COVID-19 Complicated with Arterial Thrombosis Resulting Acute Limb Ischemia: A Case Report from Bangladesh

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Abstract

COVID-19 (Corona virus disease 2019), which starts from Wuhan, China on December, 2019 spread rapidly to different countries of the world including Bangladesh. It affects huge impact on health care system. It’s a new disease with multisystem involvement. Physicians are experiencing new presentation of different cases and rare complication including arterial thrombosis. Few data is available regarding arterial thrombosis in SARS-CoV-2 infected patients. We are currently fighting with a 60 year old lady suffering from COVID-19 pneumonia with other co-morbidities developed severe arterial occlusion of right leg despite of taking anti platelet for long time for another cause. Patient developed irreversible right lower limb ischemia not improving with continuous infusion of unfractionated heparin followed by severe pulmonary embolism. So further study and recommendations will need to evaluate the cases and treatment in COVID-19 Patients with rare presentation. [Bangladesh Journal of Infectious Diseases, October 2020;7(suppl_2):S50-S56]

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Introduction

Novel coronavirus (2019-nCoV) was first reported in Wuhan, China. Since then SARS-CoV-2 has generated 16207130 confirmed cases of COVID-19 worldwide with a confirmed death of 648513 cases till July 26, 2020. The total numbers of confirmed COVID-19 cases in Bangladesh are 221178 with total confirmed death of 2874 till July 26, 2020.

Unusual presentations of COVID-19 were unknown when it first emerged in Wuhan, China. Initially the virus presented with high fever, cough, tiredness, sore throat and aches and pains. Subsequently cases of diarrhoea, conjunctivitis, headache and loss of smell were often accompanying the illness.

Although respiratory failure is the main cause of death of moderate to severe COVID-19 disease, several cardiovascular complications and numerous cases of thromboembolic disease have been reported. Coagulopathy is an emerging and often lethal complications. However, venous thromboembolism (VTE) is common in COVID-19 patients. Despite the pathophysiology of an underlying prothrombotic state, data and regarding the risk of acute arterial thrombotic events are still rare and only a few reports of arterial thromboembolism. COVID-19 with multiple comorbidities associated with severe disease and increase mortality. The most common comorbidities found were obesity, hypertension and diabetes mellitus. Older adults and people of any age, who have underlying medical conditions such as hypertension and diabetes, have shown worse prognosis. The aim was to report this case to describe the clinical characteristics of the patient during presentation, treatment response of the case, choice of anti-thrombotic and to familiarize our fellow colleague to share the experience of an unusual presentation of a COVID-19 Pneumonia with multiple co-morbidities.

Case Presentation

A 60 years old obese (BMI -39) woman presented to the hospital on July 11, 2020 with the complaints of fever for 11 days which was intermittent, high grade, highest recorded temperature was 104°F, she have to take antipyretic paracetamol for relieving her fever, cough with expectoration of scanty sputum but not any history of haemoptysis, shortness of breath and generalized weakness for same duration. She admitted with a positive report of Corona by RT PCR from nasopharyngeal swab 5 days before. She had no history of headache, diarrhea, arthralgia or any other unusual symptoms. She denied any contact with positive COVID-19 patients. Exploration of past medical history included hypertension for 5 years, chronic persistent bronchial asthma controlled on medication for 5 years, hypothyroidism for 4 years, and ischemic heart disease for 2 years taking anti ischemic drugs and dyslipidaemia taking lipid lowering drug, atorvastatin 20 mg daily for 3 years. She reported no previous history of cerebrovascular or peripheral vascular disease. On admission physical examinations revealed a temperature of 104°F, Blood pressure of 150/90 mm of Hg, pulse of 102/min with normal rhythm and volume, respiratory rate was 22 breath per minute and oxygen saturation of 88% on room air immediately put on supplemental oxygen though she was not in acute distress, there is bilateral pitting oedema of the both legs. Lung auscultation showed few scattered course crackles over the both lung field with polyphonic rhonchi. There was no evidence of VTE on examinations. Initial Chest X ray showed bilateral interstitial pneumonitis (Figure I).

![Figure I: Chest X ray posterior-anterior view on admission showing Bilateral Interstitial pneumonitis with peripheral distribution](image)

High resolution computed tomography of chest(HRCT of chest) (Figure II and III) was performed which revealed multifocal ground glass density areas intermixed with multifocal sub segmental consolidations, irregular attenuated areas and fibrotic bands are seen at multiple segments of both lungs predominantly distributed at peripheral, peribronchoalveolar and sub pleural regions. The ground glass opacity and consolidations involved approximately 30% of lung volume.
Figure 2 (A and B): HRCT of chest coronal view showing crazy paving with ground glass opacity and consolidations in the both lungs involved approximately 30% of lung volume

Figure 3: (A, B and C) HRCT of chest coronal view showing multifocal ground glass density areas intermixed with multifocal sub segmental consolidations, irregular attenuated areas and fibrotic bands are seen at multiple segments of both lungs predominantly distributed at peripheral, peribronchialveolar and sub-pleural regions.

Other significant laboratory findings included haemoglobin was 7.6gm/dl, erythrocyte sedimentation rate (ESR) was 74 mm in 1st hour, and Total white blood cell count (WBC) was 14,000/cmm with 74% neutrophils and 13.0% lymphocyte in differential count. Packed cell volume(PCV) was 24.2%, serum creatinine was 2.4mg/dl with estimated GFR was 56 ml/min/1.73m², c reactive protein(CRP) was 64 mg/L, serum ferritin was 711 ng/ml, D-dimer was 0.81 mg/l ,Alanine aminotransferase was 23 U/L, serum urea 23 mg/dl, blood urea nitrogen was 22.7 mg/dl, serum calcium was 6.1mg/dl, phosphate was 5.9 mg/dl, peripheral blood film showed microcytic hypochromic anemia with neutrophilic leukocytosis. She was started on enoxaparin 60mg subcutaneous 12 hourly, oral favipiravir 1600 mg loading dose followed by maintenance dose 600 mg 12 hourly for 10 days, intravenous meropenem 500mg 3times daily and oral clarithromycin 500mg twice daily along with her regular antihypertensive medications amlodipine5mg,olmesartan 20mg, clopidogrel75mg, nitroglycerine 2.6mg twice daily, trimetazidine 35 mg twice daily, bisoprolol 5mg daily, atorvastatin 20 mg daily and regular antiasthma medication metered dose inhaler formeterol/ Beclomethasone combination along with salbutamol and montelukast 10mg daily along with levothyroxine 100micgm daily. She was admitted to an isolation unit and started on supplemental oxygen via simple face mask at 5-6L/min. She was nor screened for VTE at admission. Her symptoms and vital signs remained stable in the first 1-4 days following admission although she continued to require supplemental oxygen. On hospital day 6, she began complaining of right lower extremity pain which increasing with time. After that thorough physical examination was done and found absent dorsalis pedis, posterior tibial and feeble anterior tibial artery pulse in her right foot and leg which was remain cooler than her contralateral foot. The intensity of pain increasing with time. She was found to have diminished sensation also in her right foot, anterior and posterior aspect of the right leg, consistent with Rutherford Class III ALI. After that emergency duplex study was performed (Figure IV) and found arterial spectral flow on the right femoral artery PsV: 48cm/sec, right popliteal artery was PsV: 19 cm/sec, no recordable blood flow was seen right anterior tibial, posterior tibial and dorsalis pedis arteries, in the left side which were normal.
Figure 4(A, B and C): Duplex ultrasound of the Lower limb vessels Showing no recordable blood flow in the Right anterior tibial, posterior tibial and Dorsalis pedis arteries, Contralateral arteries were normal. The spectral flow pattern of the venous system was normal in both side.
The spectral flow pattern of the venous system was normal. Normal respiratory variance was seen. Calf compression test was normal on both sides. CT angiography of lower extremities was planned but cannot possible due to rapid deterioration of the patient. Echocardiography showed concentric left ventricular hypertrophy with anterior regional wall motion abnormality with ejection fraction 64% and normal right ventricular systolic function. Anti-nuclear antibody (ANA) and anti-phospholipid antibody was found negative. After that she was started with unfractionated heparin 5000 IU loading dose followed by continuous infusion of 1000 IU /hr but her condition worsened with increasing breathlessness, she became increasingly tachypneic with respiratory rate more than 28 with fluctuation saturation 80-90% put on non-rebreather mask with supplemental oxygen 12-15L/min. Two units of packed cells and 200 ml of convalescent plasma given during this period. All other investigation reviewed and found markedly elevated D-dimer with other parameters. She was seen by a surgeon but postponed any procedure due to her worsening condition. After that she was also started with antiviral, Remdesivir 100mg daily along with other drugs. Activated plasma thromboplastin time (APTT) was found within normal limit in the follow up. But her condition not improved at all rather increasing pain in the right leg with gradual blackening of the toes and developed blister over the anterior surface of the foot (Figure V).

Increasing breathlessness and desaturation requiring more oxygen, put on high flow nasal canola to provide 50L/min oxygen. Following two days her saturation was maintained above 92% but pain and pulsation in the right legs not improved. She was also started intravenous methylprednisolone 250 mg that time daily. But on day 16 July 25, 2020 in the hospital her condition become worsened with fall of oxygen saturation and put on ventilation. Planned for computed tomography pulmonary angiography (CTPA) and CT angiogram of the bilateral lower extremities but not possible due to patient condition. A portable X-ray chest was taken (Figure VI) which showing bilateral extensive involvement of both lungs. On July 26, 2020 at 10 pm she developed hypotension followed by cardiac arrest leading to initiation of nor-epinephrine and cardiopulmonary resuscitation but cannot recovered. Informed consent was obtained from the patient for publication of this case report.

Figure 6: Chest X ray Anterior-posterior view Showing Extensive Bilateral Involvement of both Lungs (July 25, 2020)

Figure 5(A and B): Showing blackening of big toe including other toes(A) and blister formation on the dorsum of the foot with blackening of skin(B)
Table 1: Clinical Laboratory findings from hospital, (Day 1 to 14) (July 11-July 25, 2020)

| Measurement (Normal Reference range) | Hospital Day 1 | Hospital Day 4 | Hospital Day 10 | Hospital Day 14 |
|--------------------------------------|---------------|---------------|----------------|---------------|
| Haemoglobin                          | 7.6mg/dL      | 7.5mg/dL      | 9.1gm/dL       | 6.2gm/dL      |
| ESR (0-15 mm in 1st hour)            | 74mm in 2st hr| 87mm in 1st hr| 70mm in 1st hr | 140mm in 1st hr|
| WBC (4000-11,000/cmm)                | 14,000/cmm    | 13,700/cmm    | 17,000/cmm     | 15,600/cmm    |
| Neutrophils (Differentials) (40-75%) | 70.0%         | 79.0%         | 89.0%          | 85.0%         |
| Lymphocytes (Differential)           | 13.0%         | 14.0%         | 18.0%          | 6.0%          |
| Haematocrit (37-47%)                 | 24.2%         | 24.8%         | 20.0%          |               |
| Platelet Count (150,000-400,00/cmm)  | 172,000/cmm   | 191,000/cmm   | 112,000/cmm    | 96,000/cmm    |
| Sodium (135-145nmol/L)               | 133.4nmol/L   | 138nmol/L     | 132nmol/L      | 133nmol/L     |
| Potassium (3.5-5.0nmol/L)            | 4.22nmol/L    | 4.5nmol/L     | 4.9nmol/L      | 5.8nmol/L     |
| Chloride (98-107nmol/L)              | 96.6nmol/L    | 101nmol/L     | 105nmol/L      |               |
| S. Calcium(8.1-10.4mg/dl)            | 6.1mg/dl      |               |                |               |
| S. creatinine(0.5-1.2mg/dl)          | 2.4mg/dl      | 2.7mg/dl      | 2.2mg/dl       | 3.4mg/dl      |
| Phosphate (2.5-5.0mg/dl)             | 5.9mg/dl      |               |                |               |
| BUN (6.0-21mg/dl)                    | 22.7mg/dl     |               |                | 39mg/dl       |
| Total Billirubin (0.2-1.0 mg/dl)     | 1.2mg/dl      | 1.6mg/dl      |                | 1.7mg/dl      |
| S. Albumin (3.8-5.1d/l/dl)           | 5.1gm/dl      |               | 4.5gm/dl       | 4.6gm/dl      |
| Prothrombin time (Control 13 sec)    | 17.0 sec      | 14.0sec       | 18.0 sec       |               |
| Alanine aminotransferase (Female up to 32 U/L) | 54U/L      | 102U/L       | 99U/L          |               |
| CRP (less than 6mg/L)                | 48mg/l        | 51mg/l        | 75mg/ml        | 211mg/ml      |
| D-dimer (<0.5 mg/ml)                 | 0.81mg/l      | 2.1mg/l       | 1.86mg/l       | 13.0mg/l      |
| APTT (25-35)                         | Control:32    | Patient:27    | Control:32     | Patient:33    |
| Troponin I (<0.1ng/ml)               | 0.08ng/ml     | 0.06ng/ml     | <0.01ng/ml     |               |
| Serum Ferritin (Adult Female 15-120ng/ml) | 711ng/ml   | 198ng/ml      | >1000ng/ml     |               |
| N terminal Pro BNP (<300pg/ml HF unlikely) | 513pg/ml | 477pg/ml | 910pg/ml | |
| Lactate dehydrogenase (200-400U/L)   | 410U/L        |               | 973U/L         |               |
| 24 hour Urine Protein (Up to 0.15gm/24 hrs) | 0.54gm/24hrs | | | |
| S Procalcitonin (<0.1ng/ml)          | <0.05ng/ml    |               | 2.7ng/ml       |               |
| TSH (0.3-5.05µIU/ml)                 | 1.93µIU/ml    |               | 2.08µIU/ml     |               |
| Malarial Parasite                    | Not found     |               |               |               |
| NS1 antigen for Dengue               | Negative      |               |               |               |
| Electrocardiogram(ECG)               | Anterior ischaemia | Atrial Fibrillation with rapid ventricular response |
| Seroimmunological Test for Salmonella, Brucella and Rickettsia | Not significant | | | |
| Blood culture                        | No growth     |               |               |               |
Discussion

COVID-19 appears to be associated with a strong thrombotic tendency due to thrombo-inflammation, probably driven by distinct mechanism that still require explanation. In this case provides that how arterial thrombosis leads to very poor outcome in a patient with COVID-19 pneumonia. First, the case developed severe pneumonia starting antiviral and antibiotic for possible co-infection, thromboprophylaxis with high dose low molecular weight heparin, enoxaparin, subsequently developed arterial thrombosis of the right leg started promptly unfractoned heparin in continuous infusion. Presence of additional risk factor obesity, hypothyroidism, ischemic heart disease, hypertension, renal impairment also contributes to the condition and making it very difficult to manage. Further deterioration due to respiratory failure may be due to involvement of the pulmonary arterial thrombosis.

This case also shows the diagnostic challenges in patients with COVID-19 and in particular that deteriorate rapidly. We feel an impossible situation to differentiate between respiratory failure due to progression of severe pneumonia, acute respiratory distress syndrome in one side and pulmonary embolism in other side. In our case showed both, rapid progression of COVID-19 pneumonia, arterial thrombosis not responding to unfractoned heparin and probably consequent development of severe pulmonary embolism. Patient condition and facility does not make possible to confirm it by computed angiography (CTPA) in a severely ill patient.

One study suggest that the combination of D-dimer levels increasing progressively and clinical worsening is suggestive for pulmonary embolism and D-dimer elevations associated with poor prognosis which were similar to our case. Acute limb ischemia is a limb threatening thromboembolic event that is considered as surgical emergency. A retrospective study suggests that patients who had undergone lower extremity revascularization procedures for acute limb ischemia revealed that 40.0% had some evidence of hypercoagulable state. An arterial thrombosis can easily retrieve with an open embolectomy procedure with prompt restoration of flow to the foot. In this case, revascularization cannot possible due to rapid deterioration of the patient. At last combined cascade make our dedicated team hopeless and to lose the patient on July 26, 2020.

Conclusion

This case emphasizes hypercoagulability as a major contributor to COVID-19 related complications and suggests that early diagnostic and therapeutic approaches as must implemented promptly to ameliorate the risk of thromboembolic events, prompt intervention to remove thrombus and control of co morbid condition. Further study should require for a clear recommendation for this dangerous complications related to COVID-19 to reduce morbidity and mortality. Interim rapid guideline also needed for the physicians to combat the situations.

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