Thrombotic thrombocytopenic purpura

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Once formerly thought to be a rare disorder, thrombotic thrombocytopenic purpura (TTP) is becoming increasingly recognized. It is characterized by a pentad of clinical findings, including microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic and renal abnormalities, and fever. Following a case report, the major clinical findings, pathophysiologic findings, diagnoses, and use of various therapeutic modalities are discussed.

Thrombotic thrombocytopenic purpura (TTP) is characterized by microangiopathic hemolytic anemia, thrombocytopenic purpura, fluctuating neurologic dysfunction, fever, and progressive renal impairment. Although a relatively rare disorder, TTP has received considerable attention in the medical literature within the last several years. In the past, it has been described as a rapidly progressive, mortal disease. However, recent reports¹⁻⁴ suggest that it is not always fatal; improved survival rates may reflect recognition of less severe forms of the disease as well as more effective treatment modalities.

Report of case

During a routine physical examination, a 44-year-old man was found to have anemia, thrombocytopenia, and microscopic hematuria. Two weeks before admission, the patient noted slight bruising of the extremities following minimal trauma. Twelve days later, he noticed petechial eruptions at the sites of electrocardiographic suction cups.

Four months prior to admission, the patient had presented with sudden-onset, right-sided pure motor hemiparesis. Computed tomographic scanning of the brain and noninvasive carotid studies had negative results, but a magnetic resonance imaging (MRI) procedure detected a solitary hyperdensity of the left corona radiata, which was thought to be consistent with a small lacunar infarction (Fig 1). Routine laboratory results were unremarkable. The patient was placed on a regi-

men of oral dipyridamole (50 mg three times daily) and aspirin (325 mg per day.) His symptoms resolved completely after a few days, and there were no residual effects.

The past medical history was negative for hypertension, diabetes mellitus, or other significant illness. The patient had had no hematologic problems and had received no transfusions. He had a 60 pack-year smoking history and did not use alcohol.

Physical examination revealed an afebrile, normotensive patient who appeared slightly icteric. Petechiae were noted on the chest and the anterior tibia bilaterally. A large ecchymotic area was seen on the left triceps area, the site of a vitamin B₁₂ injection administered on the day of admission. There were no other physical findings.

Laboratory results included a hematocrit value of 37%, white blood cell count of 8,700/cu mm, reticulocyte count of 0.7%, and platelet count of 63,000/cu mm; the red blood count indices and coagulation values were normal. Indirect and direct Coombs' tests were negative. The lactate dehydrogenase level was elevated to 1,025 IU/L and subsequently rose to 2,012 IU/L. The fibrinogen level was 468 mg/dL, and the fibrin split products were non-diagnostic.

One day after admission, the peripheral blood smear revealed marked schistocytes (Fig 2). The platelet count and hematocrit value eventually decreased to 5,000/cu mm and 26.9%, respectively. Bone marrow aspiration revealed a normal level of megakaryocytes, with no evidence of malignancy. The serum creatinine level was 1.3 mg/dL. Urinalysis showed 3+ proteinuria, a large amount of occult blood, and 15 to 20 red blood cells without casts.

On the same day, the patient was noted to have fever, renal abnormalities, microangiopathic hemolytic anemia, and thrombocytopenia. He was transferred to a tertiary medical center, where daily plasmapheresis and plasma exchange were performed in conjunction with a rapidly tapered regimen of glucocorticoids. Within one week, the platelet count rose to 292,000/cu mm, and the hematocrit value to 34.6%. The peripheral blood smear returned to normal.

The frequency of the plasmapheresis was decreased to every other day, and the patient was discharged on the eleventh hospital day. The hematologic parameters have remained normal, and the patient is asymptomatic. He is maintained on 75 mg of dipyridamole three times daily and 325 mg of aspirin daily.

Fig 1. MRI scan shows left-sided lacunar infarct.

Fig 2. Peripheral blood smear demonstrates a large number of schistocytes, helmet cells, and decreased platelet count.

Discussion

TTP was first described by Moschowitz in 1925.⁵ The original triad of hemolytic anemia, thrombocytopenic purpura, and neurologic disease was expanded to include fever and renal disease by Lukes and associates⁶ in 1961; this presentation was reinforced by Amorosi and Ultmann⁷ in 1966. The disease was considered universally fatal in these early cases, with the clinical course ranging from hours to several weeks in duration.

Although the exact pathophysiology remains unclear, treatment advances have been made using a multimodality approach, which has led several investigators¹⁻⁴ to report remission rates approaching 60% to 90% percent. TTP can occur at any age; however, the disease most commonly affects adults

aged 20 to 40 years. Approximately 60% to 70% of patients are women.⁸ This entity has been seen in pregnant and postpartum women.

Etiology

Several causative and precipitating factors have been suggested, including genetic predisposition, immune mechanisms, tumors, viral infections, and the use of certain drugs, most notably oral contraceptives.⁹

The apparent association of TTP with autoimmune diseases, such as systemic lupus erythematosus and Sjögren's syndrome, as well as other immunologic diseases also has been described.¹⁰ The majority of cases, however, occur without any known causal event or associated disease process.

Clinical findings

A pentad of clinical findings—thrombocytopenic purpura, microangiopathic hemolytic anemia, fever, renal impairment, and neurologic involvement—occur in approximately 40% of TTP cases.⁹ A more common presentation (75%) is the triad of microangiopathic hemolytic anemia, thrombocytopenic purpura, and neurologic dysfunction.⁹ Patients usually present because of neurologic symptoms, bleeding, symptoms of anemia (weakness, pallor), or abdominal complaints.

The neurologic findings are peculiar and often diverse. The most prominent aspect is that a host of deficits, including seizures, aphasia, dysarthrias, paresis, and mental status changes,¹¹ usually are evanescent.

The majority of hemorrhagic manifestations occur in the skin in the form of petechiae, ecchymoses, and purpura. Genitourinary, gastrointestinal, and retinal hemorrhage also are common.

Laboratory findings

The laboratory manifestations in TTP often are dramatic (Table 1). The hallmark of the disorder is a severe microangiopathic hemolytic anemia, which is characterized by reticulocytosis and red cell fragmentation on the peripheral smear (Fig 2).

The Coombs' tests typically are negative. Severe thrombocytopenia is the rule and, together with a short platelet half-life, accounts for the bleeding. In most cases, platelet counts are <20,000/cu mm. Leukocytosis without a shift to the left also is common. The bone marrow may contain increased numbers of megakaryocytes. Coagulation values, including prothrombin time, partial thromboplastin time, and fibrinogen and fibrin split product levels usually are normal. An increase in the indirect fraction of bilirubin and clinical evidence of jaundice also reflect red cell hemolysis.

Gross or microscopic hematuria is the most common renal abnormality found. Nonnephrotic-range proteinuria also is encountered, as are mild elevation of blood urea nitrogen and serum creatinine values.

Pathogenesis

The reasons for the formation of the diffuse microvascular thrombosis of TTP remains unknown. Present evidence lends support to the theory that a plasma abnormality is primarily responsible for platelet hyperaggregability and the initiation of thrombus formation.

One such proposal¹² suggested that prostacyclin, which is the most potent endogenous inhibitor of platelet aggregation (PAFI), is absent from the serum of patients with TTP. This, in turn, would lead to unopposed platelet aggregating factor (PAF)-induced platelet aggregation and microcirculatory thrombosis. It was postulated that the success of plasmapheresis and plasma exchange in these cases is attributable to replacement of PAFI or deletion of PAF, or both.

Along those same lines, it has been proposed that a deficiency of IgG immunoglobulin, which inhibits PAF present in normal plasma, is responsible for inappropriate and excess platelet activation.¹³

Other authors¹⁴ have noted that patients with chronic, relapsing TTP have increased amounts of unusually large multimers of von Willebrand factor (vWF) in their plasma. The PAF may interact with these large multimers to cause platelet aggregation. Certain patients may be more susceptible to the agglutinating factor because of an inability to convert these large vWF to the vWF forms normally present in the circulation of normal platelets.¹⁵

Glas-Greenwalt and colleagues¹⁶ postulated that a defect in the fibrin clearing system permits thrombus formation to occur and to proceed in an unchallenged fashion, thereby contributing to the complex events leading to arterial ischemia in vital organs.

It appears that the bulk of evidence regarding the underlying mechanisms of TTP supports a type of plasma abnormality as being primarily responsible for the platelet hyperaggregability and the initiation of thrombus formation.

Pathologic findings

The histopathology of TTP is characterized by the formation of hyaline thrombi, which are composed mainly of platelets and fibrin. These thrombi are found throughout the vasculature, with predominant involvement of the brain, heart, kidneys, pancreas, and adrenal glands. Electron-microscopy has

TABLE 1. LABORATORY FEATURES OF THROMBOTIC THROMBOCYTOPENIC PURPURA.

Microangiopathic hemolytic anemia
Severe anemia (normochromic, normocytic)
Reticulocytosis
Fragmented red blood cells
Elevated lactate dehydrogenase value
Unconjugated hyperbilirubinemia
Negative Coombs' test
Severe thrombocytopenia
Normal coagulation study results
Abnormal urinary sediment

revealed a variety of findings, including endothelial cell swelling, vessels with open lumens but subendothelial deposits of hyaline material, vessels with lumens occluded by loose platelets aggregates, and, finally, occlusive thrombi.

Diagnosis

TTP should be considered in any patient who presents with the multisystemic clinical features of fluctuating neurologic abnormalities, progressive renal failure, fever, thrombotic lesions, microangiopathic hemolytic anemia, and thrombocytopenia.

Tissue biopsy as a diagnostic tool in TTP has been studied. However, because of the unpredictable nature of organ involvement, this procedure may yield negative results. Gingiva, skin, and bone marrow have all been examined, with varying success rates (39%, 55%, and 30%, respectively).¹⁷ Therefore, a negative biopsy finding despite a correlating clinical history should not detract from the diagnosis.

The differential diagnosis of TTP is lengthy (Table 2). The majority of cases are fairly distinctive, and the diagnosis is straightforward.

Treatment

In the past, therapy mostly was empiric, primarily because the exact pathogenesis was unknown. Patients were treated with many different approaches, including splenectomy, glucocorticoids, and antiplatelet agents (aspirin and dipyridamole) either alone or in combination. The multimodality approach used today evolved from these combinations of therapies.

Considerable progress was made in the mid-1970s, when the use of exchange transfusions was reported to induce remission in approximately 60% of patients.¹⁻³ Cuttner and coworkers⁴ reported remission rates of 87% in 18 patients treated with splenectomy, glucocorticoids, and dextran 70. Since then, numerous reports have indicated that some

form of plasma manipulation is essential in achieving high remission rates.

Plasmapheresis and plasma exchange have now been shown to be highly effective in the initial management of TTP. A recent report¹⁸ suggests that the addition of aggressive plasma exchange to plasmapheresis will result in a high response rate. It should be noted that glucocorticoids were used as adjunctive therapy in many cases, thus making it impossible to state whether plasmapheresis and plasma exchange alone would have induced remission.

The exact mechanism by which plasmapheresis and plasma exchange function is not known. They may act either by removal of a platelet aggregating factor or immune complex, or by restoring an inhibitor of platelet aggregation present in normal plasma. The amount and duration of this therapy remains empiric as well. Plasmapheresis is continued until the patient achieves clinical and hematologic remission.

It appears that splenectomy may be beneficial in patients who do not respond initially to plasmapheresis.^{19,20} The use of vincristine also has been studied²¹ as adjunctive therapy, but its impact is unclear at this time. Other agents that have shown promise in small series include Epoprostenol (prostacyclin) infusions,²² nafazatrom,²³ and high-dose immunoglobulins.²⁴

A reasonable approach would be to treat all patients with TTP initially by plasmapheresis and plasma exchange. Corticosteroids, although not proved to be effective when given alone, probably should be administered in high doses but tapered rapidly. If these fail, treatment would proceed to splenectomy, steroids, and dextran 70. Further plasmapheresis and plasma exchange, vincristine, and perhaps antiplatelet agents would then be used for patients not responding to splenectomy.

Recent reports^{8,13,18} suggest maintaining the patient on aspirin (600 mg to 1,200 mg daily) and dipyridamole (400 mg daily) indefinitely in the post-plasmapheresis period. However, this patient is still doing well 2 years post-diagnosis despite being on no medication.

Comment

Two aspects of the present case make it noteworthy. First, the patient developed documented lacunar infarction with resulting right hemiparesis, although he did not have any risk factors (hypertension, diabetes mellitus) for this type of event. This episode cleared rapidly and without sequelae.

Second, the patient was then treated with aspirin and dipyridamole, both of which have been used in the treatment of TTP. Although the majority

TABLE 2. DIFFERENTIAL DIAGNOSIS OF THROMBOTIC THROMBOCYTOPENIA PURPURA.

Disseminated intravascular coagulation
Evans' syndrome
Vasculitis (systemic lupus erythematosus, severe glomerulonephritis)
TTP-like syndromes
Hemolytic-uremic syndrome
Postpartum acute renal failure
Eclampsia
Other causes of microangiopathic hemolytic anemia
Vascular malformations
Malignant hypertension
Prosthetic valves
Metastatic adenocarcinoma

of studies suggest that antiplatelet agents by themselves are not successful in the treatment of this disorder, there is at least one report²⁵ of a remission achieved by this modality.

Although it cannot be proved, it is possible that the lacunar infarct may have been a subtle early manifestation of TTP. Further, it has been noted that the natural history of TTP in some patients can include active or subclinical disease of weeks' to months' duration. The antiplatelet agents the patient received may have prevented clinical relapse up until the time he developed the full-blown syndrome.

Summary

A disease of unknown cause, thrombotic thrombocytopenic purpura is characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, changing neurologic abnormalities, and renal impairment. Widespread microvascular hyaline thrombi and endothelial lesions are characteristic and are responsible for many of the clinical complications.

While TTP once was considered a highly fatal disease, increased understanding about the pathogenesis has led to improved survival rates. Plasmapheresis and plasma exchange in the initial treatment phase appears to be the essential element in producing remission of the disorder. If this is unsuccessful, the previously mentioned modalities may be used. It is clear that early diagnosis and an aggressive therapeutic approach will likely lead to remission in large numbers of TTP patients.

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BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Seldane (terfenadine) is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, gelatin, lactose, magnesium stearate, and sodium bicarbonate.

INDICATIONS AND USAGE

Seldane is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

CONTRAINDICATIONS

Seldane is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

PRECAUTIONS

Information for patients

Patients taking Seldane should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting Seldane therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should be instructed to take Seldane only as needed and not to exceed the prescribed dose. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, mutagenesis, impairment of fertility

Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C

There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Seldane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Seldane is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to Seldane only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use

Safety and effectiveness of Seldane in children below the age of 12 years have not been established.

General

Consideration should be given to potential anticholinergic (drying) effects in patients with lower airway disease, including asthma.

ADVERSE REACTIONS

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received Seldane, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported

adverse effects in patients receiving Seldane was similar to that reported in patients receiving placebo (See Table below.)

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

Adverse Event	Percent of Patients Reporting			All Clinical Studies	
	Seldane N = 781	Placebo N = 665	Control N = 626**	Seldane N = 2462	Placebo N = 147
Central Nervous System					
Drowsiness	9.0	8.1	18.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.6	0.5
Appetite Increase	0.6	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress					
(Abdominal distress,					
Nausea, Vomiting,					
Change in Bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/ Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash					
and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

*Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 DAYS.

**Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.

***CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (1 patients)

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of Seldane that warrant listing as possibly associated with drug administration. These include: alopecia, (hair loss or thinning), anaphylaxis, angioedema, arrhythmia (including ventricular tachyarrhythmia), bradycardia, confusion, depression, galactorrhea, hypotension, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, palpitation, paresthesia, photosensitivity, prolonged QT interval, seizures, sweating, syncope, tachycardia, tremor, urinary frequency, and visual disturbances. In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving Seldane. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis in most cases available information is incomplete. In neither the clinical trials nor marketing experience is a causal relationship of liver abnormalities to Seldane use clear.

OVERDOSAGE

Information concerning possible overdosage and its treatment appears in Full Prescribing Information.

DOSAGE AND ADMINISTRATION

The usual dosage for adults and children 12 years and older is 60 mg (1 tablet) twice daily.

Product Information as of June, 1988

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