CASE REPORT

COVID-19 and thrombotic thrombocytopenic purpura: A case report

Muhammad Zain Mushtaq[1], Saad Bin Zafar Mahmood[2], Syed Ahsan Ali[3], Muhammad Usman Shaikh[4]

Abstract

The clinical presentation of COVID-19 varies from being asymptomatic to developing acute respiratory distress syndrome and multi-organ dysfunction. The diffuse microvascular thrombi in multiple organs seen in the autopsy of COVID-19 patients are similar to that of thrombotic microangiopathy (TMA). TMA is characterised by thrombus formation in the microvasculature with laboratory findings of microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. A 49-year-old male presented to the Aga Khan University Hospital, Karachi. with fever, diarrhoea, altered level of consciousness, and a positive nasopharyngeal swab for SARS-CoV-2. He developed severe thrombocytopenia, MAHA with 5.8% schistocytes, and worsening renal function on the sixth day of admission. Diagnosis of thrombotic thrombocytopenic purpura (TTP) was established based on PLASMIC score, and he was successfully treated with intravenous (IV) Methylprednisolone, therapeutic plasma exchange and IV Rituximab. The case emphasises the need to keep TTP in the differential diagnosis when a patient with COVID-19 develops severe thrombocytopenia, acute renal failure, or impaired level of consciousness, since prompt diagnosis and treatment is necessary to gain favourable outcome.

Keywords: COVID-19, thrombotic thrombocytopenic purpura (TTP), Rituximab, PLASMIC score.

DOI: https://doi.org/10.47391/JPMA.4992

Submission completion date: 20-11-2021

Acceptance date: 01-06-2022

Introduction

Thrombotic microangiopathy (TMA) is a clinical entity encompassing thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome (HUS), and secondary TMAs. TMA is characterised by thrombus formation in the microvasculature (mainly arterioles) with laboratory findings of microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia.[1] The classical pentad of TTP includes thrombocytopenia, MAHA, fever, altered mental state, and acute kidney injury and is primarily caused by a depletion of a disintegrin and metalloproteinase (ADAMTS13) which results in increased release of Von Willebrand Factor (VWF) leading to endothelial damage.[1] It is hypothesised that like other viral infections, Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) stimulates the release of VWF and Factor VIII.[2] Literature reports sporadic cases of TTP associated with Coronavirus disease 2019 (COVID-19).[3] Here we report the first case of TTP successfully treated in a patient with COVID-19 from South Asia.

[1-3]Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan; [4]Department of Oncology, Aga Khan University Hospital, Karachi, Pakistan.

Correspondence: Muhammad Zain Mushtaq. e-mail: zain.mushtaq@aku.edu ORCID ID. 0000-0001-5988-577X

Case Report

A 49-year-old male, with no prior comorbid conditions presented to the Aga Khan University Hospital, Karachi, in July 2020 with high grade fever (max 38.8°C) for three days, loose stools (six to seven episodes) that were watery in consistency with no blood or mucus for two days, and decreased level of consciousness for a few hours. He was only taking paracetamol for fever at home. On examination in ED, the patient was dehydrated, tachycardic, and had a Glasgow Coma Scale (GCS) of three with pinpoint pupils and decerebrate posture on pain stimulus. The neck was supple with no signs of meningeal irritation and planters were equivocal. The rest of the vitals and systemic examination was unremarkable. He was intubated and kept on mechanical ventilator for airway protection.

Blood tests on admission revealed haemoglobin of 11.7 g/dL (12.3-16.6 g/dL) and platelets of 69 x10^9/L (154-433 x10^9/L), white blood cell count (WBC) of 13.4 x10^9/L (4.8-11.3 x10^9/L) with 85.1% (34.9%-76.2%) neutrophils, and creatinine of 1.7 mg/dL (0.9-1.3 mg/dL). His blood urea nitrogen was 11 mg/dL (6-20 mg/dL), total bilirubin was 0.8 mg/dL (0.1-1.2 mg/dL), alanine transaminase was 223 IU/L (<45 IU/L), aspartate transaminase was 378 IU/L (<35 IU/L), alkaline phosphatase was 59 IU/L (45-129 IU/L), and prothrombin time was 12.2s (9.3-12.8s). Chest X-Ray was unremarkable. Considering the ongoing pandemic, nasopharyngeal swab for SARS-CoV-2 was done which was positive. Malarial parasite was not seen on peripheral blood film and dengue antigen was negative. Urine toxicology screening did not reveal any toxic substances. CT scan of the head ruled out intracranial bleeding or infarction.

Inflammatory markers done for COVID-19 were as follows: C-reactive protein 0.38mg/L (0-10 mg/L), ferritin 292 ng/ml (22-322 ng/ml), lactate dehydrogenase (LDH) 807 IU/L (120-246 IU/L), and d-dimer 4.7 mg/L FEU (<0.5

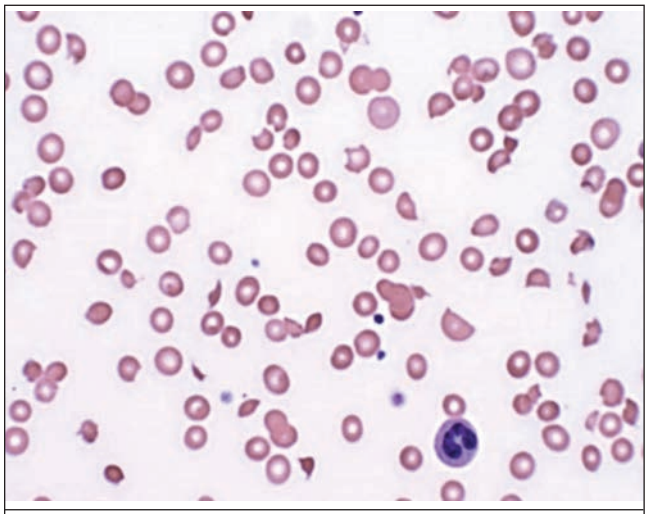

Figure Peripheral film on the sixth day of hospital stay.

mg/L FEU). He was started on high dose of empiric intravenous (IV) Ceftriaxone and Vancomycin to treat the presumed meningoencephalitis and IV hydration for acute kidney injury. He remained on minimal ventilatory settings (FiO2 of 40% and PEEP of 5) for five days. However, on the sixth day of intensive care unit (ICU) stay, renal function deteriorated and a drop in haemoglobin and platelets was noted. Labs showed haemoglobin at 7.2 mg/dL (12.3-16.6 mg/dL), platelets at 17 x10^9/L (154-433 x10^9/L), creatinine at 2.5mg/dL which later increased to 3.3mg/dL (0.9-1.3 mg/dL), LDH of 974 IU/L (120-246 IU/L), total and indirect bilirubin at 3.1 mg/dL (0.1-1.2 mg/dL) and 2.3 mg/dL (0.1-0.8 mg/dL), respectively, alanine transaminase at 128 IU/L (<45 IU/L), aspartate transaminase at 104 IU/L (<35 IU/L), and reticulocyte counts at 2.6% (0.6% to 2.4%). Direct Coombs test was weakly positive, while peripheral blood smear revealed presence of 5.8% schistocytes (Figure). Thrombotic thrombocytopenic purpura (TTP) was considered as the top differential considering the haematological, renal, and liver derangements and prompt management was started once the diagnosis was confirmed. Due to unavailability of ADAMTS13 level, PLASMIC score was calculated to estimate ADAMTS13 deficiency. A score of 5 meant the patient was in intermediate risk group with 6% chance of severe ADAMTS13 deficiency; based on this result TTP was diagnosed. Immediate treatment in the form of intravenous Methylprednisolone pulse (1 gram) was started for three days and five sessions of plasma exchange (PLEX) was also instituted. The patient received one dose of IV Rituximab at 375mg/m^2. The patient's haemoglobin and schistocytes started to improve along with improvement in platelets, LDH creatinine, and urine output. Labs showed haemoglobin at 7.9 mg/dL (12.3-16.6 mg/dL), platelets at 79 x10^9/L (154-433 x10^9/L), LDH at 431 IU/L (120-246 IU/L), and creatinine at 3.1 mg/dL (0.9-1.3 mg/dL). Since the target platelet count was not achieved after five sessions of PLEX, two additional sessions were done. The patient was extubated after the third session of PLEX. During his stay in ICU, the patient developed ventilator-associated pneumonia (*Escherichia coli* and *Pseudomonas aeruginosa*), which was treated with IV Meropenem, and Candidaemia (*Candida glabrata*) for which IV Amphotericin B was administered. The patient was discharged on the 16th day of admission with a haemoglobin of 8.3 g/dL (12.3-16.6 g/dL), platelets of 480 x10^9/L (154-433 x10^9/L), and creatinine of 3.1 mg/dL (0.9-1.3 mg/dL). He had no disability at the time of discharge, and was functional class I. Upon follow-up after 10 days, his creatinine had improved to 2.1 mg/dL (0.9-1.3 mg/dL), with haemoglobin of 9.5 g/dL (12.3-16.6 g/dL), and platelets of 265×10^9/L (154-433 x10^9/L). His LDH and liver function tests had normalised, and he was allowed to resume his work.

Discussion

Here we have presented the case of COVID-19 which was complicated by TTP which is a rare occurrence. The widespread thrombus formation in COVID-19 together with low grade MAHA signified by low haemoglobin, raised LDH and bilirubin, and the presence of schistocytes mimics TTP which is a part of TMA.[1] TTP is classified as either primary/idiopathic or secondary/acquired, with acquired being the more common variant of the disease.[4] TTP has been seen to be precipitated by infections with literature citing case reports showing association between TTP and H1N1 as well as between TTP and Arboviruses.[2,5] SARS-CoV-2 has also been associated with TTP. Literature review shows that there have been some differences in the presentation, diagnostics, and management of such patients.[3,6-9] Majority of the cases had prior history of diabetes, hypertension, or malignancy.[3,6,7] All the cases reported so far have shown to have bicytopenia, with only two case reporting disturbances in haematological, renal, and neurological parameters[7,8] with one needing admission to ICU.[7] Two patients developed ischaemic stroke as a complication of TTP.[6,7] Our case is unique as it did not have any past medical or surgical history but presented with all the features of TTP including haematological, renal, and neurological parameters. However, our patient did not develop any ischaemic complications.

Though most of the cases have reported the use of ADAMTS13 in the diagnosis of TTP, two cases made use of PLASMIC score.[6,9] The use of PLASMIC score in the management of TTP has been propagated as a cost-effective method in literature.[10] The PLASMIC score has turned out to be a valuable tool for the early diagnosis of

TTP associated with ADAMTS13 deficiency. It gives one point to each variable: platelets < 30 x10^9/L, haemolysis (any of the following—reticulocyte count > 2.5%, undetectable haptoglobin, or indirect bilirubin > 2.0 mg/dL), no active cancer, no history of solid-organ or stem-cell transplant, prothrombin time > 15s, creatinine < 2.0mg/dL, and a mean corpuscular volume of < 90fL. A score of 0-4 is labelled as low risk with 0% risk of severe ADAMTS13 deficiency, while a score of 5 is labelled as intermediate risk group with 6% chance of severe ADAMTS13 deficiency. Score above 5 is characterised as high-risk group with a 72% chance of ADAMTS13 deficiency.[10] Unfortunately, due to the non-availability of ADAMTS13 levels at our institute, we were unable to test for it but made use of PLASMIC score in diagnosing TTP and characterising the severity of ADAMTS13 deficiency.

Regarding treatment, literature shows that most cases have been treated with PLEX and glucocorticoids apart from one case where due to lack of PLEX, IVIG and fresh frozen plasma were used.[3] However, the number and volume of PLEX varies according to the severity. The use of monoclonal antibodies has become common in treating COVID-19 associated TTP. Rituximab and Caplacizumab both have been used with success in these patients.[3,6,8,9] Our patient also received the standard regimen of glucocorticoids and PLEX which was increased due to refractory thrombocytopenia. The standard treatment was supported by the use of a single dose of Rituximab.

Conclusion

Haematological complications of COVID-19 are increasingly being acknowledged. Our case highlights the need for timely recognition of these complications to achieve favourable outcomes and the absence of other possible causes suggests role of COVID-19 in the development of TTP in our case as it had all the typical features of anaemia, thrombocytopenia, and deranged renal functions. Our case also shows the importance of using Rituximab to achieve a good remission as follow up of the patient showed normal levels of platelets and improving renal functions.

Consent: Consent for publication of the case report was obtained from the family members of the patient.

Disclaimer: None.

Conflict of interest: None.

Funding disclosure: None.

References

1. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of Covid-19 coagulopathy. Crit Care 2020;24:360. doi: 10.1186/s13054-020-03077-0.
2. Bastos MLA, Araújo RMO, Oliveira DS, Cavalcante ANM, Silva Junior GBD. Thrombotic thrombocytopenic purpura associated with dengue and chikungunya virus coinfection: case report during an epidemic period. Rev Inst Med Trop Sao Paulo 2018;60:e48. doi: 10.1590/s1678-9946201860048
3. Tehrani HA, Darnahal M, Vaezi M, Haghighi S. Covid-19 associated thrombotic thrombocytopenic purpura (TTP); A case series and mini-review. Int Immunopharmacol 2021;93:107397. doi: 10.1016/j.intimp.2021.107397.
4. Vacca VM Jr. Acquired autoimmune thrombotic thrombocytopenic purpura. Nursing 2019;49:22-9. doi: 10.1097/01.NURSE.0000549721.69197.4d
5. Koh YR, Hwang SH, Chang CL, Lee EY, Son HC, Kim HH. Thrombotic thrombocytopenic purpura triggered by influenza A virus subtype H1N1 infection. Transfus Apher Sci 2012;46:25-8. doi: 10.1016/j.transci.2011.10.024.
6. Altowyan E, Alnujeidi O, Alhujilan A, Alkathlan M. Covid-19 presenting as thrombotic thrombocytopenic purpura (TTP). BMJ Case Rep 2020;13:e238026. doi: 10.1136/bcr-2020-238026
7. Al-Ansari RY, Bakkar M, Abdalla L, Sewify K. Critical Care Covid-19 Patient with a Picture of Thrombotic Thrombocytopenic Purpura. Eur J Case Rep Intern Med 2020;7:e002143. doi: 10.12890/2020_002143.
8. Nicolotti D, Bignami EG, Rossi S, Vezzani A. A case of thrombotic thrombocytopenic purpura associated with COVID-19. J Thrombolysis 2021;52:468-70. doi: 10.1007/s11239-020-02362-7.
9. Shankar K, Huffman DL, Peterson C, Yasir M, Kaplan R. A Case of COVID-19 Induced Thrombotic Thrombocytopenic Purpura. Cureus 2021;13:e16311. doi: 10.7759/cureus.16311.
10. Upadhyay VA, Geisler BP, Sun L, Uhl L, Kaufman RM, Stowell C, et alUtilising a PLASMIC score-based approach in the management of suspected immune thrombotic thrombocytopenic purpura: a cost minimisation analysis within the Harvard TMA Research Collaborative. Br J Haematol 2019;186:490-8. doi: 10.1111/bjh.15932