the clinical course of the disease and the development of long COVID. Confirmation of these data might drive a change in the management of SARS-CoV-2 infection and additional insights in COVID-19 pathophysiology.

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