A fatal case of progressive steatohepatitis, possibly chemotherapy- associated steatohepatitis related to gemcitabine

- Case Report –

A fatal case of progressive steatohepatitis, possibly chemotherapy-associated steatohepatitis related to gemcitabine

Xiangshan Ren[1.2], Kenichi Harada,[1] Seiichi Yoshikawa,[1] Saya Igarashi,[1] Takeshi Urabe[3], Shinya Yamada[4], Kazuyoshi Katayanagi[5], Hiroshi Kurumaya[5], and Yasuni Nakanuma[1]

1. Departments of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan.
2. Department of Pathology, Yanbian University College of Medicine, Yanji-City, China
3. Department of Gastroenterology, Public Central Hospital of Matto-Ishikawa, Hakusan, Japan.
4. Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan.
5. Department of Pathology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan.

Short title: **chemotherapy-associated steatohepatitis**

Address correspondence to: Kenichi Harada, M.D.
Department of Human Pathology, Kanazawa University
Graduate School of Medicine, Kanazawa 920-8640, Japan
Tel: +81-76-265-2199
Fax: +81-76-234-4229
E-mail: kenichih@med.kanazawa-u.ac.jp

ABSTRACT

We report the case of an 80-year-old female suffering from pancreatic cancer who developed severe non-alcoholic steatohepatitis (NASH) resulting in fatal hepatic failure after anti-cancer chemotherapy with gemcitabine. Hepatic encephalopathy appeared one year after the chemotherapy and the patient developed progressive liver failure and eventually died. Radiological examination showed severe fatty liver. Histopathological examination of a liver needle necropsy showed almost panlobular macrovesicular fatty change. Ballooning degeneration and necrosis of hepatocytes accompanying neutrophil infiltration, Mallory bodies, and a few bile plugs were found in zone 3. Marked perivenular and pericellular/perisinusoidal fibrosis and extensive bridging fibrosis were also found. Together, these findings indicated steatohepatitis at a precirrhotic stage. Because the patient had no history of drinking in excess, we made a diagnosis of NASH, in particular, chemotherapy-associated steatohepatitis (CASH). Gemcitabine is a pyrimidine nucleoside antimetabolite with anti-cancer activity. A few reports have mentioned fatal hepatotoxicity caused by gemcitabine but, to our knowledge, this is the first report of steatohepatitis, possibly associated with gemcitabine. Physicians treating patients with this drug should be aware of the possibility of steatohepatitis.

Key words: gemcitabine, chemotherapy-associated steatohepatitis**,** non-alcoholic steatohepatitis, liver failure

INTRODUCTION

Steatohepatitis can be categorized as alcoholic steatohepatitis (ASH) or non-alcoholic steatohepatitis (NASH), based on its etiopathogenesis.[1] Ludwig primarily introduced NASH to describe a form of liver disease that is histologically indistinguishable from ASH, but occurs in patients that do not consume excess alcohol.[2] Recently, NASH has been recognized as a hepatic manifestation of metabolic syndrome, associated with obesity, diabetic mellitus, and hyperlipidemia. This type of NASH is known as primary NASH.[1] In contrast, secondary NASH is caused by jejunoileal bypass surgery, total parenteral nutrition, drugs, and industrial toxins. As for drug-induced steatohepatitis, consistent with the term 'NASH', the term "chemotherapy associated steatohepatitis" (CASH) has been proposed. Cases of drug-induced liver damage as well as the kinds of causative drugs have been increasing recently, but drug-induced liver injury showing the clinicopathological features of steatohepatitis is very rare.[2] This is because in complex medical conditions, the diagnosis may be confounding, and the potential hepatotoxicity of chemotherapeutic agents may be easily overlooked.

In this report, a fatal case of CASH which was possibly associated with anti-cancer chemotherapy using gemcitabine is introduced. Such case reports are extremely rare.

CASE PRESENTATION

Clinical history

The patient was an 80-year-old Japanese female. She had a history of hysterectomy for hysteromyoma, cholecystectomy for cholecystolithiasis, Basedow's disease, and autonomic dystonia and had regularly gone to the hospital to treat autonomic dystonia. She was not a drinker. CT scan imaging revealed the presence of mass formation suggesting pancreatic cancer in the pancreatic head and the absence of definite fatty liver (Fig.1A) and the patient was admitted to initial hospital for the treatment in July

2004. Laboratory data at admission were follows; AST 29 [normal range, 12-36 IU/L], ALT 18 [3-32 IU/L], γGTP 17 [9-71 IU]), ALP 351 [114-394 IU/L], Amylase 166 [58-166 IU/L], Pancreatic type 68 % [28-72%], Blood glucose level 111 [70-110 mg/dl], Total cholesterol 176 [130-230], Triglyceride 81 [70-180 mg/dl], Platelet 17 [15-35 $x10^4$], IgG 1180.0 [917-1850 mg/dl], IgM 86.7 [80-272 mg/dl], Viral markers for hepatitis (-), ANA <x40, CA19-9 54 [<37]. Obesity (68.3kg, BMI 29) and mild impaired glucose tolerance was found, but she had no prior medical history of hepatic disease and no sign of impaired liver function at this time. After admission, the peak weight was 70kg (BMI 29.9). Because the patient refused an operation, anti-cancer chemotherapy with gemcitabine (Gemzar®) in addition to camostat mesilate (Foipan®), Domperidone (Nauzelin®), loxoprofen sodium hydrate (Loxonin®), and tiquizium bromide (Thiaton®), had started at September 2004. Her symptoms partially improved during this anti-cancer treatment. However, because severe liver dysfunction and cognitive impairment, probably due to hepatic encephalopathy, appeared in October 2005 (13 months later after chemotherapy), chemotherapy was discontinued (Fig.2). Radiological findings concerning the pancreatic cancer did not changed, but severe fatty change was detected in the liver (Fig.1B). Then, she was admitted to next hospital for further examination of liver dysfunction, but she died of progressive hepatic failure 3 months after second admission. Liver function data just before death were follows; AST 78, ALT 46, total bilirubin 3.43, ALP 517, platelet 17.1, prothrombin time 35%, and albumin 2.4 g/dl. A liver needle necropsy was performed.

Histology of liver necropsy

Histopathological examination of the liver revealed a pan-lobular fatty change, predominantly macrovesicular, involving approximately 90% of lobules (Fig.3). Ballooning degeneration and necrosis of hepatocytes accompanying neutrophil infiltration and bile plugs were found in zone 3 admixed with steatosis (Fig.4). These ballooned hepatocytes contained typical Mallory bodies consisting of dense and ropy hyaline (Fig.4). Portal tracts were fibrously expanded, and perivenular and

pericellular/perisinusoidal fibrosis in zone 3 was also prominent (Fig.5). Extensive bridging fibrosis connecting central veins with other central veins and with portal tracts had developed, resulting in partial nodular remodeling and a pre-cirrhotic state (Fig.5). In portal tracts, mild infiltration of lymphocytes and neutrophils and mild interface hepatitis were found. We made a diagnosis of NASH (Grade 3, Stage 3),[3] probably CASH associated with gemcitabine.

DISCUSSION

Recently, cases of NASH are increasing and its etiology and mechanisms have been examined. Moreover, cases of drug-induced liver injury are also increasing and many drugs causing hepatic damage have been reported. Steatosis is one common pathological feature of drug-induced liver injury, but cases of steatohepatitis are very rare.[2]

The liver histology of the patient described in this report was typical of steatohepatitis and alcohol history was not applicable in this case. Therefore, we made a diagnosis of NASH. In general, ASH and NASH are thought to have a similar histology.[4] In fact, the two can be indistinguishable in terms of macrovesicular fatty change, fibers, and hepatocellular ballooning. However, detailed histological differences between ASH and NASH, particularly ASH and primary NASH, have been reported. For example, in cases of ASH, a typical Mallory body is found, but in cases of primary NASH, an atypical Mallory body that is ‘poorly formed’ and lacks the dense ropy quality of hyaline is seen.[5] Moreover, neutrophil infiltration and hepatocellular necrosis are thought to be prominent in ASH, compared with NASH. Patients with ASH, therefore, generally show severe liver dysfunction. The histological features of secondary NASH including CASH depend on the etiology and drugs involved.

Several drugs including nifedipine,[6] tamoxifen,[2] estrogen,[2] corticosteroid,[7] and methotrexate[8] have been reported as causative of NASH. Among them, the anti-estrogen drug tamoxifen, is most well-known. Methotrexate, an antimetabolite,

has also been reported as a reagent causing NASH and liver fibrosis.[8] In general, antimetabolites show hepatotoxicity. Gemcitabine (Gemzar®) is a novel analogue of deoxycytidine which inhibits DNA synthesis and acts as an antimetabolite with broad-spectrum anti-cancer activity including against pancreatic cancer.[9] It is used as a standard medication for many cancers including pancreatic cancer and non-small cell lung cancer. Hepatotoxicity due to gemcitabine is known, but has repeatedly been described as a slight, transient, asymptomatic, and rapidly reversible elevation of AST and ALT levels.[10,11] Therefore, gemcitabine does not have severe toxicity; however, fatal cases of liver injury involving veno-occlusive diseases[12] and cholestatic liver failure[13,14] that developed after treatment with gemcitabine have been reported.[13,15]

This patient had obesity (BMI 29 at peak) and mild impaired glucose tolerance, but no fatty liver was found before the chemotherapy. Because the radiological findings of pancreatic cancer did not changed before and after the chemotherapy and no liver metastasis was not found, cancer-associated liver dysfunction causing the fatal course was unlikely in this case. Intrahepatic cholestasis as well as steatosis, moreover, was also found in the liver, suggesting the drug-associated liver injury. Therefore, the possibilities of other factors causing steatohepatitis are raised in this case, but the association of chemotherapy is likely in the pathogenesis of steatohepatitis. As mentioned above, two fatal cases of cholestatic liver failure related to gemcitabine therapy have been reported.[13,14] The reason why this patient died of hepatic failure is unknown, but we speculated that the combined hepatocellular damage associated with steatohepatitis and cholestasis caused hepatic decompensation.

The histological features of secondary NASH including CASH depend on the etiology and drugs involved. Several drugs including methotrexate, tamoxifen, and aminodarone, initially induce mitochondrial dysfunction through an impairment of beta-oxidation, which plays a central role in the pathogenesis of drug-induced steatosis and steatohepatitis and also in that of alcoholic cytotoxicity.[2] Therefore, drug-induced steatohepatitis could show an ASH-like histology. This case also showed ASH-like histological features; typical Mallory bodies, prominent

neutrophilic infiltration and hepatocellular necrosis, and severe liver dysfunction resulting in lethal liver failure. These findings suggest that the cytotoxicity of gemcitabine is induced by a similar mechanism to that of ethanol.

To our knowledge, this is the first case of possibly gemcitabine-induced steatohepatitis encountered during the treatment of pancreatic cancer. Recently, drug-induced hepatic damage has been broadly recognized, but as a special type of liver injury, physicians treating patients with this antitumor drug should be alert to the possibility of CASH.

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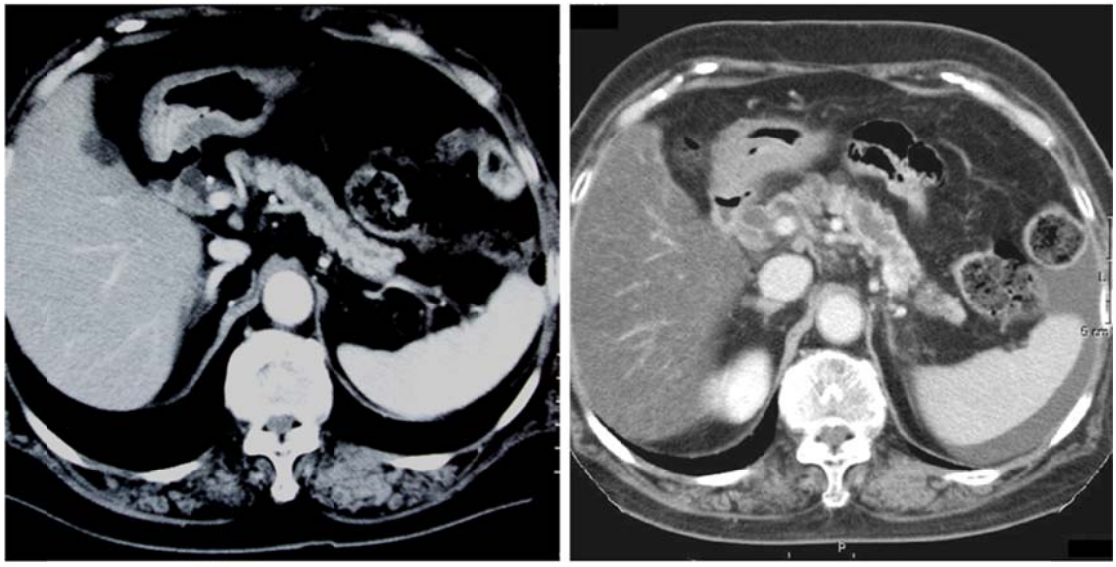
FIGURES and LEGENDS

Fig.1



A B

Fig.1

Dynamic CT scan reveal no definite fatty change of the liver in August, 2004 (A, before chemotherapy), but the presence of clear fatty liver and ascots in November, 2005 (B, after discontinuance of anti-cancer chemotherapy). Moreover, dilatation of main pancreatic duct is visualized in the pancreatic body and tail.

Fig.2

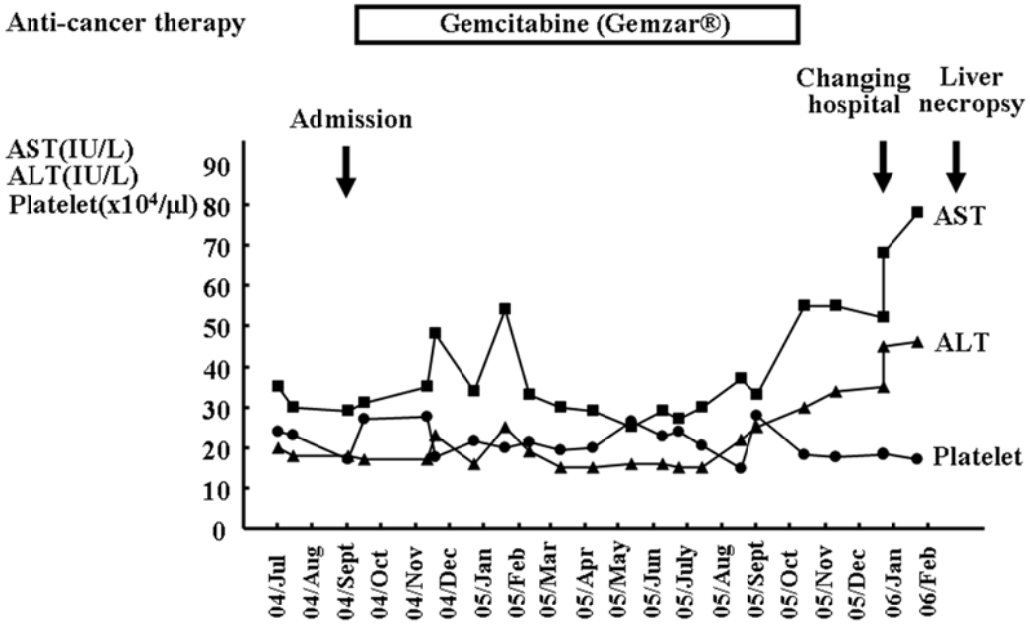
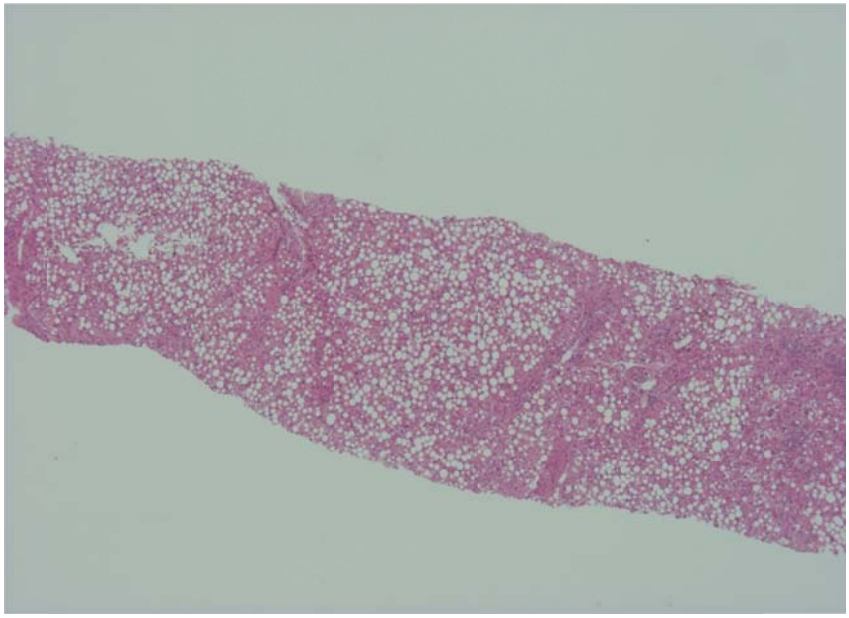


Fig.2

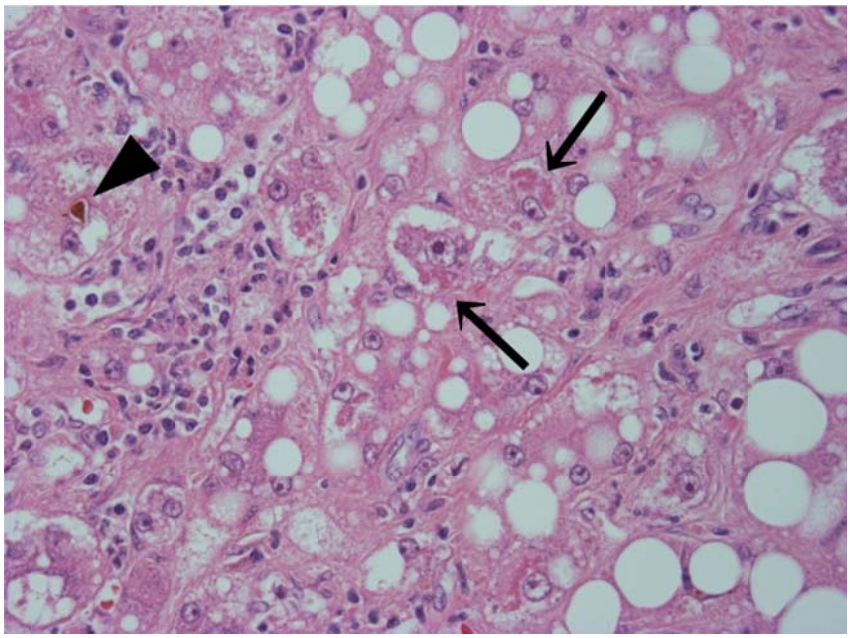
Clinical chart and serial studies of transaminases and platelet counts.

Fig.3



Lower magnification of liver necropsy. Almost panlobular fatty change (approximately 90%) is found in liver parenchyma. H&E staining.

Fig.4



Ballooned hepatocytes containing Mallory bodies (arrows), neutrophilic infiltration, and bile plugs (arrowhead) are found in zone 3 admixed with steatosis. H&E staining.