Progressive COVID-19-Associated Coagulopathy Despite Treatment with Therapeutic Anticoagulation and Thrombolysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDE 1   I. Gusti Ngurah Mahaalit Aribawa
BCD 1   Leonard Hidayat
BCD 2   Putu Utami Dewi
AEF 1   Christopher Ryalino

1 Department of Anesthesiology and Intensive Care, Faculty of Medicine, Udayana University/Udayana University Hospital, Denpasar, Bali, Indonesia
2 Department of Radiology, Faculty of Medicine, Udayana University/Udayana University Hospital, Denpasar, Bali, Indonesia

Corresponding Author: I Gusti Ngurah Mahaalit Aribawa, e-mail: mahaalit@unud.ac.id
Conflict of interest: None declared

Patient:	**Male, 72-year-old**
Final Diagnosis:	**COVID provoked thromboembolism**
Symptoms:	**Desaturation • fever • hypotension • non productive cough • shortness of breath • unconsciousness**
Medication:	**—**
Clinical Procedure:	**—**
Specialty:	**Anesthesiology • Critical Care Medicine • Radiology**

Objective: Unusual clinical course

Background: Coronavirus Disease 2019 (COVID-19) has been associated with a hypercoagulability state. Clinical presentation can range from asymptomatic to severe illness and mortality. Thrombotic complications in COVID-19 have been associated with mortality. The incidence of systemic hypercoagulation in COVID-19 is associated with the process of severe inflammation. The majority of severely ill patients have developed coagulopathy, and this condition is associated with poor outcomes.

Case Report: A 72-year-old man presented with respiratory symptoms and was diagnosed with a COVID-19 infection. He presented with tachypnea, tachycardia, increased blood pressure, and 74% peripheral oxygen saturation under 15 L/min oxygen per non-rebreather mask. Initial laboratory test results showed severe hypoxemia as per blood gas analysis (pH 7.42, pCO_2 23 mmHg, pO_2 43 mmHg, HCO_3 15 mmol/L, base deficit -9 mmol/L), with increased procalcitonin, high-sensitivity C-reactive protein, D-dimer, fibrinogen, creatine kinase myocardial band, and Troponin I. He subsequently developed thrombosis of the pulmonary arteries and multiple branches of the pulmonary vein despite therapeutic anticoagulation. We initiated heparin therapy (average dose 25 191 units per day, mean activated partial thromboplastin time, 64.35 seconds). Radiological investigations revealed multiple thromboses on pulmonary arteries and pulmonary veins, as well as multiple locations of brain infarction. Rescue thrombolytic therapy was given, but unfortunately, the patient died due to multiple end-organ failures.

Conclusions: Controlling coagulopathy, and thrombolytic therapy type and timing, are critical issues, and new strategies must be sought to lower its morbidity and mortality rates further.

Keywords: **Brain Infarction • COVID-19 • Pulmonary Embolism • Thrombolytic Therapy**

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/930667
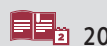
📄 2265   ▦ —   📊 2   📚 20

Background

Coronavirus Disease 2019 (COVID-19) cases were first reported in Wuhan City, China, in December 2019. As of September 5, 2020, more than 26 million confirmed cases had been reported, including more than 865 000 deaths worldwide [1]. The incubation period for COVID-19 is up to 14 days from the time of exposure, with a median period of 4 to 5 days [2]. Clinical presentation can range from asymptomatic to severe illness and mortality.

Some reports propose numerous treatment choices involving fibrinolytic drugs for severe COVID-19 cases. Thrombotic complications in COVID-19 have been associated with mortality [3,4]. The incidence of systemic hypercoagulation in COVID-19 is associated with severe inflammation. The lung is the likely site of thrombosis in most cases of COVID-19 [4]. Pulmonary thrombosis in severe COVID-19 can be described as macroscopic or microscopic thrombosis. The majority of severely ill patients develop coagulopathy associated with poor outcomes [3,4]. Therefore, early detection and management for coagulopathy must always be considered.

Case Report

A 72-year-old man (82 kg, 28.4 kg/m^2) was referred to our emergency department from a private hospital. He had a history of fever and non-productive cough for a week prior to admission and reported shortness of breath with gradual onset and increasing severity. His past medical history was unremarkable, and he had no history of malignancy, diabetes, or cardiovascular disease. A polymerase chain reaction (PCR)-based test for SARS-CoV-2 had been performed the previous week and the result was positive.

Upon admission, his respiratory rate was 55 breaths per minute with 74% peripheral oxygen saturation (SpO$_2$) under 15 L/min oxygen with a non-rebreather mask. His blood pressure was 144/91 mmHg, heart rate was 145 beats per minute, and body temperature 36.8°C. Blood investigation showed an increased white cell count (15 840 cells/μL) with 8% lymphocytes and a normal platelet count (192 000 platelets/μL). Blood gas analysis with a non-rebreather mask showed a pH of 7.42, pCO$_2$ 23 mmHg, pO$_2$ 43 mmHg, HCO$_3$ 15 mmol/L, base deficit -9 mmol/L, and lactic acid 7.46 mmol/L. Serum biochemical analysis showed blood urea nitrogen (BUN) 36 mg/dL, creatinine 1.4 mg/dL, alanine aminotransferase (ALT) 169 U/L, and aspartate aminotransferase (AST) 238 U/L. We also found increased procalcitonin (51.36 ng/mL) and high-sensitivity C-reactive protein (hs-CRP, 391 mg/L). Additional laboratory findings included elevated D-dimer (>50 000 ng/mL fibrinogen equivalent units; FEU) and increased fibrinogen (439 mg/dL). Cardiac

biomarkers showed elevation for creatine kinase myocardial band (CKMB, 31.8 ng/mL) and troponin I (0.61 ng/mL). The patient's electrocardiogram showed sinus tachycardia. His chest X-ray revealed heterogenous consolidation on both the middle and lower lung field. We also obtained a blood culture, which came back a few days later as negative (no bacterial growth).

We initiated high-flow nasal oxygen (HFNO) therapy with an oxygen flow of 40 liters/minute and 100% fractional inspired oxygen (FiO$_2$). HFNO therapy clinically improved his oxygen saturation to 92%, respiratory rate to 26 breaths per minute, blood pressure to 130/80 mmHg, and heart rate to 120 beats per minute. Informed consent was obtained for central venous catheter and arterial catheter placement. The patient was treated with aspirin, clopidogrel, and infusion with a therapeutic dose of intravenous unfractionated heparin (UFH). His activated partial thromboplastin time (aPTT) was routinely checked every 6 hours with a target range 2 to 2.5 times the control value. He was then transferred to the negative-pressure intensive care unit (ICU) for further management.

Initially, the management in the ICU included meropenem (1 gram every 8 h), levofloxacin (750 mg/day), dexamethasone (5 mg every 12 h), famotidine (20 mg/day), vitamin D (400 IU/day), ascorbic acid (500 mg every 8 h), zinc (100 mg/day), atorvastatin (40 mg/day), N-acetyl cysteine (NAC) (200 mg every 8 h), and nebulized lidocaine.

The average dose of UFH was 25 191 units per day with mean aPTT value of 64.35 seconds. His condition improved, and oxygen supplementation was gradually down-titrated to a simple face mask at 6 liters/minute at the beginning of the 12th day of treatment. Blood gas analysis showed pH 7.41, pCO$_2$ 37 mmHg, pO$_2$ 74 mmHg, HCO$_3$ 24 mmol/L, base deficit -1 mmol/L, and lactic acid 1.36 mmol/L. Follow-up investigations showed improvement of procalcitonin (decreased to 7.4 ng/mL), hs-CRP (decreased to 0.13 mg/dL), and D-dimer levels (decreased to 5308 ng/mL FEU). In comparison to initial lab results, we also found increased fibrinogen (523 mg/dL) and reduced ALT and AST (153 U/L and 62 U/L, respectively).

In the evening of the same day, the patient had a sudden clinical deterioration with labored breathing, desaturation, hypotension, and altered mental status. We performed endotracheal intubation and started inotropic and vasopressor agents. The next day, computed tomography-pulmonary angiography (CTPA, **Figure 1**) revealed thrombosis in bilateral pulmonary arteries and multiple branches of pulmonary veins. A brain CT scan (**Figure 2**) showed an infarct on the cortical-subcortical left parietal lobe, pons, and left part of the cerebellum. Rescue thrombolytic therapy was commenced with streptokinase 250 000 IU as a loading dose over 30 minutes followed by 100 000 IU/hour over 12 hours.
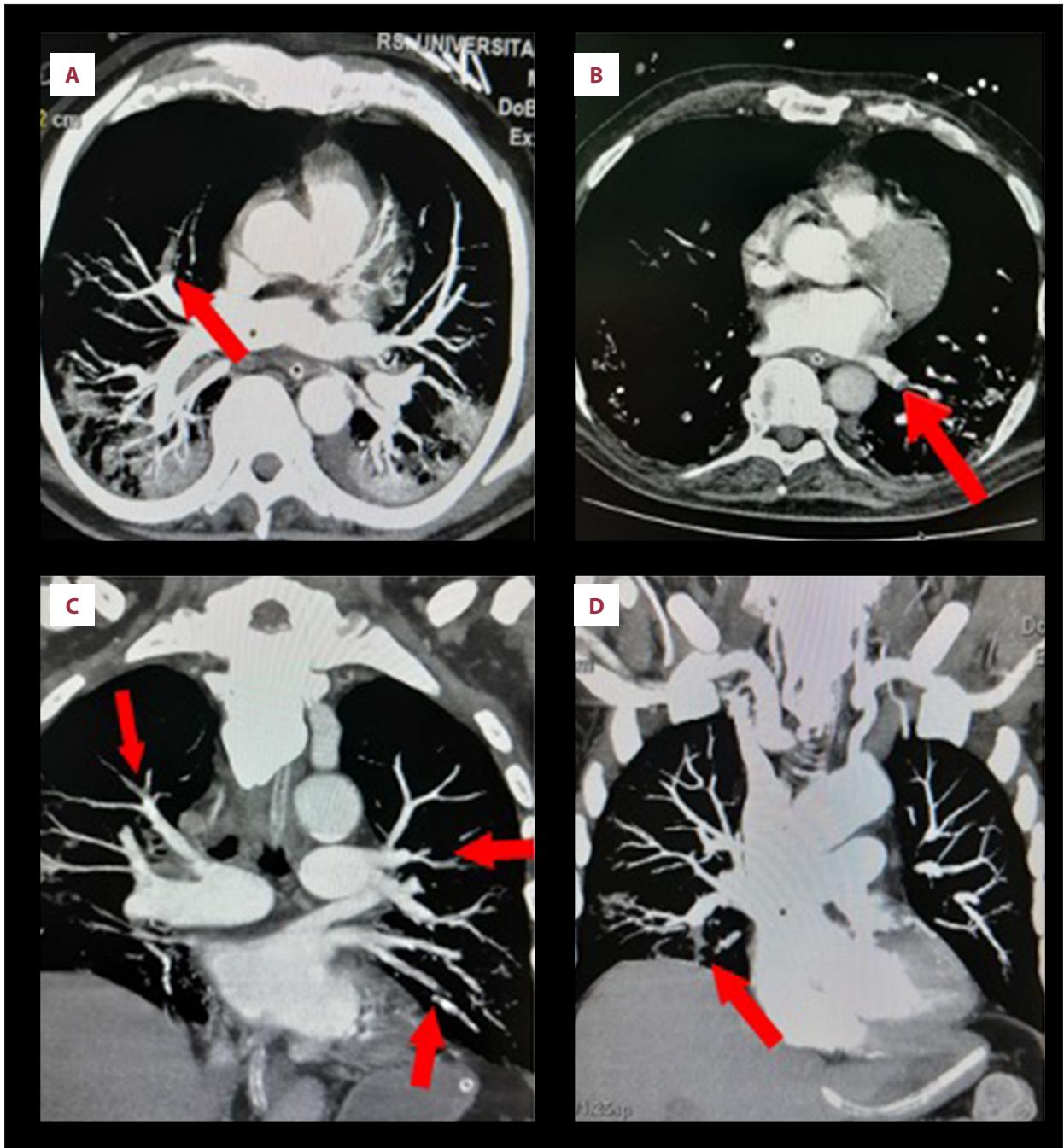
Figure 1. CT-pulmonary angiography showing multiple pulmonary thromboses. (**A**) Filling defect in the apical branch of the superior right pulmonary artery. (**B**) Filling defect in the left pulmonary vein. (**C**) Irregularity and filling defect in the lateral basal, lingular, and posterior basal branches of the left pulmonary artery. (**D**) Filling defect in the anterior basal branch of the right pulmonary artery.
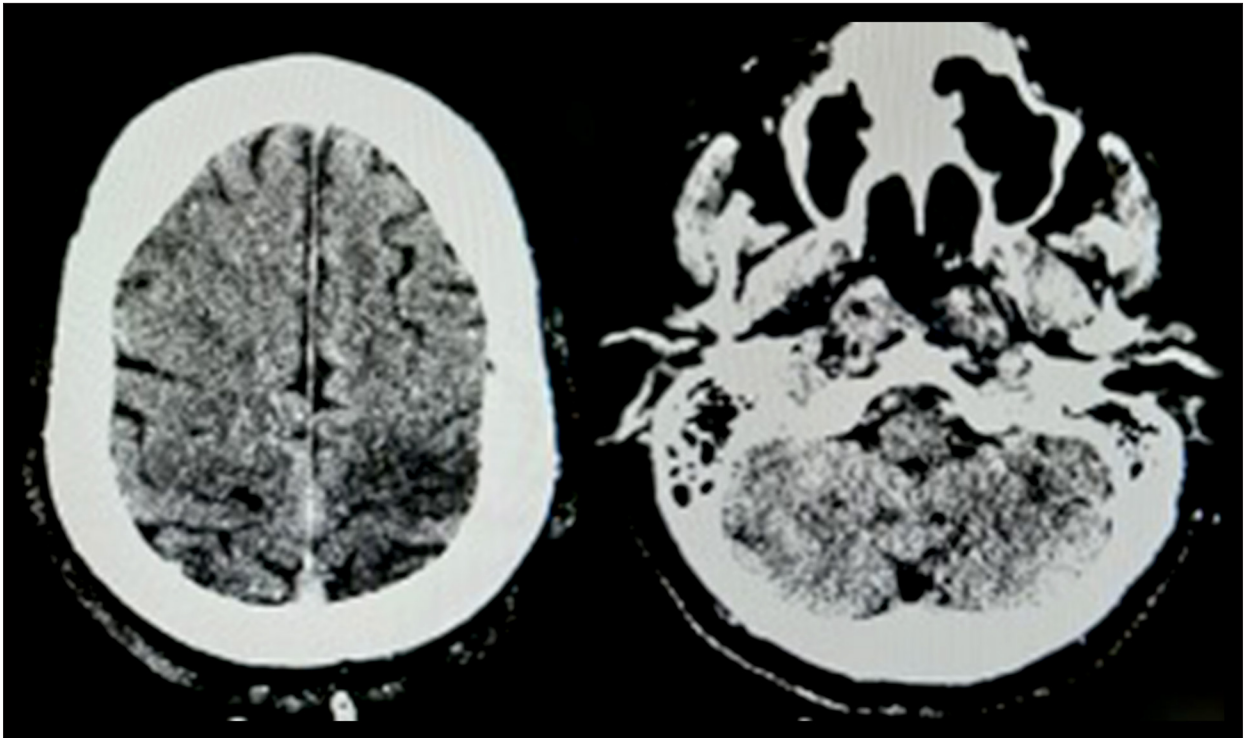
Figure 2. Infarct in the cortical-subcortical left parietal lobe, pons, and left part of the cerebellum.

On day 14, he was still in critical condition and showed no improvement after thrombolytic therapy. Further investigations showed hs-CRP of 221.1 mg/dL, ferritin of >15,000 µg/L, D-dimer level of 2597 ng/mL FEU, and fibrinogen of 634 mg/dL. Tocilizumab 600 mg was infused over a period of 1 hour. The patient died due to multiple end-organ failure on the 18th day of hospitalization.

Discussion

Severe acute respiratory distress syndrome accompanied by multiorgan dysfunction syndrome has been recognized as a cause of death in most COVID-19 patients. Coagulopathy has been observed in these patients and is consistently associated with poor prognosis [5]. The mechanism of infection from SARS-CoV-2 involves angiotensin-converting enzyme 2 (ACE-2) receptors on human cells, including endothelial cells. Viral binding to ACE-2 receptors on endothelial cells will disrupt angiotensin-II metabolism, with a resulting increase in plasma angiotensin-II, and exert vasoconstriction, inflammation, and release of tissue factor, plasminogen activator inhibitor 1 (PAI-1), and cytokines (tumor necrosis factor [TNF]-α and interleukins [IL-1, IL-2, and IL-6]). In other words, viral binding to ACE-2 receptors leads to coagulation activity [6,7].

Neutrophil extracellular traps are the other pathogenic pathway, which has a protective function against pathogens but can cause thrombo-inflammation and enhance thrombin generation [6,8]. Complement activation has been shown to activate coagulopathy through an inflammatory response and direct pro-thrombotic effect by activating platelets and endothelial cells and increasing tissue factor and von Willebrand factor expression [6]. In addition to previous mechanisms, several risk factors can contribute to a hypercoagulable state, including immobilization, cancer, diabetes, cardiovascular disorders, inherited thrombophilia, central vein catheters, advanced age, and obesity [6,7].

Coagulation abnormalities are typically found in patients with severe COVID-19 and are associated with intense inflammation. Elevated D-dimer and fibrinogen levels are the hallmark laboratory findings of COVID-19-associated coagulopathy (CAC) [8,9]. D-dimer levels greatly increase due to the release of urokinase-type plasminogen activator by alveolar macrophages, causing upregulation of local fibrinolysis in alveoli. The second mechanism is direct infection of endothelial cells, leading to a massive release of plasminogen activators [8,10]. In sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC), there is excessive production of PAI-1 so that fibrinolysis is often suppressed, and, as an implication, D-dimer levels are usually not as high as in CAC [8,9].

Progressive fibrin clot formation will lead to microthrombi and multiple organ dysfunction. Typical SIC/DIC coagulation disorders manifest as a decrease in platelet count and increase in

prothrombin time due to continued consumption and subsequent exhaustion of platelets and plasma coagulation proteins. However, that type of coagulopathy does not usually occur in COVID-19 in its early phase. IL-1β and IL-6 induce thrombocytosis and hyperfibrinogenemia, and sustained inflammation may maintain the production of these factors. Nevertheless, CAC potentially proceeds toward SIC/DIC [8].

Emphasizing the hypercoagulable state seen in COVID-19, venous and arterial thromboembolism can manifest as arterial thrombus, pulmonary embolism, myocardial infarction, stroke, venous embolism, and thrombotic microangiopathy [11]. Patients with severe clinical manifestations can deteriorate rapidly, and evaluation should include radiological investigations, electrocardiogram, complete blood count, differential leukocyte count, liver and renal function tests, inflammatory and coagulation markers, and other metabolic investigations [2].

Management approaches for CAC vary greatly among institutions and always balance the risks and benefits of given therapies. Although there are differences, heparin seems to be the clear answer to this hypercoagulable state. In addition to its antithrombotic effect, it has anti-inflammatory, anti-complement, and direct antiviral effects that may be advantageous in COVID-19 [12]. Heparin appears to be a promising therapy for COVID-19, but Maatman et al conclude that standard prophylactic anticoagulation doses may be inadequate to prevent thromboembolism in high-risk patients [13]. Higher prophylactic or therapeutic dosing must be prescribed for patients who may benefit without suffering bleeding complications [12].

White et al, interestingly, described heparin resistance in COVID-19 patients in the ICU. Heparin resistance was defined as requiring >35 000 units of heparin per day for those on UFH. For patients on low molecular weight heparin (LMWH), expected anti-Xa was defined as a 2-4 hour peak of anti-Xa activity from 0.6-1.0 IU/mL for those on twice-daily dosing and >0.1 IU/mL LMWH for those on once-a-day dosing. Heparin resistance most likely occurs due to high fibrinogen and factor VIII and low anti-thrombin levels in COVID-19 patients [14,15]. In our case, UFH was chosen over LMWH because it may be a better choice for thrombosis in COVID-19 patients to ensure therapeutic anticoagulation is achieved. In severe cases, the half-life of LMWH will be significantly prolonged due to renal failure. The bleeding risk will increase if LMWH has to be given with tissue plasminogen activator (tPA) for critically ill patients who develop pulmonary embolism complications [15]. The average dose of 25 191 units per day of UFH and mean aPTT value of 64.35 seconds led us to conclude that our patient did not have heparin resistance.

Initially, our patient showed clinical improvement, but experienced sudden deterioration on the 12th day of hospitalization.

Such a clinical course strongly suggests the possibility of acute thrombosis. Radiological findings showed infarcts on the cortical-subcortical left parietal lobe, pons, and left part of the cerebellum. CTPA was performed and revealed pulmonary artery and pulmonary vein thrombosis. Pulmonary embolism (PE) is the most common thrombotic complication of COVID-19 [11]. The diagnosis of PE is challenging because symptoms of PE can overlap with COVID-19. PE should be suspected in acute worsening of hypoxemia, drop in blood pressure, tachycardia, increased oxygen requirement, and ventilatory settings disproportionate to the severity of pneumonia on chest imaging. CTPA is the criterion standard for diagnosing PE, and a great number of hospital resources were utilized in shifting the patient to the radiology unit [5]. In the setting of rapid hemodynamic deterioration on anticoagulant treatment, thrombolytic rescue therapy came into consideration [16].

Interestingly, thrombolytic therapy may be clinically useful in severe cases of COVID-19 because pulmonary thromboembolism incidence is high even in patients without prior classic thrombotic risk factors. In terms of pathology, refractory respiratory failure in these patients could be caused mainly by pulmonary thrombosis. Pulmonary thrombosis will exhibit abnormal gas exchange, and thrombolytic agents could be a better alternative to promote necessary clot lysis [17]. Approved regimens for PE are recombinant tissue-type plasminogen activator (rtPA) or first-generation thrombolytic agents (streptokinase and urokinase) [16]. Alteplase is the only approved rtPA for acute PE. The third-generation thrombolytics, tenecteplase and reteplase, are approved for acute coronary syndrome but not for acute PE [16,18]. Compared with streptokinase, alteplase activates plasminogen on the clot surface and is classified as fibrin-specific [18]. This could be the reason why, in our case, thrombolytic therapy using streptokinase showed no clinical improvement. Nevertheless, this requires confirmation by solid evidence of efficacy and safety, especially for COVID-19 patients.

Strategies to mitigate severe inflammatory responses that could lead to lung injury and multiorgan dysfunction were implemented as well. Corticosteroids have shown lower 28-day all-cause mortality in critically ill patients with COVID-19 but have been associated with delayed virus clearance [2,19]. Tocilizumab, a recombinant humanized anti-IL-6-receptor monoclonal antibody, modulates IL-6, which is a pro-inflammatory cytokine produced by various cell types, and thereby alter the course of the disease. Ascorbic acid is an antioxidant and free-radical scavenger with anti-inflammatory properties that influences cellular immunity and vascular integrity. Vitamin D supplementation is based on its immunomodulatory effect, which could potentially protect against COVID-19 infection. Increased intracellular zinc concentrations efficiently impair RNA virus replication, but long-term supplementation can cause copper

deficiency [2]. Zinc can stimulate coagulation by potentiating platelet aggregation and fibrin clot formation, but it has secondary effects on the anticoagulant pathway and fibrinolysis, which dampen the procoagulant response.

Consequently, zinc serves as a regulatory switch in hemostasis [20]. Considering all of these factors, the benefits of therapies given need to significantly outweigh the potential risks. Finally, when there is suspicion of secondary bacterial infection or sepsis, empiric antimicrobial drugs must be given and re-evaluated daily until no bacterial infection is detected; only then can the antimicrobial drugs be de-escalated or stopped [2]. In the present case, although all intensive effort was made to control systemic inflammation and coagulopathy, the progression of CAC still occurred, and this explained the patient's final deterioration.

Conclusions

COVID-19-associated coagulopathy frequently occurs in severe COVID-19 infection. Progressive CAC will lead to massive thrombosis, multiorgan dysfunction, and increased mortality. Heparin has beneficial effects in treating CAC, but more studies are needed to assess the best approach to stop CAC progression. Because there is a high possibility of thromboembolism, thrombolytic drugs should be carefully considered in the management of critically ill COVID-19 patients. COVID-19 infection predisposes the patient to both arterial and venous thrombosis and can lead to multiorgan dysfunction and mortality.

Conflict of Interest

None.

References:

1. Ryalino C. How indonesia copes with coronavirus disease 2019 so far (part two): Is the country ready for the new norm? Bali J Anaesthesiol. 2020;4:89

2. Senapathi TGA, Ryalino C, Raju A, et al. Perioperative management for cesarean section in COVID-19 patients. Bali J Anaesthesiol. 2020;4(Suppl 1.):13-16

3. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-26

4. Ordi Ros J, Camprubi Sociats I, Ordi Q. Covid-19 infection and thrombosis. Int J Intern Emerg Med. 2020;3(2):1-5

5. Aggarwal M, Dass J, Mahapatra M. Hemostatic abnormalities in COVID-19: An update. Indian J Hematol Blood Transfus. 2020;36(4):1-11

6. Franchini M, Marano G, Cruciani M, et al. COVID-19-associated coagulopathy. Diagnosis (Berl). 2020;7(4):357-63

7. Miesbach W, Makris M. COVID-19: Coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clin Appl Thromb Hemost. 2020;26:1076029620938149

8. Iba T, Levy JH, Connors JM, et al. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):360

9. Marietta M, Coluccio V, Luppi M. COVID-19, coagulopathy and venous thromboembolism: More questions than answers. Intern Emerg Med. 2020;15(8):1375-87

10. Ibañez C, Perdomo J, Calvo A, et al. High D dimers and low global fibrinolysis coexist in COVID19 patients: what is going on in there? J Thromb Thrombolysis. 2021;51(2):308-12

11. Abou-Ismail MY, Diamond A, Kapoor S, et al. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020;194:101-15

12. Mucha SR, Dugar S, McCrae K, et al. Coagulopathy in COVID-19: Manifestations and management. Cleve Clin J Med. 2020;87(8):461-68

13. Maatman TK, Jalali F, Feizpour C, et al. Routine venous thromboembolism prophylaxis may be inadequate in the hypercoagulable state of severe coronavirus disease 2019. Crit Care Med. 2020;48(9):e783-90

14. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. J Thromb Thrombolysis. 2020;50(2):287-91

15. Turshudzhyan A. Anticoagulation options for coronavirus disease 2019 (COVID-19)-induced coagulopathy. Cureus. 2020;12(5):e8150

16. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603

17. Bornstein R, Páramo JA. Can fibrinolytic therapy be clinically useful in severe pneumonia caused by COVID-19? J Thromb Thrombolysis. 2020;51(3):633-36

18. Martin C, Sobolewski K, Bridgeman P, et al. Systemic thrombolysis for pulmonary embolism: A review. P T. 2016;41(12):770-75

19. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA. 2020;324(13):1330-41

20. Vu TT, Fredenburgh JC, Weitz JI. Zinc: An important cofactor in haemostasis and thrombosis. Thromb Haemost. 2013;109(3):421-30