Beneficial Effects of Pioglitazone on Cholangiohepatitis Induced by Bile Duct Carcinoma

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Abstract

Cholangiocarcinoma is a predominantly fatal cancer, which can be difficult to treat. We report a 73-year-old man who developed cholangiocarcinoma with cholangiohepatitis and diabetes. Administration of pioglitazone, peroxisome proliferator-activated receptor γ (PPARγ) agonist, improved not only diabetic control, but also the tumor-induced cholangiohepatitis, and improved the patient’s quality of life. Although he finally died of obstructive jaundice, thiazolidinedione should be considered for treatment of tumor-induced hepatitis in the presence of diabetes, unless severe side effects occur.

Key words: PPAR, cholangiocarcinoma, pioglitazone, diabetes, thiazolidinedione

Introduction

Pioglitazone is one pharmacological ligand for PPARγ and it has been shown to increase insulin sensitivity in patients with diabetes (1). The action of the ligand is initiated through binding to its nuclear receptors and gene activation (2). In addition to the increase in insulin sensitivity, a variety of pharmacological effects of the ligand have been reported. The PPARγ ligand prevents cancer formation, atherosclerosis, cytokine-induced inflammation, and non-alcoholic steatohepatitis (NASH), although the precise molecular mechanisms of these effects are unknown (3, 4). Cholangiocarcinoma is a predominantly fatal cancer, which can be difficult to treat (5). Complete resection is the only cure for cholangiocarcinoma. To date, the results of chemotherapy and radiotherapy have been disappointing.

Here, we report a patient with cholangiocarcinoma whose biochemical evidence of cholangiohepatocellular injury, diabetes, and tumor markers were improved by treatment with pioglitazone. Although the patient eventually died of obstructive jaundice, his plasma glucose level, tumor progression, and hepatic damage were controlled well by the PPARγ ligand. This ligand may be useful for the management of cancers unless side effects are a critical issue.

Case Report

A 60-year-old man received routine medical care for diabetes in our outpatient clinic. Familial and past histories were not remarkable. Fair diabetic control was maintained with 60 mg gliclazide daily until March 2003 at the age of 73. There were no diabetic complications. Fair diabetic control was maintained with 60 mg gliclazide daily until March 2003 at the age of 73. There were no diabetic complications. Between March and April 2003, the patient showed a weight loss of 2 kg with deterioration of diabetic control. Although the concentration of carbohydrate antigen 19-9 (CA19-9) was within the normal range, abdominal ultrasonography demonstrated a solitary space-occupying lesion in the liver. Further examinations with CT and MRI indicated cholangiocarcinoma of the liver. Between March and August 2003, the concentrations of hepatic enzymes and CA19-9 increased abruptly, while his diabetes worsened. There were no lymph metastases or distant metastases detected on CT and MRI and the tumor was considered curatively resectable. However, the patient refused surgical treatment. We recommended insulin injection as a treatment for diabetic control. However, he also refused insulin injection because of the complexity of the self-injection procedure. The potential side effects of pioglitazone administration, especially the risk of pioglitazone-induced hepatitis, were fully explained to the

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the dose of pioglitazone to 45 mg on July 5, 2005. How-

ever, there was no change in the elevated hepatic enzyme concentrations. Thus, we discontinued pioglitazone administration because it was possibly the cause of hepatitis. The patient was admitted to our hospital and began insulin injection to control the plasma glucose level. The elevation of CA19-9 and the hepatic enzymes including ALP persisted, and the serum concentration of direct bilirubin increased. Percutaneous transhepatic cholangiography and drainage was considered in order to relieve obstruction of the bile duct. As several obstructive lesions in the hepatic bile ducts were observed on CT, we judged that the procedure would not improve the obstructive jaundice. He was discharged without palliative therapy 2 weeks after control of the plasma glucose level was achieved with insulin injection. One month later, the patient was re-admitted because of diarrhea probably due to obstructive jaundice, and he died on November 11, 2005.

Autopsy showed that the main cause of death was ob-

structive jaundice due to intrahepatic highly differentiated cholangiocarcinoma at the hilum of the liver (Fig. 3). Components of multicystic intraductal adenoma/adenocarcinoma were seen frequently, suggesting that invasive carcinoma had arisen from bile duct cystadenocarcinoma. The cancer cells were immunohistochemically positive for anti-CA19-9 anti-

Fig. 1a. Serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidase (γ-GTP) and alkaline phosphatase (ALP) from March 2003 through September 2004 are shown in the upper panel. The HbA1c and serum concentration of CA19-9 are shown in the lower panel.

Fig. 1b. The serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidase (γ-GTP) and alkaline phosphatase (ALP) from September 2004 through August 2005 are shown in the upper panel. The HbA1c and serum concentration of CA19-9 are shown in the lower panel.
Fig. 2. MRIs in July 2003 (a), March 2004 (b), and March 2005 (c), showed the tumor in the liver. There were no remarkable changes in tumor size between (a) and (b). Overt progression can be seen in (c).

Discussion

At the first screening, tumor was identified in the liver. As markers of cholangiohepatic injury, the hepatic enzyme concentrations were elevated with an increase in CA19-9 concentration (7). These data suggest that cholangiohepatitis may have been induced by the progression of cholangiocarcinoma. Abnormal elevation of the serum concentration of hepatic enzymes between April and July 2003 was suppressed by daily treatment with 15 mg of pioglitazone. It has been reported that 15 mg or a lower dose of pioglitazone is clinically sufficient to achieve pharmacological effects including diabetic control (8). In contrast to the effect on the initial elevation, re-elevation after September 2004 was unaffected by the agent. The difference in responses to pioglitazone suggests that different mechanisms underlying cholangiohepatitis development were present in this case.

CA 19-9 is a tumor marker that is predominantly expressed in pancreatic, gastric and colon cancers (9). Thiazolidinedione was initially reported to suppress prostate specific antigen as a circulating tumor marker for prostate cancer (10). This is the first report indicating that the agent may directly suppress the CA19-9 level originating from cholangiocarcinoma. The CA19-9 is a glycogenic protein, which may be affected by the plasma glucose concentration (11). During the suppression of CA19-9 concentration by pioglitazone, the agent also controlled the plasma glucose level. Thus, it is possible that suppression of CA19-9 may have been due to a decrease in the plasma glucose level.

However, suppression of the serum concentration of hepatic enzymes indicated that the tumor-induced cholangiohepatitis was improved by treatment with this agent. Moreover, medical care was possible without insulin injection, cytotoxic chemotherapy, and/or liver protecting agents. As a result, we could improve the patient’s quality of life by administration of pioglitazone.

Although the molecular mechanisms of the PPAR ligands have been clarified, the biological effects of the ligand, especially the anti-carcinogenesis effect of the ligand, remain controversial (12). Thiazolidinediones inhibit growth and produce terminal differentiation of human tumor cells (13). Recently, it was reported that pioglitazone could suppress proliferation and induce apoptosis in cholangiocarcinoma cell lines (14). However, two studies showed that PPARγ activator promoted colon tumor and polyp development in mice (15, 16). Clinically, thiazolidinediones are reported to be useful as suppressive agents against malignant tumors including breast and prostate cancers as well as liposarcoma (17-20).

As increased ALP is not observed in subjects with fatty liver, the elevated ALP in this case was probably due to tumor-mediated cholangiohepatitis. Moreover, the autopsy findings demonstrated that there was no evidence of fatty liver or NASH, suggesting that hepatic injury was at least in part associated with cholangiocarcinoma in this case. Furthermore, the PPARγ ligand is reported to be useful for the treatment of NASH (21). Taken together, we consider that there are two possible mechanisms to explain the initial improvement of hepatitis: the PPARγ ligand may have directly suppressed the abnormal cell growth, or the PPARγ ligand may have indirectly suppressed tumor growth after the ligand improved hepatitis and/or diabetes.

The re-elevation of the hepatic enzymes was not suppressed despite raising the dose of the agent. Elevated serum
concentration of CA19-9 has been reported in a case of biliary obstruction (22). Thus, we speculate that the re-elevation may have mainly been due to mechanical obstruction of the bile duct by the tumor, or that the agent itself promoted tumor progression during the terminal stages.

In conclusion, the PPARγ ligand improved the diabetes but also suppressed the hepatitis along with the malignant tumors. We recommend thiazolidinediones to improve diabetic condition and tumor-induced hepatitis, unless serious side effects develop.

References


