AHUS mistaken for TTP associated with COVID-19: a case report

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Case Report

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Abstract

Thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS) are both thrombotic microangiopathies that share several clinical traits including microangiopathic hemolytic anemia, thrombocytopenia, and organic damage. There is inherent opportunity for misdiagnosis. As thrombocytopenia and thrombus are strongly related to COVID-19, it may be more difficult to tell an aHUS from a TTP when COVID-19 is present. Thus, we describe a patient presenting with severe COVID-19 who was misdiagnosed with TTP but in the end corrected to aHUS. We suggest that perform detection to ADAMTS-13 activity and complement gene mutation as soon as possible is necessary.

Background

Thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS) are both thrombotic microangiopathies (TMA) that share many clinical features including microangiopathic hemolytic anemia (MAHA), thrombocytopenia and organic damage[1], thus there is inherent opportunity for misdiagnosis.

TTP and aHUS are two distinct diseases with different pathophysiology[2]. TTP is characterized by MAHA, thrombocytopenia, neuropsychiatric symptoms, fever, and renal involvement, but acute kidney injury is uncommon[3, 4]. It's pathogenesis mainly involves the deficiency of ADAMTS13 activity, which leads to the failure of timely degradation of the abnormally released super-large molecule VWF, and resulting in ischemia, hypoxia, and organ dysfunction[4]. AHUS, a complement-mediated thrombotic microangiopathy (CM-TMA), is caused by a genetic abnormality in the complement alternative pathway, that primarily affects the kidney[5]. The development of molecular diagnostic techniques has improved the accuracy of distinguishing aHUS from TTP[6].

COVID-19, the disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is linked to thrombocytopenia and thrombus[7, 8]. During the novel coronavirus pneumonia pandemic, to distinguishing different TMA types such as TTP and aHUS seems harder. Thus, we describe the case of a patient presenting with severe COVID-19 who was misdiagnosed with TTP but in the end corrected to aHUS.

Case Presentation

A 54-year-old Chinese male with thrombocytopenia was admitted to our hospital at the end of 2022. He was initially diagnosed of TTP in 2014 and was treated by plasmapheresis and prednisone with no relapse since then. Four days before to admission to the hospital, the patient developed a fever. Physical examination revealed no significant abnormalities. Blood tests showed severe thrombocytopenia (PLT 12x10^9/L), mild anemia (Hb 99g/L), renal insufficiency (creatinine 291µmol/L), VWF 219.1%, ragged-red fiber 1.4% (Fig. 1b) and hypocomplementemia (complement C3 0.54g/L and complement C4 0.08 g/L). Other laboratory results included CRP 19.1mg/L, D-Dimer 9968ng/ml, LDH 1919U/L, direct bilirubin 17
µmol/L, indirect bilirubin 36.6 µmol/L. Arterial blood gas indicated acute hypoxic respiratory failure, urinalysis showed microalbuminuria 599mg/L and blood 3 +. The COVID-19 nucleic acid test was negative. Computed tomography (CT) of the chest revealed pneumonia and bilateral pleural effusions Fig. 1(c). Consanguineous marriage was confirmed in his parents. His brother and sister both had a history of thrombocytopenia, and one went through nephrectomy. So a whole exome sequencing (WES) was performed for him.

With a PLASMIC score of 6, TTP was strongly suspected, and daily plasmapheresis for him was started immediately along with high-dose prednisone impulsion and human immunoglobulin infusion therapy. Blood samples for measuring ADAMTS13 activity and inhibitor levels were collected after a course of plasmapheresis and the ADAMTS13 activity was 33.8% (by fluorescence resonance energy transfer; normal: 70–120%) with an antibody titer of 0 (by enzyme-linked immunosorbent assay; normal: indetectable).

The patient responded to eight plasmapheresis courses while developed hypotension and hypoxemia during the first week. We conducted a tracheoscopy on him and discovered SARS-CoV-2 novel coronavirus in his bronchoalveolar lavage fluid (Fig. 1d), and he was given antiviral medication immediately. On the 5th week of hospitalization, the patient became refractory with decreasing platelet count since the prednisone being reduced from 100mg to 60mg per day. Treatment was intensified with a course of rituximab (375 mg/m2) but there were no signs of PLT increasing. On the 6th week, he accepted oral thrombopoietin receptor agonist (TPO-RA) maleate avatrombopag. Two weeks later, his PLT level has been on the rise. And the patient was discharged on prednisone and maleate avatrombopag. The trend of PLT level was showed in Fig. 1a. Soon afterwards the patient discharged, his report of WES came out showing membrane cofactor protein (CD46) and complement factor H (CFH) gene mutation, confirming the diagnosis of aHUS (Fig. 1e).

Discussion

To best of our knowledge, this is the first case of aHUS in the setting of COVID-19 with declining ADAMTS13 activity. The patient was initially diagnosed of TTP was later changed to aHUS. Against the backdrop of the Omicron COVID-19 pandemic, despite the patient’s nucleic acid testing was negative for many times, we clinically suspected that he has been infected based on the pulmonary infection and hypoxemia. Bronchoalveolar lavage and NGS assisted us in determining the outcome, and we proposed that COVID-19 was the most possible reason for inducing this TMA. The current case represents is the only one encountered in our department.

Since the outbreak of COVID-19 in 2019, several cases of aHUS and TTP have been reported[9,10], the mechanism by which COVID-19 induces TMA remains unclear. Coagulation activation is common in patients with severe COVID-19, and coagulation biomarkers including FVIII and VWF are independent predictors of increased oxygen requirement in COVID-19 patients[11,12]. COVID-19 patients with severe inflammatory reaction have high blood C5a serum levels, indicating vigorous complement activation that
resulted in systemic TMA\textsuperscript{[13]}. Recent studies\textsuperscript{[14, 15]} have also found a significant increase in the VWF:Ag/ADAMTS13 ratio secondary to COVID-19 infection, which can explain the decrease of ADAMTS13 level in our report.

Despite having completely different pathogenetic mechanisms, both aHUS and TTP can develop TMA, and both are challenging to diagnose clinically. Because the blood sample has not been taken before plasma exchange, the result of ADAMTS13 level might be inaccurate for this patient. On the other side, consanguineous marriages allow the defective genes to remain in the family, so we performed WES and eventually found gene mutations of CD46 and CFH, complement regulatory protein, which was the most frequently affected in aHUS\textsuperscript{[16]}. Agnieszka Furmanczyk-Zawiska et al. showed a series of cases from a single family whose five members were affected by aHUS with next-generation sequencing revealing combined mutations in both CFH and CD46\textsuperscript{[17]}. A report also demonstrates a high frequency of CD46 mutations in aHUS, closely mimicking relapsing/remitting TTP\textsuperscript{[6]}. A study published in \textit{BLOOD} demonstrate that SARS-CoV-2 spike protein can activate the alternative pathway of complement\textsuperscript{[18]}. Notably, COVID-19 likely act as a second hit of aHUS that manifests in genetically predisposed individuals (“two-hit hypothesis”). Therefore, the role of ADAMTS-13 activity and genetic screening for complement abnormalities is important in differentiating aHUS and TTP.

The patient’s mutation result was delayed and the standard such as plasmapheresis and prednisone were used. Nonetheless, the outcome was dismal. This occurrence may be related to the ongoing attack of COVID-19. Anti-complement treatment, including eculizumab and ravulizumab, is said to be successful in treating aHUS\textsuperscript{[19, 20]}. Noteworthily, the PLT of the patient began to improve progressively after using maleate avatrombopag, an oral-small-molecule second-generation TPO-RA, which has not been previously reported in the therapy of TMA. More research is required because we assume maleate avatrombopag might play an importantly role in the treatment of refractory TMA-associated disorders.

**Conclusion**

Although being two separate entities with differing pathophysiologies, TTP and aHUS are both TMAs. COVID-19 act as a second hit for aHUS that manifests in genetically predisposed individuals. The COVID-19 background makes it more difficult to distinguish between TTP and aHUS. Far more crucial are the identification of ADAMTS-13 activity and complement gene mutation.

**Abbreviations**

- Thrombotic thrombocytopenic purpura (TTP)
- Atypical hemolytic uremic syndrome (aHUS)
- Thrombotic microangiopathies (TMA)
- Microangiopathic hemolytic anemia (MAHA)
complement-mediated thrombotic microangiopathy (CM-TMA)
severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)
Computed tomography (CT)
whole exome sequencing (WES)
thrombopoietin receptor agonist (TPO-RA)
cofactor protein (CD46)
complement factor H (CFH)

Declarations

Ethics approval and consent to participate:
This study was approved by the Ethics Committee of the First Affiliated Hospital of Ningbo University and was in accordance with the Declaration of Helsinki.

Availability of data and materials:
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests:
The authors declare that they have no competing interests.

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Authors' contributions:
AW collected data and drafted the article. JW, CS, XY co-interpreted the data. GO and LS designed the work and substantively revised the manuscript. All authors read and approved the final manuscript.

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**Figures**
Figure 1

(a) Response in platelets and creatinine indices during treatment. (b) Chest CT scan images. (c) Ragged-red fiber on smear. (d) SARS-CoV-2 novel coronavirus was discovered through the next generation sequencing in bronchoalveolar lavage fluid. (e) The CD46 and CFH gene mutation by WES.