Case report

A case of severe COVID-19 pneumonia with right common femoral vein thrombosis, positive lupus anticoagulant and low ADAMTS-13 level

Wichean Mongkonsritragoon[1] and Wimwipa Monkonsritragoon[2]

[1]Horizon Cancer Center, Department of Medicine, Bumrungrad International Hospital; [2]Department of Pediatrics, Faculty of Medicine, Chulalongkorn University

Abstract:

A Thai male, aged 58 years old presented respiratory symptoms, myalgia and acute fever. He had just returned from an endemic area of COVID-19 infection outside Thailand. He was diagnosed with pneumonia from SARS-CoV-2 virus confirmed by nasal swab real time PCR and CT-scan of chest. He was treated with darunavia, ritonavia, favipiravir, azithromycin, chloroquine and intravenous immunoglobulin (IVIg). He also received antibiotics (levofloxacin, meropenem, vancomycin) and antifungal agent (micafungin). The pneumonia improved determined from chest X-ray and respirator setting. During treatment, the patient developed deep vein thrombosis of the right common iliac vein and was treated with unfractionated heparin infusion. The investigations of thrombophilia found positive lupus anticoagulant and low ADAMTS-13 level. The patient developed sudden cardiac arrest which EKG showed prolonged QT with acute anterolateral wall infarction. He passed away after cardiopulmonary resuscitation failed.

Keywords : ● *COVID-19* ● *Lupus anticoagulant* ● *ADAMTS-13*

J Hematol Transfus Med. 2020;30:297-305.

Received 18 May 2020 Corrected 17 June 2020 Accepted 1 September 2020

Correspondence should be addressed to Assoc. Prof. Wichean Mongkonsritragoon, MD., Horizon Cancer Center, Department of Medicine, Bumrungrad International Hospital, Bangkok 10110

รายงานผู้ป่วย

ผู้ป่วยโคโรน่าไวรัส-19 พบการเกิดลิ่มเลือดในหลอดเลือดดำร่วมกับลูปัสแอนตี้โคแอ็กกูแลนท์ (Lupus anticoagulant) และระดับของอดัมส์ 13 (ADAMTS-13) ต่ำ

วิเชียร มงคลศรีตระกูล[1] และ วิมพ์วิภา มงคลศรีตระกูล[2]

ศูนย์มะเร็งฮอริซัน แผนกอายุรกรรม โรงพยาบาลบำรุงราษฎร์[1], ภาควิชากุมารเวชศาตร์ คณะแพทย์ศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย[2]

บทคัดย่อ

ผู้ป่วยชายชาวไทยอายุ 58 ปี มาพบแพทย์ด้วยอาการของระบบทางเดินหายใจ ปวดกล้ามเนื้อและไข้ หลังจากที่กลับจากพื้นที่ระบาดของโรคโควิดไวรัสจากต่างประเทศ ตรวจพบปอดอักเสบจากเชื้อ SARS-CoV-2 ไวรัสจากการป้ายสารคัดหลั่งหลังโพรงจมูกโดยเทคนิค real time PCR ร่วมกับการทำเอกซเรย์คอมพิวเตอร์ของปอด คนไข้ได้รับการรักษาด้วยยา darunavia, ritonavia, favipiravir, azithromycin, chloroquine และ intravenous immunoglobulin (IVIgG) ร่วมกับยาปฏิชีวนะ (levofloxacin, meropenem, vancomycin) และยาต้านเชื้อรา (micafungin) อาการปอดอักเสบดีขึ้นจากการตรวจด้วยเอกซเรย์ปอดและการตั้งค่าเครื่องช่วยหายใจ ระหว่างการดำเนินของโรคผู้ป่วยเกิดภาวะลิ่มเลือดอุดตันที่เส้นเลือดดำขาขวา (common iliac vein)และได้รับการรักษาด้วยยาเฮปาริน ผลการตรวจเลือดพบมีลูปัสแอนตี้โคแอกกูแลนท์ (lupus anticoagulant) และระดับของอดัมส์-13 (ADAMTS-13) ต่ำ ผู้ป่วยเกิดภาวะหัวใจหยุดเต้นเฉียบพลันโดยที่คลื่นหัวใจแสดง QT ยาวร่วมกับกล้ามเนื้อหัวใจขาดเลือดเฉียบพลัน (prolonged QT with acute anterolateral wall infarction) ผู้ป่วยเสียชีวิตหลังจากการกู้ชีพล้มเหลว

คำสำคัญ : ● *โควิท-19* ● *ลูปัสแอนตี้โคแอ็กกูแลนท์* ● *อดัมส์-13*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2563;30:297-305.

Introduction

The outbreak of pneumonia from a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, previously known as 2019-nCoV) first appeared in Wuhan, China in December 2019 and was later announced by the World Health Organization to be have reached pandemic level. Up until midMay 2020, a total of more than 4.4 million cases had been reported all over the world (1,430,348 cases in the USA, 271,095 cases in Spain, 252,245 cases in Russia, 229,705 cases in the UK and 222,104 cases in Italy), including 45,931 severe cases and 298,323 reported deaths. The relatively high infectivity, rapid progression of lung involvement and ongoing lack of definite effective treatment make it urgent to develop new antiviral agents, alternative medicine and vaccines. SARS-CoV-2 enters cells by endocytosis after binding to the transmembrane angiotensin converting enzyme-2 (ACE-2) protein on cells in the lungs, heart, blood vessels, kidneys and gastro-intestinal tract[1]. The diagnosis of COVID-19 is confirmed by a positive reverse transcriptase polymerase chain reaction (RT-PCR) from the nose, throat, sputum or broncho-alveolar lavage. The sensitivity of this test is suboptimal (50 to 80%), probably due to sampling error, low viral loads as well as timing of the sample in the disease course[2,3]. Among most patients with COVID-19, noncontrast chest CT scanning shows bilateral ground glass opacities with a peripheral and basal distribution. The sensitivity of CT imaging, not specificity, may be higher than the standard nasopharyngeal swab RT-PCR[4]. Many empirical therapeutic options have introduced several recommendations including chloroquine, azithromycin, some old antiretrovirals and also intravenous immunoglobulin (IVIg)[5].

Based on recent reports that have demonstrated a strong association between elevated D-dimer levels and poor prognosis, concerns have risen about thrombotic complications among patients with COVID-19. Up to 31% incidence of thrombotic complications among ICU patients with COVID-19 infection is remarkably high[6]. Some reinforce the recommendation to strictly apply pharmacological thrombosis prophylaxis among all patients with COVID-19 admitted to the ICU, and strongly suggest increasing the prophylaxis toward high prophylactic doses, even in the absence of randomized evidence. COVID-19 most likely causes a hypercoaguable state; however, the prevalence of acute venous thromboembolism remains an evolving area. D-dimer is a nonspecific acute phase reactant and limited data suggest pulmonary microvascular thrombosis may play a role in progressive respiratory failure. A report of three patients with COVID-19, evaluated for anti-phospholipid antibody,[7] detected anticardiolipin (aCL) IgA antibodies, anti-β_2-glycoprotein I IgA and IgG antibodies. However, lupus anticoagulant (LAC) was undetected in any of the patients. In contrast, an investigation from France during the recent COVID-19 outbreak in Mulhouse, studied 56 patients diagnosed with COVID-19 using polymerase chain reaction (n = 50) or chest computed tomography scan (n = 6), for the presence of LAC with dilute Russell's viper venom time and sensitive activated partial thromboplastin time tests. Twenty-five cases (45%) were LAC positive, whereas aCL or a β_2 glycoprotein I (β_2GPI) was detected in only 5 of 50 tested patients (10%, three related to LAC) using immunoglobulin G and immunoglobulin M detection. Acute infections are known to be sometimes associated with transient LAC, and anticoagulant therapy is usually unnecessary. Detecting LAC with or without aCL or β_2GPI among these critically patients, who are characterized by having many thrombosis risk factors, highlights the importance of an early anticoagulant therapy[8].

We reported a case of severe pneumonia from COVID-19 with very good response to darunavia, ritonavia, favipiravir, azithromycin, chloroquine and intravenous immunoglobulin (IVIg). Deep vein thrombosis of the right iliac vein was detected with positive LAC and low ADAMTS-13. He was complicated with myocardial infarction (MI) and passed away after unsuccessful resuscitation.

Case report

A 58-year-old Thai man with body weight 104 kg flew from England the previous day. He presented three to four days of sore throat, acute fever, myalgia and headache with productive cough. He had no underlying disease and did not smoke or consume alcohol. Physical examination showed no acute distress, no pallor and no jaundice but injected pharynx. He had no lymphadenopathy with clear breathing and normal heart sounds. The abdomen was soft with no hepatosplenomegaly, no mass and no tenderness. The patient presented normal neurological signs. Because of coming from an endemic area of COVID-19, he was then investigated and observed for this new virus infection. The chest X-ray showed mild interstitial opacity at left perihilar, left upper and lower lung zones and suspected infiltration with mild cardiomegaly (Figure 1).

Laboratory tests:

Hb 11.1 g/dL, Hct 33.3%, WBC 8.7 x10^9/L, PMN 8%, L 92%, Platelet 323 x10^9/L

Electrolyte, BUN/Creatinine, liver function test were within normal limit

Ferritin 3,085 ng/mL (25-370)

ESR > 130 mm/h (28/3), CRP 33.67 mg/dL (0-0.5)

Real-time PCR for novel coronavirus (nCo-V2): detectable

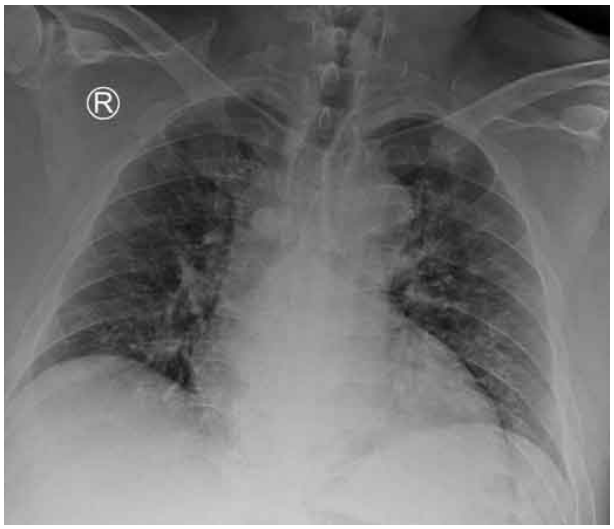

Figure 1 Chest X-ray on 17 March 2020: mild interstitial opacity at left perihilar, left upper and lower lung zone; suspected infiltration with mild cardiomegaly

Darunavia 600 mg oral twice a day and ritonavia 200 mg oral twice daily were started.

The next day of admission (18 Mar 2020), he still presented fever, more dyspnea, fatigue and showed bilateral rales on physical examination. The chest CT scan (Figure 2) showed multifocal ground glass opacity at the peripheral sides of both lungs with interlobular and interlobular septal thickening (crazy paving) in both

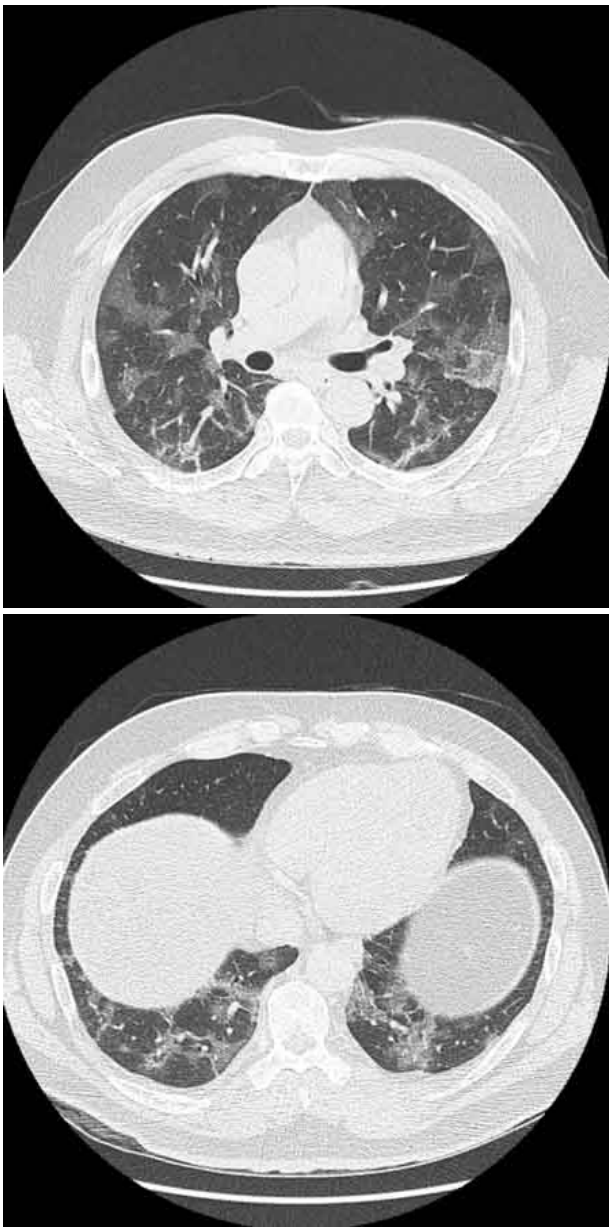

Figure 2 CT scan of chest 18 March 2020: Multifocal ground glass opacity at periphery of both lungs with interlobular and intralobular septal thickening (crazy paving) in both lower lobes. Mild peribronchial thickening was detected considering diffuse pneumonia. Few mediastinal lymph nodes were found, likely reactive node.

lower lobes. In addition, mild peribronchial thickening was detected, suggesting diffuse pneumonia. Few mediastinal lymph nodes were found, likely reactive nodes. The patient was transferred under observation in the ICU and favipiravir was started when available on the next day (19 May 2020). The patient still presented fever and levofloxacin was added on the night of 21 May 2020. Respiration still fluctuated, and chest X-ray gradually worsened. On 23 May 2020, the patient developed acute hypoxic respiratory failure with SpO2 91 to 96%. ET intubation was performed using full precautions with PPE and PAPR. He was pre-oxygenated for 5 minutes via mask with bag, O2 flow 10 LPM and sedated with midazolam 2 mg, propofol 100 mg then succinylcholine 200 mg intravenous. Full sedation and all life supports were used to maintain good oxygenation to prevent acute respiratory failure with ARDS from COVID-19 pneumonitis.

On that day our team inserted venous and arterial lines on the left leg and the right common iliac vein thrombus was found (Figure 3). Low molecular weight heparin (enoxaparin) was started.

The next day, urine output decreased and serum creatinine level increased from 1 to 3.5 mg/dL. Hemodialysis was initiated via right internal jugular vein and a hematologist was consulted to manage the thrombo-embolic event and anticoagulant. The enoxaparine was changed to intravenous unfractionated heparin and activated partial thromboplastin time was maintained about twice that of baseline. Anemia and thrombophilia were investigated. The CBC showed hemoglobin 11.2 g/dL, hematocrit 33.5%, WBC 8.7 $x10^9$/L neutrophil 8%, lymphocyte 92% and platelet count 323 $x10^9$/L. The peripheral blood smear did not demonstrate micro-angiopathic hemolytic anemia feature. LDH 425 mg/dL

Direct Coombs' test negative

D-dimer 87953 ng/mL (0-500)

APTT 38.3 second (25-36.6), PT 14.9 second (9.9 -12.4),

Fibrinogen 545 mg/mL

Immunoglobulin G 1241 mg/dL (540-1,822)

Immunoglobulin A 197 mg/dL (63-484)

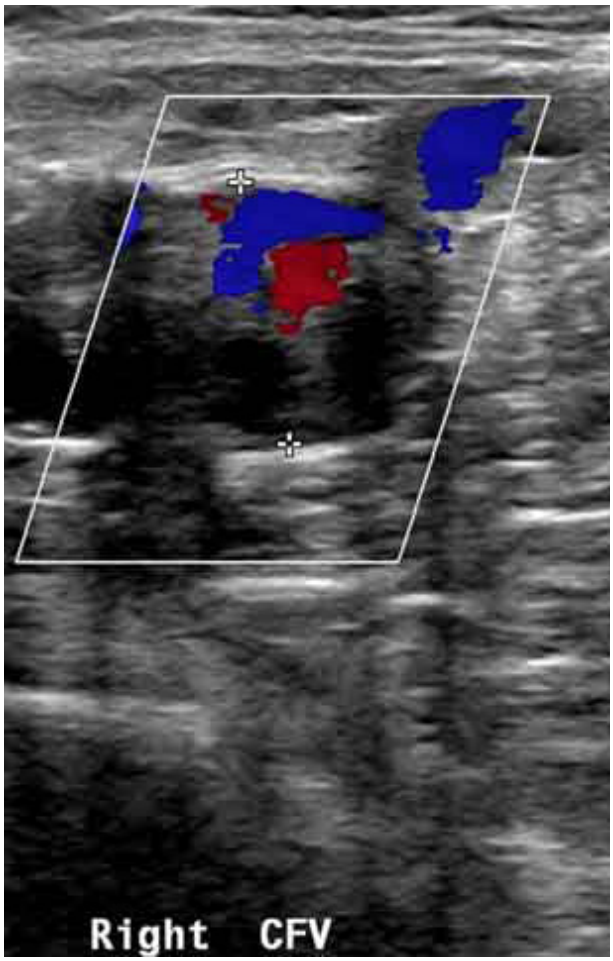

Figure 3 Doppler ultrasound of right leg showed acute deep vein thrombosis of the common femoral vein

Immunoglobulin M 132 mg/dL (22-240)

NT pro B-Natriuretic peptide 9486 pg/mL (0-300)

Toponin T 0.144 ng/mL (0-0.013)

Creatine Kinase MB Mass 0.37 ng/mL (0-6.22)

Doppler ultrasound of the right leg showed acute deep vein thrombosis of the right common femoral vein, causing partial venous obstruction

On 25 March 2020, anti-interleukin-6 receptor antibody (Actemra) 800 mg was injected intravenously.

On 26 March 2020, Interleukin 6 level was 319 pg/mL (0-7), and the clinical signs of ARDS did not improve, so our team decided to add intravenous immunoglobulin (IVIg) 400 mg/kg/d for 5 days.

ARDS conditions and respirator parameters gradually improved, commencing 27 March 2020. The chest X-ray showed significant improvement 28 March 2020. D-dimer decreased from 87,953 to 15,692 ng/mL, LDH dropped from 425 to 373 mg/dL, CRP reduced from 33.67

to 10.89 mg/mL and serum ferritin declined from 3,737 to 3,435 ng/mL. The blood showed Interleukin 6 level 1302 pg/mL (0-7) and positive for LAC with ADAMTS-13 (functional) level 18.0 U/dL (73-164) 29 March 2020.

From 26 to 30 March 2020, the patient's conditions gradually improved, but on the night of 30 March, the patient became unstable as EKG suddenly changed to ST elevation with prolonged QT interval rapidly progressing to severe bradycardia with hypotension. The chest X-ray appeared stable. CPR was unsuccessfully performed and the patient passed away. The clinical progression and treatment chart are showed in Figures 4 to 6

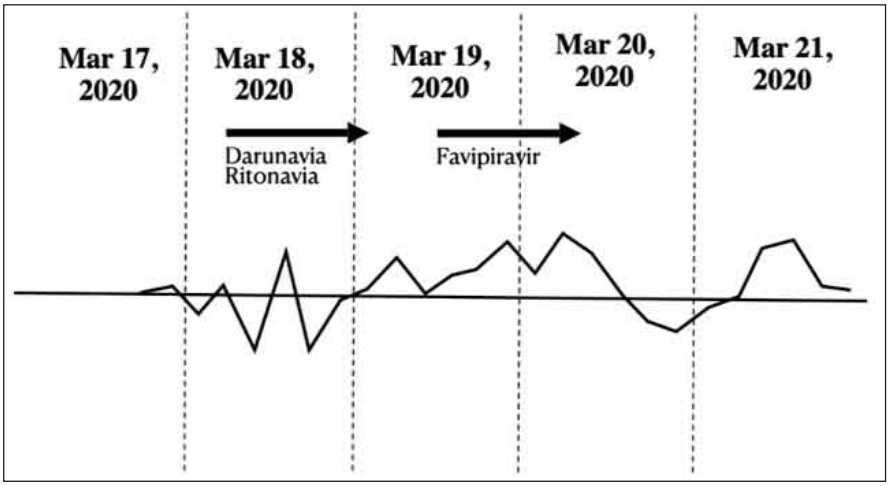

Figure 4 Clinical chart during 17-21 Mar 2020

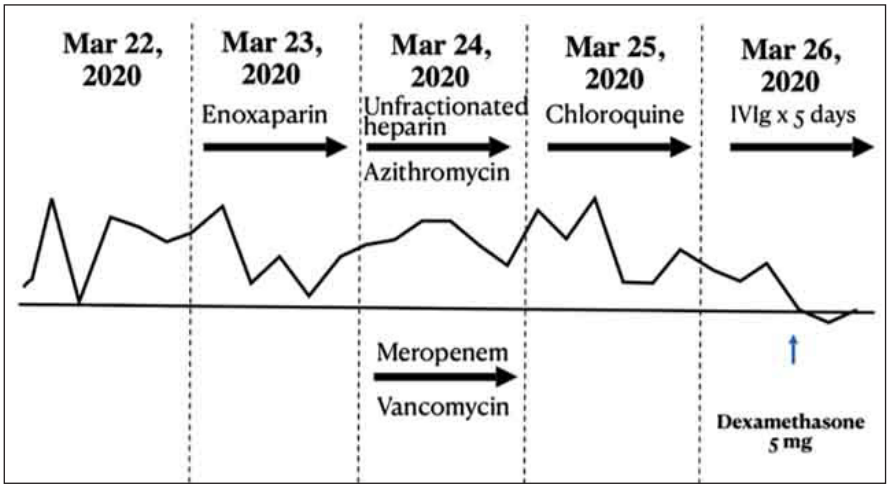

Figure 5 Clinical chart during 22-26 Mar 2020

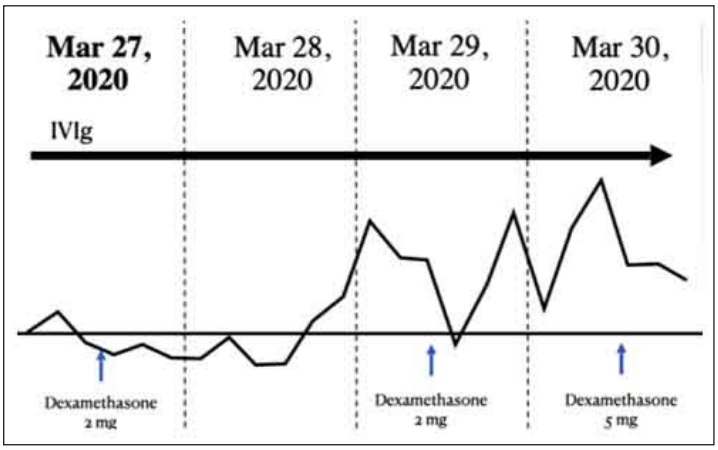

Figure 6 Clinical chart during 27-30 Mar 2020

Discussion

This constitutes a case of classical severe COVID-19 pneumonia wherein lung complications were significantly improved with multiple antiviral, chloroquine, azithromycin and IVIg.

IVIg was introduced for patients with COVID-19 because it has been used successfully among patients with SARS[9], MERS[10] and pandemic influenza infection[11,12]. Among those who rapidly progressed to critical conditions, reduced peripheral lymphocyte count and elevated inflammatory factors were observed, indicating an overwhelming immune response[13,14]. Previous experiences with SARS showed that the main pathogenesis of organ dysfunction lay in the overall cytokine dysregulation. A report by Yun Xie et al. (1) regarding effects of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia included 58 patients with a diagnosis of severe COVID-19. Twenty-three (39.6%) critically ill patients died within 28 days. All patients were treated with IVIg within 48 hours of admission. Not only was ventilator use reduced, but also hospital and ICU length of stay decreased, ultimately improving 28-day mortality.

Concerning thrombotic phenomena found in COVID-19, one report of 184 patients in three Dutch hospitals[6] evaluated incidence of the composite outcome of symptomatic acute pulmonary embolism (PE), deep vein thrombosis, ischemic stroke, MI, or systemic arterial embolism of patients with COVID-19 admitted to the ICU. All patients received at least standard doses of thromboprophylaxis, and cumulative incidence of thrombosis was 31%. PE, the most common thrombotic complication, was observed among 25 patients (81%). Some reports found increased positive LAC in COVID-19. From a report of 216 patients with SARS-COV-2, 20% had a prolonged APTT[15]. Demographic characteristics of the patients involved included mean age 57 years, 71% were male involving one case of PE and clinical suspicion of thrombosis. In all, 35 patients underwent the evaluation. None presented factor VIII and IX deficiency, 5 exhibited a marginal reduction in factor XI but without clinical significance, 16 patients showed reduced factor XII levels and 31/34 patients (91%) were positive for LAC. Some case reports demonstrated immune thrombotic thrombocytopenia purpura (iTTP) among patients with COVID-19. In our case, no TTP features were found in peripheral blood smear but the patient showed positive LAC with low ADAMTS-13 level. One report demonstrated complement-associated microvascular injury and thrombosis in the pathogenesis of COVID-19 infection[16]. Their demonstration of the striking deposition of C5b-9, C4d and MASP2 in the microvasculature of two organ systems was consistent with profound and generalized activation of both alternative and lectin-based pathways. It provided a foundation to further explore the pathophysiologic importance of complement in COVID-19, and could suggest targets for specific interventions. SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lungs, heart, kidneys and intestines. ACE2 receptors are also expressed by endothelial cells[17]. Whether vascular derangements in COVID-19 are due to endothelial cell involvement by the virus remains currently unknown. Intriguingly, SARS-CoV-2 can directly infect engineered human blood vessel organoids in vitro[18]. Additionally, endothelial cell involvement (also call endotheliitis) was observed across vascular beds of different organs in a series of patients with COVID-19.

The possibility of thrombo-embolic events involving COVID-19 should be multifactorial. The first may be because immune dysfunction causes positive anticoagulant. The second may be from vascular injury to the viral infected particle itself. A third possibility could be the vascular injury may cause low ADAMTS-13 because endothelial cells produce and secrete ADAMTS-13 in blood circulation[19].

Our patient likely expired because of cardiac complication leading to cardiac arrest. The electrocardiogram showed acute anterolateral wall infarct with prolonged QT and marked bradycardia. Disruption of the angiotensin converting enzyme-2 receptor might have be a possible cause leading to cardiomyopathy, cardiac dysfunction and heart failure. Literature exploring cardiac involvement in SARS-CoV-2 is expanding. Myocardial injury is one of the important pathogenic features of COVID-19. As a surrogate for myocardial injury, multiple studies have shown increased cardiac biomarkers mainly cardiac troponins I and T among infected patients especially those with severe disease. Myocarditis is depicted as another cause of morbidity among COVID-19 patients. The exact mechanisms of how SARS-CoV-2 can cause myocardial injury are not clearly understood. Disruption of ACE-2 leads to an age-dependent cardiomyopathy, cardiac dysfunction and heart failure[20,21]. Oudit et al. hypothesized that the interaction between SARS-CoV and ACE-2 in the heart could contribute to SARS-mediated myocardial inflammation and damage. They reported that the SARS-CoV viral RNA was detected in autopsied human heart samples suggesting direct myocyte invasion of the virus. They further indicated marked downregulation of ACE-2 and reduced ACE-2 protein in the heart samples. Moreover, they reported significant myocardial macrophage infiltration of postmortem heart samples[22]. The detrimental effect of ACE-2 downregulation would impede cardioprotective effects of angiotensin 1 to 7 leading to increased TNF-α production[20,23]. TNF-α is a common inflammatory cytokine and many researchers have shown that the inflammatory response may be at least partially responsible for the myocardial damage[24].

Another possibility of cardiac event in this case might be thrombotic event from hypercoagulable stage or arrhythmia triggered from many kinds of medicine. Medicines which can cause QT prolong include chloroquine, azithromycin, antiretrovirals and others.

Conclusion

This patient with COVID-19 presented severe pneumonia complicated with deep vein thrombosis on the right common iliac vein which may have been induced by the immunologic process of LAC and low ADAMTS-13 level. The pneumonia indicated a very good response to antiretrovirals and IVIgG therapy. The patient developed an acute cardiac event with undetermined definite cause. The virus particle itself, the thrombo-embolic event or drug induced arrhythmia might have been the possible cause.

References

1. *Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen KY, Wang Q, Zhou H, Yan J, Qi J. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell 2020; https://doi.org/10.1016/j.cell.2020.03.045. Published April 9, 2020.*
2. *Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020; doi: 10.1001/jama.2020.3786. Published March 11, 2020.*
3. *Xu H, Yan L, Qiu CM, Jiao B, Chen Y, Tan X, et al. Analysis and prediction of false negative results for sars-cov-2 detection with pharyngeal swab specimen in covid-19 patients: a retrospective study. MedRxiv 2020; doi: https://doi.org/10.1101/2020.03.26.20043042. Published March 30, 2020.*
4. *Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020;200642. doi: 10.1148/radiol.2020200642.*
5. *Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patient with COVID-19. J Infect. 2020 Apr 10; S0163-4453(20)30172-9.*
6. *Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critical ill ICU patients with COVID-19. Thromb Res. 2020, 191:145-7.*
7. *Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. N Engl J Med. 2020 Apr 23;382(17):e38. Epub 2020 Apr 8*
8. *Harzallah I, Debliquis A, Drénou B. Lupus anticoagulant is frequent in patients with Covid-19. J Thromb Haemost. 2020 Apr 23:10.1111/jth.14867. doi: 10.1111/jth.14867. Epub ahead of print. PMID: 32324958; PMCID: PMC7264773*

9. *Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006 Sep;3(9):e343. doi: 10.1371/journal.pmed.0030343. PMID: 16968120; PMCID: PMC1564166.*
10. *Mustafa S, Balkhy H, Gabere MN. Current treatment options and the role of peptides as potential therapeutic components for Middle East Respiratory Syndrome (MERS): A review. J Infect Public Health, 2017;11:9-17.*
11. *Rockman S, Lowther S, Camuglia S, Vandenberg K, Taylor S, Fabri L, et al. Intravenous immunoglobulin protects against severe pandemic influenza infection. EBioMedicine. 2017;19:119-27.*
12. *Hung IFN, To KKW, Lee CK, Lee KL, Yan WW, Chan K, et al. Hyperimmune IV Immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza a(h1n1) infection. Chest, 2013,144:464-73*
13. *Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.*
14. *Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-33.*
15. *Bowles L, Platton S, Yartey N, Dave M, Lee K, Hart DP, et al. Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19. N Engl J Med. 2020 May 5:NEJMc2013656. doi: 10.1056/NEJMc2013656. Epub ahead of print. PMID: 32369280; PMCID: PMC7217555*
16. *Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe Covid-19 infection: a report of five cases. Transl Res. 2020 Jun;220:1-13. doi: 10.1016/j.trsl.2020.04.007. Epub 2020 Apr 15. PMID: 32299776; PMCID: PMC7158248*
17. *Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111:2605-10.*
18. *Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 2020 May 14;181(4):905-913.e7. doi: 10.1016/j.cell.2020.04.004. Epub 2020 Apr 24. PMID: 32333836; PMCID: PMC7181998.*
19. *Gaultier A, Cousin H, Darribere T, Alfandari D. ADAM13 disintegrin and cysteine-rish domains bind to the second heparin-binding domain of fibronectin. J Bio Chem. 2002;277:23336-44.*
20. *Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, et al. Angiotensin- converting enzyme 2 is an essential regulator of heart function. Nature. 2002;417:822-8.*
21. *Yamamoto K, Ohishi M, Katsuya T, Ito N, Ikushima M, Kaibe M, et al. Deletion of angiotensin- converting enzyme 2 accelerates pressure overload-induced cardiac dysfunction by increasing local angiotensin II, Hypertension. 2006;47:718-26.*
22. *Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Investig. 2009;39:618-25.*
23. *Oudit GY, Kassiri Z, Patel MP, Chappell M, Butany J, Backx PH, et al. Angiotensin II-mediated oxidative stress and inflammation mediate the age-dependent cardiomyopathy in ACE2 null mice, Cardiovasc. Res. 2007;75:29-39.*
24. *Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiol. 2020 Mar 27:e201017. doi: 10.1001/jamacardio.2020.1017. Epub ahead of print. PMID: 32219356; PMCID: PMC7101506.*