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THROMBOTIC MANIFESTATIONS OF COVID-19: A CASE SERIES AND REVIEW OF THE LITERATURE

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ABSTRACT

The coronavirus 2019 (COVID-19) pandemic has affected millions around the world. The severe form of the disease is associated with respiratory distress and thromboembolic manifestations. Inflammatory markers like C reactive protein (CRP) and D dimer have an independent effect on disease severity and carry prognostic importance and outcomes. We describe a series of four cases of COVID-19 patients who had unusual manifestations of thrombosis. The sole aim is to bring forward the atypical causes and manifestations of COVID induced thrombotic events. Our Case Series showed rare thrombotic presentations in patients with COVID 19 with the use of immunomodulators, prolonged ICU stays with few having thrombotic events as sole presentation.

Keywords: COVID-19 infection, COVID thrombosis, Immunomodulators

INTRODUCTION

Corona virus 2019 (COVID-19) pandemic has affected millions around the world. The severe form of the disease is associated with respiratory distress and thromboembolic manifestations **[1, 2]**. The pathophysiology is predominantly uncontrolled inflammatory response resulting in these manifestations **[2]**. Endothelial inflammation and deranged coagulation are one of the primary methods by which the virus affects the body leading to a hyper thrombotic state **[3]**. Inflammatory markers like C reactive protein (CRP) and D dimer have the independent effect of disease severity and carry prognostic importance and outcomes. Anticoagulation was mandated as a part of treatment protocol but still, the

incidence of thrombotic events is 14.7% to 22.1% in COVID-19 patients **[3, 4]**. The process itself can impart risk of future thrombosis both short term and long term. There have been various case reports and studies on pulmonary thromboembolism and deep vein thrombosis in COVID-19 **[5, 6]**. We describe a series of four cases of COVID-19 patients who had unusual manifestations of thrombosis.

Case Series

The first case is of a 55-year-old male who was admitted with Covid 19 symptoms and started on standard therapy (Inj Dexamethasone 6mg IV, Inj Enoxioarin 60mg SC). He was admitted to the intensive care unit (ICU) for 35 days before getting discharged. On non-invasive ventilation (NIV) for 7 days during ICU stay and fifteen days after discharging that patient presented with right-sided weakness. CT scan of the brain showed a left-sided stroke. (Image-1) The patient was discharged after two weeks of admission with the advice of dabigatran 110 mg per oral twice daily. The patient was again admitted on day 74 with features of pain abdomen. A CT scan was done, which revealed thrombosis of Superior Mesenteric Artery (SMA) (image-2) and splenic infarct. (Image-3) The main risk factors in this patient were patient had a prolonged stay in the ICU in the first admission, and the patient had received Baricitinib for the treatment of COVID-19. The second case is of a 46-year-old male a known diabetic on insulin therapy. The patient presented with shortness of breath for 4 days turned out to be Covid-19 positive started on NIV therapy and institutional standard therapy and with an abrupt increase in C reactive protein, normal procalcitonin, and with no source of septic focus, Inj Tocilizumab 400mg IV was given and continued enoxaparin prophylactic dose. The patient was gradually weaned from a non-invasive ventilator over 14 days and stayed in the hospital for 30days. The patient developed swelling and the left arm for which ultrasound revealed left axillary and brachial veins were completely thrombosed. He was started on Heparin infusion with protocolized targeting of APTT. DVT screening was negative and possibly other sources of thrombosis were ruled out as a part of the protocol. On Day 2 of symptoms, the patient had sudden onset tachycardia and tachypnea, and sudden desaturation. Point of care ultrasound (POCUS) showed dilated right atrium, dilated right ventricle with severe tricuspid regurgitation. CT pulmonary angiography showed venous thromboembolism. (Image-4) Planned for thrombolysis suspecting pulmonary embolism but succumbed to death. The third case is that of a 29-year-old male who had presented to the emergency with left-side hemiparesis and intubated in view of low GCS (5/15) and incidentally found to be Covid-19 positive.

NCCT brain revealed right-sided MCA territory infarct. (Image- 5) Incidentally found to be COVID-19 positive. Started on Tab Ecospirin and tab Atorvastatin and mechanically ventilated. The patient was having D-dimers of 5 times the baseline, other sites for thrombosis had been ruled out. Tracheostomized and gradually weaned from the mechanical ventilator and discharged. The last case was a 26-year-old female a known case of mitral stenosis. She had features of mild upper respiratory tract infection, fever & sore throat for seven days. She was admitted to the emergency with abdominal pain and features of respiratory distress. Laboratory investigations revealed elevated CRP and D-dimers 10 times the baseline. The CT scan of the abdomen revealed there was thrombosis of the left renal artery with an infarct of the left kidney. (Image-6) Started on heparin anticoagulation and switched on to enoxaparin subcutaneous dose. Repeat radiological investigations showed resolutions The patient did not have any other significant risk factors for this thrombosis. Patient discharged with anticoagulation with Dabigatran.

DISCUSSION

COVID-19 is associated with a wide variation in clinical presentation ranging from asymptomatic to patients with multi-organ failure. The Coronavirus belongs to a family of enveloped, single-stranded RNA viruses, It gains access inside the human cells predominantly by attaching itself to the ACE2 receptor **[1, 5]**. The rate of thromboembolism in COVID 19 cases reported in the literature is diversified. Some report 30% while others are up to 70%. Hyper-coagulability and thromboembolic complications have been associated with more severe disease and a higher risk for mortality **[4, 5]**. The association though well documented it is still not conclusive as there are still many patients with deranged parameters but no clinical abnormalities. The variation in the population, the duration of follow up and self-reporting of symptoms may have affected the ambiguity in the lack of association. D-dimers values indirectly predict prothrombotic pathogenesis with a more negative predictive value. All cases in the series have increased D-dimers and which predicts the severity of disease but it might not reflect as clinical manifestation **[7]**. In a systemic review conducted by *Panagiotis Paliogiannis* 1,807 patients (585 with severe disease) The pooled results of all studies revealed that the D-dimer concentrations were significantly higher in patients with more severe COVID-19 disease ($p < 0.0001$). The heterogeneity was moderate ($I2 = 46.5\%$; $p = 0.033$) which concluded that D-dimer concentrations in patients with severe COVID-19 are significantly higher when compared to those with non-severe forms **[8]**. COVID-19 related deaths and debility is high in correlating with increasing infection rates.

COVID-19 pathophysiology is still being deciphered. Involvement of the endothelial system specifically is expected to contribute significantly to worse outcomes. The elevated risk of thromboembolism is one of the important factors for death. Numerous mechanisms have been seen to contribute to this increased thromboembolism risk of these patients. The inflammatory response associated with the viral invasion of the respiratory epithelium and endothelium is the main reason for thromboembolism **[1, 9, 10]**. One important factor is the de novo generation of thrombi in the micro-vasculature rather than embolism from a peripheral site **[11]**. To deal with this pro-thrombotic state associated with COVID-19, the International Society of Thrombosis and Hemostasis (ISTH) interim recommendations on recognition and management of coagulopathy in COVID-19 states prophylactic dose low molecular weight heparin (LMWH) should be considered in all patients (including non-critically ill) who require hospital admission for COVID-19 infection. This may not be given to those with contraindications **[12, 13]**. There have been some case reports regarding SMA thrombosis in COVID-19 **[6]**. In our case the patient presented after more than two months and also has a stroke episode in between. The impact of Baricitinib cannot be ruled out. *Juliana Setiawan* reported thromboembolic events with JAK-STAT inhibitors, the calculated adverse drug reactions (ADR) pairs with higher than expected incidence among them baricitinib contributed to Deep vein thrombosis and pulmonary embolism with a reporting odds ratio (ROR) 14.84 [9.64–22.84] and empirical Bayesian geometric mean (EBGM) 9.49 [5.91] **[14]**. The incidence of upper limb deep vein thrombosis (DVT) is very low with only a few cases reported worldwide. The second case reported one such case who stayed in ICU for more than a month. The patient in this case had additional risk factors of uncontrolled diabetes and received injection Tocilizumab. A retrospective analysis by *Chan et al* focused on thrombophilic effects of tocilizumab with elevated D-dimers after drug administration and hypothesized that IL6 receptor antagonists have an interplay with thromboembolic events **[15]**. In this case we can't impart tocilizumab as a sole cause of thromboembolic phenomenon as the baseline D-dimers were high and this interplay between Il6 and thromboembolic events has paucity in the literature. The third case was of a thrombus in the middle cerebral artery (MCA). This case underlines the fact that patients with no respiratory issues can directly present with thrombotic events in COVID-19. The final case had renal artery thrombosis and abdominal pain. We found only one case of renal artery thrombosis associated with COVID-19 **[16]**. This case also signifies the

link of mild to moderate COVID illness for significant thrombotic manifestations. A meta-analysis conducted by *Malas MB* in 42 studies including 8271 patients was published. They showed overall venous thromboembolism (VTE) rate was 21%, with a DVT rate of 20% and pulmonary embolism (PE) rate of 13% while arterial thromboembolism (ATE) rate was 2%. Among ICU patients, the VTE rate was 31%, DVT rate was 28%, PE rate was 19%, and ATE rate was 5%. Thromboembolism significantly increased the odds of mortality by as high as 74%. Our case series highlights the rare manifestations of covid thrombosis and the lack of association with severe respiratory disease **[17]**. The thrombotic manifestations are common in severe disease which had been proved by many clinical trials and RCTs. But we would like to highlight those thrombotic events might be sole presentations without respiratory prodrome (case-3). It could be a part of adverse drug reactions with baricitinib or tocilizumab. (case1, 2). Prolonged ICU stays and failed protocolized anti coagulation post-discharge might be a cause (case1, 2). It can be associated with mild disease (case 4). This case series lacks evidence for the pertained cause, as thrombotic events could be multifactorial. The sole aim is to bring forward the atypical causes and manifestations of covid induced thrombotic events. Further studies and large RCTs and platform trials are needed to evaluate the risk factors in this field.

CONCLUSION

Our Case Series showed rare thrombotic presentations in patients with COVID 19. The use of immunomodulators was associated with thrombosis. Most cases had mild to moderate respiratory disease though they all presented with life threatening thrombosis. There was no association between age and duration of illness.

Conflict of Interest: Nil

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REFERENCES

[1] Klok FA, Kruip MJHA, van der Meer NJM, *et al*. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020; 191: 148-150.

[2] Middeldorp S, Coppens M, van Haaps TF, *et al*. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020; 18: 1995-2002.

[3] Smilowitz NR, Kunichoff D, Garshick M, *et al*. C-reactive protein and clinical outcomes in patients with COVID-19. Eur Heart J 2021; 42: 2270-2279

[4] The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in

critically ill patients with Covid-19. N Engl J Med 2021Aug; 385: 777-789.

[5] Mahajan P, Dass B, Radhakrishnan N, McCullough PA. COVID-19-associated systemic thromboembolism: a case report and review of the literature. Cardiorenal Med. 2020 oct; 10(6): 462–469

[6] Karna ST, Panda R, Maurya AP, Kumari S. Superior Mesenteric Artery Thrombosis in COVID-19 Pneumonia: an Underestimated Diagnosis-First Case Report in Asia. Indian J Surg. 2020 Oct 19:1-3.

[7] Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, *et al*. (2021) D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLOS ONE.2021Aug; 16(8).

[8] Paliogiannis P, Mangoni AA, Dettori P, Nasrallah GK, Pintus G, Zinellu A. D-Dimer Concentrations and COVID-19 Severity: A Systematic Review and Meta-Analysis. Front Public Health. 2020 Aug 4; 8: 432.

[9] Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar; 395: 1054-1062.

[10] Al-Samkari H, Karp Leaf RS, Dzik WH, *et al*. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020Jul; 136: 489-500.

[11] Ionescu F, Jaiyesimi I, Petrescu I, *et al*. Association of anticoagulation dose and survival in hospitalized COVID-19 patients: a retrospective propensity score-weighted analysis. Eur J Haematol 2021Feb; 106: 165-174.

[12] Marietta M, Ageno W, Artoni A, De Candia E, Gresele P, Marchetti M, Marcucci R, Tripodi A. COVID-19, and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus. 2020 May; 18(3): 167-169.

[13] J. Thachil, N. Tang, S. Gando, A. Fal anga, M. Cattaneo, M. Levi, *et al.* ISTH interim guidance on recognition and management of coagulopathy in COVID-19 J Thromb Haemost. 2020Mar; 18: 1023-1026.

[14] Setyawan J, Azimi N, Strand V, Yarur A, Fridman M. Reporting of Thromboembolic Events with JAK Inhibitors: Analysis of the FAERS

Database 2010-2019. Drug Saf. 2021 Aug; 44(8): 889-897.

[15] Chan K, Patel B, Podel B, *et al*. (May 24, 2021) Tocilizumab and Thromboembolism in COVID-19: A Retrospective Hospital-Based Cohort Analysis. Cureus. 2021May; 13(5): e15208. doi:10.7759/cureus.15208.

[16] Acharya S, Anwar S, Siddiqui FS, Shabih S, Manchandani U, Dalezman S. Renal artery thrombosis in COVID-19. *ID Cases*. 2020Sep; 22: e00968. doi:10.1016/j.idcr.2020.e00968.

[17] Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. E Clinical Medicine. 2020, Dec; 29: 100639.