[^{18}F] FDG-PET/CT revealing aortic hypermetabolism in patients with chest pain after COVID-19: a retrospective study.

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ABSTRACT

Background: Long-term consequences of SARS-CoV-2 infection are still poorly known and will become a major issue in the coming years.

Objective/Design: We performed a retrospective study including patients with a proven previous SARS-CoV-2 infection, who underwent a ^{18}F-FDG PET/CT scan in our center to explore symptoms that persisted more than three weeks after the acute infection. We incidentally discovered aortic hypermetabolism in 10 of these patients and compared their clinical characteristics to 37 controls with persistent symptoms and no aortic hypermetabolism.

Results: In these 10 patients, aortic SUV values were between 2.52 and 4.45, and aortic/liver values were between 0.88 and 1.18. The thoracic aorta was involved in all patients. Four patients had a new ^{18}F-FDG PET/CT scan at between four and six months of follow-up and showed persisting or increasing aortic hypermetabolism. When compared with the 37 controls, patients with aortic hypermetabolism were less frequently active tobacco smokers, (P=0.001), and less frequently had experienced dyspnoea (11% vs 52%, p=0.02) and ageusia (0 vs 37.8%, p=0.02) during the acute phase of the illness. Patients complained more frequently of chest pain at re-evaluation (60% vs 19%, P=0.017). Chest pain and the absence of active tobacco smoking were also associated with aortic hypermetabolism in univariate and multivariate analyses (ß=0.4; 95% CI: 0.185-0.7; P=0.002 and ß $= 0.5,$ 95% CI: 0.175-0.453 respectively).

Conclusions: SARS-Cov-2 can infect endothelial cells and its ability to cause post infectious chronic vascular inflammation has already been suggested by previous reports. Further studies and close follow-up of these patients are needed to better understand this new entity and its future consequences. Clinicians should search for aortic hypermetabolism in patients presenting with persistent chest pain after COVID-19.

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INTRODUCTION

The COVID-19 pandemic that started in December 2019 in Wuhan, Hubei Province, China, due to SARS-CoV-2, has already caused 83,910,386 confirmed cases and 1,839,660 deaths around the world (1). With clinical presentation initially suggesting a flu-like syndrome, COVID-19 has revealed multiple unexpected extra-pulmonary complications such as thrombosis, cardiac injuries, anosmia, ageusia, dizziness, encephalitis, strokes, diarrhoea, hepatitis, colitis, acute kidneys injuries, myocarditis, cutaneous ecchymosis or rashes, and vasculitis (2).

We are now seeing the emerging challenge of long-term persisting symptoms and sequelae in patients with a proven COVID-19 infection. This new clinical entity has been referred to as "long COVID" by some authors, but remains to be fully characterised (3–5). A recent cohort study assessed the most frequent syndromes after COVID-19 and found a high prevalence of fatigue, muscle weakness, and sleep difficulties (6). Patients who were more severely ill had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations (6). Several dimensions can be identified among persisting symptoms. The question of respiratory sequelae and the hypothesis of evolution to post-infectious chronic fibrotic interstitial lung disease, remains unanswered (7,8). Post-infectious persisting anosmia is increasingly reported, and patients may benefit from olfactory training in this situation (9). Finally, the viral neurotropism of SARS-CoV-2 through the olfactory bulb is a potential explanation for neurocognitive persisting symptoms, and we recently identified cerebral hypometabolic patterns in these patients (11).

In this context, as part of a previous study, we performed brain and full body ^{18}F-FDG PET/CT scans on confirmed post COVID-19 patients with persisting symptoms, to search for persistent inflammatory lesions (11). Among these patients, we retrospectively and

incidentally identified 10 patients with significant aortic hypermetabolism. Here we report and describe these patients, their clinical and imaging characteristics, and their follow-up when available, compared to the other 37 patients undergoing an ^{18}F-FDG PET/CT scan.

MATERIAL AND METHODS:

Inclusion criteria

Following the two SARS-CoV-2 outbreaks in Marseille (April–March 2020 and October-November 2020), 51 consecutive patients presented at our center, complaining of persisting symptoms (fatigue, dyspnoea, hyposmia, anosmia, dysgeusia, ageusia, memory/cognitive impairment, insomnia, pain) and received a full body ^{18}F-FDG PET/CT scan to search for post-infectious residual inflammatory lesions. We included in our retrospective analysis all patients with symptoms evolving more than three weeks after an initial proven SARS-CoV-2 infection (i.e., with a positive RT-PCR at the onset of symptoms, or a positive serology for SARS-CoV-2 after the initial acute symptoms). After identification of aortic hypermetabolism, patients were recalled for a new ^{18}F-FDG PET scan for follow-up, and a dedicated aortic CT-scan.

Patient data was anonymised. The data collection was retrospective with no ethical approvement requirement other than informed consent, according to French and European regulations. These data were extracted from a study which was GPDR (General Data Protection Regulation) compliant, registered under the following reference code: PADS20-296.

^{18}F-FDG PET imaging

^{18}F-FDG PET scans were acquired in the same center using an acquisition protocol which conformed to European guidelines, in a resting state, in fasting subjects for at least four hours with a controlled, normal glycaemic level, using an integrated PET/CT General Electric

camera (Waukesha, WI), after intravenous administration of 150 MBq per 15-minute acquisition at 30-minutes post-injection. Images were reconstructed on a 192×192 matrix using the ordered subsets expectation maximisation algorithm and corrected for attenuation using a CT transmission scan. The interpretation was performed by an experienced nuclear medicine radiologist within our center (SC). Hypermetabolic regions were described based on the ^{18}F-FDG uptake compared with the liver. After identification of abnormal hypermetabolic aortic patterns in ten patients, it was suggested controlling the ^{18}F-FDG PET scans six months after the initial episode.

Aortic CT angiography

After identification of aortic hypermetabolism, patients were invited to undergo computed tomography angiography to measure aortic diameters and volumes. The patients underwent preprocedural computed tomography angiography (CTA, Revolution EVO, GE Healthcare, Chicago, USA). CTA scans were performed after administration of a bolus of 1 cc/kg of a non-ionic contrast medium flushed with a bolus of 30 cc of a saline solution. The acquisition parameters were as follows: slice thickness = 0.6 mm; pitch = 1.3; reconstruction slice thickness = 0.6 mm; peak voltage = 120 kV; and automatic modulation of mAs.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the means ± SD (standard deviation). Comparative analyses were first established using a bivariate analysis Pearson test, using SPSS Statistics Software 20. Univariate and multivariate analyses were also performed using SPSS Statistics Software 20. We use the data previously collected by our team in the study cited above (11) to make a comparative analysis between patients with aortic hypermetabolism and patients without.

RESULTS

Within the group of 51 patients who underwent ^{18}F-FDG PET/ CT scan for persisting symptoms, two were retrospectively excluded from our observational study because no proof of SARS-CoV-2 infection was available. Two other patients were excluded from the analysis due to a lack of clinical data in the clinical files, resulting in a cohort of 47 patients. The results of the ten patients showing aortic hypermetabolism are described, and the clinical data were compared with the 37 patients not showing aortic hypermetabolism (controls).

Initial ^{18}F-FDG PET/CT description of patients and follow-up

Aortic hypermetabolism was incidentally detected in ten patients (Figure 1) with aortic SUV values comprised between 2.52 and 4.45 and aortic/liver values between 0.88 and 1.18 (Table 1). The thoracic aorta was involved in these ten patients, and abdominal aortic hypermetabolism was associated in three patients, the detail of the localisation of hypermetabolisms is shown in Figure 2. For four patients, a second ^{18}F-FDG PET/CT scan was performed at between four and six months of follow-up. Table 1 summarises the SUV values and aorta/liver ratios of ^{18}F-FDG uptake.

CT aortic angiography

For three patients for whom we conducted a second ^{18}F-FDG PET/CT scan, an aortic angiography CT scan was performed, and no patient showed significant parietal thickening on ascending or descending thoracic aorta nor on abdominal aorta.

Clinical characteristics and potential risk factors

The clinical characteristics of the ten patients are summarised in Table 2 and were compared with those of the 37 patients not showing aortic hypermetabolism. Of the ten patients, six were women, corresponding to a 0.6 men/women ratio. The mean age was 55 years old (44–71), the mean BMI was 25 (23–29). Four patients were previous smokers (22.5 median pack-years), one was an active smoker, and five patients had no current or past

smoking history. Only one patient had a cardiovascular medical history (arrythmia and stroke). One patient had rheumatoid arthritis, and another had thyroiditis, no patients had diabetes. At the onset of COVID-19 symptoms, two patients had a prognosis NEWS (12,13) score > 5. Sixty percent of patients had chest pain, 11% had dyspnoea and 14% had a severe chest CT during the acute phase of the disease. Regarding the treatment of the acute illness, 40% received a combination of hydroxychloroquine and azithromycin and no patients had corticosteroids (Table 2). The most frequent symptoms at the clinical re-evaluation after more than three weeks were dyspnoea (70%), chest pain (60%) and memory loss (60%) (Table 2). All patients had a normal C-Reactive protein rate when ^{18}F-FDG PET /CT scan was performed.

When the ten patients presenting aortic hypermetabolism were compared with the 37 controls, we found significant differences regarding the absence of active tobacco smoking at baseline (50% vs 83%, p=0.001), dyspnoea during the acute stage of the disease (11% vs 52%, p=0.02) and absence of ageusia (Table 2). Regarding symptoms at re-evaluation, patients with aortic hypermetabolism complained more frequently of chest pain more than three weeks after the acute illness (60% vs 19%) (Table 2). The only variables that were still associated with aortic hypermetabolism in univariate and multivariate analyses were the presence of a chest pain at re-evaluation (ß=0.4; 95% CI: 0.185-0.7; P=0.002) and the absence of active tobacco smoking ($ß = 0.5$, 95% CI: 0.175-0.453).

DISCUSSION

We report the largest clinical case series of aortic hypermetabolism in patients with persisting complaints more than three weeks after COVID 19 infection. We found these vascular hypermetabolisms incidentally by performing systematic exploratory ^{18}F-FDG PET/CT scans in patients with persisting symptoms following COVID-19. However, the high proportion of this feature in our cohort (21%) makes us think that this phenomenon is not due

to chance. The global epidemiology of aortitis is poorly known, but Japan has the highest incidence in the world, with 0.01 cases per 100,000 children per year, and its incidence in the US and European populations has been estimated at 1–3 new cases per million per year (14,15). Moreover, Sollini *et al.* recently reported ten patients who had recovered from SARS-COV-2 with persisting symptoms who underwent an ^{18}F-FDG PET/CT scan (16). Of them, six patients had an increased ^{18}F-FDG uptake in blood vessels and the target-to-blood pool ratio was significantly higher than controls in the following three vascular regions: thoracic aorta, right iliac artery and femoral arteries (16). Four other case reports showing signs of thoracic aortitis after SARS-CoV-2 infection can be found in the literature and are presented in Table 3. These data may reinforce the hypothesis of a SARS-CoV-2 post-infectious aortic inflammation.

When CT aortic angiography was performed, we did not find any significant aortic morphological changes in our patients, indicating that this may be a very early inflammatory phenomenon. However, when ^{18}F-FDG PET/CT re-evaluation was conducted for four patients (after 4–6 months of follow-up), hypermetabolism was still present, suggesting a persisting inflammation process.

This study is retrospective and, consequently, suffers from several biases. No previous ^{18}F-FDG PET/CT scan was available for the patients, so that we could not exclude the possibility that some of our patients had a previous aortic hypermetabolism and differential diagnosis could not be properly assessed. However, our patients had no more cardiovascular risks factors than the controls, on the contrary, they were less frequently active smokers ($p=0.001$), and no diabetic patients were found, suggesting that aortic hypermetabolism was probably not due to previous unknown atherosclerotic lesions. Moreover, this cohort was limited in size that may have prevented us from identifying more risk factors for patients with

aortic hypermetabolism after COVID-19. Additionally, differential diagnosis would have to be eliminated through biological analysis which we did not perform.

The pathophysiological mechanism for this post-infectious vascular inflammation is unknown. Endothelial cells have ACE2 receptors that could bring SARS-CoV-2 into the cytoplasm (17) and viral particles have been described in the vascular wall by Varga *et al* (18). Consequently, it could be asked whether the inflammatory phenomenon is the result of post-infectious inflammation of whether viral persistence is involved, as is described in syphilis infection (19,20).

Surprisingly, common ^{18}F-FDG PET/CT images found in proven primary syphilitic infection looks very similar to the images we found in COVID-19 infected patients (21,22), with the same moderately increased metabolic activity in the aortic wall (23). As is the case in syphilitic aortitis (20,24), the hypermetabolism seen in our patients appears to particularly affect the thoracic segment. In 2018, Yuan *et al* described clinical sign panels in 52 patients with a syphilitic aortic aneurysm (20), and the main symptoms were chest pain, as we found in our cohort.

Cases of large-vessel aortic inflammation due to viral infections have already been reported in the literature. In 2016, Don Gilden and colleagues described an autopsy case series of 11 patients infected with Varicella Zoster Virus (VZV) and compared them to 28 controls. 11/11 of the aortas had the VZV antigen detected by immunohistochemistry and PCR, associated with pathologically-verified granulomatous arteritis (25). As a well-known phenomenon, cases of HIV-related aortitis have also been described, as Takayasu-like disease, mainly on large and medium vessels, with a high risk of aortas an cerebral aneurysms (26). Finally, we found rare case reports of aortitis secondary to Hepatitis C virus (HCV)-associated cryoglobulinemia (27), aorta mesoarteritis with media destruction in Chronic

Active Epstein-Barr Virus (EBV) infection, with a positive EBV PCR in the aortic wall (28), and Cytomegalovirus (CMV)-linked atherosclerotic aortitis found in mice (29).

Considering this data, there is a need for close follow-up of these ten post- COVID-19 patients with aortic hypermetabolism, to understand whether the inflammation that we have observed is a post-infectious sequelae or an ongoing process. New CT angiography should be performed in the follow-up to identify whether morphological changes occur in the aortic walls of these patients. The possible emergence of an aortic aneurysm or dissection, years after acute infection, as is the case in *Treponema pallidum* infection (20,30), is a real matter of concern, as is its potential treatment.

CONCLUSION:

Our data should prompt clinicians to use ^{18}F-FDG PET/CT scans to search for aortic hypermetabolism in patients with persisting symptoms after COVID-19, especially those complaining from atypical chest pain.

Author's contributions:

-Pierre Dudouet wrote the first draft of the MD

-Serge Camilleri and Eric Guedj interpreted the results of the 18F FDG PET/CT scan and wrote the nuclear imaging part of the MS

-Alexis Jacquier interpreted and wrote the aortic CT angiography part of the MS

-Didier Raoult revised the different versions of the MS

-Carole Eldin designed the work, performed the statistical analyses and revised the different versions of the MS

Conflicts of interest/Competing interests

The authors declare that they have no conflicts of interest

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Table 1. SUV max values and aorta/liver ratios for the ten patients

	1st PET-CT scan			2nd PET-CT scan		
	Thoracic Aortic SUV max	**Abdominal Aortic SUV max**	**Aorta/liver ratio**	**Thoracic Aortic SUV max**	**Abdominal PET-1 Aortic SUV max**	**Aorta/liver ratio**
Patient 1	3.05	//	0.9	//	//	//
Patient 2	2.52	//	0.89	//	//	//
Patient 3	3.35	3.87	0.88/0.99*	//	//	//
Patient 4	4.25	4.71	0.98/1.08*	3.65	3.85	0.89/0.94*
Patient 5	3.55	//	0.96	4.09	//	1.18
Patient 6	3.47	//	0.98	3.17	//	0.88
Patient 7	4.45	4.88	0.91/1*	3.74	4.38	0.66/0.77*
Patient 8	2.56	//	0.88	//	//	//
Patient 9	2.93	//	1.08	//	//	//
Patient 10	3.08	//	0.98	//	//	//

Legend:

1st PET-CT scan: first ^{18}F-FDG PET/CT

2nd PET-CT scan: second ^{18}F-FDG PET/CT, when available

*Thoracic aorta liver ratio/Abdominal aorta liver ratio

SUV: Standardised Uptake Value

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386 **Table 2. Clinical characteristics of patients with aortic hypermetabolism, compared to**

387 **patients without aortic hypermetabolism after COVID-19**

	Aortic hypermetabolism n= 10	**No aortic hypermetabolism n= 37**	**P (Pearson)**
Mean Age	55	52	0.4
Sex ratio (W/M)	0.6 (6/10)	0.45 (17/37)	0.6
Mean BMI	25	28	0.069
High Blood Pressure	1 (10%)	8 (2.7%)	0.4
Diabetes	0	9 (24%)	0.09
No current or past smoking	5 (50%)	31(83%)	**0.001**
Initial symptoms	**Aortic hypermetabolism n= 10**	**No aortic hypermetabolism n= 37**	**P (Pearson)**
Dyspnoea	1/9 (11%)	19/36 (52%)	**0.02**
Chest pain	3/9 (33%)	11/36 (30%)	0.5
Anosmia	2/9(22%)	13/36 (36%)	0.35
Ageusia	0	14/37(37.8%)	**0.02**
NEWS Score>= 5	2/6 (33%)	9/27(33%)	1
Severe initial Chest CT Scan	1/7(14%)	10/29 (34%)	0.22
Delay between symptoms and treatment	4.30 (0.24-8.36)	2.76 (1.66-3.86)	0.27
Delay treatment> 3 days	6/10 (60%)	18/37 (48%)	0.5
Delay treatment>5 days	3/10 (30%)	8/37 (22%)	0.6
Azithromycin	6/10 (60%)	26/34 (76%)	0.3
HCQ	5/10 (50%)	26/35(74%)	0.2
3GC	1/10 (10%)	14/32 (44%)	0.05
Other Antibiotics	2/10 (20%)	3/32 (9%)	0.35
HCQ + Azithromycin	4/10 (40%)	23/35 (66%)	0.1
HCQ + Azithromycin >72H	4/10 (40%)	23/35 (66%)	0.1

High blood pressure treatment	1/10 (10%)	7/35(20%)	0.5
Week 3 symptoms			
Dyspnoea	7/10(70%)	26/36 (72%)	0.59
Chest pain	6/10 (60%)	7/37 (19%)	**0.017**
Diffuse pain	4/10 (40%)	12/36(33%)	0.48
Anosmia	2/10 (20%)	11/36 (31%	0.139
Ageusia	1/10 (10%)	8/36 (22%)	0.36
Memory loss	6/10 (60%)	19/37 (51%)	0.45
Sleep disorders	3/9 (33%)	14/36 (38.9%)	0.5

W: Women; M: Men; BMI: Body Mass Index; PY: package-year, CT: computerised tomography, CRP: C-reactive protein, ICU: intensive care unit, HCQ: hydroxychloroquine, 3GC: 3rd generation cephalosporins H: hours

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390 **Table 3. Aortitis cases after COVID-19 in the literature.**
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	Patient A	Patient B	Patient C	Patient D
Sex, Age, country	M, 71, UK	M, 71, UK	F, 69, Spain	M, 50, Italian
Background	No	Cholecystectomy	No	No
Delay between disease and imagery	15 days	90 days	NA	90 days
Aortic segments	Thoracic	Arch	Thoracic, abdominal	Arch, descendant thoracic
Symptoms	Chest pain	Chest pain	No symptom	Chest pain, fatigue
Imagery	Injected CT Scan	Injected CT scan	^{18}F-FDG PET-TDM	^{18}F-FDG PET-TDM
Treatment	CTC	CTC	No	No
Imagery control	Regression	Regression	No	NA
Outcomes	Good	Good	Good	Good
Reference	*Shergill et al, Eur. Heart J. August 2020*	*Zou et al, Rheu adv in Pract, Oct 2020*	*Carmen Davila et al, Rev Esp Med Nucl Im Mol, 2020*	*Solini et al, Eur J Nucl med mol imaging, Oct 2020*

Table 5. Description of aortic abnormalities found in literature in confirmed COVID-19 cases. UK: United Kingdom, M: male, F: female, CTC: corticosteroids, PET: positron emission tomography, FDG: fluoro-2-deoxyglucose, CT: computerised tomography, TDM: tomodensitometry.

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Figure 1. 18F-FDG PET CT showing aortic hypermetabolism in two patients.

Panel A: 48-year-old woman (Patient 3)

Panel B: 71-year-old man (Patient 4)

Figure 2. Schematic representation of the localisation of aortic hypermetabolism for the ten patients.