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## CASE REPORT

# Clopidogrel-induced refractory thrombotic thrombocytopenic purpura successfully treated with rituximab



Sara Khodor <sup>a</sup>, Miguel Castro <sup>b</sup>, Colin McNamara <sup>a</sup>, Chakra P. Chaulagain <sup>c,\*</sup>

<sup>a</sup> Charles E. Schmidt College of Medicine, Boca Raton, FL, USA

<sup>b</sup> Department of Internal Medicine, Cleveland Clinic-Florida, Weston, FL, USA

<sup>c</sup> Taussig Cancer Institute of the Cleveland Clinic, Maroon Cancer Center, Cleveland Clinic-Florida, Weston, FL, USA

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### KEYWORDS

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ADAMTS13;  
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### Abstract

Thrombotic thrombocytopenic purpura (TTP) is a multisystem disorder characterized by microvascular aggregation of platelets and fibrin strands causing thrombocytopenia, microangiopathic hemolytic anemia, and organ dysfunction. TTP can develop as a result of a deficiency in ADAMTS13 enzyme activity due to either a genetic defect or, more commonly, the development of anti-ADAMTS13 autoantibodies. TTP can also be associated with pregnancy, organ transplant, lupus, infections, and drugs. Here, we present a case of TTP that developed shortly after the start of clopidogrel treatment for acute ischemic stroke and acute myocardial infarction, and describe the clinical presentation, refractory course of the disease, and successful induction of remission through the use of rituximab in a setting of pre-existing autoimmune diseases.

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## Introduction

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are similar disorders classified under thrombotic microangiopathy (TMA) due to the common mechanisms of platelet and red blood cells (RBC) destruction in the microvasculature, and similar histologic

\* Corresponding author at: Taussig Cancer Institute of the Cleveland Clinic, Maroon Cancer Center, Cleveland Clinic-Florida, 2950 Cleveland Clinic Boulevard, Weston, FL 33331, USA.

E-mail address: [chaulac@ccf.org](mailto:chaulac@ccf.org) (C.P. Chaulagain).

abnormalities in tissue biopsy specimens from affected organs. Both TTP and HUS are characterized by the deposition of loose platelets and fibrin strands in small vessels, causing mechanical shearing of RBCs and agglutination of platelets and resulting in microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. Although it is rare, TTP can cause chronic remitting and relapsing illness due to congenital deficiency of von Willebrand factor (vWF)-cleaving protease called ADAMTS13. However, most cases of TTP are acquired (also known as idiopathic TTP) and caused by IgG autoantibodies that inhibit ADAMTS13 enzymatic activity. Normally, ADAMTS13 regulates vWF activity by cleaving high-molecular weight vWF multimers, and prevents platelet accumulation and thrombosis in capillaries and arterioles. Failure to cleave the vWF multimers in TTP by ADAMTS13 leads to accumulation of large vWF multimers facilitating platelet accumulation and microvascular thrombosis, which results in tissue ischemia of the affected organs and leads to variable degrees of neurologic symptoms and renal impairment. The classic pentad of MAHA, thrombocytopenia, neurologic symptoms, renal failure, and fever is present in only 5% of patients, and evidence of TMA (MAHA and thrombocytopenia) without another apparent etiology is enough to make a working diagnosis of TTP/HUS.

Typical laboratory findings for TTP include decreased platelet count, elevated lactate dehydrogenase (LDH), negative direct anti-globulin test (DAT), and fragmentation hemolysis (schistocytes) on the blood smear. Levels of creatinine and blood urea nitrogen depend on the presence and severity of renal involvement. Schistocytes are characteristic for TTP, but can also be present with other causes of fragmentation hemolysis, e.g., disseminated intravascular coagulation (DIC), prosthetic valve hemolysis, malignant hypertension, preeclampsia/HELLP syndrome, and vasculitis [systemic lupus erythematosus (SLE), scleroderma]. In contrast to DIC, typically in TTP, prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer levels are normal. A severely depressed (<10%) level of ADAMTS13 activity is present in TTP, while ADAMTS13 activity is normal in HUS. This distinction is important clinically, but not required to make a working diagnosis of TTP, and to initiate lifesaving treatment with plasma exchange (PLEX).

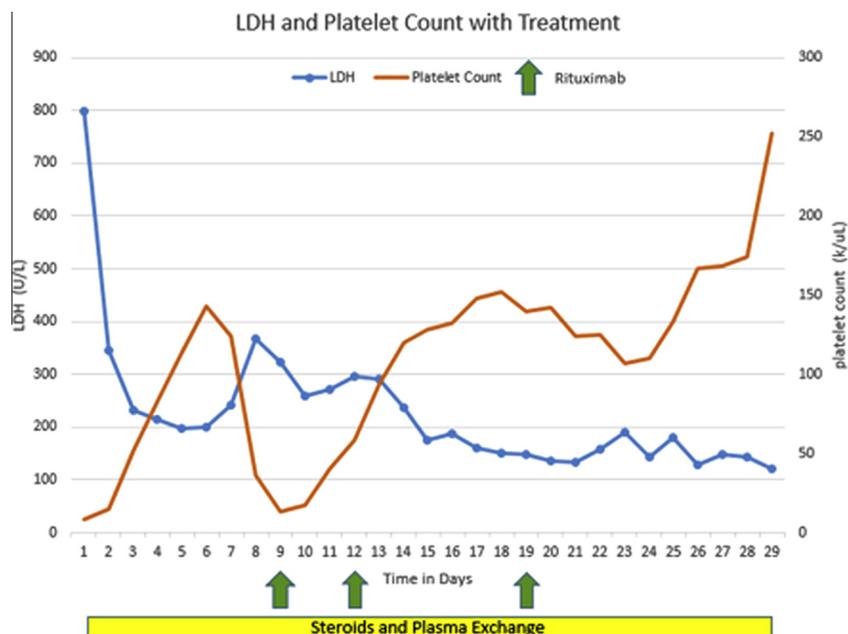
## Case report

A 43-year-old woman with past medical history of hypertension, hyperlipidemia, Sjogren's syndrome (SS), rheumatoid arthritis (RA), and obesity was admitted from the emergency room for rapid onset right-sided paresthesia from acute left-thalamic ischemic stroke. She developed angina while in the hospital, and was diagnosed with non-ST segment elevation myocardial infarction (NSTEMI). Coronary angiogram showed nonobstructive coronary artery disease, and laboratory studies revealed normal blood counts, bilirubin, and creatinine. The stroke and myocardial infarction were presumed secondary to accelerated hypertension. She was started on aspirin, atorvastatin, clopidogrel, carvedilol, and losartan, and was discharged home after 5 days of hospitalization. The patient presented again 2-weeks later with an approximately 3-day history of worsening fatigue, jaundice, and generalized rash. Physical exam was notable

for generalized petechial rash, scleral icterus, dark urine, normal mental status, and stable vital signs. Abnormal laboratory studies included a platelet count of 8000/mm<sup>3</sup>, LDH of 797 IU/L, hemoglobin of 10.5 gm/dL, creatinine of 2.3 mg/dL (against a baseline of 1.1 two-weeks prior), bilirubin of 4 mg/dL, and haptoglobin <20 mg/dL (normal range: 37–246 mg/dL). Peripheral blood smear showed three schistocytes per high power field, polychromasia, and severe thrombocytopenia. A DAT (Coomb's test) was negative. The patient was diagnosed with TTP/HUS, clopidogrel was discontinued, and she was started promptly on PLEX and 1 mg/kg prednisone. She initially responded to therapy with an improvement in both platelet counts and LDH levels, but then became refractory to PLEX on day 7, as shown in Figure 1. She also deteriorated clinically on day 7, with new onset anginal chest pain, which was concerning for coronary ischemia, that improved with a nitroglycerine infusion. She also complained of new right-sided paresthesia, and magnetic resonance imaging of the brain confirmed a new acute left lentiform and caudate nuclei infarcts. As a result, we started her on 375 mg/m<sup>2</sup> rituximab IV, escalated glucocorticoid therapy to 1 gram methylprednisolone IV daily, and continued daily PLEX. The concomitant use of PLEX, rituximab, and steroid was complicated by transfusion-associated circulatory overload, which responded to IV diuretics, gradual weaning off of the PLEX and steroids, and supportive care. Over the next several days, she continued to improve clinically and went into complete remission from TTP after receiving a total of 24 PLEX treatments, three weekly dosages of rituximab, and a tapering course of prednisone over 3 weeks.

## Discussion

Our patient had a positive ADAMTS13 antibody of >8 (normal: <0.5 inhibitor units), with a decrease in ADAMTS13 activity to <5 (normal: 68–163%). This was consistent with TTP, which is the disorder usually described in adults, unlike HUS, which is more common in children and associated with normal ADAMTS13 activity and absence of the inhibitor antibody. Many studies do not distinguish between TTP and HUS, and combine them under the comprehensive term TTP/HUS syndrome, since their presenting features and initial management in adults are essentially the same. Although the levels of ADAMTS13 activity and inhibitor antibody help differentiate between TTP and HUS, one should not wait for the results of these tests to start therapy. When neurological manifestations are more dominant, with renal abnormalities being minimal or absent, the condition is more likely to be TTP; whereas, when acute renal failure is the dominant clinical manifestation, the condition is more likely to be HUS. HUS often presents in children, following bloody diarrhea due to a shiga-toxin producing strain of *Escherichia coli* (O157:H7), and resolves spontaneously with supportive care (D+ HUS). Some HUS patients can present without diarrheal prodrome, and are classified to have D- HUS or atypical HUS. HUS occurs due to dysregulation of complement regulatory proteins. In TTP, in addition to renal and neurologic abnormalities, patients may rarely present with cardiac involvement secondary to platelet thrombi, leading to arrhythmias, myocardial infarctions, heart failure, or even



**Figure 1** Lactate dehydrogenase and platelet count versus time with medical management.

sudden death [1]. Congenital TTP is rare and results from a genetic defect of ADAMTS13, leading to reduced ADAMTS13 activity [2]. However, there have been cases reported of patients with severely reduced ADAMTS13 activity who have no hematologic abnormalities, as well as cases of patients who have persistent reduced ADAMTS13 activity, even after recovery from TTP [3,4]. Additionally, mouse-model studies of homozygous ADAMTS13 deficiency demonstrated the need for inflammatory or prothrombotic stimuli to initiate a clinical syndrome resembling TTP [5,6].

However, the reduced ADAMTS13 activity in acquired TTP is the result of an autoimmune process, wherein inhibitory autoantibodies are produced against ADAMTS13. Severely reduced ADAMTS13 activity was also associated with other autoimmune disorders, such as SLE, suggesting a linkage to broader autoimmune disorders and/or relationships to HLA regions [7]. TTP was also described as being associated with other conditions, including pregnancy, organ transplant, infections, and disseminated malignancy. TTP-like syndromes can be caused by certain drugs, such as ticlopidine (frequency: 1 in 2000 to 5000), clopidogrel (frequency: <1 in 20,000), quinine, trimethoprim, interferon, simvastatin, tacrolimus, mitomycin C, and gemcitabine [8]. The pathogenesis of drug-induced TTP is diverse, but some are associated with autoantibodies to ADAMTS13, while many others are due to other mechanisms, such as direct endothelial injury. In the case of our patient, we believed that TTP was induced by clopidogrel, as the patient developed TTP 2 weeks after initiation of this drug. The mechanism of clopidogrel-induced TTP is not fully understood, as many of these patients have decreased ADAMTS13 activity, and a minority of patients has normal ADAMTS13 activity. A contributory role for the concomitant use of statins has been suggested, but not confirmed [9]. The antiplatelet drug ticlopidine has fallen out of favor due to higher association with TTP. TTP caused by clopidogrel is very rare, typically occurring 2-weeks

postadministration, and responds well to PLEX in the majority of cases, but can relapse in some cases [10]. The fact that our patient had severely decreased ADAMTS13 activity and high titer ADAMTS13 autoantibodies may suggest the possibility of contributions from pre-existing autoimmune processes (SS and/or RA) to trigger ADAMTS13-antibody production, with clopidogrel acting as a hapten. This raises the question of whether the initial presentation of stroke and NSTEMI by our patient shortly before development of TTP was also related to the underlying autoimmunity, and that TTP was provoked or accelerated by clopidogrel use. It is unknown how clopidogrel induces production of ADAMTS13 autoantibodies in some cases, and can cause TTP independent of ADAMTS13 in others.

The standard treatment for TTP relies upon therapeutic PLEX, which replaces ADAMTS13 and removes circulating inhibitory autoantibodies. Mortality from TTP was previously very high (>90%) before the advent of PLEX, but has decreased to <20% with PLEX treatment. Our patient initially responded with a decline in LDH levels and a rise in platelet count during the 1st week of steroid and daily PLEX treatments (Figure 1). However, the patient became refractory to PLEX on day 7. While PLEX treatment is successful in many patients, 10–20% will have a transient or incomplete response to therapy, and this group of TTP patients are at high risk of death [11]. Case reports and small studies have documented success with the use of rituximab in the treatment of such refractory cases, with substantial improvement in the outcomes [12,13]. Rituximab, a humanized monoclonal antibody against CD20 antigen on the surface of B-lymphocytes, can cause depletion of CD20-expressing B lymphocytes, which would otherwise differentiate into plasma cells that secrete the inhibitory antibodies. The mechanisms proposed for lymphocyte depletion include complement-dependent cytotoxicity, direct apoptosis, and antibody-dependent cellular cytotoxicity. Rituximab is generally well tolerated, aside from the risk of infusion

**Table 1** ADAMTS13 activity and ADAMTS13 inhibitor with duration of therapy.

| Days | ADAMTS13 activity (%) | ADAMTS13 inhibitor titer (inhibitor unit) |
|------|-----------------------|---|
| 1    | <5                    | >8  |
| 8    | 9                     | 0.9                                       |
| 16   | 11                    | >1.1                                      |
| 30   | 105                   | NA  |
| 60   | 89                    | NA  |
| 90   | >188                  | NA  |
| 120  | 94                    | NA  |

*Note:* Normal ADAMTS13 activity is >67% (range: 68–163%), and the normal titer for ADAMTS13 inhibitor antibody is <0.5 inhibitor units. ADAMTS13 activity was ordered with reflex testing for the inhibitor in case of low ADAMTS13 activity. NA = not applicable.

reactions and increased risk of infections. The majority of patients who are refractory to PLEX respond to a single dose of rituximab and improvement is seen within 2 weeks, but the exact dosage and duration of rituximab therapy required is unknown, and long-term follow up data are still evolving. Our patient continued to show increasing ADAMTS13 activity and decreasing ADAMTS13 inhibitor during the first 3 weeks (Table 1), and required three weekly doses of rituximab to induce complete remission. Also unknown is whether there is any role for maintenance therapy using rituximab to prevent TTP relapse. Others have advocated preemptive rituximab infusions after remission in order to prevent relapses in patients with persistent severe ADAMTS13 deficiency (<10%), because such patients are known for higher relapses [13]. We administered five additional weekly dosages of rituximab for consolidation and did not offer any maintenance rituximab therapy. The patient remains in complete remission with complete renal and neurologic recovery after 13 months of follow up.

In conclusion, despite prompt recognition and immediate PLEX treatment, some TTP patients fail to respond, or respond only transiently. Such patients are at high risk of early death, and rituximab therapy in this situation can be lifesaving. Clopidogrel-induced TTP is very rare and usually responds to PLEX treatment. However, in refractory cases, response to rituximab has been observed with sustained remission. Clopidogrel-induced TTP should be considered in an acutely ill patient with thrombocytopenia, especially in the first few weeks after drug treatment is initiated.

## Conflicts of interest

The authors declare no conflicts of interest.

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