Large vessel stroke in six patients following SARS-CoV-2 infection: a retrospective case study series of acute thrombotic complications on stable underlying atherosclerotic disease

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\textbf{Introduction}

The pandemic outbreak of coronavirus disease 19 (COVID-19) was first described as a flu-like syndrome with respiratory symptoms [1]. However, neurological symptoms have been reported in 31\% of cases, with 6\% of cerebrovascular disease [2]. A limited number of strokes associated with COVID-19 have been described, either occurring in young patients (n = 5) or associated with antiphospholipid antibodies or hypercoagulability (n = 9) [3–5]. The cause of stroke was suggested to be related to the coagulopathy induced by COVID-19 infection and the associated inflammation [6].

Here, healthcare providers are warned about the catastrophic association of stable atherosclerotic disease and COVID-19 infection which may precipitate acute stroke.

Accordingly, six cases of patients with SARS-CoV-2 infection who developed large vessel ischaemic stroke, all with large intraluminal thrombus and mildly, stable, underlying atherosclerotic lesions are reported here.
The demographic, clinical, radiological and laboratory characteristics of six consecutive patients admitted for ischaemic stroke associated with SARS-CoV-2 infection are described.

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of Foch Hospital. Oral consent was obtained from patients or next of kin.

**Results**

A retrospective analysis of stroke related to large vessel occlusion was conducted amongst patients with SARS-CoV-2 infection and underlying mild atherosclerotic disease.

Six cases of large vessel occlusion on mild atherosclerotic lesions were admitted during the study period between 19 March and 19 April 2020 in six different stroke centers in the Ile-de-France area, France.

The median age was 52 years, median body mass index (BMI) was 29.5 kg/m². All patients displayed previous vascular risk factors such as high blood pressure, diabetes, dyslipidemia or BMI > 25.

The delay between the first respiratory symptoms of COVID-19 and stroke was 11.5 days. The diagnosis of SARS-CoV-2 infection was asserted by polymerase chain reaction or thoracic computed tomography (CT) scan for all patients. Four of the six reported cases displayed no/mild respiratory symptoms. All the patients showed an increase in inflammatory markers and a hypercoagulability state (elevation of D-dimer or C-reactive protein).

At baseline, all had tandem occlusions, i.e. intracerebral and extracerebral thrombi assessed by CT or magnetic resonance imaging. All cases except one (patient 1) displayed a large thrombus in the cervical carotid artery with underlying mild non-stenosing atheroma, after an etiological workup based on angiographic imaging and/or cervical echography. They were classified as stroke of undetermined etiology according to the TOAST classification. Although no underlying atherosclerotic lesion was found, patient 1 displayed BMI = 33, high blood pressure and diabetes in his medical history. The rest of the etiological workup was negative for these patients (Fig. 1, Table 1).

Concerning the outcome, three patients had died and three were discharged to a rehabilitation center.

**Discussion**

The mechanisms of ischaemic stroke associated with SARS-CoV-2 infection are poorly understood [6–8].

The prothrombotic state associated with COVID-19 infection has been proposed to be responsible, as for pulmonary embolism [9]. Furthermore, circulating inflammatory factors (e.g. interleukin and C-reactive protein) are responsible for early molecular events triggered by coagulation abnormalities.

Major prognostic factors of the SARS-CoV-2 infection encompass a medical history of vascular disease and risk factors of atherosclerotic disease (obesity, high blood pressure, diabetes). Our observations of acute ischaemic stroke in patients with SARS-CoV-2 infection are in accordance with the reported high-risk profile of patients admitted with the most severe form of SARS-CoV-2 infection [1,10].

Our observations illustrate large vessel occlusion associated with clotting induced by SARS-CoV-2 infection complicating underlying stable atherosclerotic disease. Complications of atherosclerotic disease by viral infection have previously been described [11,12] but the heavy burden of the current COVID
| Case number | 1        | 2        | 3        | 4        | 5        | 6        |
|-------------|----------|----------|----------|----------|----------|----------|
| Age (years) | 42       | 60       | 50       | 45       | 60       | 54       |
| Sex         | Male     | Female   | Male     | Female   | Male     | Male     |
| Medical history | HBP, diabetes | Dyslipidemia | HBP, diabetes | None | HBP, diabetes | None |
| Symptoms at disease onset | Aphasia and right hemiplegia | Right hemiplegia confusion | Hemiplegia limb ischaemia | Aphasia and right hemiplegia | |
| Days from disease onset to ischaemic stroke | 11 | 11 | 13 | 4 | 12 | 13 |
| BMI | 33 | 35 | 33 | 14 | 26 | 26 |
| NIHSS at stroke onset | 20 | 22 | 21 | 26 | 4 | 4 |
| Site of occlusion | Common and external and internal carotid artery and MCA | Tandem occlusion with terminus carotid artery and MCA | Tandem occlusion with terminus carotid artery and MCA | Tandem occlusion with terminus carotid artery and MCA | Tandem occlusion with terminus carotid artery and MCA | Tandem occlusion with terminus carotid artery and MCA |
| Stroke topography | Anterior | Anterior | Anterior | Anterior | Anterior | Anterior |
| Side of stroke | Left | Left | Right | Right | No | No |
| Symptoms of COVID-19 severity | Mild (cough) | Severe | Severe (pulmonary embolism) | No | Severe (ARDS) | Cough |
| COVID diagnosis | Thorax CT scanner | Thorax CT scanner | PCR + | Thorax CT scan + PCR+ | PCR+ | Thorax CT scan |
| D-dimers (µg/ml) | 19461 | 5315 | 13010 | 11970 | 137.9 | 4 |
| High-sensitivity C-reactive protein (mg/ml) | 30 | 158 | 211 000 | 371 000 | 325 000 | 424 000 |
| Platelet count | 279 000 | 253 000 | Not done | Negative/negative | Negative/negative | Not done |
| Antiphospholipid antibodies/anti B2-glycoprotein 1 | Negative/negative | IgM 15/B2GP1 = 23 | Not done | Negative/negative | Negative/negative | Not done |
| Lupus anticoagulant | Negative | Negative | Not done | Positive | Positive | Not done |
| Acute stroke treatment | IVT and EVT | Heparin IV | EVT | Normal, except a thin atheromatous plaque | Normal, except a thin atheromatous plaque | Normal, except a thin atheromatous plaque |
| Etiology work-up | Cryptogenetic | Stroke of undetermined etiology | Stroke of undetermined etiology | Stroke of undetermined etiology | Stroke of undetermined etiology | Stroke of undetermined etiology |
| Etiology classification (TOAST) | Stroke of undetermined etiology | Stroke of undetermined etiology | Stroke of undetermined etiology | Stroke of undetermined etiology | Stroke of undetermined etiology | Stroke of undetermined etiology |
| Clinical follow-up | Death | Death | Death | Discharge to rehabilitation center | Discharge to rehabilitation center | Discharge to rehabilitation center |

ARDS, acute respiratory distress syndrome; B2GP1, beta-2 glycoprotein 1; BMI, body mass index; CT, computed tomography; EVT, endovascular treatment; HBP, high blood pressure; IgM, immunoglobulin M; IVT, intravenous thrombolysis; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCR, polymerase chain reaction.
outbreak has permitted an infrequent complication of atheroma associated with viral infection to be described. Direct (invasion by virus) or indirect mechanisms (inflammatory/procoagulant status) have also been debated [7,13]. Our report does not provide definitive evidence whether the clotting in the internal carotid artery is related to the underlying atherosclerosis or whether this is simply an epiphenomenon, given the high prevalence of atherosclerotic disease. However, in the reported cases, clotting was described only at the surface of the atherosclerotic plaque and in the downstream circulation. Multiple clotting in different arteries was not observed in these cases, supporting the potential causal effect of the underlying atherosclerotic lesion.

The observation of these large vessel occlusions amongst COVID patients with mild atherosclerotic disease could represent important clinical findings to warn healthcare providers about the high-risk profile of patients with vascular risk factors. Thus, the community needs to be alerted on the risk of precipitating severe complications due to underlying atheroma.

This study has several limitations. It is a retrospective report. Whilst it may not be generalizable, our study should alert clinicians to scrutinize any new onset of ischaemic stroke during COVID-19 infection, mainly in patients with vascular risk factors or underlying atherosclerotic lesions.

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Disclosure

The authors declare no financial or other conflicts of interest.

Data availability statement

The data will be available to others on reasonable requests to the corresponding author.

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