Hepatic Xanthoma Associated with Pasireotide Administration: A First Case Report

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Abstract

Hepatic xanthoma is an extremely rare lesion worldwide. We herein present a case of hepatic xanthoma that developed in a 27-year-old Taiwanese man who had participated in a clinical trial of pasireotide. This is, to the best of our knowledge, the first case of pasireotide-induced hepatic xanthoma. Following discontinuation of the drug, the tumor continued to decrease in size (98.2% decrease in tumor volume). We suggest that, in patients receiving pasireotide, the liver should be checked using periodic radiological examinations, even if the patient does not exhibit any risk factors, and that medical or surgical intervention may not be needed.

Key words: hepatic xanthoma, pasireotide


Introduction

Xanthomas are rare, benign and asymptomatic lesions (1, 2) that often occur in the digestive system. The possible risk factors for xanthomas include homozygous familial hypercholesterolemia (3) and hyperlipidemia (4). The incidence of upper gastrointestinal (UGI) xanthomas was reported to be 0.23% among 7,320 patients based on the results of UGI endoscopy (1). The most common location of UGI xanthomas is the stomach (76%), followed by the esophagus (12%) and duodenum (12%) (1). Meanwhile, hepatic xanthomas are extremely rare lesions, and the present case is, to the best of our knowledge, only the second case reported in the literature and the first case of pasireotide-induced formation of a hepatic xanthoma. The previous case was that of a 61-year-old Korean woman with a history of multiple myeloma, hyperlipidemia, fatty liver disease, viral hepatitis, homozygous familial hypercholesterolemia or any hereditary metabolic storage disorders. There were no significant findings from his family history. He denied having a smoking or drinking habit or taking any other drugs before or after exposure to pasireotide.

Case Report

The patient was a 27-year-old Taiwanese man (height: 176 cm, weight: 80 kg, BMI: 25.8) who had normal health before he entered a clinical trial for pasireotide. He had no history of diabetes mellitus, hyperlipidemia, fatty liver disease, viral hepatitis, homozygous familial hypercholesterolemia or any hereditary metabolic storage disorders. There were no significant findings from his family history. He denied having a smoking or drinking habit or taking any other drugs before or after exposure to pasireotide.

The patient was asymptomatic with no signs of a poor appetite, fatigue, abdominal pain, nausea, general malaise, weight loss, skin xanthomas, fever or yellow skin discoloration before the clinical trial. Approximately one and five months prior to the clinical trial, he received a series of examinations that showed negative serology results and no size of the lesion gradually decreased without any medical or surgical treatment. Although surgical intervention may not be necessary, conservative observation with psychological support for the patient’s mental well-being is recommended.
signs of fatty liver or hepatic lesions on abdominal sonography (Fig. 1a).

The clinical trial was a single-center, open-label phase I study conducted to assess the pharmacokinetics and safety of single and multiple doses of subcutaneously injected and single doses of long-acting release (LAR) formulations of pasireotide in healthy Taiwanese male volunteers. The clinical trial lasted 33 days. Before the study started, the protocol was approved by the Institutional Review Board, and informed consent was obtained from all participants. In the clinical trial, a total of 45 male volunteers were randomized to receive one of nine treatment regimens, with five volunteers per regimen.

Our patient followed a treatment regimen in which his first dose was a single s.c. dose of 900 μg of pasireotide on day 1, followed by a 2-week washout period from days 1 to 14. This was followed by multiple s.c. doses of 900 μg bid (twice a day) on days 15 to 18. Another single s.c. dose of 900 μg was given on the morning of day 19, followed by a 2-week washout period from days 19 to 32. The final administration was a single intramuscular (i.m.) dose of 40 mg of pasireotide LAR on day 33.

Approximately three months after the first day of the trial, abdominal sonography performed during a follow-up visit revealed a homogeneous hypoechoic mass-like lesion with an irregular shape in segment 6 over the right lobe of the liver (Fig. 1b). For diagnostic purposes, abdominal computed tomography (CT) with contrast enhancement was performed. The lesion (approximately 3.8×3.0×3.0 cm) (Fig. 2a, b) showed poor contrast enhancement on arterial phase and delayed phase images. This made a diagnosis of hepatocellular carcinoma or hemangioma unlikely; however, cholangiocarcinoma, metastatic tumors and inflammatory pseudotumors could not be ruled out. On abdominal T1WI, T2WI and diffusion weighted image (DWI) magnetic resonance imaging (MRI) images, the lesion presented with hypointensity (Fig. 3a-c). The findings were highly indicative of an inflammatory pseudotumor, although cholangiocarcinoma could not be ruled out. The tumor marker levels were unremarkable (Alphafetoprotein: <3.00 ng/mL, Carcinoembryonic antigen: 1.12 ng/mL, Carbohydrate antigen 19-9: <1.00 unit/mL), and the results of a diagnostic tumor biopsy with a histological examination revealed extensive, foamy histiocytic aggregation (Fig. 4a-d). Positive CD68 staining of the histiocytes led to the final diagnosis of xanthomatous foamy histiocytic infiltration. After making the diagnosis, the patient received close follow-up attention with no medical or surgical intervention.
At the 6-month follow-up examination, an MRI image showed that the lesion had decreased in size from 3.8×3.0×3.0 cm to 1.8×1.3×1.4 cm (Fig. 3b). At the 10-month follow-up, the tumor had continued to decrease in size and measured only 1.5×0.8×0.5 cm (Fig. 3c).

**Discussion**

Pasireotide (6, 7), a multireceptor ligand somatostatin analogue, is a cyclohexapeptide engineered to bind to somatostatin receptor subtypes 1, 2, 3 and 5 and mimics the action of natural somatostatin. In the clinical setting, octreotide shows poor efficacy for treating Cushing’s disease and some carcinoid tumors. Compared with octreotide, pasireotide has an *in vitro* binding affinity that is 40-, 30- and 5-fold higher for somatostatin receptor subtypes 5, 1 and 3, respectively. Pasireotide potently suppresses growth hormone (GH), insulin-like growth factor (IGF)-I and adrenocorticotropic hormone (ACTH) secretion, indicating that it has potential efficacy for treating acromegaly, Cushing’s disease and gastroenteropancreatic neuroendocrine tumors resistant or refractory to octreotide (7). Moreover, *in vitro* studies...
with pasireotide have shown that the drug has both direct and indirect antitumor activity and significantly inhibits vascular endothelial growth factor (VEGF)-stimulated proliferation in human endothelial cells, suggesting that it may have a role in antiangiogenic therapy different from that of octreotide (7). Due to the above advantages, pasireotide is likely to be widely used in the future. Pasireotide elimination occurs primarily via hepatic clearance. Pasireotide is also associated with elevated fasting and postprandial plasma glucose levels, decreased cholecystokinin levels and dose-dependent increases in stool fat (8). The most common adverse effects of pasireotide given subcutaneously or intramuscularly are gastrointestinal symptoms, including mild diarrhea (58%) and nausea (52%), as well as hyperglycemia-related events (40%), cholicolithiasis (30%) and transient elevated liver enzymes (29%) (8). However, no hyperlipidemia or formation of hepatic xanthoma has been previously reported in the literature.

Hepatic xanthomas are extremely rare lesions. Like all upper gastrointestinal tract xanthomas, they are asymptomatic. The diagnosis of these tumors is based on histological examinations of liver tissue biopsies, in which the lesions appear as clusters of large foamy cells, termed xanthomatous. The diagnosis of these tumors is based on histological examination, the incidence, risk factors, mortality rate and true etiology of hepatic xanthoma remain unknown. However, as indicated in other published studies, treatment with Sandostatin LAR (a somatostatin analog) in patients with acromegaly (9) shows that somatostatin increases the activity of lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL), both of which are related to the production of low-density lipoprotein (LDL) from very-low-density lipoprotein (VLDL). Therefore, the amount of LDL deposited in the liver via the LDL receptor may increase upon exposure to somatostatin. When oxidized LDL is engulfed by macrophages, foamy cells are formed (10). Some published studies have shown that LDL is associated with the development of tendon xanthoma (11), gastric xanthoma (12) and cerebrotendinous xanthoma (13). Because pasireotide is more potent than somatostatin, the risk of formation of foamy cells may be even greater for pasireotide, which may subsequently induce the formation of a hepatic xanthoma.

After the present patient discontinued the drug, the size of the hepatic xanthoma decreased gradually and spontaneously from 3.8×3.0×3.0 cm to 1.5×0.8×0.5 cm (98.2% decrease in tumor volume) within approximately 10 months without medical or surgical treatment. Accordingly, we feel that the formation of hepatic xanthomas is a possible adverse side effect of pasireotide.

In addition, the event happened after the clinical trial of pasireotide; hence, we had the responsibility to console the patient and provide him guidance and sufficient health education in this situation. We told that patient that he has no malignant lesions in the liver and that we will arrange for regular follow-up with abdominal imaging.

Based on the present case findings, we have some suggestions regarding pasireotide prescription. First, before prescribing pasireotide, the patient should be checked for possible risk factors for xanthomas, such as homozygous familial hypercholesterolemia, hyperlipidemia (9) and hereditary metabolic storage disorders. Second, in patients receiving pasireotide, the liver should be checked using periodic radiological examinations, even if the patient does not exhibit any risk factors. Third, if hepatic xanthomas are found, medical or surgical intervention may not be needed because the lesion can decrease in size gradually and spontaneously upon discontinuation of pasireotide use, although providing conservative observation with abdominal radiological imaging and sufficient health education for the patient is still required.

To the best of our knowledge, the present case is the first case of hepatic xanthoma development that may have been induced by pasireotide, although the true etiology of hepatic xanthomas remains unknown. From our observations, we believe that spontaneous or gradual discontinuation of the drug, along with conservative observation with abdominal radiological imaging and health education, is sufficient.

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

References


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