Clinical Article

Thrombotic Thrombocytopenic Purpura, Moschcowitz Syndrome

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Abstract

The authors present a case of a 16-year-old boy, who was referred to the hospital due to thrombocytopenia, anemia, proteinuria and hyperbilirubinemia. Based on the clinical picture and the laboratory data, thrombotic thrombocytopenic purpura (TTP) was diagnosed. The adequate therapy was immediately started. TTP is quite a rare entity. The etiology and the pathogenesis are not well defined. The authors summarize the different pathomechanisms, which may play a role in the development of TTP. Similarity to the hemolytic uremic syndrome (HUS), therapeutic possibilities, prognosis and the outcome are also discussed. The importance of the early diagnosis of TTP in childhood, and life-saving effect of the adequate treatment are emphasized. *Int Pediatr. 2001;16(3):144-149.*

Key words: thrombotic thrombocytopenic purpura (TTP), plasmapheresis, plasma exchange (PEX)

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a severe multisystemic disorder characterized by the same tetrad of clinical findings as hemolytic uremic syndrome (HUS) (thrombocytopenia, microangiopathic hemolytic anemia, fluctuating neurological symptoms and impaired renal function) with the addition of fever.[1] Although it is a disorder of unknown cause, a variety of clinical events have been identified as possible precipitating factors. Infections are the most common precipitation factors, followed by pregnancy.[2,3] Without treatment, TTP has a mortality rate in excess of 90% due to multi-organ failure.[4] The authors recognized the clinical signs and the laboratory data on a 16-year-old patient, and after setting the diagnosis of thrombotic thrombocytopenic purpura, adequate therapy was started immediately on the basis of the current literature. For five months this patient has received combined therapy. He is now symptom- and complaint-free.

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Case Report

A 16-year-old boy is presented. He is the first child of his family, after a normal delivery. At the age of 8-months, he had salmonellosis, and later varicella and mumps. There was no family history of an inherited disease or bleeding disorder. Both his parents and his younger brother were healthy. At 16 years of age, the previously healthy boy had diarrhea. One day later he had fever and vomited.

These symptoms had disappeared in three days. Two days later, his family doctor referred him to the hospital because of proteinuria. In the hospital, anemia, thrombocytopenia, indirect hyperbilirubinemia, severe proteinuria were recognized, and an unclear structure of the kidneys was seen by an abdominal ultrasound.

During the first physical examination, he appeared pale, scleral and skin jaundice. Petechia, and some ecchymosis, and submandibular lymphadenomegaly were detected. His liver was 2 cm under the costal arch.

On his first admission at another institution, he had profound thrombocytopenia (18.000 G/l), anemia (Hb 9.2 g/dl) with numerous schistocytes (Fig 1). The patient also had an elevated LDH activity (2116 U/l), indirect hyperbilirubinemia (65 μmol/l), decreased level of serum fibrinogen (125 mg/dl), hypocalcemia (1.9 mmol/l), and proteinuria. The boy's urine sediment contained 4-5 red blood cells and 1-1 leukocytes could be detected.

Microangiopathic hemolytic anemia was diagnosed based on the clinical findings and laboratory results. The treatment was symptomatic with forced fluid therapy (in a dose of 3000 ml/m^2), which included infusions of fresh frozen plasma (FFP).

On the second day of his admission, his hemoglobin level decreased, the platelet count was stable but low. Therefore a treatment with regular plasma exchange (PEX) by plasmapheresis was initiated.

Due to the daily PEX, with replacement of cryosupernatant, a quick improvement was observed. His LDH level became normal, serum bilirubin-level decreased, hemolysis alleviated, and platelet count increased. Reticulocytosis was seen as a compensation of the bone marrow (Fig 2).

After the seventh PEX, severe spastic abdominal pain occurred; only opioid analgetics were effective. As a cause of this acute symptom, in addition to the manifestation of his primary disease, bowel ischemia, hypocalcemia, inspis-

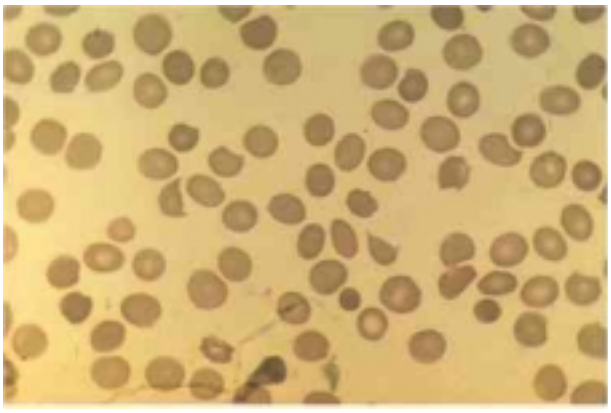

Fig 1. - Blood smear of our patient, showing red cell fragmentation (schistocytosis) and marked deficiency of platelet.

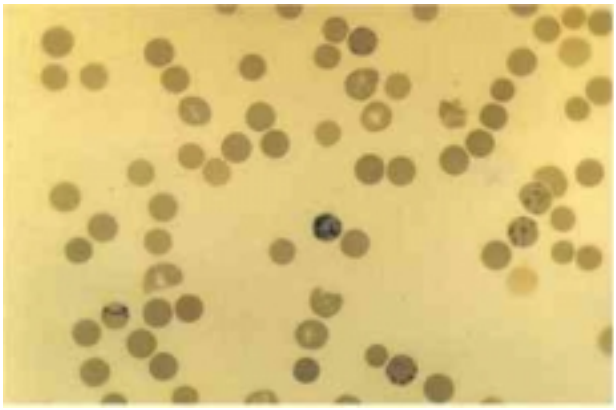

Fig 2. - Blood smear of our patient, showing reticulocytosis, reflecting the bone marrow response to hemolysis.

sated bile syndrome and gallbladder dysfunction had arise, but none of them could have been proved.

PEX was given to our patient 12 times. All together, 33 liters of plasma were removed, and just as many cryosupernatants were transfused. One week later, the platelet count has decreased again without any sign for hemolysis; therefore oral corticosteroid was given. During the third week, his nursing therapy was completed with azathioprine and 4 times a day transfusion with cryosupernatant (Fig 3).

The result of this combined therapy, the blood work and the laboratory results of our patient became normal, but still, no clinical finding was recognized. He was treated with methylprednisolone for 11 weeks and with azathioprine for 19 weeks. Remarkably, at six months after setting the diagnosis, he had acute purulent appendicitis, and three months later, he was admitted to the hospital because of mastoiditis associated with meningitis. During this period, the laboratory results were those for acute bacterial infection. At his last ambulatory control, he was symptom- and complaint-free; his blood work and laboratory results were normal, with no sign of hemolysis or relapse of the primary disease.

Discussion

In 1925 Moschcowitz observed widespread hyaline thrombi in capillaries and arterioles now established as the pathologic hallmark of TTP. Moschcowitz regarded these lesions as the result of circulating toxin affecting platelets and red cells.[1]

The etiology is unknown, but a variety of clinical events have been identified as possible precipitating factors (serotoxin-producing enteropathogenic Escherichia coli and Shigella dysenteriae infections,[2] pregnancy or oral-contraceptive related,[3] malignancy, chemotherapy, marrow transplantation, drug-dependent antibodies and connective tissue disease).

The pathogenesis of TTP is heterogeneous. Several markers and hypothesis have been described in the literature. Histological findings point to the pathological interaction between vascular endothelium and platelets, which leads to enhance platelet aggregation and endothelial damage. Autopsy findings in TTP reveal multiple small hyalin-like thrombi occluding capillaries and arterioles in a variety of organs (most frequently the kidneys, brain, pancreas, heart, spleen and adrenal glands).

Immunohistochemical stains have shown that the thrombi contain platelets and fibrin and frequently immunoglobulin and complement. Cytotoxic effects on endothelial cells have been induced by sera from patients with TTP.[4] Abnormalities of prostacyclin (PGI_2), the platelet-inhibiting eicosanoid synthesized by endothelial cells, have also been described in TTP. Plasma from some patients, in contrast to normal plasma, was unable to stimulate PGI_2 synthesis in endothelial cells. ß-thromboglobulin, a platelet α-granule protein secreted upon platelet activation, can inhibit endothelial PGI_2 synthesis and is a candidate for this activity in patients with TTP. Others have suggested that a PGI_2 deficiency may be caused by deficiency of a PGI_2-stabilizing protein, with excessive PGI_2 degradation.[5] Detection of abnormally large multimers of the von Willebrand factor in the plasma of patients with TTP links endothelial cell damage with a mechanism of platelet aggregation.[6] These multimers are very effective in binding to glycoproteins (Ib and II/IIIa) on the endothelial cell surface and inducing platelet aggregation. An intracellular cysteine protease, calpain, has been found in the plasma of many patients with acute TTP. High molecular weight kininogen is one of the primary plasma inhibitors of calpain. Kelton et al observed that the high molecular weight kininogen in plasma samples from patients with acute TTP was proteolysed.[7,8]

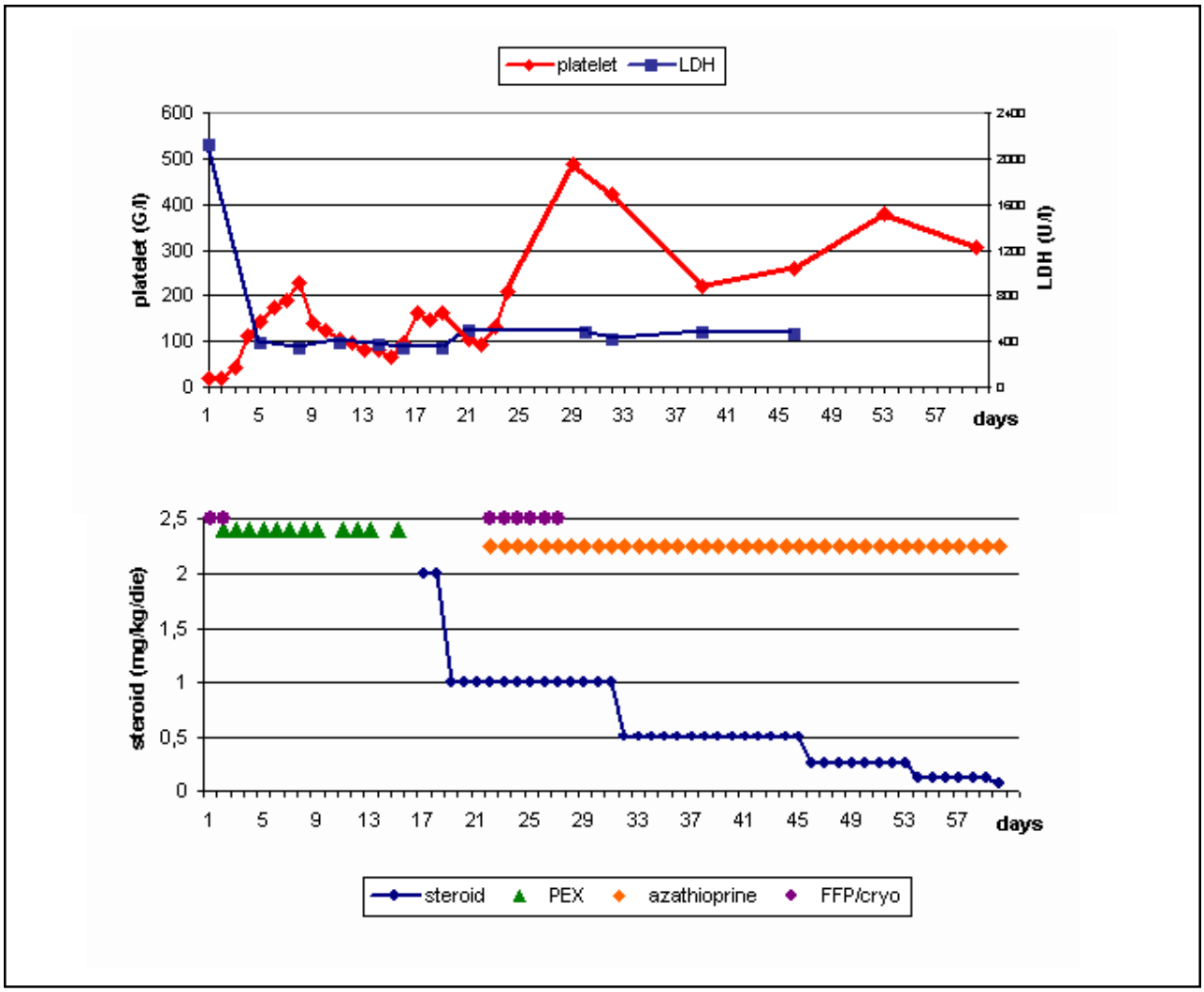

Fig 3. - Time course of platelet count and LDH values during the hospital courses of our patient with different treatment modalities.

Fibrinolytic activity is depressed at the site of microthrombi formation. Decreased level of protein C also has been reported in TTP plasma. Impaired fibrinolysis may contribute to the stability of the platelet plug and enhance tissue injury.[9]

The classic pentad of clinical findings is (1) fever, (2) thrombocytopenia, (3) microangiopathic hemolytic anemia, (4) neurologic abnormalities, and (5) renal involvement (Table 1). This disease is similar to HUS except that it occurs most often in young adults, involves more organ systems, neurologic symptoms are prominent, renal dysfunction is less severe, and the mortality rate is higher (Table 2). A variety of manifestations due to damage of multiple organs are present. Damage to the central nervous system is most common. Headaches, confusion, seizures and coma reflect cerebral lesions. Symptoms may be reversible, if treated early. Jaundice reflects both hemolysis and liver damage. The widespread thrombotic process results in visual defects, heart failure, abdominal pain, and damage to the pancreas and adrenal glands.

Four different types of TTP have been recognized: (1) single-episode TTP (most common); (2) relapsing TTP, which characterized by episodes that recur after healthy periods of months or years; (3) chronic TTP, which is characterized by very frequent recurrent episodes; (4) childhood/familial TTP, which is very rare.

Laboratory Findings

TTP is usually apparent from the initial blood count and examination of blood film. The hemoglobin is usually less than 10.5 g/dl (average 8 to 9 g/dl). MCV may be

Table 1. - Evolution of diagnostic criteria for TTP

Clinical signs	Percent of patients		
	Amorosi et al[18]	Ridolfi et al[19]	Rock et al[13]
Microangiopathic hemolytic anemia	96	98	100
Thrombocytopenia	96	96	100
Neurologic symptoms	92	84	63
Renal disease	88	76	59
Fever	98	59	24

Table 2. - Differences between HUS and TTP.

	HUS	TTP
Peak age incidence	1-4 years	20-25 years
Male:Female ratio	1 : 1	1 : 2
Prodromal illness	Usual	Variable
Fever	Rare	Usual
Neurologic abnormalities	Variability related to renal failure	Usual
Renal disease	Usual	Usual
Renal failure	Common	Rare
Hypertension	Common	Rare
Major organs affected	Kidneys	Kidneys, brain, heart, pancreas, adrenals
Prognosis	Relatively good	Relatively poor

normal; decreased, if there is marked erythrocyte fragmentation; or increased, depending on the degree of reticulocytosis. MCH and MCHC are normal. Reticulocytes are increased, and nucleated erythrocytes are found in the peripheral blood, reflecting the bone marrow response to hemolysis. The most striking blood finding is the abundance of schistocytes (Fig 4).

Thrombocytopenia is typically severe (8 to 44 /µl) due to consumption of platelets in the formation of microthrombi. Platelet survival is very short, and platelet sequestration studies demonstrate hepatosplenic uptake. Megakaryocytes are abundant in the bone marrow. The bleeding time may be prolonged if the platelet count is less than 100 G/l. Leukocytosis with counts more than 20 G/l occur in 50% of patients and usually accompanied by a shift to the left. Hemoglobinemia, hemoglobinuria, decreased haptoglobin levels and increased serum bilirubin are direct evidence of intravascular hemolysis. Coagulation tests are usually normal or only mildly disturbed in TTP, which helps to differentiate TTP from disseminated intravascular coagulation.

Treatment

Due to the rarity of the condition, several different treatment modalities have been used. Among them, plasma exchange recently became the standard therapeutic management for this disease.[10] Plasma exchange regiments for TTP should begin with single plasma volume exchange (40 ml/kg body mass) on a daily basis. Daily treatments should continue until the resolution of the thrombocytopenia, neurological abnormalities, the stabilization of the hemoglobin, and the normalization of LDH level. The standard replacement fluid is FFP, however several recent reports described successful use of cryosupernatant (which is the residual plasma fraction after the separation of cryoprecipitate and is mostly depleted of vWF, fibrinogen, fibronectin and factor XIII).[11]

Solvent-detergent processing of plasma also removes the highest multimers of vWF, so this product may also be particularly suitable for the treatment of TTP.[12] Patients undergoing plasma exchange have shown a higher response rate and lower mortality rate than those given only plasma infusions.[13] Antiplatelet agents such as acetylsali-

Fig 4. - Scanning electron micrograph of formation of fragmented erythrocytes by fibrin strands in an in vitro model (x2100). *Bull et al. Blood. 1970;53:104.*[20]

cylic acid and dipyridamole have widespread use as platelet-inhibitor drugs. Vincristine, in combination with glucocorticoids and plasma, also has been used. Splenectomy and intravenous immunoglobulin have been reported to lead to remission in TTP patients who did not respond to plasma exchange, or those who had relapsed.[14-16]

Supportive Treatment

The prompt administration of appropriate therapy is essential.[13] It is equally important to recognize that platelet transfusions are contraindicated, despite the frequently encountered severe thrombocytopenia, which may aggravate the disease.[11] Red blood cell replacement is frequently necessary before the abatement of the hemolysis with plasma exchange therapy. The requirement is proportional to the degree of hemolysis. The packed red blood cells are depleted of platelets and can be given safely.

Acute renal failure is the result of severe injury to the renal vasculature, as a result of the primary endothelial injury or of a heavy presence of the microthrombotic lesions characteristic of TTP. The renal failure may often be severe and requires frequent hemodialysis. Renal vascular lesions in TTP leads to ischemia results in the activation of the renin-angiotensin system. In the case of severe involvement of the kidney, this activation is maximal and prompt control of severe hypertension by angiotensin converting enzyme inhibitors is needed to prevent acute hypertensive complications.

Prognosis

Before the late 1970s, almost all patients with TTP died of their illness within days or weeks. Since the introduction of corticosteroids, platelet-inhibitor drugs and splenectomy, the survival rate increased almost 50%. By means of supportive care and a variable combination of therapeutic modalities (currently including intensive plasma exchange), as many as 85-90% of patients with TTP may eventually recover. However, Sumack et al have published that more than one third of patients who survive an acute episode of TTP will have at least one relapse during the following ten years.[17]

In conclusion, TTP is a rare, but life-threatening disorder. Prognosis is good with immediate diagnosis and adequate treatment with plasma exchange.

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