

Generalized Status Epilepticus in a Patient with Acute-onset Type 1 Diabetes Mellitus Associated with Severe Kidney Dysfunction: A Case Report and Literature Review

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Abstract

A 65-year-old Japanese man with advanced chronic kidney disease (CKD) developed acute-onset type 1 diabetes mellitus (T1D) that was associated with severe acute kidney injury and was manifested by generalized tonic-clonic status epilepticus. His seizures resolved without recurrence after correcting the diabetic ketoacidosis. Although hyperglycemia is an important cause of acute symptomatic seizure (ASS), patients with ketotic hyperglycemia develop ASS less frequently. In this T1D case with CKD, severe hyperglycemia in conjunction with other metabolic insults, such as uremia, hyponatremia, and hypocalcemia, probably provoked his seizure despite the severe ketonemia.

Key words: type 1 diabetes mellitus, generalized tonic-clonic status epilepticus, diabetic ketoacidosis, acute kidney injury, chronic kidney disease, electrolyte disturbance

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Introduction

Type 1 diabetes mellitus (T1D) is characterized by the destruction of pancreatic beta cells and insulin-deficient hyperglycemia (1). The rate of beta-cell destruction varies from patient to patient, and T1D is classified as fulminant, acute-onset, or slowly progressive in Japan depending on the manner of onset and progression (2). Acute-onset T1D is characterized by diabetic ketosis or diabetic ketoacidosis (DKA) within three months after the onset of hyperglycemic symptoms, with or without islet-related autoantibodies (3). Patients may exhibit acute kidney injury (AKI) and electrolyte disturbances in association with severe dehydration when

they develop acute-onset T1D (4).

Acute symptomatic seizure (ASS) is a clinical seizure that occurs in close temporal relationship with an acute central nervous system (CNS) or systemic insult (5-7). Major insults include stroke, traumatic brain injury, CNS infections, and toxins and metabolic derangements, including hypo- or hyperglycemia, uremia, and electrolyte disturbances. ASS can involve either focal or generalized seizures, and patients may present with status epilepticus (SE) (8).

Although hyperglycemia is an important metabolic insult for ASS (5, 6, 9), patients with ketotic hyperglycemia less frequently present with ASS than those with non-ketotic hyperglycemia (10-14). Nevertheless, in several case reports, diabetic ketosis (15, 16) or DKA (17-21) was associated

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with ASS, in which the patients usually had coexistent disorders that provoked seizure. However, few studies have investigated patients with T1D and DKA associated with ASS.

We herein report a rare case of a patient who exhibited generalized SE upon the development of acute-onset T1D and DKA associated with severe AKI and pre-existing advanced chronic kidney disease (CKD). In addition, we review previously reported cases of DKA associated with ASS.

Case Report

A 65-year-old Japanese man who presented with generalized tonic-clonic SE was admitted to our hospital in February 2016 with a diagnosis of DKA and severe kidney dysfunction. His family history revealed that his father and his paternal uncle had type 2 diabetes mellitus. None of his relatives had a convulsive disorder or mitochondrial disease. The patient had smoked 10 cigarettes/day from 20 to 60 years of age, but had never consumed alcohol. The patient had no history of diabetes mellitus, collagen disease, or a CNS disorder, including head trauma, stroke, or encephalopathy. The patient was found to have kidney dysfunction [serum creatinine, 1.4 mg/dL; estimated glomerular filtration rate (eGFR) (22), 44.9 mL/min/1.73 m²] and untreated hypertension with negative urinalysis results for proteinuria, microhematuria, pyuria, and glycosuria at 42 years of age. The patient had experienced an uneventful clinical course during conservative medical treatment for CKD, except for a gradual increase in the serum creatinine level. Eight months before admission, he was referred to the nephrology department of our hospital (serum creatinine, 2.58 mg/dL; eGFR, 20.3 mL/min/1.73 m²). His height was 145 cm, weight 47 kg, and blood pressure 123/79 mmHg. There were no abnormal physical findings suggesting congenital or other disorders that caused his short stature. No dysacusis, muscle pain, joint pain or swelling, alopecia, or discoid rash was found. A urinalysis detected no protein, blood, pus, or glucose in the urine. His casual plasma glucose (96 mg/dL), glycated hemoglobin (HbA1c) (5.2%), blood lactic acid (11.0 mg/dL, reference range: 4.5-14.4 mg/dL), and serum levels of complement (CH50) (36 U/mL, reference range: 30-45 U/mL) and C-reactive protein (0.13 mg/dL) were normal. Anti-nuclear antibody was negative. Abdominal ultrasonography showed bilateral atrophic kidneys. The patient continued medical treatment with oral valsartan (40 mg/day), furosemide (20 mg/day), sodium bicarbonate (2 g/day), febuxostat (10 mg/day), calcium polystyrene sulfonate (5 g/day) and alfacalcidol (1 µg/day), and subcutaneous darbepoetin alfa (30 µg/month) for CKD-related hypertension, fluid retention, metabolic acidosis, hyperuricemia, hypocalcemia, and renal anemia, respectively. One month before admission, he weighed 47 kg, and his blood pressure was 128/79 mmHg. Blood chemistry revealed the following: venous pH, 7.359; bicarbonate, 23.6 mmol/L; red blood cells, 359×10⁴/µL; hemoglobin 11.8 g/dL; hematocrit, 34.2%; cre-

atinine, 2.54 mg/dL; eGFR, 20.7 mL/min/1.73 m²; urea nitrogen, 30.6 mg/dL; uric acid, 7.4 mg/dL; albumin, 4.1 g/dL; sodium, 142 mEq/L; potassium, 3.3 mEq/L; chloride, 104 mEq/L; calcium, 7.2 mg/dL; phosphorus, 3.0 mg/dL; and casual plasma glucose, 95 mg/dL. The patient developed a cough and sore throat 7 days before admission. Three days later, he became unusually thirsty and was polyuric. On the day of admission, he developed a generalized tonic-clonic seizure with disturbed consciousness and was brought by ambulance to our hospital.

On arrival at the hospital, the patient was comatose and presented with generalized tonic-clonic seizures that lasted several minutes and frequently recurred. His seizures were controlled with intravenous diazepam, but he rapidly developed respiratory depression, and he was placed on mechanical ventilation. A physical examination revealed body weight, body temperature, and blood pressure of 42 kg, 34.7°C, and 82/48 mmHg, respectively. His oral cavity was markedly dry. No chest rales, heart murmurs, or peripheral edema was detected. Electrocardiogram showed sinus tachycardia with a heart rate of 120 beats/min. Blood chemistry (Table 1) revealed severe hyperglycemia (casual plasma glucose, 1,272 mg/dL), ketonemia (serum 3-hydroxybutyrate, 11,210 µmol/L), renal dysfunction (serum creatinine, 6.96 mg/dL; eGFR, 6.5 mL/min/1.73 m²), uremia (serum urea nitrogen, 109.4 mg/dL), and metabolic acidosis (arterial pH, 6.992; bicarbonate, 4.7 mmol/L). The serum levels of creatinine kinase (619 IU/L), uric acid (9.1 mg/dL), potassium (5.6 mEq/L), and phosphorus (9.8 mg/dL), and those of exocrine pancreatic enzymes, including amylase, lipase, elastase-1, and phospholipase A2, were high. The serum levels of sodium (111 mEq/L) and calcium (6.4 mg/dL) were low. HbA1c (6.9%) and serum glycated albumin (37.5%) were slightly and moderately high, respectively. Computed tomography revealed no abnormalities in the brain, lungs, heart, liver, pancreas, or spleen, except for bilateral kidney atrophy. He was diagnosed with DKA, severe hypovolemia, prerenal AKI, and electrolyte disturbances, and was treated with intravenous saline, calcium gluconate, and regular insulin. His seizures were considered to be due to severe metabolic derangements, and sedation was continued using intravenous midazolam under ventilation.

His blood pressure was maintained at >100/60 mmHg, and his anuria resolved within 4 hours. His plasma glucose levels decreased at a rate of approximately 70 mg/dL/h, and his serum sodium levels increased gradually. Sixteen hours after admission, his arterial pH was 7.289, plasma glucose was 261 mg/dL, and serum sodium was 128 mEq/L. After his severe dehydration had been corrected, he received sufficient fluid volume by maintenance infusion.

Blood chemistry performed on day 7 of admission showed the following results: arterial pH, 7.426; bicarbonate, 22.4 mmol/L; creatinine, 6.03 mg/dL, eGFR, 7.6 mL/min/1.73 m²; urea nitrogen, 84.9 mg/L; uric acid, 6.7 mg/dL; albumin, 2.7 g/dL; sodium, 138 mEq/L; potassium, 3.8 mEq/L; chloride, 100 mEq/L; calcium, 7.0 mg/dL; phospho-

Table 1. Laboratory Findings at the Time of Admission (February 2016).

Hematology	
Red blood cells	363×10 ⁴ /μL (435-555)
Hemoglobin	12.0 g/dL (13.7-16.8)
Hematocrit	33.8 % (40.7-50.1)
White blood cells	13,300/μL (3,300-8,600)
Platelets	29.3×10 ⁴ /μL (15.8-34.8)
Blood chemistry	
Casual plasma glucose	1,272 mg/dL (70-139)
Glycated hemoglobin (HbA1c)	6.9 % (4.6-6.2)
Glycated albumin	37.5 % (11.6-16.4)
Acetoacetate	2,420 μmol/L (<55)
3-Hydroxybutyrate	11,210 μmol/L (<85)
Total protein	5.0 g/dL (6.6-8.1)
Albumin	3.3 g/dL (4.1-5.1)
Total cholesterol	143 mg/dL (130-220)
Triglycerides	45 mg/dL (50-130)
Aspartate aminotransferase	21 IU/L (13-30)
Alanine aminotransferase	19 IU/L (10-42)
Gamma-glutamyl transferase	16 IU/L (13-64)
Amylase	276 IU/L (44-132)
Lipase	249 U/L (17-57)
Elastase-1	1,363 ng/mL (72-432)
Phospholipase A2	1,684 ng/dL (130-400)
Creatine kinase	619 IU/L (59-248)
Urea nitrogen	109.4 mg/dL (8.0-18.4)
Creatinine	6.96 mg/dL (0.65-1.07)
eGFR*	6.5 mL/min/1.73 m ² (>90)
Uric acid	9.1 mg/dL (3.7-7.8)
Sodium	111 mEq/L (138-145)
Potassium	5.6 mEq/L (3.6-4.8)
Chloride	67 mEq/L (101-108)
Calcium	6.4 mg/dL (8.8-10.1)
Phosphorus	9.8 mg/dL (2.7-4.6)
Magnesium	1.89 mg/dL (1.7-2.3)
C-reactive protein	1.33 mg/dL (0-0.14)
Intact-parathyroid hormone	84 pg/mL (10-65)
Arterial blood gas analysis on artificial respiration	
pH	6.992 (7.35-7.45)
Partial carbon dioxide pressure	19.3 mmHg (32-48)
Partial oxygen pressure	393.0 mmHg (83-108)
Bicarbonate	4.7 mmol/L (21-28)

The reference range for each parameter is shown in parentheses.

*Estimated glomerular filtration rate was calculated using the published Japanese equation as follows (22): $eGFR (mL/min/1.73 m^2) = 0.808 \times 175 \times \text{serum creatinine (mg/dL)}^{-1.154} \times \text{age}^{-0.203}$.

rus, 3.4 mg/dL; and casual plasma glucose, 165 mg/dL. Because his metabolic status improved, sedation therapy was terminated, and the patient was weaned from ventilatory support on the same day. He recovered consciousness and no longer presented any seizures or other neurological abnormalities.

The patient's fasting serum C-peptide levels before and 5 minutes after intravenous glucagon loading were <0.2 ng/mL and <0.2 ng/mL, respectively, indicating a diagnosis of T1D. He tested negative for islet-related autoantibodies, such as glutamic acid decarboxylase antibody (<5.0 U/mL), islet cell antibody (<1.25 JDF units), insulinoma-associated

antigen-2 antibody (<0.4 U/mL), insulin antibody (<125.0 nU/mL), and zinc transporter-8 antibody (<10.0 U/mL). He was also negative for anti-anterior pituitary, thyroid peroxidase, thyroglobulin, thyroid-stimulating hormone receptor, and anti-adrenal autoantibodies. Human leukocyte antigen (HLA) typing showed A*24/26, B*40(-), and C*08:01(-) class I genes and DRB1*08:03/15:01, DQB1*06:01/06:02, and DQA1*01:02/01:03 class II genes.

The patient regained his appetite and was started on subcutaneous insulin injection therapy on day 14 of admission. A fundoscopic examination detected no diabetic retinopathy. An electroencephalographic examination performed on day

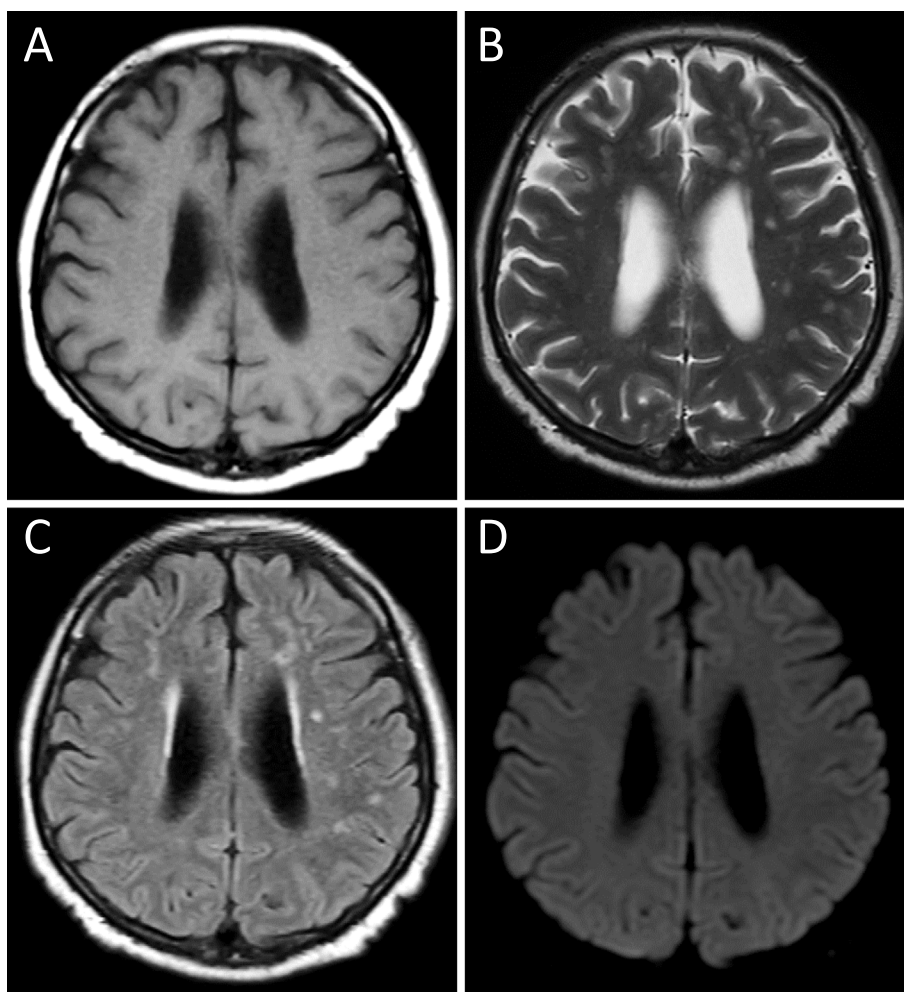


Figure. Brain magnetic resonance image (day 20 after admission in February 2016). Magnetic resonance imaging showed scattered hyperintense signals in the bilateral cerebral white matter on both T2-weighted (B) and fluid-attenuated inversion recovery (C) images, but no abnormal-intensity signals were found on T1-weighted (A) or diffusion-weighted (D) images.

18 revealed no findings suggestive of an epileptogenic disorder. Magnetic resonance imaging (MRI) of the brain performed on day 20 showed no abnormalities, except for scattered hyperintense areas in the bilateral cerebral white matter on both T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Figure). No arterial lesions were detected on magnetic resonance angiography.

The patient was discharged on day 46 of admission after completing a diabetes mellitus self-management education program. In August of the same year, he weighed 43.9 kg, and blood chemistry showed the following results: venous pH, 7.396; bicarbonate, 21.1 mmol/L; serum creatinine, 3.60 mg/dL; eGFR, 13.8 mL/min/1.73 m²; urea nitrogen, 58.1 mg/dL; uric acid, 5.3 mg/dL; albumin, 3.3 g/dL; sodium, 137 mEq/L; potassium, 3.9 mEq/L; chloride, 100 mEq/L; calcium, 7.9 mg/dL; phosphorus, 4.9 mg/dL; casual plasma glucose, 185 mg/dL; serum C-peptide, <0.2 ng/mL; HbA1c, 7.3%; and glycated albumin, 29.0%, under conventional medical treatment for CKD and multiple daily insulin injection therapy (total of 26 units/day) for diabetes mellitus. Brain MRI performed in August 2016 showed scattered hy-

perintense signals in the bilateral cerebral white matter on both T2-weighted and FLAIR images, which remained unchanged compared to those on MRI taken six months prior (Figure) and indicated asymptomatic chronic ischemic changes in relation to his aging and long-standing CKD (23). His subsequent clinical course was stable without recurrence of seizure.

Discussion

An elderly Japanese patient with advanced CKD abruptly developed T1D and DKA that was accompanied by severe AKI and manifested as generalized tonic-clonic SE. His seizures resolved after correcting the DKA, electroencephalographic examinations showed no findings suggestive of epileptogenic disorder, and brain MRI detected no remarkable findings, except for chronic cerebral white matter ischemic changes. The patient experienced no recurrence of seizures during medical treatment for T1D and CKD. This is the first reported case of proven T1D and DKA associated with ASS.

Table 2 summarizes the reported patients who exhibited

Table 2. Summary of Reported Patients who Exhibited Acute Symptomatic Seizure in Association with Diabetic Ketoacidosis.

Case	Age (years)	Sex	Type of seizure*	Etiology of diabetes mellitus**	Known duration of diabetes mellitus (years)	HbA1c (%)	Plasma glucose (mg/dL)	Serum 3-hydroxybutyrate (μmol/L)	Arterial pH	Serum creatinine (mg/dL)	Serum urea nitrogen (mg/dL)	Magnetic resonance imaging of the brain	Complicating disorders	Ref.
1	46	Female	Generalized	Undetermined	0	N.D.	890	N.D.	N.D.	N.D.	54	N.D.	Electrolyte disturbance (Severe hyponatremia)	(17)
2	49	Female	Generalized	Mitochondrial	15	10.7	1,231	1,410	7.12	1.3	49	N.D.	MELAS	(18)
3	33	Female	Focal	Mitochondrial	15	N.D.	540	1,990	6.88	N.D.	N.D.	Hyperintense areas on FLAIR images in the bilateral temporal and occipital lobes (abnormal lactic acid accumulation)	MELAS	(19)
4	44	Male	Focal	Pancreatic	0	N.D.	506	N.D.	7.28	N.D.	N.D.	Hypointensity on FLAIR images in the left subcortical precentral gyrus (possibly crossed cerebellar diaschisis) and hyperintensity in the right cerebellar hemisphere (possibly cerebral injury secondary to ASS)	Previous alcohol abuse, chronic pancreatitis	(20)
5	80	Male	Generalized	Type 2	20	14.0	608	N.D.	7.22	N.D.	N.D.	Slim subacute subdural hematomas over the bilateral occipital lobes	Theophylline intoxication, traumatic brain injury	(21)
6	59	Male	Generalized	Type 1	0	6.9	1,272	11,210	6.99	7.0	109	Scattered hyperintense areas in the bilateral cerebral white matter on T2-weighted and FLAIR images (chronic ischemic changes)	AKI on advanced CKD, electrolyte disturbance (hyponatremia and hypocalcemia)	Present case

*Seizures were divided into focal or generalized, according to the clinical presentation (8).

**Diabetes mellitus was classified as type 1, type 2, gestational, or "other specific types," based on the published etiological classification (1). "Other specific types" included pancreatic or mitochondrial diabetes mellitus. The etiology of diabetes mellitus in Case 1 was undetermined because of a lack of information regarding endogenous insulin secretory capacity, islet-related autoantibodies, or a requirement for insulin treatment to survive after the onset of diabetes mellitus.

AKI: acute kidney injury, ASS: acute symptomatic seizure, CKD: chronic kidney disease, FLAIR: fluid-attenuated inversion recovery, HbA1c: glycated hemoglobin, MELAS: mitochondrial myopathy encephalopathy lactic acidosis and stroke-like episodes, N.D.: not described

ASS in association with DKA. These cases included adults with various etiologies and durations of diabetes mellitus who presented with focal or generalized seizures. The patients had a variety of coexisting CNS or systemic disorders capable of precipitating seizures, including severe hyponatremia (17), mitochondrial myopathy encephalopathy lactic acidosis and stroke-like episodes (MELAS) syndrome (18, 19), and traumatic brain injury and theophylline intoxication in relation to the management of chronic obstructive pulmonary disease (21). In the present case, CNS insults, including traumatic brain injury and MELAS, were ruled out by the clinical, laboratory, and imaging findings.

One of the notable findings at the onset of T1D in our patient was the marked hyperglycemia and related metabolic derangements. He had more severe hyperglycemia, electrolyte disturbances including hyponatremia, AKI, uremia, ketonemia, and metabolic acidosis than typical cases of T1D (24). Studies have shown that patients with CKD exhibit insulin resistance (25), which may accelerate the rate of elevation of blood glucose levels during the reduction of endogenous insulin secretion at the development of T1D. CKD also causes non-volatile acid accumulation as a result of decreased renal excretion or disturbed acid-base homeostasis. In our patient, the advanced CKD probably increased the severity of hyperglycemia, ketonemia, and metabolic acidosis by inducing insulin resistance and acid accumulation. Simultaneously, his severe hyperglycemia and resulting osmotic diuresis led to the observed marked hypovolemic hyponatremia, prerenal AKI, and uremia.

The mechanisms underlying ASS when T1D occurred in our patient remain unclear. However, hyperglycemia is thought to decrease the seizure threshold (9), possibly through decreased levels of gamma-aminobutyric acid (GABA; the major CNS inhibitory neurotransmitter) (10-12), reduced blood flow in an area of a previously silent cerebral lesion (26), or disruption of the blood-brain barrier (27). In contrast, several lines of evidence suggest that ketone bodies have a protective effect against seizures through increased GABA production or altered neuronal responsiveness to GABA (28-31). These findings suggest that severe hyperglycemia in conjunction with other metabolic insults, such as uremia and electrolyte disturbances, including acute hypovolemic hyponatremia and chronic hypocalcemia, probably provoked the seizures despite the patient exhibiting severe ketonemia (Table 1).

CKD can be caused by a variety of renal disorders, and major causes include diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis, and collagen diseases, such as lupus nephritis (32). Our patient had no history of diabetes mellitus before he was diagnosed with CKD, and glomerulonephritis and collagen disease were ruled out based on the clinical, urinary, and serological findings. A kidney biopsy was not indicated because our patient already had advanced CKD with atrophic kidneys when he was referred to our hospital; consequently, no histopathological diagnosis was obtained. However, the presence of untreated

hypertension at the diagnosis of kidney dysfunction suggests that hypertensive nephrosclerosis was a causal factor for his CKD.

Fulminant T1D is a subtype of T1D that results from the extremely rapid and almost complete destruction of pancreatic beta cells (2). The published criteria for diagnosing this disorder require near normal HbA1c values despite high plasma glucose levels at disease onset, which reflects the abrupt occurrence of hyperglycemia within a few days (33). Our patient abruptly developed insulin-deficient hyperglycemia and DKA with an HbA1c value of 6.9% and seemed to develop fulminant T1D. However, because he had advanced CKD and anemia treated with erythropoiesis-stimulating agents, he probably showed a lower HbA1c value than one truly reflecting the average blood glucose levels over the preceding few months (34). Furthermore, his serum levels of glycated albumin, another indicator reflecting the average previous blood glucose levels, were substantially higher than is usual in cases of fulminant T1D (35). Based on these findings, we diagnosed him with acute-onset T1D.

In conclusion, we reported a patient who exhibited generalized tonic-clonic SE upon development of acute-onset T1D and DKA that was associated with severe AKI and advanced CKD. Severe hyperglycemia in conjunction with uremia, hyponatremia, and hypocalcemia probably provoked the seizure, despite the patient exhibiting severe ketonemia. The present case highlights the need for physicians to consider that ASS can be associated with DKA, including that of T1D onset, and may occur in the presence of other metabolic derangements, such as uremia and electrolyte disturbances. In addition, ASS can occur as a predominant manifestation of T1D onset, particularly when patients have pre-existing advanced kidney dysfunction.

The authors state that they have no Conflict of Interest (COI).

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