A Case of Drug-induced Hepatic Injury Associated with Sitagliptin

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Abstract

A 58-year-old man with a 10-year history of type II diabetes mellitus presented with progressive jaundice that began three days before admission. Thorough history-taking revealed that the patient had started on a new medication, sitagliptin, one month previously for the treatment of diabetes mellitus. Laboratory investigations showed severe liver dysfunction. Ultrasonography detected no extrahepatic biliary duct dilatation or gallstones. Abdominal computed tomography excluded pancreatic and hepatic focal lesions. Liver function improved upon discontinuation of sitagliptin. Drugs are an important, often unrecognized, cause of acute liver injury. This report presents a rare case in which sitagliptin was responsible for acute hepatic damage. As demonstrated, a thorough drug history is helpful in any case of unexplained liver injury.

Key words: sitagliptin, acute liver injury, electron microscopy

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Introduction

A progressive increase in the prevalence of type II diabetes mellitus has occurred over the past decade. The availability of various oral hypoglycemics has given rise to several adverse effects. Sitagliptin, is in a new class of oral anti-hyperglycemic known as dipeptidyl-peptidase (DPP)-4 inhibitors, or incretin enhancers. It is used for the treatment of type II diabetes mellitus, and it inhibits DPP-4 enzyme-induced inactivation and degradation of incretin hormones. The enhanced incretin action stimulates insulin release and decreases glucagon secretion, thereby lowering hemoglobin A1c and lowering fasting and postprandial glucose levels (1). In clinical practice, drug-induced liver injury is not a common condition in patients taking medications (2). We report this rare case of drug-induced liver injury caused by sitagliptin.

Case Report

A 58-year-old man was admitted to our hospital with progressive jaundice. He had a 10-year history of diabetes mellitus and had been treated with a regimen of glimepiride 3 mg daily and acarbose 300 mg daily, in addition to dietary and lifestyle modifications. He had drunk about 40 g/day alcohol for 10 years. Because of inadequate control of blood glucose levels, sitagliptin 100 mg daily had been started one month before presentation at our hospital. After one month of sitagliptin treatment, the patient started to develop persistent fever and nausea. He visited the local hospital. Because of the poor control of blood glucose, he was initiated on insulin 30 U/day in two divided doses. Three days before presentation at that hospital, he noticed yellowish discoloration of his eyes, and subsequently noticed darker urine and lighter colored stools. He was referred to our hospital...
for additional investigation of jaundice. On admission to our hospital, physical examination showed severe mucocutaneous jaundice. He had no eruption. His body temperature was 36.6 °C. His pulse rate was 78 beats/min, with respiration rate of 16/min and blood pressure of 117/80 mmHg. He was 178.5 cm tall, weighing 104.3 kg, with a BMI of 32.7. His abdomen was slightly distended. The liver was enlarged to 3 cm below the right costal margin; although firm, it was not tender. Blood tests showed the following: white cell count of 6.30×10^3 cells/mm^3 (neutrophil 54.4%, lymphocyte 31.2%, monocyte 12.5%, and eosinophil 1.3%), red blood cell count 588×10^4 cells/μL, hemoglobin 17.7 g/dL, prothrombin time 87%, and C-reactive protein (CRP) 0.91 mg/dL. Results of urinalysis were specific gravity 1.40 g/mL, pH 5.5, sugar >1,000, protein 100, ketone 1+, bilirubin 3+, and urobilinogen +/-. Total/direct bilirubin was 11.8/9.4 mg/dL, serum aspartate aminotransferase (AST) 1,318 IU/L, alanine aminotransferase (ALT) 1,653 IU/L, alkaline phosphatase (ALP) 814 IU/L, γ-glutamyl transpeptidase (GTP) 369 IU/L, blood urea nitrogen 8.3 mg/dL, creatinine 0.7 mg/dL, blood glucose 249 mg/dL (normal range: 70-109), and HbA1c 11.8% (normal range: 4.3-5.8) (Table 1). Pancreatic enzymes were within normal limits. Viral hepatitis serology was negative for hepatitis A virus (HAV), hepatitis B virus (HBV), but positive for hepatitis C virus (HCV). The HCV (genotype 1b) TaqMan PCR was 7.6 (normal range: <1.2) log IU/mL. Ultrasonographic evaluation showed no evidence of dilated intrahepatic or dilated extrahepatic biliary ducts. Computed tomography (CT) (axial image) demonstrated gallbladder wall thickening, lumen narrowing, no mass lesion on admission (Fig. 1a) and slight gallbladder wall thickening, lumen narrowing, with no mass lesion and 2-7 mm gallstones 6 months later. The liver-tospleen (L/S) ratio of CT was 1.0. Magnetic resonance cholangiopancreatography (MRCP) was performed, revealing irregular gall bladder wall thickening with a dark stone impacted in the neck of the gall bladder, but no stone was detected in the common bile duct. No extrahepatic biliary duct dilatation was detected (Fig. 1b).

Therefore, the impaired hepatic function was not caused by extrahepatic injury but by liver damage. After a detailed and thorough review of the patient’s history, the recent addition of sitagliptin for treatment of diabetes mellitus was suspected as the cause of liver injury. A drug-induced lymphocyte stimulation (DLST) test for sitagliptin showed a negative DLST index: 102% (<179%). A liver biopsy revealed edematous and pigmented hepatocytes around the central vein. Acute hepatocellular injury was observed as isolated (spotty necrosis), confluent necrosis, and hepatocyte pigmentation (Fig. 2a, 2b) around zone 3, with confluent and
piecemeal necrosis and confluent droplet in the portal tract (Fig. 2c, 2d). Evidence of hepatitis C infection was found in the form of portal inflammation and periportal piecemeal necrosis (Fig. 2a), but scant steatosis (Fig. 2a). These findings were consistent with drug-induced liver injury concomitant with hepatitis C. To investigate the hepatocyte pigmentation further, electron microscopy was performed. An electron microphotograph showed dilated canaliculi with deposition of bile substances, accompanied by a huge dilatation of bile canaliculi extending into the liver cell hyaloplasm (Fig. 3a, 3b). Moreover, another electron micrograph showed a pseudo-bile ductule. The adjacent bile canaliculus (Fig. 3a, 3b). Additionally, a pseudo-bile ductule was identified in the hybrid bile canaliculus extending into the liver cell hyaloplasm (Fig. 3a, 3b). Moreover, another electron micrograph showed a pseudo-bile ductule. The adjacent bile canaliculus was dilated with loss of microvilli, and thickened pericanalicular webs (supplemental data). This case showed mixed-type drug-induced hepatic injury.

The newly initiated sitagliptin was strongly suspected to be responsible for the patient’s condition. The drug-induced hepatitis status evaluation (3) gave a score of 5, which means “possible.” The progressive improvement in the patient’s condition was attributed to the discontinuation of his oral hypoglycemic medication and the start of insulin therapy for the control of blood glucose. Five days after admission, the patient’s general condition improved dramatically, but the serum bilirubin level continued to increase gradually. On the 10th hospital day, he underwent plasma exchange and dialysis for bilirubin absorption (4).

He was subsequently discharged from the hospital with the recommendation of regular follow-up for serum bilirubin and transaminases. One month after discharge, the patient’s laboratory results revealed normalization of serum bilirubin and hepatic transaminase levels. However, the serum alkaline phosphatase level normalized after two months (Fig. 4).

Discussion

Drugs are an important, often unrecognized, cause of acute liver injury. Clinicians should take detailed and thorough drug history information for any patient presenting with acute hepatic injury. Discontinuation of the offending agent will bring dramatic improvement in symptoms, and prevent adverse outcomes (2). A search of the Japanese literature (JMEDPlu) and international literature (MEDLINE) identified only a single report of elevated hepatic transaminases associated with sitagliptin monotherapy (5). The drug-induced hepatitis score (3) was evaluated to be 5: possible. A scoring system will categorize the suspicion as “definite or highly probable,” except for hepatitis C, and alcohol in this case.

In contrast, clinical trials of sitagliptin monotherapy or in combination with other oral hypoglycemic agents have indicated no change or a slight decrease from the baseline in AST or ALT with sitagliptin treatment (6, 7).

These reports include drug-induced liver injury associated with a high background rate of hepatitis C infection in diabetic patients (8, 9). A wide variety of drugs are capable of causing drug-induced liver injury (3). Cholestasis is occasionally encountered in patients with diabetes receiving sulfonylureas, especially glimepiride (10). Dipeptidyl peptidase 4 is a ubiquitous cell membrane protein expressed in many tissues and cells including lymphocytes, which has raised some concerns about the long-term effects of DPP4 inhibitors, especially on immune functions (11). In the case of type II diabetes mellitus, the nature of the disorder itself predisposes an increased risk of several organ-specific complications that might be exacerbated by drug treatment.
These include drug-induced liver injury associated with a high background rate of hepatitis C infection. Patients with type II diabetes mellitus have a high incidence of non-alcoholic fatty liver disease, and several antidiabetic agents such as acarbose, gliclazide, and metformin have been associated with drug-induced liver injury (12). In the liver, Hyaluronic acid (HA) is mostly synthesized by the hepatic stellate cells and degraded by the sinusoidal endothelial cells. HA levels are increased in chronic liver diseases (13). HA has also the potential for clinical use for detecting the earliest changes following liver injury, for screening drugs, and as a means of identifying agents that protect against liver injury (14).

Overtly drug-induced hepatotoxicity has not been reported from the use of sitagliptin. This report is the first in the relevant literature of sitagliptin-induced acute hepatocellular injury manifesting progressive jaundice for which a clear causative relation was demonstrated. Drug-induced liver injury should be suspected in any patient with type II diabetes mellitus using oral hypoglycemic agents presenting with unexplained hepatic injury. A thorough drug history should be recorded by the practitioner in any case of unexplained cholestasis. Recovery is common in these cases provided that the drug is identified and discontinued. The features of liver histology in drug-induced hepatitis are as follows: 1. demarcated perivenular (acinar zone 3) necrosis, 2. minimal hepatitis with canalicular cholestasis, 3. poorly developed portal inflammatory reaction, 4. abundant neutrophils, 5. abundant eosinophils, and 6. epithelioid-cell granulomas (15). However, liver histology in drug-induced liver injury might not be diagnostic in the majority of cases. Moreover, although centrilocular necrosis with minimal portal inflammation is characteristic of drug-induced liver injury, similar histological features can be seen in acute-onset autoimmune hepatitis. Plasma cell infiltration in portal tracts, which is often prominent in autoimmune hepatitis, might be helpful for the differential diagnosis in such cases.

In the present case, small stones might have passed from the gall bladder into the bile ducts from CT and MRCP. Mechanical obstruction of the large bile ducts results in a classic trio of portal tract changes: connective tissue edema, bile ductular proliferation, and neutrophil infiltrates. The term currently favored for these reactive portal changes in biliary disease is ductular reaction (16). This case had no slight ductular reaction. The ultrastructure of the liver in intrahepatic and extrahepatic cholestasis in humans, as investigated extensively using conventional electron microscopy, does not assist in the differential diagnosis between these two conditions (17).

The major role of histological examination is therefore to exclude other possible causes of liver injury, rather than to make a final diagnosis of drug-induced liver injury. When
using light microscopy, the liver specimen showed the presence of bile pigment in bile canaliculi and hepatocytic alterations predominantly involving the bile secretory apparatus of liver cells, especially centrilobular hepatocytes. Electron microscopy revealed bile canicular changes of cholestatic liver include liver cells arranged in pseudo-bile ductile, dilatation and ramification of bile canaliculi, disappearance and edema of microvilli, thickening of ectoplasm, and alterations of microfilaments. Diverticula from canaliculi extended into hepatocytes are observed in all forms of cholestasis (18, 19). Ultrastructural findings showed intrahepatic cholestasis. It is possible that the concomitant hepatitis C predisposed the patient to develop hepatitis.

In conclusion, we describe a rare case of sitagliptin-associated liver injury, which calls for caution in the use of sitagliptin. All patients receiving sitagliptin should have their liver function assessed periodically, especially if they have a history of liver disease. Sitagliptin administration should be discontinued immediately at the onset of abnormal liver function.

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

References
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