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Covid-19 coagulopathy – A case series of gangrenous necrosis

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Abstract

SARS -COV-2 has presented with varied symptoms and a number of factors determine clinical outcome.While hypoxemic respiratory failure remains main cause of morbidity and mortality, a hyper-inflammatory state induced endothelial injury and hypercoagulability leading to thromboembolism also is a leading cause of mortality.

Thearticle aims to present a case series of SARS –COV-2 patients who developed serious thromboembolic

complications involving the limbs, leading to severe acute gangrene. This case series analyses imaging, inflammatory markers and challenges in treatment in these patients.

Introduction

The rapid spread of COVID in India during second wave has led to an unprecedented mortality. The past 1 year of understanding of disease has led to reporting of thrombotic tendency in patients and early initiation of anti-coagulant therapy in moderate to severe disease is the norm. Despite initiation of anticoagulants, Throm Bo embolic events and complications continue to arise leading to increased morbidity and mortality [(1)]. This case series reports three cases of thromboembolism involving the extremities, leading to gangrene in patients who were already on anticoagulant therapy. All the three patients were RT-PCR confirmed COVID cases and had no features of peripheral vascular disease at presentation. They developed acute progressive gangrenous necrosis in the course of illness.

Keywords: SARS-COV-2, RT PCR, Anti-coagulants.

Case 1

A 60-year-old diabetic, hypertensive, non- smoker, male presented with complaints of cough, fever and breathlessness since 3 days. Patient presented with tachypnea and maintaining saturation of 85% on room air, CT severity score was 13/25.Patient was treated in ICU with Non-invasive ventilation,prophylactic Enoxaparin, Remdesivir and steroids. Patient's respiratory status was deteriorating and was intubated,kept on mechanical ventilator and later tracheostomy was done. During the course of illness patient developed pain over right foot which progressed to gangrene and ischemia over left foot. CT- Aortogram was done.

Figure 1: Chest x ray- alveolar opacities.

Figure 2: Right foot gangrene.

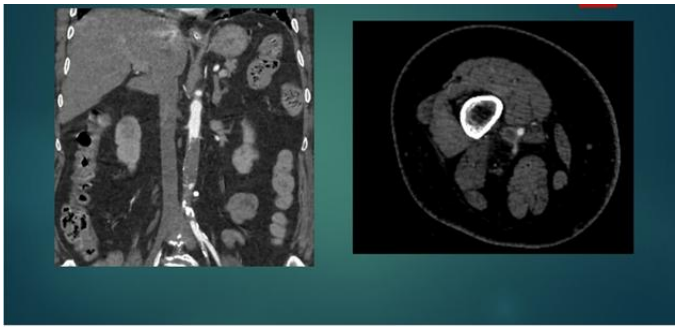

Figure 3: CT aortogram showing occlusion of infrarenal abdominal aorta

CT Aortogram done showed **c**omplete occlusion of infra-renal abdominal aorta- 5. 2cms.Partial thrombotic occlusion of Right common iliac artery -3.5cms causing 60% occlusion. Right anterior tibial artery completely occluded. Left anterior tibial artery completely occluded - 8cms with stenosis in mid and distal third of anterior tibial artery.Patient was treated with parenteral heparin, pentoxifylline. Respiratory status improved and patient-maintained saturation on Room air. Patient was explained the need for amputation plus revascularization surgery involving abdominal aorta but due to high risk of complications, patient wasn't willing for surgery and was discharged after 35 days of hospital stay.

Case 2

62-year-old male patient with no known co-morbidities, chronic smoker presented with history of fever, cough, loss of smell and taste and breathlessness since 3 days. Patient was tachypneic and maintained saturation of 90% in room air. CT severity was 17/ 25. Patient was treated in ICU with Non-invasive ventilation, prophylactic Enoxaparin, Remdesivir and steroids. Patient was stable on NRBM but complained of left ankle pain 5 days after admission followed by ischemia. Patient was started on Heparin infusion at 1000U/Hour as D -dimer increased to> 5000.CT Aortogram was done for the patient.

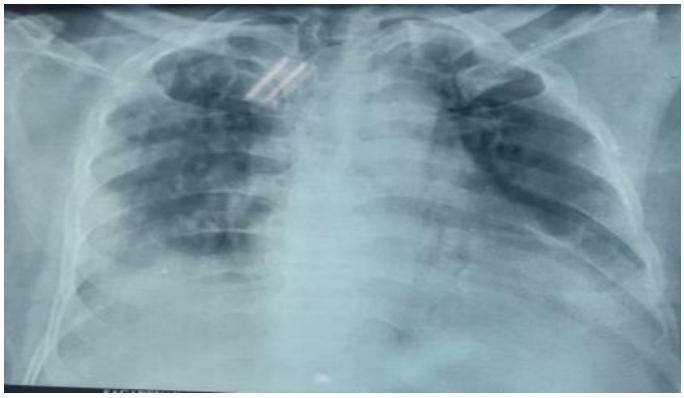

Figure 4: Chest X –Ray showing Air space opacities

Figure 5: Left limb ischemia

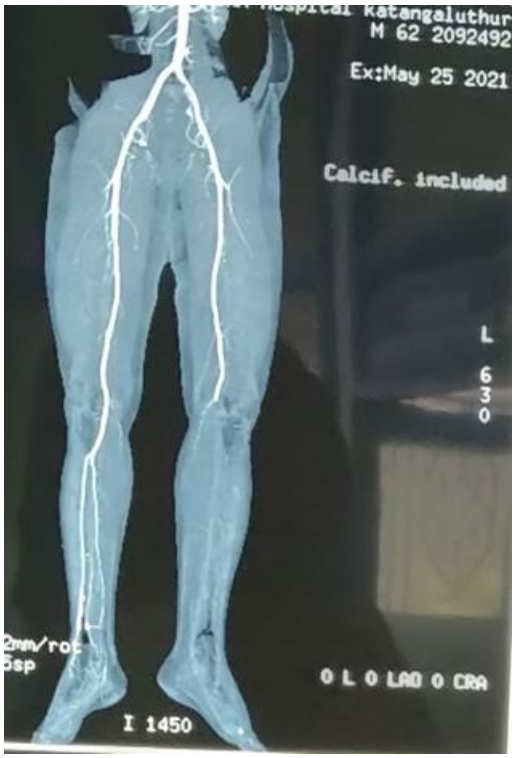

Figure 6: CT Aortogram

Partial occlusion of left common iliac artery upto bifurcation -80% luminal narrowing

Long segment stenosis of Left Internal Iliac artery for 4.7cms from its origin

Left popliteal, anterior tibial, posterior tibial and peroneal arteries show no contrast opacification- Suggestive of complete occlusion (Fig 2.3)

Patient was continued on heparin infusion along with antiplatelet, cilostazol and pentoxifylline. However, patient deteriorated with onset of sepsis and started on

NIV plus higher antibiotics. Patient was intubated, kept on mechanical ventilator.

Gangrene worsened although patient was on anticoagulant therapy. Patient developed sudden desaturation and expired after 55 days of admission with pulmonary embolism and sepsis being likely cause of death.

Figure 5 and 7:Progression ofIschemic limb to complete necrotic gangrene over 1 month in patient of ARDS on anticoagulant therapy.

Figure 7: Left foot gangrene

Case 3

82-year-old male diabetic patient with old CVA on antiplatelet treatment came with complaint of cough, sore throat and breathlessness, CT severity score was 9/15.Patient had mild breathlessness and had saturation of 92% in RA, maintaining with 6L NRBM.

Patient was started on antibiotics, steroids, antiplatelet and other supportive management. 3 days after admission, patient GCS dropped suddenly and was drowsy. CT brain was done and was found to have acute/ subacuteInfarct.

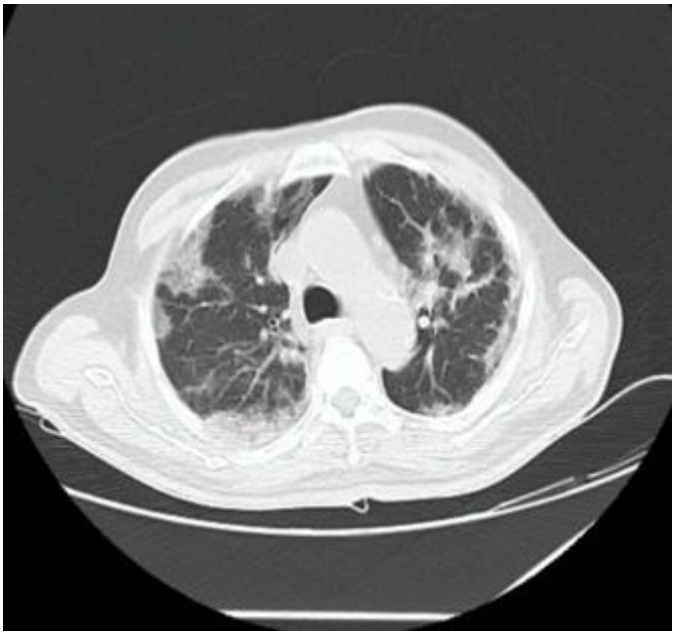

Figure 8: CT chest showing GGO s

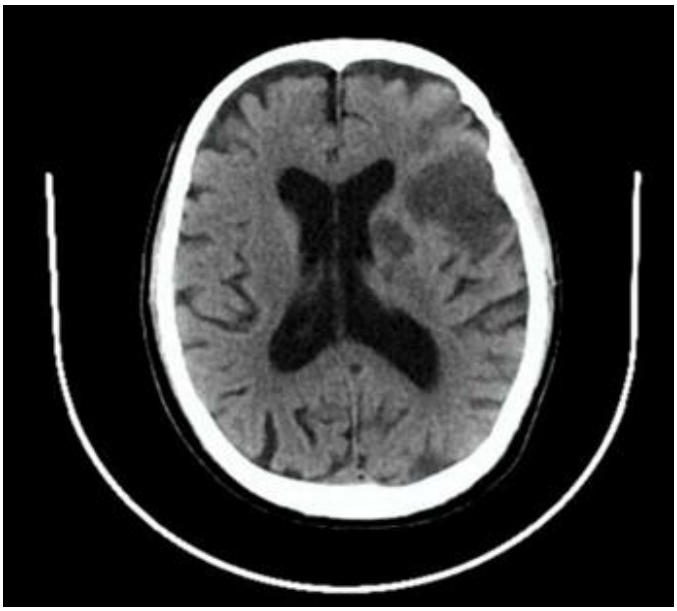

Figure 9: CTbrain-Hemorrhagic infarct.

Patient was started on intravenous heparin 5000U twice daily dose as D –dimer was persistently above 5000. Repeat CT showed hemorrhagic transformation, so patient was shifted to enoxaparin. Patient GCS further dropped and was intubated and kept on mechanical ventilator. Patient developed gangrene of 4th and 5th toe subsequently. Doppler lower limb was done.

Patient went into sepsis and acute kidney injury and was started on higher grade antibiotics. In view of gangrene plus hemorrhagic transformation of infarct, patient was kept on heparin 5000U twice daily dose.

However patient clinical condition worsened, went into bradycardia followed by cardiac arrest 13 days after admission with septic shock with multiple organ dysfunction being immediate cause of death.

Figure 10: Gangrene of 4th and 5th toe

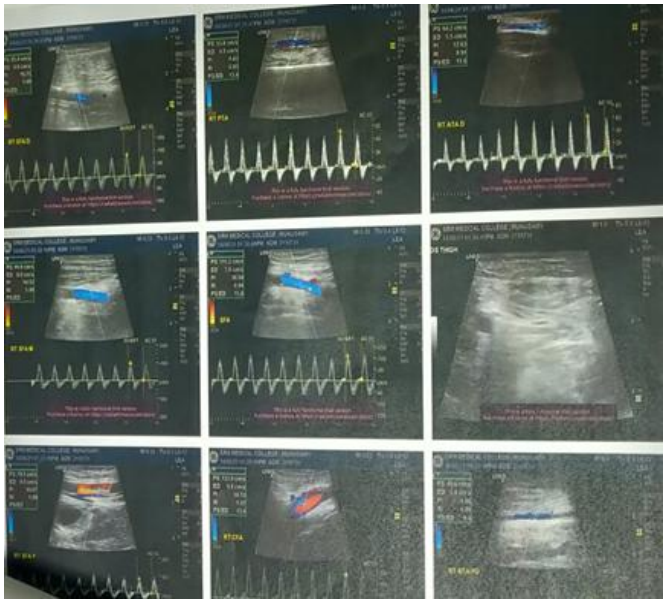

Figure 11: Doppler of Right Lower limbShowing obstruction of flow

Discussion

SARS-COV -2 pandemic has affected more than 180 million people worldwide with 4 million deaths reported in one and half years[(2)]. A number of factors including age, socio economic status, co morbidities determine the outcome in patients affected by COVID-19.

Besides respiratory failure and sepsis, thromboembolic complications, even in absence of relevant macro-thrombi is a leading cause of mortality [(3)].

In a study done by Richard Becker et al, the composite incidence of thrombotic events in patients of ICU with severe COVID- 19 was around 31%. Venous Thromboembolic events were more common accounting for 27%, majority being pulmonary embolism [(4) (5)].

A meta-analysis of various studies showed overall prevalence of venous Throm Bo embolism to be around 14.1% with arterial thrombotic events upto 3% [(6)].

The most common pattern of coagulopathy observed in patients hospitalized with COVID-19 is characterized by elevations in fibrinogen and D-dimer levels, with mild prolongation in PT/aPTT[(7)].

The most severe complications of COVID- 19 has been the acute large vessel occlusion with ischemic strokes and gangrene in patients on prophylactic anticoagulant therapy.

COVID-19 associated coagulopathy has a multifactorial association explained by interaction of coronavirus with endothelial cells, local and systemic inflammatory response and the coagulation system.

SARS- C0V-2 binds to host cells via ACE 2 receptor. A high density ofACE2R expression has been demonstrated in endothelial cells from large and small arteries, their smooth muscle cells and veins in all tissues, human tissues obtained from biopsies. This may have relevance in acute gangrenous necrosis observed.

This may lead to capillary endothelial injury and microvascular dysfunction.

The cytokine storm associated with COVID will fuel pro-inflammatory and pro-coagulation process resulting in capillary leakage, cellular dysfunction and overt activation of coagulation cascade causing high Throm botic tendency.

The case series highlights the macro-vascular complication seen in patients. All patients were managed in intensive care setting and started on prophylactic anticoagulant therapy in view of moderate to severe COVID disease.

Although Initial D-dimer levels of patients showed mild elevations, patients developed progressive elevation of D-dimer even after thromboprophylaxis with enoxaparin, DVT stockings and limb physiotherapy. All patients during course showed D-dimer above 5000 levels and subsequent development of rapid progressive gangrene.

A number of guidelines on thromboprophylaxis have been published with risk assessment and dosing of anticoagulants. However, the appropriate anticoagulant therapy and dose remains a topic for discussion.

While National Institute of health, American college of chest physicians, WHO guidelines recommend routine dose Throm boprophylaxis, international society of Throm bosis and Hemostasis, Anticoagulant forum interim clinical guidance, National institute of health and care excellence guidelines recommend increased intensity of Throm bo prophylaxis. [(6)]

Our case series highlights progression of gangrenous necrosis in patients started on routine prophylactic enoxaparin but were switched over to high dose anticoagulants, with antiplatelet along with Phosphodiesterase inhibitor, while one patient developed bleeding complication and dose of anticoagulant had to be adjusted. However, gangrene progression was irreversible once set in, implying that high degree of coagulation cascade disruption is potentially irreversible and associated with high morbidity and mortality. Based on this study, it is recommended to start increased dose of initial Throm boprophylaxis case to case basis.

Conclusion

Acute rapid progressive irreversible gangrenous necrosis due to thrombosis is a dreaded complication. With increasing Throm Bo embolic complications like acute cerebrovascular accidents, intestinal gangrene, gonadal vein thrombosis, Pulmonary embolisms, more studies are needed to formulate guidelines for Throm boprophylaxis needed in moderate to severe COVID-19 and in patients showing early signs of ischemia onset or elevated D-dimers should warrant aggressive management.

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