

Thrombotic Microangiopathy in Patients Recovering from COVID-19

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ABSTRACT

INTRODUCTION During the pandemic caused by the SARS-CoV-2 virus, some patients who develop severe forms of COVID-19 present thrombotic microangiopathy in the course of the disease's clinical progression.

METHODS Data came from direct patient observation and clinical records. We performed a kidney biopsy and used optical microscopy and immunofluorescence techniques.

RESULTS We present the case of a 78-year-old male patient, mestizo, overweight with a history of high blood pressure, ischemic cardiopathy and chronic obstructive pulmonary disease who was first admitted to the hospital due to respiratory symptoms and diarrhea related to COVID-19, from which he

recovered. He was subsequently readmitted with symptoms of acute renal dysfunction accompanied by mild anemia and thrombocytopenia; at the same time, he resulted negative for COVID-19 via a real-time polymerase chain reaction test. A kidney biopsy revealed thrombi in glomerular capillaries, acute tubular necrosis, thickening of extraglomerular blood vessel walls, and C3 deposits in the glomerular tufts.

CONCLUSIONS We describe a case of thrombotic microangiopathy with kidney biopsy in a patient recovering from COVID-19. Acute renal dysfunction is a form of thrombotic microangiopathy that has been observed in patients recovering from COVID-19.

KEYWORDS COVID-19, thrombotic microangiopathy, kidney, biopsy, Cuba

INTRODUCTION

COVID-19 presents an ongoing challenge to global public health.[1] Many patients with severe forms of COVID-19 present coagulation abnormalities, such as disseminated intravascular coagulation and thrombotic microangiopathy (TMA), with thrombi in several organs and tissues, marked endothelial damage and high mortality.[2]

Clinically, TMA is characterized by hemolytic anemia, thrombocytopenia and acute renal dysfunction. TMA development in COVID-19 has several potential causes, and its identification and prompt treatment can affect a patient's clinical progress.[3] However, reports of TMA in patients recovering from COVID-19 are not common and its diagnosis can be difficult, since clinical signs may not be pronounced.[4] The objective of this study is to present and describe a case of TMA with acute renal damage in a patient recovering from COVID-19.

METHODS

All data were collected from direct patient observation and from the patient's clinical records. Two kidney biopsy samples were taken with an automatic 16-gauge core biopsy gun. Optical microscopy (OM) was used to analyze one of the samples with the following tests: hematoxylin-eosin test, Masson's trichrome, Jones methenamine silver and periodic acid Schiff (PAS). The other was analyzed by immunofluorescence (IF) microscopy using IgA, IgG, IgM (immunoglobulins A, G, and M, respectively), C3, C1q (complement component 1q), fibrinogen, and kappa and lambda antisera.

Ethical considerations The patient provided written informed consent for his case to be presented without revealing his

identity. The study was approved by the Ethics Committee and the Scientific Council of the Dr Abelardo Buch López Nephrology Institute in Havana, Cuba.

RESULTS

The study describes a 78-year-old male patient, mestizo, overweight (BMI of 29.3 kg/m²), ex-smoker with a history of hypertension, ischemic cardiopathy and chronic obstructive pulmonary disease treated with diltiazem, enalapril and hydrochlorothiazide. He sought emergency care three days following symptom onset of productive cough, fever, weakness, diarrhea and polypnea. In the physical exam, the patient presented mild crepitations in both lung bases and a heart rate of 115 beats/min. The patient also presented hypoxemia (SO₂ of 78% without supplemental oxygen). The chest X-ray showed patches of diffuse inflammatory lesions. A real-time reverse polymerase chain reaction (RT-PCR) test for COVID-19 was conducted, which was positive. The patient was admitted to an intermediate care unit and treated with oxygen, chloroquine, α2b interferon, Kaletra (lopinavir and ritonavir), methylprednisolone and ceftriaxone.

Laboratory test results conducted upon admission are presented in Table 1. The patient recovered from the respiratory dysfunction and diarrhea without the need for mechanical ventilation. After being hospitalized for 21 days, he tested negative for COVID-19 (by RT-PCR) and was discharged (without anticoagulant therapy and with basic treatment, as previously described).

Two weeks after discharge, the patient presented asthenia, anorexia, diarrhea and reduced urine output, along with elevated levels of creatinine (746.1 μmol/L). He was readmitted (with a negative RT-PCR) and required hemodialysis (six sessions). The remaining exams are presented in Table 1. Renal ecography showed a slight rise in ecogenicity in both kidneys, and conserved perfusion. Given the acute renal dysfunction of unknown origin with

IMPORTANCE We describe Cuba's first case of thrombotic microangiopathy in a patient recovering from COVID-19.

Table 1. Laboratory test results

Test (normal values)	During first hospitalization	During second hospitalization
Hemoglobin (132–166 g/L)*	156	90
Leukocytes (4.0–11.0 x 10 ⁹ /L)	7.5	9.1
Granulocytes (55%–70%)	89.5	78.8
Lymphocytes (1.5–3.5 x 10 ⁹ /L)	7.5	18.2
Monocytes (0.2–0.8 x 10 ⁹ /L)	3	3
Platelets (150–400 x 10 ⁹ /L)	181	121
Peripheral lamina		Absence of schistocytes or fragmented red cells
Coombs test		Negative
Creatinine (65.4–119.3 μmol/L)*	107.8	746.1
Uric acid (202–416 μmol/L)*	439	659
Urea (2.1–8.5 mmol/L)		20.86
Cholesterol (<5.18 mmol/L)	3.41	5.61
Triglycerides (<1.7 mmol/L)	3.39	3.19
Total proteins (60–83 g/L)		48.6
Albumin (38–64 g/L)		23.21
Total alkaline phosphatase (25–290 U/L)		96
ALT (≤49 U/L)		10
AST (≤49 U/L)		16
LDH (200–400 U/L)		467
Gamma-glutamyl-transpeptidase (10–45 U/L)		45
Total bilirubin (≤1.2 mg/dL)		1.2
Indirect bilirubin (≤0.94 mg/dL)		0.82
Direct bilirubin (≤0.3 mg/dL)		0.38
Blood glucose (4.20–6.11 mmol/L) (RV:)		3.49
Creatine phosphokinase [CPK] (24–195 U/L)		42.5
VDRL (Serology for syphilis)		Negative
Coagulogram		PT:14.4 sec (control: 12.6 sec) aPTT:27.3 sec (control 27.1 sec) Retracting clot Bleeding time: 1 min Coagulation time: 8 min
C3 (0.9–1.8 g/L)		1.3
C4 (0.1–0.4 g/L)		0.3
Nuclear antibodies		Negative
2-hour Addis count (elements/min)		Red blood cells: 55,000 Leukocytes: 21,000 Casts: 0
Proteinuria 24 hours (g/day)		0.57
Protein/creatinine ratio (g/g)		0.76
Stool culture		Negative
Fresh fecal sample		Negative
Hepatitis C antibodies		Negative
HIV antibodies		Negative
Hepatitis B surface antigen		Negative

*Normal range for adult males

ALT: Alanine aminotransferase; aPTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; PT: Prothrombin time

hematuria, mild anemia (no schistocytes) and thrombocytopenia, a kidney biopsy was performed.

In the kidney biopsy sample analyzed by OM, 11 glomeruli were found (two were obsolescent, one had an area of sclerosis, and several others had dilated glomerular capillaries and intracapillary thrombi) (Figures 1A, 1B, 1C and 1D). The tubular epithelium was simplified with loss of brush border and sloughing of cells toward the tubular lumen (Figure 1A). The extraglomerular blood vessels had marked thickening of the walls, vacuolization and intimal myxoid degeneration (Figures 1E and 1F). In the IF technique, diffuse deposits of C3 were observed, as well as traces of IgG, and lambda and fibrin light chain depositions in glomerular capillaries lumens (Figure 1C). The anatomical–pathological conclusion was TMA with acute tubular necrosis.

In the differential diagnosis to determine the origin of acute renal failure associated with COVID-19, multiple potential causes should be considered, such as collapsing glomerulopathy, interstitial nephritis, TMA, and acute tubular necrosis (ATN). [5] ATN in this case was most likely associated with renal hypoperfusion secondary to diarrheal episodes in an older patient with extremely damaged renal vasculature. The patient showed no signs of rhabdomyolysis (normal CPK), which has been described as a cause of ATN in COVID-19.[5] TMA was undoubtedly the most notable finding of the kidney biopsy; the literature has reported cases of COVID-19–associated TMA identified by kidney biopsy, one of which was in a recovering patient.[4,6]

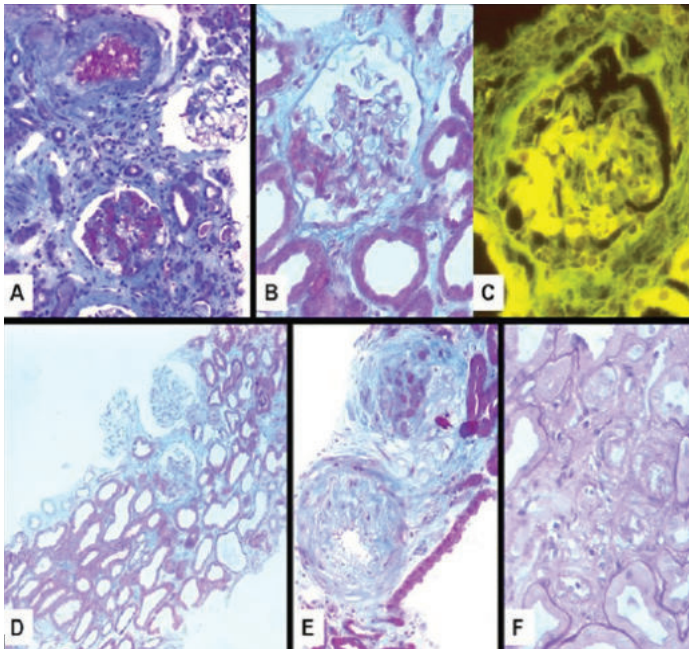
While the TMA's clinical profile was atypical (with no evidence of schistocytes in the peripheral lamina, mild thrombocytopenia, and only moderately elevated LDH—lactate dehydrogenase—levels) the biopsy findings left no doubt. Other reports are incomplete when it comes to recording clinical manifestations of COVID-19–associated TMA.[7]

TMA's origin is particularly important for preventing damage in these patients. Possible origins include antiphospholipid syndrome, thrombotic thrombocytopenic purpura (TTP) (due to deficiencies in disintegrin and metalloprotease with thrombospondin type 1 motif 13 [ADAMTS-13]), typical and

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atypical hemolytic-uremic syndrome (HUS) and multisystem inflammatory syndrome (MIS).[2]

Figure 1: **A.** Thrombi in glomerular capillaries and small arteries. Area of interstitial fibrosis and tubular atrophy. Masson's trichrome X200. **B.** Glomeruli with intracapillary thrombi. Masson's trichrome X400. **C.** Thrombi in glomerular capillaries. IF technique X400. **D.** Area of acute diffuse tubular necrosis. **E.** Extraglomerular blood vessels with severe thickening of the wall. Masson's trichrome. X200. **F.** Twisted arterioles with marked thickening of the wall and partial obliteration of the vascular lumen. PAS X400.



Antiphospholipid syndrome has been described in patients with COVID-19. However, it is unlikely that this was the trigger in this case, for several reasons. There were no signs of macrothrombosis; serology was negative for syphilis (cardiolipin antibodies), which, while not a measure of phospholipid antibodies, tends to be positive in patients with no history or signs of autoimmune disease; and nuclear antibodies were negative.[8]

This syndrome cannot be completely ruled out as an initiating cause, however, since phospholipid antibodies were not directly measured (in any case, not an ideal test since these antibodies can fluctuate upward during the course of an infection or exposure to drugs).[9] Antibody presence 12 weeks following symptom onset must be identified to confirm this diagnosis.[10]

Thrombotic thrombocytopenic purpura secondary to ADAMTS-13 deficiency is another potential diagnosis in cases of patients recovering from SARS-CoV-2 infection. A lack of resources made measuring ADAMTS-13 levels infeasible, so it cannot be ruled out. In the present case, however, the PLASMIC score[11] (at <5) suggests no notable enzyme deficiency.


Another plausible diagnosis in this case is typical HUS with diarrhea, as the patient presented with diarrhea at symptom onset and again when readmitted. HUS is more common in children and tends to affect other systems. For this patient, no other organs were affected, stool samples were negative, and the diarrhea did not contain blood.[12]

Another potential diagnosis previously identified in patients with COVID-19 is atypical HUS with activation of an alternative complementary pathway,[2] generally caused by mutations in gene coding for complementary proteins such as C3 and the H, B, and I factors; or by antibodies against complementary regulatory factors.[2,6] However, atypical HUS has been described as secondary to infections that directly cause endothelial damage or that deregulate the alternative complementary pathway with heavy deposits of C3 in the kidney biopsy, as occurred with this patient.[13] Atypical HUS is a probable diagnosis, despite the patient's normal C3 levels. It is important to keep in mind that fewer than half of atypical HUS cases have low C3 levels.[12,14]

MIS (multi-syndrome inflammatory syndrome)—a Kawasaki-like disease—has been described in children recovering from COVID-19, and one report describes an adult with COVID-19-associated TMA. While that case shares some similarities with ours, absence of any extra-renal abnormalities suggests that MIS is an unlikely diagnosis. [4,15]

Despite the shortage of diagnostic resources needed to determine a more accurate differential diagnosis, all indications point to basic vascular damage due to age, adverse lipid profile and excess weight, which worsened due to the vascular cytopathic effect of SARS-CoV-2 infection, as observed in the kidney biopsy. During convalescence, the pro-thrombotic condition caused by COVID-19 triggered TMA following secondary atypical HUS.

CONCLUSIONS

We describe TMA in a patient recovering from COVID-19, demonstrating that TMA should be considered a possible cause of renal dysfunction in patients with COVID-19 and in those recovering from the disease. 

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