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Case Report

A unique tale of COVID-19 induced concomitant overt disseminated intravascular coagulation and acute bilateral pulmonary embolism

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), a novel coronavirus, originated as an epidemic respiratory illness in Wuhan, China. COVID-19 eventually spread to almost all countries and has now been declared a global pandemic disease by the World Health Organisation. A plethora of research has explored the dynamics of different clinical entities related to SARS-COV-2, in particular, COVID-19 associated coagulopathy. A large scale of patients have been reported to have developed pulmonary embolism without any other standard triggers or risk factors, leading to speculation that COVID-19 is an independent risk factor for venous thromboembolism.

In addition to the development of thromboembolic complications such as pulmonary embolism, COVID-19 has also been reported to have triggered disseminated intravascular coagulation (DIC); however, it is unclear whether pulmonary embolism was due to COVID-19-induced thrombosis or a result of coagulopathy secondary to DIC.

We describe a unique case of a COVID-19 associated coagulopathy in a patient with confirmed pulmonary embolism along with an overt DIC. Following diagnosis, the challenge was to identify the appropriate treatment modality for this unique situation. The patient was treated with anticoagulants and steroids along with blood products. The patient's condition markedly improved and was clinically stable on discharge.

Case presentation

A priority call was initiated in the emergency triaging area when paramedics brought in a 65-year-old woman with an oxygen saturation of 65% on room air. She was given full flow oxygen at 15 L through a non-rebreathing mask, which elevated her saturation to 92–95%. Upon stabilising the patient, history revealed that she had been experiencing viral prodrome for the past 7 days. Her symptoms were primarily fever, chest pain, cough with clear expectoration, and intermittent shortness of breath on exertion. She had been monitoring her oxygen saturations at home and noted them to be approximately 60–65% on room air. She had no gastrointestinal symptoms nor smell/taste alterations that are common with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV2). Her past medical history included Type II Diabetes Mellitus and she was taking oral hypoglycemics. She reported being otherwise fit and well and a non-smoker.

During a general examination, the patient was noted to have pleuritic sounding chest pain and was markedly dyspnoeic, tachycardic and tachypnoeic, and had an oxygen saturation of 92–95% on a 15 L non-rebreathing mask. She was unable to speak in full sentences due to breathlessness. Auscultation during chest examination revealed pleural rub along with bi-basal crackles without any wheeze. Other systemic examinations were normal. A 12 lead electrocardiogram showed a right bundle branch block (RBBB) with sinus tachycardia (Figure 1). A bedside echocardiogram ruled out right ventricular strain. Arterial blood gas showed hypoxic respiratory failure.

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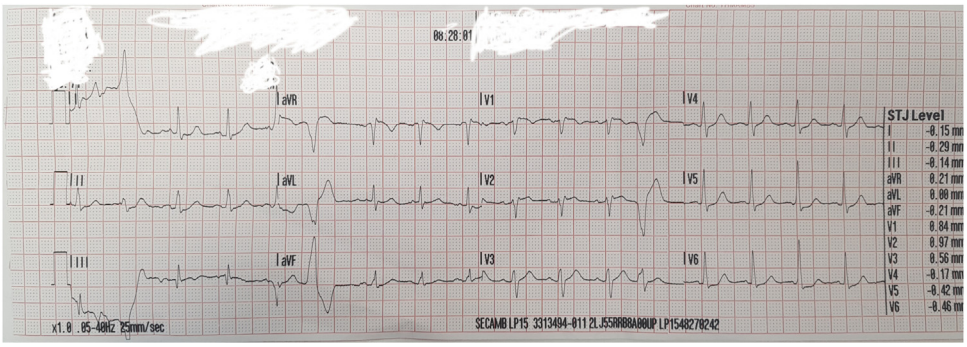

Figure 1. ECG showing sinus tachycardia with right bundle branch block and ectopics.

Investigations

Blood results showed a deranged clotting screen with a prothrombin time (PT) of 65 s (12–16 s), an activated partial thromboplastin time (APTT) of 105 s (22–35 s), and fibrinogen level of 1.6 g/L (1.9–4.3 g/L). She had a haemoglobin level of 140 g/L (110−150 g/L) with an elevated white cell count of 12.4 × 10^9/l (4.0−11 × 10^9/l) showing marked lymphopenia at 0.6 × 10^9/l (1.5–4.0 × 10^9/l). Her platelet count was 32 × 10^9/l (150–400,10^9/l) and the D-dimer level was elevated at 6.35 mg/L. C-reactive protein (CRP) was 125 mg/L (0.0−10 mg/L). Her liver and renal function were unremarkable. Her International Society of Thrombosis and Haemostasis disseminated intravascular coagulation (DIC) score was 6. The prolongation of clotting factors makes the case for an overt DIC. Her chest x-ray revealed bilateral opacities with prominent right pulmonary trunk highly suspicious for COVID-19 pneumonitis (Figure 2). These symptoms and signs such as pleuritic chest pain, tachycardia, and shortness of breath along with an elevated D-dimer level placed her Wells score for pulmonary embolism (PE) at 4.5, prompting a CT Pulmonary Angiogram which revealed bilateral ground-glass opacities along with bilateral pulmonary embolism as the diagnosis (Figures 3 and 4).

The working diagnosis for the patient was that she had bilateral PE and an overt DIC. The patient had no previous history or other risk factors for thromboembolic disorders other than COVID-19 and has no family history of similar ailments.

Treatment

The patient was treated with therapeutic Low Molecular Weight Heparin (LMWH) at a 50% dose reduction after discussion with haematology. Initially, no blood products were transfused as she was continuously clinically monitored and had no signs of any active bleeding. However, further blood tests revealed that her platelet count had a progressive decline from 32 × 10^9/l to 18 × 10^9/l (repeated 6 h post initial baseline platelet count), which

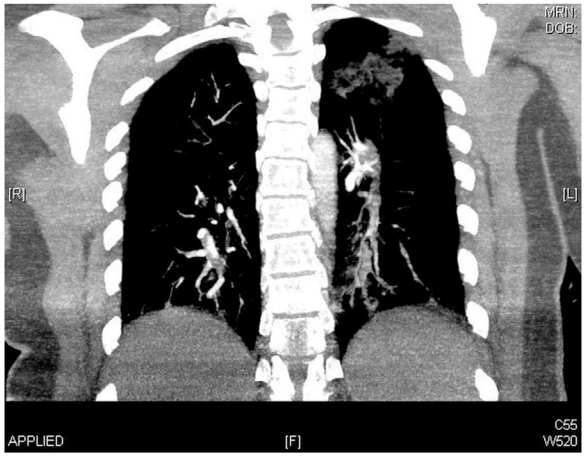

Figure 3. CT-pulmonary angiogram demonstrating bi-lateral pulmonary embolism.

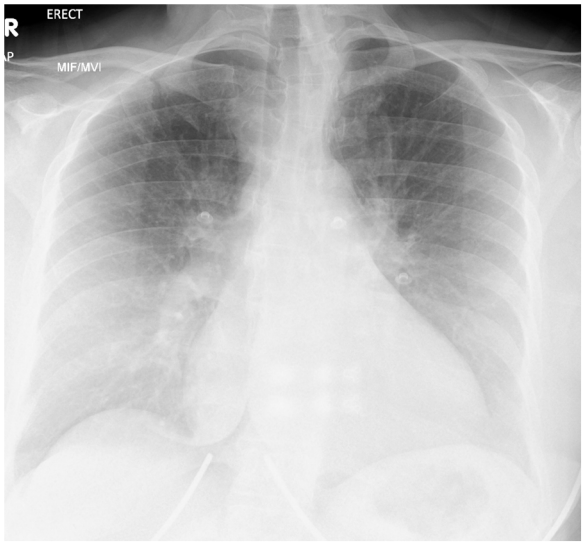

Figure 2. X-Ray chest revealing bi-lateral opacities with prominant right pulmonary trunk.

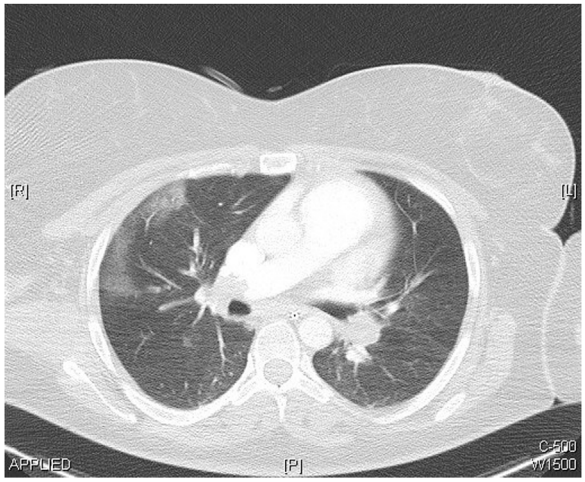

Figure 4. CT-pulmonary angiogram demonstrating ground glass opacities suggestive of COVID-19 pneumonitis.

subsequently dropped to 8 × 10^9/l (repeated 3 h after the second blood sample was taken to follow up platelet count), still without any bleeding manifestations. Though she was not clinically bleeding, she was transfused with 1 unit of single donor platelet as clinically mandated. This elevated her platelet count to 52 × 10^9/l, which remained relatively stable for the duration of her hospital stay and rose to 212 × 10^9/l on the day of her discharge with normalisation of the clotting screen. Her anti-coagulation dose was increased to the full therapeutic dose (1.5 mg/kg body weight) on the third day of treatment as her platelet count remained above 50 × 10^9/l after 1 unit platelet apheresis. Her D-dimer level came down to 0.35 mg/L on the day of discharge (after 9 days of treatment in the hospital). Her blood levels were regularly monitored throughout her hospital stay.

Supplementary oxygen was provided as needed and titrated according to the patient's oxygen needs. Antibiotics were administered as the patient's infective markers were elevated and in order to provide cover for any secondary bacterial infections. Oral dexamethasone 6 mg was prescribed once a day for the duration of her hospital stay. Non-invasive ventilation requirements were negligible as she improved clinically. She was given chest physiotherapy and received regular input from the nutritionist to maintain optimal nutritional status.

After 9 days the patient was discharged following her improved clinical condition with improved breathing and blood parameters. The patient declined to participate in any of the ongoing national recovery trials.

Discussion

We will discuss the factors that led to the development of DIC and PE. The pathophysiology of a PE with a concomitant DIC has been explored in non-COVID-19 patients. However, limited studies explore this phenomenon in patients where coagulopathies are triggered by COVID-19. Coagulopathy remains a very common biochemical picture, with features of elevated D-dimer/fibrin degradation product/fibrin alongside prolongation of PT/APTT and low platelet/fibrinogen, when COVID-19 induced DIC develops, with a more frequent tendency to form clots in the pulmonary arteries (Jean and Levy, 2020; Sakr et al., 2020). Approximately 2.6%–8.9% of hospitalised patients have concomitant PE with higher rates for patients in intensive care units (ICU) despite standard prophylactic anticoagulation treatment (Sakr et al., 2020). COVID-19 triggered thrombotic disorders are likely a consequence of the viral infection causing complement activation, cytokine release, and endothelial dysfunction, however, the mechanism is yet to be proven (Gian et al., 2020).

Although no conclusive evidence exists for coagulopathy in COVID-19, it is postulated that the 3 major contributing factors are endothelial injury, stasis, and hypercoagulability (Virchow's Triad) (Jean and Levy, 2020; Leisman et al., 2020; Prakash et al., 2020; Sakr et al., 2020). The endothelial injury occurs secondary to viral penetration of endothelial cells, resulting in cytokine release and its subsequent effect on vascular endothelium (Gaertner and Massberg, 2016; De Lorenzo et al., 2020). This is followed by the release of Von-Willebrand Factor (vWF) by the endothelial cells (Gaertner and Massberg, 2016; De Lorenzo et al., 2020). The endothelial cells are key for viral entry as they contain angiotensin-converting enzyme 2 receptor along with Protease 2 and Sialic Acid receptor (Gaertner and Massberg, 2016; De Lorenzo et al., 2020).

Following the endothelial cell injury, pro-inflammatory cytokines promote vascular endothelial cell apoptosis causing vascular leakage, alveolar oedema and hypoxia (De Lorenzo et al., 2020). Studies have shown that COVID-19 confirmed patients have a marked increase in pro-inflammatory markers such as interleukin (IL)2, IL6, IL7, IL8, granulocyte-colony stimulating factor, interferon gamma induced protein 10, monocyte chemotactic protein-1, macrophage inflammatory protein 1A and tumour necrosis factor alpha (Sakr et al., 2020). These markers give rise to a haemophagocytic lymphohistiocytosis with activation of blood coagulopathy eventually resulting in micro thrombus formation (Sakr et al., 2020). Subsequent exocytosis of ultra-large vWF bodies in the endothelial cells and insufficient ADAMTS13 results in endothelial injury (Varatharajah and Rajah, 2020). This phenomenon of increasing pro-inflammatory markers has been confirmed by a study undertaken in Wuhan which showed elevated markers in ICU patients compared to non-ICU patients (Huang et al., 2020). In Virchow's triad, the hypercoagulable state is brought about by a variety of factors such as hypoxia, DIC etc. Hypoxia raises the blood viscosity through the hypoxia-inducible transcription factor-dependent signalling pathway (Sakr et al., 2020). While IL6 has been regarded as the potential cause for endothelial injury, the abnormal activation of the clotting cascade results in a hypercoagulable state (Kerr et al., 2001). Various blood cell interactions play a critical pro-coagulant role (Sakr et al., 2020), for example, platelet activation upon antigen recognition may facilitate the clearance of the pathogen by white blood cell activation resulting in clot formation (Giannis et al., 2020; Sakr et al., 2020). Another theory proposed is that neutrophil extracellular traps induced by platelets can play a role in sepsis-associated hypercoagulopathy (Sakr et al., 2020; Zucoloto and Jenne, 2019). Poissy et al. reported 20.6% of patients admitted to a French ICU had PE within 6 days of ICU admission despite anticoagulation treatment (Poissy et al., 2020). One French observation study involving 2 hospitals reported 16.7% of patients developing PE despite thromboprophylaxis (Helms et al., 2020).

DIC, along with other thrombotic disorders, manifests as one of the most common biochemical abnormalities associated with COVID-19. A study in Wuhan, China reported that approximately 71.4% of COVID-19 non-survivors and 0.6% of survivors met the DIC criteria during their hospital stay (Ning et al., 2020).

The mechanism of evolution of the DIC in COVID-19 is not conventional as it is often associated with elevated D-dimer level and a relatively lower degree of thrombocytopenia. Two studies found that only 5% of non-COVID-19 patients with DIC showed marked thrombocytopenia (<100 × 10^9/l) whereas 70–95% had a platelet count between 100 × 10^9/l and 150 × 10^9/l (Guan et al., 2020; Huang et al., 2020). In addition to thrombocytopenia, the elevated D-dimer level could also stem from the pronounced inflammation caused by COVID-19, thereby activating coagulation pathways. This activation of coagulation pathways is demonstrated by the following studies. A study by Tong et al. demonstrates an elevation of fibrinogen levels in COVID-19 pneumonia patients on admission to hospital (Ning et al., 2020). A targeted study by Ranucci et al. on 16 COVID-19 patients with Acute Respiratory Distress Syndrome on mechanical ventilation reported elevated fibrinogen and D-dimer levels along with increased levels of IL6 (Ranucci et al., 2020). As this study explores the correlation between IL6 and fibrinogen, it helps us to understand the link between inflammation and pro-coagulant changes. A higher level of D-dimer and a relatively lower degree of thrombocytopenia perhaps explains the reason for more predominant thromboembolic events compared to bleeding tendency (Sakr et al., 2020).

In our case study, clinically apparent bleeding was not observed in the patient even though the blood values would have indicated otherwise. D-dimer is highly sensitive (more than 266 mcg/L) but not specific for identification of PE in COVID-19 patients (Sakr et al., 2020). Although elevated D-dimer levels are not specific for thromboembolic events like PE, Cui et al. have demonstrated that a D-dimer value of 3.0 mcg/mL is a predictor of venous thromboembolism (VTE) (sensitivity, specificity and negative predictive values of 76.9%, 94.9% and 92.5% to predict VTE respectively) (Cui et al.,

2020). Another mechanism is that cellular activation triggered by viruses causes D-dimer elevation which is a true reflection of thrombosis (Sakr et al., 2020). Mortality is almost 18 times higher in patients with a mean D-dimer level of 1 mcg/L . A study in China of 183 patients reported a mean D-dimer of 0.6 mcg/L in COVID-19 survivors compared to 2.12 mcg/L among non-survivors (Ning et al., 2020). The D-dimer levels decrease consistently when treated with anticoagulants.

Other factors to discuss are the elevated PT and APTT levels along with low fibrinogen that is often noted in COVID-19 triggered DIC. In conventional DIC, the values of PT and APTT can be elevated and the fibrinogen levels low. However, these values can also be normal due to the presence of circulating activated clotting factors like thrombin and Factor 10a which accelerate thrombin formation (Levi et al., 2009). One study found that approximately 57% of patients with non-COVID triggered DIC had normal fibrinogen levels (Levi et al., 2009)

This case study is unique in that the patient developed both PE and overt DIC simultaneously with more pronounced thrombocytopenia than is usually observed in patients with COVID-19. This warranted devising new treatment protocols. Treatment for any major bleeding with tachycardia (heart rate >110 beats/min) and decreased blood pressure (systolic <90 mm hg) is to give blood products or they may be given before any invasive procedure (Levi et al., 2009). Conventional wisdom dictates that a transfusion of blood products is essential based on clinical values and parameters even when the patient is not actively bleeding. Fresh frozen plasma (FFP) can be prescribed at an initial dose of 12−15 mL/kg (4 units for 1 adult and 1 bag for every 20 kg of body weight) (Levi et al., 2009). Further FFP requirements will depend on the follow-up PT levels (may be given if follow up PT/INR is above 1.5 or APTT above 1.5) (Levi et al., 2009). Usually, 4 units transfusion can raise fibrinogen levels to 1 g/L (Levi et al., 2009). If there is actively bleeding and fibrinogen levels are below 1.5 g/L it can also be replaced by cryoprecipitate (2 cryoprecipitates or as 3 g concentration) (Levi et al., 2009). For non-bleeding patients we aim to transfuse platelets if the count is 10,000–20,000, for actively bleeding patients the threshold is <50,000 (Levi et al., 2009). If indicated, 1 platelet apheresis should be provided and later will depend upon the response.

Further treatment is by anticoagulation with therapeutic dose LMWH. This is based on the bleeding status and platelet count of the patient. If the patient is not actively bleeding and the platelet count is above 50 × 10^9/l a full dose of LMWH is prescribed according to body weight (Mariasanta et al., 2018). However, if the patient is bleeding and the platelet count is between 30 × 10^9/l and 50 × 10^9/l then a dose reduction of 50% should be considered for LMWH (Mariasanta et al., 2018). If the platelet count is well below 30 × 10^9/l then a prophylactic dose of LMWH is given. However, clinicians should be wary of this situation as an actively bleeding patient at 30 × 10^9/l platelets may require urgent transfusions and an inferior vena cava filter insertion by the interventional radiologist (Mariasanta et al., 2018). Other than LMWH, in a hospital setting, unfractionated heparin can be considered as it has a very short half-life and efficient reversibility (Levi et al., 2009). Weight adjusted dose (10 mcg/kg/hr) has also been suggested without the intention of prolonging APTT ratio to 1.5–2.5 times the control (Levi et al., 2009). A usual prophylactic dose of LMWH/heparin is recommended for VTE prophylaxis for patients who have no active thromboembolic disorders.

Conflict of interest

No conflict of interest amongst the authors.

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Ethical approval

No ethical approval required.

Informed consent

Written informed consent for the paper to be published (including case history, image) was obtained from the patient.

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