

Recurrent Stroke in A Young Patient with Transient Positivity for Lupus Anticoagulant and Covid-19 Infection

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune disorder diagnosed using clinical and laboratory criteria. Thrombotic manifestations of APS are variable, not limited to deep vein thrombosis (DVT), stroke, and transient ischemic attacks.

COVID-19-associated coagulopathy (CAC) is an evolving diagnosis during the coronavirus disease (COVID-19) pandemic, and it seems to differ from those seen in patients with bacterial sepsis-induced coagulopathy or disseminated intravascular coagulation. Clinical and laboratory features of CAC do have some overlap, however, with hemophagocytic syndrome, APS, and thrombotic microangiopathy.

For better understanding of the role of anti-phospholipid (aPL) antibodies in COVID-19-associated thrombosis, we present a case of a young male whose quiescent COVID-19 course was followed by a complicated hospitalization due to recurrent strokes, likely provoked by the transient presence of aPL antibodies. His case is then followed by a review of relevant literature.

Keywords: COVID-19, stroke, antiphospholipid syndrome, lupus anticoagulant, autoimmune disease.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder diagnosed using clinical and laboratory criteria (Table 1). Persistent positivity for lupus anticoagulant (LAC), anticardiolipin (aCL), or antibeta2-glycoprotein I (a β 2GPI) IgG or IgM antibodies are current laboratory criteria for the diagnosis of APS [1]. In one large cohort, the prevalence of APS was estimated to be 50 per 100,000 in the population [2].

Thrombotic manifestations of APS are variable, with deep vein thrombosis (DVT) accounting for approximately 32% of cases and stroke and transient ischemic attacks accounting for 13% and 7% of cases, respectively. Pulmonary embolism is present in 9% of thrombotic cases, while fetal loss and superficial thrombophlebitis account for 8% and 9%, respectively [3]. Thus, the most common thrombotic events in APS include venous

thromboembolism and cerebral ischemia (i.e., stroke or transient ischemic attacks) [4].

The exact pathogenesis of APS is complex; however, a more simplistic explanation is that the procoagulant state induced by anti-phospholipid (aPL) antibodies (first hit) can lead to thrombotic events in patients in whom an inciting factor (second hit), such as infection, malignancy, or use of certain medications [5], occurs. An increased risk of developing aPL antibodies during certain types of infections, particularly viral ones, has been described.

Among APS manifestations, stroke carries a high burden of morbidity. In one systematic review, the frequency of aPL antibodies in young patients with cerebrovascular events was approximately 17%, and patients with aPL antibodies seemed to carry a fivefold higher risk of developing stroke or TIA than the controls [6].

Thrombotic complications and coagulopathies have frequently been documented in patients with coronavirus disease 2019 (COVID-19). Characteristics of this COVID-19-associated coagulopathy (CAC) seem to differ from those seen in patients with bacterial sepsis-induced coagulopathy or disseminated intravascular coagulation. Clinical and laboratory features of CAC do have some overlap, however, with hemophagocytic syndrome, APS, and thrombotic microangiopathy [7].

To further understand the role of aPL antibodies in COVID-19-associated thrombosis, we present a case of quiescent COVID-19 course followed by recurrent strokes, likely caused by the transient presence of aPL antibodies. His case is then followed by a review of relevant literature.

Case presentation

A 30-year-old male with no reported past medical history presented to the emergency department with a 5-day history of fever, dry cough, headache, and throat pain. He was confirmed to have a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by reverse transcription polymerase chain reaction (RT-PCR) of a nasopharyngeal swab. He was thereafter transferred to a quarantine facility where he was managed for mild COVID-19.

Two weeks after his initial presentation, the patient was brought back to the emergency department from the quarantine facility due to the acute onset of an inability to speak, right-sided facial droop, and right-sided hemiplegia of 3-hour duration. On examination, he was afebrile, with a blood pressure of 102/68 mm Hg, a tachypneic respiratory rate of 26 breaths per minutes, and a 92% oxygen saturation on room air. Neurological examination demonstrated a Glasgow Coma Scale score of 11, global aphasia, right-sided hemianopia with a left-sided gaze deviation, right-sided facial weakness, and a hemiplegia affecting the right upper and lower extremities. His sensation was intact, with preserved deep tendon reflexes and a positive Babinski sign on the right side. His National Institutes of Health Stroke Scale score was 22. Cardiac, respiratory, and abdominal examinations were unremarkable.

Emergent computed tomography (CT) imaging of the head showed a subtle hyperdensity in the left middle cerebral artery (MCA). CT perfusion studies showed flow-volume mismatch in the left cerebral hemisphere, with CT angiography demonstrating a nonocclusive filling defect in the left common carotid artery (CCA) proximal to the bifurcation, with narrowing of the petrous and cavernous segments of the internal carotid artery (ICA). There were also partial filling defects in the left external carotid artery (ECA) and the M1 segment of the left MCA (Figure 1).

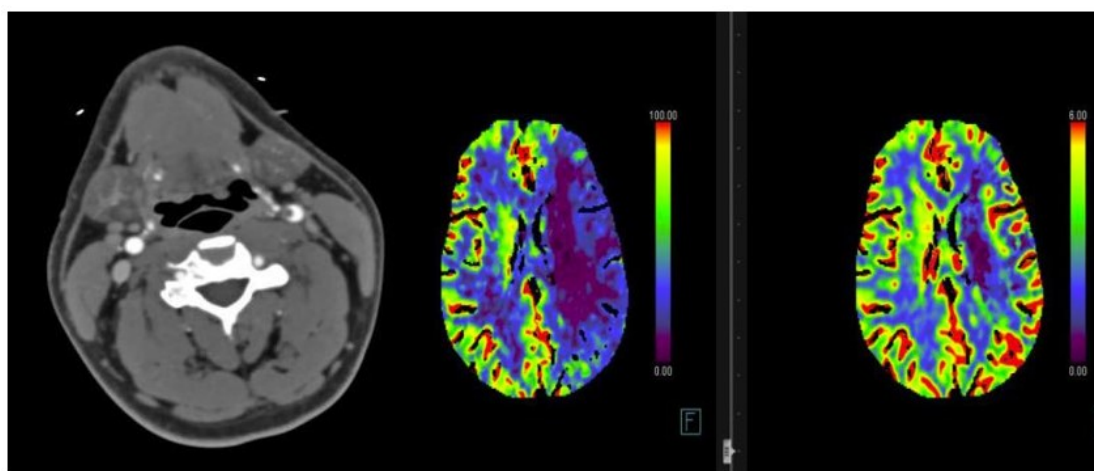


Figure 1: Axial computed tomography (CT) angiography demonstrating a nonocclusive thrombus in the left common carotid artery (CCA). Cerebral blood flow (CBF) and cerebral blood volume (CBV) sequences of CT perfusion studies demonstrated mismatch in the territory of the left middle cerebral artery (MCA).

The patient underwent intravenous thrombolysis with Alteplase and was transferred to the catheter lab for mechanical thrombectomy. During this procedure, the thrombus in the left CCA was aspirated. There was also total occlusion of the left ICA and the left MCA by a large

thrombus. A combination of aspiration and stent-retriever thrombectomy were used for achieving recanalization, with a thrombolysis in cerebral infarction (TICI) score of 3 (Figure 2).

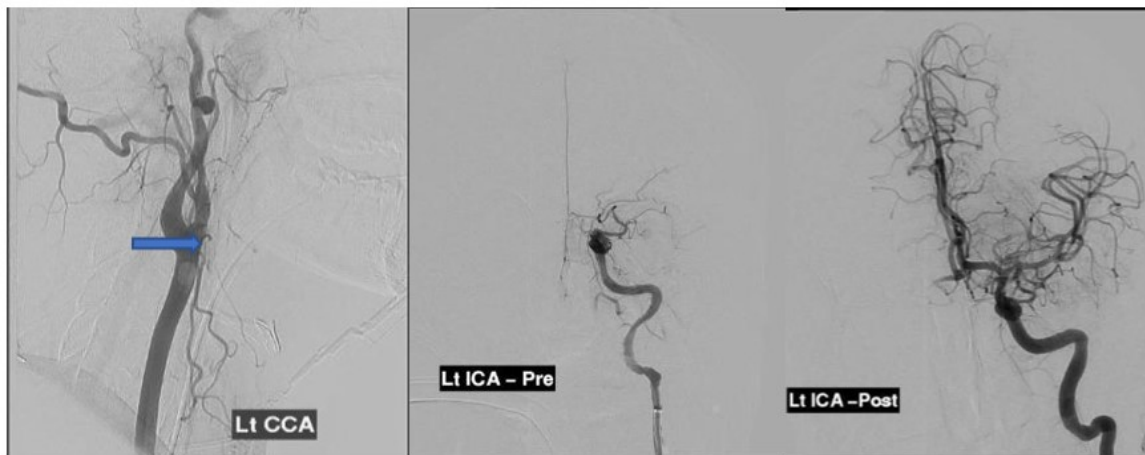


Figure 2: A conventional angiography and mechanical thrombectomy image on the left demonstrates a nonocclusive thrombus (blue arrow) of the left common carotid artery (CCA), with poor flow into the internal carotid artery (ICA). The middle image demonstrates irregularities in the distal ICA and occlusion intracranially, with complete recanalization noted in the right image.

The patient was then transferred to the medical intensive care unit (MICU) for further observation, where urgent transthoracic echocardiography showed no clear thrombus in his left ventricle and was otherwise unremarkable. On the following day, postprocedural CT imaging of the head showed evidence of mild hemorrhagic transformation. At this point, only aspirin was commenced, while statins were held due to a transaminitis.

Over the next 4 days, the patient's hospital course was unremarkable, and atorvastatin was introduced as his liver function began to improve. Laboratory testing demonstrated a mild transaminitis, as well as continued detection of SARS-CoV-2 by RT-PCR of nasopharyngeal

swabs. Complete blood count, basic metabolic panel, toxicology, coagulation profile, and thyroid function tests were within normal limits. An autoimmune panel was significant only for a weakly positive aCL IgM antibody value of 12, while his aCL IgG antibody value of 1.7 was considered negative. LAC was also negative.

Due to the absence of neurological improvement, the patient underwent repeat CT imaging of the head with angiography on the 5th day of his admission, revealing a new total occlusion of the left ECA and the left ICA from its origin all the way to the distal branches of the left MCA, with maintenance of some intracranial flow likely from retrograde collateral circulation (Fig. 3 and 4).

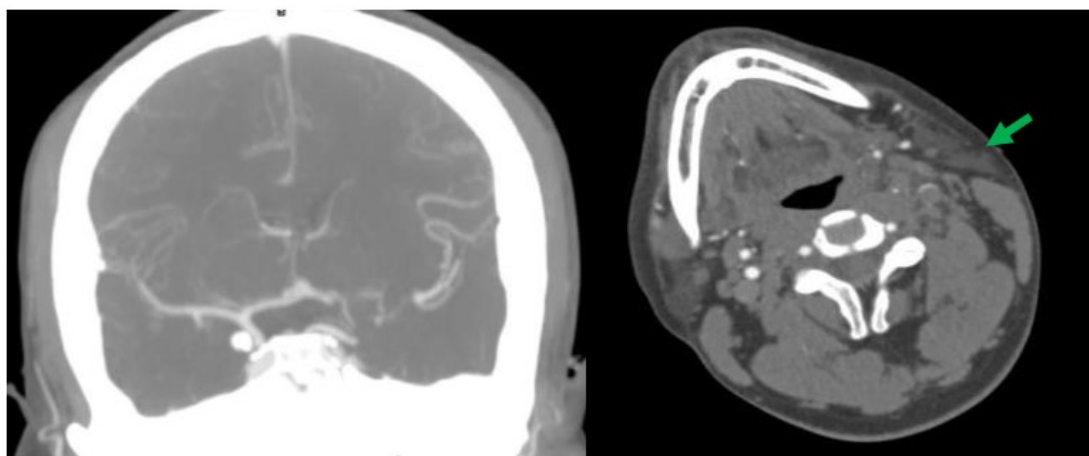


Figure 3: Computed tomography (CT) angiography demonstrating left internal carotid artery (ICA) occlusion on an intracranial coronal section (blue arrow) and an almost complete occlusion of the left cervical segment on an axial section (green arrow).

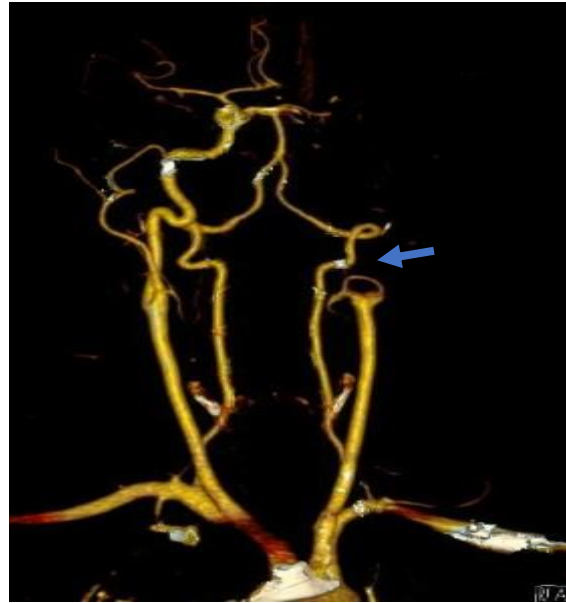


Figure 4: Three-dimensional reconstruction of the computed tomography (CT) angiogram demonstrating occlusion of the left internal carotid artery (ICA) and the external carotid artery (ECA) at their origins (blue arrow).

His autoimmune panel was repeated and was significant for a positive LAC value of 65 and a positive $\text{a}\beta 2\text{GPI}$ IgM antibody value of 13, while his $\text{a}\beta 2\text{GPI}$ IgG antibody value of 1.3 was considered negative. He also had a weakly positive aCL IgM antibody value of 34, while his aCL IgG antibody value of 9.4 was considered negative.

Based on these results, the patient was diagnosed with SARS-CoV-2-induced APS complicated by left hemispheric strokes. He was thereafter started on anticoagulation with a therapeutic dose of enoxaparin and was bridged to warfarin to achieve a therapeutic international normalized ratio of 2–3. The patient remained stable without evidence of hemorrhagic transformation or clinical worsening and was subsequently transferred to a rehabilitation facility for continuity of care. Repeated APS serology performed 12 weeks after the initial test showed negativity for antibodies to LAC, $\text{a}\beta 2\text{GP}$, and aCL.

Literature review

This literature review was conducted to review the current knowledge regarding the implications of positivity for aPL antibodies in patients with COVID-19-associated strokes. We conducted a search of PubMed from January to September of 2020 and identified 35 articles generally related to COVID-19-related thrombosis. Here, we summarize the reported cases of stroke in COVID-19 patients proven to have positivity for any aPL antibodies.

In a case series of six patients with COVID-19 and stroke, five had positivity for LAC, while one had a medium titer for aCL IgM antibodies and low titers for $\text{a}\beta 2\text{GPI}$ IgG and IgM antibodies. These patients were all above 50 years of age and all had moderate-to-severe courses of COVID-19 [8]. Another case series from China described three patients with COVID-19, stroke, and positivity for aPL antibodies. These patients were all > 65 years of age and all had critical courses of COVID-19. One of these patients had positivity for aCL IgA antibodies and $\text{a}\beta 2\text{GPI}$ IgA and IgG antibodies, while the other two patients were positive for aCL IgA antibodies, as well as $\text{a}\beta 2\text{GPI}$ IgA and IgG antibodies. None of these cases were positive for LAC [9].

In addition, two patients with stroke and COVID-19 were reported by Zeyat et al. One of these patients, a 74-year-old male, was positive for aCL IgM antibodies [10]. Goldberg et al. described a 64-year-old with COVID-19, right MCA and bilateral ACA infarcts, and elevation in aCL IgM antibodies [11]. Ten patients with COVID-19 and ischemic stroke were also reported by Sujana et al. One of these patients, a 39-year-old female, was found to have elevated aCL antibodies without meeting the criteria for APS [12]. Fara et al. also reported three COVID-19 patients with subocclusive severe stenoses of the CCA and strokes within that distribution. One of these patients was found to have positivity for aCL antibodies [13]. Finally, Gemciogulu et al. reported a young female who developed an MCA stroke a few days after developing COVID-19 symptoms and was found to have positivity for LAC [14].

Author	Journal citation	Patient age & gender	Comorbidities	COVID-19 course	Site of thrombosis	Antiphospholipid antibodies
Beyrouiti et al.	J Neurol Neurosurg Psychiatry 2020;91:889-891	64, male	None	Severe	Left vertebral artery and left posterior-inferior cerebellar artery territory infarction	Medium titer anticardiolipin IgM, low titers anti- β 2-glycoprotein I IgM and IgG, positive lupus anticoagulant
Beyrouiti et al.	J Neurol Neurosurg Psychiatry 2020;91:889-891	53, female	Hypertension, diabetes mellitus, mitral valve replacement, atrial fibrillation, HF with a permanent pacemaker	Critical	Right parietal cortical and left cerebellar infarct	Positive lupus anticoagulant
Beyrouiti et al.	J Neurol Neurosurg Psychiatry 2020;91:889-891	61, male	Hypertension, stroke, chronic leg ulcers	Moderate	Right middle cerebral artery	Positive lupus anticoagulant
Beyrouiti et al.	J Neurol Neurosurg Psychiatry 2020;91:889-891	83, male	Hypertension, diabetes, ischemic heart disease, smoking and alcohol consumption	Severe	Right middle cerebral artery	Positive lupus anticoagulant
Beyrouiti et al.	J Neurol Neurosurg Psychiatry 2020;91:889-891	73, male	Gastric carcinoma (resected), benign essential tremor	Severe	Right basilar artery and bilateral mild-to-moderate P2 segment stenosis	Positive lupus anticoagulant
Zhang et al.	N Engl J Med 2020;382:e38	69, male	Hypertension, diabetes mellitus, stroke	Critical	Multiple cerebral infarctions in bilateral frontal, parietal, and occipital lobes, as well as bilateral basal ganglia and cerebellar hemispheres and the brain stem	Anticardiolipin IgA, anti- β 2-glycoprotein I IgA and IgG
Zhang et al.	N Engl J Med 2020;382:e38	65, female	Hypertension, diabetes, coronary artery disease, no history of thrombosis	Critical	Multiple cerebral infarctions in the right frontal and bilateral parietal lobes	Anticardiolipin IgA, anti- β 2-glycoprotein I IgA and IgG
Zhang et al.	N Engl J Med 2020;382:e38	70, male	Hypertension, emphysema, nasopharyngeal carcinoma, stroke	Critical	Multiple cerebral infarctions in the frontal lobe; right frontal, parietal, temporal, and occipital lobes; and bilateral cerebellar hemispheres	Anticardiolipin IgA, anti- β 2-glycoprotein I IgA and IgG
Zayet et al.	Emerg Infect Dis	84, male	Diabetes mellitus,	Moderate	Multiple vascular areas	Anticardiolipin IgM

	2020;26:2258-2269		hypertension, coronary artery disease, peripheral vascular disease, atrial fibrillation			
Goldberg et al.	AJNR AM J Neuroradiol 2020;41:1170-1172	64, male	Hypertension, aplastic anemia, splenectomy	Mild	Anterior cerebral infarct	Anticardiolipin IgM
Sujan et al.	Case Rep Neurol 2020	39, female	None	Mild	Left middle cerebral artery	Anticardiolipin
Fara et al.	J Thromb Haemost 2020;18:2031-2033				Common carotid artery	Anticardiolipin
Gemcioglu et al.	J Clin Rheumatol 2020;26:236-237		None	Mild	Middle cerebral artery	Positive lupus anticoagulant
Our patient		30, male	None	Mild	Our patient	

Discussion

While thrombosis is a life-threatening complication of COVID-19, the exact mechanism underlying this phenomenon is not yet fully understood. A notable connection with APS is, however, being documented in the literature. CAC currently accounts for 6% of all COVID-19-related deaths [15]; thus, understanding the underlying pathogenesis and appropriate management strategies for this disease is becoming more and more crucial.

Stroke, one manifestation of CAC, carries a high burden of morbidity and mortality in patients. In a recently published cohort study, stroke was reported in 1.6% of adults with COVID-19 who visited the emergency department or were hospitalized, which is a higher rate than observed in a cohort of patients with influenza [16].

Possible links between COVID-19 and stroke include a hyperinflammatory state or the cytokine storm associated with increased IL-6 levels in this infection, resulting in hyperviscosity and stroke [17]. Another suggested mechanism is that infection-associated vascular endothelial damage results in an increased risk of intracerebral hemorrhage, microthromboses of small penetrating arteries, and arterial dissection of larger arteries [18]. Although it is difficult to be certain, these mechanisms do not appear to provide an explanation for the strokes that occurred in our patient, given that he had a relatively stable course of COVID-19 from pulmonary and systemic standpoints and did not have evidence of organ damage.

APS is a well-established pathology underlying stroke, especially in young patients without obvious risk factors. Understanding the potential involvement of aPL antibodies in patients with stroke and COVID-19, however, is of utmost importance considering the current public health crisis. The prevalence of aPL antibodies in these patients has varied between different reports; however, they have been reported in up to 47.0% of critically ill patients without

Although the clinical implications of elevated aPL antibodies in patients with COVID-19 is not yet clear, the

being detected as commonly in patients in noncritical condition [19].

In a recent cohort of 187 patients who had LAC testing ordered, 119 were not tested or tested negative for COVID-19 using RT-PCR. The LAC-positive rate in patients who tested negative for COVID-19 was 22% (27 of 119). In contrast, the LAC-positive rate in patients who tested positive for COVID-19 was 44% (30 of 68) ($P = .002$) [20].

Being critically ill is one risk factor for developing APL, as has been described in many previous reports. Our patient, however, was in a stable condition and had an uncomplicated course of COVID-19 for the 2 weeks prior to developing stroke. Therefore, this patient had a rather unique presentation, and his case raises the suspicion that COVID-19 may independently trigger the development of a "COVID-19-induced, APS-like syndrome." This case supports the existence of this unique disease entity due to the patient's seroconversion from LAC negativity to positivity, as well as the clinical and temporal associations between these antibodies and the occurrence of two consecutive strokes in a young male without any obvious risk factors or alternative etiologies uncovered by laboratory testing, neuroimaging, or echocardiography.

Conclusion

Here, we have presented the case of a young male who developed two strokes during his otherwise mild COVID-19 course. In this patient, an extensive workup revealed the presence of positivity for LAC, despite initial negativity, as his only risk factor for stroke. Moreover, at 12 weeks after his last positive serology, he was again found to be negative for this antibody. In the context of COVID-19, three major diagnostic possibilities should be considered in this patient, including either the presence of aPL antibodies without associated thrombosis, COVID-19-induced APS with significant thrombosis, or chronic APS being detected at the time of infection. Our patient likely falls into the second category.

potential pathogenic role of these autoantibodies in inducing thromboembolic manifestations during SARS-

CoV-2 infection should not be underestimated. We believe that screening for APS in young patients with thrombosis in the setting of COVID-19 is warranted. Moreover, repeating serologic testing within 12 weeks after positivity in these cases may improve patient management and prognosis.

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