Case Report

Coronavirus Disease 2019-Associated Thrombotic Microangiopathy

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Abstract

Coronavirus disease 2019 (COVID-19) has spread tremendously since its first appearance in December 2019. Infected individuals can experience a wide range of systemic complications, including thrombotic microangiopathy (TMA). Like the other forms of TMA, COVID-19-associated TMA is characterized by thrombocytopenia, hemolytic anemia, and organ failure (such as acute kidney injury). The role of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in COVID-19-associated TMA is most probably dual: it can act either as a trigger to an underlying condition or as a cause of TMA. As opposed to the majority of other reported cases, it may be that in our case COVID-19 was the only cause of TMA. We present a case of a 32-year-old previously healthy man who was treated for acute kidney injury associated with TMA, which we believe was caused by COVID-19. Thrombotic thrombocytopenic purpura, as well as other possible known causes of typical and atypical hemolytic-uremic syndrome, was excluded. During his hospitalization, three negative nasopharyngeal swabs for SARS-CoV-2 were obtained, but serological tests showed the presence of IgG and IgA antibodies. After initial treatment known to be helpful in other forms of TMA (therapeutic plasma exchange and methylprednisolone), his renal function and platelet count recovered completely. Our case illustrates the importance of quickly recognizing this life-threatening complication of COVID-19 and applying treatment that has been shown to be beneficial in other forms of TMA. Future studies of the pathophysiology and subsequent targeted treatment of this novel disease are needed.

Keywords: Thrombotic microangiopathy; COVID-19; Acute kidney injury

Introduction

Since the first case of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was diagnosed in December 2019, the disease has spread tremendously. As the prevalence of COVID-19 has increased, we now know that infected individuals can experience a wide range of systemic complications beyond just pulmonary involvement. COVID-19 has been shown to cause complications in every organ system [1]. Although acute kidney injury (AKI) is common in patients with COVID-19 [2], its exact mechanism remains unclear. While acute tubular injury appears to be the most common histopathological finding on renal biopsy [3, 4], it has been suggested that thrombotic microangiopathy (TMA) can also occur [5].

TMA is a group of exceptionally diversified syndromes. Like the other TMA syndromes, COVID-19-associated TMA is characterized by key pathological and clinical features. The key pathological element is widespread microvascular injury, including thrombi of platelets and fibrin in capillaries and arterioles [6]. These lesions have clinical consequences, such as microangiopathic hemolytic anemia, thrombocytopenia, and organ injury (AKI, neurological abnormalities). Microangiopathic hemolytic anemia is identified by occurrence of schistocytes (fragmented erythrocytes) on peripheral blood film microscopy. Schistocytes emerge in areas of turbulent flow in the microcirculation due to partial occlusion by platelet aggregates. Platelet aggregation and consumption result in thrombocytopenia. Presentation with AKI reflects the consequences of ischemia in the kidney [7].

Here we present a case of a 32-year-old previously healthy man who was treated for AKI associated with TMA that occurred after infection with SARS-CoV-2. This case illustrates the importance of quickly recognizing this life-threatening complication of COVID-19 and applying treatment that has been shown to be beneficial in other forms of TMA.

Case Report

Investigations

We present a case of a 32-year-old Caucasian man who was admitted to our department in September 2021 with a history of fatigue, mild abdominal pain, nausea, vomiting, and low-grade fever (up to 37.5°C) for about 10 days prior to admission. He had no neurological symptoms or diarrhea. His past medical history was insignificant. On physical examination, we found no significant abnormalities. He was in sinus rhythm...
with a frequency of 62 beats per minute, had a blood pressure of 140/75 mm Hg, and oxygen saturation on room air was 98%. He was stable and not in acute distress.

**Diagnosis**

Laboratory findings were conclusive for TMA: thrombocytopenia (platelet count 86 × 10^9/L), AKI (serum creatinine 441 µmol/L and blood urea nitrogen (BUN) 40.3 mmol/L) and hemolytic anemia (hemoglobin 5.09 mmol/L, lactate dehydrogenase (LDH) level elevated four times the upper normal limit, undetectable haptoglobin, and 7.7% schistocytes in a peripheral blood smear). In the urine, we observed hematuria and mild proteinuria (0.85 g/day). Inflammatory markers (C-reactive protein and procalcitonin) were not elevated. Chest radiograph was normal and nasopharyngeal swab taken at admission was found to be negative for SARS-CoV-2 by polymerase chain reaction (PCR)-based test. Ultrasonography of the kidneys showed signs of acute injury with increased resistivity index but an increase in velocity during systole, which basically ruled out renal artery stenosis. There were no signs of urinary tract obstruction.

According to the clinical picture of hemolytic uremic syndrome, we followed a broad diagnostic protocol to exclude the known causes of primary and secondary TMA. We observed the normal activity of ADATMS13 (74.8%), which excluded thrombotic thrombocytopenic purpura (TTP). Shiga toxin-mediated hemolytic-uremic syndrome (STEC-HUS) was excluded by the absence of Shiga toxin in the stool. Serological tests for hantavirus, leptospirosis, hepatitis B and C, and human immunodeficiency virus were all negative. Complement components 3 and 4 (C3 and C4) were within the normal range. A detailed functional complement analysis also showed normal activation of the complement system in all three pathways (classical, lectin, and alternative); complement factors B, H, and I were within the normal range; urinary and serum C5b-9 levels were also normal. Workup for autoimmune diseases was negative: there were no antibodies to cardiolipin, beta2-glycoprotein I, prothrombin, as well as no anti-nuclear, anti-glomerular basement membrane and anti-neutrophil cytoplasmic antibodies. Coagulation parameters were normal. There were no specific drug exposures (including hydroxychloroquine) suggestive of drug-induced TMA. No malignancy was detected. Autoimmune hemolytic anemia was ruled out by a negative Coombs test, which was done later in the course of hospitalization due to persistent hemolytic anemia. His PLASMIC score was 5.

**Treatment**

After this initial clinical and laboratory examination, we were unable to determine the specific cause of the TMA. We decided to start the patient on therapeutic plasma exchange (TPE) with fresh frozen plasma immediately after admission. After only one TPE procedure, there was a steady increase in platelet count, decrease in LDH and schistocytes, and rapid recovery of renal function. He did not require further TPE or hemodialysis. However, due to persistent hemolytic anemia, oral methyldprednisolone was administered at a dose of 1 mg/kg/day for 10 days (started on day 8 when hemoglobin was 4.65 mmol/L).

Following our hospital’s COVID-19 protocols, we performed two more PCR swabs for SARS-CoV-2 after admission (on day 3 and day 5), both of which were negative. He had not been vaccinated against SARS-CoV-2. However, serological testing by enzyme-linked immunosorbent assays for SARS-CoV-2 (Euroimmun AG, Lubeck, Germany) revealed the presence of IgG (optical density (OD) value of 5.54; values above 1.1 are interpreted as positive) and IgA (OD value of 2.57; values above 1.1 are interpreted as positive) antibodies. This test is 99.6% specific and 94.5% sensitive for detecting IgG antibodies and 98.3% specific and 96.9% sensitive for detecting IgA antibodies. With the prevalence of SARS-CoV-2 infection in our country at that time being approximately 13.87%, the estimated false positive rate of the test was low: 0.4% for IgG antibodies and 1.7% for IgA antibodies. The negative PCR swabs and positive serology for SARS-CoV-2 were consistent with the timing of the patient’s gastrointestinal symptoms, which occurred before admission. Moreover, in the month prior to admission, he was staying in a highly endemic country at that time (Serbia).

On day 11, he was discharged in good general condition with near normal renal function (serum creatinine 111 µmol/L and BUN 6.5 mmol/L), platelet count of 353 × 10^9/L and anemia (hemoglobin 4.96 mmol/L).

**Follow-up and outcomes**

Four weeks after discharge, he had normal renal function (serum creatinine 90 µmol/L and BUN 3.7 mmol/L), a normal platelet count of 205 × 10^9/L, and a hemoglobin of 7.88 mmol/L. We observed minimal hematuria, while proteinuria reduced to 0.35 g/day. By ruling out a wide variety of other possible causes of TMA, we concluded that the patient suffered from COVID-19-associated TMA.

**Discussion**

To our knowledge, several cases of TMA associated with COVID-19 have already been reported to date [8-13]. Interestingly, in a significant proportion of the reported cases (including ours), the patients had no respiratory symptoms of COVID-19, but presented with gastrointestinal symptoms, such as nausea, vomiting and abdominal discomfort [14-17]. The majority of presented patients had positive nasopharyngeal swabs for SARS-CoV-2 by PCR-based test. However, in our and some other cases, TMA emerged after virus clearance (negative PCR-based test and positive serological testing for SARS-CoV-2) [11, 18, 19].

As with other infections, it has been assumed that COVID-19 can trigger TTP [8, 18, 20, 21]. Furthermore, it is believed that COVID-19 can unmask an underlying complement defect and trigger atypical hemolytic-uremic syndrome (aHUS): it can cause either a relapse of a known aHUS [15], or...
a presentation of a previously undiagnosed aHUS [16]. However, it is questionable whether COVID-19 acts as the sole cause of these reported TMAs, as other possible TMA-causing factors were also present in the majority of cases published to date. For example, in a subset of the reported cases, concomitant hydroxychloroquine use could cause drug-induced TMA [22, 23], which has been pointed out by other colleagues [24]. A unique case of coexistence of SARS-CoV-2 infection, hydroxychloroquine intake and pregnancy, where all three conditions could contribute to the development of TMA, has also been reported [25]. Another group of cases reported is COVID-19-associated TMA, which has been found in patients with transplanted kidneys [14, 23, 26] treated with calcineurin inhibitors or sirolimus. Here, it is possible that not only COVID-19 but both drug- and virus-associated factors were involved in TMA. In addition, a case of TMA was described in a patient with COVID-19 and concurrent metastatic cholangiocarcinoma treated with gemcitabine, and both malignancy and gemcitabine could be associated with the occurrence of TMA [27, 28]. Last but not least, there is a report of COVID-19-associated TMA in which hypertensive crisis could act as an accompanying cause of TMA [29].

It may be that in our case COVID-19 was the only cause of TMA, while we have ruled out a variety of other possible causes of TMA (as mentioned in the case presentation). Besides the patient presented here, the case recently reported by Boudhabhay et al [18] seems to be the only case so far in which COVID-19 may indeed be the only plausible explanation for triggering the multisystemic inflammatory syndrome after COVID-19 with biopsy-proven renal TMA. Although genetic testing did not reveal any rare variants in the six complement genes implicated in aHUS, in this case the TMA was thought to be complement-mediated because elevated soluble C5b-9 levels were found in the presence of low C4 and normal C3 levels in serum.

In our case, the possible underlying mechanism of TMA remains unknown, as we did not detect any abnormalities in complement or ADAMTS13 activity or in immunodiagnostics including antiphospholipid antibodies. Interestingly, even after the TMA resolved and serum creatinine levels normalized in our patient, minimal hematuria and mild proteinuria (0.35 g/day) persisted. In general, there are many types of renal injury besides TMA, which infection with SARS-CoV-2 can cause, including hemodynamically mediated acute renal failure because of hypotension; direct infection of the renal tubular epithelium and glomerulus through the attachment of the virus to the angiotensin-converting enzyme 2 (ACE2) receptor in the podocytes and glomerular basement membrane [30]; collapsing glomerulopathy [31]. Moreover, COVID-19 can also act as a trigger of a form of secondary TMA associated with glomerular disease, for example IgA nephropathy, the increased incidence of which has been associated with COVID-19 era [32]. Based on this, it is tempting to speculate that our patient may have underlying undiagnosed renal disease. Since we do not have a urine specimen collected prior to the development of the TMA and he does not currently meet the criteria for a diagnostic renal biopsy, it is impossible to rule out underlying renal disease with certainty. On the other hand, persisting minimal proteinuria with hematuria could be a consequence of direct viral infection on its own. To conclude, TMA seems to be the leading cause of renal injury in our patient, since the clinical picture began to improve with the treatment of TPE, but it is possible that other forms of renal injury co-occurred. Unfortunately, renal biopsy was not performed, so these are only speculations. Also, it is important to emphasize that there is always the possibility that an association between an observed TMA and a positive serology for SARS-CoV-2 infection is a coincidence rather than a causal relationship, since SARS-CoV-2 infections are very common nowadays.

The pattern that seems to emerge from the previous reports suggests a logical classification of COVID-19-associated TMA into two groups: in the first group we recognize COVID-19 as the cause of TMA (first hit), whereas in the second group we consider COVID-19 as the trigger of an underlying defect (second hit), for example, hereditary abnormalities in the activity of the alternative complement pathway. Rapid identification of TMA and application of appropriate treatment can lead to better outcomes. The challenge, of course, is to identify the exact pathophysiological mechanism of COVID-19 associated with TMA, which would lead to targeted treatment. In general, the most likely mechanisms in TMA associated with viral infections are thought to be related to direct endothelial damage, acquired inhibitors of ADAMTS13 or the presence of lupus anticoagulants [33].

Initial treatment of TMA generally relies on four modalities: TPE, corticosteroids, symptomatic measures to protect organ function, and treatment of the underlying cause/triggering factor (e.g., treatment of infection, elimination of medications associated with TMA). Other therapeutic options include immunosuppression [34], targeted anti-von Willebrand factor (vWF) or anti-complement therapy [35].

Historically, the most commonly used first-line therapeutic approach in patients with TTP has been a combination of TPE and glucocorticoids. Glucocorticoids, which are used to achieve rapid immunosuppression in patients with TMA, have a multifactorial mechanism of action: suppression of endothelial inflammation [36]; inhibition of acquired inhibitors of ADAMTS13 and anti-factor H antibodies [34]; inhibition of activation of the alternative complement pathway [37]. TPE has been shown to be useful in the treatment of almost all types of TMA (not just TTP). It replaces the defective or deficient protein (such as ADAMTS13, complement, etc.) with a functional one [38].

The unique pathophysiology of the COVID-19 infection offers additional ways through which TPE can have favorable effect. It was shown that cell entry of coronaviruses depends on binding of the viral spike proteins to cellular receptors and on spike protein priming by host cell proteases [39, 40] through a mechanism by which anti-spike protein antibodies are responsible for the immune system cells infection [41, 42]. As these antibodies could be removed by TPE [43], it was proposed that TPE would be of benefit in critically ill COVID-19-infected patients in general, not only in those with TMA [44]. A meta-analysis of several case reports and small series confirmed the beneficial effects of TPE in COVID-19 [45]. However, a newly published large-scale prospective study of the use of TPE in COVID-19 was not as positive [46]. They compared 42 patients with SARS-CoV-2 who had failed conventional therapy
and were treated with TPE to a control group of 147 patients with acute renal failure from COVID-19 who received only hemodialysis: although there was a survival advantage (43.9% vs. 50.7%, P = 0.004), mortality was still greater than 40%. The main finding of the study was the improvement in inflammatory parameters as a result of the TPE. However, since our patient did not show signs of active COVID-19 infection (he did not have elevated inflammatory parameters), it seems reasonable to speculate that he did not benefit from TPE through the described mechanism.

Judging from the experience gathered from clinical cases published to date, further management of a patient with COVID-19-associated TMA generally followed the principles of treatment based on differentiation of the underlying disease, which may be either TTP or aHUS. Rituximab, a B-cell-depleting monoclonal antibody, has been used as adjunctive therapy in a few patients with COVID-19-associated TTP [10, 21, 47, 48]. Another option in patients with TTP is caplacizumab, a humanized bivalent immunoglobulin fragment against vWF. It inhibits the interaction between vWF multimers and platelets and prevents the formation of new microthrombi [49]. It is particularly important for the treatment of infection-related TTP because it is not an immunosuppressant and has been already successfully used in some patients with COVID-19-associated TTP [10, 11, 21, 50].

Consistent with the proposed complement-mediated nature of the disease [51], anti-complement therapy may be used in patients with aHUS to supplement TPE and prevent progression of renal failure. In some cases of COVID-19-associated TMA, the use of eculizumab [18, 29] and recently ravulizumab [13], both anti-C5 monoclonal antibodies, led to positive results.

Our patient showed signs of rapid recovery of renal function and platelet count after TPE and a modest dose of oral methylprednisolone. The mechanism by which these two therapeutic options acted is not fully understood. Regardless of the exact role of COVID-19 in the development of TMA in the patient presented here, there is no doubt that early recognition of TMA as a life-threatening complication of COVID-19 and the use of treatment that has been shown to be beneficial in other forms of TMA resulted in favorable outcome.

Learning points

In summary, we present the case of a young, previously healthy man who was treated in our department for AKI associated with TMA, which we believe was a case of COVID-19 post-viral TMA. After initial treatment, his renal function and platelet count recovered completely. Therefore, it seems that treatment with TPE and oral steroids may be of use, but this of course cannot be conclusive judging just from one case. Future studies of the pathophysiology and subsequent targeted treatment of this novel disease are needed.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Written informed consent has been obtained from the patient to publish this paper.

Author Contributions

Conceptualization and original draft preparation were done by MMV. Supervision, review and editing were done by ZVH. All authors read and approved the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

ACE2: angiotensin-converting enzyme 2; aHUS: atypical hemolytic-uremic syndrome; AKI: acute kidney injury; COVID-19: coronavirus disease 2019; LDH: lactate dehydrogenase; OD: optical density; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; STEC-HUS: Shiga toxin-mediated hemolytic-uremic syndrome; TMA: thrombotic microangiopathy; TPE: therapeutic plasma exchange; TTP: thrombotic thrombocytopenic purpura; vWF: von Willebrand factor

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