

SARS-CoV-2 infection and delayed multilevel thrombosis

Sorina Iordache¹, Eugen Țieranu², Alexandru Rocșoreanu², Despina Toader¹, Ionuț Donoiu²

¹ Cardiology Department, Emergency County Hospital, Craiova, Romania

² Cardiology Department, University of Medicine and Pharmacy, Craiova, Romania

ABSTRACT

COVID-19 is a systemic disease encompassing a wide spectrum of manifestations, from asymptomatic to severe organ dysfunction and death. Thromboembolic complications are frequent, but there is a great variability of individual risk and severity. We present the case of an adult male with recovered SARS-CoV-2 infection, which developed late thrombosis in several arterial and venous sites, with unfavorable outcome. The mechanisms involved in COVID-19 hypercoagulable state are discussed.

Keywords: COVID-19, thrombosis, embolism, echocardiography

INTRODUCTION

After the first reports on SARS-CoV-2 infection it was considered primarily a respiratory pathology, but with the epidemiologic development towards a pandemic, it can be asserted that COVID-19 is a systemic disease with a pulmonary starting point. It was shown that it also causes neurological, digestive, kidney, cardiac or vascular manifestations, with a remarkable predisposition for vascular thrombosis. Usually, thrombi originate in the deep venous system of the lower limbs, in patients with risk factors like surgery, fractures, stroke, malignant tumors, etc., and could embolize in pulmonary circulation. Infections are categorized as moderate risk factors, particularly pneumonia, urinary tract infections or HIV infection (1). The cause of thrombosis in a specific patient is difficult to elucidate, given that some patients remain asymptomatic, being accidentally diagnosed, or, conversely, the onset is with sudden cardiac death. As a parallel, in 2004, estimates based on an epidemiological model showed that out of 317,000 deaths caused by pulmonary arterial thrombosis, only 7% occurred at diagnosed patients. Furthermore, in patients with concomitant respiratory disease the diagnosis of pulmonary thromboembolism is challenging.

CASE PRESENTATION

We present the case of a 50-year-old patient, smoker, alcohol consumer, who was previously diagnosed with a severe form of SARS-CoV-2 infection for which he was hospitalized, with good response to therapy and apparently favorable evolution, after 20 days being discharged at home.

Approximately five weeks later, the patient arrived in the Emergency Unit for dyspnea at rest with orthopnea, abdominal distension and diffuse abdominal pain. Clinical exam showed a severely dyspneic patient with a blood pressure of 100/60 mmHg, heart rate of 90 bpm, jugular veins distension, bibasilar crackles at the base of the lungs, and distended abdomen with ascites.

The electrocardiogram revealed abnormal Q waves suggesting myocardial necrosis with minimal ST elevation and negative T waves in the inferior-lateral area (Figure 1).

Laboratory tests showed: creatinine = 0.7 mg/dl, urea = 36 mg/dl, gamma-glutamyl transferase = 24 U/l, glutamic oxaloacetic transaminase (GOT) = 25 U/l, glutamic pyruvic transaminase (GPT) = 11 U/l, total bilirubin = 0.3 mg/dl, direct bilirubin = 0.1 mg/dl, total cholesterol = 93 mg/dl, glycemia = 93 mg/dl. D-dimers were > 5 µg/l and markers of myocardial

Corresponding author:

Eugen Țieranu

E-mail: eugen.tieranu@umfcv.ro

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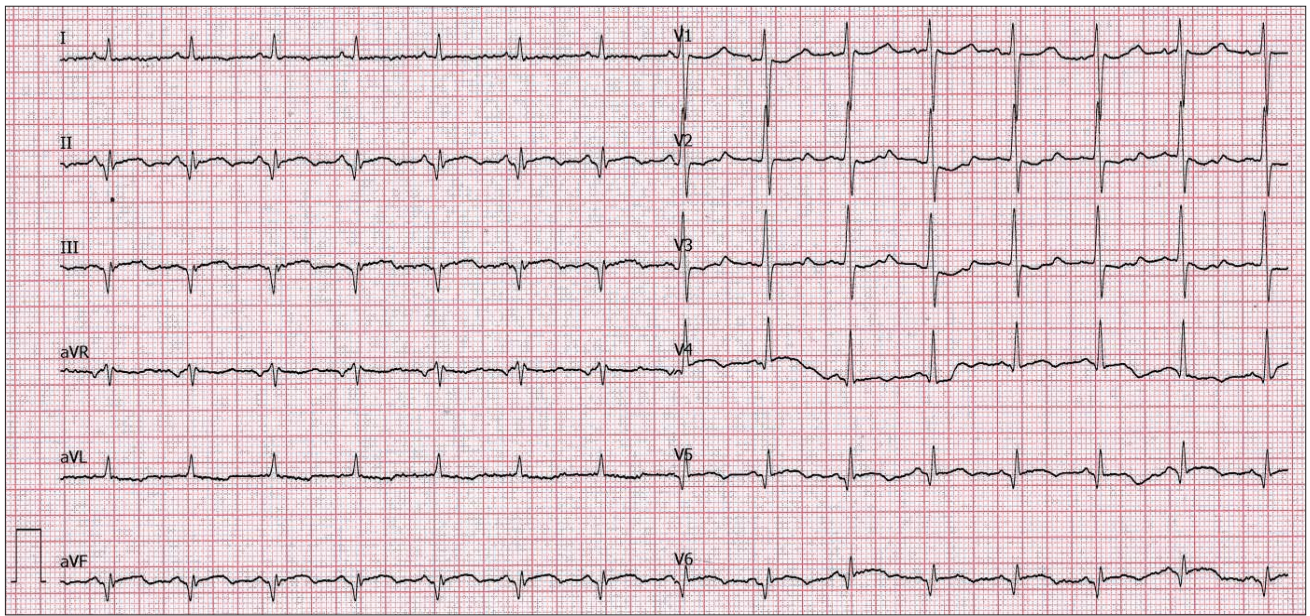


FIGURE 1. Electrocardiogram at presentation: sinus rhythm, Q waves of myocardial necrosis with minimal ST segment elevation in DII, DIII, aVF, V5, V6, R > S wave in V2

necrosis (creatinkinase MB, and high-sensitivity troponin I) were negative.

Transthoracic echocardiography showed a slightly dilated left ventricle, with an ejection fraction of 35%, with akinesia in the basal to mid segments of the inferior and inferolateral wall, and a moderate mitral regurgitation. Also, a large hyperechoic image suggesting a thrombus of approximately 4.5/3 cm was noted at the base of the left ventricle, with a semilunar shape covering the posterior mitral ring (Figure 2).

A CT scan of the chest and abdomen was performed, showing thrombosis in the right pulmonary artery almost completely obstructive, with the extension in the upper and middle lobe artery and partially obstructive thrombosis with extension to the lower lobe artery (Figure 3). At the level of the left ventricle, it was noted a hypodense image of

20/45 mm highly suggestive of intracavitary thrombus. Moreover, well-defined, hypodense, non-iodophilic areas with the appearance of renal infarctions were identified (Figure 4).

The patient was admitted in the Critical Care Unit of the Cardiology department with the diagnosis of left ventricular thrombosis, old inferior myocardial infarction, embolic renal infarctions, and pulmonary embolism. Treatment was started with continuous intravenous infusion of unfractionated heparin, oral anticoagulant (Acenocoumarin), antiplatelet agent (Aspirin), lipid-lowering therapy (Atorvastatin), beta-blocker (Metoprolol succinate), anti-aldosterone diuretic (Spironolactone), loop diuretic (Furosemide), albumin substitution, oxygen therapy, hydroelectrolytic and hemodynamic rebalancing.

Subsequent laboratory analysis results showed increased serum amylase (2,600 U/l), and serum li-

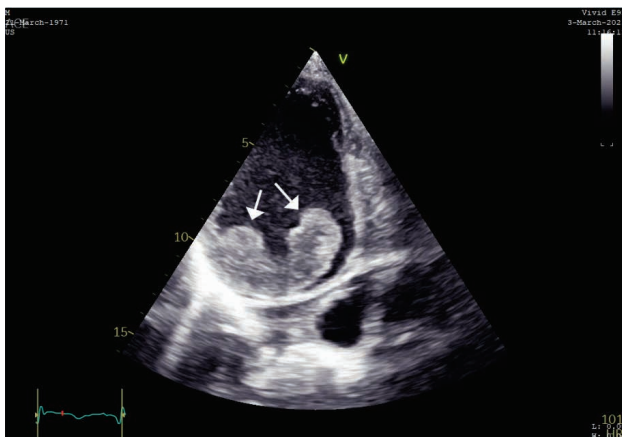


FIGURE 2. Transthoracic echocardiography: modified parasternal short-axis view showing the semilunar shape of the thrombus, at the base of the left ventricle (arrows)

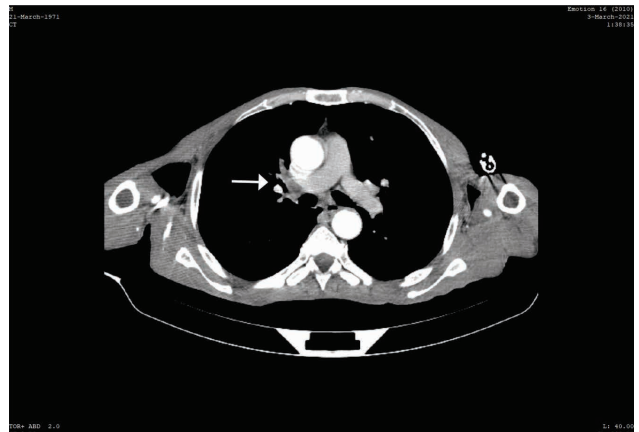


FIGURE 3. Contrast computed tomography of the chest showing thrombus in the right pulmonary artery (arrow)

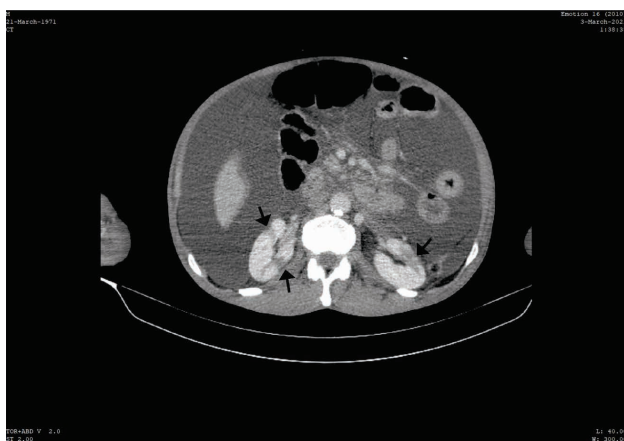


FIGURE 4. Contrast computed tomography of the abdomen showing multiple renal infarctions (arrows)

pase (1200 U/l), raising the suspicion of an acute pancreatitis, but the gastroenterologist considered there were not enough arguments sustaining it (atypical symptoms, no changes on ultrasound and CT scan). Also, there was a nonspecific inflammatory syndrome, hypoalbuminemia, hypocalcemia, mild leukocytosis with lymphopenia, normal result of urinalysis and microbiological examination of sputum, usual thrombophilia tests with negative results. Paracentesis was performed with a negative result for Koch bacillus, negative Rivalta reaction and microbiological examination of the fluid. The cytological examination identified smears with reactive mesothelial cells, an aspect encountered in viral or bacterial infections.

Three days after admission, the patient presents sudden deterioration with respiratory arrest, followed by cardiac arrest through electromechanical dissociation. Orotracheal intubation was performed, and he was mechanically ventilated with initial response to resuscitation maneuvers, being transferred to the intensive care clinic for assisted ventilation. Six days after admission in intensive care unit, the patient had an unfavorable evolution with cardiac arrest through asystole, without any response to resuscitation maneuvers.

DISCUSSION

We presented a patient with multiple thrombosis (at the level of pulmonary arteries, left ventricle, and branches of the renal arteries), diagnosed approximately 7-8 weeks after SARS-CoV-2 infection. COVID-19 is a systemic disease encompassing a wide spectrum of manifestations, from asymptomatic to severe organ dysfunction and death (2). Initial studies with COVID-19 patients emphasized the increased risk venous thromboembolism, but recent data seem to report a greater risk of arterial thrombosis as well (3). A meta-analysis of observational studies describing the prevalence of venous

and arterial thromboembolism up to 30 September 2020 which included 102 studies with 64,503 patients found a prevalence of 14.7% for venous thromboembolism: 7.8% being with pulmonary embolism and 11.2% with deep vein thrombosis (4). As for arterial thromboembolic events, its overall prevalence was 3.9%, with 1.9% for acute coronary syndrome, and 0.9% for stroke.

If the mechanisms of microvascular thrombosis appear to be well explained by direct infection and endothelial cells injury, the mechanisms of macrovascular arterial thrombosis are less clear. Any of these situations seems to be based on the involvement of the immune system, therefore a recently created term, immunothrombosis, could be appropriately applied as it suggests the relationship between the disproportionate immune response and the formation of thrombus during severe infection (5). More precisely, a “storm” of cytokines is released, including the tumor necrosis factor- α , interleukin (IL)-1 β , IL-6, IL-8, and C-reactive protein, with complement activation, the lysis of infected cells associated with biochemical changes that cause local vasoconstriction induced by hypoxemia (6-11).

Regarding the case we presented, arguments must be brought in favor of acute thrombosis compared to an old, organized thrombus. In addition to the devastating hemodynamic impact, some of the criteria are based on the existence of calcification in the walls and the lumen of the vessel or the development of collateral vessels. If in our patient the relation between arterial thrombosis and COVID-19 is based on the disproportionate immune response generated by the infection, the thrombus in the left ventricle may be derived from the significant left ventricular regional contractility disorders resulting from myocardial infarction (possibly by thrombus at the level of the right or circumflex coronary artery), with the development of an aneurysm at the level of the inferior left ventricular wall, over which occur all the aforementioned mechanisms which potentiate the development of intracavitary thrombus within an environment associating hypercoagulable disorders in COVID-19 context.

It appears that the risk of thrombosis persists after discharge in high-risk patients hospitalized for COVID-19, so International Society on Thrombosis and Hemostasis recommends discharge thromboprophylaxis with low molecular weight heparin or new oral anticoagulants to all hospitalized patients with severe SARS-CoV-2 infection which have a low risk of bleeding, up to 14 or 30 days, although the optimal period of time still remains unclear (6). The association between the severe systemic inflammatory reaction together with the respiratory compromise within COVID-19 pathology determines a high-

er prevalence of thrombotic complications. Currently all these data are still undergoing a continuous process of refining through observational and prospective studies.

CONCLUSIONS

The particularity of the case consists in thrombosis of both systemic and pulmonary circulation with multiple localization in a patient recently recovered with COVID-19, in the absence of any other predisposing factors that could have been identified dur-

ing hospitalization, with unfavorable evolution despite all medical efforts. Until present time, relevant data are lacking to provide insights on the best approach for these patients, therefore a better understanding of the pathophysiology behind the association of SARS-CoV-2 infection with coagulation disorders is highly essential for the development of effective therapeutic strategies. The focus towards the understanding of this pathology is necessary given the fact that at this moment the diagnosis and treatment of these patients is clearly difficult.

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