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Thrombotic microangiopathy following acute pancreatitis

Akut pankreatit sonrası trombotik mikroanjiyopati

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Summary

Acute pancreatitis as a potential triggering event for an acute episode of thrombotic microangiopathy and is a rare phenomenon. A 22-year-old female patient was hospitalized with a diagnosis of recurrent acute biliary pancreatitis. Confusion, anemia, thrombocytopenia, an increase in serum lactate dehydrogenase and acute renal failure developed within the next three days. With these findings, thrombotic microangiopathy was diagnosed. Continuous hemodiafiltration and fresh frozen plasma transfusions with intravenous methylprednisolone were applied. There was a full recovery.

Acute pancreatitis should be suspected when there are other biological and clinical signs of thrombotic microangiopathy including acute renal failure. Early institution of plasma based therapies will improve prognosis and long term renal function

Key Words: Thrombotic microangiopathy, acute pancreatitis.

Özet

Akut pankreatitin, trombotik mikroanjiyopatinin akut atağının potansiyel tetikleyicisi olması nadir bir durumdur. Tekrarlayan akut biliyer atakları olan 22 yaşındaki kadın hasta hospitalize edildi. Akut pankreatitin takip eden üç günlük gerileme dönemi sonrasında konfüzyon, anemi, trombositopeni, serum laktat dehidrogenaz seviyesinde artış ve akut böbrek yetmezliği gelişti. Bu bulgularla trombotik mikroanjiyopati tanısı konuldu. Devamlı hemofiltrasyon, taze donmuş plazma transfüzyonu ve intravenöz prednizolon tedavisi başlandı. Hasta sorunsuz bir şekilde taburcu edildi.

Akut böbrek yetmezliği dâhil trombotik mikroanjiyopatinin biyolojik ve klinik bulguları olan akut pankreatit olgularında, trombotik mikroanjiyopatiden şüphelenilmelidir. Plazma temelli tedavilerin erken başlanmasının, prognoz ve uzun dönemli renal fonksiyonlar üzerinde olumlu etkisi vardır.

Anahtar Sözcükler: *Trombotik mikroanjiyopati, akut pankreatit.*

Introduction

Acute pancreatitis (AP) and thrombotic microangiopathy (TMA) are separate diseases that have diverse recognized etiologies, clinical manifestations, associated conditions, and risk factors. The pancreas is an organ which is frequently and severely involved in patients with TMA. It is believed that the ischemic changes on the pancreas which occurs during the course of TMA cause AP and its common symptom of abdominal pain (1,2).

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Therefore, the development of AP as a result of TMA is a known entity, but TMA following AP is a relatively rare phenomenon with unknown pathophysiology (1,3-5).

In this report, we describe TMA in a young woman following an acute biliary pancreatitis attack highlighting the importance of an early diagnosis and appropriate treatment.

Case Report

A 22-year-old female patient was hospitalized with a diagnosis of acute biliary pancreatitis. She presented with two-day history of severe epigastric pain, associated with nausea and vomiting. Her medical history revealed previous acute biliary pancreatitis episode one and half year before while she was

pregnant, and she refused the proposed cholecystectomy afterwards. Her body temperature was 37.1°C and physical examination was normal except right upper quadrant tenderness. On admission, laboratory evaluation revealed the following abnormal results: direct bilirubin 0.4 mg/dL, indirect bilirubin 0.4 mg/dL, aspartate aminotransferase 242 U/L, alanine aminotransferase 334 U/L, amylase 2155 U/L, lipase 1358 U/L and lactate dehydrogenase 658 U/L (Table 1). White blood cell count and C-reactive protein level were 6.7 K/uL and 1.0 mg/dL, respectively. Ultrasonography showed multiple small stones in the gallbladder, minimal dilatation of the external biliary tree, and pancreatic edema with peri-pancreatic fluid collection. She was diagnosed as AP with these findings. After conservative management, AP resolved clinically.

Confusion, severe anemia, thrombocytopenia, an increase in serum lactate dehydrogenase and acute renal failure developed during the next three days. Her hemotocrit level and platelet count dropped to 7.1% from 37.1% and to 42000 K/uL from 455000 K/uL, respectively. Her blood urea nitrogen and serum creatinine levels increased to 148 mg/dL from 28 mg/dL and to 2.0 mg/dL from 0.8 mg/dL, respectively (Table-1).

Table-1. Laboratory values of the patient from induction of AP (day 0) to induction (day 3) and progress of TMA (day 4).

Parameter	Day 0	Day 3	Day 4
Hematocrit (%)	37.1	24.6	7.1
Platelet count (K/uL)	455	71	42
BUN* (mg/dL)	28	100	148
Creatinine (mg/dL)	0.8	2.0	1.7
LDH¶ (U/L)	658	2076	3654
Amylase (U/L)	2155	1493	248
ALT§ (U/L)	334	157	71
AST¥ (U/L)	242	109	69
Direct bilirubin (mg/dL)	0.4	1.0	0.9
Indirect bilirubin (mg/dL)	0.4	2.3	1.7

*: blood urea nitrogen
¶: lactate dehydrogenase
§: alanine aminotransferase
¥: aspartate aminotransferase

The Coomb's test was negative. Bacterial examination of the blood was sterile. Prothrombin time, activated prothrombin time, d-dimer, and fibrinogen levels were normal. Peripheral blood film revealed numerous fragmented red cells and schistocytes. Abdominal computed tomography showed mild peri-pancreatic edema without necrosis. With these findings, TMA following AP was diagnosed. Continuous hemodiafiltration (for nine days) and fresh frozen plasma transfusions (15 mg/kg/day for one week) with intravenous methylprednisolone (initially 250 mg/day, terminated by tapering doses in one week) were applied. Severe hypotension and tachycardia were treated with intravenous fluid replacement, erythrocyte transfusions and inotropic support. With progressive disturbance on her respiratory status, intubation was applied and mechanical ventilation was started. Chest X-ray showed bilateral pulmonary infiltrates. In absence of cardiogenic pulmonary edema, presence of severe hypoxemia and PaO_2/FiO_2 ratio less than 200 revealed diagnosis of adult respiratory distress syndrome. After full recovery, she was transferred to the surgical ward on the 27th day. Later she was discharged with normal laboratory findings, and elective laparoscopic cholecystectomy was performed on the 8th weeks after her discharge. There were no medical problems over the following one year.

Informed consent with regard to presentation of the case was taken from the patient.

Discussion

Microangiopathy is a pathological condition characterized by the presence of hemolytic anemia, thrombocytopenia and generalized microvascular occlusion, especially in kidneys and the central nervous system (2,6,7). There are two classical phenotypic presentations namely thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). HUS is characterized most commonly by renal involvement beside the above mentioned three clinical signs. Fever and neurological impairment in addition to the criteria above are usually seen in TTP.

Identification of ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type I repeats, the von Willebrand factor cleaving protease) deficiency in adult idiopathic TTP, and abnormal control of the alternative complement pathway in adult HUS (atypical HUS) improved the understanding of the pathogenesis of TMA, and helped to distinguish HUS from TTP (6-9). We could not measure the level of ADAMTS13 for this patient, because of the lacking availability of the test in our setting. Although such molecular markers for identification of TTP and HUS have been described, the wide spread clinical use is not established as in these cases. Even severe ADAMTS13 deficiency does not account for all cases of idiopathic TTP. Pregnancy, infections and several inflammatory conditions may also trigger acute episodes of TTP which are not associated with ADAMTS13 deficiency (1,10). So, it should be kept in mind that either deficiency of ADAMTS13 or deficiency of complement regulators is sufficient for the development of TTP or atypical HUS, respectively. In the

light of these evidences, differential diagnosis of TTP and HUS that is based only on clinical and laboratory findings is usually very difficult. Therefore, we and other authors prefer to use the term “TMA” rather than the terms “TTP” and “HUS” (3,6-9).

The acute inflammatory response to pancreatitis may trigger the onset of TMA. Although the exact mechanism of TMA following pancreatitis is not known, possible mechanisms have been evoked (1,3,5,7,8). The interval between AP and TMA as short as 2 to 3 days, as in our case, raises the hypothesis that the inflammatory consequence of pancreatitis has a direct impact on the pathogenesis of TMA (1,8,11).

Presence of a severe bacterial infection such as cholangitis may be another triggering etiology for TMA. It is well-known that TMA is usually caused by bacterial infections (7,10). However, normal levels of the laboratory markers of inflammation including white blood cell count and C-reactive protein in an afebrile patient, and lack of imaging findings suggestive of acute cholecystitis or cholangitis were regarded as criteria for absence of a severe bacterial infection. There are several criteria to consider pancreatitis as a triggering event for an acute episode of TMA: pancreatitis with recognized etiology preceded the presence of diagnostic criteria for TMA and resolution of pancreatitis when the diagnostic criteria of TMA occurred (1,3,4). In the present case, when biliary AP was diagnosed, there was no microangiopathic hemolysis or thrombocytopenia, indicating AP as a potential trigger for TMA.

Acute renal failure is one of the most commonly seen complications during the course of AP (3). Particular attention must be paid to differentiate whether this complication is caused by TMA or multiple organ failure that is seen in AP. Presence of other clinical signs of TMA such as severe hemolytic anemia, thrombocytopenia, neurological disturbances, and indirect findings of intravascular hemolysis including indirect hyperbilirubinemia and increase in LDH help to diagnose the former condition in accordance with this case (1,3).

The treatment of TMA following AP is usually supportive with plasma based therapies which includes plasma exchange, hemodialysis/filtration, fresh frozen plasma (1-4). The effect of corticosteroids is controversial (1,3,7,8,10). It was shown that the prognosis may be improved by early administration of plasma based therapy, especially within the first 24 hours of the presentation (3,4,6). Hemodiafiltration with fresh frozen plasma transfusions should be given in cases in which plasma exchange cannot be applied in a timely manner. Clinical response to treatment can be determined by platelet count and serum LDH levels (4,10). We observed the recovery of TMA in our patient after the induction of continuous hemodiafiltration used for both TMA and acute renal failure, and fresh frozen plasma therapy. Recovery of TMA after induction of this therapy also supports the hypothesis in which AP may cause development of TMA.

In conclusion, AP is a possible trigger for TMA. It should be suspected when there are other biological and clinical signs of TMA including acute renal failure during the course of AP. Early institution of plasma based therapies will improve prognosis and long term renal function.

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