

# Gemcitabine-related fatal cholestatic hepatitis

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## Abstract

**Introduction.** Gemcitabine is used in treatment of such cancers as pancreatic cancer and biliary tract cancer and has been shown to improve progression-free survival in patients with pancreatic cancer when administered as adjuvant chemotherapy. Low-grade elevations in liver enzymes are generally among the known toxicities of gemcitabine. However, it has also been associated with serious and fatal hepatic failure.

**Case report.** A 71-year-old male patient with pancreatic cancer developed fatal cholestatic hepatitis after six cycles of gemcitabine given as adjuvant chemotherapy.

**Management and outcome.** A fatal gemcitabine-associated cholestatic hepatitis in a patient receiving adjuvant gemcitabine monotherapy for pancreatic cancer.

**Discussion.** Our case differs from those reported in the literature. In our patient, 10 days after the 6<sup>th</sup> course of gemcitabine administration, elevated liver enzymes, increased bilirubin, and jaundice were observed. Gemcitabine-induced cholestatic hepatitis was diagnosed because there was no other drug use that could have triggered this reaction.

**Keywords:** cholestatic hepatitis, gemcitabine, pancreatic cancer

## Introduction

Gemcitabine is a pyrimidine anti-metabolite with broad-spectrum antitumor activity used in the treatment of pancreatic cancer, non-small cell lung cancer, breast cancer, prostate cancer, and biliary tract cancer [1, 2]. Side effects of gemcitabine are common due to myelosuppression. Infections due to leukopenia, weakness and shortness of breath due to anemia, and bleeding due to thrombocytopenia are frequent. In addition, after gemcitabine treatment, side effects such as nausea, diarrhea, constipation, stomatitis, elevated liver enzymes, proteinuria, hematuria, alopecia, skin rashes, myalgia, and flu-like symptoms may also occur [2]. Elevated liver transaminase can be seen. This transaminase elevation is usually low-grade, rapidly reversible, and transient [1]. We report a fatal case

of cholestatic liver failure caused by adjuvant gemcitabine after pancreaticoduodenectomy for pancreatic cancer (PC).

## Case

A 71-year-old male patient was admitted to the hospital with abdominal pain in February 2022. He had hypertension and atherosclerotic cardiovascular disease. Abdominal ultrasonography (USG) revealed a hypodense, nodular lesion, approximately 1.5 centimeters (cm) long, with irregular contours in the pancreatic head. An endosonography-guided biopsy was performed, and immunohistochemical staining of tumor cells showed pan-cytokeratin positivity and synaptophysin negativity. Additionally, histochemical mucin was positive, leading to the diagnosis of pancreatic adenocarcinoma. Abdominal and thoracic computed tomography (CT) showed no distant metastases; the tumor was resectable. In addition, the liver had a normal density on CT. The tumor did not invade any adjacent tissues except the portal vein. The mass infiltrated

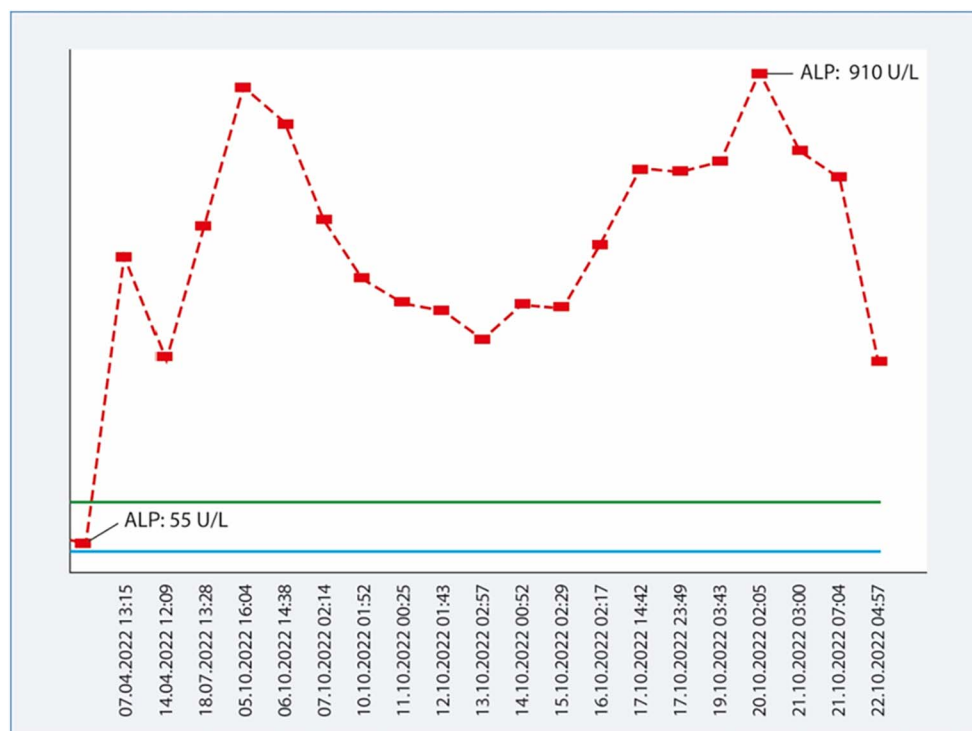
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the portal vein in an area of approximately 5 mm. A 5 mm defect in the portal vein wall was continuously sutured with 4/0 prolene.

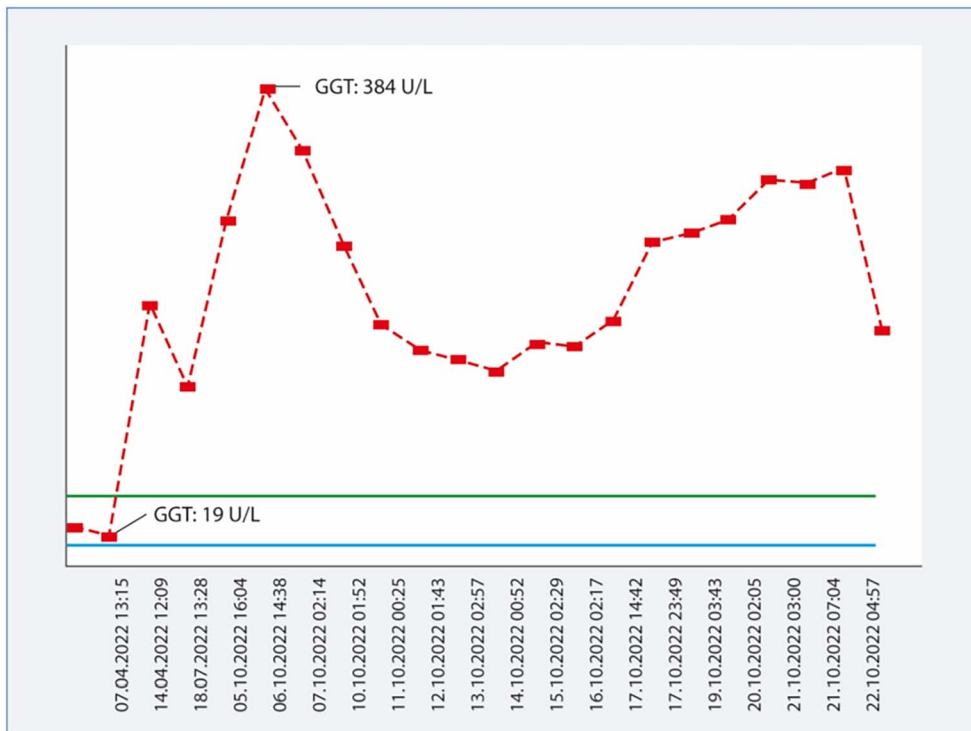
Pancreaticoduodenectomy was performed in March 2022. In pathological examination, the tumor size was 2 × 1.7 × 1.2 cm. All 15 dissected lymph nodes were reactive. No tumor was detected in the surgical margins. The pathological staging after pancreaticoduodenectomy was determined to be stage 1A disease, according to the American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8<sup>th</sup> ed., 2017). Six cycles of gemcitabine were given as adjuvant chemotherapy [1250 mg/m<sup>2</sup>, intravenous (*i.v.*) infusion on days 1, 8, and 5, repeated every 28 days]. Ten days after the sixth cycle, the patient presented with jaundice. There was an increase in liver enzymes and a significant increase in bilirubin values. His blood test showed the following results: alanine aminotransferase (ALT) 92 IU/L (5–34), aspartate aminotransferase (AST) 127 IU/L (0–55), total bilirubin 21.18 mg/dL (0.2–1.2), direct bilirubin 18.75 mg/dL (0–0.30), alkaline phosphatase (ALP) 720 IU/L (40–129), gamma-glutamyl transpeptidase (GGT) 393 IU/L (0–60), lactate dehydrogenase (LDH) 674 IU/L (135–225), total protein 42.4 g/L (64–83), serum albumin 21.2 g/L (35–52), white blood cells 11.03 × 10<sup>9</sup>/L (4.5 to 11.0 × 10<sup>9</sup>/L), hemoglobin 10 g/dL (12.1–17.2), platelets 81.00 × 10<sup>3</sup> u/L (150–400). On abdominal USG, the liver appeared natural, and the biliary tract was normal. Abdominal CT showed ascites, but there was no

evidence of peritoneal carcinomatosis or metastases in other organs, including the liver. No thrombus was detected in the hepatic artery or portal vein.

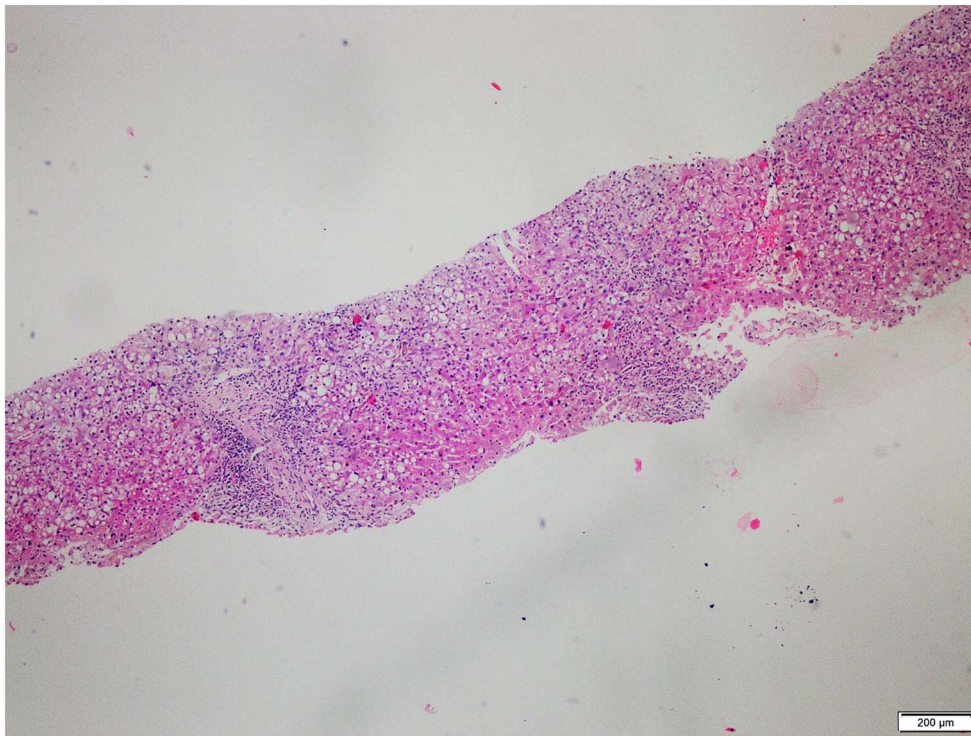
In addition, magnetic resonance cholangiopancreatography (MRCP) was performed. No additional evidence was found to explain the elevated levels of bilirubin and liver enzymes. In ascites sampling, the serum ascites albumin gradient was calculated at 2.4 g/dL. Ascites cytology was reported as benign. Ascites was not caused by malignancy. The patient had no history of exposure to drugs, toxins, alcohol, or other alternative or complementary drugs. Before adjuvant gemcitabine, laboratory data were within the normal reference range. The patient was admitted to the hospital. During the clinical follow-up of the patient, cholestatic enzymes, liver enzymes, and total and direct bilirubin continued to increase (Fig. 1 and 2). Hepatitis A virus-specific immunoglobulin M (IgM) antibody, hepatitis B surface antigen, hepatitis C virus antibody, viral capsid antigen IgM, human immunodeficiency virus (HIV) antibody, and cytomegalovirus antigen were negative. His rheumatological examination was normal, and only antinuclear antibody (ANA) was positive for the immunological markers. In the follow-up, the patient developed hepato-renal syndrome, hepatic encephalopathy, and coagulation disorders after bilirubin elevation. Albumin and terlipressin were given for hepato-renal syndrome. Furthermore, hepatoprotective agents such as ursodeoxycholic acid, liver extracts, and mixed solutions of glycine, glycyrrhizin,



**Figure 1.** Concentration of alkaline phosphatase (ALP)



**Figure 2.** Concentration of gamma-glutamyl transferase (GGT)

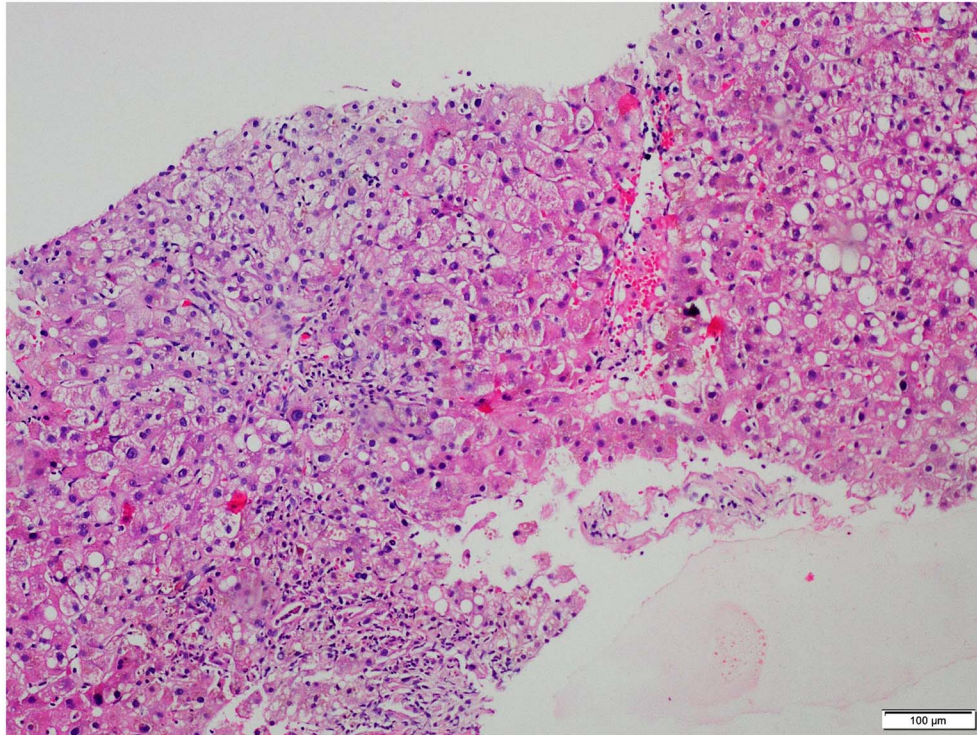


**Figure 3.** Marked inflammatory changes were observed in the liver parenchyma, along with signs of steatosis

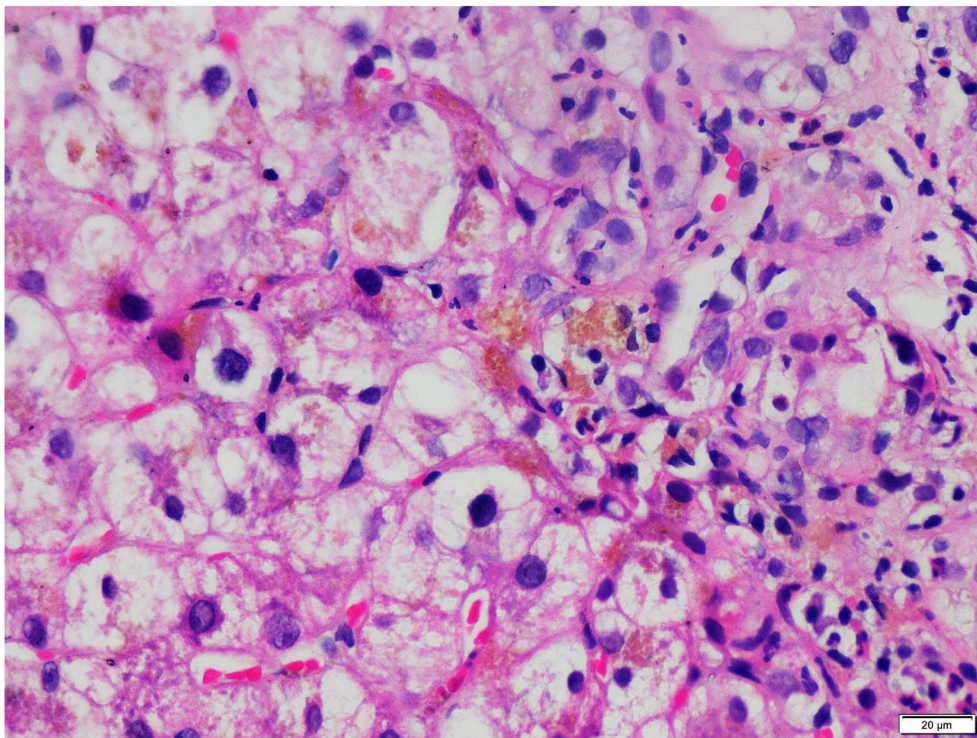
and L-cysteine were administered for hepatic encephalopathy.

On October 10, 2022, a biopsy was performed to determine the etiology of acute hepatic failure.

The liver biopsy revealed significant inflammatory changes and steatosis findings in the liver (Fig. 3), the appearance of lymphocyte, neutrophil, polymorph, and eosinophil-rich inflammation and lobular



**Figure 4.** The parenchyma exhibits inflammation rich in lymphocytes, neutrophils, polymorphs, and eosinophils, as well as an appearance of lobular cholestasis



**Figure 5.** Accumulation of bile segments is concentrated in the ducts and hepatocyte cytoplasm

cholestasis in the parenchyma (Fig. 4), and bile pigment deposits in canaliculi and hepatocyte cytoplasm (Fig. 5). As a result, the pathological examination

was evaluated as compatible with cholestatic hepatitis and drug-induced hepatocellular damage. Therefore, 1 mg/kg *i.v.* methylprednisolone was given for 5 days.

The patient's liver enzymes, total bilirubin, and direct bilirubin values showed a tendency to decrease with methylprednisolone. Despite receiving the best palliative treatment, the patient developed multiple organ failure and died on 22/10/22.

## Discussion

Gemcitabine is used as adjuvant therapy in PC patients and significantly prolongs overall survival [3]. Gemcitabine causes adverse reactions such as myelosuppression, nausea, vomiting, fever, fatigue, rashes, anaphylactoid reactions, transient liver enzyme elevation, and flu-like symptoms [4]. Serum aminotransferase elevation is observed in 30–90% of patients receiving gemcitabine. Patients are generally asymptomatic, and transaminase elevation is usually self-limiting. AST and ALT are elevated more than 5 times the normal value in 1–4% of patients. Elevated serum alkaline phosphatase and serum bilirubin are even rarer and are usually mild and transient. However, fatal acute cholestatic liver disease due to gemcitabine has occasionally been reported.

Cholestatic hepatitis is characterized by hepatocellular injury, prominent cholestasis, and portal inflammation [5, 6]. Coeman et al. [7] published a report on a 75-year-old man with non-small cell lung cancer (NSCLC) who developed fatal cholestatic liver failure related to gemcitabine (1000 mg/m<sup>2</sup>) used as a palliative treatment. A severe cholestatic liver injury was observed, with elevations of total bilirubin and ALP. The patient died of multiple organ failure due to liver failure [7].

Okada et al. [4] published a study on severe cholestatic liver failure associated with gemcitabine monotherapy after pancreaticoduodenectomy for patients with advanced PC.

Kagohashi et al. [8] published a report on a 57-year-old man with large-cell lung cancer receiving gemcitabine 800 mg/m<sup>2</sup> and vinorelbine 20 mg/m<sup>2</sup>. After this treatment, the patient died from severe hepatic failure, accompanied by an increase in AST, ALT, and total bilirubin.

Some authors have stated that patients with pre-existing liver damage or liver metastases have a dose-dependent increased risk of fatal hepatic failure. Matsuda et al. published a report on a 79-year-old man with PC who received 13 cycles of gemcitabine 800–1000 mg/m<sup>2</sup>. The patient had chronic hepatitis C and type 2 diabetes. Chemoradiotherapy was planned for the patient who could not be operated on. A severe liver injury was observed, with elevations of total bilirubin and ALP. Abdominal CT showed no evidence of liver metastases or obstructive jaundice. Hepatocyte necrosis due to gemcitabine was suspected, and systemic prednisolone (50 mg/day)

was given. The patient died of multiple organ failure due to liver failure. An autopsy revealed diffuse hepatic necrosis suggestive of drug-induced hepatocellular injury associated with chronic hepatitis [9].

Samłowski et al. [10] published a case of a patient with metastatic squamous cell carcinoma of the head and neck who developed liver failure 14 days after a single dose of gemcitabine. The patient died of multiple organ failure due to liver failure [10]. Robinson et al. published a report on a 45-year-old woman with metastatic breast cancer receiving carboplatin 450 mg/m<sup>2</sup> and gemcitabine 1300 mg/m<sup>2</sup>. The patient who received combined chemotherapy developed cholestatic liver disease after chemotherapy. The patient progressed to hepatic coma and died [11]. In addition, Dobbie et al. [12] published a case of gemcitabine-related hepatic veno-occlusive disease in a female with viral hepatitis. The patient received a total of 11 applications of gemcitabine (1000/m<sup>2</sup>). She was hospitalized one week after the last dose. That patient also progressed to hepatic coma and died [12].

We scored our case using the Naranjo Adverse Drug Reactions Probability Scale. Adverse drug reactions are assigned to a probability category from the total score as follows: definite if the total score is 9 or greater, probable for a score of 5–8, possible for a score of 1–4, and finally unlikely for a score of 0. In our case, we calculated a score of 6. Our case differs from those reported in the literature. In our patient, 10 days after the 6<sup>th</sup> course of gemcitabine administration, elevated liver enzymes, increased bilirubin, and jaundice were observed. No obstruction was observed in the biliary tract, portal vein, or hepatic artery on USG, CT, or magnetic resonance imaging (MRI). There was also no liver metastasis or peritonitis carcinomatosis. Viral serological markers were negative. The liver biopsy was compatible with cholestatic hepatitis. Gemcitabine-induced cholestatic hepatitis was diagnosed because there the patient received only gemcitabine and no other drug could be related to his worsening condition. Despite palliative support and steroid therapy, the patient died.

In conclusion, it is well known that gemcitabine can cause a mild and transient elevation of serum aminotransferase. However, it should be kept in mind that if jaundice develops in patients receiving gemcitabine, fatal cholestatic liver failure may occur. Therefore, liver enzyme monitoring should be considered during gemcitabine therapy.

## Article Information and Declarations

### Ethics statement

Written informed consent was obtained from the patient.

### Author contributions

O.Y.: concept, design, supervision, data collection and/or processing, literature search, writing, critical reviews; M.K.E.: concept, design, supervision, literature search, writing, critical reviews; A.F.G.: supervision, analysis and/or interpretation, critical reviews; M.U.: supervision, analysis and/or interpretation, literature search, critical reviews; S.T.A.: supervision, critical reviews; M.Araz: supervision, data collection and/or processing, critical reviews; M. Artaç: supervision, data collection and/or processing, analysis and/or interpretation, critical reviews.

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### Conflict of interest

Authors declare no conflict of interest.

### Supplementary material

None.

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