
Review

COVID-19 Associated Thrombotic Thrombocytopenic Purpura: A Case Report and Systematic Review

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Abstract: Introduction: The proliferation of literature regarding COVID-19 pandemic has served to highlight a wide spectrum of disease manifestations and complications like thrombotic microangiopathies. Our review with a brief case presentation highlights the increasing recognition of TTP in COVID-19 and describes its salient characteristics. **Methods:** We screened the available literature in Pubmed, EMBASE and Cochrane database from inception till April 2022 of articles mentioning COVID-19 associated TTP in English Language. **Results:** From 404 records, we included 8 articles mentioning data of 11 patients in our review. TTP was predominantly reported in females (72%) with a mean age of 48.2 years (SD 15.1). Dyspnea was the most common symptom in 1/3rd of patients (36.6%). Neurological symptoms were reported in 27.3% of cases. The time to diagnosis of TTP was 10 days (SD: 5.8) from onset of Covid-19. All 11 cases underwent plasma exchange (PLEX), with a mean of 12 sessions per patient, whereas six cases received Rituximab (54.5%), and three received Caplacizumab (27.3%). One patient died from the illness. **Conclusion:** This review of available literature highlights the atypical and refractory nature of COVID-19 associated TTP. It required longer sessions of PLEX with half of the patients receiving at least one immunosuppressant.

Keywords: SARS-COV-2; COVID-19; TTP; refractory; thrombotic microangiopathies

What is the new aspect of your work?

This is the first systematic review combining the available data on the rare association of COVID-19 triggered thrombotic thrombocytopenic purpura.

What is the central finding of your work?

COVID-19 associated TTP had atypical mode of presentation with none reporting fever and only 27.3 % patients had neurological symptoms. The development of TTP was unrelated to severity of COVID-19 in our review with a mean from COVID-19 symptoms to TTP diagnosis of 10 days. In terms of management, it required a mean of 12 plasma exchange sessions per patient with more than half requiring immunosuppressive therapies. This may signify the refractory nature of TTP.

What is (or could be) the specific clinical relevance of your work?

The pathophysiology and management of TTP in COVID-19 remains an evolving field. This review of available literature highlights the atypical and refractory nature of COVID-19 associated TTP that needs early recognition and appropriate management of this life-threatening condition.

1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is part of a broad spectrum of thrombotic microangiopathies (TMAs) that presents with significant manifestations of hemolytic anemia. The pathophysiology of this entity is endothelial dysfunction characterized by thrombocytopenia, hemolytic anemia, schistocytes, and tissue injury, which are caused by the deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), allowing the unregulated proliferation of microthrombi composed of von Willebrand factor and platelets. Only a small percentage of patients present with the characteristic pentad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, neurologic manifestations, fever, and renal failure [1]. The central nervous system and the kidneys are the two organ systems most afflicted by TTP [2].

The Oklahoma TTP-HUS registry approximates the incidence of TTP as 3 per 1 million adults year with a median age of diagnosis as 41 years [3]. TTP is a medical emergency with a 90% death rate if not diagnosed and treated promptly. It can be challenging to diagnose immune mediated TTP since its clinical manifestations are similar to those of other TMAs, including moderate to severe thrombocytopenia, MAHA, and indications of ischemia and end-organ destruction. Although diagnosis is made clinically, the activity of ADAMTS13, which is <10% in acute TTP, is measured to support the diagnosis [4]. However, ADAMTS13 testing is not readily available in many hospitals, and results can take several days, which may be impractical for a timely diagnosis.

As COVID-19 pandemic rapidly spread around the globe, many scientific facts, and pieces of data about the pathogenicity of this virus were discovered. Deep venous thrombosis, pulmonary thromboembolism, and TMAs are some of the conditions associated with COVID-19 coagulopathy [4]. The association between TTP and COVID-19 has been rarely described to date. This systematic review focused on data from adult patients who were diagnosed with COVID-19 associated TTP. This review aims to provide a comprehensive summary of the available evidence with regard to COVID-19 associated TTP with a brief mention of a case at our healthcare center.

2. Case Presentation

A 33-year-old, previously vaccinated female was diagnosed with COVID-19 infection via nasopharyngeal PCR after experiencing flu-like symptoms. She did not require any treatment at that time. On day 10 from symptom onset, she presented to the hospital with increased bruising and heavy menstrual flow along with ecchymosis and petechiae on her arms and chest. She was afebrile, with a regular pulse of 89 beats/min, respiratory rate 15 breaths/min, blood pressure of 124/79mmHg, and saturation of 100% on ambient air. Laboratory evaluation revealed hemoglobin of 9.1g/dl, platelets of 9.0×10^3 /microL, haptoglobin <30mg/dl, LDH 695 IU/L, bilirubin 3.0 mg/dl, creatinine of 0.52 mg/dl, and marked schistocytes on peripheral smear with a negative coombs test. She had negative ANA, lupus anticoagulant, CMV serology, parasite smear, HIV, Hepatitis B, and pregnancy test.

With a high clinical suspicion of immune TTP, and a PLASMIC score of 7, treatment was initiated with Prednisone 1mg/kg/day. She also received five sessions of plasmapheresis (PLEX), and one dose of Rituximab (RTX). On day 5 of admission, her platelet count improved to 181×10^3 IU/L. ADAMTS13 activity level, that had been drawn prior to starting PLEX, was <0.03 % (normal > 60%) and with ADAMTS13 inhibitor value of 2.3 BU (normal < 0.5 BU).

She was discharged from the hospital on a prednisone taper. Follow up in our clinic the following week showed a decline in platelet count to 85×10^3 IU/L. Repeat ADAMTS13 level was still undetectable, and ADAMTS13 inhibitor was 1.4 BU. Patient was readmitted and reinitiated on PLEX and RTX with addition of pulse dose methylprednisolone 1 g daily x3 days followed by 1 mg/kg prednisone daily, and Caplacizumab (CZB). After the fifth day, platelets improved over 150×10^3 IU/L and she was discharged home with a

plan to complete CZB daily for thirty days along with Rituximab for a total of four doses with successful recovery.

3. Methods

3.1. Search strategy

We performed a comprehensive database search on MEDLINE (via PubMed), EMBASE, and Cochrane database for published articles describing the association of COVID-19 and TTP from inception until February 2022. Search strategy was performed using a concise vocabulary as shown in **Supplementary File 1**. The search strategy was designed and performed by an experienced librarian with input from the principal investigator. We limited our search to articles published in English language only.

3.2. Study selection and characteristics

All articles in English were screened by two authors individually, HC and UN. The extracted articles were screened by their title and abstract. Articles not meeting the inclusion criteria or without confirmation of TTP with ADAMTS 13 levels were not included. We restricted our inclusion to adults aged 18 and older. We excluded the articles reporting a relapse of TTP in previously diagnosed immune TTP. We also excluded articles reporting TTP associated with COVID-19 vaccination. Full text articles were reviewed after the initial screening. Commentaries, review articles and abstracts without full texts were excluded as well. We included 8 articles including the data of 11 patients with COVID-19 associated TTP [5-12] as depicted in PRISMA flow diagram (**Figure 1**).

3.3. Quality Assessment of Articles

All the included articles were case reports and series. The case reports were assessed for quality by using the Joanna Briggs Index (JBI) Critical Appraisal Checklist for Case Reports available at <https://wiki.joannabriggs.org/display/MANUAL/Appendix+7.4+Critical+appraisal+checklist+for+case+reports> (**Supplementary File 2**).

4. Results

4.1. Patient Characteristics

As depicted in **Table 1**, the cases of COVID-19 induced TTP had a female predominance (n=8, 72.7%) with a mean age of 48.4 years (SD: 15.1 years). Two cases had previous diagnosis of locally advanced breast cancer in remission and one patient was pregnant. Dyspnea was the most common symptom at presentation present in more than 1/3rd of the patients (n=4, 36.6%), with neurological symptoms being the second most common (n=3, 27.3%) of whom two presented with seizures (18.2%). One patient presented with back pain, while one patient presented with rectal bleeding. None of the patients had febrile illness with onset of TTP. The mean duration from the onset of COVID-19 to diagnosis of TTP was 10 days (SD: 5.8).

(i)	25/F	Pregnant	Severe respiratory symptoms	Not mentioned	Dexamethasone 8 mg BID daily x 14 days	10 days sessions	No	No
(ii)	56/F	Locally advanced breast cancer/In remission	Severe respiratory symptoms	Not mentioned	Dexamethasone 8 mg BID daily x 14 days	14 days sessions exchange	Yes	No
(iii)	57/F	None	Severe respiratory symptoms	Not mentioned	Dexamethasone 8 mg BID daily x 14 days	14 sessions	No	No
(iv)	38/M	None	Rectal bleeding	Not mentioned	Dexamethasone 8 mg BID x 21 days	21 sessions	Yes	No

(CZB= Caplacizumab, FFP = Fresh Frozen Plasma, PLEX = Plasmapheresis, RTX = Rituximab).

4.2. Laboratory Parameters

The mean hemoglobin (Hb) at the time of TTP diagnosis was 7.6 g/dl (SD: 2.1), mean platelet level was 25.8×10^3 /microL (SD: 26.3×10^3), median LDH level was 1422 U/L (range: 545-10,977 U/L). All of the included eleven cases had a reported ADAMTS13 activity of less than 10%. Eight (72%) cases had elevated ADAMTS 13 inhibitor or antibody levels with the exception of three cases [6,11,12]. The pertinent laboratory investigations with other inflammatory markers and radiological findings are as summarized in **Table 2**

4.3. Treatment

All 11 cases underwent PLEX, with an average number of 12 sessions (SD: 4.36) per patient (n=10). All patients received steroids, six patients (54.5%) received dexamethasone with an average dose of 16 mg/day (equivalent methyl prednisone dose = 85.3mg/day), and five patients (41.7%) receiving prednisone/methylprednisone with an average dose of 1mg/kg/day. Two cases did not mention the steroid dosage used. Out of 11 cases, six received RTX (54.5%) [5,7,9,10,12] while three received CZB (27.3%), including two cases that received it in addition to RTX [9,10] (Table 2). Almost half of the patients did not receive additional immunosuppressants with PLEX despite more than 5 sessions of PLEX.

Table 2. Laboratory findings in patients with COVID-19 associated TTP.

Study/ year	Hb in g/dL	Plt count x 10 ³ /m L	INR	LDH (U/L)	ADAMTS 13 activity (%)	ADAMTS 13 inhibitor level (normal <12 U/ml; <0.5BU)	ADAMTS 13 antibody titer (normal <15 U/ml)	CT/CXR of lung findings
Albiol et al. 2021[5]	6.9	13	N/A	1594	2.0%	5.2 BU	-	CT thorax Normal
Beaulieu et al. 2021[6]	6.0	18	1.1	1422	<10%	-	0.5	CXR normal
Dhingra et al. 2021[7]	8.3	20	N/A	10,977	undetectable	3.0 BU	-	n/a
Hindilerden et al. 2020 [8]	6.6	48	Normal	1108	0.2%	>90 U/mL	-	Patchy peripheral bibasilar ground glass opacities in both lungs. MRI brain normal
Law et al. 2021[9]	7.0	14	1.1	788	<5.0%	63 U/ml	-	n/a
Nicolotti et al. 2021[10]	6.0	7	Normal	2961	<5.0%	57 U/mL	-	Interstitial pneumonia involving 25% of lung parenchyma
Shankar et al. 2021[11]	13.7	9	Normal	1068	3.0%	0.60 BU	-	n/a
Tehrani et al. [12]								
(i)	7.0	10.5	1.4	3465	8.0%	-	85	Patchy infiltration
(ii)	6.0	41	1.2	1520	0.01%	-	36.2	Patchy bilateral infiltration
(iii)	7.9	98	1.5	1150	0.86%	-	25.3	Not mentioned
(iv)	8.0	5.0	1.3.	545	0.06%	-	14	Patchy infiltration in the right upper lobe

ADAMTS-13= A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, CT = computed tomography; BU= Bethesda unit; CXR= Chest X-ray; CRP = C-reactive protein; Hb= hemoglobin; INR= International normalized ratio; LDH= Lactate Dehydrogenase, Plt = platelets.

4.4. Outcome

Majority of cases (90.9%) had favorable outcome with no mention of early relapse. There was one reported death [12]. The median length of hospital stay was 18.5 days (7-

51). The duration of ICU stay was only reported in two cases with one patient requiring three weeks of intensive care.

5. Discussion

Our review highlights the increasing recognition of TTP in COVID-19 infections and summarizes important features of COVID-19 associated TTP. TTP was predominantly reported in females (72%), neurological symptoms were present in 27.3% of cases with absence of fever at the time of TTP diagnosis amongst all. The mean number of days for diagnosis of TTP was 10 days (SD: 5.8) from onset of COVID-19 symptoms. The type and dose of steroid therapy was inconsistent in majority cases, more than half received Dexamethasone 16mg/day. All 11 cases underwent PLEX with a mean of 12 sessions (SD 4.36) per patient, whereas six cases received RTX (54.5%) and three cases received CZB (27.3%) in addition to PLEX and corticosteroid therapy.

These findings may suggest a refractory nature of COVID-19 associated TTP. The current practice for management of acquired TTP is to perform at least 5 sessions of PLEX or until platelet and hemolysis parameters normalize for two consecutive days [13,14]. The cases requiring more than 4-7 sessions are labeled as refractory. The relapse rate in acquired TTP varies from 10-40%, with response rates of nearly 100% in those who receive RTX shown in a few observational studies [15]. These findings have not been replicated in our review. Although majority of the cases required more than 5 days of PLEX, nearly half of them received RTX. The lack of robust data favoring this approach and concomitant COVID-19 infection may have guided decision-making in these cases, as effects of RTX on COVID-19 infection can be detrimental. Interestingly, clinicians opted to use RTX in two of the reported cases despite severe COVID-19 infection and had favourable outcome in one [10,12].

CZB, a novel monoclonal therapy that inhibits the binding of vWF to glycoprotein 1b present on platelets, has been increasingly used as part of the treatment strategy for severe TTP. CZB has been shown to decrease rates of relapse and time to platelet recovery in a randomized double-blind study [16]. Our review showed that 3 cases (27.3%) required CZB, with triple therapy comprising PLEX, RTX and CZB in only two of these [9-11]. In one case by Nicolotti et al. CZB was added owing to inadequate response after 11 PLEX sessions and 2 doses of RTX. One case by Law et al. also had minimal response to frontline RTX, leading to addition of CZB with PLEX on day 17[9]. None of the cases from this review mentioned an early relapse on follow up. However, our patient had an early relapse with 5 sessions of PLEX and 2 weeks of RTX therapy requiring addition of CZB. The triple therapy is supported by a recent prospective study supporting the role of RTX and CZB as complementary in the management of acquired TTP [17]. Another consideration in the management of refractory TTP cases in COVID-19 infection may be widespread activation of complement mediated endothelial injury causing micro thrombosis. One series of 5 cases showed evidence of complement deposition in vascular tissue without viral cytopathic effects on endothelium [18]. These cases can be difficult to differentiate from acquired TTP and appear to be more consistent with a COVID-19 induced complement mediated TMA. In these cases, role of complement inhibition may be effective. However, this was not reported in any of our reviewed cases.

Although a causal relation remains to be elucidated, viral infections are a known trigger for secondary or immune TTP with proposed mechanisms including both direct endothelial injury and creation of ADAMTS13 auto-antibodies [19,20]. The hypercoagulable state conferred by COVID-19 has also been postulated to be direct cytopathic injury to endothelial cells mediated by entry via ACE-2 receptors as well [21]. Small scale studies have also shown decreased ADAMTS13 levels secondary to COVID-19 inflammation [22]. We hypothesize that these multiple mechanisms may explain the refractory nature of COVID-19 associated TTP. Two recent studies by Mancini et al. [22] and by Pascreau et al. [23] including 120 patients showed the correlation of decreased ADAMTS13 activity with severity of COVID-19 illness. Interestingly, most reviewed cases (81.8%) with

confirmed TTP had undetectable ADAMTS-13 activity (i.e., < 10%) without clinically severe COVID-19 infection.

The combination of elevated vWF, Factor VIII, fibrinogen, and D-dimer levels in COVID-19 infections have also been noted in studies [24]. This in turn has led to a spectrum of thrombotic disorders including COVID-19 induced micro thrombotic disease which differs from TTP or other primary TMAs in the absence of MAHA and thrombocytopenia. When present, severe thrombocytopenia and hemolytic anemia could be representative of disseminated intravascular coagulation (DIC), HUS or drug related TMA which are also not uncommonly noted in Covid-19 infections [25]. These often clinically overlapping conditions highlight the need for prompt recognition of TTP as mortality in untreated patients can be over 90% and <10% if appropriate timely therapy is initiated [25].

This is the first systematic review combining all the data regarding disease characteristics and outcomes of confirmed TTP cases in COVID-19 patients to the best of our knowledge. However, we do note some limitations. First, none of the articles clearly mentioned if the patients were unvaccinated against COVID-19. This is important because the development of TTP secondary to COVID-19 vaccination has been previously reported. Whether the previous immunity against COVID-19 prevents the development of TTP after disease exposure is unknown. Second, the characteristics of COVID-19 severity were also not clearly defined in some of the articles. It may be worth exploring if severe COVID-19 infection is a risk factor for development of TTP as severe endothelial inflammation leading to vWF release may have a role to play. Finally, an inherent limitation is the rarity of this association with small number of cases reported to date which warrants further large-scale studies.

6. Conclusion

In summary, the pathophysiology and management of TTP in COVID-19 remains an evolving field. This review of available literature highlights the atypical and refractory nature of COVID-19 associated TTP. It required longer sessions of PLEX with half of the patients receiving at least one immunosuppressant.

Acknowledgments: The authors are grateful to the Reading Hospital librarian Ms. Alexandra Short for her expertise in devising the search strategy.

Funding: Authors did not receive any funding for this study.

Disclosure: All authors declare no conflicts of interest

Author's Contributions: HC conceptualization and design of the study, project manager, manuscript writing, literature search, data curation, analysis and editing. UN manuscript writing, literature search, data curation and analysis. KS, ML, CR, PS data collection, manuscript review and editing. RR manuscript review. NS critical review and editing. All authors approved the final manuscript

Informed Consent: Patients consent for case presentation was obtained. No identifiable information is presented.

Institutional Review Board Approval: Not required as it was a systematic review.

Ethical Compliance with Human/Animal Study. Not applicable as data is gathered from published articles.

Data Availability. The authors declare that data supporting the findings of this study are available online.

Financial Disclosures: All authors declare no financial conflicts; no funding was received for this article.

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