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Case Report

Multiple ischemic stroke with pulmonary embolism revealing severe COVID-19 infection in a young healthy patient ☆,☆☆

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ABSTRACT

Coronavirus 2019 (COVID-19) disease has caused significant morbidity and mortality worldwide since its emergence in December 2019. Despite its respiratory tropism; there is a non-trivial relationship between this virus and the neurovascular system exposing patients to higher morbidity and mortality. We report the case of a young patient admitted for hemiplegia with acute respiratory failure, in whom imaging found multiple ischemic strokes with pulmonary embolism and severe involvement suggestive of COVID-19 pneumopathy. Stroke in the context of COVID-19 infection has distinct characteristics in terms of disease mechanism, patient demographics, but also clinical, biological, and neuroradiological specificities. The pathogenesis and optimal management of COVID-19-associated ischemic stroke remain unclear, but the coagulopathy and endotheliopathy triggered by the cytokine storm represent possible target mechanisms.

Introduction

First appearing in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the 2019 coronavirus disease (COVID-19), which the World Health Organization (WHO) has declared a pandemic in MARS 2020.

Although the majority of the focus is on respiratory symptomatology, neurological complications, which are more frequent and complex than originally envisioned, may manifest subtly and add considerably to the severity of the disease [1,2].

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Acute ischemic stroke is an important but under-recognized neurovascular complication of SARS-CoV2 infection, with clinical presentations that vary widely from subject to subject [3,4].

A review of data from patients with COVID-19-associated stroke has highlighted specificities regarding disease mechanism, patient demographics, but also clinical, biological, and neuroradiological specificities [5].

The pathogenesis and optimal management of COVID-19 associated ischemic stroke remain unclear, but emerging evidence suggests that cytokine storm-triggered coagulopathy and endotheliopathy represent possible targetable mechanisms [5].

Cases presentation

This is a 44-year-old patient originating from Oujda (oriental of morocco) whose number of confirmed cases was 2860 with as dominant variant: the delta variant not vaccinated against COVID-19 due to the unavailability of the vaccine during the period of his admission, without any particular history, the history of the disease goes back 12 days before the date of her admission by the appearance of an influenza-like syndrome made of asthenia, myalgia, fever and cough.

The evolution was marked by the installation of a right hemiplegia 2 days after her admission neglected by the family and a respiratory discomfort motivating her consultation at the emergency room of the Mohammed VI University Hospital.

The clinical examination found a conscious patient, tachycardia at 125 bpm, BP = 140/65 mm Hg Polypneic at 30 cycles/min SpO2 at 60% on room air 80% under 15 L/min with signs of struggles. Neurological examination a right hemiplegia, without speech disorders, without cranial pairs involvement, with confusional syndrome and notion of auditory and visual hallucinations, fluctuating during the day, without meningeal stiffness or other associated signs. NIHSS: 10.

Patient hospitalized in the ICU and received and given the neurological and respiratory symptomatology the patient benefited from:

- C- brain CT showed hypodense left temporal and frontal cortico-subcortical areas associated with effacement of the cortical sulci opposite (Fig. 1). Cerebral MRI (Fig. 2) showed diffusion hypersignal with low ADC in the left temporal, left frontal and right frontal cortico-subcortical areas and left cerebellar punctiform. All lesions are in Flair and T2 hypersignal. No hemorrhagic stigma on the T2* sequence. Analysis of the 3D TOF sequence revealed a complete polygon of Willis without any image of stenosis. Minimal vascular leukopathy grade 1 according to the FAZEKAS scale: Multiple bilateral sylvian ischemic strokes and left PICA.
- Thoracic angioscan (Fig. 3) bilateral alveolar-interstitial lung disease suggestive of SARS COV-2 PNP classified as CORADS 5 with critical involvement (>75%). Segmental pulmonary embolism in the right lower lobe and left upper lobe.

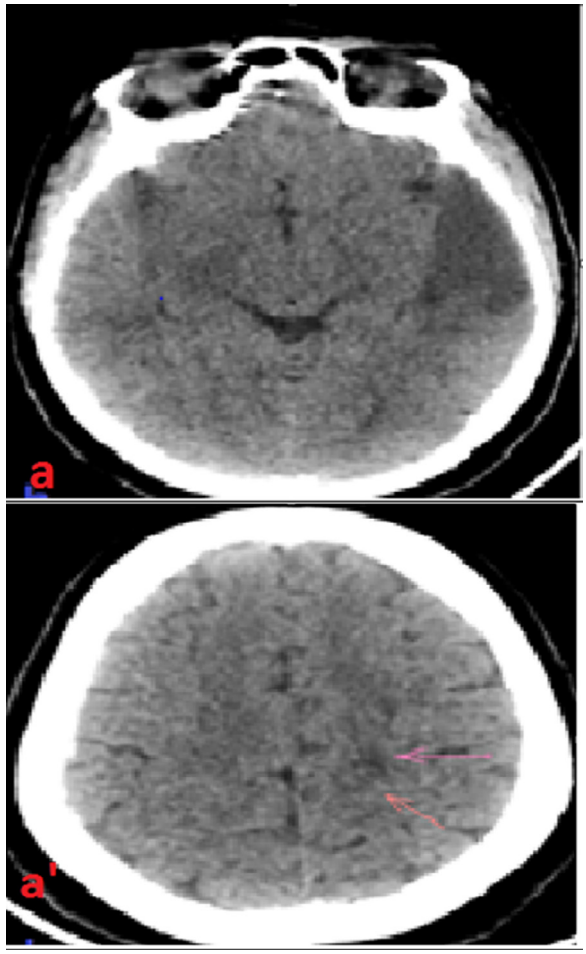

Fig. 1 – Axial section of a brain scan without injection (a); hypodense temporal and left frontal cortico-subcortical areas associated with effacement of the cortical sulci opposite (a').

- Biological findings lymphopenia (900/μL NR: 1000-4000/μL), and elevation of D-Dimers at 35.2 mg/L (NR: 0-0.5mg/L), and given the pandemic context, an RT-PCR with COVID-19 was performed, which came back positive. The ECG showed no rhythm or conduction disorders Trans Thoracic Echocardiography was normal.
- The patient was put on: oxygen therapy (Optiflow), Azithromycin: 500 mg the first day then 250 mg for 6 days, Triaxone 2 g/d, Ciprofloxacin 200 mg/12 h, PPI 40 mg/d, Medrol 32 mg/d, Vit C 1 g x 2/d, Zinc 45 mg 1cp/d, Nicardipine (Loxen according to BP), Paracetamol 1g/6h if fever and curative anticoagulation Low Molecular Weight Heparin 6000 UI/12 h. On the neurological level, the patient was put on Levetiracetam: Keppra 250 mg: 0-0-1 for 03 days, then 1-0-1 for 03 days, then 1-0-2 for 03 days, then Keppra 500: 1-0-1, with monitoring of liver function, and Anti platelet therapy: Coplavix 75/100 mg: day for 03 weeks, then Kardégic 160 mg/d.

After a 12-day hospitalization in intensive care, the evolution was marked by a clinical and biological improvement.

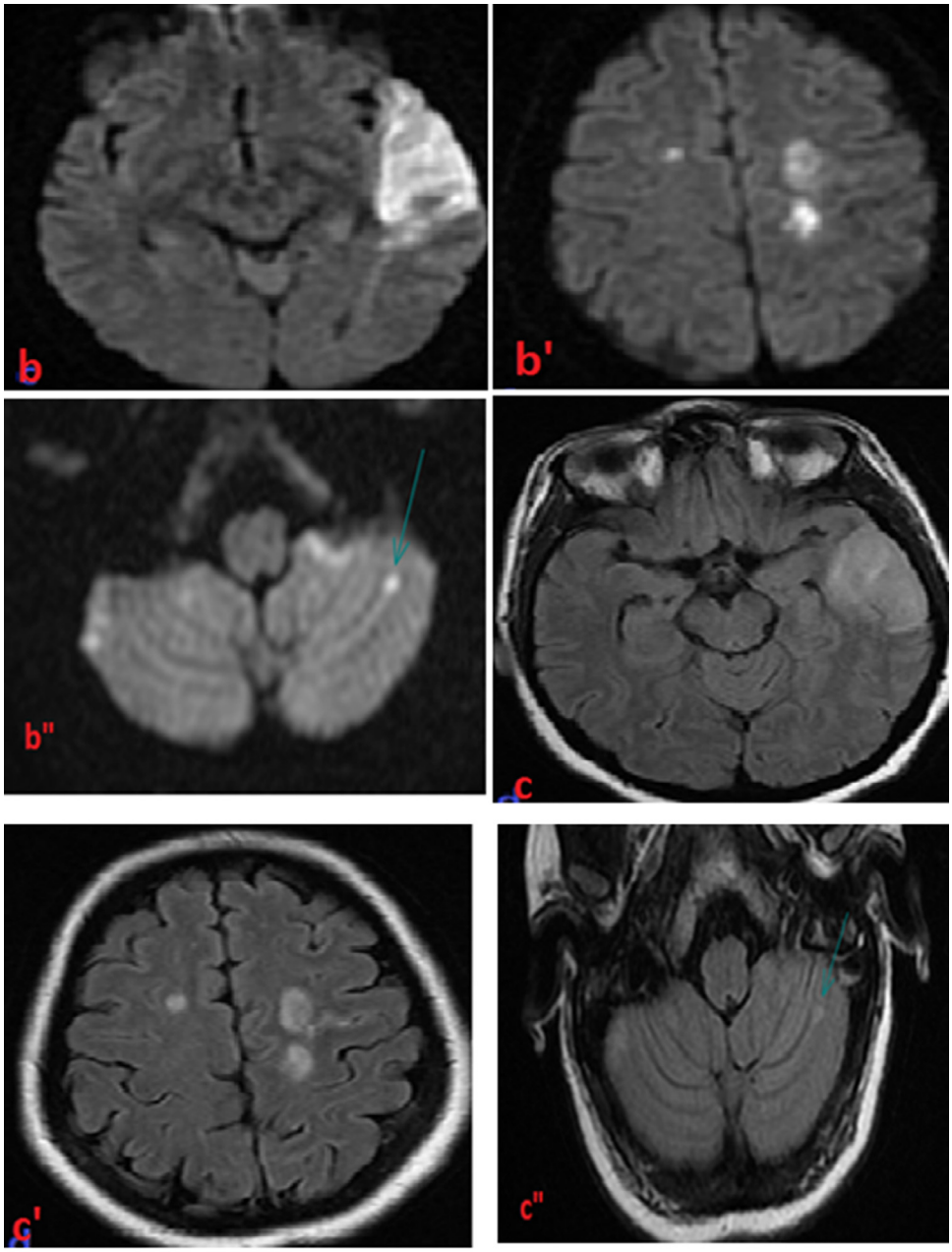

Fig. 2 – Axial MRI sections in diffusion sequence (b)(b')'(b''), T2 FLAIR showing multiple bilateral sylvian subacute ischemic strokes and left PICA Absence of hemorrhagic remodeling. (c)(c')(c'').

The patient was discharged at home with good respiratory progress, and persistence of a sensory-motor deficit, then the patient was referred to a physical rehabilitation service.

Discussion

Most patients with ischemic stroke in COVID-19 were older than 60 years and had vascular risk factors. But, younger patients without known risk factors were also reported. These patients had predominantly large vessel occlusion, multiple vascular territory involvement, and neurological deficit that were severe at the time of presentation. Concomitant cases of deep vein thrombosis and pulmonary embolism were described. On the biological level, an elevation of D-dimer and inflammatory balance was marked as well as anti-phospholipid antibodies [5].

The authors also found that cryptogenic stroke was twice as common in COVID-19 positive patients compared with COVID-19 negative patients (65.6% vs 30.4%, respectively) [6], and it has been proposed that COVID-19-associated cryptogenic stroke represents a unique mechanism of stroke associated with a higher likelihood of early mortality [7,8].

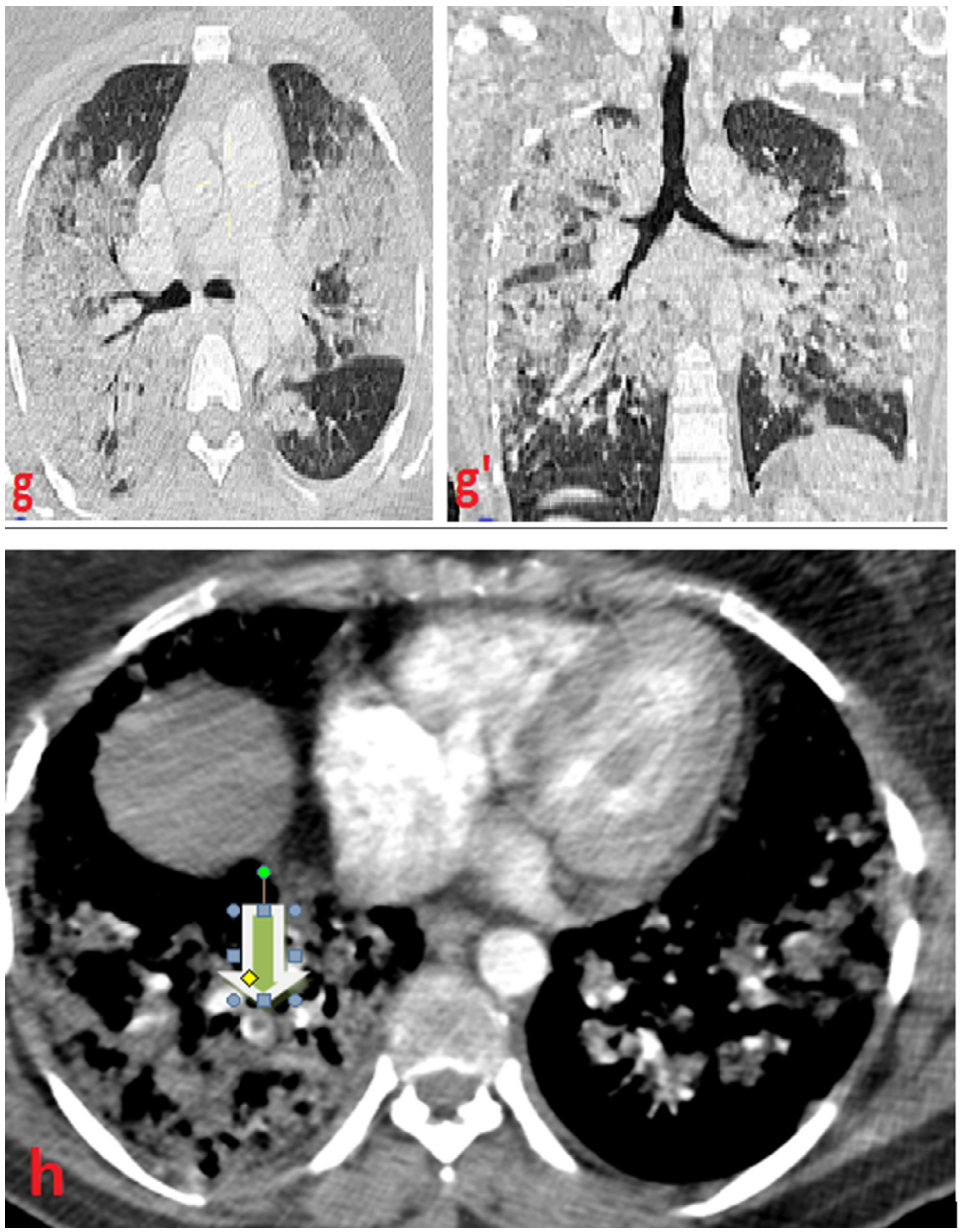

Fig. 3 – Axial (g) and coronal (g') thoracic CT: CORADS 5 lung disease, critical impairment (h), thoracic angioscan showing segmental pulmonary embolism in the lower lobar region.

The first study (Benali et al.) to link SARS-CoV-2 to acute stroke showed that COVID-19 infection was found to be independently and significantly associated with patients with acute ischemic stroke [9].

The pathogenesis of stroke during SARS-CoV-2 infection is complex and not fully understood, but current data indicate the combined effect of several factors, among them:

Infection results in the recruitment of mononuclear cells. These cells secrete pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) that promote the release of plasminogen activator inhibitor (PAI-1) and inhibit natural anticoagulants. They promote the activation of coagulation through the generation of tissue factor, as well as the activation of platelets and their interaction with the activated endothelium [10].The interaction between IL-6 secretion and the pro-coagulant phenotype of patients with SARS-CoV-2 is described in an Italian study with a significant association between fibrinogen and IL-6 levels [11]. This hyper-activation of coagulation is coupled with hypo-fibrinolysis. The role of fibrinolysis is to degrade fibrin, thanks to the action of plasmin. Plasmin is itself derived from plasminogen, and is dependent on tissue plasminogen activator and urokinase. Both of these enzymes are disrupted in inflammatory situations [12] and are inhibited by plasminogen activator inhibitor type I (PAI-1). In SARS, high blood levels of PAI-1 were found in patients [13]. This hypofibrinolysis was further analyzed in critically ill COVID-19 patients, and it was shown in such a retrospective analysis comparing COVID-19 and non-COVID-19 patients

that D-dimer and fibrinogen levels were higher in the former [13] and that COVID-19 stroke patients have dramatically elevated D-dimer and fibrinogen levels [14,15].

In addition to its role in thrombogenesis through activation and exposure of pro-thrombotic elements such as collagen, tissue factor, and platelet adhesion molecules [16]. Inflammation leads to instability and vulnerability to atherosclerotic plaque rupture Inflammation and plaque vulnerability [17]. The presence of proteolytic enzymes such as metalloproteinases (MMPs) and cysteine proteases cathepsins (CCPs), which are secreted by the bloodstream, is a major factor in the development of inflammation. The presence of proteolytic enzymes such as metalloproteinases (MMPs) and cysteine proteases cathepsins (CCPs), which are secreted by activated macrophages, promote extracellular matrix degradation and plaque fragility and may lead to thromboembolism, while making acute ischemic stroke a likely event in the potential trajectories of patients with systemic COVID-19 infection [18]. This hyperinflammatory state is shown by marked increases in various biomarkers such as neutrophil/lymphocyte ratio (NLR), C-reactive protein, and serum ferritin in COVID-19 patients with DALYs [15,19].In addition to CRP being a marker of inflammation, a meta-analysis also confirms its role in thromboembolic events [20]. On the other hand, serum ferritin, an inflammatory biomarker, also predicts the degree of neuronal damage in patients with AIS, as shown by its correlation with markers of blood-brain barrier damage such as glutamate, interleukin-6, metalloproteinase-9, and cellular fibronectin [21,22]. COVID-19 infection is also associated with deregulation of neutrophil extracellular traps (NETs) [23]. These traps are extracellular networks of chromatin, proteins, and oxidative enzymes produced by activated neutrophils and serve to contain infection, but they also play a role in thrombus formation [24]. There is evidence that in patients with COVID-19 infection, there is an increase in NET production that further propagates inflammation and thrombosis [6]. Evidence for the role of NETs in AIS is well described, Laridan et al examined thrombi from patients undergoing endovascular thrombectomy and found that Cit-H3, the hallmark of NETs, was observed in the majority of samples [25–27].

A characteristic feature of SARS-CoV2 infection is its interaction with ACE2 receptors, which significantly affect the RAAS [28]. This disruption of RAAS axes is likely to contribute to the pathogenesis of stroke by promoting inflammation, vasoconstriction, and organ damage [29].

Various COVID-19 registries have shown that there is an increased mortality rate in patients with preexisting cardiovascular disease such as hypertension and diabetes [30]. Similarly, a majority of AIS and COVID-19 patients report hypertension as a classic risk factor [31]. The contribution of hypertension to the outcomes of COVID-19 patients is likely explained by a variety of mechanisms. Nevertheless, classical RAAS overactivity as well as virus-induced endothelial vasoconstriction may be contributing factors to the neurological exacerbation of COVID infection [30].

It has been shown in recent publications that antiphospholipid antibodies are positive in patients severely infected with sars-CoV-2 and presenting with multiple stroke [15,32]. Thus, COVID-19 disease may trigger a transient or permanent antiphospholipid antibody syndrome resulting in vasculitis and cerebral and endothelial disease predisposing to a thromboembolic state .However, it is possible that SARS-CoV-2 interacts directly with cerebral endothelial cells that express the ACE-2 receptor leading to excessive and prolonged activation of the coagulation cascade, as well as activation of immune cells [33,34].

Conclusion

COVID-19 is a global pandemic caused by SARS-CoV-2 that is causing significant morbidity and mortality worldwide, making it the most significant health crisis of the decade.

And as the pandemic continues to grow, various neurological manifestations have become evident, among them ischemic strokes.

The COVID-19 virus has become a risk factor for stroke, especially in the absence of a pre-existing medical condition, which has proven to be very aggressive with a high case fatality rate. Hence the interest in systematically searching for an underlying viral infection such as COVID-19 in cryptogenic strokes.

Patient consent

Informed consent was obtained from the patient.

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