COVID-19 Associated Coagulopathy In The Setting of Underlying Malignancy

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Case Report

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Abstract

Coronavirus Disease 2019 (COVID-19) associated coagulopathy is growingly recognized as the predictor for morbidity and mortality in COVID-19 patients. Deep vein thrombosis (DVT) and pulmonary embolism (PE) have been increasingly observed in COVID-19 patients. Nonetheless, there are no consensus guidelines on the use of therapeutic coagulation in this group of patients. We herein presenting a unique case of a COVID-19 patient with metastatic ovarian cancer who presented with DVT/PE despite being on therapeutic anticoagulation, highlighting the unpredictability of COVID-19 associated coagulopathy. This is to raise the awareness that thrombophilic state in metastatic malignancies is potentially augmented by COVID-19. We also discussed the complexity of making anticoagulation treatment decision in COVID-19 patients in the absence of evidence-based guidelines.

Introduction

Coronavirus Disease 2019 (COVID-19) has reached a global public health emergency with more than 4.2 million cases and 290,000 deaths reported worldwide as of May 14th, 2020 [1] . COVID-19 has multifaceted presentations with close to 70-80% of patients who are asymptomatic or only present with mild symptoms [2]. COVID-19 associated coagulopathy is growingly recognized as the predictor for morbidity and mortality in COVID-19 patients. To our knowledge, there are still no consensus guidelines on the management of this group of patients including the choice of anticoagulation, the specific cut off for D-dimer, fibrinogen or coagulation markers, the duration of treatment and follow up recommendations. Majority of the data was on the severe COVID-19 patients with exuberant inflammatory response associated with complications related to cytokine storm or hyperinflammatory phase but not much data on asymptomatic or mild disease, which comprised the majority of the patients. We herein report a case of a 60-year-old female with metastatic ovarian cancer who tested positive for COVID-19 RT-PCR, developed deep vein thrombosis (DVT) and pulmonary embolism (PE) on Day 15 of the COVID-19 despite being on therapeutic anticoagulation with Apixaban 5mg BID as outpatient and low molecular weight heparin as inpatient. This highlights the important of aggressive therapeutic anticoagulation in COVID-19 patients with active malignancy and further raises the discussion on the choice of anticoagulation in this group of patients.

Case Report

A 60-year-old female with a past medical history of Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) diagnosed 8 months ago, who was on apixaban 5 mg twice daily. She was newly diagnosed with metastatic ovarian cancer with peritoneal carcinomatosis and tested positive for COVID-19. She was readmitted two days after discharge presented with failure to thrive, constipation and abdominal distention. Initial vital signs on admission showed temperature 98.2 °F, blood pressure 123/86 mmHg, tachycardia with heart rate 121/min, respiratory rate normal 18/min and she was saturating 99%

on room air. Her BMI was 22.3 kg/m2. Complete blood count showed WBC 8.3 x 10*3/uL, platelets 359, PTT 33.7, PT 14.4, and Procalcitonin 0.1 ng/mL (0-0.5 ng/mL). EKG shows sinus tachycardic with left axis deviation. CXR shows bilateral pleural effusion with bibasilar atelectasis. Her CT angiogram (CTA) done on previous admission (April 20th, 2020) showed no evidence of pulmonary embolism, with moderate bilateral pleural effusion, multiple pulmonary nodules and 15mm right pleural mass which may represent metastatic disease with axillary and hilar lymphadenopathy. Paracentesis was done which showed metastatic carcinoma immunophenotypically consistent with ovarian origin. Her inflammatory markers on last admission were: D-dimer 5329 ng/ml (0-500 ng/ml), fibrinogen 530 mg/dL (200-393 mg/dL), LDH 569 U/L (122-222 U/L), CRP 17.5 mg/dL (0-0.8 mg/dL), ferritin 829.3 ng/mL. D-dimer decreased to 1859 ng/ml on present admission, ferritin 852.8 ng/mL, LDH 587 U/L, CRP 13.8 mg/dL. She received therapeutic enoxaparin 60mg every 12 hours during the hospital course in light of history of DVT/PE. She was doing well, and inflammatory makers were trending down. On Day 8 of admission (Day 15 of COVID-19 symptoms), D-dimer was trending up to 7786 ng/ml. In addition, she has persistent tachycardia with increase oxygen requirement. Although she was already on anticoagulation, but in light of multiple comorbidities and COVID-19 associated coagulopathy, repeat CTA was performed and showed pulmonary emboli throughout the right lung, with the greatest clot burden at the right middle lobe, in addition to wedge-shaped opacities at the right middle lobe, which may represent developing pulmonary infarction. Venous doppler was performed and showed acute DVT in both lower extremities. Echocardiogram showed left ventricular ejection fraction (LVEF) 50-55%, right ventricle was moderately hypokinetic, moderate pulmonary hypertension, along with interventricular septal flattening, suggestive of right ventricular strain from pulmonary embolism. IVC filter was placed and she was discharged to subacute rehab center with apixaban and will continue palliative chemotherapy on carboplatinum and paclitaxel as outpatient.

Discussion

Venous Thromboembolism is common in acutely ill COVID-19 patients despite the use of prophylactic anticoagulation. It was reported that about 20-43% of VTE, mostly PE developed in ICU patients [3–5]. Data are limited for inpatients admitted to regular medical floor. The pathophysiology of COVID-19 associated coagulopathy remains unclear. Two autopsy studies on post-mortem examination of COVID-19 individuals revealed that common causes of death are hypercoagulability and inflammation [6,7]. One of the autopsy study revealed 7 out of 12 patients (58%) had DVT and PE and this was the direct cause of death in 4 patients [7]. Here, we reported a case of asymptomatic COVID-19 patient with underlying malignancy and previous history of VTE who developed an acute VTE (both DVT and PE) despite being on therapeutic anticoagulation. Her inflammatory markers were all elevated. Initially, the patient's Ddimer was trending down to 1859 ng/ml, later on, there was an increasing trend of Ddimer to 7786 ng/ml on day 8 of admission which prompted the suspicion of acute VTE. The initial CTA was negative which suggested that the previous PE had resolved.

Although this patient has multiple risk factors for VTE which included malignancy, immobility and previous history of VTE, the inflammation and severe endothelial dysfunction secondary to COVID-19 may trigger and worsen the hypercoagulable state despite the use of therapeutic dose of enoxaparin. Interestingly, the late presentation of VTE in COVID-19 patients also suggests that the hypercoagulable state persist even in recovery phase and also in asymptomatic patients. High Ddimer is an independent predictor of mortality in hospitalized patients with COVID-19 [8]. However, it is also important to trend Ddimer in asymptomatic COVID-19 patients in the hospital.

Recent study from Mount Sinai Hospital shows that therapeutic dose anticoagulation improved survival among hospitalized COVID-19 patient both in and out of ICU [9]. Due to lack of data, the use of therapeutic anticoagulation in individuals with no documented VTE still remains controversial. American Society of Hematology (ASH) recommends the use of prophylactic anticoagulation for those who have not had confirmed VTE unless in patients with high risk probability in whom confirmatory test could not be performed. If VTE is suspected, confirmatory testing should be sought if possible. Despite the lack of evidence, many institutions have used an intermediate dose or therapeutic dose of anticoagulation on managing COVID-19 coagulopathy. Therefore, current clinical trials are focusing on studying the therapeutic or prophylactic dose of anticoagulation in preventing VTE in critically ill COVID-19 patients. It is also crucial to understand which phase of disease is associated with the highest risk of VTE to know the optimal timing and duration for therapeutic anticoagulation. It will be interesting to study the incidence of VTE in asymptomatic COVID-19 patients with high risk as well. In regards to the duration of anticoagulation, it is important to consider extended thromboprophylaxis after discharge depends on patient's VTE risk factors.

Heparins have been reported to have an anti-inflammatory and anti-viral activity in COVID-19. It binds tightly to COVID-19 spike proteins, downregulate IL-6 and directly dampens immune activation[10–12]. To date, no study compares whether unfractionated heparin (UFH) is better than low molecular weight heparin (LMWH) in COVID-19 coagulopathy. Koenig et al. reported that heparin, in addition to anticoagulation, has effects on the blocking of P- and L-selectin, which are being reduced or even eliminated by the switch to the low-molecular-weight heparins. P- and L-selectin, are a group of glycoproteins important in mediating the inflammation and interactions of endothelium in reperfusion injury[13]. Moreover, P-selectin ligation has been demonstrated to play a role in platelets activation as well as thrombus formation and micro-aggregation[14]. Although there is no direct comparison between heparin and LMWH, but it seems that heparin have more functional roles that have been reduced with conversion to LMWH and synthetic polysaccharides. Nonetheless, LMWH has more practical use due to less frequent dosing and omit the need for frequent monitoring of activated partial thromboplastin time (aPTT). However, UFH has better anti-inflammatory activity and is preferred in patients who may need reversibility for urgent intervention, morbid obesity or renal impairment. The other indication to use UFH is in patients who progressed despite being on anticoagulant therapy. More studies are still needed to dissect the roles and differences of UFH versus LMWH on its anti-inflammatory activity especially on COVID-19.

Conclusion

In conclusion, we presented a case of COVID-19 infection which triggered the coagulation cascade in an asymptomatic high-risk patient despite being on therapeutic anticoagulation. It highlighted that the risk of VTE persisted until late phase of disease. This shows the importance of early recognition of acute VTE with immediate treatment even in recovery phase to decrease mortality. It also emphasizes the role of extended anticoagulation after discharge in the future management of COVID-19 patients who are at high risk of VTE.

Declarations

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The case study is approved by Saint Michael's Medical Center ethics committee. Patient consent to publish the case.

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