Thrombotic thrombocytopenic purpura with COVID-19 as an unforeseen complication: A case report.

Muhammad Zain Mushtaq[1], Saad Bin Zafar Mahmood[1], Usman Shaikh[2], and Syed Ahsan Ali[3]

[1]The Aga Khan University
[2]Affiliation not available
[3]Aga Khan University Hospital

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Abstract

This article reports an association of thrombotic thrombocytopenic purpura(TTP) with COVID-19. A 49-year old male presented with fever, diarrhea and altered mentation, was found to have COVID-19. On sixth hospital day, he developed thrombocytopenia, microangiopathic hemolytic anemia with schistocytes on peripheral blood film and worsening renal function signifying TTP.

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Authors:

1. Muhammad Zain Mushtaq FCPS(Medicine), Senior Instructor, Department of Medicine, Aga Khan University Hospital, Karachi.
2. Saad Bin Zafar Mahmood MBBS, Chief Resident, Department of Medicine, Aga Khan University Hospital, Karachi.
3. Usman Shaikh FCPS(Hematology), Associate Professor and Section Head, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital, Karachi.
4. Syed Ahsan Ali FCPS(Medicine), Assistant Professor, Department of Medicine, Aga Khan University Hospital, Karachi.

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Corresponding Author:

Muhammad Zain Mushtaq

Mailing Address: Faculty Office Building, 1st floor, Department of Medicine, Aga Khan University Hospital, Stadium Road, Karachi.

Postal Code: 74800

Contact Number: +923337622902

zain.mushtaq@aku.edu

ORCID ID: 0000-0001-5988-577X

Introduction:

COVID-19 infection which was declared as a pandemic in March 2020 has now affected millions around the globe. The clinical features of COVID-19 vary widely from being purely asymptomatic to developing multi-organ dysfunction. The diffuse microvascular thrombi in multiple organs in autopsy cases of COVID-19 are similar to that of thrombotic microangiopathy (TMA).[1] TMA is a clinical entity encompassing thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and secondary TMAs. The classical pentad of TTP includes thrombocytopenia, MAHA, fever, altered mental status and acute kidney injury.[2]

TTP is primarily caused by a depletion of a disintegrin and metalloproteinase (ADAMTS13) which results in increase release of Von Willebrand Factor (VWF) leading to endothelial damage.[3] It is hypothesized that like other viral infections, SARS-CoV-2 virus itself stimulates the release of VWF and Factor VIII.[4] Initially TTP was almost universally fatal but improved treatment measures including exchange transfusions have reduced the mortality rate to 10-20%.[5]

Case report:

A 49-year-old male, motor mechanic by profession and with no prior comorbid conditions presented with high grade fever (102@ F) for three days, watery stools with no blood or mucus for two days and decreased level of consciousness for few hours. His drug history was only significant for paracetamol which he was taking for fever at home. On examination patient was dehydrated and tachycardic. On neurological examination, he had a Glasgow Coma Scale (GCS) of three with pinpoint pupils and decerebrate posture on pain stimulus. Neck was supple with no signs of meningeal irritation and planters were equivocal. Rest of vitals and systemic examination was unremarkable.

Differential diagnosis, investigations and treatment:

Our patient presented with fever and altered level of consciousness raising suspicion of meningoencephalitis. Patient on examination was obtunded, had pinpoint pupils and lost consciousness acutely, hence organophosphorus poisoning was another differential. Malaria and Dengue were ruled out. Urine toxicology screening did not reveal any toxic substances in urine. During the hospital stay when patient developed anemia, severe thrombocytopenia and acute kidney injury, Thrombotic thrombocytopenic purpura (TTP) was our top differential considering the hematological, renal and liver derangements and immediate hematological consultation was sought and prompt management was started on lines of TTP once diagnosis was confirmed.

Routine laboratory workup on first day of admission including complete blood count, renal and liver functions test and inflammatory markers are given in Table 1. Chest X-Ray was unremarkable. Considering the ongoing pandemic, nasopharyngeal swab for SARS-CoV-2 (polymerase chain reaction) was done which was positive. Malarial parasite was not seen on peripheral blood film and Dengue antigen was negative. CAT (computerized axial tomography) scan brain ruled out intracranial bleed or infarct. Patient was managed on lines of COVID pneumonia (mild) and presumed meningoencephalitis. Upon presentation to emergency room, patient was intubated for airway protection and was kept on mechanical ventilator. He was started on high dose of intravenous ceftriaxone and vancomycin to treat presumed meningoencephalitis. Cerebrospinal

fluid analysis was normal hence doses of antibiotics were reduced. During ICU stay patient was on minimal ventilatory settings (Fraction of inspired Oxygen [FiO2] of 40% and Positive End Expiratory Pressure [PEEP of 5]). Mild acute kidney injury on presentation got resolved with intravenous hydration.

On sixth day of hospital stay patient developed anemia, severe thrombocytopenia and acute kidney injury. Laboratory workup including reticulocytes, Direct Coombs, renal and liver function tests are shown in Table 1. Peripheral film on sixth day of hospital stay showed schistocytes as shown in Figure 1. Due to unavailability of ADAMTS13 levels at our center, Plasmic score was calculated to estimate ADAMTS13 deficiency. A score of 5 showed patient to be in intermediate risk group with 6% chance of severe ADAMTS13 deficiency (severe ADAMTS13 deficiency is defined as activity of less than 15%). Lactate dehydrogenase (LDH), total and indirect bilirubin and reticulocyte counts were raised. Direct Coombs test came out to be weakly positive while peripheral blood smear showed presence of schistocytes (5.8%) and thrombocytopenia (as mentioned in Table 1). Immediate hematological consultation was sought and prompt management was started on lines of TTP. Intravenous methylprednisolone pulse (1 gram) and plasma exchange (PLEX) was instituted. Steroid therapy was continued for three days and seven sessions of PLEX were done. Patient also received one dose of IV rituximab at a dose of 375mg/m^2. Patient's hemoglobin and platelet count started to increase after first session of PLEX. Renal function along with urine output also started to improve. Since target platelet count was not achieved after five sessions of PLEX, two additional sessions were done. Patient was extubated after third session of PLEX. However hospital stay got complicated with development of ventilator associated pneumonia (tracheal secretions showed growth of*Escherichia coli* and *Pseudomonas aeruginosa*) and candidemia (blood culture showed growth of *Candida glabrata*) which was treated with intravenous meropenem and IV Amphotericin B.

Outcome and follow-up:

On 16$^{\text{th}}$ day of hospital stay patient was discharged home with normal hematological laboratory parameters and slightly deranged renal function (creatinine of 3.1 mg/dl). Patient was sent home on Amphotericin B for candidemia. He had no disability on discharge. Upon clinic visit after 10 days, his renal function had improved to 2.1 mg/dl, with hemoglobin of 9.5 g/dl and platelets of 265,000/µL. His LDH and liver function tests had also normalized and he was allowed to resume his work. Figure 2 and Figure 3 show the trend of hemoglobin, platelets, lactate dehydrogenase (LDH) and schistocytes percentage over the course of hospital stay as well as on follow-up. Patient's creatinine had decreased to 1.0 mg/dl and hemoglobin had increased to 11.9 g/dl after 3 weeks of discharge.

Discussion:

Here we present a case of COVID-19 which was complicated by TTP which is an extremely rare complication of COVID-19 as per the current information available in the literature. The widespread thrombus formation in COVID-19 together with low grade MAHA signified by low hemoglobin, raised LDH, increase in bilirubin and presence of schistocytes mimics TTP which is a part of TMA.[3]

TTP is classified as either primary/idiopathic or secondary/acquired, with acquired being the more common variant of the disease.[6] Acquired TTP has female preponderance and affects women intra and postpartum with an estimated prevalence of 1 in 25,000 pregnancies.[6, 7] Autoantibody induced destruction or suppression of a disintegrin and metalloproteinase with a thrombospondin type I motif, member 13 (ADAMTS13), an enzyme that splits large multimers of von willebrand factor, is considered the precursor for TTP. TTP can also be precipitated by infections with literature citing case reports showing association between TTP and *H1N1* as well as between TTP and*Arboviruses.* [8, 9] SARS-CoV-2 has also been associated with TTP and literature review has revealed three such cases.

A case of relapsing TTP (history of TTP 30 years ago) due to COVID was reported by Capecchi et al in a 55 year old male patient from Italy with generalized weakness, shortness of breath and chest discomfort. TTP was suspected due to rapidly dropping platelet counts 184,000/µL to 14000/µL, along with decrease in hemoglobin level 11.4 to 7.4 g/dl and presence of schistocytes on peripheral blood smear. Plasma ADAMTS13 levels were undetectable and PLEX was initiated promptly in combination with Caplacizumab, a humanized

antibody against von willebrand factor. In this patient two nasopharyngeal PCR for SARS-CoV-2 were negative but COVID antibody against SARS-CoV-2 was positive. Hospital stay got complicated because of acute right parietal lobe infarct and hemoptysis due to ectatic artery with a fistulous tract in right main bronchus for which angioembolization of culprit artery was performed. 14 sessions of PLEX were done and glucocorticoids along with Caplacizumab were continued for 12 days. Patient was discharged home after 31 days with normal platelet counts.[10]

Albiol et al reported a case of 57-year old Spanish woman with history of breast cancer who presented with fever and anosmia. Two nasopharyngeal samples for SARS-CoV-2 were negative but IgG antibodies for SARS-CoV-2 were positive. On 5th day of hospital stay patient developed severe thrombocytopenia and low hemoglobin. TTP was established on the basis of MAHA, low platelet counts and very low activity of ADAMTS13. Patient responded to PLEX and was discharged home.[11]

Similarly, Hindilerden et al from Turkey reported a case of 74-year old lady who presented with cough and generalized weakness. PCR for SARS-CoV-2 was positive. On arrival, she had hemoglobin of 6.6 g/dl and platelet counts of 48,000/μL. Peripheral blood smear showed schistocytes. Patient was managed on lines of presumed acquired TTP by initiation of PLEX and methylprednisolone pulse therapy. ADAMTS13 levels were reported to be $< 0.2\%$ and ADAMTS13 inhibitor concentration was more than 90%. Patient received 11 sessions of PLEX and was discharged home on a hemoglobin levels of 10.6g/dl and platelet counts of 398,000/μL.[12]

To the best of our knowledge this is the fourth case of TTP associated with COVID 19 and first from South Asia. Our patient is unique in several aspects as our patient had no comorbid conditions prior to this illness. He presented with fever and decreased level of consciousness. He was intubated and managed in intensive care unit. Our patient developed low hemoglobin, platelets and deranged renal function on 6th hospital stay. The 3 case reports mentioned in literature predominately showed hematological manifestations of TTP while deranged renal function and neurological symptoms have not been described. Our patient demonstrated significant renal dysfunction and neurological symptoms along with hematological derangements of TTP. All the symptoms either resolved completely or improved with treatment. However, in our case we were not able to do ADAMTS13 levels because of unavailability of this test in our institute. However, Plasmic score was calculated in order to estimate ADAMTS13 deficiency. Our patient responded well to PLEX and glucocorticoids and a seven sessions of PLEX were done in total. COVID-19 was treated symptomatically as patient had no overt respiratory symptoms. A retrospective study done at our hospital included 25 patients with TTP treated with PLEX. The study concluded that neurological and renal involvement in TTP was a strong predictor of outcomes and clinical improvement. However, a delay in initiation of PLEX due to late presentation was a major obstacle.[13] Our patient also received one dose of Rituximab at a dose of 375 g/m^2. A study done in China showed that adding rituximab to PLEX and steroids increases the platelet counts in approximately 80% of patients and also reduces mean time to attain a normal platelet count.[14] This study also illustrated that prognosis is better if rituximab is administered within 3 days of treatment initiation. Rituximab was originally used in TTP for refractory disease but it is now used as first line with PLEX based on observational studies signifying that rituximab may accelerate recovery and reduces the risk of relapse.[15]Further doses of Rituximab were withheld due to development of hospital acquired infections. Hospital stay got complicated with *Candida glabrata* in blood for which intravenous Amphotericin B was started. Of the three previous studies only one has described any complication but none has shown hospital acquired infections.

Ethical considerations

The authors verify that they have obtained all appropriate patient consent forms. In the form, next of kin has given his consent for images and other clinical information to be reported in the journal. Next of kin understands that names and initials will not be published and efforts will be made to hide patient's identity. Furthermore, permission for case report was granted by the ethical review committee of the institution.

Authorship List:

1. Muhammad Zain Mushtaq made substantial contributions to conception, drafting the manuscript and revising it critically.
2. Saad Bin Zafar Mahmood was involved in drafting the manuscript and revising it critically.
3. Usman Shaikh gave the final approval of the version to be published.
4. Syed Ahsan Ali helped in reviewing the final version of the manuscript.

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Tables

Table 1: Laboratory investigations on day 1 and day 6

Hemoglobin (g/dL)	1
White Blood Cell count (x10^9/L)	1
Platelets (x10^9/L)	6
Prothrombin time (seconds) Activated partial thromboplastin time (seconds) Fibrinogen level (mg/dL) Schistocytes (%)	1
Reticulocytes (%)	-
Direct Coombs	-
Blood Urea Nitrogen (mg/dL)	1
Creatinine (mg/dL)	1
C-Reactive Protein (mg/L)	0
Ferritin (ng/mL)	2
Lactate dehydrogenase (IU/L)	8
D-dimer (mg/L FEU)	4
Procalcitonin (ng/mL)	0
Total bilirubin (mg/dL)	0
Direct bilirubin (mg/dL)	0
Gamma-glutamyl transferase (IU/L)	3
Alanine transaminase (IU/L)	2
Aspartate transaminase (IU/L)	1
Alkaline phosphatase (IU/L)	8

Figures (Illustrations)

Figure 1: Peripheral film on 6^{th} day of hospital stay

Figure 2: Trend of Hemoglobin (Hb) and Schistocytes during hospital stay

Figure 3: Trend of Lactate Dehydrogenase (LDH) and Platelets (Plt) during hospital stay