Concurrent Stroke and Myocardial Infarction After Mild COVID-19 Infection

Gerardo Ruiz-Ares, MD, PhD, Santiago Jimenez-Valero, MD,†*
Andrés Fernández-Prieto, MD,‡ Emilio Arbas-Redondo, MD,†
Beatriz Díaz-Pollán, MD,§ Pedro Navia, MD,‡ Pablo Meras, MD,†
Maria Alonso de Leciñana, MD, PhD, Jorge R.P. de Donebún, MD,**
Ricardo Rigual, MD, Blanca Fuentes, MD, PhD,**
*and Exuperio Díez-Tejedor, MD, PhD**

Introduction: The concurrency of both, acute stroke and acute myocardial infarction in normal conditions, outside the pandemic is rare. Coagulopathy has been associated with the inflammatory phase of coronavirus disease (COVID-19) and might be involved in this concurrency.

Cases Report: We describe 2 patients with previous mild or no symptoms of COVID-19, admitted for acute stroke with recent/simultaneous myocardial infarction in whom admission polymerase chain reaction was negative but serologic testing diagnosed COVID-19. In these patients, concurrent stroke and myocardial infarction could have been promoted by COVID-19 infection. Management and evolution are detailed, and their contacts to confirm the COVID-19 infection. Pathogenic analysis of possible hypercoagulation state is described suggesting the hypothesis of endothelial dysfunction as the strongest mechanism involved in thrombus formation after the acute phase of COVID-19 infection.

Conclusions: Our experience with these cases suggests that patients with mild symptoms can also present thromboembolic complications once the acute phase of COVID-19 infection has passed.

Key Words: stroke, COVID-19, hypercoagulation state, myocardial infarction, thrombolysis

(*The Neurologist* 2021;26:86–89)

On January 30, 2020, the World Health Organization declared the Chinese outbreak of coronavirus disease (COVID-19) to be a public health emergency of international concern. The symptoms of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) range from minimal symptoms to severe respiratory failure with multiple organ failure.[1] Organ dysfunction and generalized coagulopathy, are associated with the highest mortality.[2] In fact, a state of hypercoagulation has been associated with the inflammatory phase of COVID-19,[3] which might be involved in the risk of stroke that has been reported in this context.

From the *Department of Neurology, Stroke Center; †Department of Cardiology; ‡Section of Neuro-Radiology; and §Infectious Diseases Unit, Internal Medicine Service; La Paz University Hospital – IdiPaz Health Research Institute, Autonoma University of Madrid, Madrid, Spain.

The authors declare no conflict of interest.

Correspondence to: Gerardo Ruiz-Ares, MD, PhD, Department of Neurology, Stroke Centre, La Paz University Hospital, Autonoma University of Madrid, Paseo de la Castellana, 261, Madrid 28046, Spain. E-mail: adalbertog.ruiz@salud.madrid.org.

ISSN: 2331-2637/21/2603-0086
DOI: 10.1097/NRL.0000000000000311

The concurrency of acute stroke and acute myocardial infarction in normal conditions, outside the pandemic, has been reported to be as rare as 0.009%.[4] The same state of hypercoagulation secondary to COVID-19 could promote this concurrence. Moreover, some carriers are asymptomatic,[5] and the proportion and risk of related complications of this group are unclear. We describe 2 patients admitted for acute stroke with recent/simultaneous myocardial infarction in whom reverse transcription-polymerase chain reaction (RT-PCR) was negative at admission, but serological testing diagnosed COVID-19.

CASE PRESENTATIONS

Patient 1

A 43-year-old man with a smoking habit and no other prior condition developed acute onset of speech impairment with good comprehension and mild right-sided weakness in April 2020. After stroke code activation, he was admitted to a primary stroke center. The initial examination showed predominant motor aphasia and right mild hemiparesis, scoring 5 points on the National Institute of Health Stroke Scale (NIHSS). Noncontrast brain computed tomography (CT) scan showed early signs of ischemia in left middle cerebral artery (MCA) territory, and a CT angiogram demonstrated a complicated carotid atheromatous plaque with a superficial thrombus causing a 90% stenosis in the left proximal internal carotid artery (ICA) (Fig. 1A). No intracranial artery occlusion was found and intravenous thrombolysis (IVT) was started at 2 hours 25 minutes of symptom onset. Significant ST-segment elevations in V3-V6 and inferior leads were observed on the electrocardiogram at admission, and whereas IVT treatment was administered, an urgent echocardiogram showed left ventricular apical akinesia.

The absence of clinical improvement despite IVT, the visualization of poor vascularization in the left frontal lobe suggesting hypoperfusion at CT angiogram, and the obvious danger of thrombus migration to the brain from left ICA was treated by mechanical thrombectomy. Although a complicated carotid plaque was nonstenotic, it was deemed to be at high risk for new embolisms, given it showed a broken surface and traces of thrombus (Fig. 1B). Therefore, to prevent early stroke recurrences, a double layer self-expandable stent was placed from ICA to CCA, with perfect final angiographic results.

Once the mechanical thrombectomy was completed, a coronary angiography was performed by the same femoral artery access. It showed a thrombus in the middle segment of the right coronary artery with distal flow preserved; thus aspiration with a catheter was conducted, subsequently verifying the absence of an atherosclerosis plaque underneath (Figs. 1C, D). Troponin-I levels peaked at 24 hours, at 5201.5 ng/L with subsequent decline. A new echocardiogram confirmed the apical akinesia and a right-to-left shunt detection test was performed, which was negative. No other cause of the stroke was identified after an extensive workup, including a thrombophilia study.

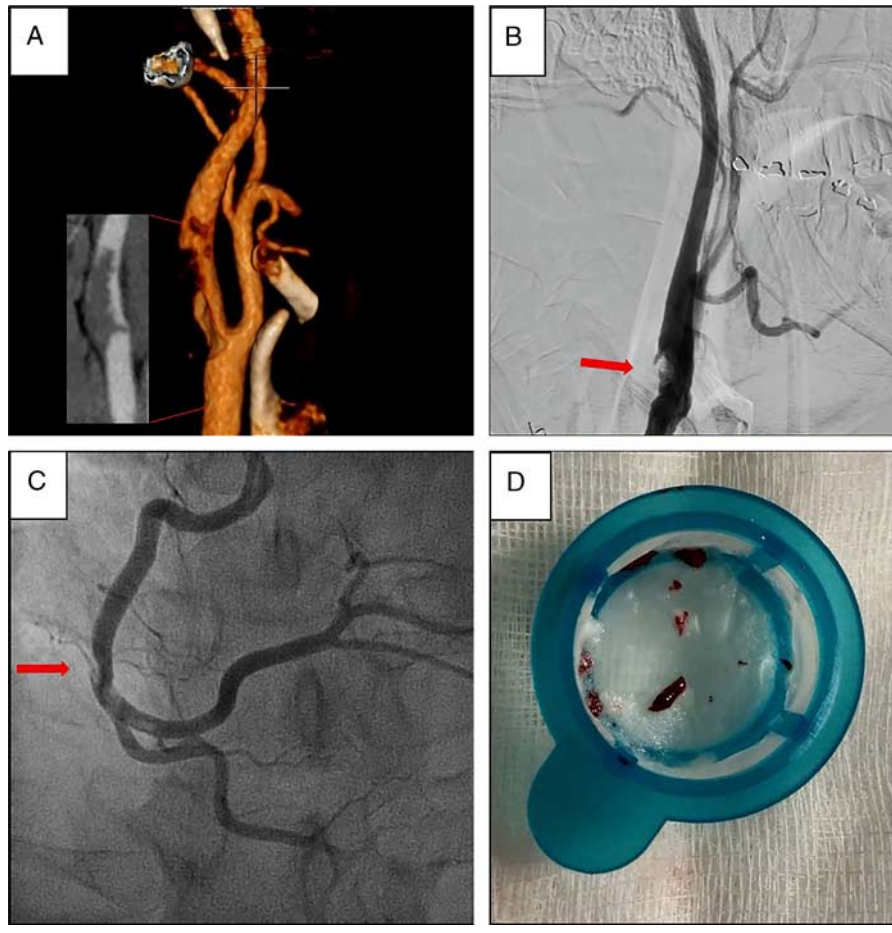

FIGURE 1. Images of case 1. A, 3-Dimensional (3D) computed tomography angiogram (CTA) demonstrating left internal carotid artery (ICA) origin stenosis and filling defect because of the floating thrombus. In the emergent box, 2D MIP CTA shows thrombus progression inside the vessel lumen. B, Digital subtraction angiography of left ICA after thrombectomy showing the broken surface plaque and traces of thrombus on it (arrow). C, Coronariography image of right coronary artery showing nonocclusive thrombus and traces of smaller embolus (arrow). D, Image of the main thrombus retired of right coronary artery with some fragments. MIP indicates maximum intensity pixel.

RT-PCR for SARS-CoV-2 was negative on admission, and chest CT ruled out inflammatory/infectious signs in the lung parenchyma. The patient improved until he was able to express himself, at which time he denied experiencing any respiratory or other symptoms compatible with COVID-19 infection or chest pain. He was treated with double antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg) plus prophylactic lower weight heparin and discharged home, scoring 1 point on the NIHSS. Four weeks later, validated serological studies identified positive immunoglobulin M (IgM) and immunoglobulin G (IgG) for COVID-19. The patient then reported that despite being secluded in his home for a few weeks before hospital admission, he often went out to the supermarket and saw his brother who lives nearby. His brother had been diagnosed with multiple sclerosis. Given he is immunosuppressed, a serological test was performed, showing positive results for IgM and IgG for COVID-19. Neither sibling presented symptoms suggestive of COVID-19 infection.

Patient 2

A 64-year-old woman with a history of hypercholesterolemia was admitted to the stroke center because of the acute onset of impaired speech aphasia. Initial examination showed changes in nomination and reduction in language fluency, and mild right facial paresis, with an NIHSS score of 2. Noncontrast brain CT scan showed focal hyperdensity in distal left MCA (M1) without parenchymal abnormalities, and a CT angiogram demonstrated a distal left MCA segment occlusion (Figs. 2A, B). IVT was started within less than 2 hours 40 minutes of symptom onset, and was admitted to the stroke unit. The patient improved in the following hours and achieved a complete recovery.

The transthoracic echocardiogram showed inferior akinesia and posterior hypokinesia of the left ventricle, although high-sensitivity troponin-I levels were normal and coronary CT angiography showed no signs of atherosclerosis (Figs. 2C, D). A previous transthoracic echocardiogram was reviewed, which had been performed 4 months previously as a workup study for palpitations, showing no cardiac abnormalities. Therefore, these new regional wall motion abnormalities were attributed to a silent myocardial infarction that might have occurred within the last 4 months, probably explained by a coronary thrombus with subsequent reperfusion. Other cardiac sources for embolism were ruled out after electrocardiogram monitoring.

No respiratory or other symptoms compatible with COVID-19 infection or chest pain were initially reported. Chest CT ruled out inflammatory/infectious signs in the lung parenchyma, and RT-PCR for SARS-CoV-2 was negative on admission; however, the serological studies identified positive IgM and IgG for COVID-19.

The patient works in a bakery with 7 other people. Three had had mild symptoms of COVID-19 in March 2020 and were isolated once the symptoms started, without any diagnostic tests. Since March 30, the patient reported mild headache, asthenia, and a painful rash of erythematous papules similar to hives in the upper region of the left thigh lasting for 3 weeks; 2 weeks later, stroke occurred.

The patient's demographic and clinical characteristics, and laboratory findings, are summarized in Table 1.

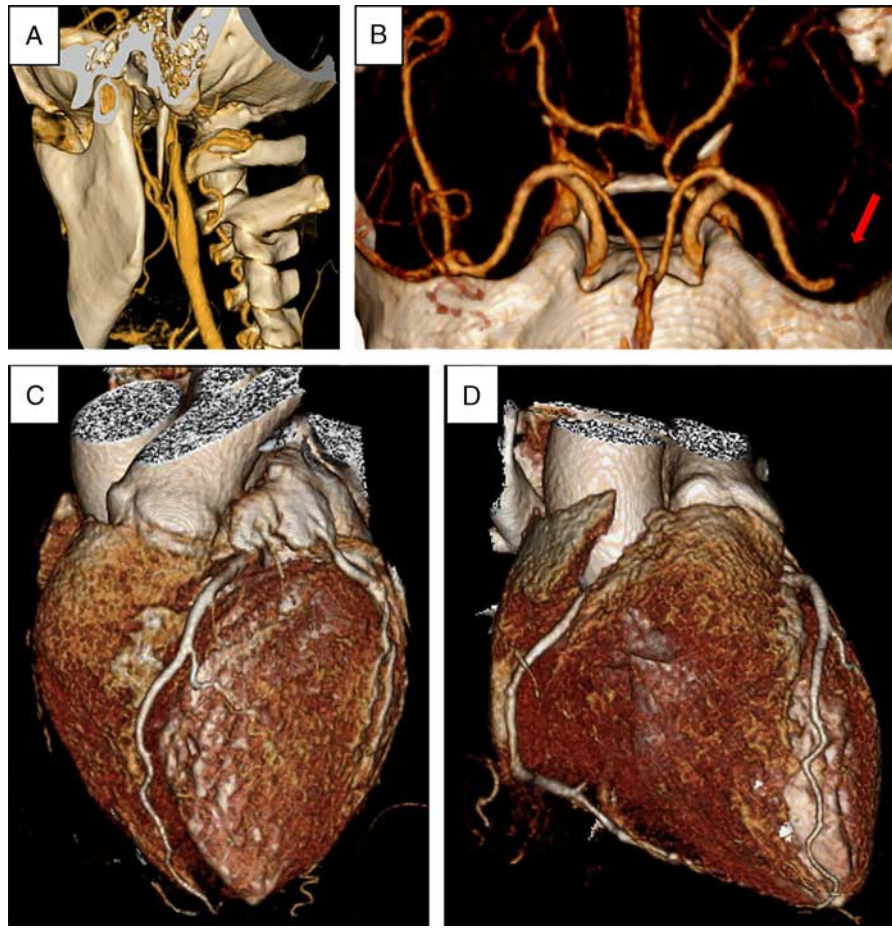

FIGURE 2. Complementary examinations images of case 2. A, 3-Dimensional (3D) computed tomography angiogram (CTA) demonstrating left internal carotid artery shows nonatherosclerotic pathology. B, 3D CTA demonstrating left middle cerebral artery (distal M1 segment) occlusion (arrow). C and D, 3D CTA showing no signs of atherosclerosis with permeability of all 3 main coronary vessels.

DISCUSSION

In these patients reported here, concurrent stroke and myocardial infarction could have been promoted by COVID-19 infection. The fact that both patients had positive IgG and IgM supports this hypothesis, and during a detailed epidemiological anamnesis, they reported close contact with other patients with COVID-19 before stroke.

Given the clinical manifestations of COVID-19 range from asymptomatic to severe illness,[5] presentation forms and complications are not fully clarified. We do not know which individuals are asymptomatic carriers because universal testing has not been used in our country. However, potential transmission from asymptomatic or minimally symptomatic patients has been suggested.[6,7] Thus, asymptomatic or mildly symptomatic patients could be at risk of the same complications from the infection.

A classification of COVID-19 disease states has been proposed, with 3 escalating phases of COVID-19 disease progression: stage I, early infection; stage II, pulmonary involvement; and stage III, systemic hyperinflammation. Some authors have suggested that thrombotic complications were related to thrombocytopenia, elevated D-dimer, and a prolongation of the prothrombin time, have been more frequent in patients with severe COVID-19 disease.[2,5] Although the approximate duration of each phase is not specified, thrombotic events can occur in the final and most severe phase of the disease. The data thus far reported are suggestive of low-grade intravascular clotting activation, which is evident particularly in patients with severe disease. In patients with stage III disease, markers of systemic inflammation, such as interleukin (IL)-2, IL-6, IL-7, granulocyte colony-stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α, C-reactive protein, ferritin, and D-dimer are significantly elevated.[8] In this context, microangiopathy and endothelial dysfunction contribute to a hypercoagulative state, which predisposes the patient to experience thrombotic events in coronary and cerebral trees or in any other territory, including the lung and kidney.[9–11] Interestingly, endothelial cells express angiotensin-converting enzyme 2, the receptor for SARS-CoV-2, and their interaction has been associated with endothelial damage, that increases the risk of thrombotic events.[2,12] A recent case report found the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death suggesting that SARS-CoV-2 infection facilitates the induction of endothelitis in several organs as a direct consequence of viral involvement and of the host inflammatory response.[13,14] Furthermore, COVID-19 can trigger an intense inflammatory response, which could also

TABLE 1. Demographic and Clinical Characteristics and Laboratory Findings

Characteristic	Patient 1	Patient 2
Demographic characteristics		
Age (y)	43	64
Sex	Male	Female
Initial findings		
Medical history	Smoker	Hypercholesterolemia, palpitations
Laboratory findings		
White cell count (per mm^3)	5940	7520
Differential count (per mm^3)		
Total neutrophils	3830	4160
Total lymphocytes	1440	2460
Total monocytes	420	380
Platelet count (per mm^3)	265,000	321,000
Hemoglobin (g/dL)	15.7	13.4
Creatinine (mg/dL)	1.02	0.54
EGFR (ml/min/1.73 m^2)	90	> 90
High-sensitivity cardiac troponin-I (ng/L)	109.8–5201.5	2.9
Prothrombin time (s)	10.7	10.3
Activated partial-thromboplastin time (s)	23.4	25.0
Fibrinogen (mg/dL)	367	286
D-dimer (ng/mL)	740	330
Serum ferritin (ng/mL)	—	43
High-sensitivity C-reactive protein (mg/L)	4.6	4.0
Total cholesterol	175	224
High-density lipoprotein cholesterol	37	61
Low-density lipoprotein cholesterol	114	148
Triglycerides	121	74
PCR SARS-CoV-2	Negative	Negative
IgM COVID-19	Positive	Positive
IgG COVID-19	Positive	Positive

EGFR denotes estimated glomerular filtration rate; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR SARS-CoV-2, polymerase chain reaction severe acute respiratory syndrome coronavirus 2.

increase the risk of plaque rupture.[10,15] However, given the way in which our cases presented, it is impossible to classify them as to which phase they were in, and the absence of alterations in coagulation is striking. These findings suggest that endothelial dysfunction could be the most probable mechanism involved in the thrombotic events of our patients.

Our experience with these cases suggests that patients with mild symptoms can also present thromboembolic complications once the acute phase of COVID-19 infection has passed. Further studies focusing on arterial thrombotic complications are needed to characterize the arterial consequences of coronavirus in order to propose appropriate management.

REFERENCES

1. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol*. 2020;215:108427.
2. Levi M, Thachil J, Iba T, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol*. 2020;7: e438–e440.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.
4. Yeo LLL, Andersson T, Yee KW, et al. Synchronous cardiocerebral infarction in the era of endovascular therapy: which to treat first? *J Thromb Thrombolysis*. 2017;44:104–111.
5. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–1720.
6. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-NCOV infection from an asymptomatic contact in Germany. *N Engl J Med*. 2020;382:970–971.
7. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med*. 2020;382:1175–1177.
8. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Hear Lung Transplant*. 2020;39:405–407.
9. Violi F, Pastori D, Cangemi R, et al. Hypercoagulation and antithrombotic treatment in coronavirus 2019: a new challenge. *Thromb Haemost*. 2020;120:949–956.
10. Boukhris M, Hillani A, Moroni F, et al. Cardiovascular implications of the COVID-19 pandemic: a global perspective. *Can J Cardiol*. 2020;36:1068–1080.
11. Liu PP, Blet A, Smyth D, et al. The science underlying COVID-19: implications for the cardiovascular system. *Circulation*. 2020;142: 68–78.
12. Sohrabi C, Alsafi Z, Neill NO, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. 2020;76:71–76.
13. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417–1418.
14. Fara MG, Stein LK, Skliut M, et al. Macrothrombosis and stroke in patients with mild Covid-19 infection. *J Thromb Haemost*. 2020;18: 2031–2033.
15. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. 2020; 75:2950–2973.