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CASE REPORT

Gemcitabine-induced haemolytic uremic syndrome, although infrequent, can it be prevented: A case report and review of literature

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Abstract

Gemcitabine is an antineoplastic used to treat several malignancies including pancreatic cancer. Its toxicity profile is well known with myelotoxicity, increased vascular permeability and peripheral oedema as most frequent adverse events. However, several cases of acute renal failure have been reported and haemolytic uremic syndrome (HUS) seems to be the underlying process. The cause of HUS remains unknown but its consequences can be lethal. Therefore, a high grade of suspicion is crucial to diagnose it and promptly treat it. This hopefully will reduce its morbidity. HUS is characterized by progressive renal failure associated with microangiopathic haemolytic anaemia and thrombocytopenia. The primary event is damage to endothelial cells and thrombotic microangiopathy (TMA) is the histopathological lesion. TMA affects mainly renal microvasculature. However, some cases evolve with central nervous or cardiovascular systems involvement. We present here a case of gemcitabine-induced HUS, with renal and cardiovascul-

ar system affected at the time of diagnosis which to our knowledge this is the first time of such case to be reported.

Key words: Thrombocytopenia; Haemolytic uremic syndrome; Thrombotic microangiopathy; Gemcitabine; Microangiopathic haemolytic anaemia

Core tip: Gemcitabine has a well-known toxicity profile though rare cases of acute renal failure caused by haemolytic uremic syndrome (HUS) have also been reported. The cause of HUS remains unknown but its consequences may be lethal. HUS consists of progressive renal failure with microangiopathic haemolytic anaemia and thrombocytopenia. Thrombotic microangiopathy is the histopathological lesion and this affects mainly renal microvasculature. We present a case of gemcitabine-induced HUS and review literature to make professionals fully aware of its existence, thus a high grade of suspicion might help with early diagnosis and prompt treatment which hopefully will reduce its morbidity.

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INTRODUCTION

Gemcitabine is an antimetabolite drug used in the treatment of several malignancies including pancreatic cancer[1]. Although it has got multiple adverse effects, the most relevant ones include myelotoxicity, increased vascular permeability and peripheral oedema. Unfortunately, several cases of acute renal failure have also been reported and haemolytic uremic syndrome (HUS) appears to be the underlying process. The cause of this syndrome and its treatment remain unknown[2] but its consequences may be lethal.

HUS is characterized by progressive renal failure associated with microangiopathic haemolytic anaemia and thrombocytopenia. The primary event in this syndrome's pathology is damage to endothelial cells. Thrombotic microangiopathy (TMA) is the key histopathological lesion for which the features are thickening and inflammation of the walls of arterioles and capillaries, disengagement of endothelial cells, accumulation of proteins and cellular debris in the endothelium, and the formation of platelet thrombi that obstruct the vessels lumen[3]. TMA involves mainly the renal microvasculature but involvement of the central nervous system, cardiovascular system, lungs, skin, skeletal muscle and gastrointestinal tract occurs in 20% of patients[4].

The most frequent cause of HUS is an infection by *Escherichia coli* which produces Shiga toxin. This is known as "typical HUS"[5]. However, other factors can also cause HUS, known as "secondary HUS". Among these factors, pregnancy, organ transplantation, other infections and medical treatments such as gemcitabine can be named[6].

The association of HUS with gemcitabine has been reported several times in the literature but to our knowledge this is the first case with cardiovascular system involvement at the time of diagnosis. The incidence of this complication seems to be low, but underreporting is also a possibility[7]. Although infrequent, HUS is a serious complication and a high grade of suspicion is needed to diagnose it early and initiate treatment. Uncertainty exists regarding the best treatment to apply, although discontinuation of gemcitabine is agreed as the first step. We present here a recent case seen in our Department. The patient has survived but unfortunately she remains dialysis dependent.

CASE REPORT

In April 2017, a 66-year-old Caucasian female with a history of a deep vein thrombosis after an air flight a few years back, was admitted due to extreme fatigue, peripheral oedema and general malaise. She had been previously diagnosed with an ampullary adenocarcinoma and underwent a Whipple's procedure (pancreatico-duodenectomy and splenectomy) in June 2016. Pathological results showed a pT4pN1 (3/5) R0 adenocarcinoma. Her postoperative period was a little difficult. She complained of restless legs, sleeplessness, occasional diarrhoea and vomiting not following any pattern. She required expert dietician to support. On the suspicion of pancreatic insufficiency, her pancreatic enzymes were increased. She was also started on Quinine Sulphate to help with restless legs and continued to take Omeprazole, Metoclopramide, Zopiclone and Erythromycin.

A few months after her surgery, she was started on adjuvant treatment with gemcitabine. Initially she had been planned for a combination with capecitabine but due to her diarrhoea, this plan was abandoned. The dose of gemcitabine was reduced for the first cycle in view of her long postoperative period to recover up to an acceptable level of fitness to start her adjuvant chemotherapy. The plan was to re-evaluate at the second visit.

She developed diarrhoea (3 episodes daily) and mild fatigue, phlebitis post-cannulation in arms and phlebitis in legs which were painful and hard to touch. She was then started on Rivaroxaban 10 mg daily and recommended to apply topical Hydrocortisone. She declined a PICC line. She also developed one episode of a prolonged chest infection without any neutropenia. This

was treated with Doxycycline and needed a delay of her planned 2nd cycle.

Due to all these side-effects, we decided to keep the dose reduced by 20% as performed for the first cycle. After cycle 4, she complained of sore mouth CTC (Common Terminology Criteria for Adverse Events used by oncologists to classify the intensity of side-effects (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm) grade 2 and continued with her usual diarrhoea although only CTC grade 1. Her haemoglobin levels had been fluctuating between 123 g/L and 95 g/L and her creatinine between 69 μmol/L and 107 μmol/L. At her pre-chemotherapy appointment for cycle 6 (last cycle), she complained of extreme fatigue and significant peripheral oedema lasting for the previous 2 wk. On the day of the appointment she was feeling significantly better and the oedema had significantly resolved. Following discussion with the patient about the risks of having the final cycle *vs* discontinuation, she proceeded with day 1 and day 15th, but to avoid day 8th as she would be on holidays.

Her haemoglobin was 78 g/L and her creatinine levels had increased to 146 μmol/L. At the time these were considered to be due to bone marrow toxicity with gemcitabine itself and the increased creatinine levels as being pre-renal cause, resulting from suboptimal fluid intake.

She went ahead with day 1 and received two units of blood with clinical benefit. Two weeks later, before day 15th, she presented to the acute medical oncology department with a complaint of extreme fatigue and weakness, peripheral oedema and feeling generally unwell, with mild dizziness and mild chest pain. On examination, she was tachycardic with a pulse of 120 bpm, blood pressure of 202/83 mmHg, respiratory rate of 18 and afebrile. She looked pale, dehydrated and with significant peripheral oedemas. She did not have any skin rash or purpura. Laboratory workup showed a creatinine of 392 μmol/L (baseline of 69 μmol/L), which gradually went up to 759 μmol/L in 48 h. Full blood count (FBC) showed haemoglobin of 92 g/L, hematocrit of 0.275 L/L, reticulocytosis of 3.2% and a white cell count of 22 × 10^9/L. Her platelet count was 77 × 10^9/L. Troponin was 509 ng/L and the electrocardiogram showed a NSTEMI with widespread T-wave inversion.

An echocardiogram showed all apical regions akinetic, with an ejection fraction of 45%, moderate diastolic impairment and a chest X-ray reported a mild left pleural effusion. Urinalysis showed mild proteinuria. The patient was intensively managed according to the unit relevant protocols. Her lactate dehydrogenase (LDH) level was elevated to 2328 iU/L (90-275) and haptoglobin was < 0.10 g/L (0.5-2.40). Her ADAMTS-13 levels were 87 (64-132). Peripheral smear was examined and showed anisocytosis, poikilocytosis, microspherocytes, rouleaux formation and few platelet clumps. An ultrasound of the renal tract demonstrated normal kidneys with non-obstructing features. A CT scan showed doubts with peritoneal metastases. The working diagnosis of HUS probably induced by gemcitabine was made as the patient had not had evidence of malignant recurrence. Her cardiology issues were optimised and she was started on steroids (high dose prednisolone) and although initially the patient was very reluctant to other treatments, eventually she accepted haemodialysis. She has been under close follow up and continues free of recurrence eighteen months after this episode. Her echocardiogram has shown improvement with hypokinesis of a single mid-septal segment. The remaining wall motion appears normal with globally preserved ejection fraction (> 55%) and left ventricular diastolic function is moderately impaired. She had received a total cumulative dose of 23940 mg of gemcitabine before cycle 6 and received cycle 6 day 1 as her haemoglobin drop was put in relation to gemcitabine haematological toxicity as mentioned above. The patient now feels clinically well although this has impacted negatively on her quality of life as she remains dialysis-dependant.

DISCUSSION

Gemcitabine is an antineoplastic agent commonly used in the treatment of several cancers such as pancreatic, lung, breast and other tumours. It is an analog of deoxycytidine and works as a pro-drug. Once transported into the cell, it must be phosphorylated by deoxycytidine kinase to change it into the active form that will inhibit DNA synthesis[1,8]. Several phase I studies of gemcitabine as single agent have recommended 1000 mg/m^2 administered as a 30 min infusion[8,9].

With this regimen, the toxicity profile is low, with myelosuppression as most frequent adverse event[10]. Other studies have shown similar efficacy with prolonged infusions[11], although some have suggested that it could increase cytotoxicity and survival[12]. However, it clearly increases the rate of haematological toxicities grade 3-4. Therefore, it continues to be administered as a 30 min infusion[13] in pancreatic adenocarcinoma.

Other side-effects include mainly increased vascular permeability and peripheral oedema but several cases of HUS have been documented as well[2]. It is difficult to estimate HUS incidence as it is easily underreported but the literature have published 0.078% in clinical trials and 4% when taken from spontaneous sources[14,15]. HUS is characterized by renal failure, thrombocytopenia and microangiopathic hemolytic anemia (MAHA), proteinuria and haematuria. MAHA consists of increased levels of LDH, low haptoglobin and the presence of schistocytes on the peripheral blood smear. Unfortunately HUS diagnosis is often delayed due to the fact that anaemia and thrombocytopenia might be attributed to myelotoxicity of the drug itself[16]. However, when these toxicities are combined with renal insufficiency, a high index of suspicion is needed to prompt a laboratory workup looking for signs of haemolysis[17].

There are other reasons leading to the difficulties

in diagnosis. The lack of physicians' awareness or the patients' poor oral intake, diarrhoeas, older age or co-morbid diseases such as hypertension, diabetes, or vascular disease, may contribute. Glezerman *et al*[18] reviewed 29 patients with gemcitabine nephrotoxicity and described new onset or worsening hypertension in 26; oedema, shortness of breath and congestive heart failure in 21, 15 and 7 patients respectively[18]. All of them developed anaemia, thrombocytopenia and elevated serum LDH. Haptoglobin was low and schistocytes were present in most of them[18]. These authors concluded that gemcitabine-induced HUS presents as new-onset renal failure with hypertension, thrombocytopenia and MAHA, but agree that the final diagnosis is not easy and emphasise again the relevance of a high index of suspicion[18].

In addition to this, there could be patients showing only a small decrease in renal function. In these patients, an increase in serum creatinine might be the only sign of HUS[19]. However, physicians need to know that mild renal deterioration resolving quickly on rehydration is not related to HUS. To add even more difficulties, some patients develop livedo reticularis in lower extremities or digital necrosis as an early sign of HUS[20]. We have recently published a review of 157 patients on adjuvant gemcitabine for pancreatic adenocarcinoma. Two patients developed gemcitabine-HUS. Both had a drop in haemoglobin of 37% and 34% from the baseline levels and a drop in creatinine clearance of 41% and 31%. Logistic regression analysis showed that a drop in haemoglobin > 25% and in creatinine clearance > 30% from baseline, increased significantly the chances of ending on hemodyalisis (P = 0.0001)[21]. We proposed that in those suspicious cases, gemcitabine should be at least delayed to undertake all those extra laboratory tests and confirm or dismiss this diagnosis before a final decision regarding gemcitabine continuity is made[21].

Serke *et al*[17] recommended reticulocyte-counting if patients develop anaemia or thrombocytopenia. If strongly elevated, this supports hyperregenerative anaemia due to haemolysis, ruling out myelotoxicity. Coombs test can also be performed and it should be negative if renal insufficiency is not related to HUS[22]. Finally, in some cases, a renal biopsy could be considered to be able to confirm this complication[22]. In the case presented here, we established the diagnosis based on clinic-analytical parameters and although a renal biopsy was considered and discussed, this was finally abandoned. To throw more challenges to the diagnosis, timing and cumulative dose behind HUS are variable[7,14,15,23,24]. Whereas Fung *at al*[15] documented HUS within 1 to 2 mo of the last infusion with a median of cumulative dose of 18252 mg/m^2, Flombaum *et al*[25] reported a broad range of cumulative doses, from 2450 to 48000 mg/m^2. None of these authors found a dose-response relationship[24]. HUS may also occur many months after the last infusion[25,26]. As such this variability further clouds the its' recognition and so encourages awareness that it is a risk, possibly serious of this treatment. Unfortunately its prognosis is poor, with mortality rates ranging from 10% to 40% in most series[27] to as high as 60%-70% in others[23].

Although gemcitabine-induced HUS occurs in early and advanced disease, older literature reviews indicate that it is more frequent when the patient is free of disease or has minimal tumour burden[25]. However, HUS could be cancer associated as well but this is more frequent with metastatic disease[25,27]. The mechanism or mechanisms behind HUS are unknown, but one hypothesis propose a micro vascular endothelial injury as the key. This may be *via* a direct gemcitabine interaction or indirectly following neutrophil or platelet activation[28,29].

Others are inclined to think that the origin is immunologic, following the observation that there appears to be benefit from treatments that remove circulating immunocomplexes or from immunosuppressants[30]. Reduced complement and partial reduction in the activity of ADAMTS13 (< 60% of normal activity) have been documented in most patients with atypical HUS, respectively. This has led to the proposal that functional tests of ADAMTS13 should be considered in these patients[31]. Consistent with this observation, metastatic cancers may have reduced serum ADAMTS13 activity[32]. Another mechanism taken into consideration is the activation of the clotting pathway following gemcitabine drug-induced endothelial injury[33].

In addition platelet activation may be a secondary response to endothelial injury[34]. In TMA, the renal and cerebral vessels are commonly involved, while the pulmonary and hepatic microvasculature is usually spared. Evidence also indicates that acute myocardial infarction is an early, frequent and severe complication during TMA[35]. A study with 74 patients with TMA (not associated with gemcitabine) showed that 18% had acute myocardial infarctions, 9 non- and 5 ST-segment elevation. All these episodes happened 5 ± 3 d after the TMA diagnosis predominantly in thrombotic thrombocytopenic purpura. This caused left ventricular dysfunction in 3 of 8 survivors[36].

Cardiac complications are frequently seen in thrombotic thrombocytopenic purpura and also occur in atypical HUS. Therefore these patients should be assessed for cardiac sequelae[36]. Our patient showed signs of myocardial infarction in the context of haemolysis which we have not seen reported before in gemcitabine-induced HUS, and this was an early complication. Another issue with gemcitabine-induced HUS is the optimal management. Immediate discontinuation[19] seems appropriate as first step, although it is unknown whether this ameliorates the course of the syndrome. Other interventions include steroids, transfusions, dialysis, plasmapheresis, vincristine, rituximab and more recently eculizumab[5,29] with limited effectiveness[16,30,31]. Plasmapharesis has shown to modify the evolution of haemolytic anaemia but not in renal impairment[5,29].

Recent studies have explored the use of Rituximab

(an anti-CD20 monoclonal antibody) and Eculizumab. Eculizumab is a recombinant humanized monoclonal antibody that binds to complement C5 protein and inhibits its cleavage, preventing the generation of the inflammatory peptide C5a and the cytotoxic membrane-attack complex C5b[9,37]. The most frequent side-effects are headache, anaemia and diarrhea[38]. Neisseria meningitidis vaccination is also indicated at least two weeks prior to treatment[39]. It has shown a fast and sustained interruption of the TMA process in patients with non-atypical HUS, including those with drug-induced HUS[40] and it has been associated with significant long-term improvements in renal function, the interruption of plasmapheresis and important reductions in the need for dialysis[6]. Al Ustwani *et al*[19] have reported resolution of the haemolysis and thrombocytopenia in four patients with gemcitabine-induced HUS. Renal function improved significantly although it did not return to baseline and only one patient required temporary haemodialysis, but renal function subsequently improved[19]. Although Eculizumab has been recently approved by FDA for atypical HUS, its role in malignancy or chemotherapy induced HUS has not been defined[41,42] and its current cost limits accessibility[19].

Bharthuar *et al*[43] presented a case of gemcitabine-induced HUS which was aggressively treated with plasmapheresis, high-dose steroids, vincristine and rituximab. The patient improved clinically and the platelets recovered concurrently with administration of rituximab but needed aggressive supportive measures to manage renal failure (haemodialysis) and hypertension.

Ritchie *et al*[44] reported their experience of managing three patients with pancreatic adenocarcinoma who developed gemcitabine-induced HUS. One patient showed some benefit with plasmapheresis and rituximab resulted in durable resolution of HUS in the others. These authors concluded that immune based therapies seem to reverse haemolysis and stabilise renal function[44].

Although there is an urgent need for better therapy, it seems that immunotherapy offers promise but requires more evaluation. In the case reported here, we did not see any significant benefit with steroids but the patient was very reluctant to receive any other treatments. She was not keen on trying any other options after knowing potential side-effects and the uncertain benefits. Rituximab and Eculizumab were mentioned in the discussion but finally abandoned for these reasons. It was only after several long discussions with the patient and a significant clinical deterioration that she finally accepted haemodialysis. We can conclude here that gemcitabine-induced HUS is a rare but serious toxicity with significant morbidity and mortality that requires prompt diagnosis and intervention. We hope that this article would help all professionals, making them aware of this extremely serious syndrome. Subtle signs such as increase level of serum creatinine or a significant drop in haemoglobin should flag an alert. Gemcitabine should then be withheld to undertake all the required laboratory workup to confirm or dismiss this diagnosis. However, as previously discussed, it is unknown if this measure would be able to stop or minimize the damage already initiated.

ARTICLE HIGHLIGHTS

Case characteristics

A 66-year-old female developed a significant renal impairment and anaemia while receiving adjuvant Gemcitabine.

Clinical diagnosis

She was diagnosed with haemolytic uremic syndrome.

Laboratory diagnosis

Her laboratory tests showed haemolysis and ruled out any myelotoxicity.

Imaging diagnosis

An electrocardiogram showed a NSTEMI with widespread T-wave inversion. A renal US did not show any evidence of lesion or cortical damage.

Pathological diagnosis

Although considered a renal biopsy, this was finally declined.

Differential diagnosis

Myelotoxicity and general decline with low intake and dehydration but these were ruled out immediately after receiving results showing haemolysis. Myocardial infarction as the cause but ruled out after parameters showing haemolysis, and considered a consequence of the haemolysis as part of the thrombotic microangiopathy (TMA).

Treatment

Steroids were tried and she was also started on aspirin. Haemodialysis was needed.

Term explanation

HUS: Haemolytic uremic syndrome; TMA: Thrombotic microangiopathy.

Experiences and lessons

Subtle signs such as increase level of serum creatinine or a significant drop in haemoglobin should flag an alert in patients on Gemcitabine. Although it is unknown if by withholding Gemcitabine this would be able to stop or minimize the damage already initiated, this should be done until all the laboratory workup to confirm or dismiss the diagnosis has been performed and received.

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