

# Catastrophic Thrombotic Thrombocytopenic Purpura Accompanying Recurrent Acute Pancreatitis Attacks and Splenic Vein Rupture

## *Rekürren Akut Pankreatit Atakları ve Splenik Ven Rüptürüne Eşlik Eden, Katastrofik Seyirli Trombotik Trombositopenik Purpura*

### ABSTRACT

Acute pancreatitis can be encountered as a rare complication of thrombotic thrombocytopenic purpura and it has been associated with recurrent thrombotic thrombocytopenic purpura. In this report, we present a case of thrombotic thrombocytopenic purpura closely followed for recurrent acute pancreatitis attacks and having a lethal clinical picture due to splenic vein rupture in spite of plasmapheresis and steroid treatments.

**KEY WORDS:** Thrombotic thrombocytopenic purpura, Acute pancreatitis, Splenic vein rupture

### ÖZ

Akut pankreatit, trombotik trombositopenik purpuranın (TTP) nadir görülen bir komplikasyonu olarak karşımıza çıkabileceği gibi; TTP'nin nüksüyle de ilişkilendirilmiştir. Biz, yeni TTP tanısı almış ve tekrarlayan akut pankreatit ataklarına bağlı sık nüks nedeniyle izlenen; plazmaferez ve steroid tedavilerine rağmen, splenik ven rüptürü sonucu mortal seyreden bir hastayı sunuyoruz.

**ANAHTAR SÖZCÜKLER:** Trombotik trombositopenik purpura, Akut pankreatit, Splenik ven rüptürü

### INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare condition characterized by fever, thrombocytopenia, renal failure, microangiopathic haemolytic anaemia and neurological involvement (convulsions, coma and unconsciousness) (1). Despite treatment, recurrences may appear in some cases. In fact, they occur in 21%-64% of the cases and in the first year of the disease in general. The cases not responding to plasmapheresis, the method first resorted for the treatment of the condition, are considered relapsing-refractory to treatment and it is recommended that immunomodulatory agents should be added in such cases (2). Relapses usually appear in cases of secondary TTP associated with infections (e.g. HIV), pregnancy, cancer, drugs, bone marrow transplantations and surgery. Severe ADAMTS 13 deficiency has also been associated with relapses and poor prognosis

of the condition (3). Prognosis is poor in cases of relapse and the reported mortality in patient series is 5%-18% (4). Involvement of the gastrointestinal system in TTP is rare. Abdominal pain, nausea and vomiting are frequent symptoms in the presence of gastrointestinal involvement. Complications develop due to ischemia of the organs in gastrointestinal involvement (5). There have been few cases of acalculosis cholecystitis and acute pancreatitis due to ischemia (6-7).

In this report, a patient presenting to the emergency department with high blood pressure and diagnosed as TTP based on clinical signs and laboratory investigations was found to have gastrointestinal involvement when investigated for abdominal pain. The lethal picture of TTP due to frequent relapses and splenic vein rupture caused by recurrent pancreatitis attacks despite effective and sufficient therapy has been reviewed in light of the literature.

**Mesudiye BULUT<sup>1</sup>**  
**Ebru GÖK OĞUZ<sup>2</sup>**  
**Müge EREK<sup>1</sup>**  
**Didem TURGUT<sup>1</sup>**  
**Nihal ÖZKAYAR<sup>1</sup>**  
**Serhan PİŞKİNPASA<sup>1</sup>**  
**Fatih DEDE<sup>1</sup>**

- 1 Numune Training and Research Hospital, Department of Nephrology, Ankara, Turkey
- 2 Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Nephrology, Ankara, Turkey



Received : 07.06.2013

Accepted : 15.09.2013

Correspondence Address:

**Ebru GÖK OĞUZ**  
 Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Nefroloji Bölümü, Ankara, Turkey  
 Phone : + 90 312 341 03 00  
 E-mail : ebrugokoguz@hotmail.com

## CASE

A twenty-seven year old woman presented to the emergency department with headache, nausea and vomiting. On physical examination, the patient was conscious, her blood pressure was 190/90 mmHg, her heart rate was 78/min, her respiratory rate was 16/min, she was pale and there were inspiratory rales bilaterally. History showed no abnormality except for hypertension for the past one year. Laboratory investigations showed that erythrocyte-sedimentation rate was 30 mm/hr, white-cell count 11920/mm<sup>3</sup>, haemoglobin 9,9 gr/dl, thrombocyte count 75000/mm<sup>3</sup>, BUN 98 mg/dl, creatinine 2.12 mg/dl AST 98U/L, ALT 55 U/L, INR 0.9, LDH 1915 U/L, indirect bilirubin 1.43 mg/dl, direct bilirubin 0.42 mg/dl and amylase 106 U/L. Other biochemical findings were normal. Fully automated urine analysis revealed that urine density was 1018, protein 300 mg/dL, white cell count 1/HPF (high power field) and erythrocyte count 5/HPF. The patient was first diagnosed as acute renal damage and hypertension and admitted to hospital. Investigations for the differential diagnosis of renal dysfunction showed that spot urine protein/creatinine was 332/196 (1.7) mg/mg. Urine culture showed no abnormality. AntiHIV, AntiHCV and HbsAg were negative. IgG, IgA, IgM, C3 and C4 were normal and ANA, anti-ds-DNA, p and c ANCA were negative. On ultrasonography of the urinary system, sizes of bilateral kidneys, thickness of the parenchyma and renal echogenicity were normal. Direct and indirect Coombs tests were negative, the reticulocyte count was high and peripheral blood film showed occasional fragmented erythrocytes. Examination of the fundus oculi showed stage 4 hypertensive retinopathy and the patient's blood pressure was kept under control with oral antihypertensive treatment. A renal biopsy was performed to investigate the aetiology of renal failure and it suggested thrombotic microangiopathic nephropathy involving chronic glomerular and tubulointerstitial damage. Based on the findings, the patient was diagnosed as TTP and plasmapheresis (three sessions of 40 ml/kg/day) and methylprednisolone 1mg/kg/day were initiated. At the end of the attack lasting for three days, creatinine decreased to 2.8 mg/dl. Planning to decrease the dose of steroids and then to withdraw it, we discharged the patient. Fifteen days after her discharge, the patient presented again with the second attack of TTP (abdominal pain accompanied by signs of haemolysis, thrombocytopenia and increased serum creatinine levels). In addition to plasmapheresis (three sessions of 40 ml/kg/day), renal replacement therapy was instituted. The dose of steroid treatment was increased to 1 mg/kg/day. The attack subsided within one week. Three days later, the patient had the third TTP attack (signs of haemolysis, thrombocytopenia and increased serum creatinine levels) accompanied by abdominal pain and vomiting. For the treatment of TTP attack, plasmapheresis (three sessions of 40 ml/kg/day) was performed in addition to steroid treatment at 1 mg/kg/day. Renal replacement therapy was continued. Tests for mesenteric ischemia performed to search for aetiology of abdominal pain showed no abnormality.

Endoscopy demonstrated nodular gastritis. Abdominal ultrasonography revealed stones a few millimetres in size in the gallbladder and abdominal ascites, which were not detected on the previous ultrasonography. The patient, having an amylase level of 202 U/L and LDH 5 isoenzyme level of 518 IU/L, was thought to have acute pancreatitis. Abdominal tomography demonstrated that the gallbladder was at the upper limit of its normal size and the ductus choledochus was larger than normal. Ductus choledochus measured 15 mm in the proximal section and the diameter of the duct was considerably decreased in the distal section. There were widespread liquid collections in the peripancreatic fat tissue having a cystic appearance and irregular contours, about 10HU in density and 29mmx18mm in size in the pancreatic body that seemed to be connected with the ductus choledochus. Oral intake was discontinued and intravenous antibiotic therapy was initiated. On ERCP, multiple pigmented stones were removed from the ductus choledochus. The high enzyme levels indicative of acute pancreatitis decreased on follow-up. Signs of haemolysis subsided, the thrombocyte count increased and LDH levels returned to normal within five days, accompanied by a decrease in the severity of gastrointestinal complaints. However, the abdominal pain started again one week later. The patient was diagnosed as recurrent acute pancreatitis and abdominal computed tomography demonstrated pseudocysts in the pancreas and an increase in the size of cystic lesions compared to their size on the previous tomography. Meanwhile, the patient developed the fourth TTP attack (signs of haemolysis and thrombocytopenia), suggestive of refractory TTP. Therefore, apart from plasmapheresis, the patient was initiated rituximab as an immunosuppressive treatment. Renal replacement therapy was also continued. When the vital signs of the patient became unstable, she could not be given rituximab and was transferred to the intensive care unit. Upon a decrease in blood pressure and haemoglobin, laboratory investigations were performed and the patient was diagnosed with splenic vein rupture. The patient died before emergency surgery was performed for the rupture.

## DISCUSSION

Acute pancreatitis and splenic vein rupture are quite rare during the course of TTP. Acute pancreatitis can appear as a complication of TTP (8) and can also be a triggering factor for relapses of TTP. Although there have only been a few cases, it can be suggested that there is a 1-2 week interval between acute pancreatitis and TTP and that the frequency of TTP is increased during recurrent attacks of pancreatitis (9). TTP is characterized by microvascular thrombi connected with Von Willebrand factor (vWf) multimers larger than normal in the endothelium and thrombocytes and tissue ischemia. Normally, abnormal vWf is deactivated by a metalloprotease ADAMTS 13 and is not released into the circulation. Acquired or congenital impairment of this metalloprotease causes aggregation and adhesion of thrombocytes in the circulation depending on abnormal vWf multimers (10). Haematological changes indicative of

a poor prognosis such as thrombocytopenia and disseminated intravascular coagulation may appear in the course of acute pancreatitis. However, severe thrombocytopenia is not normal (11). In a series of 12 patients whose TTP was triggered by acute pancreatitis, three patients had normal levels of ADAMTS 13, but only two patients had severe deficiency of this enzyme and it was therefore postulated that the association between TTP and acute pancreatitis cannot be explained only by enzyme deficiency (12). The main reason why TTP triggers acute pancreatitis is ischemia due to microvascular thrombi (13). It has been suggested that increased IL-6, IL-1, IL-8 and TNF- $\alpha$  levels in acute pancreatitis lead to release of large vWf multimers from endothelial cells, which in turn cause a relative deficiency of ADAMTS 13 and development of TTP (14). Another mechanism incriminated for pathogenesis of TTP due to acute pancreatitis is a decrease in the release of nitric oxide (NO) from pancreatic cells. It is known that endothelial NO is a strong anti-aggregating agent; decreased NO levels in acute pancreatitis may trigger TTP development (15). As in other rare cases (16,17), TTP relapses accompanied the acute pancreatitis attacks in the case presented here. Thanks to treatment of bile duct stones and pancreatic pseudocysts that cause pancreatitis, the gastrointestinal complaints subsided, signs of haemolysis disappeared, LDH levels decreased and thrombocyte levels increased. The case reported here died of splenic vein rupture developing as a complication. Although the spleen is close to the pancreas, splenic complications rarely occur in pancreatitis. These complications are splenic vein thrombosis, arterial pseudoaneurysm, intrasplenic pancreatic pseudocyst and splenic rupture and are encountered in 1-5% of the cases (18). Cases of splenic rupture due to pancreatitis have been reported, though rarely (19,20). In addition, there have been cases of splenic vein rupture during pregnancy and the puerperium (21). Thrombocyte aggregation due to activation of pancreatic enzymes is incriminated for splenic vein thrombosis and splenic vein rupture in acute and chronic pancreatitis (22). In the case presented here, the pressure of the thrombus associated with microangiopathy due to TTP relapses and pseudocyst due to attacks of pancreatitis on the splenic hilus might have caused splenic vein rupture.

TTP may have a clinical picture characterized by life-threatening complications. Acute pancreatitis developing during the course of TTP can be responsible for relapses, but can also be a complication developing during the course of the disease. In cases in which pancreatitis develops as a result of insufficient treatment and/or impairments in the coagulation cascade due to TTP, splenic vein rupture can be lethal; early diagnosis and treatment in suspected cases can therefore be of great importance for survival.

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