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CASE REPORT

Hemolytic-Uremic Syndrome Associated with Gemcitabine: A Case Report and Review of Literature

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ABSTRACT

Context Hemolytic uremic syndrome is a rare condition compromising the clinical triad of acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. Hemolytic uremic syndrome may be associated with a variety of etiologies, and chemotherapeutic agents have also been reported to be associated with hemolytic uremic syndrome, including mitomycin, cisplatin, bleomycin, and most recently gemcitabine.

Case report A 72-year-old Caucasian male treated with four cycles of gemcitabine at 1,000 mg/m^2 developed clinical and laboratory findings compatible with hemolytic uremic syndrome. He developed microangiopathic hemolysis, rapidly declining renal function with proteinuria and hematuria, and renal biopsy revealed thrombotic microangiopathy. Hemodialysis, plasmapheresis, and corticosteroid therapy were utilized but the process ultimately was irreversible.

Conclusion With multiple reports of hemolytic uremic syndrome complicating gemcitabine therapy, it is imperative that clinicians heighten their awareness of this potentially lethal complication.

INTRODUCTION

Hemolytic uremic syndrome (HUS) is a rare condition compromising the clinical triad of acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia [1, 2]. Originally described in children with a preceding gastrointestinal infection with bloody diarrhea, it is now known that HUS may be associated with a variety of etiologies, and in adults is rarely associated with diarrheal illness [3, 4]. Etiologies associated with HUS include acute bacterial and viral infections, HIV disease, collagen vascular diseases, pregnancy and post-partum state, estrogen therapy, malignancy, and chemotherapeutic agents [5, 6, 7]. HUS has been associated with a variety of malignancies, most often metastatic adenocarcinomas including those from the stomach, colorectum, lung, breast, and pancreas [8, 9, 10, 11, 12, 13]. Mitomycin C (MMC) is the chemotherapeutic, most commonly known to be associated with HUS [14], but the exact pathophysiology of HUS with MMC is not clear. Additional chemotherapeutic agents have been reported to be associated with HUS, including cisplatin, bleomycin, and most recently gemcitabine [15, 16, 17].

Gemcitabine is a nucleoside analog structurally related to cytarabine [18] that is indicated for use in pancreatic and non-small

cell lung cancer, and utilized in a variety of malignancies including urothelial and ovarian cancers. The incidence of HUS in patients receiving gemcitabine is approximately 0.15% based on the reported cases in the literature [19]. We report here a patient with unresectable, locally advanced pancreatic cancer who developed a clinical picture consistent with HUS after 4 months of gemcitabine therapy and review the literature.

CASE REPORT

In October 2001, a 72-year-old Caucasian male with a history of coronary artery disease and hypertension noted changes in his skin color associated with dark urine and clay colored stools. He was admitted to an outside facility and underwent radiographic imaging that revealed a 2.8 cm mass in the head of the pancreas. The mass was noted to partially encase the superior mesenteric artery and vein. Endoscopic ultrasound with biopsy was performed revealing adenocarcinoma of the pancreas. His condition deteriorated over the following 2 weeks with onset of worsening abdominal pain and symptoms of indigestion and he was transferred to the Gastrointestinal Surgical Service at our facility. Following transfer in early December 2001, he was taken to the operating room for exploratory laparotomy and was deemed unresectable. The postoperative course was complicated by pneumonia and the patient required admission to the surgical ICU. He was evaluated by medical and radiation oncology at that time, confirming that the patient had locally advanced, unresectable pancreatic adenocarcinoma and was scheduled for outpatient evaluation following discharge.

The patient was seen in follow up on January 24th, 2002, and at that time was noted to have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 secondary to residual fatigue and generalized weakness. He was otherwise asymptomatic. Past medical history was as stated above and also included longstanding hypertension. Active medications included atenolol, simvastatin, aspirin, and sertraline. The patient denied known allergies. Physical exam noted emaciation and an intact jejunostomy tube, but was otherwise unremarkable. The patient's weight was 64.5 kg and was estimated to be 13.6 kg below his weight prior to becoming ill. Initial laboratory evaluation revealed hemoglobin of 10.6 g/dL (reference range: 13.5- 17.0 g/dL) with normal indices of anemia related to cancer (platelet count of 389,000 mm^{-3}, reference range: 150,000-400,000 mm^{-3}; serum creatinine of 0.9 mg/dL; reference range: 0.7-1.2 mg/dL) as well as, normal LDH, liver enzymes, and coagulation parameters. CA 19-9 was measured at a baseline value of 614 U/mL (reference range: 0-37 U/mL). Repeat abdominal CT scan revealed an increase in size of the pancreatic mass to 3.3x2.7 cm, along with portal caval nodal involvement, and new attenuation of the anterior duodenum.

Radiation oncology was again consulted and combined therapy with 5-fluorouracil (5-FU) and radiation therapy was considered. However, based on the patient's performance status, combined chemoradiotherapy was ultimately felt to be too intensive. After detailed discussion with the patient and his family, the decision was made to start single agent gemcitabine therapy. Gemcitabine was initiated at 1000 mg/m^2 i.v. weekly every three of four weeks. Additional supportive medications included megestrol and prochlorperazine as needed. He was also started on erythropoetin therapy at 40,000 U subcutaneously every week.

The patient was re-evaluated after 2 cycles of gemcitabine and found to have stable disease radiographically with a drop in his CA 19-9 from 614 to 350 U/mL. The patients overall performance status had not changed significantly and his weight remained stable. Review of systems revealed mild diarrhea as the only new problem, and this was well controlled with loperamide. The hemoglobin was stable at 10.2 g/dL, platelet count at 647,000 mm^{-3}, and serum creatinine at 1.0 mg/dL. Liver enzymes again were normal. The decision was made to continue with cycle three and four of gemcitabine therapy.

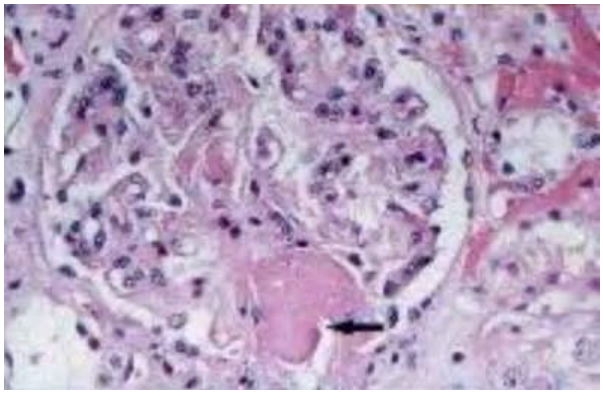

Figure 1. Findings of renal biopsy consistent with thrombotic microangiopathy (microvascular damages with arterioles and small arteries occluded by eosinophilic hyaline thrombi containing fibrin and platelet aggregates).

Therapy was continued through week two of cycle four. On May 23rd, 2002 (week 3 of cycle four), the patient was noted to have an elevated serum creatinine at 1.3 mg/dL, a hemoglobin of 8.3 g/dL, and a platelet count of 3,000 mm^{-3}. Evaluation revealed a normal fibrinogen level, normal coagulation parameters, reticulocyte count of 0.1% (reference range: 0.7-2.4%), and it was felt that his thrombocytopenia and anemia were likely due to bone marrow toxicity. One unit of apheresed platelets and two units of packed red blood cells were transfused with an appropriate one-hour response in the platelet count to 52,000 mm^{-3}. Two days later, the patient had repeat platelet count of 23,000 mm^{-3}, and a stable hemoglobin of 11.3 g/dL, but was noted to have a further decline in renal function with a serum creatinine of 2.4 mg/dL, a BUN of 38 mg/dL (reference range: 6-19 mg/dL), and new onset proteinuria and hematuria. There was no evidence of bleeding on physical exam, but the patient had developed 2+ bilateral lower extremity edema. Further laboratory evaluation revealed an elevated bilirubin at 1.2 mg/dL (reference range: 0-1.0 mg/dL), primarily indirect, normal coagulation studies, and normal fibrinogen. The reticulocyte count was 1.8%, and LDH elevated at 700 IU/L (reference range: 120-240 IU/L). The peripheral smear was evaluated and revealed numerous schistocytes per high power field. The patient was admitted for supportive care and workup for suspected HUS.

After admission to the hospital, the Nephrology Service was consulted as the patient continued to have decline in his renal function with the serum creatinine rising to 2.6 mg/dL. Creatinine clearance was measured at 18 mL/min (reference range: 97-137 mL/min), and urinary protein excretion totaled 4.8 g/24h (reference range: 0-0.15 g/24h). Renal ultrasound was normal. Renal biopsy was performed and findings were consistent with thrombotic microangiopathy (Figure 1). Plasmapheresis was initiated in a daily fashion and the platelet count and LDH remained essentially stable, however with continued worsening of the patient's hemoglobin and renal function, plasmapheresis was discontinued after five total treatments. With worsening uremia and volume overload, hemodialysis was warranted, and was continued as palliative therapy in the outpatient setting three times weekly.

DISCUSSION

Gemcitabine is a commonly used chemotherapeutic agent for cancers of the pancreas, breast, lung and many others. HUS associated with gemcitabine has been identified, but poorly described. The crude incidence of HUS associated with gemcitabine ranges from 0.078% (6 of 7,654) in the clinical trials to 0.008% (6 of 71,200) reported from spontaneous sources, with an overall incidence of 0.015% (12 of 78,854) [20, 21]. Potential underreporting is possible, especially from spontaneous sources, but when compared with the incidence rates ranging from 2.6-13.0% cited in the literature for either malignancy-induced or chemotherapy-induced HUS [20, 21], the incidence of HUS associated with gemcitabine is relatively rare. The median duration of therapy with gemcitabine in the literature is reported at 5.8 months, with the majority of patients developing HUS within 1 to 2 months month of the last infusion of gemcitabine [21].

Majority of reported cases who developed HUS had been receiving gemcitabine for few months to more than one year, and initially presented with mild to moderate elevation of BUN and creatinine levels [21]. Other findings included thrombocytopenia, and hemolytic anemia (fragmented red blood cells; an elevated LDH, bilirubin, and reticulocyte count; and decreased haptoglobin). Urinalysis showed mild proteinuria, microscopic hematuria, and cylindruria. A renal biopsy showed thrombotic microangiopathic changes. The patients were treated with plasmapheresis, corticosteroids, and/or hemodialysis. The outcome was dismal in most cases. In contrast to MMC, where a dose response relation is well documented for MMC-induced HUS [14], no such a correlation for gemcitabine has been observed.

The etiology of HUS perhaps is immunologic as demonstrated by improvement with therapies aimed at removing circulating immunocomplexes [1, 2, 22, 23] while others believe that microvascular injury is the cause of the condition [24, 25]. No such mechanism is known to gemcitabine-associated HUS. MMC is an antibiotic that contains quinone, urethane, and aziridine groups [14]. It is activated chemically and metabolically to a variety of alkylating moieties. However, gemcitabine is a pyrimidine antimetabolite [18] and no structural or pharmacological similarity between MMC and gemcitabine has been found. Similarly, cisplatin, bleomycin, and 5-FU (with which HUS occasionally has been reported to be associated) have no structural similarity with gemcitabine [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. On the other hand, cytarabine that contains a cytidine base like gemcitabine, has not been reported to cause HUS [18, 19, 21]. This indicates that HUS associated with gemcitabine is not a drug class effect.

Treatment modalities employed for HUS include immunocomplex removal (plasma-pheresis, immunoadsorption, hemodialysis, or exchange transfusion), antiplatelet/anti-coagulant therapies (antiplatelet drugs, heparin, prostacyclin, or splenectomy), immunosuppressive therapies (corticosteroids, vincristine, or azathioprine), and others (fresh frozen plasma transfusion) [1, 2, 21]. Most of such modalities of treatment are safe and quite effective, in particular if performed in a specialized setting.

Despite the availability of these treatments, the outcome with HUS is poor with a high mortality. Mortality rates rage from 10 to 40% in the majority of series [1, 2] to as high as 60-70% in others [20, 26]. Such a high mortality rate approaching 50% is not surprising because the majority of these patients had advanced disease.

It can be a challenge to discriminate between HUS associated with underlying malignancy versus that caused by chemotherapy [27, 28]. Review of literature suggests that cancer-associated HUS usually occurs during widespread metastatic disease or poorly controlled carcinomas, whereas chemo-therapy-associated HUS is more common when the patient is in disease remission or has minimal tumor burden [27, 28]. However, the discrimination is not always clear. Murgo [28] attempted to distinguish the characteristics of malignancy-induced and chemotherapy-induced HUS and identified several features to separate the two while Gordon and Kwaan [27] showed that there are more similarities than differences. Some researchers suggest the level of serum factors such as tumor necrosis factor-alpha, interleukin-1, and interleukin-6 as well as von Willebrand factor (vWF) antigen and low molecular weight vWF multimers may be used to distinguish between malignancy-associated HUS and chemotherapy-associated HUS [5, 24, 25, 29, 30]. However, such studies remain experimental and are not readily available in the majority of community settings.

Reasons for under diagnosis may include lack of high vigilance on the part of physician, unfamiliarity with this complication of the drug, myelosuppression related to chemotherapy, poor oral intake in an already ill patient, third spacing (ascites), older age or comorbid conditions (hypertension, diabetes, vascular disease). One must develop a high degree of suspicion in patients who develop

renal insufficiency in the presence of myelosuppression. One must look for laboratory suggestion of hemolysis with microangiopathy (fragmented red blood cells; schistocytes; burr cells; increased reticulocyte count, indirect bilirubin, and LDH; or fibrin split products) to distinguish isolated renal insufficiency in the presence of myelotoxicity from a true case of HUS. In addition, the Coombs' test should be negative in patients with renal insufficiency unrelated to HUS and the anemia and thrombocytopenia from myelosuppression should be more severe. A renal biopsy, if performed, will confirm the diagnosis by revealing the classic microvascular damages with arterioles and small arteries occluded by eosinophilic hyaline thrombi containing fibrin and platelet aggregates (Figure 1). In addition, the mild renal insufficiency should resolve quickly or return to baseline on rehydration or treatment of the underlying prerenal state.

CONCLUSIONS

HUS associated with gemcitabine is quite rare and no consistent risk factors have been identified. Confounding etiologies, including the primary malignancies or other underlying conditions may have contributed to some of these cases. There is no structural similarity between gemcitabine and MMC or other chemotherapeutic agents known to cause HUS. No difference in the incidence or mechanism related to different schedules (30-minute versus fixed dose rate (FDR)) is known. Clinicians caring patients who receive gemcitabine should be aware of this complication. Management with plasma-pheresis, hemodialysis, or corticosteroids should be undertaken after confirming diagnosis, consulting nephrologists, and weighing the appropriate risk *versus* benefit ratio.

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Abbreviations 5-FU: 5-flourouracil; ECOG: Eastern Cooperative Oncology Group; FDR: fixed dose rate; HUS: hemolytic uremic syndrome; MMC: mitomycin C; vWF: von Willebrand factor

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