Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Aortic ^{18}F-FDG PET/CT hypermetabolism in patients with long COVID: a retrospective study

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To the Editor,

Long COVID is defined by the French National Health Authority as persisting symptoms more than 4 weeks after COVID-19 [1]. Recently, Sollini et al. described an increased ^{18}F-FDG vascular uptake in six patients with long COVID [2]. We retrospectively searched for vascular hypermetabolism among patients consulting for long COVID who had a whole body ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) as part of routine exploration. This retrospective study was approved by the hospital board (AP-HM) on reference PADSVJWVK7, and data extracted respecting the French GPDR (General Data Protection Regulation). One hundred and sixteen patients consulted for long COVID in our centre between May and December 2020. Fifty-one patients had ^{18}F-FDG PET/CT, two were excluded because no proof of SARS-CoV2 infection was available and two because of a lack of clinical data, resulting in a cohort of 47 patients. The 47 patients had persisting symptoms more than 4 four weeks after a positive RT-PCR naso-pharyngeal test for SARS-CoV-2 infection (70% with dyspnoea, 27% with hyposmia/anosmia, 19% with dysgeusia/ageusia, 27% with chest pain, 53% with cognitive disorders and 36% with sleeping disorders).

^{18}F-FDG PET/CT were acquired in fasting subjects for at least 6 hr with a controlled glycaemic level, using GE discovery 710 PET/CT, 60 min after intravenous administration of 3 MBq/kg of ^{18}F-FDG. Comparative analyses were done using the Fisher exact test with SPSS Statistics Software 20.

Aortic hypermetabolism was visually detected in ten patients, with an aortic mean Standardized Uptake Value (SUV_{max}) measured at 3.36 (SD = 0.63) (Fig. 1). The thoracic aorta segment was involved in all patients. Abdominal aortic hypermetabolism was additionally found in three patients. Five patients were checked with a second ^{18}F-FDG PET/CT scan (mean delay 152 days). Four out of five showed persistent aortic hypermetabolism. The mean aortic SUV_{max} in the ten aortic hypermetabolism patients was higher than in the 37 non-aortic hypermetabolism patients (3.36, SD 0.63; and 2.51, SD 0.18, respectively, p 0.002). Three out of ten patients had a thoracic CT angiography to measure aortic diameters and volumes. No significant parietal thickening on the ascending or descending thoracic aorta nor on the abdominal aorta was found on CT angiography.

The group of ten patients with aortic hypermetabolism was composed of six women (6/10), with mean age of 55 years (44–71), and mean body mass index ($Kg.m^{-2}$) of 25 (23–29). Five patients were smokers (one active and four former smokers). One patient had high blood pressure and one patient had past cardiovascular events (arrythmia and stroke). Three patients had chest pain during acute COVID-19 (3/9), one patient had dyspnoea (1/9), and one had a severe lesion on chest CT scan (1/7). The clinical features of long COVID were dyspnoea (7/10), chest pain (6/10) and cognitive complains (6/10). When compared with the 37 controls with negative aortic PET, we found significant differences regarding

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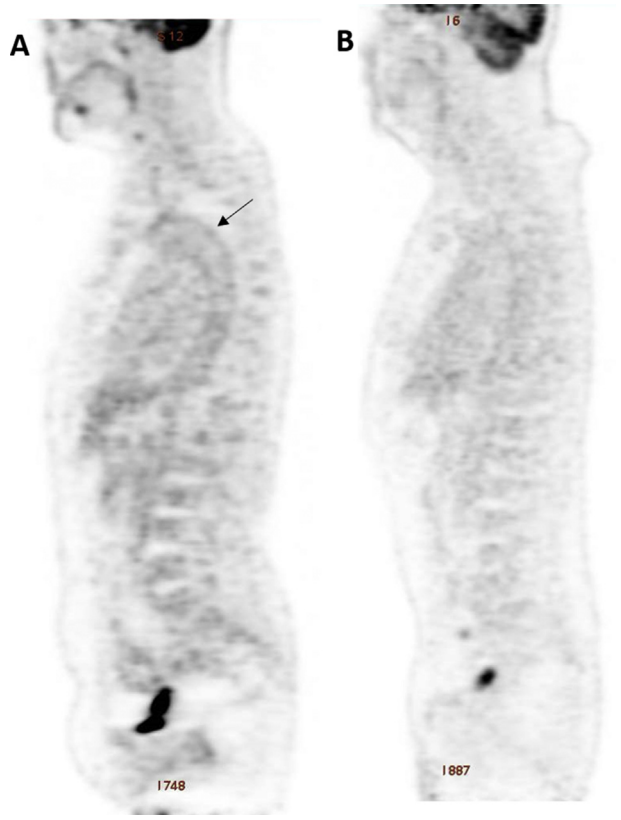

Fig. 1. ^{18}F-FDG PET sagittal views 60 min after injection. Mean of SUV_{max} was measured at 3.36 with 0.63 SD in aortic hypermetabolism patients and 2.51 with 0.18 SD in non-aortic hypermetabolism patients. (A) Long COVID patient with aortic hypermetabolism. The arrow points to hypermetabolism of the aortic wall. (B) Long COVID patient without aortic hypermetabolism.

tobacco smoking at baseline (5/10; 50% vs. 31/37; 83%, p 0.04), dyspnoea during the acute stage (1/9; 11% vs. 19/36; 52%, p 0.03), persistent ageusia (0/10 vs. 14/37; 38%, p 0.02) and persistent chest pain (6/10; 60% vs. 7/37; 19%, p 0.017). No other significant differences were found between the two groups. Biologically, all patients had a normal C-reactive protein rate, and we performed *Treponema pallidum* serology on six patients, and all were negative.

In summary, we retrospectively found aortic hypermetabolism in ten out of 47 patients with long COVID who had an ^{18}F-FDG PET/CT scan, with more frequent chest pain in this group (6/10; 60% vs. 7/37; 19%, p 0.017). The high proportion of aortic hypermetabolism in our cohort (21%) makes us think that this phenomenon is not incidental. To have an idea of the prevalence of an incidental finding of thoracic aortic hypermetabolism, we compared thoracic aortic uptakes between our long COVID patients, and a non-COVID-19 control group of 20 randomly selected patients with negative SARS-CoV-2 RT-PCR and serology, who had an ^{18}F-FDG PET/CT scan for oncological indications. No patients in this control group had visually detected aortic hypermetabolism and comparative analysis with a non-parametric Kruskall–Wallis test showed significant differences in mean aortic SUV_{max} between our ten patients with aortic hypermetabolism and the non-COVID-19 control group (3.36, (SD 0.63) and 2.15 (SD 0.59), respectively; $p < .0001$).

This study is retrospective and, consequently, suffers from several biases. No previous ^{18}F-FDG PET/CT scan was available for the patients, and we could not exclude the possibility that some had a pre-existing aortic hypermetabolism. Nonetheless, they had no more cardiovascular risks factors than the controls, including tobacco and age, suggesting that aortic hypermetabolism was probably not due to previous unknown atherosclerotic lesions. However, we found significant differences between small groups of patients, and the relevance of our results needs to be confirmed by further studies on larger samples.

We nevertheless confirm the findings of Sollini et al. and of four other case reports showing signs of thoracic aortitis after SARS-Cov2 infection, all presenting with chest pain, reinforcing the hypothesis of SARS-COV 2 post-infectious aortic inflammation [3–6]. Supported by the SARS-CoV-2 pathophysiological mechanism of entry, which uses the ACE2 receptor present on endothelial cells, evidence of SARS-CoV2 virions inside vascular tissues is now emerging [7]. Nonetheless, it is still not clear whether this FDG/PET inflammation means active endothelial viral replication, passive viral persistence without endothelial damage, post-infectious aortic inflammation mechanism or sequelae. ^{18}F-FDG PET/CT thoracic aortic hypermetabolism found in primary syphilitic infection, long before the development of aortic aneurysm, looks very similar to the images we found in COVID-19-infected patients, suggesting similar pathogenesis [8].

There is a need for close long-term follow-up of these patients with aortic hypermetabolism, to understand whether the inflammation that we observed is a sequela or an ongoing process, with possible emergence of an aortic aneurysm or dissection, years after acute infection. CT angiography should be performed at follow-up to identify if morphological changes occur in the aortic wall of these patients. Further prospective multicentric studies are needed to better understand the risk factors and prognosis of post-COVID-19 thoracic aortic inflammation.

Transparency declaration

The authors declare that they have no conflicts of interest. No external funding was received for this study.

Author contributions

Pierre Dudouet proceeded to patient examination, wrote the first draft, revised the present MS, collected and analysed data; 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.

Ethical considerations

Use of all data was secured by password protection of all folders, and was approved by the legal General Data Protection Regulation team from the “Assistance Publique des Hôpitaux de Marseille”, the Marseille university hospital as a retrospective study without need of ethics committee declaration in current French regulatory rules. Specific Secure Data Access Portal was created with the number VJWVK7.

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