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CASE REPORT

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SGLT2 inhibitor in a type 2 diabetes mellitus patient coexisted with central diabetes insipidus following hyperosmolar hyperglycemic state

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Abstract

Background Central diabetes insipidus (CDI) is a rare complication following a hyperglycemic hyperosmolar state (HHS) in patients with type 2 diabetes mellitus (T2DM). The coexistence of T2DM and CDI can lead to diagnostic challenges, particularly when the patients present with persistent hypernatremia without a sense of thirst.

Case presentation This case report describes a young woman with T2DM and HHS who developed persistent hypernatremia without thirst. The diagnosis of CDI was delayed until she exhibited polydipsia, consuming up to 10 L of water per day, following the administration of dapagliflozin for glucose control. Initially, the low specific gravity of urine was not evident during dapagliflozin treatment. However, after discontinuing dapagliflozin for 48 h, CDI was confirmed through a water deprivation test, which revealed polyuria with low urine specific gravity and osmolality. The patient was successfully treated with oral desmopressin.

Conclusions This case highlights that SGLT2 inhibitors, such as dapagliflozin, may accelerate polyuria and alter urine osmolality by inhibiting glucose and sodium reabsorption in the proximal tubular. Therefore, it is crucial to discontinue SGLT2 inhibitors when CDI is suspected or diagnosed.

Keywords T2DM, Hyperosmolar hyperglycemic state, Central diabetes insipidus, SGLT2 inhibitors

Background

The development of central diabetes insipidus (CDI) in patients with type 2 diabetes mellitus(T2DM) complicated by hyperosmolar hyperglycemic state (HHS) is a rare occurrence [1]. HSS is most commonly observed in elderly patients with T2DM and is associated with a mortality rate 10 times higher than that of diabetic ketoacidosis [2].

Sodium-glucose cotransport 2 (SGLT2) inhibitors, a class of glucose-lowering agents, work by inhibiting glucose reabsorption in the renal tubules, thereby promoting glucosuria [3]. Their diuretic effect is thought to result from mild osmotic diuresis and natriuresis [4]. Emerging evidence suggests that SGLT2 inhibitors also confer cardiorenal benefits, even in individuals without T2DM, by influencing salt and water homeostasis [5]. However, the appropriateness of SGLT2 inhibitors in patients with T2DM who also have coexisting CDI remains unclear. This case highlights the potential challenges in

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diagnosing and managing CDI in the context of T2DM and HHS, particularly when SGLT2 inhibitors are used, as they may mask or exacerbate CDI symptoms. Further research is needed to clarify the safety and efficacy of SGLT2 inhibitors in this unique patient population.

Case presentation

A 22-year-old woman was incidentally found to have hyperglycemia during a routine medical examination, despite the absence of polydipsia or polyuria. She was diagnosed with T2DM based on a fasting blood glucose level of 9.8mmol/L, glycated hemoglobulin (HbA_{1C}) of 9.5%, a positive family history of diabetes in second-degree relatives, negative islet antibodies, and obesity with a body mass index (BMI) of 32.1 kg/m^2 (height 165 cm, weight 87.5 kg). She was initially prescribed metformin (1000 mg twice daily) and advised to adopt intensive lifestyle modifications, including dietary energy restriction and regular exercise. Two months later, she discontinued metformin upon discovering she was five weeks pregnant. At seven weeks of pregnancy, she presented to the emergency room with a three-day history of hyperemesis, generalized weakness, progressive polydipsia, and a urine output of 2–3 L/day. HHS was diagnosed based on the following findings: blood glucose of 75.9 mmol/L, HbA_{1C} of 11.58%, corrected serum sodium of 166.96 mmol/L, negative urinary ketones, serum creatinine of 300.53μmol/L, uric acid of 1183.13μmol/L and arterial blood gas showing PH 7.34, bicarbonate 20.4mmol/L, base excess −3.5mmol/L, lactic acid 3.93mmol/L. Additional laboratory data are summarized in Table 1. Within two hours of admission, she developed mental confusion and subsequently fell into a coma. She was transferred to the intensive care unit and managed according to the HHS protocol. Her consciousness was restored within 24 h following successful fluid resuscitation and continuous intravenous insulin therapy. During her hospitalization, she complained of abdominal pain, and severe acute pancreatitis was confirmed by elevated serum amylase and lipase levels, as well as a CT of pancreas. On the second day of admission, she experienced a spontaneous abortion. Her treatment included intravenous norepinephrine for shock, continuous renal replacement therapy for acute kidney injury, enteral nutrition support, octreotide, antibiotic, and triglyceride-lowering drugs (triglyceride level: 10.95 mmol/L), and anticoagulation. By day 10 of admission, Her HHS and pancreatitis had significantly improved; however, hypernatremia unexpectedly recurred and persisted despite intravenous fluid replacement (Table 1). Fluid balance was closely monitored and maintained with timely supplementation. Her urine output increased to 10 L/day, accompanied with a decline in urine specific gravity, which was initially attributed to the polyuria phase of acute kidney injury. She was discharged without any specific intervention and continued enteral nutrition support with 2000 kcal/day of intacted protein enteral nutrition powder for three weeks. Basal insulin (14 units daily) was irregularly administered for glycemic control.

Following discharge, she experienced abdominal distension even with minimal food and water intake after removal of the enteral tube at a local hospital. Her urine output remained at 2 L/day, matching her fluid intake. She had lost 12.5 kg since her initial admission. She was subsequently admitted to our endocrinology department for persistent hypernatremia and poorly controlled

Table 1 Laboratories on the first admission

Laboratory (reference range)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 9	Day 10	Day 15
Glucose(mmol/L)	75.9	8.59	7.71	12.38	8.74	7.45	/	4.58	/	9.74
Blood urea nitrogen (2.6-7.5 mmol/L)	15.89	10.03	8.83	9.66	7.88	6.63	5.02	10.02	/	6.06
Creatinine (41-73 μmol/L)	300.53	173.67	197.34	237.66	208.34	188.62	153.3	172.49	/	74
Uric acid (135-425 μmol/L)	1183.13	1055.29	505.63	242.94	149.97	137.59	115.83	392.18	/	85
WBC (3.5-9.5*10^9/L)	25.93	20.77	15.22	10.23	10.32	8.75	8.62	8.83	/	8.52
NEUT% (40-75%)	86.7	76.60	80.70	78.00	77.30	68.4	69.2	72.00	/	70.9
Hb (115-150 g/L)	200	153	132	112	86	86	92	85	/	78
HCT (35-45 L/L)	61.6	45.6	39.00	32.6	25.2	25.3	27.7	27.10	/	24.5
Serum osmolality(mOsm/kg)†	378.06	344.19	317.83	304.88	302.32	298.57		302.58		319.22
Sodium (137-147 mmol/L)	146.7	164.5	151.4	142.8	142.8	141.8	139.2	144.3	153.3	150.8
Corrected serum sodium (mmol/L)*	166.96	165.37	152.02	144.77	143.72	142.35	/	144.02	/	152.01
Potassium (3.5-5.3 mmol/L)	4.38	3.30	3.66	3.45	3.99	3.76	4.10	4.7	4.47	3.94
Calcium (2.11-2.52 mmol/L)	2.79	2.59	2.24	2.12	2.00	2.14	2.19	2.08	2.13	2.08
Urinaly analysis										
urine specific gravity	/	>1. 030	>1. 030	>1. 030	1.020	1.015	1.010	<1. 005	/	<1. 006
glucouria	3+	-	-	-	-	-	-	-	/	1+
urine ketones	-	-	-	-	-	-	-	-	/	-
urine protein	2+	2+	2+	2+	1+	1+	1+	±	/	-
hematouria	1+	1+	3+	3+	3+	3+	3+	2+	/	-

*[Na]Corrected, mmol/L=[Na]+0.016×([Glu mg/dl])-100), †serum effective osmolality=2×([Na]+[K])+[Glu]

diabetes. Laboratory tests revealed a serum natremia level of 165.7 mmol/L (corrected for a random blood glucose of 27.39mmol/L), which remained uncorrected despite a daily fluid intake of 4 L, including intravenously hypotonic fluids and scheduled oral hydration, due to the absence of thirst. Her HbA_{1C} had risen to10.3%, reflecting poor dietary adherence and irregular insulin use. A fasting C-peptide level of 1.87 ng/ml (reference range: 0.6-3.4ng/ml) was detected. Renal function had recovered, with blood urea nitrogen at 5.18 mmol/L and serum creatinine at 66 μmol/L. Adipsic diabetes insipidus (DI) was suspected. Magnetic resonance imaging (MRI) of the pituitary gland revealed the absence of the posterior pituitary bright spot on T1-weighted images (Fig. 1), with no abnormalities in the anterior pituitary or stalk. Anterior pituitary hormone levels and their target hormones were within normal ranges, ruling out adenohypophysis insufficiency. The details were as follows: corticotropic hormone (ACTH), 12.9 (7.2–63.3 pg/ml) at 8 am; serum cortisol, 31.0 (5–28 μg/dl) at 8 am,

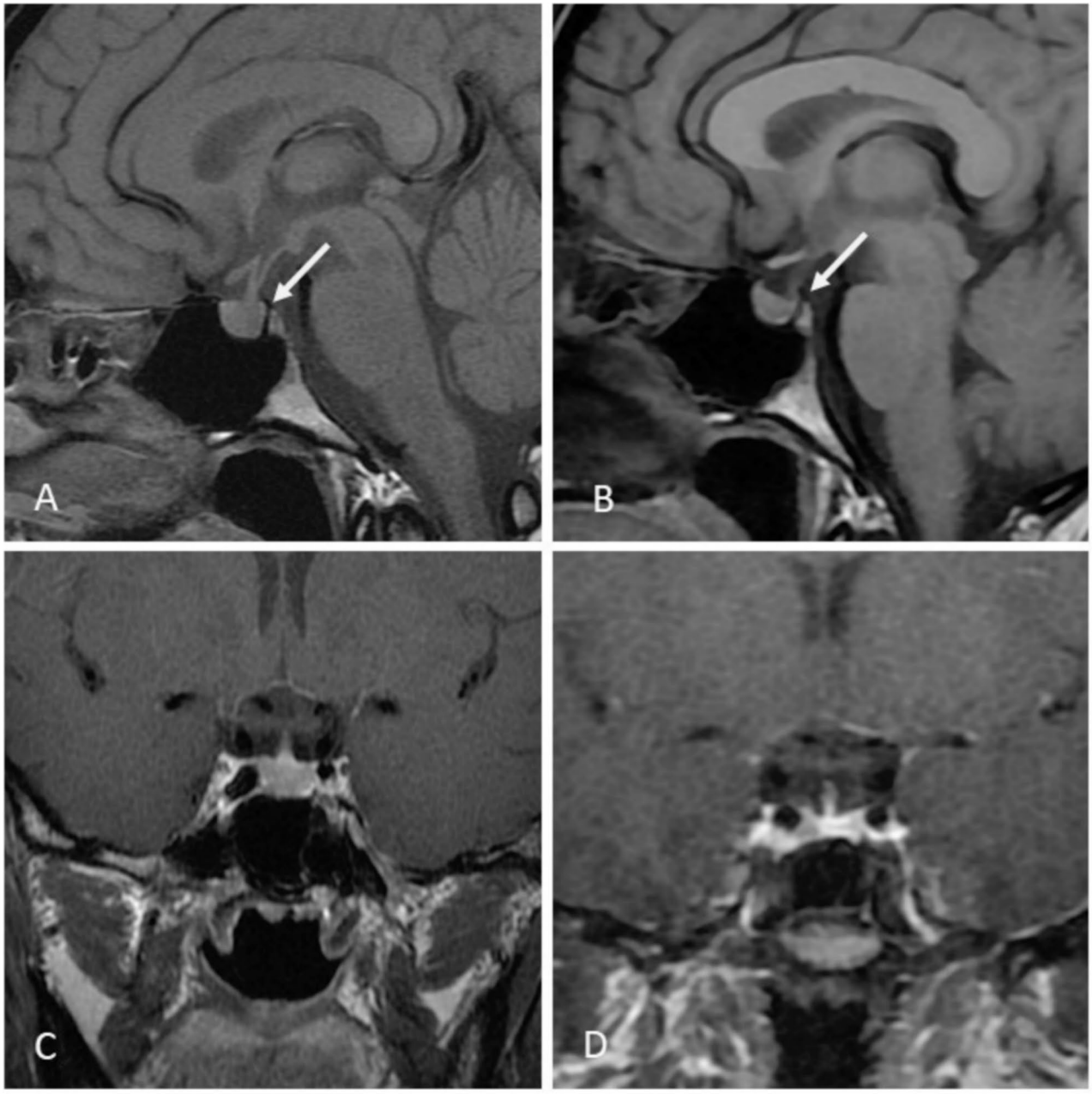

Fig. 1 Magnetic resonance imaging scan of pituitary in sagittal view (**A**, **B**) and contrast-enhanced in coronal view (**C**, **D**), which were conducted at first month (**A**, **C**) and six months (**B**, **D**) since abortion, respectively. Both **A** and **B** showed an absence of posterior pituitary bright spot on the T1-weighted images. **C** showed slight pituitary hyperplasia in response to estrogen stimulation and recovered later (**D**)

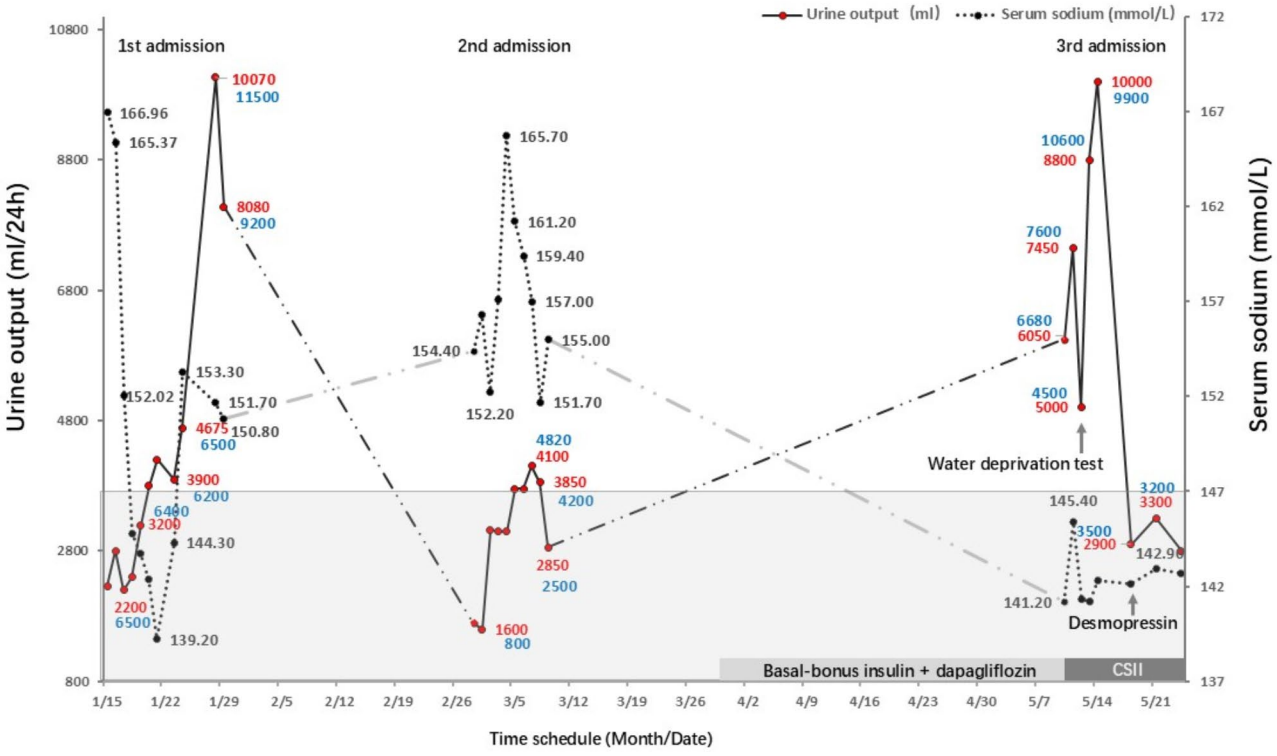

Fig. 2 Trend of serum sodium and urine output throughout each hospitalization. The blue numbers in the figure indicate the corresponding fluid intake volumes (ml)

24.8 μg/dl at 4 pm; growth hormone, 0.251(0–8 ng/ml); insulin growth factor-1(IGF-1), 104(116–358 μg/ml); estradiol (E2), 164.7 pmol/L; luteinizing hormone (LH), 1.160 mIU/ml; follicle stimulating hormone (FSH), 2.750 mIU/ml; prolactin (PRL), 18.83(4.79–23.3 ng/ml); thyrotrophic hormone (TSH), 1.84(0.27–4.2 μIU/ml) and free T4, 14.3(12–22 pmol/L). To evaluate potential rheumatologic and autoimmune diseases, a preliminary assessment was conducted during the second admission, including autoantibodies profiles, immunoglobulin testing, thyroid-associated antibodies, and inflammatory markers. Specifically, anti-nuclear antibodies (ANA) and anti-double-stranded DNA (dsDNA) antibodies were tested to assess for systemic lupus erythematosus (SLE); Anti-neutrophil cytoplasmic antibodies (ANCA) were measured to valuate vasculitis; Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were analyzed to screen for systemic inflammation; and Anti-thyroid peroxidase (TPO) antibodies and anti-thyroglobulin (Tg) antibodies were tested to assess autoimmune thyroiditis. These investigations did not indicate the presence of underlying autoimmune conditions that could potentially explain the patient's symptoms. Due to the local COVID-19 outbreak, she was discharged prematurely and managed with a basal-bolus insulin regimen.

As her gastrointestinal function improved, increased food intake led to a 5 kg weight gain (body weight: 80 kg) and worsening glycemic control despite higher insulin doses. Dapagliflozin (10 mg daily) was added to her regimen at a local hospital to address obesity and hyperglycemia. Shortly, after initiating dapagliflozin, she developed progressive thirst and polydipsia, with a daily fluid intake of up to 10 L (Fig. 2). Notably, her hypernatremia resolved during this period. She was readmitted to our endocrinology department for evaluation of hyperglycemia, polydipsia, and polyuria. Her HbA_{1C} had risen to13.6%, and random blood glucose was 36.07 mmol/L with negative urinary ketones. Continuous subcutaneous insulin infusion (CSII) was initiated to optimize glycemic control. Urine specific gravity, measured every three hours, fluctuated between 1.008 and 1.018, with a total 24-hour urine output of 7.45 L. The maximum urine specific gravity exceeded 1.015, which was inconsistent with the expected low specific gravity (<1.015) in diabetes insipidus. We hypothesized that the hypotonic polyuria characteristic of diabetes insipidus was masked by excessive urinary glucose excretion due to both diabetes and SGLT2 inhibitor use. Dapagliflozin was discontinued, and after 48 h, a water deprivation test was performed. Serum osmolality increased from 306.06 to 330.08 mOsm/kg, while urine osmolality rose minimally from 19 to 86 mOsm/kg. The plateau phase was achieved with a stable urine output and a maximum specific gravity of 1.010. A vasopressin challenge test was not performed

due to the patient's intolerable thirst. Then CDI was confirmed, and oral desmopressin (0.05 mg nocte) was initiated, later increased to 0.05 mg twice daily. Her urine output decreased markedly to 3 L/24 hours, with no nocturnal polyuria, and urinary osmolality increased to 388 mOsm/kg. She was discharged on a basal-bolus insulin regimen and desmopressin. At follow-up, her blood glucose was well-controlled with basal insulin and metformin. Desmopressin (0.05 mg twice daily) was continued, maintaining a urine output of 2 L/day and normal serum sodium levels. Two years later, desmopressin remains essential, as attempts to reduce or discontinue it result in a urine output of 5–6 L/day.

Discussion and conclusions

The coexistence of T2DM and CDI is rare in clinical practice. Potential causes of CDI include conditions such as craniopharyngioma, pituitary metastases, and Wolfram syndrome [6]. The etiology of CDI in this case remains unclear, but it may be linked to a series of pathophysiological disturbances, including hemodynamic instability, pregnancy, and a significant increase in serum osmolality. Wolfram syndrome is a rare genetic disorder typically diagnosed based on the presence of diabetes mellitus and optic atrophy, along with additional features such as diabetes insipidus and sensorineural hearing loss. In this case, the absence of optic or hearing abnormalities makes late-onset Wolfram syndrome a less likely etiology; however, it cannot be entirely ruled out without genetic testing. During pregnancy, the presence of placental vasopressinase can markedly alter vasopressin physiology by increasing hormone clearance rates [7]. Gestational diabetes insipidus (GDI) may occur in cases with reduced arginine vasopressin (AVP) preservation or partial renal responsiveness to AVP. It typically affects women during the second or third trimester. Symptoms of GDI usually resolve 4–6 weeks postpartum as vasopressinase activity declines [8]. However, in this patient, CDI was diagnosed during the first trimester and persisted for more than two years after her abortion, thereby ruling out GDI as a potential cause.

Pregnancy can also trigger autoimmune disorders, such as lymphocytic hypophysitis, which may lead to CDI [9]. This patient showed no evidence of adenohypophysis insufficiency or pituitary gland abnormalities on MRI, nor were there signs of other autoimmune disorders, making lymphocytic hypophysitis an unlikely explanation. Another possible contributing factor was hypovolemic shock resulting from severe fluid loss and hypotension secondary to a systemic inflammation caused by acute pancreatitis. Although rare, CDI has been reported in cases of severe hemorrhage [10] and in an older diabetic patient with HHS [1]. Similarly, Melegari et al. reported that CDI could be triggered by septic shock, which led to permanent posterior pituitary damage resulting from a cascade of pathological events, including hypotension, exsiccosis, hemoconcentration, and local venous thrombosis [11]. We hypothesize that hypovolemic shock or severe dehydration may have impaired cranial perfusion, disrupting the synthesis, transport, or storage of AVP in the hypothalamus, pituitary stalk, or posterior pituitary. The reoccurrence of hypernatremia with polyuria and low urine specific gravity during her initial admission supports the development of CDI following severe HHS and hypovolemia. Although the exact cause of CDI in this patient remains uncertain, impaired AVP release likely played a key role. Clinicians should consider CDI in patients with prolonged hypernatremia following HHS.

CDI is characterized by hypotonic polyuria due to impaired vasopressin physiology often accompanied by hypernatremia and hyperosmolality if fluid losses are not adequately replaced [12]. Discriminating CDI from primary polydipsia can be challenging. A water deprivation test remains a valuable tool for differential diagnosis. In this case, polyuria was not initially associated with hypotonic urine (maximum specific urine gravity: 1.018) while the patient was on dapagliflozin. However, two days after discontinuing dapagliflozin, hypotonic polyuria became evident, and a water deprivation test confirmed CDI, showing an increase in urine specific gravity from 1.005 to 1.010 and urine osmolality from 19 to 86 mOsm/kg.

Several intriguing features were observed in this patient. During her second admission, she presented with hypernatremia without thirst, but by her third admission, she developed significant polydipsia (up to 10 L/day). This transient adipsia may have resulted from temporary damage to thirst-regulating neurons and osmoreceptors due to hypovolemia, which resolved over time. Additionally, the osmotic diuresis caused by poorly controlled diabetes and the use of SGLT2 inhibitors likely exacerbated her polydipsia and polyuria. SGLT2 inhibitors reduce glucose and sodium reabsorption in the proximal tubule, contributing to osmotic diuresis. A similar case was reported in a patient with adipsic CDI following traumatic brain injury, where empagliflozin obscured low urine osmolality (a relatively high urine osmolality: 529mOsm/kg) and partially attenuated the antidiuretic effect of desmopressin [13]. Five days after discontinuing empagliflozin, a second desmopressin test exhibited a significant reduction in urine volume. Refardt et al. also demonstrated that empagliflozin increased urinary excretion (total urinary excretion of 579 ml ± 194.8 ml in empagliflozin treatment for 8 h versus 367 ml ± 158.8 ml in the placebo group, $p = 0.017$.) in healthy volunteers with artificially induced syndrome of inappropriate antidiuretic hormone secretion by administration of desmopressin [14]. These findings suggest that SGLT2

inhibitors can influence urine osmolality and may slightly reduce the efficacy of desmopressin. Therefore, SGLT2 inhibitors should be discontinued when evaluating urine osmolality to differentiate polyuria.

SGLT2 inhibitors inhibit sodium and glucose reabsorption in the proximal tubule, leading to glycosuria and natriuresis, both of which can affect urine osmolality and contribute to osmotic diuresis. Vasopressin acts on V2 receptor (V2R) in the collecting duct, facilitating water reabsorption via aquaporin-2 (AQP2) channels [15]. Dysregulation of the vasopressin-V2R-AQP2 axis is central to both CDI and nephrogenic diabetes insipidus. Studies in diabetic rats have shown that empagliflozin downregulates AQP2 expression in the kidney [16]. In CDI, the lack of vasopressin release impairs urine concentration, and SGLT2 inhibitors may exacerbate this defect by further downregulation of AQP2. In this patient, the marked increase in polydipsia following dapagliflozin administration supports this hypothesis.

A limitation should be considered in the interpretation of our case. The inability to routinely measure AVP and copeptin levels at our institution, due to both technical limitations and existing clinical protocols, represents a key constraint. This lack of quantitative neuroendocrine data restricts our capacity to establish precise correlation between observed clinical manifestations and their underlying biochemical mechanisms.

In conclusion, CDI should be considered in T2DM patients with persistent hypernatremia following resolution of HHS. SGLT2 inhibitors may complicate the diagnosis and management of CDI by masking hypotonic polyuria and altering urine osmolality. Discontinuation of SGLT2 inhibitors is recommended when evaluating patients with suspected of CDI to ensure accurate diagnosis and effective treatment.

Abbreviations

AVP	Arginine vasopressin
BMI	Body mass index
CDI	Central diabetes insipidus
CSII	Continuous subcutaneous insulin infusion
DI	Diabetes insipidus
GDI	Gestational diabetes insipidus
HHS	Hyperglycemic hyperosmolar state
HbA1C	Glycated hemoglobulin
MRI	Magnetic resonance imaging
SGLT2	Sodium-glucose cotransport 2
T2DM	Type 2 diabetes mellitus

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Author contributions
LS was the major contributor to the writing of the manuscript text. CWQ, MSH and ZYR collected the clinical information and prepared figures and the table. GH and SBY is the main responsible for the patient management and contributed to the writing of the manuscript text. All authors reviewed and approved the final manuscript.

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Data availability
All the data generated and/or analyzed during this study are included in this published article.

Declarations

Consent for publication
Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Competing interests
The authors declare no competing interests.

Ethic approval and consent to participate
The Institutional Ethics Committee of our hospital approved the publication of the case.

Clinical trial number
Not applicable

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