CASE REPORT

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Gemcitabine-Induced Hemolytic Uremic Syndrome in Pancreatic Cancer: A Case Report and Review of the Literature

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Hemolytic uremic syndrome (HUS) is a rare thrombotic complication characterized by a triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. HUS may be caused by several different conditions, including infection, malignancy, and chemotherapeutic agents, such as mitomycin, cisplatin, and most recently, gemcitabine. The outcome of gemcitabine-induced HUS is poor, and the disease has a high mortality rate. This study reports a case of gemcitabine-induced HUS in a patient with pancreatic cancer in Korea. **(Gut Liver 2014;8:109-112)**

Key Words: Hemolytic-uremic syndrome; Gemcitabine; Pancreatic neoplasms

INTRODUCTION

Gemcitabine-induced hemolytic uremic syndrome (HUS) is rare but can often be fatal. Early detection of HUS is critical so that contributing chemotherapeutic agents, such as gemcitabine, can be discontinued. In clinical trials, HUS is characterized by renal failure, microangiopathic hemolytic anemia (MAHA), and thrombocytopenia.[1] In addition, the onset of new and uncontrolled hypertension can be diagnostic for HUS.[2]

While a few cases of gemcitabine-induced HUS have been reported globally, but only a single Korean case of HUS in a lung cancer patient is known.[3] With the increase in gemcitabine use in pancreatobiliary cancer, early detection of gemcitabine-induced HUS is essential. Herein, we describe the first case of HUS in a pancreatic cancer patient, associated with gemcitabine use in a Korean hospital.

CASE REPORT

In June 2011, a 56-year-old male visited a local hospital complaining of dyspepsia and back pain. Contrast-enhanced computed tomography (CT) revealed a 4.4 cm mass at the head of his pancreas (Fig. 1). He was referred to our hospital, where we found the mass had invaded the main portal vein, common hepatic artery, and stomach. An endoscopic biopsy revealed moderately differentiated adenocarcinoma. The patient was diagnosed with locally advanced, unresectable pancreatic cancer (cT4N1M0). Laboratory tests showed serum hemoglobin level of 14.9 g/dL, platelet count of 166,000/μL, blood urea nitrogen of 21.3 mg/dL, and serum creatinine level of 1.28 mg/dL. The carcinoembryonic antigen level was 2.34 ng/mL (normal range, 0 to 5 ng/mL) and carbohydrate antigen 19-9 was 798 U/mL (normal range, 0 to 37 U/mL).

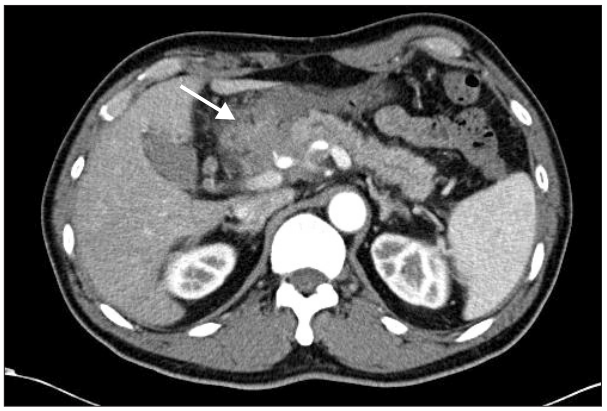

Fig. 1. Contrast-enhanced computed tomography revealed a 4.4-cm mass at the head of the pancreas, as indicated by the arrow.

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Concurrent chemoradiotherapy (CCRT) with original gemcitabine weekly (1,000 mg/m^2 per week, day 1, 8, 15, 22, and 29) and 25 radiation therapy (total radiation dose, 4,500 cGy) was performed from June 30 to August 3, 2011. One month after CCRT, a repeat abdominal CT showed that the pancreatic mass had decreased from 4.4 to 3.0 cm but remained unresectable. The tumor response was considered a partial response to treatment. On October 21, 2011, gemcitabine therapy was administered weekly (1,000 mg/m^2 per week, day 1, 8, and 15) for 3 out of 4 weeks. A cumulative dose of gemcitabine from June 30, 2011 was 26,250 mg.

In February 2012 during week 2 of cycle 5, the patient was admitted for generalized edema and general weakness. He developed acute renal failure and had an elevated serum creatinine level of 2.08 mg/dL (normal range, 0.5 to 1.40 mg/dL). On physical examination, the patient had dyspnea on exertion, lower extremity pitting edema, and a blood pressure of 200/140 mm Hg. The patient's hemoglobin level had decreased to 7.7 g/dL (normal range, 13.0 to 17.0 g/dL) and a platelet count of 87,000/μL (normal range, 150,000 to 400,000/μL). The reticulocyte count was 11.69% (normal range, 0.5% to 2.31%), with a corrected reticulocyte count of 6.6% and an elevated lactate dehydrogenase (LDH) level of 459 IU/L (normal range, 110 to 247 IU/L). A peripheral blood smear showed macrocytic hypochromic anemia with mild anisopoikilocytosis composed of schistocytes and acanthocytes (Fig. 2). There was no evidence of proteinuria or hematuria, but the patient was positive for urine hemoglobin. The patient's total bilirubin, obtained from an indirect Coombs test, was normal and the patient's haptoglobin level was <10 mg/dL.

The laboratory tests confirmed MAHA, thrombocytopenia, and acute renal failure–leading to a diagnosis of gemcitabine-induced HUS. The patient started plasmapheresis due to oliguria and bilateral pleural effusion. After 19 plasmapheresis treatments, the patient's creatinine level decreased to 2.02 mg/dL and he was able to maintain self-urine output. The patient declined further chemotherapy due to his poor general condition after HUS treatment. He was transferred to a nursing home for hospice care and has continued with outpatient palliative therapy.

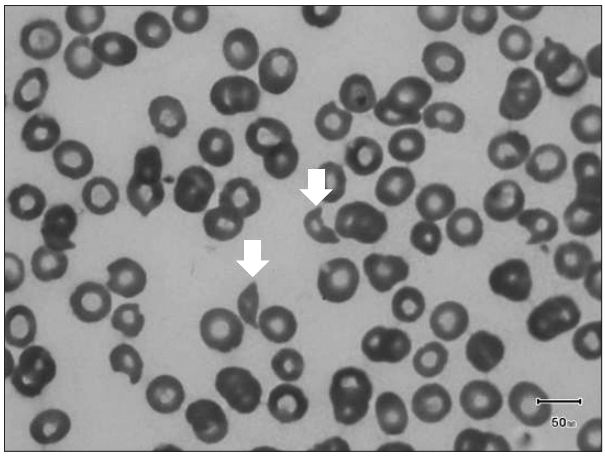

Fig. 2. The peripheral blood smear showed macrocytic hypochromic anemia with schistocytes, as indicated by the arrows.

DISCUSSION

HUS is characterized by renal failure, thrombocytopenia and MAHA characterized by a trio of classic symptoms–elevated LDH, low haptoglobin, and schistocytes on the peripheral blood smear. Five typical HUS cases were first described by Gasser *et al*. in a pediatric patient with hemorrhagic diarrhea and enterocolitis caused by verotoxin-producing *Escherichia coli*.[4] In 1979, a gastric cancer patient developed chemotherapy-related HUS associated with mitomycin C (MMC) and 5-fluorouracil.[5] The causes of atypical HUS include infectious diseases, malignancy, antineoplastic agents such as MMC, antiplatelet agents, pregnancy, hemolytic anemia, elevated liver enzymes, and low platelet syndrome (HELLP syndrome), malignant hypertension, systemic lupus erythematosus, and antiphospholipid syndrome.

The incidence of gemcitabine-induced HUS is low (0.015% to 0.31%), but the mortality rate is as high as 50% in these patients. There have been previous reported cases in patients with nonsmall cell lung cancer, ovarian cancer, and metastatic breast cancer.[6-8] A review of the literature revealed only 15 patients of gemcitabine-induced HUS in pancreatic cancer. These 15 cases are summarized in Table 1.[1,2,9-15] Our case is noteworthy because of the first reported case in Korea. The mechanism of gemcitabine-induced HUS is unclear with hypotheses including microvascular endothelial damage or immunocomplex mediation.[9] An increase of von Willebrand factor levels in HUS suggests a potential role in HUS, but further investigation is needed.[5] In the literature, the median duration of gemcibatine therapy was 5.8 months, with the majority of patients developing HUS within 1 to 2 months of the last gemcitabine infusion.[1] The median time between initiation of chemotherapy and onset of gemcitabine-induced HUS was 7.4 months.[16] Gemcitabine-induced HUS developed after an estimated median cumulative dose of 20,000 mg/m^2 with a broad range from 2,450 to 48,000 mg/m^2 with no clear dose-response relationship.[11] Our patient began developing symptoms of peripheral edema and hypertensive emergency after 7 months of therapy and a cumulative dose of 26,250 mg.

In patients treated with gemcitabine, HUS must be considered when uncontrolled hypertension or worsening preexisting hypertension develops, and it is important to monitor blood pressure to detect any early indication of gemcitabine-induced HUS. Although there is currently no consensus as to the best treatment for gemcitabine-induced HUS, immediate discontinuation of gemcitabine is accepted as the initial step.[17] Other treatment modalities include corticosteroids, transfusion of fresh frozen plasma, plasmapheresis, or hemodialysis. However, plasmapher-

Table 1. A Summary of the Previous Published Case Reports of Gemcitabine-Induced Hemolytic Uremic Syndrome in Pancreatic Cancer

Case	Reference	Age/ Sex	Clinical symptoms	The lowest platelet count, $\times 10^9$/L	Peak creatinine, mg/dL	Treatment	Outcome
1	Saif *et al*.[1]	72/M	Peripheral edema	3	2.6	Plasmapheresis	Continued hemodialysis
2	Humphreys *et al*.[2]	58/M	Worsened hypertension	68	1.9	None	Died
3	Humphreys *et al*.[2]	43/M	Worsened hypertension	40	2.3	Plasmapheresis	Died
4	Fung *et al*.[9]	59/M	None	NA	NA	None	Unknown
5	Fung *et al*.[9]	52/F	Pulmonary edema, confusion	NA	NA	None	Died
6	Fung *et al*.[9]	73/F	None	NA	NA	Plasmapheresis	Died
7	Fung *et al*.[9]	62/M	Dyspnea, pulmonary edema	NA	NA	Plasmaperesis	Died
8	Fung *et al*.[9]	52/F	New onset hypertension	NA	NA	Plasmapheresis, intravenous immunoglobulin	Recovered
9	Lhotta *et al*.[10]	26/M	Hypertension, dyspnea	125	5.2	Steroids	Recovered
10	Flombaum *et al*.[11]	67/F	Peripheral edema	92	3.1	Steroids	Recovered
11	Flombaum *et al*.[11]	63/F	Peripheral erythematous rash	56	1.9	Plasmapheresis	Recovered
12	Casper *et al*.[12]	65/M	New onset hypertension	119	2.2	None	Died
13	De Smet *et al*.[13]	71/F	Gastrointestinal bleeding	11	4.6	None	Died
14	Boeck *et al*.[14]	64/F	Dyspnea, hypertension	93	2.5	Plasmapheresis	Continued hemodialysis
15	Wato *et al*.[15]	63/M	None	NA	NA	Plasmapheresis	Continued hemodialysis

M, male; NA, not available; F, female.

esis reportedly had no direct therapeutic effect, which was attributed to discontinuing gemcitabine administration.[18]

To confirm a diagnosis of HUS, a renal biopsy can be performed to show microvascular damage of arterioles and small arteries occluded by eosinophilic hyaline thrombi containing fibrin and platelet aggregates.[1] Generally, the histopathology of renal tissue in patients with HUS shows characteristic thrombotic microangiopathy consisting of thrombi in blood vessels, glomerular mesangiolysis, and widening of the subendothelial space with detachment of endothelial cells from the glomerular basement membrane.[4] A renal biopsy was scheduled for the patient in this case but he decided to cancel the procedure due to the high risk of bleeding. It is possible that a diagnosis of HUS may be delayed because anemia and thrombocytopenia can also be induced by myelotoxicity secondary to chemotherapy. In particular, an elevated reticulocyte count could differentiate between anemia due to myelotoxicity of gemcitabine and gemcitabine induced-HUS.[19] Furthermore, a sudden decrease in hemoglobin, sudden renal failure, uncontrolled hypertension, pulmonary congestion, peripheral edema, and thrombocytopenia should alert clinicians of the possibility of HUS. When HUS is suspected, peripheral blood smears should be screened for the presence of fragmented red blood cells and elevated LDH level.[20]

In conclusion, few cases of gemcitabine-associated HUS have been described. With the increase is the use of gemcitabine therapy for pancreatic cancer, it is important to quickly and accurately diagnose gemcitabine-associated HUS. This case report demonstrates that a patient could overcome this life-threatening crisis with early clinical detection and immediate discontinuation of gemcitabine.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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