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【 CASE REPORT 】

Hamman Syndrome Caused by a Sodium Glucose Cotransporter 2 Inhibitor in an Elderly Patient with Diabetes Which Mimicked of Boerhaave Syndrome

Kai Korekawa[1], Hiroaki Mitsugashira[2,3], Yoshiyuki Yashima[2] and Takeshi Asakura[2]

Abstract:

A 70-year-old man with diabetes was treated with a sodium glucose cotransporter 2 (SGLT2) inhibitor. He developed vomiting and epigastric pain and was diagnosed with diabetic ketoacidosis (DKA). Computed tomography (CT) revealed mediastinal emphysema. As Boerhaave syndrome could not be ruled out, treatment was initiated in parallel with DKA treatment. After the DKA healed, the mediastinal emphysema disappeared. DKA combined with mediastinal emphysema is known as Hamman syndrome. There have been no reports of Hamman syndrome in elderly patients with diabetes caused by SGLT2 inhibitors. His symptoms mimicked the course of Boerhaave syndrome, and such cases have a high risk of misdiagnosis.

Key words: sodium glucose cotransporter 2 inhibitors, mediastinal emphysema, diabetic ketoacidosis, Hamman syndrome, Boerhaave syndrome

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Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are novel oral hypoglycemic agents with specific mechanisms of action. SGLT2 inhibitors act on SGLT2 in the renal proximal tubules to lower blood glucose levels in an insulin-independent manner by inhibiting glucose reabsorption and promoting the urinary excretion of glucose (1). Diabetic ketoacidosis (DKA) is a serious adverse event associated with the use of SGLT2 inhibitors use (2, 3). DKA should be differentiated when diagnosing acute abdomen, as it frequently produces gastrointestinal symptoms, such as vomiting, abdominal pain, and chest pain (4, 5).

DKA is a common complication and it is relatively easy to diagnose if suspected, as it is characterized by the results of a blood gas analysis and urinalysis. Thus, DKA may be associated with spontaneous mediastinal emphysema. This condition was first described in 1937 and is referred to as Hamman syndrome (6). Two previous studies summarized the clinical features of Hamman syndrome. One report stated that the mean age of onset was 20 years (7), whereas another reported a median age of onset of 41 years (8). In terms of sex, both studies reported that the disease was more common in male patients (7, 8). Although the type of diabetes was not specified in these reports, previous case reports of Hamman syndrome have only described its association with type 1 diabetes (9, 10). However, with the availability of SGLT2 inhibitors, the frequency of DKA occurring at relatively low blood glucose levels in patients with diabetes has increased, without any reports of an association with Hamman syndrome, and the clinical features have not yet been clarified.

When combined with clinical manifestations (vomiting, chest pain, and abdominal pain), the complications of mediastinal emphysema make differentiation from Boerhaave syndrome difficult.

A misdiagnosis must be avoided at all costs in such cases, as Hamman syndrome and Boerhaave syndrome have different treatment strategies, and both diseases can lead to death if the initial treatment is incorrect.

Hamman syndrome has not been reported in older pa-

[1]Department of Gastroenterology, Kesen-numa City Hospital, Japan, [2]Department of Surgery, Kesen-numa City Hospital, Japan and [3]Department of Surgery, Tohoku University Graduate School of Medicine, Japan
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Correspondence to Dr. Kai Korekawa, kai.rekawa@gmail.com

tients with diabetes treated with SGLT2 inhibitor monotherapy. We encountered a case of Hamman syndrome with epidemiological and clinical features that were similar to those of Boerhaave syndrome. Gastroenterologists are expected to encounter Hamman syndrome more frequently in the future, and the concept of this disease should therefore be remembered. In this paper, we report an educational case.

Case Report

A 70-year-old man had been treated for type 2 diabetes for 10 years by a primary physician. He had been taking a SGLT2 inhibitor (canagliflozin hydrate, 100 mg/day) orally for two years. He developed nausea in the morning and experienced vomiting ten times at noon. He then began to experience epigastric pain and visited the emergency department of our hospital in the same evening because of unbearable pain.

The vital signs at presentation were: blood pressure, 162/81 mmHg; heart rate, 130 beats per minute (atrial fibrillation); body temperature, 36.4°C; respiratory rate, 28/min (Kussmaul breathing); and saturation of percutaneous oxygen, 96% (on ambient air). His level of consciousness was determined using the Glasgow Coma Scale (E4V5M6). A physiological examination of the abdomen revealed tenderness in the pericardial area without any symptoms of peritoneal irritation.

We closely examined the patient for acute abdomen. Blood tests revealed hyperglycemia, a blood gas analysis revealed high anion gap metabolic acidosis, and urinalysis showed urinary ketones of 3+ (Table), which led to the diagnosis of DKA. We also noted mediastinal emphysema on computed tomography (CT) (Fig. 1).

The patient vomited several times in quick succession, several hours before visiting our hospital, followed by epigastric pain. The vomiting in the hospital revealed a black liquid; we deduced that an acute esophageal mucosal lesion or Mallory-Weiss syndrome had occurred. Furthermore, considering the CT confirmation of mediastinal emphysema (no subcutaneous emphysema was identified), due to the lack of reports on Hamman syndrome in older patients with diabetes treated with a SGLT2 inhibitor with high lactic acid levels at 2.1 μmmol/L, we also could not rule out Boerhaave syndrome.

Boerhaave syndrome is often associated with pain refractory to analgesics, pleural effusion, and mediastinitis on CT. However, the patient did not present with any of these features. Despite this, we started decompression with a nasogastric tube and antibiotics (tazobactam/piperacillin) for Boerhaave syndrome while treating him mainly with DKA. After consulting with surgeons at the time of the initial consultation, it was decided that surgery would not be performed because of the mild degree of inflammation, even if the patient had Boerhaave syndrome.

We initiated high-volume infusion, continuous insulin administration, and electrolyte correction to treat the DKA. The epigastric pain and nausea improved the day after treatment initiation. On day 10 after admission, the DKA was cured. The total insulin dose required to cure DKA was 97.9 U and the glucose content was 510 g. After the blood tests confirmed that the inflammatory reaction was no longer present, a second CT scan was performed on day 11. Since the mediastinal emphysema had resolved (Fig. 2), esophagogastroduodenoscopy was performed on day 12, which revealed no mucosal damage suggestive of esophageal perforation (Fig. 3a, b). Furthermore, as an esophagogram with amidotriazoic acid did not reveal any leakage into the mediastinum (Fig. 3c, d), the patient was ultimately diagnosed with Hamman syndrome and spontaneous mediastinal emphysema associated with DKA. The course of treatment was good, and the patient was discharged on day 27. The SGLT2 inhibitor was discontinued, insulin therapy was introduced during hospitalization, and the patient continued to be treated for diabetes. Basal bolus insulin therapy was effective, and hemoglobin A1c (HbA1c), improved to 9.2% after one month of treatment and to 7.2% after two months.

Discussion

Our patient had been treated for type 2 diabetes by a primary physician. We re-examined diabetes in parallel with DKA treatment. Anti-glutamic acid decarboxylase (GAD) and anti-insulinoma-associated protein-2 (IA-2) antibodies were negative, and there was no family history of diabetes.

Assessment of insulin secretory capacity showed that the patient was insulin-dependent, with decreased C-peptide levels in the blood and urine. It had been approximately 10 years since he started treatment for type 2 diabetes. However, information regarding his primary physician's diagnosis of type 2 diabetes is not known; assuming type 2 diabetes, becoming insulin-dependent, as in this case within 10 years, is atypical. We suggest that the patient was diagnosed with diabetes 10 years previously when he visited the hospital; however, he had likely developed diabetes much earlier. The relatively rapid course of the disease, which we noted, led us to consider the possibility of fulminant type 1 diabetes as well as type 2 diabetes: a report in 2000 showed that some types of type 1 diabetes manifest negative diabetes-related antibodies, which is also consistent with the characteristics of this case (11). However, assuming fulminant type 1 diabetes, a high HbA1c of 10.1%, as in the present case, was difficult to explain from a pathophysiological point of view and could not be ruled out as type 1 diabetes. Based on these results, it is difficult to determine the type of diabetes in this patient.

DKA can be caused by triggers such as infection, myocardial infarction, or interruption of insulin therapy (12). In the current case, insulin therapy was not administered and the patient had no history of lifestyle deterioration, pancreatic cancer, or acute pancreatitis that could be identified on CT. We strongly suspected that the use of SGLT2 inhibitors in the presence of decreased endogenous insulin secretion

Table. Laboratory Data.

[Blood chemistry]		[Blood gas analysis]	
TP	6.0 g/dL	pH	7.103
Alb	4.0 g/dL	pO_2	150 mmHg
AST (GOT)	22 IU/L	pCO_2	8.6 mmHg
ALT (GPT)	25 IU/L	HCO_3^-	2.7 mEq/L
LD	217 IU/L	BE	-24.5 mEq/L
T-Bil	0.7 mg/dL	Anion gap	30 mEq/L
D-Bil	0.1 mg/dL		
ALP	89 IU/L	[Data related diabetes mellitus]	
BUN	37.3 mg/dL	HbA1c	10.1 %
Cre	1.89 mg/dL	Casual blood glucose	438 mg/dL
eGFR	27.9 mL/min/1.73 m^2	Anti-GAD antibody	<5.0 U/mL
UA	6.5 mg/dL	Anti-IA-2 antibody	<0.6 U/mL
Amylase	638 U/L	C-peptide (serum)	0.1 ng/mL
Lipase	36 U/L	Urinary C-peptide	3.9 μg/day
Na	137 mEq/L	Urinary microalbumin	197.1 μg/dL
K	5.4 mEq/L	Lactic acid	2.1 mmol/L
Cl	87 mEq/L		
Ca	10 mg/dL	[Endocrinology]	
CPK	52 IU/L	TSH	0.41 μIU/mL
CRP	0.46 mg/dL	Free T4	1.16 ng/dL
Posm	332 mOsm/L	Free T3	1.99 ng/dL
T-Chol	124 mg/dL		
HDL-C	49.7 mg/dL	[Urianalysis]	
TG	59 mg/dL	Urine specific gravity	1.025
[Peripheral blood]			
WBC	15,800 cells/μL		
RBC	59.4 $\times 10^4$ cells/μL		
Hb	19.5 g/dL		
Hct	60.3 %		
Plt	174 $\times 10^3$/μL		

TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine transaminase, LD: lactate dehydrogenase, T-Bil: total bilirubin, D-Bil: direct bilirubin, ALP: alkaline phosphatase, BUN: blood urea nitrogen, Cre: creatinine, eGFR: estimated glomerular filtration rate, UA: uric acid, Na: sodium, K: potassium, Cl: chlorine, CPK: creatine phosphorus kinase, Posm: plasma osotic pressure, T-Chol: total cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, Plt: platelet, BE: base excess, HCO_3^-: bicarbonate ion, HbA1c: hemoglobin A1c, Anti-GAD: antibody anti-glutamic acid decarboxylase antibody, Anti-IA-2: antibody anti-insulinoma associated protein-2 antibody, TSH: thyroid stimulating hormone, Free T4: free thyroxin, Free T3: free triodothyronine

had thus been the cause of DKA.

In clinical studies on type 2 diabetes, the incidence of DKA associated with SGLT2 inhibitors was less than 0.1% (13, 14). However, the reported incidence in actual practice is 0.2-0.5%, with a risk of incidence that is 2.2-7 times higher than that of dipeptidyl peptidase4 inhibitors (3, 15, 16). Furthermore, careful monitoring is essential during SGLT2 inhibitor use, as there are reports of an increased risk of DKA in patients with type 2 diabetes over the age of 60, taking SGLT2 inhibitors for >52 weeks (17).

In addition to DKA, a condition termed as euglycemic DKA (euDKA) has also been reported in patients taking SGLT2 inhibitors. To date, no unified diagnostic criteria have been established. However, the condition is considered to present with a blood glucose level below 300 mg/dL and DKA, according to Munro's definition (18). Although hyperglycemia is an important point of suspicion for DKA, we suggest that normal blood glucose levels make the diagnosis of DKA by gastroenterologists even more difficult.

DKA can also cause diabetic pseudo-peritonitis, which causes severe abdominal pain and may require experimental laparotomy (19). In our opinion, the present case most likely had Hamman syndrome, a typical case of DKA. However, in the case of spontaneous mediastinal emphysema in euDKA, making a diagnosis without prior knowledge of Hamman syndrome is much more difficult; the risk of misdiagnosis of Boerhaave syndrome is even higher. Indeed, it is important to note that there has been a report of a patient

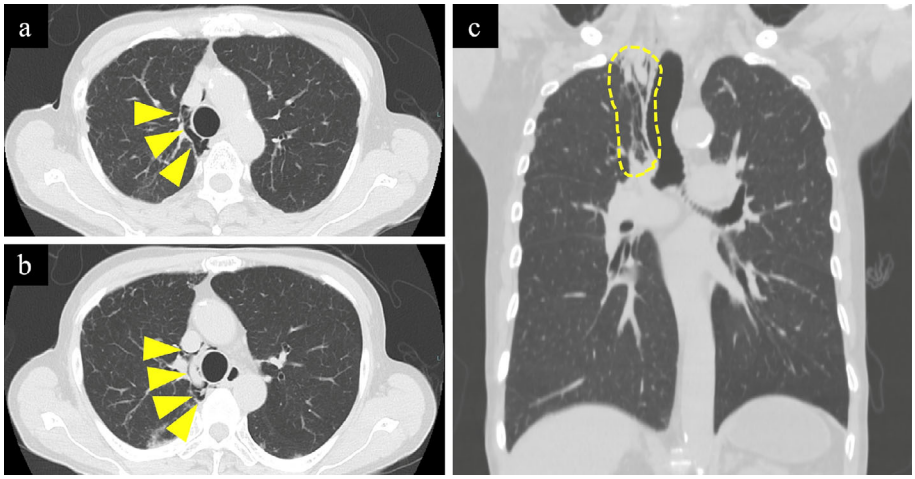

Figure 1. **CT on the day of the hospital visit (day 0). a) Axial view: Lower thoracic esophagus. Mediastinal emphysema could be identified (yellow arrowheads); no findings near the EG junction suggested any perforation. b) Axial view: The mediastinal emphysema extended into the middle thoracic esophagus (yellow arrowheads). c) Coronal view: Mediastinal emphysema was present almost evenly over the entire esophagus (yellow dotted line frame).**

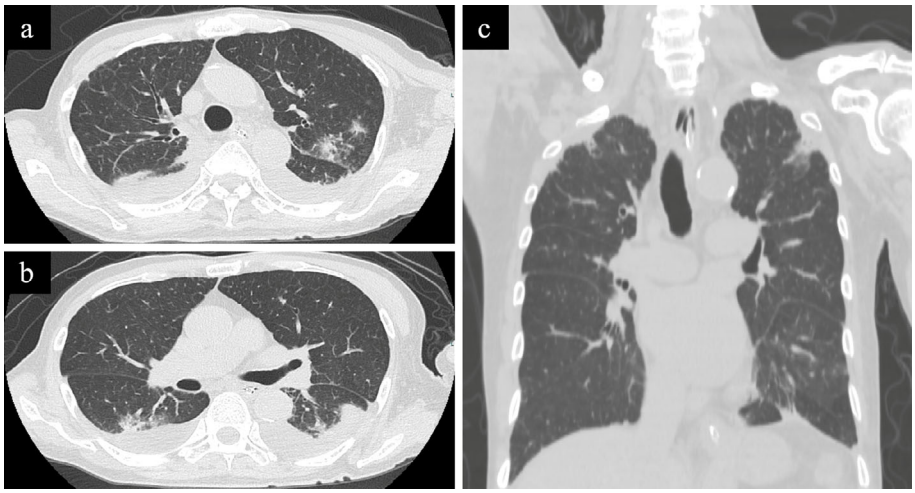

Figure 2. **Follow-up CT (day 11). a) Axial view: Lower thoracic esophagus. The mediastinal emphysema had disappeared, as had the emphysema in the neck of the esophagus. b) Axial view: All emphysema in the mediastinum had disappeared. c) Coronal view: All emphysema in the mediastinum had disappeared.**

with Hamman syndrome who was misdiagnosed with Boerhaave syndrome and thus had his abdomen opened up to undergo exploratory surgery (20). Regarding Boerhaave syndrome, the left wall of the lower third of the esophagus, an anatomically vulnerable site, is the most common site, with some studies reporting 84% (21). Therefore, mediastinal emphysema is expected to be more often distributed in the left mediastinum. The present case of right-sided mediastinal emphysema only showed characteristics different from those of the common Boerhaave syndrome. However, no perforation was observed in the left wall of the esophagus; therefore, the localization of mediastinal emphysema should not be used to differentiate between Hamman syndrome and Boerhaave syndrome.

The mechanisms underlying the development of mediastinal emphysema are still not fully understood. However, the prevailing theory postulates that Kussmaul breathing and frequent vomiting associated with DKA rapidly alter the intrapressure of the thoracic cavity, causing an increase in intra-alveolar pressure, which leads to an alveolar rupture and the development of mediastinal emphysema (22). Kussmaul breathing was observed in the present case, thus suggesting that intrapressure in the thoracic cavity was elevated.

Characteristic physical examination findings include a characteristic auscultatory finding which is called Hamman's sign (a systolic clicking and "crunching" sound) (23). Hamman's sign is typically caused by mediastinal emphysema with cardiac pulsation sounds. In the present case, although auscultation was performed daily until the DKA healed, no sounds were heard. Since mediastinal emphysema was on

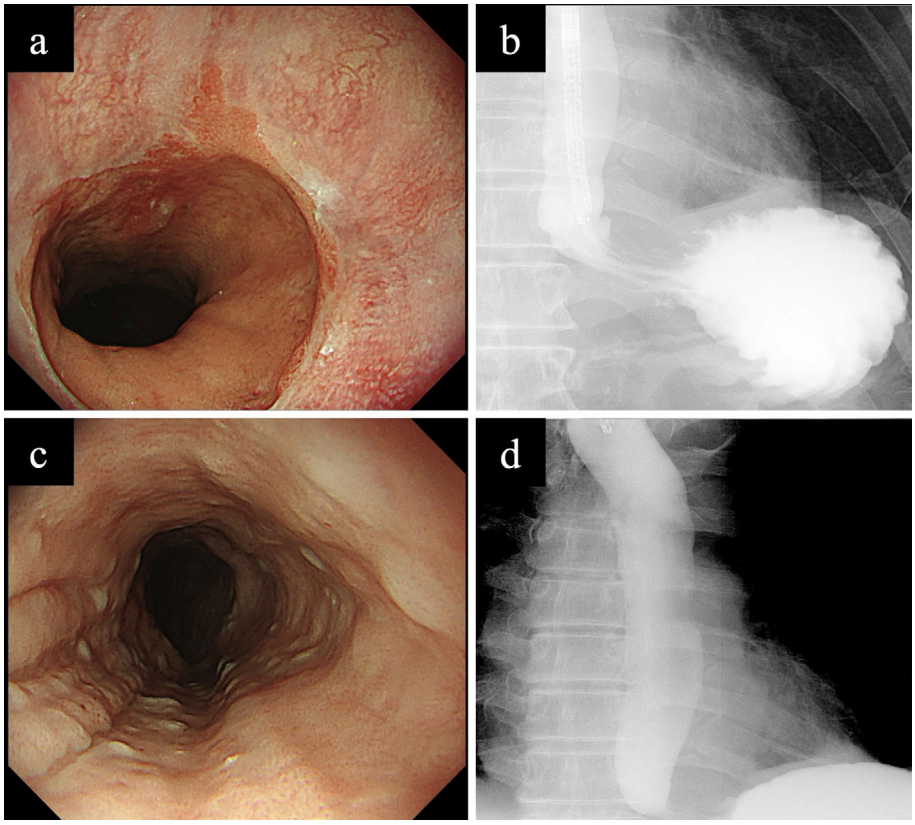

Figure 3. **EGD and esophagography (day 12). a) In Boerhaave syndrome, perforation sites are often present near the EGJ; however, no mucosal injury was found. b) Contrast was performed near the EGJ. No leakage was observed. c) The entire esophagus was observed on EGD. No perforation was observed. d) Contrast from the thoracic esophagus did not reveal any leakage.**

the right side of the upper esophagus, Hamman's sign might not have occurred.

To the best of our knowledge, there are no reports of Hamman syndrome in older patients with diabetes or those receiving long-term treatment with a SGLT2 inhibitor, as in this case. Mediastinal emphysema in patients with Hamman syndrome resolves spontaneously and is self-limiting in all patients without mediastinitis (9). Therefore, DKA is the mainstay of treatment. In the present case, mediastinal emphysema resolved on CT on day 11. However, an earlier review of 40 cases of Hamman syndrome did not report the duration of mediastinal emphysema resolution (8).

Therefore, our experience has identified several issues such as how to appropriately monitor mediastinal emphysema and when it should be differentiated from diseases that produce mediastinal emphysema other than Hamman's syndrome. SGLT2 inhibitors are drugs with expanded indications beyond diabetes, including chronic heart failure (HF) and chronic kidney disease (CKD) (24), and they are increasingly prescribed by physicians who do not specialize in people with diabetes. The incidence of SGLT2 inhibitor-related DKA in patients with CKD and HF, but without diabetes is unknown. Therefore, we suggest that ketoacidosis in patients treated with SGLT2 inhibitors should be assumed in practice. SGLT2 inhibitors have not only increased the chances of encountering DKA but also revealed the presence of multiple factors that could lead to a misdiagnosis, including euDKA and Hamman syndrome. Gastroenterologists who frequently treat patients with abdominal emergencies should ensure that they possess appropriate knowledge to make an accurate diagnosis.

Conclusion

This case provides educational insights into the occurrence of Hamman syndrome in older patients with diabetes and highlights the fact that when Boerhaave syndrome is suspected, Hamman syndrome should always be included in the differential diagnoses.

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

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