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SHORT COMMUNICATION

Rituximab-based therapy for gemcitabine-induced hemolytic uremic syndrome in a patient with metastatic pancreatic adenocarcinoma: a case report

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Abstract
Purpose The purpose of this report is to describe the management and outcome of an unusual complication of a commonly used chemotherapeutic agent. Gemcitabine is a known risk factor for hemolytic uremic syndrome (HUS), which can often have a rapidly fatal clinical course despite intervention with steroids, plasmapheresis and hemodialysis.
Methods A retrospective report of the first case of gemcitabine-related HUS, in a patient with metastatic pancreatic adenocarcinoma, treated with a variety of standard therapies in addition to rituximab is presented. The hematologic response parameters and clinical outcomes to each of the therapies given are described.
Results Chemotherapy-induced HUS was aggressively treated with plasmapheresis, high-dose steroids, vincristine and rituximab. Platelet recovery and clinical improvement coincided with administration of rituximab. In addition, aggressive supportive measures to manage renal failure (hemodialysis) and labile hypertension, allowed this patient to have an extended survival as a result of successful therapy for this complication despite an underlying rapidly fatal malignancy.
Conclusion This case highlights the importance of timely application of aggressive measures even in patients with known diagnosis of a fatal malignancy as these interventions can prolong life and be of palliative benefit.

Keywords Pancreatic cancer · Rituximab · HUS · Gemcitabine · Chemotherapy

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Introduction

Gemcitabine or 2′, 2′-difluorodeoxycytidine is a pyrimidine antimetabolite that was introduced in 1987, for treatment of solid tumors. The first case of gemcitabine-related hemolytic uremic syndrome (HUS) was reported in 1994 [1], and since then there have been numerous other case reports describing this association. Gemcitabine is now an acknowledged etiological risk factor of non-diarrheal adult hemolytic uremic syndrome, making this a well-recognized though poorly understood phenomenon. The incidence varies between 0.008 and 0.078% [2], but in some series it has been as high as 2.2% [3].

The severity of gemcitabine-related hemolytic uremic syndrome, however, is difficult to predict. In some cases, patients improve simply by discontinuation of the drug and supportive care [4, 5], while other patients require plasmapheresis, steroids, hemodialysis [6–8]; and despite aggressive care, this complication often proves to be fatal. Occasionally, patients who recover can develop irreversible renal failure, and require hemodialysis for prolonged periods of time that can in poor prognosis patients extend the end of their lives [6, 7].

Thrombotic microangiopathy is a spectrum of diseases that includes HUS and thrombotic thrombocytopenic purpura (TTP), and is characterized by microangiopathic hemolytic

anemia, thrombocytopenia and acute renal failure. It is difficult to distinguish between the two, but fever and altered mental status are the more dominating symptoms in TTP, while renal failure is more typical of HUS. The histology and pathophysiology of each is believed to be different [9, 10]. There are no randomized controlled trials that can guide us in the management of thrombotic microangiopathy, but from information and research gleaned across the years, it has been felt that the endothelial cell damage that leads to platelet aggregation, fibrin formation and thrombus deposition seen in this disorder has an underlying immunological basis [11, 12]. The emerging trend now is to use immunosuppressive agents if the clinical course manifests itself as refractory or relapsing in nature, such that it does not respond to plasmapheresis and steroids.

In this context, there have been two case reports where rituximab, an anti-CD20 monoclonal antibody was used with success for treatment of HUS. The first case was of a 36-year-old female with familial HUS, who developed recurrent HUS after kidney transplant, and was treated with multiple courses of two weekly infusions of rituximab [13]. The second case was of a 26-year-old man who developed HUS after undergoing matched sibling allogeneic transplant for acute lymphoblastic leukemia and achieved complete resolution of HUS after four doses of daily rituximab [14]. Rituximab has also been used with excellent results in multiple cases of life threatening and chronic TTP, either alone or in combination with cyclophosphamide or vincristine [15–18]. Plasmapheresis is of questionable benefit in chemotherapy-associated HUS and we report the first case of gemcitabine-related HUS treated successfully with rituximab after failure to respond to plasmapheresis, steroids, hemodialysis and vincristine.

Case report

A 47-year-old Caucasian woman was diagnosed with metastatic pancreatic adenocarcinoma in August 2006, when she presented to a local emergency room with symptoms of progressively worsening epigastric discomfort and back pain that began eight months prior. CT scan of the abdomen and pelvis revealed numerous hypodense lesions throughout the liver, the largest one measuring 4 cm × 3.7 cm, and a 2.2 cm × 1.6 cm mass in the uncinate process of the pancreas. She was evaluated at our institute, and an ultrasound-guided needle biopsy of the liver lesion was performed, which revealed poorly differentiated carcinoma. On immunohistochemistry the tumor was an adenocarcinoma CK7 positive, CK20 negative, CA19-9 positive, AE1/3 positive and TTF1 negative, and serum CA 19-9 was elevated at 1592, consistent with metastases from the primary pancreatic tumor.

Palliative chemotherapy was initiated with gemcitabine, capecitabine and bevacizumab on a multi-center phase II clinical trial for advanced pancreatic cancer patients in September 2006. She received six and a half cycles on this protocol until January 2007. Gemcitabine was given as a weekly infusion for 2 weeks followed by 1 week off, at a dose of 1,000 mg/m^2 and bevacizumab was given intravenously 15 mg/m^2 every 3 weeks. Capecitabine was dosed at 825 mg/m^2 orally twice a day for 2 weeks, followed by 1 week off.

Restaging CT scans showed response to therapy with decrease in size of the liver lesions and pancreatic head mass consistent with stable disease per RECIST [19] criteria and CA19-9 response was also seen (Fig. 1). However, in January 2007, she developed grade 3 hypertension and grade 4 proteinuria consistent with nephrotic syndrome, attributed to bevacizumab—the anti-vascular endothelial growth factor (VEGF) therapy, and was then taken off this trial. Echocardiogram done at this time showed an ejection fraction of 70%. She was treated with a combination of three anti-hypertensive drugs and diuretics. On discontinuation of the bevacizumab, her hypertension gradually improved and two of the three anti-hypertensive agents were slowly tapered off.

The tumor marker, CA19-9 at this time started to trend upwards again, though restaging CT scans in January 2007 remained unchanged. She was then treated off protocol with gemcitabine and capecitabine. Gemcitabine was given at the same dose at 1,000 mg/m^2 weekly infusion for 2 weeks followed by 1 week off and capecitabine was dose-reduced to 750 mg/m^2 orally twice a day for 2 weeks followed by a week off due to prior mucositis and grade 2 neutropenia. She received another six cycles on this regimen from January to June 2007. Interim imaging continued to show stable disease and the serum CA19-9 started to trend down again.

In late May 2007, she reported new onset lower extremity edema. She had been taking furosemide 40 mg orally and this was increased to 60 mg/day with no improvement. It was felt that this fluid retention was secondary to gemcitabine, and dexamethasone 4 mg orally twice a day was

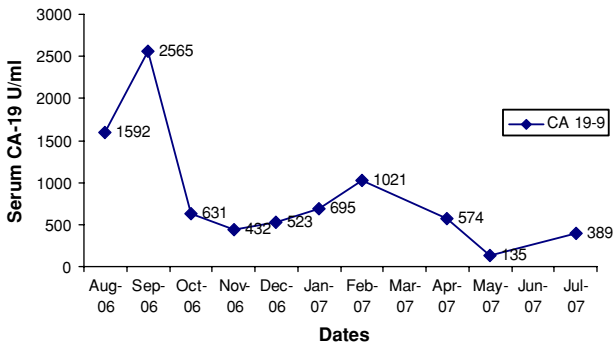

Fig. 1 CA19-9 Trend

added on days one to three of the chemotherapy cycle. However the peripheral edema continued to worsen and she developed facial and abdominal fluid retention and swelling, and also reported exertional dyspnea. In early June she was found to have a sudden decrease in her hemoglobin to 7.7 g/dL, for which she was transfused with packed red blood cells. Gemcitabine was discontinued at this time. One week later, she also developed thrombocytopenia with platelet count of 56,000/mm^3 and renal failure with serum creatinine of 1.9 mg/dL, and progressively worsening dyspnea, necessitating hospitalization. Physical examination including chest auscultation was unremarkable except for 2+ pitting edema of both lower extremities. Vital signs revealed a blood pressure of 174/91 mmHg, heart rate of 91/min at rest and 114–144/min with ambulation, respiratory rate of 24/min and pulse oximetry at rest of 96%, that decreased to 89% with ambulation. Ventilation-perfusion lung scan did not show any segmental defect consistent for pulmonary embolus, 12-lead electrocardiogram was normal and repeat echocardiogram showed normal ejection fraction and ventricular function. Chest x-ray showed evidence of bilateral pleural effusions with prominence of the pulmonary vascular markings compatible with congestive heart failure or fluid overload. Laboratory results showed a reticulocyte count of 6.8%, haptoglobin 2 mg/dL, lactate dehydrogenase (LDH) 4,686 U/L, platelet count 21,000/mm^3, serum creatinine 2.1 mg/dL, total bilirubin 2 mg/dL, direct bilirubin < 0.1 mg/dL, negative direct Coomb's, prothrombin time 13.8, activated partial thromboplastin time 45.2, CA19-9 135 U/L, and >300 mg protein and red blood cells >100 on urine analysis. Peripheral smear revealed schistocytes (Fig. 2) and given the clinical triad of hemolytic anemia, thrombocytopenia and renal failure, the patient was diagnosed with hemolytic uremic syndrome. Von Willebrand factor-cleaving protease (ADAMTS-13) enzyme level was normal.

She was initially treated with methylprednisolone 125 mg intravenously twice a day and plasma exchange. The plasma exchanges were performed via central line using a Fresenius AS 104 and FFP as the replacement fluid. She received thirteen procedures in fourteen days. This helped her dyspnea, but her serum creatinine continued to increase to 5.1 mg/dL, the LDH remained elevated and thrombocytopenia did not improve. Hemodialysis three times per week was initiated after eight plasma exchanges for management of non-oliguric renal failure, and although additional plasma exchange procedures were performed, it was eventually discontinued as the patient's parameters continued to worsen. She also had an episode hypertensive emergency with grand mal seizures, which were managed with intravenous labetolol infusion and phenytoin. Multiple anti-hypertensive agents were used to control her blood pressure, which was extremely labile. In the third week of her hospitalization vincristine was initiated at a dose of 2 mg intravenously once a week for 2 weeks. After the first infusion there was only minimal improvement; the LDH initially started to trend downwards but then started to climb again and the thrombocytopenia continued to worsen; and a decision to switch to rituximab was made. After the first dose of rituximab, the first signs of increase in her platelet count were seen, which was reinforced after the second infusion of rituximab 375 mg/m^2 1 week later. Normalization of the platelet count occurred on day fifteen after the first dose of vincristine, and ten days after the first rituximab dose and was accompanied by improvement in several clinical and laboratory parameters. Besides reversal of the thrombocytopenia, LDH started to rapidly trend downwards, plasmapheresis was no longer required, and steroids were able to be tapered (Fig. 3). She did not recover renal function however, and continued to require thrice weekly hemodialysis for the remaining months of her life. After a month long hospital stay for management of this life threatening complication she maintained a good quality of life on discharge, despite not receiving any further chemotherapy, and passed away four months later in November 2007.

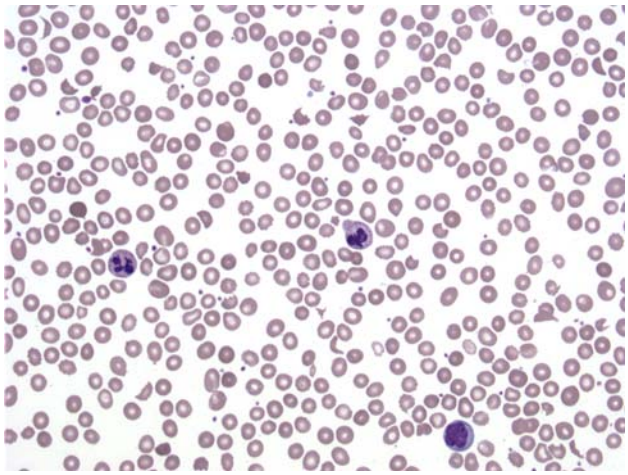

Fig. 2 Peripheral blood smear. Red blood cells show marked anisopoikilocytosis with frequent schistocytes (fragmented red blood cells) (Wright–Giemsa stain, ×400)

Discussion

Gemcitabine-related HUS is now a well recognized entity. It is vital for medical professionals caring for cancer patients to be aware of and cognizant of this rare but potentially fatal side effect of gemcitabine. Diagnosis may often be delayed as anemia and thrombocytopenia are attributed to myelosuppression secondary to chemotherapy, which is definitely more common [20]. However, a sudden drop in

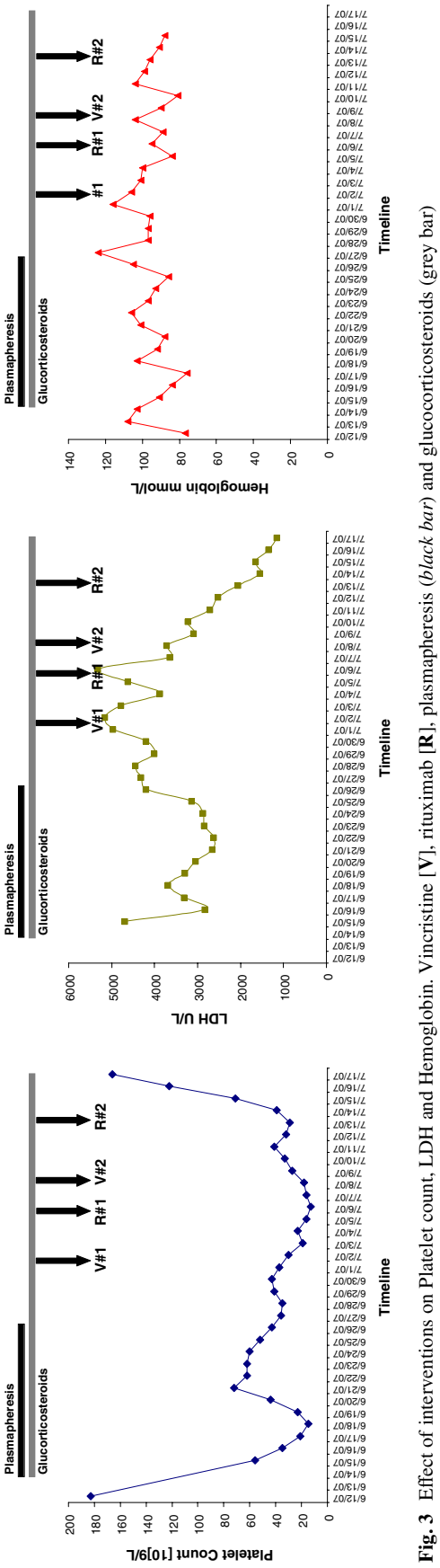

Fig. 3 Effect of interventions on Platelet count, LDH and Hemoglobin. Vincristine [**V**], rituximab [**R**], plasmapheresis (*black bar*) and glucocorticosteroids (grey bar)

hemoglobin, new-onset renal failure, new or worsening hypertension, pulmonary congestion, peripheral edema and dramatic decline in platelet count are warning signs that should alert providers to work up the patient for HUS/TTP. Workup should include reticulocyte count, LDH, peripheral smear for schistocytes and ADAMTS-13 antibody. ADAMTS-13, a disintegrin and metalloprotease with thrombospondin type 1 motif, cleaves ultra-large von Willebrand Factor (ULVWF) soon after secretion from endothelial cells. ULVWF is secreted into the circulation on endothelial damage and forms ligands with platelets and the endothelium leading to formation of occlusive platelet aggregates [21]. ADAMTS-13 is responsible for cleaving these large multimers, preventing formation of platelet-rich thrombi. Patients with TTP have either genetic or acquired deficiency or absence of this enzyme [12], but it is usually normal in patients with HUS. This has led to the belief that the inciting factor for endothelial damage seen in HUS is different from TTP, and may be attributed to dysregulation and activation of the complement cascade by deficient Factor H, which is a regulatory protein that inhibits complement activation via the alternative pathway [10]. Another hypothesis for cancer and chemotherapy-related HUS is the generation of soluble circulating immune complexes that trigger aggregation and deposition of platelets around areas of toxin-related endothelial damage in the kidney microvasculature [22].

There are only two case reports of rituximab use in HUS and ours is the third such case, though it has been much more widely used for treatment of TTP. The fact that this has been used successfully in both these conditions suggests that the etiopathogenesis of TTP and HUS are similar and that these indeed are part of the same clinical spectrum. There are no specific guidelines for treatment of HUS/TTP, and rituximab is used after failure of other strategies. Platelet response to rituximab when used for TTP has been as rapid as 1 week [18] and in HUS has been as early as 2–3 days [13, 14]. First signs of hematologic response to vincristine is also fairly rapid and occurs within a few days [23, 24]. Our patient had a swift clinical decline hence different therapies were attempted sequentially. Therefore a clear association between each therapy and response is difficult to discern. There were no signs of clinical or hematologic improvement after her initial vincristine dose, these appeared only after the first rituximab infusion and recovery was accelerated after the second rituximab infusion 1 week later. The authors believe that rituximab likely played a major role in the reversal of the underlying process causing her HUS. In view of our experience, we postulate that early intervention with rituximab may alter the clinical course and decrease morbidity and mortality of this disease, and if further experience consolidate our findings this may become the ‘standard of care’ for treatment of this complication. The

exact mechanism by which rituximab alters the downward spiral seen in HUS however remains unclear, although most likely this decreases circulating immune complexes by targeting the B cell lymphocytes. This reiterates the fact that the etiopathogenesis of HUS may be explained by an inciting agent (e.g. chemotherapy drug) that sets of an autoimmune process.

The life expectancy of a patient receiving palliative chemotherapy with gemcitabine for metastatic pancreatic adenocarcinoma is approximately 6 months [25]; however, our patient's survival on palliative chemotherapy was 8 months and with the aggressive measures employed to treat the treatment related toxicity, she survived for an additional five months without chemotherapy. Many patients with terminal illnesses are not offered aggressive and expensive interventions, as it is felt that the benefit would be minimal. This case highlights that therapies intended to be palliative can prove to be life-threatening. In these cases, aggressive interventions such as plasmapheresis, timely use of hemodialysis and off-label use of rituximab, can prolong life and have palliative benefit and hence maybe justified despite an underlying diagnosis of a rapidly fatal malignancy.

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