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Case Report

Coagulopathy Associated with COVID-19 Pneumonia

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Abstract

Individuals with COVID-19 may have thrombotic and coagulation abnormalities, which can result in an increased number of thrombotic and thromboembolic events. In hospitalized patients, the rate of thrombotic events is ≈16%, varying between 11.5% to 29.4% in intensive care unit. Patients with severe forms of COVID-19 can present with both arterial and venous thrombotic events, in consequence of a hypercoagulable state. COVID-19–associated coagulopathy, represents a major component of the pathophysiology of this infectious disease, leading to widespread thrombosis. We present a clinical case of a patient with COVID-19 associated coagulopathy, manifested through systemic thrombosis and concomitant nasal bleeding due to intravascular disseminated coagulation syndrome.

Keywords: COVID-19; Coagulopathy; Bleeding; Thrombotic Events

Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome-Related Coronavirus 2; DIC: Disseminated Intravascular Coagulation; ACE2: Angiotensin-converting Enzyme 2; ICU: Intensive Care Unit; PT: Prothrombin Time; aPTT: Activated Partial Thromboplastin Time; LMWH: Low Molecular Weight Heparin; VTE: Venous Thromboembolism; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; IL: Interleukin; CC: Consumption Coagulopathy; TMA: Thrombotic Microangiopathy

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which has posed a significant threat to global health [24]. The pathology of COVID-19 is exacerbated by the progression of thrombosis, disseminated intravascular coagulation (DIC), and cytokine storm [7].

Angiotensin-converting enzyme 2 (ACE2) has been found as being a functional receptor for COVID-19. Infection by SARS-CoV-2 is mediated by binding of its spike protein to ACE2, which is highly expressed in type II pneumocytes in the respiratory system and in the cardiovascular system [23]. This is the possible cause of cardiovascular implication in COVID-19 [5,10,22].

Elevations in fibrinogen and D-dimer levels, and mild prolongation of PT/aPTT has been observed in hospitalized patiens with

COVID-19. Increased D-dimer levels (3- to 4-fold) are associated with a higher mortality and with higher rates of infection/sepsis, cytokine storm and organ failure [1,3,4].

Therefore, low molecular weight heparin (LMWH) has become an important part of the treatment of hospitalized COVID-19 patients. We describe a clinical case of pronounced epistaxis in hospitalized patients with bilateral interstitial pneumonia and SARS-CoV-2 PCR test positive, with a severe coagulopathy treated with anticoagulants.

Case Presentation

A 61 year-old male, presented at the Emergency Department with dyspnoea, extreme fatigue, fever (38.8°C), diarrhea (6 times/day), hypotension (BP 95/60 mmHg) and oliguria. He was discharged from COVID-19 Department four days before, where he was treated for severe pneumonia during 3 weeks. The patient´s co-morbidities included type 2 diabetes mellitus, coronary heart disease, arterial hypertension and persistent atrial flutter.

On admission, patient´s laboratory tests revealed severe leukocytosis (WBC-26.8 x 10^9/L) and hyperkalemia (K-7.0 mmol/L), D-dimers were in reference values. Chest X-rays showed opacities in the right middle lobe (segments 4 and 5) and in the left upper lobe (segment 2). The list of presumptive diagnoses included slowly resolving bilateral community-acquired pneumonia caused by SARS-CoV-2, pseudomembranous colitis, complicated by hypotension and prerenal acute kidney failure. Intravenous infusion therapy, oral Metronidazole, followed by oral Vancomycin, anticoagulant treatment with Warfarin (2.5 mg/day) was initiated, under coagulation control.

After the initial improvement on day 3, the patient´s condition worsened on day 8 when epistaxis, vertigo and headache developed, accompanied by changes in the coagulation tests (prothrombin index -18% (N 85 - 100%), INR-5.43). Warfarin was discontinued and hemostatic treatment was initiated, including anterior nasal tamponade.

Due to the persistence of fever, headache and vertigo, left cavernous sinus thrombosis was suspected and brain CT was recommended. The findings of computed tomography suggested cerebral angiopathy represented by subcortical gliotic foci, with no signs of thrombosis.

Despite the treatment, the patient continued to present fever, dyspnoea, muco-purulent cough and diarrhea 4 - 5 times/day. The presence of colitis was confirmed on abdominal CT. Due to periodic hypotension, dyspnoea and chest pain the hypothesis of pulmonary embolism was proposed. Chest CT and angiography revealed signs of bilateral polyfocal pneumonia (foci of consolidation and ground glass opacities), bilateral pleural effusion with emphasis on the right and absence of thrombus in pulmonary artery branches. To rule out acute coronary syndrome, heart ultrasound was performed, where the hypokinesia of the basal segment of the interventricular sept and posterior wall of the left ventricle, moderate elevation of systolic pressure in pulmonary artery and diastolic dysfunction of the left ventricle were determined. The diagnosis of old myocardial infarction was established because the cardiac necrosis markers were normal. Persistent fever was the reason to suspect infectious endocarditis, but vegetations on the valves were not detected.

The presence of multiple subcutaneous bruising and repeated episodes of epistaxis accompanied by laboratory findings (decreased total protein-44 g/L, decreased albumin-28 g/L, decreased prothrombin index-18%, INR-5.45, Hb-57 g/L, prolonged aPTT 155 seconds), as well as absence of any anticoagulant treatment for more than 2 weeks suggested malabsorption syndrome secondary to colitis and posthemorrhagic anemia. Substitution treatment with fresh frozen plasma, erythrocyte mass and albumin were initiated. Under the treatment the patient´s condition and laboratory data improved. But on day 29 of hospitalization, the patient´s condition suddenly worsened and severe dyspnea, cyanosis, tachycardia and arterial hypotension developed. The suspected diagnosis was massive pulmonary embolism as a part of disseminated intravascular coagulation syndrome, but the emergent treatment was not efficient and the patient died. The autopsy was not performed for religious concerns of patient´s relatives.

Results and Discussion

In ICU patients with severe COVID-19, the prevalence of venous thromboembolism (VTE), especially pulmonary embolism (PE), varies from 17% to 47%, despite thromboprophylaxis. Also, PE can

be found without associated DVT. In a retrospective study analyzing thrombotic events in hospitalized patients, of the 28 patients who presented with any thrombotic complication, 25% had isolated PE [11].

In COVID-19 hospitalized patients a coagulation profile should be made, including D-dimer, partial thromboplastin, *partial thromboplastin* time, platelet count, and fibrinogen, which levels can be elevated 7 - 11 days after the first symptoms. Repeating these coagulopathy parameters every 2-3 days is recommended in patients with severe COVID-19 [5,16,18,19].

Reduced platelet number and elevation of D-dimer, are associated with a higher rate of mechanical ventilation, admission to intensive care unit, and death. Studies show that elderly and patients with cardiac comorbidities have a higher risk of in-hospital mortality [9,18].

In severe stages of COVID-19, there is an increase in inflammatory cytokines (*tumor necrosis factor and interleukins: IL-1 and IL-6*). IL-6 induces expression of tissue factor in macrophages, that initiates the activation of coagulation and generation of thrombin. Tumor necrosis factor and IL-1 are mediators of the suppression of the endogenous coagulation cascade. Cytokine storm in COVID-19 is characterized by high concentrations of proinflammatory cytokines and chemokines, recent studies show [9,12].

The prevalence of VTE varies in different patients and depends on the COVID-19 severity, being more frequent in severe cases. The main risk factors that can lead to VTE are long-time immobilization, acute inflammatory state, hypoxia, and endothelial cell damage [6,15]. Wang., *et al*. reported that about 40% of hospitalized patients with COVID-19 had a high risk of VTE [17,20,21].

Studies suggest that patients who received prophylactic doses of anticoagulants had a survival benefit [8]. Anyway, a recent retrospective study showed that COVID-19 patients treated with antithrombotic drugs are at increased risk of bleeding [13]. The most common type of bleeding was gastrointestinal bleeding with possible mechanisms: stress ulcer formation from hospitalization, hemorrhagic colitis possibly secondary to SARS-CoV-2 or disseminated intravascular coagulation-induced bleeding [2].

Epistaxis has also an increased incidence in patients that receive anticoagulation. This group of patients often will subsequently be treated with anticoagulation and antiplatelet therapy. Additionally, severe patients often need supplemental oxygen via nasal cannula, which dries the nasal passages and can lead to bleeding [14].

Laboratory parameters	Day 1	Day 2	Day 12	Day 15	Day 19	Day 22	Day 23	Day 24	Day 28
WBC ($x10^9$/L)	26.85	25.84	17.8	8.71	6.63	10.12	9.58	9.08	7.93
RBC ($x10^{12}$/L)	4.58	4.47	1.93	2.23	1.95	2.53	3.32	3.75	3.51
HB (g/L)	133	129	57	62	58	76	99	113	105
HCT (%)	40.5	40.0	18.0	19.3	17.6	23.3	30.2	34.3	33.2
PLT ($x10^9$/L)	130	119	338	269	173	156	168	246	262
Neutrophiles (%)	-	91.6	78.7	82.2	91.8	73.7	82.1	73.5	51.6
Lymphocytes (%)	-	4.2	13.3	7.6	5.6	20.2	12.5	19.4	35.4
ESR (mm/h)	-	24	28	43	42	-	35	-	47

Table 1: Laboratory data dynamics.

	Day 2	Day 9	Day 13	Day 15	Day 16	Day 19	Day 29
BUN (mmol/L)	24.1			28.5	16.9		9.9
Creatinine (mmol/L)	200			340	165		154
Glucose (mmol/L)	7.7	9.8	5.0	5.75	8.1		4.9
Total protein (g/L)		44					
Albumin (g/L)		28					
CRP (mg/dL)		96	384				
K (mmol/L)	7.0	5.6			5.0		4.7
Na (mmol/L)	136	138			140		141
Prothrombin index (%)			30	25	24	56	
Fibrinogen (g/L)			2.4	2.4	5.5	4.2	
APTT (s)					115		
D-dimers (mg/L)	0.2						
INR		11.0	3.27	3.98	4.2	1.76	

Table 2: Biochemistry data dynamics.

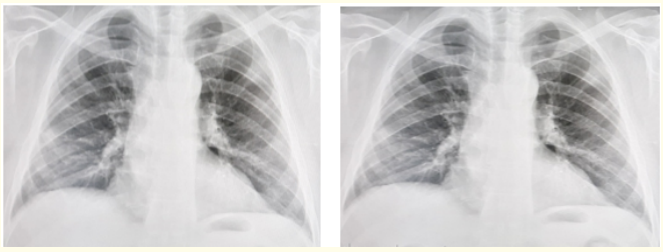

Figure 1: Chest X-ray (day 1 of hospitalization)-Bilateral opacities: on the right in S4-5 and on the left in S2. In dynamics (day 19 of hospitalization)-without significant changes in comparison with day 1.

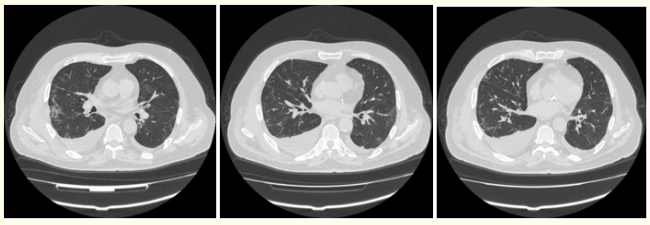

Figure 2: Chest computed tomography (day 26 of hospitalization): bilateral polyfocal ground glass opacities and consolidations. Bilateral pleural effusion. Minimal exudative pericarditis.

Conclusion

Coagulopathy is a common characteristic of severe COVID-19 disease as part of the systemic inflammatory response syndrome. Hematological changes that can occur are: *elevated D-dimer, prolonged PT and aPTT, thrombocytopenia, and/or elevated fibrinogen levels*. COVID-19 is more characterized by thrombotic events that are associated with coagulopathy, especia*lly* venous thromboembolism. Hemorrhagic events are not so frequent in the course of the disease. The severity of COVID-19 infection is represented by the worsening of laboratory parameters related to coagulation, while the improvement of these parameters, together with the relief of symptoms suggests a positive evolution of the disease.

Conflict of Interest

There is no conflict of interest in this study.

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