COVID-19 as a Potential Trigger for Immune Thrombotic Thrombocytopenic Purpura and Reason for an Unusual Treatment: A Case Report

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Abstract

Immune thrombotic thrombocytopenic purpura (iTTP) is a rare autoimmune disorder characterized by severely reduced activity of the von Willebrand factor (VWF)-cleaving protease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) due to autoantibodies. This leads to the development of pathogenic multimers of VWF, causing a thrombotic microangiopathy with decreased number of platelets, hemolysis, and life-threatening tissue ischemia of mostly brain, heart, and kidneys. Standard treatment of iTTP involves daily plasma exchange to remove ultra large multimers of VWF, inhibitors, substituting ADAMTS13, and the accompaniment of an immunosuppressive treatment with steroids. Recently, caplacizumab was approved for iTTP. Caplacizumab is a nanobody binding the A1 domain of VWF, blocking its interaction with glycoprotein Ib–IX–V platelet receptor and therefore preventing platelet aggregation. VWF activities may serve as therapeutic drug monitoring of caplacizumab, whereas ADAMTS13 activities may be used for biomarkers to guide caplacizumab treatment modalities and overall treatment duration. Additional immunosuppressive treatment by inhibiting autoantibody formation (e.g., the use of Rituximab, a chimeric monoclonal antibody directed against the B-cell antigen CD20) is a further treatment option. Infections are well-known causes for an acute episode for patients with iTTP. The novel SARS-CoV-2 virus is mainly associated with acute respiratory distress as well as diffuse endothelial inflammation and increased coagulopathy. However, little is known about an infection with SARS-CoV-2 virus triggering iTTP relapses. We herein report the case of an acute iTTP episode accompanying a SARS-CoV-2 infection.

Keywords

- COVID-19
- thrombotic thrombocytopenic purpura
- caplacizumab

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Case Presentation

The patient is a 35-year-old female with history of 16 episodes of immune thrombotic thrombocytopenic purpura (iTTP) following her initial diagnosis in 2002. Apart from obesity and nicotine abuse, no other relevant secondary diagnoses are known. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) mutations have not been found in this patient, and during remission she had normal ADAMTS13 activity; therefore, a congenital TTP (Upshaw–Schulman syndrome) could be excluded.

At the age of 17 years, the first episode of TTP was triggered by pregnancy, and was successfully treated with corticosteroids and plasma exchange (PEX).[1,2] In 2009, the monoclonal antibody rituximab was first added to the treatment of her sixth acute TTP episode.[1,2] In December 2019, she had her last episode of TTP, triggered by an infection with rhinovirus and was treated with corticosteroids, PEX, and rituximab. Additionally, caplacizumab was introduced for the first time, administered for a period of 2 weeks, given at a daily dose of 10 mg subcutaneously.[3]

The patient is enrolled in the German TTP Registry and she attends a regular follow-up every 3 months. ADAMTS13 activity (FRETS-VWF73[4]) was tested in August 2020, with 66% (normal range) and normal blood count. Three months later, during the ongoing COVID-19 pandemic in Germany, she had a tooth extraction without any bleeding symptoms. Following this intervention, her sense of smell and taste was missing for 3 days. A week later, platelet counts dropped in an outpatient routine control. The same day, laboratory results at our emergency department showed thrombocytopenia (platelet count 33/nL), hemolysis (increased lactate dehydrogenase [LDH] at 345 U/L, increased bilirubin at 1.5 mg/dL, suppressed haptoglobin at <0.08 g/dL, and increased schistocytes), and increased D-dimer at 0.72 mg/L. Serum creatinine level was normal (0.78 mg/dL). Physical examination showed discrete bleeding signs (hematoma, petechiae), but no neurological symptoms or signs of an acute infection (CRP: 2.0 mg/L, leucocytes: 8.95/nL), especially no typical signs of COVID-19 (cough, fever, diarrhea, dyspnea, or sore throat). An X-ray of the chest did not reveal pathological findings. However, a routine nasopharyngeal swab for SARS-CoV-2 (POCT-PCR SARS-CoV-2) revealed a positive test result that was confirmed 1 day later (multiplex 4 RT PCR). Without any symptoms, a specific COVID-19 therapy was not required. The PLASMIC score revealed high risk (72%) for severe ADAMTS13 deficiency (hemolysis, INR <1.5, serum creatinine <2.0 mg/dL, MCV $<9.0\times10$–14 L [$<$90 fL], no history of solid-organ or stem-cell transplant, no active cancer, platelet count not $<30\times109$/L). Indeed, plasma ADAMTS13 activity was only 4.4%. Together with the presence of an ADAMTS13 inhibitor (0.9 BE), we confirmed an acute iTTP relapse associated with SARS-CoV-2. The local center for transfusion medicine could not perform an immediate PEX, due to the SARS-CoV-2 infection of the patient, as immediate hygienic precautions were not feasible at the interventional ward. Furthermore, the patient initially refused to take prednisolone due to concerns regarding side effects. Therefore, we could not perform the immediate iTTP standard therapy. We promptly started caplacizumab (10 mg/d intravenously) on the day of admission. Only 12 hours after the first injection, the platelet count increased to 51/nL (►Fig. 1) and bleeding symptoms stopped. LDH and bilirubin were normal, D-dimer decreased to 0.57 mg/L, the count of erythrocyte fragments was reduced, and the plasma ADAMTS13 activity slightly increased to 5.5% with no more presence of an ADAMTS13 inhibitor. Therefore, alternative methods to perform PEX were not pursued. Given as monotherapy, the second dose of caplacizumab was also administered intravenously (off label), 12 hours after the first injection (off label). Due to the concern of long-lasting immunosuppression with COVID-19, we decided against the use of rituximab and the patient then consented to start prednisolone. Starting on day +2, caplacizumab was given every 24 hours. The initial four applications were given intravenously (instead of subcutaneously as labeled), and all further applications were administered subcutaneously. The platelet count increased to 95/nL on day +2. After 6 days of treatment, the patient reached a normal platelet count. Prophylaxis with low-molecular-weight heparin (dalteparin 5000 IU/d) was administered daily and caplacizumab was then given every other day subcutaneously, in relation to VWF activity (off label). Bleeding symptoms resolved completely, and the patient showed no other symptoms throughout the hospitalization period. After 11 days of treatment and two subsequent negative nasopharyngeal swabs for SARS-CoV-2, the patient was discharged in good general condition in early november with a maintenance dose of 75 mg prednisolone per day and caplacizumab 10 mg every other day. At her follow-up visits in our outpatient clinic, she showed a normal blood count and ADAMTS13 activity of 9.8% (day +13), 31.2% (day +21), and finally a normal range with 71.4% (day +28). The dose of prednisolone was reduced to 50 mg/d on day +14 and tapered every 5 days during further follow-up. Caplacizumab was stopped on day +35.

Discussion and Conclusions

With this clinical case report, we demonstrate a rare case of an acute relapse of iTTP most likely triggered by a SARS-CoV-2 infection. In our registry, iTTP patients are quarterly followed up for ADAMTS13 activity and usually, this period is sufficient to detect an enzyme decline and to prevent the impending relapse. In this patient, we measured a normal ADAMTS13 activity in August 2020, then a rapid decline to less than 10% within 2 months with immediate onset of relapse, possibly triggered and accelerated by the viral infection. However, we cannot exclude that the tooth extraction with local anesthetics might also have been another triggering factor. TTP bouts associated with COVID-19 have been reported earlier in several case reports.[5–7] In contrast to these reports, our patient did not take additional concomitant medication, for example, hydroxychloroquine for the treatment of COVID-19 that might have contributed to the

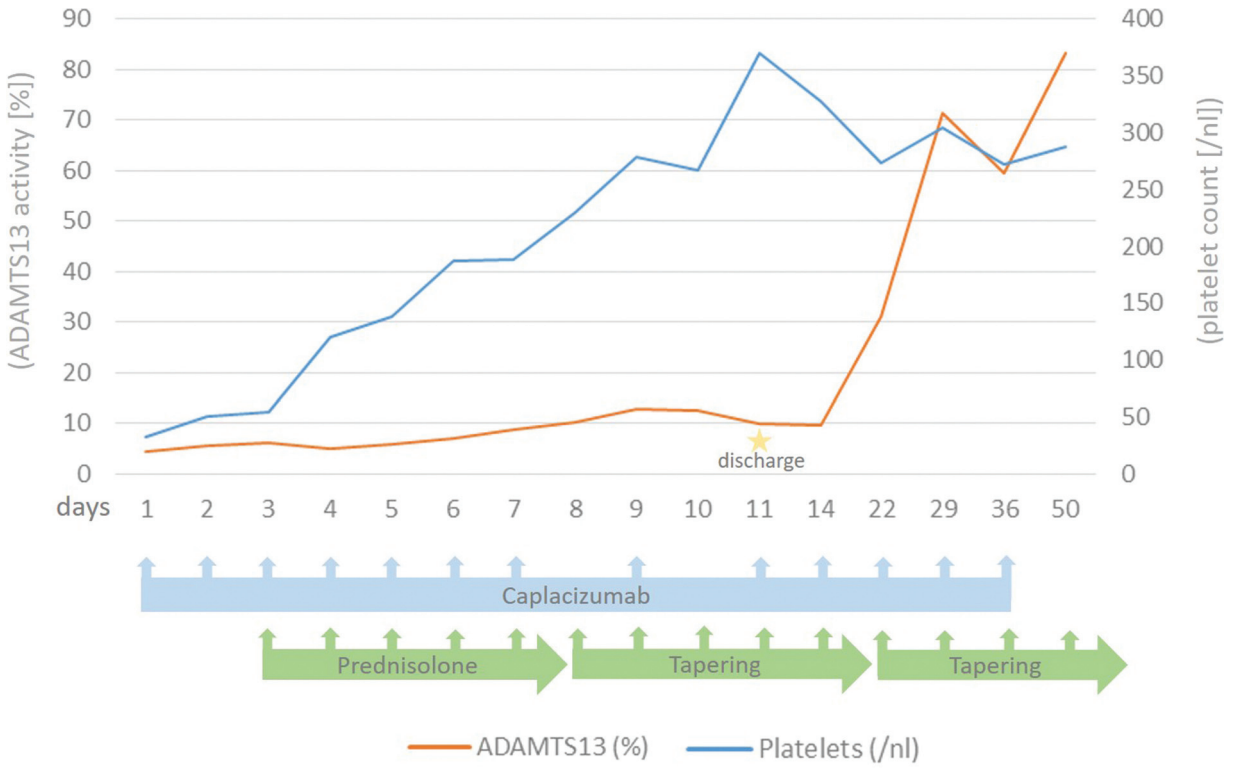

Fig. 1 Timeline of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity (FRETS-VWF73[4]) (orange), platelet counts (blue) in relation to the treatment regimen during hospitalization (until day 11) and follow-up.

onset or continuance of the iTTP relapse. The patient was treated effectively only with a monotherapy with caplacizumab on the first day of admission and a dual therapy of caplacizumab and corticosteroids during further hospitalization. Caplacizumab is licensed for the treatment of acute iTTP in addition to the standard therapy of PEX and prednisolone. In Germany, the first dose of Caplacizumab 10 mg should be given intravenously, and further applications should be done subcutaneously, approximately every 24 hours. Our patient could not receive the standard therapy with PEX and prednisolone and therefore we decided for a caplacizumab monotherapy (off label). As she was overweight and showed very little bleeding symptoms, we decided for an additional off-label approach for caplacizumab with regard to a shorter first-time interval and intravenous route of administration of the first four applications. Recent retrospective data indicate that ADAMTS13 activity measurements may help identify individual timing when to stop caplacizumab to prevent overtreatment and undertreatment and to hereby tailor disease management.[8] In our patient, too, ADAMTS13 activity measurements as well as VWF activity served as landmarks to guide caplacizumab treatment modalities. In this case, the quick initiation of the treatment with caplacizumab enabled us to avoid an emergency PEX as well as additional immunosuppressive therapy with rituximab. To our knowledge, this is the first case of an acute relapse of iTTP potentially triggered by an infection with coronavirus, which was successfully treated by caplacizumab and corticosteroids only. Other case reports and case series support the possibility of a PEX-free treatment of iTTP relapses; however, achieving stable remissions requires immunosuppression to block the production of autoantibodies against ADAMTS13.[9] In selected patients, it seems feasible to omit PEX if platelet counts increase and organ function is stable after the start of caplacizumab therapy.[10] Without any complications, our patient achieved complete remission after only 6 days. This highlights the importance of quick diagnostics and decision-making in patients with suspected relapse of iTTP. An infection with SARS-CoV-2 is concomitant with an increased coagulopathy and therefore, the risk of dramatic microangiopathic thrombotic events may be further increased.[11] Our case highlights the present challenges in the treatment of COVID-19 patients, where standard therapy is often impossible and off-label modifications are crucial. Further case series or retrospective data regarding acute relapse of TTP triggered by SARS-CoV-2 are needed to understand pathomechanisms involved, and to optimize treatment strategies in patients with a very high risk for microangiopathic thrombotic events.[11,12]

Competing Interests

The authors have no competing interests.

Ethics Approval

Not applicable.

Consent to Participate

Informed consent was obtained from all individual participants included.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Marie-Kristin Schwaegermann and Charis von Auer. The first draft of the manuscript was written by Marie-Kristin Schwaegermann and amended by Charis von Auer. Lukas Hobohm prepared the diagram for laboratory results. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

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