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Thrombotic Microangiopathic Syndrome: A Novel Complication of Diabetic Ketoacidosis

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Thrombotic microangiopathic syndrome secondary to diabetic ketoacidosis is an under reported entity in children. We describe 2 girls who developed thrombotic thrombocytopenic purpura (TTP) and thrombocytopenia associated multi organ failure (TAMOF) in new onset diabetes. Both patients presented with classical findings of DKA and were intubated due to low GCS, admitted in PICU and managed according to DKA guidelines. Later on, both patients developed thrombocytopenia, acute kidney injury, and low hemoglobin along with evidence of microangiopathy on peripheral smear. One patient developed paraparesis while other patient had high LDH levels. The clinical diagnosis of TTP and TAMOF was made respectively. Both patients were treated with plasmapharesis and renal replacement therapy. Both gradually improved and were discharged.

Keywords: Diabetes mellitus, Microangiopathy, Thrombosis, Ketacidosis.

Potential complications of diabetic ketoacidosis include dehydration, cerebral venous thrombosis, mucormycosis, pancreatitis, sepsis and electrolyte imbalance like hypokalemia and hypophosphatemia [1]. Acute kidney injury is fatal complication of diabetic ketoacidosis and development of renal failure in DKA is associated with high mortality in pediatric age group [1,2]. Thrombotic complications like thrombotic thrombocytopenic purpura (TTP) secondary to DKA are under-reported. Recently, a new thrombotic microangiopathic syndrome, called thrombocytopenia associated multi organ failure (TAMOF), has been described in literature. TTP is now considered to be a part of this syndrome. This syndrome is defined by presence of various clinical and laboratory markers including multi-organ dysfunction, new onset thrombocytopenia and elevated lactate dehydrogenase (LDH) levels [3]. Untreated TAMOF/TTP is associated with high mortality. Early diagnosis is the most important step for prompt intervention like plasmapharesis, which can be lifesaving. Therefore, pediatricians must be aware of microangiopathic complication of DKA. We report the development of this fatal syndrome in two girls presenting with diabetic ketoacidosis.

CASE-REPORTS

Case 1: A 14-year old girl presented with one day history of fever, vomiting, respiratory difficulty and altered state of consciousness. This was preceded by a 2-3 weeks history of polyuria, polydipsia, increased appetite and undocumented weight loss. On examination, she had tachycardia, hypotension, and altered sensorium with Glasgow Coma Scale of 4/15. She had evidence of severe dehydration, gasping respiratory efforts with oxygen saturation of 85-90% on room air. Initial investigations revealed hyperglycemia (random blood sugar=947 mg/dL), severe metabolic acidosis (pH of 7.00, bicarbonate 5.0), glycosuria and ketonuria. Blood counts were normal. She was intubated and started on insulin infusion along with fluid resuscitation. She was mechanically ventilated. The ketoacidosis resolved within 48 hours and she was switched to subcutaneous insulin. She was extubated on 3rd day of admission. Subsequently, she developed evidence of renal insufficiency (serum creatinine 4.4 mg/dL). Ultrasound kidneys, ureters, bladder (KUB) was reported normal. Continuous renal replacement therapy (CRRT) was started. Subsequently, she developed paraparesis along with low hemoglobin, low platelet count with evidence of microangiopathy on peripheral smear. A, clinical diagnosis of thrombotic thrombocytopenic purpura (TTP) was made. Plasmapharesis and hemodialysis were started. 5 cycles of plasmapharesis were done. She gradually improved, microangiopathy resolved and her platelet count returned

to normal. She was discharged in stable condition on insulin.

Case 2: A 13-year-old girl presented with short history of vomiting and loss of consciousness few hours prior to presentation. There was history of polyuria, polydipsia and weight loss for last 4 weeks. On examination, she was tachycardiac, afebrile and drowsy with GCS of 7/15. She had deep acidotic breathing and moderate to severe dehydration. She was also intubated in emergency room and shifted to PICU for further management. Investigation revealed blood sugar level of 289 mg/dL, severe metabolic acidosis with pH. of 6.98 and bicarbonate level of 5.8. Fluid resuscitation was started along with insulin infusion. Inotropic support was started. She developed thrombocytopenia (45,000 per mm), high LDH of 1439 and renal insufficiency (serum creatinine 3.5 mg/dL). Peripheral smear also showed evidence of microangiopathy. These findings were consistent with thrombocytopenia associated multi-organ failure. The patient underwent CRRT and 3 cycles of plasmapharesis. The clinical condition gradually improved. She was extubated and finally discharged on subcutaneous insulin in stable clinical condition.

Laboratory findings of both patients at the time of admission and development of microangiopathic syndrome are summarized in ***Table* I**.

DISCUSSION

Thrombotic thrombocytopenic purpura characterized by sudden onset of formation of platelet rich thrombi in blood vessels, leading to thrombocytopenia and dramatic response to plasma infusion. Since the identification of this disorder, cases of TTP are gradually increasing with reported incidence of 2-7 per million person-years [4]. Despite rarity, it is considered to be a fatal disorder with mortality rate of >90% in untreated patients [5].

In intensive care settings, thrombocytopenia has been identified as an important risk factor for the development of multi-organ failure and a predictor of guarded outcome in critically ill children [6]. Thrombocytopenia associated multiple organ dysfunction (TAMOF) includes a spectrum of pathologic disorders. In addition to thrombotic thrombocytopenic purpura (TTP), thrombotic microangiopathy (TMA) and disseminated intravascular coagulation (DIC) are also considered to be a part of this syndrome [3]. At times, some overlap may be evident in these clinical phenotypes. Deficiency of von Willebrand factor cleaving protease (i.e. ADAMTS13) has been linked to be associated with platelets aggregation and formation of microthrombi in the circulation which lead to thrombotic microangiopathy and clinical manifestations of TAMOF and TTP [7]. Various secondary conditions like exposure to toxins/ radiation, systemic infections, malignancies, vasculitis, chemotherapy, immunosuppressive drugs like cyclosporine A, organ transplantation and cardiopulmonary bypass have also been associated with TAMOF/TTP but endocrine causes are rarely reported.

Renal failure alone is not sufficient to establish the diagnosis of TTP or TAMOF. Clinically, thrombotic

TABLE I LABORATORY FINDINGS OF TWO PATIENTS ON ADMISSION, BEFORE AND AFTER PLASMAPHARESIS

Laboratory findings	**Patient 1**			**Patient 2**		
	Baseline	*before plasma-pharesis*	*after plasma-pharesis*	*Baseline*	*before plasma-pharesis*	*after plasma-pharesis*
Hemoglobin (g/dL)	13.5	7.0	10.4	14.7	8.7	14.0
Platelets (per mm^3)	189,000	42,000	154,000	152,000	45,000	210,000
TLC (per mm^3)	14,300	8,700	9400	33,700	15,600	5300
LDH (U/L)	–	1223	593	—	1439	
PT(s)	11.7	11	Normal	15.6	11	Normal
aPTT(s)	32.5	30	Normal	63	30	Normal
BUN (mg/dL)	52	75	31	4	39	10
Serum creatinine (mg/dL)	3.4	4.4	3.6	1.0	3.5	0.6
Peripheral smear	Normal	Burr cells, helmet cells, target cells, spherocytes	Normal	Normal	Target cells, nucleated RBC's	Normal

TLC: total leucocyte count; PT: prothrombin time; aPTT: activated partial thromboplastin time (sec) *aPTT(s); BUN: blood urea nitrogen; S; serum*

thrombocytopenic purpura is defined by the presence of pentad of symptoms. These include thrombocytopenia, renal failure, seizure/abnormal CNS condition, microangiopathic anemia along with fever [8]. Evidence of microangiopathy may be evident on peripheral blood smear or elevated lactate dehydrogenase. Both of our patients developed these clinical symptoms and relevant laboratory findings during the course of hospitalization.

In adults, sufficient data is available highlighting the association of TAMOF with various conditions but TTP associated with DKA has been reported in one case only [9]. Only one case of TAMOF has been recently reported in a child with diabetic ketoacidosis but in that case, there was also associated pancreatitis which may have contributed to the development of microangiopathy and TAMOF [10]. No other risk factor except diabetic ketoacidosis was identified in our case series which may have led to the development of TAMOF/TTP.

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Neonatal Zygomycosis with Gastric Perforation

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Zygomycosis is a rare infection in neonates. The clinical presentation is non-specific and diagnosis most often is made at autopsy. Surgical debridement performed early improves survival. We report a case of neonatal zygomycosis with gastric perforation.

Keywords: *Neonate, Zygomycosis, Intestinal perforation.*

Neonatal zygomycosis occurs rarely with only 59 cases described in English literature till 2007 [1,2]. Skin is the most common point of entry for these patients. Premature infants represent 72% of cases and the overall mortality rate varies from 64-75% [1,2]. Gastrointestinal tract (GIT) involvement results from ingestion of fungal spores and prematurity is an important predisposing factor [1,3]. Early initiation of therapy is crucial in maximising outcomes and optimal management strategies have not been defined [4]. We present a case of neonatal zygomycosis with gastric perforation.

CASE REPORT

A four-day-old male baby weighing 1880 grams presented with abdominal distension for 30 hours. He was born vaginally at 34 weeks in a private nursing home and had cried immediately after birth. He received oxygen, intravenous fluids and intravenous amikacin and piperacillin-tazobactum for tachypnea, and formula feeds by nasogastric tube by day 2 of life. The baby developed abdominal distension on day 3 and feeds were stopped.