Alerts, Notices, and Case Reports

Thrombotic Thrombocytopenic Purpura Associated With Histamine H_2-Receptor Antagonist Therapy

SUSAN M. KALLAL, PharmD
MAKAU LEE, MD, PhD
San Antonio, Texas

FIRST DESCRIBED in 1924, thrombotic thrombocytopenic purpura (TTP) is an uncommon disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurologic deficits, renal dysfunction, and fever.[1-3] In this report, we describe a case of TTP associated with the use of famotidine, a histamine H_2-receptor antagonist. To our knowledge, this is the first documented case of TTP due to an H_2-receptor antagonist.

Report of a Case

The patient, a 63-year-old man, was admitted to the hospital because of the acute onset of slurred speech and left-sided weakness on the day of admission. He did not have fever, headache, blurred vision, incontinence, seizures, hematuria, or skin discoloration. A week before his admission, the patient began taking famotidine (20 mg orally once a day) for gastroesophageal reflux symptoms. His medical history was relevant for an episode of TTP 14 years before this admission during which he was taking cimetidine for peptic ulcer disease. This earlier episode of TTP began about five weeks after the initiation of cimetidine therapy, and the TTP resolved completely after steroid therapy, blood transfusion, and the discontinuation of cimetidine.

On admission, the patient's temperature was 37.2°C (99°F), his pulse rate was 84 beats per minute, and his blood pressure was 170/80 mm of mercury. On physical examination, the patient had slurred speech and mild weakness in his left leg; the rest of the physical and neurologic findings were unremarkable. Pertinent laboratory studies included a complete blood count showing a hematocrit of 0.219 (21.9%) with a reticulocyte fraction of 0.134 (13.4%) and a platelet count of 14×10^9 per liter (14,000 per μl); a peripheral blood smear showing pronounced anisopoikilocytosis, including numerous nucleated erythrocytes, schistocytes, helmet cells, tear drop cells, and fragmented erythrocytes; total serum bilirubin level, 34 μmol per liter (2 mg per dl) (normal, 3.4 to 20.5 μmol per liter); serum lactate dehydrogenase (LDH) level, 1,207 units per liter (normal 100 to 225 units per liter); and urinalysis showing 2+ blood. The remainder of blood chemistry tests, liver function tests, and coagulation studies (including fibrinogen and fibrin-split products) were within normal limits; a direct Coombs' test was negative. An emergency computed tomographic scan of the head revealed no acute infarction or hemorrhage. A subsequent bone marrow biopsy revealed pronounced normocytic erythroid hyperplasia, a substantial increase in the number of megakaryocytes, maintenance of a trilineage maturation pattern, and no evidence of any infiltrative processes. Thus, a diagnosis of TTP was made.

The patient was treated with corticosteroids, the transfusion of red blood cells, and daily plasmapheresis with fresh-frozen plasma, in addition to the discontinuation of famotidine. His hospital course was uncomplicated, with gradual and complete resolution of his neurologic signs and hematologic abnormalities over several days. He was well and asymptomatic with no recurrence of any neurologic problems at one-year follow-up.

Discussion

Thrombotic thrombocytopenic purpura is more common in women than men by a ratio of 3:2 and occurs most often in the third decade of life.[3,4] The onset of symptoms in patients with TTP is typically abrupt.[2] About 30% of patients present with the five characteristic manifestations, whereas 70% to 80% of patients present with thrombocytopenia, hemolytic anemia, and neurologic dysfunction.[4,5] The most common initial presentations of TTP are neurologic deficits and hemorrhage.[1,2] On laboratory examination, TTP patients show hemolytic anemia and thrombocytopenia. Severe anemia is common, and about 40% of patients have a hemoglobin of 65 grams per liter (6.5 grams per dl) or less.[1,4] Platelet counts are often less than 20×10^9 per liter (20,000 per μl).[4,6] Leukocytosis may be present in about 80% of patients.[3] Peripheral blood smears show schistocytes without spherocytes, consistent with a nonimmune hemolytic anemia.[6] Serum LDH levels are markedly elevated and have been used in conjunction with the platelet count as a marker for disease progression and efficacy of therapy.[2,4,5] Coagulation studies differentiate TTP from disseminated intravascular coagulation (DIC); fibrin-degradation products present in patients with DIC are lacking in those with TTP.[4,7] In addition, prothrombin time, partial thromboplastin time, and fibrinogen values are usually normal in patients with TTP, in contrast to the abnormalities noted in patients with DIC.[4,7]

The clinical manifestations of TTP represent damage to various organ systems due to widespread thrombosis of

(Kallal SM, Lee M: Thrombotic thrombocytopenic purpura associated with histamine H_2-receptor antagonist therapy. West J Med 1996; 164:446-448)

From the Department of Medicine, University of Texas Health Science Center, San Antonio.

Reprint requests to Makau Lee, MD, PhD, Division of Gastroenterology, Dept of Medicine, University of Texas Health Science Center, 7703 Floyd Curl Dr, San Antonio, TX 78284-7878.

ABBREVIATIONS USED IN TEXT

DIC = disseminated intravascular coagulation
LDH = lactate dehydrogenase
TTP = thrombotic thrombocytopenic purpura

the microvasculature.[2,8] Possible stimuli for intravascular thrombus formation include diffuse endothelial damage and abnormally large von Willebrand factor multimers.[2,6,7] Available data from experimental studies indicate that various noxious stimuli produce endothelial injury, a transient release of platelet-agglutinating factors, and unusually large multimers of factor VIII:von Willebrand factor from injured endothelium, resulting in abnormal platelet aggregation and producing the syndrome of TTP.[6-8] Other factors implicated in the pathogenesis of TTP include impaired fibrinolytic activity, immune complex formation and deposition, abnormalities of endothelial prostacyclin production, and a deficiency in platelet-aggregating factor inhibitor.[2,6,7] An autoimmune cause has also been postulated because TTP has been associated with several autoimmune disorders, including Sjögren's syndrome, polymyositis, systemic lupus erythematosus, and rheumatoid arthritis.[7-9]

Thrombotic thrombocytopenic purpura has also been associated with pregnancy; allograft rejection; vaccines[2]; bacterial, viral, and fungal infections[10]; carcinomas[10]; a dog bite[11]; a beesting[10]; and carbon monoxide poisoning.[12] In addition, the following drugs have been reported to cause this disorder: penicillin,[13] sulfonamides,[10] rifampicin,[14] metronidazole, quinine, cyclosporin,[15] penicillamine,[16] ticlopidine,[17] defibrotide,[18] oral contraceptive agents,[2,10] chemotherapeutic agents,[10,15] and cocaine.[15] A review of the English-language literature between 1966 and 1995 did not reveal any cases of TTP related to H_2-receptor antagonist therapy. Moreover, a computer search of the 1995 Drugdex database revealed that although the use of H_2-receptor antagonists has been associated with various hematologic abnormalities (Table 1), none have been reported to cause TTP.[19] To our knowledge, our patient represents the first documented case of TTP associated with H_2-receptor antagonists. Although the pathogenesis of the hematologic adverse effects associated with H_2-receptor antagonists (Table 1) remains unclear, experimental studies suggest that these adverse effects are probably due to either direct toxicity for various hemopoietic cells or drug-induced immune reaction.[20,21] In the present case, we speculate that the H_2-receptor antagonists cimetidine and famotidine probably initiated endothelial damage and abnormal platelet aggregation, resulting in TTP.

At the time of presentation, our patient was taking no medications other than famotidine. The temporal relationship of the onset of symptoms in our patient correlates with the initiation of famotidine therapy. We speculate that he had TTP 14 years earlier while taking cimetidine, thus the initiation of famotidine seven days before this admission resulted in an inadvertent rechallenge with another H_2-receptor antagonist and recurrence of the TTP. We recognize, however, that about 30% of patients with TTP may have a recurrence during the first ten years after the initial episode[22]; hence, we cannot exclude the possibility that this patient simply had a relapse that was not related to the coincidental use of famotidine.

Finally, the treatment of TTP has been largely empiric. Over the past two decades, plasmapheresis or plasma exchange has become the treatment of choice for this disorder. In the 1960s, the mortality due to TTP was greater than 90%[1,4]; however, the introduction of plasmapheresis and improved supportive care during the past two decades have led to an overall survival rate of greater than 80%.[4,5,15] In a recent prospective trial of 108 patients with TTP treated with plasmapheresis and prednisone, a one-year survival rate of 91% was reported.[23] It remains unclear, however, whether plasmapheresis is effective due to the removal of a harmful substance or to the replacement of a deficient substance. Although plasmapheresis is the current treatment of choice, other adjunctive therapies that have been reported to be effective in individual cases include glucocorticoids, antiplatelet agents (such as aspirin, dipyridamole, sulfinpyrazone, or dextran), prostacyclin infusions, intravenous immune globulin therapy, vincristine sulfate, and splenectomy.[2,6,8] The relative benefit of these adjunctive treatments in conjunction with plasmapheresis or plasma exchange remains uncertain due to the

TABLE 1.—*Hematologic Adverse Effects Associated With Histamine H_2-Receptor Antagonists**

	H_2 Receptor Antagonists			
Hematologic Toxicity	*Cimetidine*	*Ranitidine*	*Famotidine*	*Nizatidine*
Agranulocytosis	X	X		
Neutropenia	X	X	X	
Leukopenia		X		X
Eosinophilia	X	X		
Aplastic anemia	X	X		
Pancytopenia	X	X		
Thrombocytopenia	X	X	X	X
Leukemoid reaction		X		
Hemolytic anemia		X		
Anemia				X

*From the Drugdex.[19]

rarity of the disease and the lack of prospective, controlled clinical trials. Heparin use is generally contraindicated in patients with TTP because the thrombotic occlusions are not thrombin-mediated.[24] Platelet transfusions have resulted in fatal cerebral infarction due to platelet aggregates in the brain and are not recommended.[2,25]

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Anorectal Melanoma
Successful Palliation in a 59-Year-Old Woman

SAM P. MOSTAFAPOUR, MD
JOHN MORRIS, MD
JOHN P. SHERCK, MD
San Jose, California

ALTHOUGH THE ANUS is the most common site for gastrointestinal melanoma, anorectal melanoma is an uncommon disease, with about 500 reported cases since it was first described by Moore in 1857.[1] The prognosis for melanoma in this location is poor, with five-year survival rates generally less than 10% despite surgical resection. Indeed, survival is often measured in months following diagnosis. The poor prognosis in patients with this disease may be attibutable to the aggressive nature of the tumor as well as its advanced stage at the time of diagnosis. We report a case of advanced anorectal melanoma and review the literature, with special emphasis on the treatment options available to patients with this disease.

Report of a Case

The patient, a 59-year-old woman, presented to the emergency department with weakness, fatigue, weight loss, and intermittent rectal bleeding of several weeks' duration. On physical examination, she was found to have a pigmented lesion on the right lateral aspect of her anus that was large (7 cm × 7 cm), necrotic, fungating, and nontender (Figure 1). There was bleeding from the mass. No hepatomegaly, splenomegaly, or abdominal masses were noted. She had unilateral 3+ pitting edema of her left lower extremity. Laboratory studies revealed a hematocrit of 0.16 (16%), and liver function test results were within normal limits.

The patient was taken to the surgery department for sigmoidoscopic examination under anesthesia. On close examination, the mass was found to arise on the right lateral region of the anal canal and was nearly circumferential. The mass extended 7 cm superiorly into the rectum, with involvement of the anterior, left lateral, and posterior sides. No rectovesical or rectovaginal fistulas were found.

Histopathologic analysis of a biopsy specimen revealed loosely packed sheets of pleomorphic cells, with an abundance of pigment-containing melanotic cells (not shown). The depth of the tumor locally was greater than 3 to 4 mm, which was the maximum depth of the biopsy specimen.

A computed tomographic scan from the lower thorax through the pelvis was obtained that showed the previ-

(Mostafapour SP, Morris J, Sherck JP: Anorectal melanoma—Successful palliation in a 59-year-old woman. West J Med 1996; 164:448-450)

From the Department of Surgery, Stanford University School of Medicine, Stanford, and the Division of General Surgery, Santa Clara Valley Medical Center, San Jose, California.

Reprint requests to John P. Sherck, MD, Div of General Surgery, Santa Clara Valley Medical Center, 751 Bascom Ave, San Jose, CA 95128.