

# ADAMTS13 Deficiency and Thrombotic Thrombocytopenic Purpura Associated with Trimethoprim-Sulfamethoxazole

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**Running header:** TTP, TMP-SMX and ADAMTS13 deficiency

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Received: June 27, 2012  
Revised: November 15, 2012  
Accepted: November 28, 2012

doi:10.3121/cmr.2012.1105

**Abstract**

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Thrombotic thrombocytopenic purpura (TTP) is a hematological disease characterized by microangiopathic hemolytic anemia and thrombocytopenia. Although the link between ADAMTS13 deficiency and idiopathic TTP has been well-established, the role of trimethoprim-sulfamethoxazole (TMP-SMX) in the pathogenesis of TTP is not yet well elucidated. To the best of our knowledge, there have been only two previous reports linking this medication with the development of TTP. We present the case of a 26-year-old healthy woman who developed TTP during TMP-SMX therapy for urinary tract infection. She was found to have ADAMTS13 deficiency with anti-ADAMTS13 antibodies. Her condition responded to discontinuation of the TMP-SMX, plasmapheresis, and rituximab therapy. We speculate that the acquired ADAMTS13 deficiency might have been triggered by the TMP-SMX therapy.

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**Key Words:** ADAM proteins; Autoimmune Diseases/epidemiology; Purpura, Thrombotic Thrombocytopenic; Trimethoprim-sulfamethoxazole

## Case Presentation

A previously healthy female patient, aged 26-years, presented with abdominal pain, progressive fatigue, and purpuric skin rash over the extremities that began 7 days after beginning a treatment with trimethoprim-sulfamethoxazole (TMP-SMX) for a *Klebsiella pneumoniae* urinary tract infection. She also complained of exertional shortness of breath with no cough, hemoptysis, or other cardiopulmonary symptoms. No history of bleeding gums or hematochezia was present. A detailed interrogation did not demonstrate any other recent clinical complaints or the administration of any other type of medication beyond TMP-SMX. Physical examination revealed a young woman in no obvious distress, with a body mass index of 27 and stable vital signs. She had pallor and icterus of the mucus membranes but had no bleeding gums or rectal bleeding. She had a non-itchy, purpuric skin rash over her extremities, as well as petechiae. The rest of her physical examination was unremarkable.

Significant laboratory findings included a leucocyte count  $6.5 \times 10^3/\text{u/L}$  [reference range 4.5-13.5  $\times 10^3/\text{u/L}$ ], hemoglobin 8.9 g/dL (which had been 12.7g/dL just one week earlier) [reference range 12.0-15.5 g/dL], hematocrit 25% [reference range 35-45%], platelets  $8,000/\text{mm}^3$  ( $314,000/\text{mm}^3$  one week earlier) [reference range  $150-450 \times 10^3/\text{u/L}$ ], and a creatinine level of 1.5 mg/dl [reference range 0.4-1.0 mg/dl] which was elevated compared to her baseline value of 0.6 mg/dl. Further workup showed lactate dehydrogenase (LDH) level of 797 U/L [reference range 81-190 U/L] and reticulocytes of 2.64% [reference range 0.50-1.77%]. Direct anti-globulin test as well as blood and urine cultures were negative. Transaminases and disseminated intravascular coagulation panel were all normal. A peripheral blood smear showed the characteristic findings of microangiopathic hemolytic anemia (figure 1).

Evaluation of ADAMTS13 (A Disintegrin And Metalloproteinase with ThromboSpondin motifs, 13 ) activity measured by fluorescence resonance energy transfer (FRET)-based kinetic assay was reported as less than 5% [reference range  $\geq 67\%$ ]; levels less than 10% of normal activity make the diagnosis of severe deficiency.<sup>1</sup> ADAMTS13 antibodies, measured using ELISA (enzyme linked immune sorbant assay) were elevated at 1.2 inhibitor units [reference range:  $\leq 0.4$ ].

The diagnosis of thrombotic thrombocytopenic purpura (TTP) was established, and plasmapheresis therapy was initiated. Five consecutive days of plasmapheresis before discharge were accomplished. This therapy was continued thereafter on an outpatient basis. After failure to achieve a complete hematological response with plasmapheresis, a 4-week course of rituximab was added, resulting in a complete clinical and hematological remission (figures 2 and 3). The ADAMTS13 enzyme assays done at the end of therapy with rituximab reported an activity of 94%, with a platelet count of  $282,000/\text{mm}^3$ , hemoglobin 12.9 g/dL, and lactate dehydrogenase 167 U/L. The patient remains in remission 8 months (240 days) after discontinuation of plasmapheresis and rituximab therapies.

## Discussion

Thrombotic thrombocytopenic purpura (TTP) is a type of thrombotic microangiopathy characterized by systemic microvascular platelet aggregation and erythrocyte destruction. Since it was first described by Moschcowitz in 1924,<sup>2</sup> our understanding of this unique syndrome has continuously evolved, especially from the etiologic viewpoint. The incidence, according to the

Oklahoma TTP-HUS registry, is around 4 to 11 cases per one million per year. TTP is characterized by systemic microvascular thrombi formation resulting in multi-organ damage, predominantly the skin, cardiac, renal, and central nervous systems.<sup>3-5</sup> Historically, the diagnosis of TTP had relied on the presence of a pentad that included fever, microangiopathic hemolytic anemia, thrombocytopenia, renal failure, and central nervous involvement.<sup>5</sup> However, at the present time, only the dyad of otherwise unexplained thrombocytopenia and microangiopathic hemolytic anemia is required to establish a diagnosis and initiate treatment.<sup>6</sup>

Thrombotic thrombocytopenic purpura can be congenital or acquired;<sup>6</sup> the congenital type usually manifests in early childhood as chronic relapsing TTP.<sup>7</sup> The etiology of acquired TTP is predominantly idiopathic, representing around 40% of all cases,<sup>8</sup> but it can be associated with drugs,<sup>9,10</sup> pregnancy,<sup>11</sup> infections,<sup>12</sup> and malignancies.<sup>13</sup> The idiopathic type of TTP has been found to be related to a deficiency of a vital metalloproteinase enzyme referred to as ADAMTS13, which is responsible for the cleavage of the Von Willebrand factor (vWF) multimers.<sup>14-17</sup>

Drug-associated TTP represents about 12% of all cases.<sup>8</sup> The most common medications associated with TTP include quinine, thienopyridines, vaccines, H-2 receptor antagonists, nonsteroidal anti-inflammatory drugs, antineoplastic agents, and hormonal therapies. Antibiotics like cephalosporins, ampicillin, clarithromycin, metronidazole, oxytetracycline, penicillin, rifampicin, sulfisoxazole, and trimethoprim-sulfamethoxazole have been also linked to the development of TTP.<sup>8-19</sup>

Drugs may cause TTP via two mechanisms: a dose related toxicity and/or an immune mediated reaction.<sup>9,10,18</sup> In the particular association between TMP-SMX and TTP, very limited data is available to explain the possible mechanism by which TMP-SMX might be a trigger for TTP. There are three possible hypotheses. The first is that TMP-SMX causes an immune mediated injury to the small vessels, resulting in leucocytoclastic vasculitis that triggers a microangiopathic hemolytic process and eventually thrombosis. The second hypothesis is the likelihood that TMP-SMX-dependent antibodies destroy the ADAMTS 13, leading to the accumulation of vWF multimers and subsequently TTP. The third hypothesis is that TTP occurs as a complication of a hypersensitivity reaction to TMP-SMX.<sup>20-24</sup>

To the best of our knowledge, there are only two previous reports published linking TMP-SMX with TTP. One of those reports suggests that a hypersensitivity reaction involving diffuse endothelial injury or vasculitis is the most likely mechanism in the genesis of TTP, based on the normal level of ADAM TS 13 activity and the absence of TMP-SMX dependent antibodies.<sup>20</sup> The other report, which groups two cases, suggests that TTP associated with TMP-SMX is an idiosyncratic drug reaction, although neither ADAMTS 13 activity nor antibody levels or TMP-SMX dependent antibodies were evaluated.<sup>21</sup> In our case, the patient was found to have a severe ADAMTS13 deficiency and inhibitory autoantibodies against ADAMTS13. These inhibitory antibodies are found in 44% to 93% of patients with acquired TTP and are believed to be involved in its pathogenesis.<sup>16,25,26</sup> Their prognostic utility and the exact trigger for their production remains unknown.<sup>1,27</sup> It is feasible to postulate that TMP-SMX could be one of those triggers, since it is a known stimulus for the formation of autoantibodies in other pathological processes<sup>28</sup>

We hypothesize that the exposure to TMP-SMX induced the generation of inhibitory autoantibodies, which in turn led to the accumulation of vWF multimers and eventually triggered the episode of TTP. Whether this relationship is legitimate or purely circumstantial remains a medical query that warrants more investigation.

### **Acknowledgements**

The authors thank the Marie Fleisner of the Marshfield Clinic Research Foundation's Office of Scientific Writing and Publication for editorial assistance in the preparation of this article.

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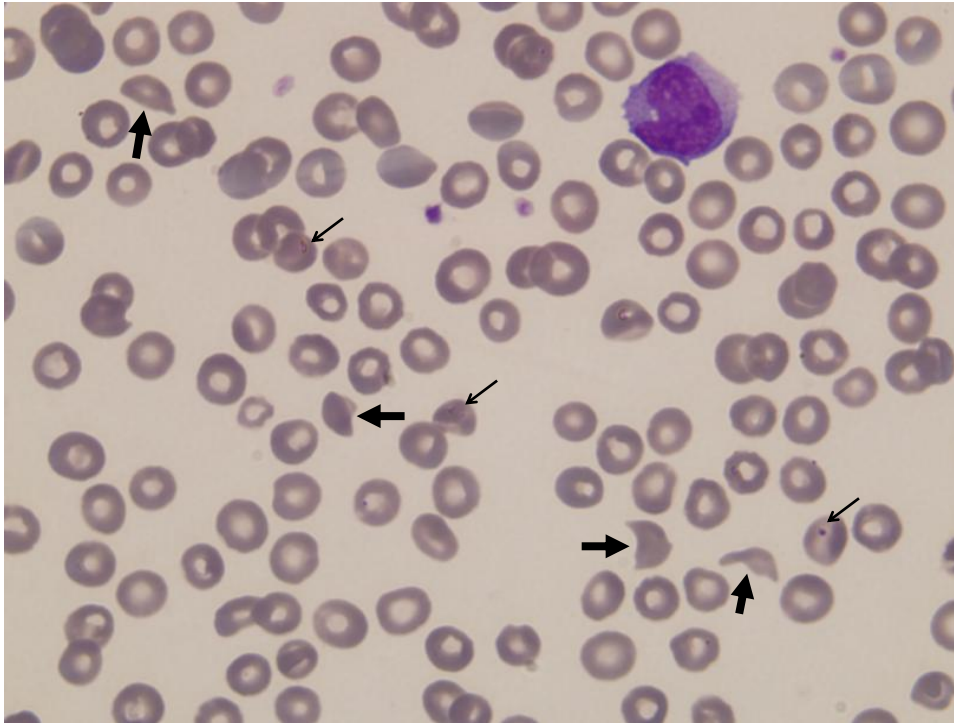
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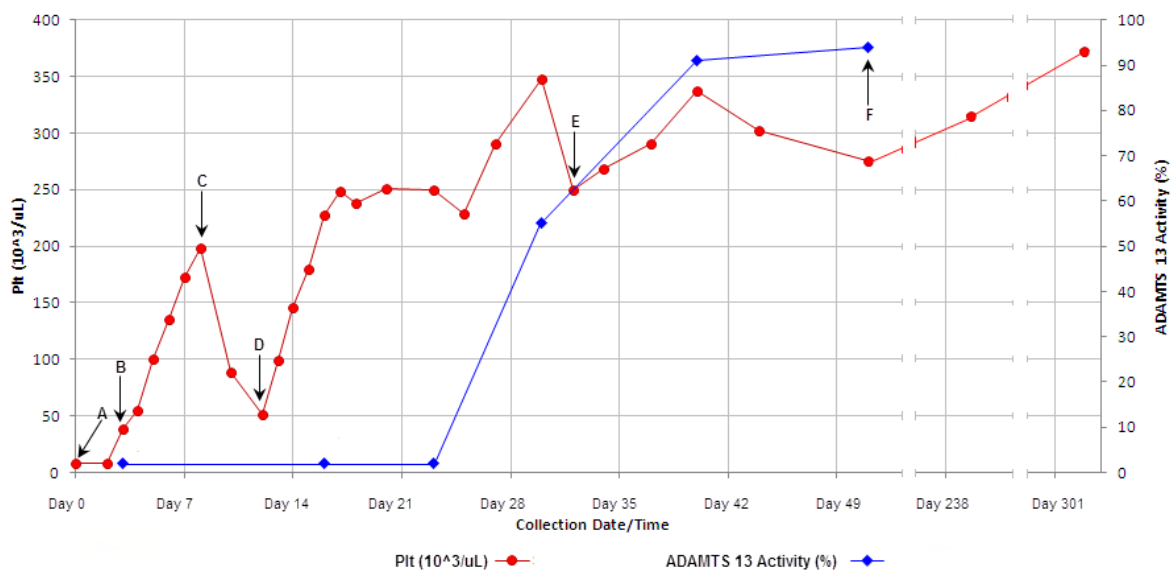
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### Figure Legends

**Figure 1.** Peripheral blood smear (under 1000\*) with Wright Giemsa stain showing Schistocytes (large arrows), basophilic stippled erythrocytes (small arrows) and reduced number of platelets.



**Figure 2.** Platelet levels and ADAMTS 13 activity during the course of the disease. (A) Diagnosis of TTP was done. (B) Daily plasmapheresis therapy was started. (C) Plasmapheresis was switched to alternate day therapy. (D) Because of the significant new reduction in platelet count, daily plasmapheresis therapy was restarted. (E) Plasmapheresis was stopped. As an incomplete recovery of the ADAMTS 13 activity was made, rituximab therapy was initiated. (F) At the end of rituximab therapy ADAMTS 13 activity returned to normal levels.



**Figure 3.** Lactate Dehydrogenase Levels. The new significant elevation observed (arrow) correlates with the period of time when plasmapheresis therapy had been switched to alternated days. A corresponding reduction on platelet count (figure 2D) required that the daily based plasmapheresis be restarted.

