CASE REPORT

Diabetic Ketoacidosis Preceding Thrombocytopenia Associated Multiple Organ Failure in a Child

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ABSTRACT

Context Thrombocytopenia associated multiple organ failure is a rare but increasingly recognized condition in children. Diabetic ketoacidosis preceding thrombocytopenia associated multiple organ failure is previously unreported in pediatric patients. **Case report** A 12-year-old female presented with diabetic ketoacidosis along with acute pancreatitis. She further developed thrombocytopenia and renal failure over the next two days. Although hemolytic uremic syndrome/thrombotic thrombocytopenic purpura spectrum was considered, the clinical picture seemed most consistent with thrombocytopenia associated multiple organ failure. The patient was treated with serial therapeutic plasma exchanges and made a complete recovery. **Conclusion** A high index of suspicion of thrombocytopenia associated multiple organ failure is required in patients with diabetic ketoacidosis or pancreatitis who present with thrombocytopenia and renal failure. Plasma exchange is a life-saving intervention in such cases.

INTRODUCTION

Thrombocytopenia associated multiple organ failure is a poorly understood syndrome in critically-ill patients. New onset thrombocytopenia is an independent risk factor for a poor outcome in critically ill patients [1]. Thrombocytopenia associated multiple organ failure is an increasingly recognized spectrum of thrombotic microangiopathic disorders which include thrombotic thrombocytopenic purpura, consumptive disseminated intravascular coagulation, and non-consumptive thrombotic microangiopathy. It is defined by a clinical triad of new onset thrombocytopenia, multi organ dysfunction, and increased lactate dehydrogenase (LDH) [2]. It has been reported secondary to sepsis, toxins, autoimmune diseases, radiation, transplantation, malignancy and cardiovascular surgery [2]. We herein describe a 12-year-old girl who presented with diabetic ketoacidosis and acute pancreatitis preceding thrombocytopenia associated multiple organ failure. To the best of our knowledge this is the first case of diabetic ketoacidosis preceding thrombocytopenia associated multiple organ failure in a pediatric patient.

Received September 1st, 2010 - Accepted November 2nd, 2010

Key words ADAMTS13 protein, human; Diabetic Ketoacidosis; Pancreatitis; Plasmapheresis; Thrombotic Microangiopathies

Abbreviations ADAMTS 13: A Disintegrin And Metalloprotease with ThromboSpondin type 1 repeats number 13

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URL http://www.serena.unina.it/index.php/jop/article/view/3382/3662

CASE REPORT

A 12-year-old previously healthy obese female presented with a 1-day history of progressive irritability and drowsiness. Her mother reported a 3-week history of polyuria, polydipsia and involuntary weight loss of 4.5 kg. She also complained of epigastric pain on the day of admission. On examination, she had tachypnea (with Kussmaul's breathing), tachycardia and hypotension. She was drowsy and had moderate dehydration on assessment (6-9% fluid deficit). Investigations revealed hyperglycemia (511 mg/dL, reference range 74-106 mg/dL), acidosis (pH: 7.07, reference range 7.35-7.45; HCO: 3.5 mmol/L, reference range 21.0-32.0 mmol/L) and positive ketones and glucose in urine. She was started on fluid resuscitation and insulin therapy. Initial complete blood count showed a hemoglobin (15.7 g/dL, reference range 12-16 g/dL), leukocytosis (17,500 μL^{-1}, reference range 4,500-13,500 μL^{-1}), and a platelet count of 238,000 μL^{-1} (reference range 142,000-405,000 μL^{-1}). Her ketoacidosis resolved within 24 hours and she was switched to subcutaneous insulin. Serum amylase and lipase were significantly elevated. Computed tomography (CT) scan of the abdomen demonstrated diffuse enlargement and hypoattenuation of pancreas with stranding of the peripancreatic fat and peripancreatic fluid collection, suggestive of pancreatitis (Figure 1). She continued to remain drowsy and was intermittently arousable to pain and verbal stimuli. A CT scan of the brain to rule out cerebral edema was negative. In spite of correction of dehydration, her blood urea nitrogen and creatinine were rising and she developed oliguria. Repeat

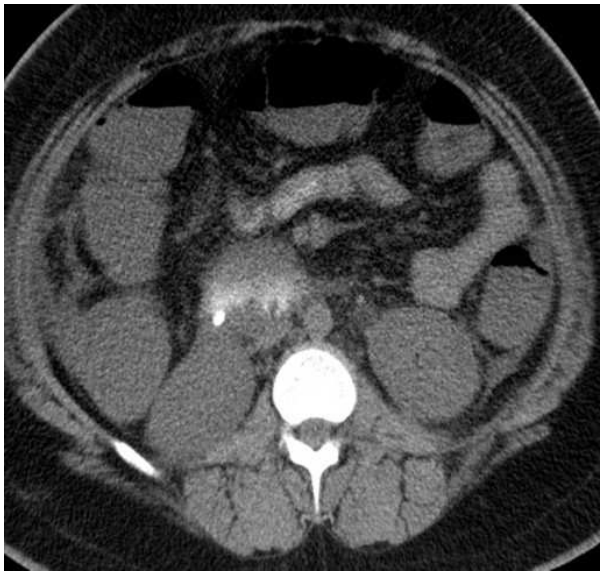

Figure 1. CT abdomen showing diffuse enlargement and hypoattenuation of pancreas with stranding of the peripancreatic fat and peripancreatic fluid collection, suggestive of pancreatitis.

complete blood count showed anemia (hemoglobin 10.6 g/dL), thrombocytopenia, and slight evidence of hemolysis (<5% schistocytes, reference range 0-5%). Her amylase and lipase were improving but LDH was slightly increased. Prothrombin time, plasma thromboplastin time, and fibrinogen were normal, while D-dimer was slightly elevated. In view of altered mental status, renal failure and thrombocytopenia, diagnosis of thrombocytopenia associated with multiple organ failure was considered. ADAMTS 13 (**A** **D**isintegrin **A**nd **M**etalloprotease with **T**hrombo**S**pondin motifs; formerly known as von Willebrand factor cleaving-protease) activity was 52% (reference range: 70-150%). She was started on plasma exchange. She responded with 3 days of plasma-pheresis with a dramatic improvement in her sensorium, renal function tests and platelet count. Table 1 shows the laboratory parameters of the patient at admission, before and after plasmapheresis.

DISCUSSION

Thrombocytopenia associated multiple organ failure is a spectrum of microangiopathic syndromes which includes thrombotic thrombocytopenic purpura, disseminated intravascular coagulation and thrombotic microangiopathy. In clinical scenarios, there might be some overlap between the three phenotypes. Thrombotic thrombocytopenic purpura is clinically described by a pentad of fever, thrombocytopenia, abnormal neurological status/seizures, renal failure, and microangiopathic hemolytic anemia [3]. Its pathophysiology has been ascribed to a decreased ADAMTS 13 activity which results in large von Willibrand factor multimers leading to a massive platelet thrombosis in multiple organs, especially brain and kidneys [4]. Typically, these patients have less than 10% of normal ADAMTS 13 activity. Hemolytic uremic syndrome is differentiated from thrombotic thrombocytopenic purpura by the presence of a normal ADAMTS 13 activity. Non-consumptive secondary thrombotic microangiopathy is distinguished from thrombotic thrombocytopenic purpura by the absence or slight evidence of hemolysis on peripheral smear. Moreover, the ADAMTS 13 activity is moderately low (10-57%) as compared to thrombotic thrombocytopenic purpura (<5%) [2]. The treatment of secondary thrombotic microangiopathy includes management of the underlying predisposing condition. Plasma exchange is the cornerstone of therapy. It works via restoration of ADAMTS 13 activity and removal of ADAMTS 13 inhibitors, thereby improving organ function. Darmon *et al*. demonstrated a drastic reduction in mortality from 40% to 0% after use of plasma exchange [5].

A very few case reports of acute pancreatitis preceding thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome have been reported [6, 7, 8, 9, 10, 11]. In each of these cases, pancreatitis preceded the diagnostic criteria of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome and there was no thrombocytopenia or microangiopathic hemolytic anemia when the pancreatitis was diagnosed. The

Table 1. Summary of the selected laboratory parameters on admission, before and after plasmapheresis.

Lab parameter	Reference range	On admission	Before plasmapheresis	After plasmapheresis
Hemoglobin (g/dL)	12.0-16.0	15.7	10.6	12.3
White blood cells (μL^{-1})	4,500-13,500	17,500	11,700	12,900
Platelets (μL^{-1})	142,000-405,000	238,000	29,000	252,000
Prothrombin time (sec)	11.3-15.2	-	16.6	14.5
Plasma thromboplastin time (sec)	24.7-35.5	-	27.4	22.4
Fibrinogen (mg/dL)	214-451	-	386	305
D-dimer (mg/dL)	0-0.50	-	17.81	4.91
LDH (U/L)	100-190	-	1,349	100
Blood urea nitrogen (mg/dL)	7-18	35	61	18
Creatinine (mg/dL)	0.6-1.3	1.8	2.2	0.6
Amylase (U/L)	25-115	782	126	37
Lipase (U/L)	74-393	8,998	664	228
Peripheral blood smear	-	Normal	Burr cell, schistocyte (<5%)	Normal

pancreatitis was resolving as evident by improving serum amylase levels, when the signs of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome first appeared. Most of these cases were described in adults. To the best of our knowledge this is the first case of diabetic ketoacidosis preceding thrombocytopenia associated multiple organ failure in pediatric age group.

Swisher *et al*. reported five adult patients who developed acute episodes of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome syndromes 1-13 days after the diagnosis of acute pancreatitis. Each of them had a recognized etiology for acute pancreatitis (choledocholithiasis or alcoholism), no evidence of hemolysis or thrombocytopenia at the time of diagnosis of acute pancreatitis and normalization of serum amylase levels at the time of diagnosis of thrombotic thrombocytopenic purpura/ hemolytic-uremic syndrome. They also defined criteria to derive a "possible" or "probable" relation for acute pancreatitis as a trigger for thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome. Sixteen previously described case reports in which acute pancreatitis preceded thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome are also reviewed. One-fourth of these patients did not have any definite etiology for acute pancreatitis [6].

Mas *et al*. described a case of thrombotic angiopathy in a 12-year-old boy following trauma-induced pancreatitis. Upper gastrointestinal endoscopy revealed vasculitis-like lesions. He improved only after initiation of plasmapheresis [8].

Acute pancreatitis is seen in about 2% children with diabetic ketoacidosis [12]. The incidence is higher in adults and the magnitude of pancreatic enzyme elevation is directly proportional to diabetic disequilibrium. Diabetic ketoacidosis causes intense dysregulation of inflammatory cytokines (IL-10, IL-6, IL-2, IL-8, TNFalpha, IL-1beta) which leads to capillary perturbation [13]. Studies have shown a profound increase in factor VIII antigen and von Willebrand factor in diabetic ketoacidosis, reflecting endothelial damage [14]. This can presumably result in thrombotic microangiopathy. Similarly, acute pancreatitis is associated with endothelial damage and massive cytokine release [15]. Thrombotic thrombocytopenic purpura has been described both as a cause and effect of acute pancreatitis [16]. Given the rarity of the condition, it is difficult to solve the "chicken or egg" conundrum.

CONCLUSION

This case describes a hitherto unreported complication of diabetic ketoacidosis: thrombocytopenia associated multiple organ failure. Physicians should consider the condition in any patient with diabetic ketoacidosis or pancreatitis presenting with renal failure and thrombocytopenia. It includes three clinical phenotypes: thrombotic thrombocytopenic purpura, consumptive disseminated intravascular coagulation, and non-consumptive thrombotic microangiopathy. Non-consumptive secondary thrombotic microangiopathy is distinguished from thrombotic thrombocytopenic purpura by the absence of hemolysis on peripheral smear and higher ADAMTS 13 activity. Plasmapheresis is the cornerstone of therapy and restores the homeostasis of procoagulant-anticoagulant factors.

Conflicts of interest The authors have no potential conflicts of interest

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