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International Immunopharmacology 93 (2021) 107397

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

COVID-19 associated thrombotic thrombocytopenic purpura (TTP) ; A case series and mini-review

Hamed Azhdari Tehrani [a], Maryam Darnahal [a], Mohammad Vaezi [b], Shirin Haghighi [a,*]

[a] Department of Hematology and Medical Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
COVID-19
Thrombotic microangiopathy
Case Series
TTP

ABSTRACT

Introduction: Thrombotic microangiopathies are a group of disorders that are mainly related to endothelial dysfunction. This category of endothelial dysfunction results of several imbalances between platelets, endothelium and immune system, also cytokine production.
Aim of this study: To report cases with thrombotic thrombocytopenic purpura (TTP) and COVID-19 and review COVID-19 endothelial dysfunction literature.
Methods: Primary laboratory data, peripheral blood smear, ADAMTS13 antigen activity level, and antibody ordered for each of these four patients. Treatments for COVID-19 administered for all patients. Traditional treatments for TTP also were administered.
Results: There were numerous schistocytes (more than 5%) in peripheral blood smears for each patient. ADAMTS13 antigen activity level was below 10%, and ADAMTS13 antibody was elevated for each patient. COVID-19 PCR was positive for all patients, and CT-Scans were indicative of the involvement of COVID-19.
Conclusion: In this case series, we reported four COVID-19 patients who presented with signs and symptoms of anemia and thrombocytopenia, resulting in thrombotic thrombocytopenic purpura.

1. Introduction

Thrombotic microangiopathies (TMA) are coagulopathies, that presented with two significant manifestations of hemolytic anemia, thrombocytopenia [1]. The most proven pathophysiology of this entity is endothelial dysfunction. TMAs are dividing further into primary and secondary [2]. Primary TMAs result from the genetically intrinsic deficiency of one or several factors such as complement regulating proteins deficiency in hemolytic uremic syndrome (HUS) or primary ADAMTS13 deficiency in primary thrombotic thrombocytopenic purpura (TTP) [3]. Secondary forms result from extrinsic triggers such as autoimmune disorders, drugs, bone marrow transplantation, pregnancy, viruses that result in acquired deficiency, and starting the TMA process such as acquired TTP, HELLP syndrome, or catastrophic anti-phospholipid syndrome [4]. However, the secondary forms do not have merely acquirable. These conditions are characterized by extremely high lethality and mortality rate due to thrombosis and organ dysfunction.

Soon after the detecting of the first case of COVID-19 in Wuhan, this virus spread throughout the world. Up to now, many facts and pieces of evidence released about the pathogenicity of this virus [5,6]. There are several manifestations of COVID-19 coagulopathy, such as deep venous thrombosis, pulmonary thromboembolism, and thrombotic microangiopathies. This paper reports four cases of COVID-19 associated thrombotic thrombocytopenic purpura (TTP), and then we discuss the probable pathogenicities of this phenomenon. Thrombotic thrombocytopenic purpura (TTP) is a rare blood disorder characterized by clotting in small blood vessels (thromboses), resulting in a low platelet count. The main manifestations of TTP are hemolytic anemia, thrombocytopenia, neurologic abnormalities. In the full-blown form, fever and renal dysfunction are also manifested. Most sporadic TTP cases appear to be associated with severe deficiency of ADAMTS13 activity due to autoantibodies against this protease. The table below, summarizes the difference between thrombotic thrombocytopenic purpura (TTP), and Disseminated intravascular coagulation (DIC) (see Table 1).

In this study, we reported four cases of TTP associated with COVID-19 disease.

2. Methods

This article reviews the pathophysiology, clinical presentation,

* Corresponding author.
E-mail address: drshirinhaghighi@sbmu.ac.ir (S. Haghighi).

https://doi.org/10.1016/j.intimp.2021.107397
Received 13 December 2020; Received in revised form 11 January 2021; Accepted 11 January 2021
Available online 22 January 2021

Table 1
Difference in hematological parameters.

Parameters	TTP	DIC
Pathogenesis	Endothelial Defects	Thrombin Excess
Clinical Condition	Usually Poor	Poor
Red Blood Cells	Schistocytes Seen	Schistocytes Seen
Prothrombin Time (PT)	Usually NL	Increased
Partial Thromboplastin Time (PTT)	Usually NL	Increased
Fibrinogen	Usually NL	Decreased
Fibrin Degradation Product (FDP)	Slightly Increased	Increased
D-Dimers	Slightly Increased	Increased
Therapy	Plasma Exchange	Treatment of Underlying Disorder

diagnosis, and evaluation of thrombotic microangiopathies, especially thrombotic thrombocytopenic purpura (TTP) in patients with COVID-19 infection. A search of MEDLINE, Google-Scholar, from January 2020 up to December 2020 was done. Terms searched included combinations of COVID-19, microangiopathies, Thrombotic thrombocytopenic purpura, pathogenesis, clinical manifestations. Randomized clinical trials, observational studies, meta-analyses, and review articles were all included in the search. All reports were in the English language.

This study aims to describe patients with anemia and thrombocytopenia in association with TTP. Anemia and thrombocytopenia are common findings among patients with COVID-19 disease, especially in severe ones. However, in these cases, we describe below, ADAMTS13 antigen activity level and antibody were correlated with TTP. These laboratory data distinguish these patients from typical findings of anemia or thrombocytopenia in COVID-19 patients (Tables 2 and 3).

3. Case 1

A 25-year-old pregnant woman in her third trimester of pregnancy, with severe respiratory symptoms, was referred to our emergency department. Vital signs in the admission were : Temperature: 38.5C axillary, Pulse Rate: 110/min, Blood Pressure: 100/70 mm/Hg, and Respiratory Rate: 22/min. In her evaluation, CT-Scan showed patchy infiltration suggestive of COVID-19 infection. In Her laboratory data, there was Bicytopenia and leukocytosis. In peripheral blood smear, there were numerous schistocytes. Coagulation tests were normal. Fibrinogen was 280 mg/dl (Normal levels between 200 and 400). Several thrombotic microangiopathies were probable for this patient. There were TTP, DIC, Pre-eclampsia, and HELLP syndrome. With regard to normal coagulation studies, DIC was excluded. With regard to normal blood pressure, HELLP syndrome and pre-eclampsia were almost excluded. However, in this patient, indirect hyper-bilirubinemia (Total Bilirubin 4 mg/dl and Direct Bilirubin 0.4 mg/dl) with a hepatocellular pattern of abnormal liver function tests (Aspartate aminotransferase 680 IU/L, Alanine aminotransferase 150 IU/L, and Alkaline phosphatase 420 U/L) were noticed. However, the gynecologist decided to terminate the pregnancy. We also checked the ADAMTS13 antigen activity level and antibody. Results were shown in Table 2. So we conclude that the TTP would be the primary cause of her Bicytopenia. After the cesarean section, plasma exchange started, and gradually patient's hemoglobin level, platelet counts began to increase [7].

4. Case 2

A 56-year-old woman with a previous history of locally advanced breast cancer now in remission, a triple negative breast cancer treated by surgical resection and adjuvant chemotherapy twenty years ago, was admitted to our hospital for severe respiratory symptoms and also Bicytopenia and leukocytosis. In peripheral blood smear, several schistocytes were seen. With a normal coagulation test, we ordered ADAMTS 13 antigen activity level and antibody. Results were shown in Table 2. With regard to these findings, plasma exchange started daily; however, hemoglobin and platelet counts did not change significantly after intensifying plasma exchange. We started Rituximab 375 mg/m2 beside plasma exchange. After two weeks, hemoglobin and platelet count became normal as shown in Table 2. With regard to deterioration of the consciousness level, a brain CT-scan showed a hemorrhagic stroke in her left frontal lobe, which led to death [8].

5. Case 3

A 57-year-old woman with severe respiratory symptoms and Bicytopenia with normal White blood cells count was referred to the emergency room. She had no past medical history and medication use. Lung CT-Scan has shown patchy bilateral infiltration suggestive of COVID-19 infection. In peripheral blood smear, schistocytes about 5% were seen. We planned to start the plasma exchange regarding ADAMTS 13 antigen activity and antibody shown in Table 2. However, only we infused fresh frozen plasma divided twice daily regarding the shortage of plasmapheresis setting. Also, Intravenous immunoglobulin (IVIG) for five days was administered. After one week of administration, the Hemoglobin level and platelet count began to rise and became normal after fourteen days (shown in Table 2).

6. Case 4

A 38-year-old man who refereed to emergency department by emergency service with complaining of rectorrhagia. Since a week ago, he had a COVID-19 infection with patchy infiltration in the right upper lobe in his lung CT-Scan. He had not any complain of respiratory symptoms. Oxygen saturation was normal. In laboratory data, there was Bicytopenia with a leukocytosis. In peripheral blood smear, schistocytes were seen in about 2% of each high-power field. However, with this schistocytes count less than 5%, the definitive diagnosis of TTP is not

Table 2
Laboratory parameters for all four patients.

	At initial diagnosis						At the time of discharge from COVID-19							
Para-metes	WBC	Hb MCV	PLT	PT	PTT	LDH	WBC	Hb	PLT	PT	PTT	LDH	ADAMTS Ag	ADAMTS Ab
Case 1	22,000	7 105	10,500	14	38	3465	15,500	10.5	145,000	14	42	359	8%	85
Case 2	14,600	6 102	41,000	12	40	1520	9520	11	155,000	13	44	413	<0.01	36.2
Case 3	7500	7.9 108	98,000	15	35	1150	13,200	12	185,000	14	39	378	0.86	25.3
Case 4	13,500	8 111	5000	13	39	545	14,000	10	145,000	12	38	290	0.06	14

WBC (White blood cells), Hb (Hemoglobin), PLT (Platelets), PT (Prothrombin time), PTT (Partial thromboplastin time), LDH (Lactate dehydrogenase), Normal ADAMTS Ab level is below 15 IU/ml.

Table 3
Treatments for COVID-19 and TTP in all four patients.

Treatments	For COVID-19	For TTP	Duration of admission	Duration of treatment for COVID-19	Duration of Treatment for TTP
Case 1	Interferon β1 : 1.2 million units + Dexamethasone 8 mg BID daily	Plasma exchange 30 cc/kg/daily	20 days	5 days for interferon β1 + 14 days for Dexamethasone	10 days
Case 2	Interferon β1 : 1.2 million units + Dexamethasone 8 mg BID	Plasma exchange + Rituximab 375 mg/m^2	15 days	5 days for interferon β1 + 14 days for Dexamethasone	14 days for plasma exchange and weekly for 2 weeks for Rituximab
Case 3	Remdesivir 200 mg in day 1 then 100 mg in days 2–5 + Dexamethasone 8 mg BID	Fresh frozen plasma 20–30 cc/kg + IVIG 20 g daily	14 days	5 days for Remdesivir + 14 days for Dexamethasone	14 days for FFP + 5 days for IVIG
Case 4	Remdesivir 200 mg in day 1 then 100 mg in days 2–5 + Dexamethasone 8 mg BID	Plasma exchange 20–30 cc/kg + Rituximab 375 mg/m2 + 40 g IVIG daily	21 days	5 days for Remdesivir + 21 days for Dexamethasone	21 days for plasma exchange + Rituximab for 4 weeks

IVIG (Intravenous immunoglobulin).

conclusive, and other diagnoses such as idiopathic thrombocytopenic purpura would be considered. Coagulation studies were normal. Lactate Dehydrogenase (LDH) was mildly elevated. Due to poor general condition, we started the plasma exchange daily. Intravenous Dexamethasone started 8 mg twice daily. Because of suspicion of idiopathic thrombocytopenic purpura (ITP) we administered IVIG daily for five consecutive days. There was no change in platelet and hemoglobin status following a plasma exchange, and hemoglobin dropped to three in the first week of admission. ADAMTS13 antigen activity level and antibody were sent after three days of plasma exchange. The results were shown in Table 2. We decided to start Rituximab 375 mg/m^2 weekly for four consecutive weeks. By continuing plasma exchange therapy and administering Rituximab platelet count and hemoglobin level, it began to rise after two weeks of admission and reached 9 g/dl for hemoglobin and 88000/μl for platelets count. After three weeks of admission, Hb and platelets reached near-normal levels (shown in Table 2).

7. Discussion

There are several manifestations of COVID-19 coagulopathy, such as deep venous thrombosis, pulmonary thromboembolism, and thrombotic microangiopathies. Out of 1008 patients with COVID-19, who underwent pulmonary CT-Angiography, Up to 40% of patients had small branches pulmonary thromboembolism [9].

There is a link between inflammation and organ damage by cytokines such as interleukin 6, interleukin 17A, tumor necrosis factor α, which are released during the cytokine storm phase of infection [10,11]. Hypercoagulability is an essential hallmark of inflammation. Pro-inflammatory cytokines lead to platelet activation and also coagulation cascade in which thrombosis occur [12]. In patients especially with moderate to severe disease especially in patients admitted to ICU, there may be several abnormalities in lab data such as thrombocytopenia, elevated prothrombin time (PT) and partial thromboplastin time (PTT), elevated D-Dimer, LDH, Fibrin degradation product (FDP), Fibrinogen and also several pro-inflammatory cytokines such as interleukin 6 [13,14]. It is also assumed that patients with more lung involvement have higher pro-inflammatory markers and, therefore, more abnormalities in platelet count and coagulation pathways [15]. Pro-inflammatory cytokines activate tissue macrophages, which express tissue factor (TF) and then platelets and factor VIII bind to TF, So the thrombin formation occurs. Also, anti-coagulation proteins such as tissue factor pathway inhibitor (TFPI) and protein C,S are functionally impaired by these cytokines [16]. The recruited platelets release further vascular endothelial growth factor (VEGF), So TF would be further expressed, and coagulation cascade amplified [17].

On the other arm, it is proven that the COVID-19 virus binds to angiotensin-converting enzyme 2 (ACE2) and then down-regulates this enzyme. So Angiotensin II increased. This increment results in vasoconstriction and also the expression of tissue factors, which leads to thrombosis [18,19].

The initiating point of all of the thrombotic microangiopathies is endothelial damage that is caused by the virus. It has been proposed that by binding SARS-COV-2 to the ACE-2 receptor, which is expressed in airway epithelial cells, vascular endothelial cells are damaged. Pro-inflammatory chemo-attractants, including C3a and C5a, are released, leading to recruiting more leukocytes [20,21]. Leukocytes being activated and release more cytokines (IL-6, TNF, IL-1). This cytokine release leads to more endothelial damage and more platelet aggregation. This is a vicious cycle. Garlinski et al. introduced SARS-COV to mice, which causes lung damage and deposition of complement proteins C3b, C4d, and C5b-9 in damaged tissues. However, when the virus was introduced to mice deficient in C3, lung damage was reduced [22].

ADAMTS13 is a protease that cleaves von Willebrand factor (VWF) multimers into small ones. This protease's inherited or acquired deficiency leads to VWF giant multimers that bind to platelets, and coagulation factors promote the coagulation cascade [23,24]. This endothelial dysfunction may lead to one of the worst outcomes, disseminated intravascular coagulation (DIC). Other COVID-19 associated thrombotic microangiopathies such as TTP or HUS may also occur, usually with the thrombotic presentation.

There are several strategies for the standard of care in patients with TMA, especially in TMAs other than DIC. All of these strategies work to modulate the immune response and balance the coagulation and anti-coagulation axis. These are high dose corticosteroids, plasma exchange, IVIG therapy, Rituximab, complement inhibitors [25–27]. Early reports in China indicated that treatment with methylprednisolone decreased the death risk in patients with COVID-19 [28]. In the RECOVERY trial, the use of Dexamethasone for patients with severe COVID-19 infection, resulted in a significantly lower 28-day mortality rate. Also, there was a trend, showing the greatest absolute and proportional benefit of Dexamethasone in patients who received mechanical ventilation [29]. In a systemic meta-analysis of seven trials, using different doses of Dexamethasone, Hydrocortisone, or Methylprednisolone, the Odds Ratio (OR) for 28 days of all-cause mortality decreased [30].

Plasma exchange is a safe procedure that removes inflammatory cytokines and thrombogenic molecules, also replenishes any deficiency in natural anti-coagulant proteins. Sometimes recovery occurs with IVIG after plasma exchange [31–33]. The use of IVIG for treatment for COVID-19 had been reported, which resulted in rapid recovery. An early study suggested that anti-coagulation with unfractionated heparin or low molecular weight heparin may have anti-inflammatory properties leading to the reduction of the 28-day mortality rate [30,34]. Glas et al. proposed the administration of anti-coagulants and protein C to reverse pulmonary microthrombi [35]. Heparin exhibits anti-inflammatory effects by neutralizing damage associated cellular proteins, thereby stabilizing endothelial cell membrane, decreasing vascular leakage, and thrombus formation [36,37]. A report from China, administration of low molecular weight heparin reduced the IL-6 levels and improved anti-coagulation indices [38].

In this case series, we reported four cases in our hematology center with anemia and thrombocytopenia. In evaluating these cases, peripheral blood smears had shown numerous schistocytes, and they had normal coagulation tests. We measured ADAMTS13 antigen activity and antibody in doubt for thrombotic thrombocytopenic purpura. All of them were positive for antibody and low level or lower limit of normal in antigen activity. Indeed, we found associated thrombotic microangiopathy except for DIC. All of the patients responded to traditional treatment of TTP, such as plasma exchange with FFP, FFP infusion, and also Rituximab therapy. So, we conclude that the main triggering factor in TTP development in these patients might be COVID-19, since this novel virus is far from completely understood. COVID-19 disease was confirmed by lung CT imaging and PCR test. It is proposed that Rituximab administration in patients, impair B lymphocytes activation, function, and antibody production [39]. Hindilerden et al. reported a 74-year-old woman with a diagnosis of COVID-19 and associated TTP. ADAMTS13 antigen activity level and antibody confirmed the diagnosis of TTP. She received daily plasma exchange and methylprednisolone [40]. Capecchi et al. reported a 55-year-old woman with a previous TTP history associated with bacterial pneumonia, thirty years ago. In a recent infection with COVID-19, she developed anemia and thrombocytopenia and schistocytes' appearance in the peripheral blood smear. ADAMTS13 antigen activity level was low and ADAMTS13 antibody was high. They started methylprednisolone and plasma exchange and also Caplacizumab [41]. Albiol et al. reported a 57-year-old woman with a previous history of breast cancer in complete remission, presented with COVID-19, anemia, and thrombocytopenia. In laboratory analysis, ADAMTS13 antigen activity level was decreased, and ADAMTS13 antibody was detected. She received plasma exchange therapy [42].

Antibodies play a role in neutralizing viral antigens. However, it may have an inverse role in the phenomenon of antibody-dependent enhancement, which leads to the production of non-neutralizing IgGs, and therefore induced more cytokine releases by macrophages [43]. Two of four cases (cases number 2,4) received Rituximab. In case number four, the patient presented with COVID-19 signs and symptoms before one week of hospital admission. He received Rituximab after one week of plasma exchange. After two consecutive weeks of administration, in new lung CT-Scan, there were new pieces of evidence of infiltration and increased bronchovascular markings. However, oxygen saturation was normal. Avouac et al. reported three cases with systemic sclerosis who had cutaneous involvement without any interestial lung disease. They had been received Rituximab about two months ago. All of them presented with COVID-19 severe infection with bilateral lung involvement. Avouac et al. assumed that Rituximab therapy without hypogammaglobulinemia might have an additional risk of infection [44]. After Rituximab therapy, case number 2 had no exacerbating COVID-19 signs or symptoms, however in case number 4 and case with classic TTP with COVID-19 infection after four weeks, they had an exacerbation in signs and symptoms of COVID-19. So, it is impossible to clearly define that Rituximab therapy may delay cytokine release or promote infection by inducing immunosuppression [45]. It needs further studies to clearly define the potential role of Rituximab therapy in COVID-19 pathogenesis, especially in patients who had disorders that fundamentally need targeting immunotherapy.

In conclusion, we reported four cases of COVID-19 who developed Bicytopenia, which was associated with thrombotic thrombocytopenic purpura. They received anti-COVID therapies besides traditional therapies for thrombotic thrombocytopenic purpura. In COVID-19 associated microangiopathies, autoimmunity besides endothelial damage, may have a crucial role in these manifestations. Plasma exchange may further improves this condition.

Study limitation

The most important limitation of this study was that we had a low population of patients with COVID-19 and associated thrombotic thrombocytopenic purpura. Therefore, no conclusions can be drawn from this treatment process.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the Helsinki declaration.

Informed Consent

Informed consent was obtained from all individuals.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

M.D; M.V; acquired data, analyzed and interpreted the data. H.A wrote the first draft of the manuscript. S.H revised the manuscript. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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