Thrombotic thrombocytopenic purpura (TTP) associated with interferon therapy of hepatitis C

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Abstract

Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) is a rare but known complication of chronic viral hepatitis C (HCV). Even less frequently treatment of HCV with interferon-alpha (INFα) may become complicated with TTP/HUS, although only a few such reports have been published. We report a 43-year-old woman who developed TTP on two separate occasions soon after beginning treatment with IFN-alpha and ribavirin for HCV.

Keywords

Thrombotic thrombocytopenic purpura (TTP); hepatitis C; interferon.

Introduction

Thrombotic thrombocytopenic purpura (TTP) was first described in 1924 by Moschovitz in a case report of sudden death of a 16-year-old girl with petechiae and anemia, who at autopsy was found to have multiple thrombi occluding small blood vessels. TTP is one of the conditions in the broad spectrum of thrombotic microangiopathy (TMA) that is characterized by the formation of thrombi in the microvasculature of various organs and has remained a syndrome with multiple unknowns until recently.

Classically TTP presents with a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia, fever, renal failure (RF) and neurological abnormalities. The presence of only thrombocytopenia and microangiopathic hemolytic anemia is however sufficient to make a diagnosis. Laboratory findings include anemia with schistocytes on peripheral blood smear, thrombocytopenia, elevated indirect bilirubin and lactate dehydrogenase (LDH). Coagulation studies (prothrombin time (PT) and partial prothrombin time (PTT)) are usually normal. The presence of neurological symptoms and RF constitute the more severe form. It is difficult to distinguish between TTP and HUS and the combined term TTP/HUS is often used. Although both conditions have TMA, renal and neurologic dysfunction, HUS is characterized by predominantly RF, whereas the neurological component is more pronounced in patients with TTP.

TTP/HUS has been reported in patients of all age groups and in both genders; the female to male ratio is 2:1. A hereditary form (Upshaw–Schulman syndrome) has been reported and occurs...
predominantly in the pediatric population\cite{2}. Although the mortality rate was extremely high in the past, the prognosis has improved significantly since plasmapheresis was introduced as a treatment modality for TTP. With this therapy the overall survival rate is 87%. Relapses are common: 40% of patients experience recurrent disease within 4 weeks of diagnosis and another 40% have late reoccurrence\cite{3}.

Subgroups of TTP with a distinct etiology are increasingly recognized. Numerous conditions are associated with TTP, namely pregnancy, autoimmune conditions, malignancy, pancreatitis, a history of organ transplantation, medications, and multiple infections. Although *Escherichia coli* (serotype O157:H7) is classically associated with TTP, *Campylobacter*, HIV, CMV, and HCV have also been linked with TTP\cite{4–9}.

We describe a woman with chronic hepatitis C virus who developed TTP on two occasions during treatment with IFN\_\_ therapy.

**Case report**

A 43-year-old African American woman had a past medical history significant for an episode of TTP during her pregnancy 15 years earlier and a history of chronic HCV genotype II. A second episode of TTP occurred much later but after plasmapheresis she had remained stable for more than a year, after which she began treatment for HCV with IFN\_\_2-b (3 Munits 3 times per week) and ribavirin (1000 mg/day).

Her laboratory data prior to initiation of treatment were: platelets 263,000/\u00b5L, aspartate aminotransferase 14 U/L, alanine aminotransferase 32 U/L, and total bilirubin 0.6 mg/dL. Within 9 days of starting treatment, she presented with headache, fever, chills, nausea, cough, abdominal pain, and generalized muscle pain. Physical examination was positive for hepatomegaly, palatal petechiae, and diffuse ecchymoses on her right hand and groin. She had a platelet count of 19,000/\u00b5L, lactate dehydrogenase (LDH) of 839 U/L, reticulocytes 3.4%, total bilirubin of 2.1 mg/dL, normal PT and PTT. Urinalysis revealed 5–10 red blood cells (RBC) per high power field (hpf). The diagnosis of TTP was made; antiviral medications were discontinued and the patient was admitted for plasma exchange therapy. Her condition improved dramatically after 6 daily cycles of plasmapheresis and at discharge, laboratory evaluation revealed a platelet count of 266,000/\u00b5L, reticulocytes 5.7%, LDH 170 U/L, and total bilirubin 0.7 mg/dL. She continued to receive plasma exchange intermittently for 2 months after discharge and remained asymptomatic with normal platelet counts for 2 years.

With the patient’s consent, a trial of pegylated IFN\_\_2-b 120 \mu g subcutaneously and ribavirin daily was begun to treat her HCV. Within 4 days, she began complaining of weakness, myalgia, nausea, vomiting, hematuria, and fever. Physical examination demonstrated muddy sclera, a systolic ejection murmur at the left sternal border, and mild right upper quadrant tenderness. Laboratory evaluation revealed a platelet count of 7000/\u00b5L, hemoglobin 9.6 g/dL, reticulocytes 5.2%, total bilirubin 3.2 mg/dL, LDH 2284 U/L, and normal PT and PTT. Reoccurrence of TTP was suspected and HCV treatment was discontinued once again. The peripheral blood smear demonstrated moderate to marked schistocytes, and urinalysis was positive for 25–30 RBC/hpf and 3–5 hyaline casts/hpf, which confirmed the diagnosis.

Plasma exchange therapy was initiated. Serum ADAMTS13 activity, measured by fluorescent resonance energy transfer (FRET) was decreased at 63% (reference range ≥67%)\cite{10}. While in the hospital, she developed a transient episode of slurred speech and hand numbness which lasted for 10 min. A transfusion of packed RBCs was administered to treat worsening anemia. The patient’s condition improved promptly in response to plasma exchange therapy. At the time of discharge her platelet count was 372,000/\u00b5L, LDH was 235 U/L, and total bilirubin was 0.8 mg/dL. She received 6 additional plasma exchanges as an outpatient and remained asymptomatic with stable platelet counts. Table 1 summarizes the laboratory findings during the various hospitalizations.

**Discussion**

Interferons are a species-specific group of naturally occurring cytokines that are produced by body tissues in response to the presence of virus as a part of the innate immune response. The presence of a substance that inhibits viral growth upon repeated exposure to virus was first described in 1954\cite{11}. A few years later, the presence of a substance that interferes with viral growth was noted when the interference of heat-inactivated influenza virus on the growth of live
influenza virus in chicken egg chorioallantoic was observed. The inhibitory substance was named interferon\[12\].

Interferons induce multiple proteins that have antiviral properties, but their exact mechanism of action is still largely unknown. INF\[12\]/C11 modulates expression of more than 100 genes, although the function is recognized for only a small proportion. Its antiproliferative, antiinflammatory, and immunomodulatory properties have been utilized in the treatment of a variety of cancers, viral infections, and autoimmune conditions\[13\]. The most common complication of INF\[12\]/C11 therapy is a flu-like syndrome and injection site reactions, but more serious reactions may also occur.

Being a protein, INF\[12\]/C11 has strong immunogenic properties and among a myriad of potential side effects are multiple autoimmune abnormalities. Thyroid disease, hematological, connective tissue, renal and vascular abnormalities are among the most commonly reported\[14,15\]. The hematological complications ascribed to therapy with INF\[12\] can be due to direct bone marrow suppression or development of antibodies that may present as autoimmune hemolytic anemia or thrombocytopenia due to immune thrombocytopenic purpura (ITP) or, infrequently, TTP\[14,16–21\]. Although very rare, INF\[12\]-induced immune thrombocytopenia can lead to disabling or life-threatening complications, such as intracranial hemorrhage or myocardial ischemia\[20,22,23\]. Occasionally these abnormalities develop long after the drug has been discontinued\[21\]. There are multiple reports of TTP during treatment of chronic myelogenous leukemia with INF\[12\]\-2b\[24,25\]. In contrast, only a few reports of TTP complicating treatment of HCV with INF\[12\] exist. The first observation of TTP complicating INF therapy for HCV, described in 1998, was a 57-year-old man with chronic HCV who was being treated with recombinant IFN\[12\]-2b\[26\]. On the 16th week of treatment, the patient experienced headache and fever and developed a markedly decreased platelet count and hemolytic anemia. He was subsequently diagnosed with TTP. In this patient the occurrence of TTP appeared to be related to the IFN treatment for his chronic HCV. The patient died on the 3rd hospital day.

The cause and pathogenesis of TTP were unknown until recently. In 1982, a very large multimer of von Willebrand factor in the plasma of patients with chronic relapsing TTP was suspected of being implicated in the pathophysiology of this condition\[27\]. In 1998, Furlan et al.\[28\] and Tsai and Lian\[29\] independently demonstrated that deficiency of the specific enzyme, metalloprotease

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<th>Table 1. Summary of laboratory findings during various hospitalizations</th>
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<td><strong>Admission labs</strong></td>
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<tr>
<td>Platelet (/L)</td>
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<td>White blood cell count(×10^3)</td>
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<td>Hematocrit (%)</td>
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<td>Blood smear</td>
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<td>Total bilirubin (mg/dL)</td>
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<td>PT/PTT/INR</td>
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<td>Urinalysis</td>
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<td>Creatinine (mg/dL)</td>
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INR, international normalized ratio.
ADAMTS13, which cleaves ultra-large von Willebrand factor (vWF) multimer at a specific site, leads to accumulation of the ultra-large vWF multimer, which, under high shear stress, leads to platelet clumping and thrombus formation. ADAMTS13 deficiency due to a congenital defect or due to the presence of inhibiting autoantibodies has been associated with many cases of idiopathic and drug-induced TTP.

Occurrence of TTP after completion of a full course of pegylated interferon (PEG-INF) was described in a 62-year-old man with transfusion-acquired HCV. The patient was treated with PEG-INF for 48 weeks and developed TTP 2 weeks after completion of his treatment. Plasma ADAMTS activity was decreased to less than 0.5% of normal and the presence of anti-ADAMTS13 IgG antibodies was detected by ELISA assay. The patient responded well to treatment with steroids and plasma exchange\[30\]. Fatal cases of TTP in the setting of the use of PEG-INF have also been reported\[31\].

HCV infection itself has been associated with multiple autoimmune phenomena, including TTP. An Italian retrospective study of 265 patients with HCV found an increased incidence of autoimmune conditions in this patient population: Sjögren’s syndrome (5.2%), thyroiditis (4.1%), rheumatoid arthritis (2.2%), autoimmune thrombocytopenia (2.6%), mixed cryoglobulinemia (1.5%), autoimmune anemia (0.3%) and oral lichen planus (0.3%)\[32\]. In viral infections (HCV, CMV, HIV), development of TTP seems to be linked to immune phenomena such as the presence of cryoglobulins and anticardiolipin antibodies as well as endothelial damage\[7\]. Our case shows a strong association between TTP and IFNα in a patient with HCV because of the short time interval between beginning treatment and symptom onset and the reoccurrence of the symptoms after a long symptom-free period following re-challenge with the drug. Although screening for preexisting ADAMTS13 deficiency or inhibitor is not readily available, this potentially fatal complication should be borne in mind when investigating thrombocytopenia in the context of interferon therapy, especially in patients with a history of TTP in the past. In our patient, ADAMTS13 activity level was mildly decreased indicating a possibility of pre-existing enzyme deficiency; however clinical features were strongly suggestive of TTP. Since ADAMTS13 activity may be artificially elevated by concurrent plasma exchange therapy, every effort should be made to retrieve a pre-treatment blood sample on which to assay for ADAMTS13.

It is possible that HCV and its treatment with interferons alter the immune system response and induce anti-ADAMTS13 antibody formation leading to an episode of TTP. Patients with a history of idiopathic TTP may have a preexisting deficiency or defect of ADAMTS13 putting them at even higher risk for development of this complication. The role of the drug in precipitating TTP has not usually been proven since re-administration of the drug offender would be unethical.

Our case is unique since INFα was re-administered at the patient’s request despite previous serious side effects, demonstrating a probable causative relationship between INF and reoccurrence of TTP in this patient.

Interferons may have bone marrow suppressive effects leading to thrombocytopenia that is usually mild and gradual in onset. A sudden drop in platelet count should prompt a thorough investigation, and TTP should be thought of in the differential diagnosis. Furthermore, patients with a history of TTP/HUS in the past are at higher risk for development of this dangerous complication while being treated with interferons, therefore, screening for ADAMTS13 deficiency prior to initiation of such therapy should be considered.

Effective use of rituximab, a monoclonal antibody directed against CD20 receptors on the surface of B cells, has been increasingly reported in the treatment of TTP associated with the presence of ADAMTS13 inhibitor in patients who have been resistant to treatment with plasma exchange. It is well tolerated and has few serious side effects. Among the most serious side effects of rituximab are infectious complications related to re-activation of latent viral infections, including HCV\[33\]. Therefore all risks and benefits should be considered very carefully before its use in patients with TTP and HCV. Pre-emptive treatment with rituximab has been successfully tried for prevention of TTP flair in patients with frequent relapses\[34\].

A novel agent, anti-vWF aptamer ARC1779, a synthetic modified DNA/RNA oligonucleotide that binds to vWF and prevents it from activating platelets, has been successfully used for treatment of TTP resistant to all types of conventional therapy, including steroids, plasmapheresis, rituximab and splenectomy\[35\]. This promising experimental medication has a low incidence of side effects, such as bleeding and unspecified toxicity. However, more studies are needed before it can be used more widely.
Teaching point

TTP presents with a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia, fever, renal failure, and neurologic abnormalities, however, the presence of only thrombocytopenia and microangiopathic hemolytic anemia is sufficient to make a diagnosis. Deficiency of a specific protein, ADAMTS13, due to a congenital defect or due to the presence of inhibiting autoantibodies has been associated with many cases of idiopathic and drug-induced TTP.

Treatment options for patients with TTP include plasma exchange therapy, and experimental therapies including rituximab, and possibly a new agent, anti-vWF aptamer ARC 1779.

TTP should be considered in the differential diagnosis of thrombocytopenia in patients undergoing therapy with interferon.

References
