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Two cases of cholangiocarcinoma in diabetes mellitus causing worsening of glycemic control and acute liver dysfunction

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ABSTRACT

This is a report of 2 cases of sudden and simultaneous worsening of glycemic control and acute liver dysfunction (biliary obstruction) suggestive of extrahepatic cholangiocarcinoma (ECC). Case 1 was a 59-year-old woman with a history of diabetes mellitus, hypertension, and hyperlipidemia who had adequate glycemic control for many years but developed worsening of glycemic control and liver dysfunction. Case 2 was a 68-year-old woman with a history of hypertension who developed worsening of glycemic control and liver dysfunction. Laboratory tests and ultrasonography revealed bile duct obstruction and computed tomography of the abdomen revealed distal common bile duct tumors in both cases. After tumor resection and pancreaticoduodenectomy, the pathological analysis revealed an adenocarcinoma in Case 1 and a rare collision cancer (adenocarcinoma and neuroendocrine carcinoma) in Case 2. These cases suggest that ECC should be suspected in patients who develop concomitant worsening of glycemic control and liver dysfunction and reiterate the need for careful clinical and radiological follow-up for the timely diagnosis and appropriate management of such rare neoplasms.

1. Introduction

Several reports of patients with diabetes mellitus (DM) developing pancreatic carcinoma have highlighted a possible cause-and-effect relationship between the 2 conditions [1,2]. However, the presentation of extrahepatic cholangiocarcinoma (ECC) with DM has rarely been reported [3–5]. There is only one report of hyperglycemic emergency in a DM patient with ECC in which it was speculated that “some factor (or factors) produced by the tumor played a role in metabolic decompensation” [6]. This report presents 2 cases in which DM patients experienced simultaneous worsening of glycemic control and liver function. Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

2. Case presentations

2.1. Case 1

A 59-year-old asymptomatic woman with DM and a history of essential hypertension, dyslipidemia, and pituitary apoplexy (from a hypothalamic infarction, 5 years ago) initially presented for routine follow-up at the outpatient clinic in March 2012. The patient had previously reported symptoms of cold and numbness in her right upper and lower limbs. She had no family history of diabetes or cancer. Physical examination showed: weight, 61.0 kg; height, 154.2 cm; body mass index, 25.6 kg/m^2; and blood pressure, 130/70 mmHg. There was no jaundice or icterus. Urinalysis showed trace amounts of glucose, normal urobilinogen, no protein or ketones, and pH 5. Results of a 75-g oral glucose tolerance test (OGTT) were abnormal (Homeostatic Model Assessment for Insulin Resistance, 2.04).

The patient was maintained on an antihypertensive drug (amlodipine 2.5 mg/day), antidiabetic drug (voglibose 0.6 mg/day), lipid-lowering drug (pitavastatin calcium 1 mg/day), and antiplatelet drug (clopidogrel sulfate 50 mg/day) and her glycated hemoglobin (HbA1c) level remained at 6.0–7.0% for 2 years. However, in 2015, her HbA1c level sharply increased to 8.9% despite no subjective symptoms of diabetes (e.g., thirst, polyuria, fatigue, weight loss). Her fasting plasma glucose (FPG) level was 200 mg/dL (Fig. 1A) and her liver function tests were abnormal (serum aspartate transaminase [AST], 163 U/L; alanine transaminase [ALT], 454 U/L; gamma-glutamyl transferase (γ-GTP), 3078 U/L; total bilirubin, 2.4 mg/dL; and serum amylase, 72 U/L (Fig. 1B). Hepatitis B antigen and hepatitis C antibody (third-generation) tests were negative, but her tumor marker levels were elevated (carcinoembryonic antigen, 7.8 μg/mL; cancer antigen, 19-9, 287.9 U/mL). Ultrasonography showed dilation of the intra- and extrahepatic bile ducts and common bile duct (CBD) but no gallstones. She was

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; CBD, common bile duct; DM, diabetes mellitus; ECC, extrahepatic cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; FPG, fasting plasma glucose; γ-GTP, gamma-glutamyl transferase; NEC, neuroendocrine carcinoma

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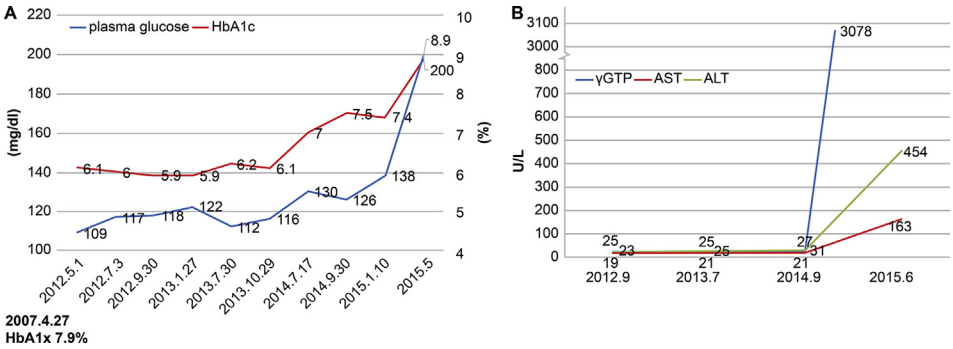

Fig. 1. Longitudinal measurement of (A) plasma glucose, glycated hemoglobin (HbA1c), and (B) liver enzyme levels showing the sudden and simultaneous onset of hyperglycemia and liver dysfunction (Case 1).

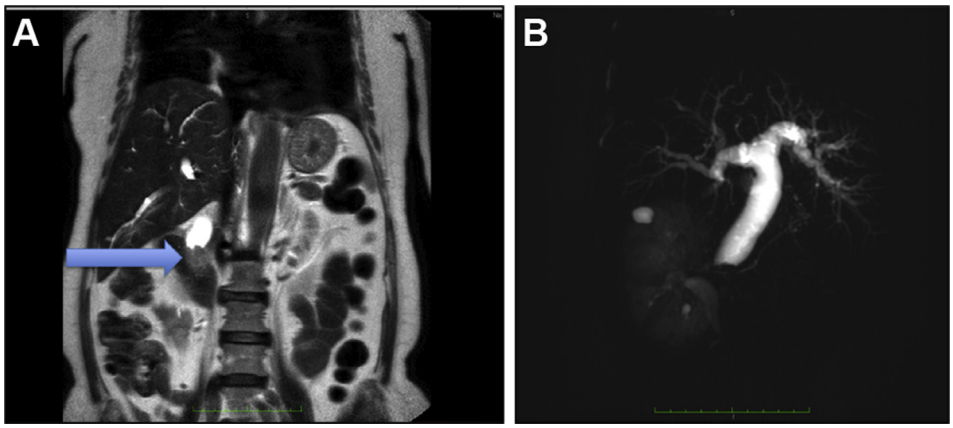

Fig. 2. (A) Magnetic resonance image of the abdomen (coronal plane) showing a 2.4 × 2.1 cm mass (arrow) at the end of the dilated common bile duct. (B) Magnetic resonance cholangiopancreatography showing obstruction of the dilated common duct and a normal appearance of the pancreatic duct (Case 1).

referred to IMS Sapporo Digestive Disease Center General Hospital, Sapporo, Japan, for further evaluation and management. Computed tomography (CT) of her abdomen revealed a 2.4 × 2.1 cm mass at the distal end of the dilated CBD. No abnormalities were detected in the pancreas, pancreatic duct, superior mesenteric vessels, portal vein, or liver. Magnetic resonance imaging (MRI) and endoscopic retrograde cholangiopancreatography (ERCP) confirmed bile duct dilatation with obstruction of the lower bile duct. An endoscopic biopsy showed adenocarcinoma at the distal CBD but no malignant involvement in the proximal bile duct (Fig. 2).

Pancreaticoduodenectomy was performed and the distal bile duct tumor (1.6 × 1.5 cm) was resected. Histopathology of the resected cholangioma showed a well-differentiated adenocarcinoma (Fig. 3) that had invaded the pancreas and duodenum but had not invaded the abdominal aorta or metastasized to the lymph nodes. There were no cancer cells at the resection margins (duodenum and pancreas). No atypical cells were found in the thickened wall of the gallbladder.

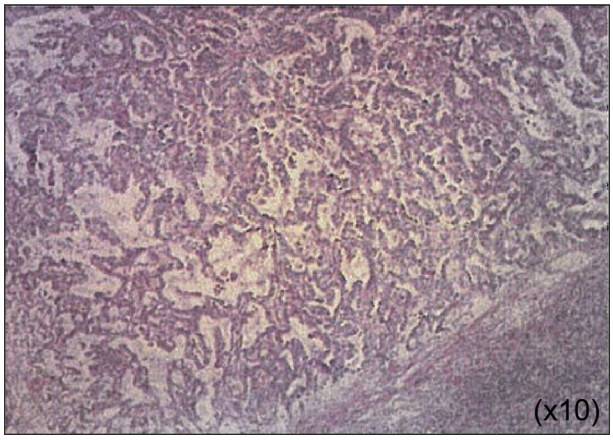

Fig. 3. Histological specimen of the tumor resected from the distal bile duct showing the features of a well-differentiated adenocarcinoma (hematoxylin-eosin stain; original magnification, ×10) (Case 1).

2.2. Case 2

A 68-year-old woman with a history of DM initially presented at the outpatient clinic with a dull occipital headache in April 2010. Physical examination showed: weight, 63.0 kg; height, 151.8 cm; body mass index, 27.3 kg/m^2; and blood pressure, 200/100 mmHg. Urinalysis showed trace amounts of glucose, normal urobilinogen, no protein or ketones, and pH 6. On June 24, 2010, her 1.5-h postprandial plasma glucose level was 285 mg/dL and HbA1c level was 7.8%. On June 30, a 75-g OGTT was performed (0 min: 175 mg/dl, 120 min: 470 mg/dl), and glimepiride (1 mg/day) was started on July 7th, 2010.

Her headache resolved with an antihypertensive agent, and her metabolic profile stabilized at about the 4-month follow-up (FPG, 102 mg/dL; HbA1c, 5.5%; total cholesterol, 191 mg/dL; high-density lipoprotein cholesterol, 50 mg/dL; low-density lipoprotein cholesterol, 107 mg/dL; triglycerides, 169 mg/dL; blood pressure, 138/70 mmHg) on Nov 1, 2010.

The patient was maintained on an antidiabetic drug (glimepiride 1 mg/day), antihypertensive drugs (amlodipine 2.5 mg/day; losartan potassium 50 mg/day; hydrochlorothiazide 12.5 mg/day), and lipid-lowering drug (rosuvastatin 2.5 mg/day) and her laboratory data remained stable for about 4 years. However, in February 2015, her glycemic and hepatic function tests suddenly became abnormal (FPG, 416 mg/dL; HbA1c, 7.8%; total bilirubin, 4.0 mg/dL; alkaline phosphatase,