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CASE REPORT

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A COVID-19 case report with low ACT(activated clotting time) and high serum D-dimer level: Antithrombin III deficiency?

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Abstract

The Coronavirus Disease 2019 (COVID-19), caused by the virus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a global public health problem in which atypical findings other than the usual fever and respiratory symptoms render early diagnosis and treatment difficult. Cases with atypical clinical and laboratory presentations continue to pose a challenge in the treatment and control of the disease. This case report aims to share our follow-up and treatment experience in a patient considered to have antithrombin III (ATIII) deficiency based on activated clotting time (ACT) levels unresponsive to heparin who was admitted to intensive care unit due to COVID-19-induced cytokine storm associated with extreme D-dimer elevation (>65,000 μg/L).

KEYWORDS
activated clotting time, COVID-19, D-dimer

INTRODUCTION

The outbreak of the SARS-CoV-2 infection has been named as the Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). While COVID-19 has been often characterized by respiratory tract infection symptoms such as fever, cough, and shortness of breath, cases where systems other than the lungs are also affected by the virus have emerged with the rapid spread of the disease.

Antithrombin III (ATIII), a plasma glycoprotein synthesized in the liver, is a highly important natural anticoagulant protein of the coagulation system. Regardless of the underlying cause, the decrease in ATIII activity leads to an increased thromboembolic risk.[1–3] ATIII is a negative acute phase reactant, and the synthesis of this protein decreases during the course of disease, even in patients with normal liver function.[4] The presence of ATIII deficiency leads to a tendency to hypercoagulopathy and eventually the development of disseminated intravascular coagulation (DIC), causing occlusions in the capillary system due to microthrombi.

The increasing number of COVID-19 cases reflects in an increased number of atypical cases, posing challenges in clinical follow-up and management. In this case report, we aimed to share the management, follow-up and evaluation of the poor clinical and laboratory presentation of a COVID-19 patient admitted to intensive care unit (ICU) due to cytokine storm with extremely high D-dimer (>65,000 μg/L) in whom we assumed ATIII deficiency based on ACT measurement as ATIII cannot be measured in our lab.[5]

CASE REPORT

A 49-year-old male patient presented to the emergency room with the complaint of shortness of breath. His medical history revealed that he had diabetes for 12 years and underwent coronary bypass surgery 9 years ago. COVID-19 polymerase chain reaction (PCR) test was performed for the patient, who reported irregular use of his medications for diabetes and coronary artery disease (CAD), as his oxygen saturation was 80%–85% (8-10 L/minute) in the emergency room. Upon thorax computed tomography (CT) showing diffuse ground-glass density (Figure 1) and a positive result in the PCR test, the patient was admitted to ICU with the diagnosis of COVID-19-related pneumonia. DIC was not considered since D-dimer was 65,300 μg/L (normal range: 80–560 μg/L) with a normal international normalized ratio

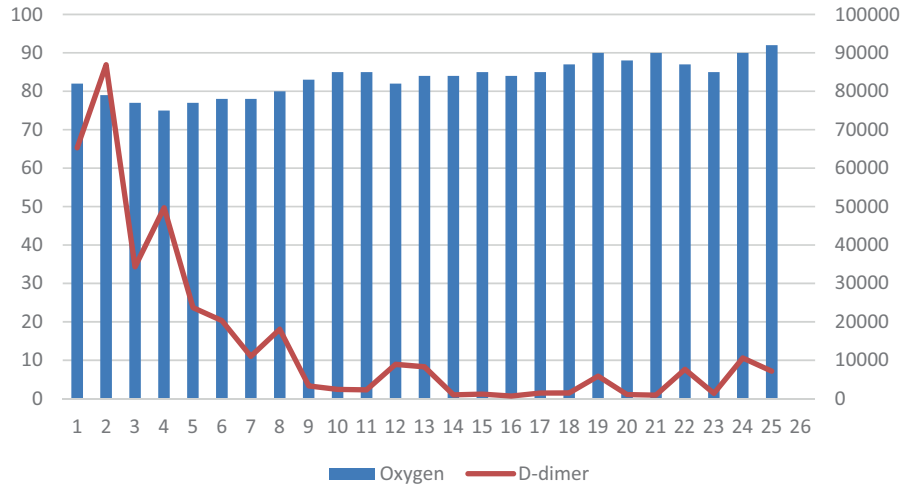

FIGURE 1 D-dimer and oxygen saturation changes by days.

TABLE 1 Changes in oxygen saturation and lab values by days.

Day	Oxygen	Support	WBC	Plt	CRP	D-dimer	Procalcitonin
1	83	HF	12,500	208	23.7	65,300	0.21
3	80	HF/CPAP	14,200	189	9.7	34,300	<0.12
5	79	CPAP	18,000	194		23,700	<0.12
7	75	CPAP	18,800	185	0.84	11,000	<0.12
9	78	CPAP	22,300	228	<0.5	11,500	<0.12
11	80	CPAP	15,900	158	<0.5	10,600	<0.12
13	85	HF/CPAP	17,300	185	<0.5	4410	<0.12
15	82	HF/CPAP	12,000	144	<0.5	3330	<0.12
17	84	HF/CPAP	15,300	129	<0.5	2310	0.49
19	84	HF	11,600	138	3.5	8290	0.15
21	87	HF	10,800	137	1.2	1200	0.13
23	88	HF/RMO	9260	160	5.5	1500	0.24
25	92	RMO	6800	186	4.9	5850	0.14

Abbreviations: CPAP, non-invasive CPAP; HFO, high-flow oxygen support; HFO/CPAP, alternate supportive therapy; PCT, procalcitonin; PLT, platelet; WBC, white blood cell.

(INR) and a normal platelet count noted during the investigations at the time of ICU admission. Thorax CT angiography could not be performed as the patient was unstable in the acute period for pulmonary thromboembolism (PTE), and PTE could not be ruled out. On Day 1 of ICU admission, tocilizumab and broad-spectrum antibiotics (imipenem, vancomycin) were added to the treatment of the patient, who was considered to have cytokine storm based on laboratory and clinical evaluation. We could not measure the ATIII level of the patient with extreme D-dimer elevation. His basal ACT was found to be 117 s, which might support the possibility of ATIII deficiency. After 10,000 units of classic heparin, the patient's ACT test was repeated, revealing a decrease to 67 s and suggesting ATIII deficiency. Because ATIII concentrate was not available, fresh frozen plasma (FFP) as 10–20 mL/kg per day was added to the treatment until the D-dimer value was <10,000 μg/L (a total of 18 units of FFP were administered). The gradual decrease in D-dimer values following the addition of FFP to treatment, and the ACT value >400 s supported our preliminary diagnosis of ATIII deficiency (Table 1). Starting from the first day of his ICU admission, the patient received low molecular weight heparin (LMWH), acetylsalicylic acid 100 mg/day and dipyridamole 2 × 75 mg/day. When oxygen levels fell below 80%, the treatment was supported with HFO-CPAP alternate therapy (high-flow oxygen and continuous positive airway pressure). The D-dimer level and other acute inflammatory markers began to improve progressively (Table 1). The patient's oxygen saturation increased as D-dimer levels decreased during the ICU admission (Figure 1). The patient, whose need of oxygen support decreased and chest radiography showed significant regression (Figures 2 and 3), was discharged from the ICU and transferred to the ward on Day 27 of inpatient care.

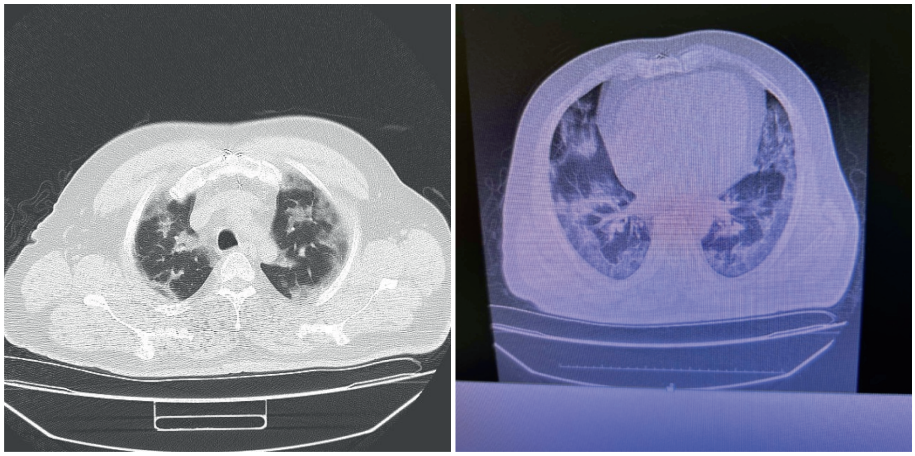

FIGURE 2 Diffuse ground-glass appearance starting from the apex in thorax CT.

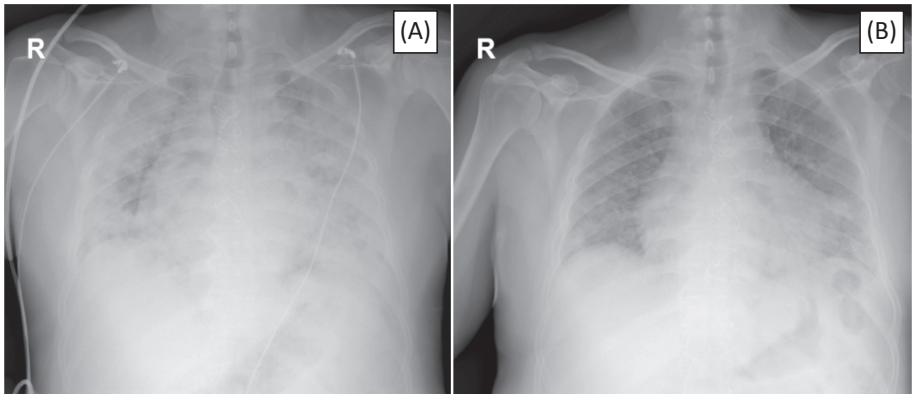

FIGURE 3 Comparison of the patient's x-rays from the apex to basal at the time of ICU admission (A) and at the time of discharge (B).

DISCUSSION

Extremely elevated D-dimer levels at the time of ICU admission in COVID-19 patients have been associated with a risk of PTE.[6] Although our patient had a high D-dimer level at the time of ICU admission, CT angiography could not be performed and PTE could not be ruled out as he was clinically unstable and had low oxygen saturation. D-dimer has a very high sensitivity but poor specificity for thrombotic disease. Several studies in patients with COVID-19 have shown a very strong association between increased D-dimer levels and serious illness/poor prognosis. Consistently, as the D-dimer level returned to normal, we observed increased oxygen saturation and a decreased need for supplemental oxygen therapy in our patient.

Currently available data suggest that the extremely high D-dimer levels observed in COVID-19 patients are not only secondary to systemic inflammation, but also reflect true thrombotic disease, possibly resulting from the cellular activation triggered by the virus.[7] In the thrombotic process, a patient with normal platelet count, normal INR, and elevated basal ACT with no ACT response after administration of 10,000 units of heparin suggests the possibility of 'heparin resistance'. However, we did not consider heparin resistance as our patient had no history of heparin use.

It is known that ACT unresponsive to heparin is associated with decreased ATIII levels and/or activity,[5] the half-life of ATIII may be reduced to 4–6 h in severe inflammatory conditions, and the decrease in ATIII activity is closely related to prognosis, therefore considered a strong prognostic predictor.[8] The acute ATIII deficiency may be severe in patients with COVID-19. The replacement of this protein proves to be important as there may be development of thrombosis as well as an impaired effectiveness of therapeutic anticoagulation in these patients. ATIII supplementation may improve the anticoagulant effect without increasing the LMWH dose. Previous studies have reported that FFP supplementation may increase ATIII levels in the absence of ATIII concentrate readily available for treatment.[9] In a study conducted in our country, the low levels of ATIII activity in COVID-19 patients were treated with daily FFP 10 mL/kg and favourable clinical results were reported.[10] In our patient presented herein, FFP 10–20 mL/kg was added to treatment until the D-dimer level fell below 10,000 μg/L. We observed a clear reflection of the laboratory and clinical improvement on oxygen saturation in our patient.

Tocilizumab has been reported to be effective in patients with severe COVID-19. Upon clinical and laboratory evaluation of the patient at the time of ICU admission, he was considered to have cytokine storm and tocilizumab was therefore added to the treatment. Cytokine storm can be irreversible unless treatment is initiated shortly after the diagnosis is established. Tocilizumab administration has been reported to improve respiratory function and decrease C-reactive protein (CRP) levels.[11] The patient presented in this report showed a positive response to treatment in terms of clinical, radiological and laboratory findings following tocilizumab administration on the day of admission to the ICU.

Previous studies have demonstrated that increased WBC count is associated with severe COVID-19 infection[12] and that WBC acceptance values may be higher in patients with severe COVID-19 compared to those with moderate infection.[13] In our case, the WBC count returned to normal range upon clinical improvement and increased oxygen saturation.

COVID-19 continues to manifest with different clinical and laboratory findings and poses an ongoing global threat. Although COVID-19 is primarily reported as an infection of the respiratory tract, emerging data suggest that it may in fact be multi-systemic disease. Cases with atypical findings pose great challenges for patient management. In our patient, who was a complex case with atypically high D-dimer, cytokine storm, low ACT and possible ATIII deficiency, we observed the desired efficacy with FFP administration instead of ATIII and we believe this is important with regard to the challenges we may encounter in COVID-19 patient management.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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