Multiple Kidney Infarctions Due to COVID-19 Infection in a Patient with Repeatedly Negative RT-PCR Tests-A Case Report

Abstract

Since the outbreak of novel coronavirus in 2019, SARS-CoV-2 has spread worldwide at an unexpected rate, becoming a major global health concern. Although respiratory tract infections represent typical clinical presentation, recently, numerous cases of acute arterial thrombosis and thromboembolic disease have been reported due to COVID-19 infection. Renal artery embolism is a condition that is easily missed due to its infrequent and nonspecific presentation. In this paper, we reported a case of a 63-year-old, previously healthy, male patient who has developed multiple right kidney infarctions due to COVID-19 infection without any respiratory or other typical clinical manifestations. Consecutive RT-PCR tests were negative and the diagnosis was set finally by serological screening. Our presentation has emphasized the necessity of clinical, laboratory, microbiological, and radiological integration in diagnostic approach to this novel and challenging disease with often unusual clinical presentations to avoid false negative discrimination.

Keywords: *Arterial thrombosis, coronavirus, hypercoagulability, infarction, kidney, SARS-CoV-2*

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Introduction

Kidney infarction is a rare condition with an estimated incidence of 0.004%–0.007% in the emergency department, although the real frequency is probably higher because its clinical presentation can mimic those of more common conditions such as infection or lithiasis.[1-4] Timely diagnosis is indispensable because renovascular hypertension and chronic kidney disease might occur consequently.[3,5] The two major causes of kidney infarction are *in situ* thrombosis and thromboembolism, including cardioembolic disease, renal artery injury, and hypercoagulable states, or it could remain idiopathic.[3] Recently, more attention has been paid to the hypercoagulable state due to the COVID-19. Almost every organ and organ system can be affected and clinical presentations are diverse and sometimes uncommon, thus posing diagnostic and treatment challenges.

Case Presentation

We report a case of a 63-year-old male Caucasian patient. Besides a long smoking history of 20 cigarettes per day, he had no past medical history, did not take any medications, and had normal blood test results. The present illness started on December 23/24, 2020 with sudden onset of very severe stabbing pain in the upper right part of the abdomen. The pain had crescendo decrescendo characteristics, migrating from below the right costal arch to the lumbar region, periumbilical and finally diffuse stretching. There was no nausea, vomiting, or stool and urination disturbances. He was afebrile, with normal room air saturation of 96% and pO2 of 9.7 kPa. Physical examination revealed a BMI of 24.28 kg/m^2, a blood pressure of 120/80 mm Hg, and a heart rate of 77 beats per minute. He had mild diffuse abdominal tenderness on palpation. There were no signs of mottled skin. ECG showed regular sinus rhythm, with no extrasystolic beats. Initial laboratory workup revealed a normal white blood cell count of 10.6 × 10^9/L with hemoglobin 136 g/dL and platelet count of 798 × 10^9/L. The biochemistry panel was noted to be unremarkable without any sign of acute kidney injury. The value of C-reactive protein at the time of admission was slightly elevated 10.7 (RR <5) mg/L. A complete urine analysis showed no evidence of microscopic or macroscopic hematuria, proteinuria within normal

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reference range, and urine culture negative for bacterial growth. The chronological review of the most of laboratory parameters are summarized in Table 1.

Abdominal X-ray was normal, but multislice computer tomography (MSCT) revealed multiple triangular hypodensities of most of the lateral contour and lower pole of the right kidney, which was supplied by two renal arteries. Contrast-enhanced imaging showed a thromboembolic incident in one of the branches of the lower renal artery. Right renal vein had normal MSCT presentation. Abdominal aorta was tortuous with thrombus immediately before the bifurcation up to 6 mm wide, which extended into the right common iliac artery, where it measured up to 8 mm. There were no filling defects, evidence of atherosclerosis/calcification, or other abnormal findings anywhere else on MSCT [Figure 1]. Irregular right-sided basal pulmonary infiltration was noticed. Chest X-ray showed bilateral peripheral, predominately lower lobe reticular parenchymal infiltrates [Figure 1].

Both SARS-CoV-2 rapid antigen detection test and RT-PCR nasopharyngeal and oropharyngeal swabs (*E-gene "SARS-like" coronaviruses, E-gen and N-gen SARS-CoV2 virus, RT-PCR, QuantStudio 5, Thermofisher Scientific*) performed on December 24 were negative. In the night from December 24 to 25, the patient became febrile, with body temperature up to 38.4°C. The patient had fever spike on December 25, but he remained afebrile after that throughout his hospital stay. After setting the diagnosis of infarction, enoxaparin subcutaneous injections twice daily were immediately ordinated. Besides anticoagulant therapy, he was treated with amoxicillin-clavulanic acid, azithromycin, analgesics, pantoprazole, and parenteral hydration with normal saline. Due to high suspicion of COVID-19, nasopharyngeal and oropharyngeal swabs were repeated on December 29 and the results arrived negative again. Finally, serological analysis was performed on January 4, 2021. The results revealed recent SARS-CoV-2 infection (positive both SARS-CoV2 IgM and IgG; ELISA). It is important to accentuate that our patient, besides two peaks of fever, did not have any other clinical manifestation of COVID-19. Control X-ray performed after 6 days showed regressive dynamics of infiltration. Meanwhile, a hypercoagulability, immunological, and malignant screening was performed. Genetic testing for Factor V Leiden and prothrombin-related thrombophilia as well as antiphospholipid syndrome markers were analyzed. All parameters were within reference range; some of these are listed here:

Table 1: Chronological review of laboratory findings

Parameter	RR	Unit	23rd Dec	25th Dec	28th Dec	29th Dec	2nd Jan	4th Jan	7th Jan
Leukocytes	3.4–9.7	$\times10^9$/L	10.6	18.4	8.5	7.6	6.9	6.9	8.7
Erythrocytes	3.86–5.08	$\times10^{12}$/L	4.35	4.32	3.46	3.84	3.77	4.23	4.30
Hemoglobin	110–157	g/L	136	138	111	122	118	134	138
Thrombocytes	158–424	$\times10^9$/L	798	683	486	601	584	545	553
Neutrophils	44–72	%	ND	78.7	63.2	59.8	54.3	47.5	48.9
Lymphocytes	20–46	%	ND	12.5	22.7	28.1	32.4	37.4	37.2
Monocytes	2–12	%	ND	7.9	11.5	9.1	8.7	10.4	8.3
Eosinophils	0–7	%	ND	0.6	1.9	2.5	0.29	3.8	4.8
Basophils	0-1	%	ND	0.2	0.7	0.4	0.04	0.9	0.8
Glucose	4.4–6.4	mmol/L	6.2	6.6	ND	5.1	ND	ND	ND
Urea	2.8–8.3	mmol/L	2.6	4.5	2.7	3.5	ND	3.8	5.6
Creatinine	64–104	µmol/L	62	91	68	66	81	72	71
eGFR-CKD-EPI		mL/min/1.73 m^2	100.4	77	96.6	98	88.0	93.7	94.3
Uric acid	182–403	µmol/L	ND	ND	150	ND	ND	ND	ND
AST	8–30	U/L	23	103	32	41	ND	22	ND
ALT	10–36	U/L	38	77	47	60	ND	38	ND
GGT	9–35	U/L	25	26	ND	50	ND	ND	ND
LDH	25–241	U/L	ND	1319	656	534	ND	266	216
Na	137–146	mmol/L	144	135	136	139	139	138	136
K	3.5–4.7	mmol/L	3.7	4.3	4.4	4.8	4.9	5.1	4.6
CRP	<5.0	mg/L	10.7	112	84.8	55.5	12.2	6.8	3.0
NT-proBNP	<386.0	pg/mL	ND	944	ND	ND	ND	ND	ND
hs-troponin T	<14	ng/L	ND	27.1	ND	ND	ND	ND	21.8
Ferritin	20–250	ng/mL	ND	ND	ND	727	ND	ND	ND
Albumin	40.6–51.4	g/L	ND	ND	ND	31.1	ND	ND	ND
D-dimers	<0.5	µg/L	5.36	4.10	ND	ND	ND	ND	1.02

RR- reference range; ND- not done

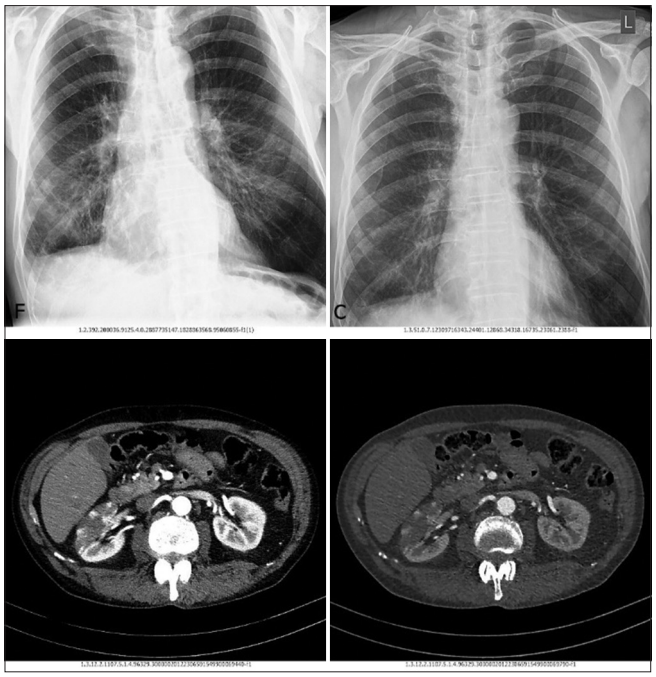

Figure 1: Radiological findings of the first chest X-ray (F) and control imaging showing regressive dynamics (C) as well as multiple right kidney infarction proven by MSCT of abdomen and small pelvis

C3 1.45 g/L (RR: 0.9–1.8 g/L) and C4 0.22 g/L (RR: 0.10–0.40 g/L), homocysteine 8.59 µmol/L (RR: <10 µmol/L), anticardiolipin antibodies IgM 0.9 (RR: <10 MPL/mL), IgG 0.8 (RR: <10 MPL/mL), B-2-glicoprotein 1 IgM 4.2, IgG 0.8 antibodies (RR: <10 AU/mL), LAC 0.94 (RR: <1.20 1/1), protein C 0.87 and protein S 1.24 (RR: 0.70–1.40 1/1), antithrombin 0.79 (RR: 0.75-1.25 1/1), and APC resistance 2.29 (RR: >2.0 FV Leiden unlikely). Further, 24-h ECG showed regular sinus rhythm and echocardiography did not reveal any thrombus, vegetations, intraluminal masses, or inter-chamber shunting. Throughout hospitalization period, our patient was hemodynamically stable, without subjective discomfort, with no respiratory problems, and was finally discharged for further ambulatory follow-up with prolonged dabigatran therapy of at least 6 months (150 mg twice daily).

Discussion

The SARS-CoV-2 virus, causing the COVID-19 disease, typically causes lung infection, and respiratory failure remains the main cause of mortality in these patients. However, lately, numerous cases of acute arterial thrombosis and thromboembolic disease have been reported due to COVID-19 infection.[6] While critical illness is known to cause a hypercoagulable state due to immobilization, mechanical ventilation, central venous access devices, and nutritional deficiencies, COVID-19 appears to cause a hypercoagulable state through unique mechanisms explained by cross-talk between thrombosis and inflammation.[7] COVID-19 leads to a severe inflammatory response that originates in the alveoli. The release of inflammatory cytokines activates epithelial cells, monocytes, and macrophages. Direct infection of the endothelial cells through the ACE2 receptor also leads to endothelial activation and dysfunction, expression of tissue factor, platelet activation, and increased levels of von Willebrand factor and factor VIII, causing thrombin generation and fibrin clot formation. However, thrombin causes inflammation through its effect on platelets, which promote neutrophil extracellular trap formation in neutrophils.[7] This bidirectional relationship also includes complement activation, cytokine storm, the presence of antiphospholipid antibodies and the immune dysregulation, dysregulated renin-angiotensin system, blood tests abnormalities, and tissue hypoperfusion.[7-10] According to different authors, thrombosis rate among COVID-19 affected patients accounts for up to 50%, especially in intensive care units, typically presenting as deep vein thrombosis and pulmonary embolism and microthrombosis in even 80% of patients proven on autopsy.[11-15] The rate of arterial thrombotic and thromboembolic events was 2%–9.6%.[16]

There is limited evidence of the risk of both arterial and venous thrombosis in patients with asymptomatic COVID-19. Furthermore, the real incidence of renal arterial thrombosis due to COVID-19 infection is still unknown, but it is an important differential diagnosis of acute kidney injury in COVID-19-infected patients. In the literature, several cases have been reported with various and sometimes bizarre clinical presentations, sometimes with multiple-organ affection and heterogeneous prognosis.[10,17] Interestingly, many patients who have presented with renal artery thrombosis and acute kidney injury have fully recovered renal function after anticoagulant therapy initiation. All of the reported cases had in common firstly proven COVID-19 disease by RT-PCR analysis of swabs. Herein, we have reported a unique case of a patient without comorbidities who developed multiple renal infarctions, with continuously normal renal function, and without previously established thrombotic risk factors besides smoking. His repeated viral RT-PCR analyses were negative and COVID-19 infection was diagnosed only afterward by using serology testing. Despite bilateral pulmonic infiltrations, he had no respiratory difficulties. Thorough hematological, immunological, and cardiological examination as well as malignant screening did not find any abnormalities. We concluded that this vascular incident was triggered by SARS-CoV-2, although long-term follow-up is needed.

In this era of novel coexistence with COVID-19, we would like to emphasize the importance of repetition and integration of several SARS-CoV-2 detection methods and having in mind this potential etiological trigger despite negative results. According to the data from the literature, rapid antigen detection (RAD) tests are only supplementary methods as RAD is 10^3-fold less sensitive than viral

culture and 10^5-fold less sensitive than RT-PCR, detecting between 11.1% and 45.7% of RT-PCR-positive samples.[18] RT-PCR detection, a standard for COVID-19 diagnosis, has a sensitivity of 65%–71% but differs according to severity of disease form, and nasopharyngeal swabs may be more reliable than oropharyngeal ones.[19] False negative or positive results cause two major problems: a failure to quarantine infected patients and containing viral transmission and quarantining disease-free persons, which can inflict economic, social, or health burdens. In such cases, imaging methods may be useful as regardless of the microbiological results. Xiao *et al*.[20] reported in a small cohort of 70 patients that 21.4% of patients experienced a "turn positive" of nucleic acid detection by RT-PCR test after two consecutive false-negative results due to prolonged nucleic acid conversion regardless of the relief in symptoms or radiography findings. Finally, serological analysis, including the IgM-IgG antibody test, represents another useful adjunct to RT-PCR detection and improves the accuracy in COVID-19 diagnosis regardless of the severity of illness. Titers of SARS-CoV-2 antibodies can reflect the progress of viral infection.

Conclusions

This case report confirmed that COVID-19 infection is associated with procoagulant state even in patients with mild COVID-19 infection and without prior medical illnesses. It is important to keep in mind this etiological trigger even if consecutive SARS-CoV-2 RT-PCR tests are negative.

Declaration of patient consent

Written informed consent has been obtained from the patient to publish this paper.

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Conflicts of interest

There are no conflicts of interest.

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