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CASE REPORT

Small-intestinal necrosis due to non-occlusive mesenteric ischemia with diabetic ketoacidosis after quetiapine treatment

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Abstract

We report a 66-year-old male who developed diabetic ketoacidosis (DKA) and necrosis of the small intestine due to non-occlusive mesenteric ischemia (NOMI), 3 months after starting quetiapine treatment. He was transferred to our hospital and diagnosed as diabetic for the first time, associated with DKA. Despite improvement in DKA, abdominal pain worsened gradually 10 h after hospitalization. Computed tomography (CT) revealed bowel emphysema, and gas out of the gut wall, in the mesenteric veins and the intrahepatic portal vein, suggesting intestinal necrosis. He survived because of resection of necrotic small-intestinal tissue and he finally required no diabetes treatment. Mesenteric arteries were patent with good palpitation without occlusion or thrombosis, and pathological findings showed ischemic enteritis, which is consistent with NOMI. DKA is a rare but serious side effect of second-generation antipsychotic medications (SGAMs) such as quetiapine, which can result in NOMI: a life-threatening complication. We must keep in mind that the plasma glucose concentration may increase in patients taking SGAMs, or that NOMI may occur concurrently if DKA develops.

Keywords Non-occlusive mesenteric ischemia (NOMI) · Diabetic ketoacidosis (DKA) · Second-generation antipsychotic medications (SGAMs) · Quetiapine

Introduction

Second-generation antipsychotic medications (SGAMs) such as quetiapine have become the main treatment for schizophrenia and delirium instead of classical major tranquilizers such as haloperidol because of their efficacy and lower risk of causing extrapyramidal side effects [1–3]. However, SGAMs also have side effects such as significant weight gain or the development of glucose intolerance. Because these side effects are not recognized sufficiently, SGAMs are often prescribed with little attention given to those complications.

The incidence of SGAM-induced hyperglycemic emergencies is 1–2 events/1000 persons/year of exposure [4]. SGAM-induced diabetic ketoacidosis (DKA) is a critical side effect which shows a mortality prevalence of ≤ 13% [5].

Necrosis of the small intestine is a rare and lethal condition, and is an unusual complication accompanied by DKA. SGAMs have not been reported to be related to mesenteric necrosis. We report a case of DKA and necrosis of the small intestine due to non-occlusive mesenteric ischemia (NOMI) after commencement of SGAM treatment.

Case report

A 66-year-old male was transferred to the emergency room of our hospital due to dizziness and a fall. At the age of 46 years, he had suffered an extradural hematoma after a fall and was diagnosed subsequently with depression. He had visited a psychiatry clinic for treatment of depression and used paroxetine, mianserin, tiapride, suvorexant and ramelteon. His only other comorbidity was internal hemorrhoids. He did not have a history of diabetes mellitus (DM), but he had not undergone a blood test for a long time. The last blood examination (3 years previously) showed a fasting plasma glucose level of 83 mg/dL and glycated hemoglobin (HbA_{1c}) of 6.3% (National

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Glycohemoglobin Standardization Program). His father had suffered from DM.

In June 2017, he had night delirium. Then, 12.5 mg of quetiapine was started from the end of July and increased to 25 mg from the beginning of August. Approximately 2 months after starting quetiapine, he began to feel thirsty and had polyuria. He did not show a current history of infection or common cold. He did not overconsume soft drinks. During these 2 months and until emergency transfer to our hospital, the plasma glucose level and body weight were not measured. His last measurement of body weight was 74 kg before 5 years. However, his waist circumference had increased after starting quetiapine because his trousers felt tighter around the waist. At the end of December, ~ 6 months after starting quetiapine treatment, he fell on his way home from a psychiatry clinic and was transferred to the emergency room of our hospital.

Upon arrival at our hospital, he did not show mental disturbance, but looked drowsy. He was 165-cm tall, weighed 62 kg, and body mass index was 22.8 kg/m^2. Blood pressure was 137/51 mmHg, pulse rate was 68 bpm, body temperature was 36.3 °C, oxygen saturation of peripheral arteries in room air was 98%, and respiratory rate was 20 beats per minute without acetone breath. He had no physical signs except for very mild pain in the left lower quadrant, which was not aggravated by palpation.

The results of laboratory examinations are shown in Table 1. The plasma glucose level was markedly high (1709 mg/dL) and HbA_{1c} was 13.1%. An arterial blood-gas test revealed metabolic acidosis with a profound increase in the anion gap. Urinary ketone was strongly positive, and the

Table 1 The results of laboratory

Urinalysis			Phosphorus	11	mg/dL
Protein	30	mg/dL	Lactate dehydrogenase	276	U/L
Glucose	100	mg/dL	Creatine kinase	3711	U/L
Occult blood	1 +		Creatine kinase-MB	33	U/L
Ketone body	4 +		Total bilirubin	0.4	mg/dL
Arterial blood gas analysis			Aspartate aminotransferase	57	U/L
pH	7.213		Alanine aminotransferase	37	U/L
PaO_2	103.0	mmHg	Alkaline phosphatase	397	U/L
$PaCO_2$	21.8	mmHg	Amylase	265	U/L
HCO_3	8.5	mmol/L	Pancreatic amylase	49	U/L
Base excess	− 18.0	mmol/L	C-reactive protein	2.1	mg/dL
Anion gap	17.0	mmol/L	Plasma glucose	1709	mg/dL
Lactate	4.9	mmol/L	HbA1c	13.1	%
Venous blood test			Serum-C peptide	3.95	ng/mL
White blood cells	10,200	/μL	Immunoreactive insulin	4.8	μIU/mL
Red blood cells	4.30	$\times 10^6$/μL	TSH	0.77	μIU/mL
Hemoglobin	13.5	g/dL	Free thyroxine	1.0	ng/dL
Platelets	201	$\times 10^3$/μL	Adrenocorticotropic hormone	40.9	pg/mL
Total protein	6.4	g/dL	Cortisol	17.2	μg/dL
Albumin	3.7	g/dL	Acetoacetic acid	1783	μmol/L
Total cholesterol	161	mg/dL	3-Hydroxybutyric acid	4090	μmol/L
Triglyceride	189	mg/dL	Total ketone body	5873	μmol/L
Blood urea nitrogen	90	mg/dL	Anti-GAD Ab	< 5.0	U/mL
Creatinine	3.60	mg/dL	Anti-IA-2 Ab	< 0.4	U/mL
Uric acid	16.3	mg/dL	Anti-insulin Ab	< 0.4	U/mL
Sodium	122	mEq/L	Anti-thyroglobulin Ab	≦ 10	IU/mL
Potassium	6.9	mEq/L	Anti-thyroid peroxidase Ab	12	IU/mL
Chloride	78	mEq/L	TSH receptor Ab	≦ 0.3	IU/L
Calcium	8.5	mg/dL			
Glucagon loading test (before discharge)					
<Before loading>			<6 min after loading>		
Serum-C peptide	2.19	ng/mL	Serum-C peptide	4.22	ng/mL
Plasma glucose	112	mg/dL	Plasma glucose	126	mg/dL

TSH thyroid stimulating hormone, *GAD* glutamic acid decarboxylase, *IA-2* insulinoma-associated protein 2

serum concentration of ketone bodies was higher than the upper limit of sensitivity of the simplified bedside ketometer. Laboratory data showed high serum osmolality with low serum levels of sodium, mild increase in inflammatory markers, exacerbation of renal function with high serum levels of potassium and phosphorus, and an increase in levels of pancreatic enzymes. Echocardiography did not show abnormality of cardiac function or collapse of the inferior vena cava. The only abnormal finding was bilateral mild enlargement of the adrenal glands according to thoraco-abdominal computed tomography (CT). Visceral fat area at umbilical slices was 146 cm^2. We diagnosed DM and DKA. He was admitted to an intensive care unit (ICU) for DKA treatment.

We started continuous intravenous infusion of human regular insulin, as well as saline infusion. The next morning, the plasma glucose level had declined gradually to 285 mg/dL and metabolic acidosis was also improved, but abdominal pain had worsened gradually. Repeat CT revealed discontinuous bowel emphysema (Fig. 1a), an increase in CT density in part, and gas out of the gut wall (Fig. 1b). Mesenteric veins and the intrahepatic portal vein also showed gas, suggesting intestinal necrosis. We could not ascertain if the cause of necrosis was mesenteric artery thrombosis or NOMI. Emergency surgery was undertaken before contrast-enhanced CT, because we suspected intestinal perforation. The small intestine had necrotized over a wide area and skip lesions were seen; we carried out partial resection of the small bowel.

Perioperative findings suggested that the cause of the intestinal necrosis was NOMI because the mesenteric arteries were patent with good palpitation without occlusion or thrombosis, and intestinal necrosis was segmental, which was not matched by thrombosis of the superior mesenteric artery. Histology revealed that a discolored part of the small intestine showed erosion, ulcers, bleeding, advanced edema of the submucosa, and infiltration of many inflammatory cells throughout the full thickness of the wall (Fig. 1c). Fibrin precipitation was observed on the serosal surface (Fig. 1d). These findings indicated ischemic enteritis, which is consistent with NOMI pathology, together with the fact that arterial thrombus was not clear microscopically.

After surgery he was given broad-spectrum antibiotics, catecholamines, oxygen, insulin infusion, recombinant thrombomodulin, and continuous hemodialysis filtration with polymyxin B-immobilized fiber for endotoxin absorption. His postoperative condition was good and he was transferred from the ICU to the general ward on postoperative day (POD)2. Continuous intravenous infusion of human regular insulin was switched to subcutaneous insulin administration on the same day. The insulin dose needed to control

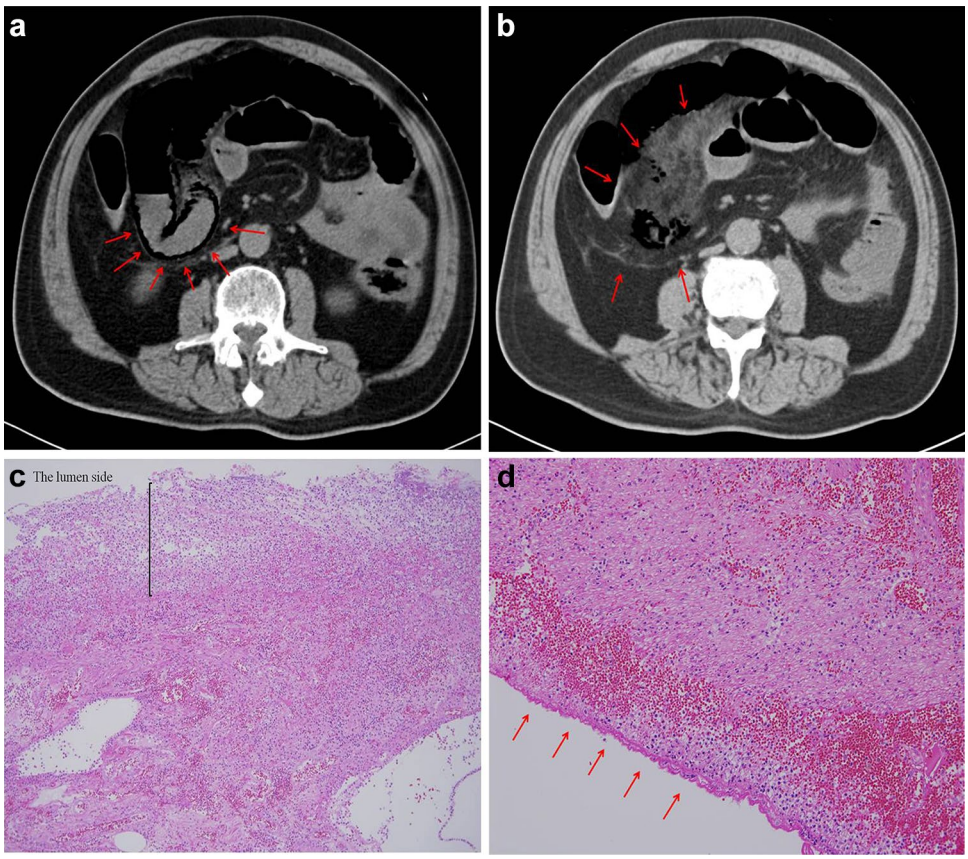

Fig. 1 Computed tomography performed on the second day of hospitalization. Bowel emphysema discontinuously appeared in the small intestine (**a** arrowhead) and an increase in CT density in part and gas out of the gut wall (**b** arrowhead). Pathohistological findings of ulcer lesion in the small intestine show that mucosal epithelium destroyed, advanced edema of the submucosa on the luminal surface (range marking) and infiltration of many inflammatory cells into all layers (**c**: hematoxylin and eosin staining × 20). Fibrin precipitation was observed on the serosal surface (**d** hematoxylin and eosin staining × 10)

the plasma glucose level was reduced gradually, and then insulin therapy stopped at POD18. DM medication was not needed until hospital discharge. The ability to secrete endogenously was maintained by a glucagon loading test (Table 1). Various antibodies for the diagnosis of T1DM were negative (Table 1). In addition, neither diabetic neuropathy, nephropathy nor retinopathy was progressing, and there was no abnormality in adrenal cortical function. Artificial anus closure was carried out in June 2018, and HbA_{1c} was 5.0% without treatment. We concluded that he had type-2 DM, and that the cause of deterioration of glucose tolerance might have been quetiapine. We resumed mianserin alone for treatment of his mental state.

Discussion

We reported a case of intestinal necrosis with DKA caused by quetiapine. Although he showed acute onset of DKA, it was likely that DM had been classified as not type-1 but type-2. Autoantibodies against pancreatic islet-related antigens were negative, insulin was not needed to maintain better control of the plasma glucose level, and the capacity to secrete insulin endogenously was preserved. He had a family history of DM. It was unclear when the plasma glucose level began to increase because laboratory tests had not been done and body weight not measured for ≥ 3 years. We speculated that the onset of overt DM was after quetiapine administration because of increased thirst, polyuria, and an increased waist circumference. The trigger for acute deterioration of DM was not overconsumption of glucose-containing beverages. We considered that quetiapine was a more likely risk factor for DM exacerbation. His past history of obesity and his family history of DM might raise the possibility of quetiapine-induced diabetes.

DKA is an important but relatively rare complication of SGAM use. Only 83 cases of DKA associated with consumption of antipsychotic agents were reported between 1994 and 2015. Olanzapine and clozapine carry a higher risk of increasing plasma glucose levels among SGAMs than quetiapine [6], but the latter continues to carry a risk. Therefore, in Japan, quetiapine is prohibited for use in patients with DM or patients with a family history of DM according to the Medicine Food Station of the Ministry of Health, Labor and Welfare [7].

Several mechanisms have been postulated for hyperglycemia onset by SGAMs. The most common mechanism is antipsychotic agent-induced increase in appetite and weight gain leading to abdominal adiposity and development of insulin resistance and DM [8]. The appetite center in humans is stimulated by 5-hydroxytryptamine-2C receptors, which promote the appetite [9]. Also, intake is increased by suppression of satiety by inhibition of histamine H_1 receptors in the small intestine [10].

Various mechanisms for increasing the blood glucose level other than appetite have been reported. Newcomer et al. showed that SGAMs enhanced insulin resistance [11]. Whether SGAMs can reduce insulin secretion is controversial. Vuk et al. reported that SGAMs that exert strong antagonism of multiple receptors employ multiple mechanisms, leading to the inhibition of insulin secretion from pancreatic islet β-cells [6]. Conversely, Sowell et al. showed no change in insulin-secreting ability even when an olanzapine oral-administration group was compared with a placebo group, indicating that SGAMs did not reduce the ability of insulin secretion directly by acting on pancreatic islet β-cells [12].

Our patient was aware that his waist circumference had increased by the tightness of his trouser waistband after starting quetiapine. Despite a normal body mass index, the visceral fat area at the umbilicus according to CT carried out on the day of hospital admission was increased (146 cm^2). We speculated that the main reason of hyperglycemia was insulin resistance exaggerated by accumulation of visceral fat due to appetite promotion by SGAMs. The mechanism by which SGAMs cause DKA is not known, and it is unclear which type of SGAM, its dose, and period of administration cause progression to DKA. The administration period has been reported to be from 10 days to 4 years from the start of oral administration [13, 14], it was 6 months in our case. DKA can be prevented by measuring the plasma glucose level. Therefore, the American Diabetes Association recommends that the fasting plasma glucose level should be measured at least at the onset, 12 weeks, and 1 year after the first oral administration of SGAMs [15].

Our case showed intestinal necrosis in the clinical course of DKA. An SGAM associated with mesenteric necrosis has never been reported. The possible cause of necrosis of the small intestine is occlusion of the superior mesenteric artery or NOMI. In our patient, the cause of necrosis was not confirmed before emergency surgery. Intraoperative findings indicated that the cause of necrosis was NOMI: the necrotized small intestine was segmental, and mesenteric arteries were not occluded. Pathology, histology and ischemic enteritis also supported NOMI as the cause of necrosis.

NOMI is gastrointestinal ischemia due to vascular spasm without obstruction of organic mesenteric arteries. The diagnosis of NOMI is usually delayed. NOMI shows early symptoms, such as abdominal pain, nausea, vomiting, fatigue, weakness and altered consciousness, but these symptoms are non-specific. There are no characteristic laboratory findings in early-stage NOMI (including blood tests). Several serum markers including lactic dehydrogenase, aspartate transaminase, creatine phosphokinase, alkaline phosphatase, D-dimer, procalcitonin and phosphorus are reported to be

useful for detecting early intestinal ischemia [16–18]. These markers were also measured in our patient, but these parameters were not conclusive but important information. This is one of the reasons why the diagnosis and treatment are often delayed, and NOMI has a mortality prevalence of ≤ 70% [19]. NOMI involves mesenteric under-perfusion due to reactive vascular spasm without demonstrable organic occlusion of the mesenteric arteries. Use of vasoconstrictor agents (e.g., digoxin, catecholamines) or inhibitors of sodium glucose co-transporter-2, long-term hemodialysis, impaired cardiac output, volume depletion, postoperative cardiac surgery, and renal failure are considered to increase the risk of NOMI [20]. Several recent case reports have described NOMI to be associated with DKA [21, 22]. It has been postulated that DKA can cause NOMI due to various factors. Hyperglycemia can cause severe dehydration, decreased vascular volume, low cardiac output, increased blood viscosity and other hemostatic changes resulting in hypoperfusion of mesenteric arteries [23]. There are other reports that DKA activates catecholamines, the renin–angiotensin system [24] and vasopressin excretion [25], which leads to spasms of mesenteric arteries. Because, to our knowledge, this is the first case report about NOMI which was caused by DKA derived from SGAM; whether DKA derived from SGAM may be more likely to develop NOMI or not remains unclear. The patients taking SGAM have increased prevalence of the metabolic syndrome, and Findikli et al. showed that using SGAs may contribute to arterial stiffness [26, 27]. These reports suggested that SGAM user with the development of arteriosclerosis might be more likely to promote the onset of NOMI.

Angiography is most useful for the diagnosis of NOMI, but multidetector-row computed tomography (MDCT) and contrast-enhanced CT can also aid the diagnosis. Mitsuyoshi et al. have proposed a new strategy for the diagnosis of NOMI. They recommend that NOMI should be suspected if three or more of the following four items are noted after cardiovascular surgery or maintenance hemodialysis in older patients: (i) abdominal symptoms (including abdominal pain and nausea) developing in the ileus; (ii) requirement for catecholamine treatment; (iii) an episode of hypotension; (iv) a slow increase in the level of transaminases. They also recommend MDCT if acute insufficiency of mesentery veins/arteries is suspected. In their strategy, continuous intravenous administration of prostaglandin (PG)E1 is the first choice if the diagnosis is NOMI [28]. Similar precautions are necessary if there are scenarios that promote mesenteric ischemia, including dehydration (e.g., DKA). In our case, we chose surgery without intravenous administration of PGE1 because a wide range of intestinal ischemia and intestinal perforation were emergency issues.

The mortality of NOMI has been reported to be extremely high but, in patients with NOMI associated with DKA, it has been reported to be relatively low [29]. The reasons are that patients with NOMI and concurrent DKA are relatively younger than those with just NOMI and do not have coexisting disorders such as cardiovascular complications, and that the time to surgery is ~ 40 h [30]. In our case, the time between hospital admission and the surgical procedure was ~ 10 h. In patients with DKA and NOMI, symptoms such as nausea, vomiting and abdominal pain are similar to each other. Hence, clinicians should pay careful attention for slight changes in symptoms (especially in an unmatched clinical course) to save lives.

In our case, DM might have developed and deteriorated to DKA upon quetiapine administration, which resulted in intestinal necrosis by NOMI through an altered circulation and metabolism. SGAMs might affect the clinical course by other direct or indirect ways. In future, obese patients with accumulated abdominal adiposity with glucose intolerance will increased more, and patients with mental disorder will also similarly increase [31, 32]. Thus, the chance of SGA administration to patients with occult glucose intolerance will be increased more. We must keep in mind that the plasma glucose concentration may increase in patients taking SGAMs, or that NOMI may occur concurrently if DKA develops.

Compliance with ethical standards

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

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained for the publication of the case report.

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