CASE REPORT

Gemcitabine-induced haemolytic uraemic syndrome in pancreatic adenocarcinoma

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SUMMARY

A woman in her mid-70s with metastatic pancreatic adenocarcinoma presented with fatigue, nausea and bilateral leg swelling, 4 days after an intravenous gemcitabine infusion. Additional examination and laboratory tests showed mild hypertension, low haemoglobin, high lactate dehydrogenase, low platelet count and high serum creatinine. The patient was subsequently diagnosed with haemolytic uraemic syndrome (HUS), and gemcitabine administration was immediately ceased. The patient received a 5-day course of methylprednisolone, with a full recovery being made 10 days after diagnosis. Clinicians should be aware of the rare but serious complication of gemcitabine-induced HUS (GiHUS), as early diagnosis and management, which includes prompt discontinuation of gemcitabine, are crucial in promptly resolving this condition. This case report describes one treatment that can be used for the treatment of GiHUS, while briefly covering some other novel treatments that have been described in other studies.

BACKGROUND

Gemcitabine, a nucleoside analogue, has commonly been used to treat pancreatic adenocarcinoma, a disease with an extremely poor prognosis and with a 5-year survival rate of approximately 5%.^{1,2} This chemotherapeutic agent has shown to have a good antitumour activity for unresectable local or metastatic pancreatic adenocarcinoma.^{3,4} Clinical trials have additionally shown increased survival in pancreatic cancer with nab-paclitaxel, in addition to gemcitabine.² Despite having a favourable toxicity profile, one rare but serious complication associated with gemcitabine is haemolytic uraemic syndrome (HUS), a thrombotic microangiopathic disorder with an approximate incidence between 0.015% and 1.4% in pancreatic adenocarcinoma patients.^{3,5–8} HUS is characterised by the following diagnostic criteria: microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury.^{9,10} There is no correlation between gemcitabine dose and gemcitabine-induced HUS (GiHUS), as even a low cumulative dose of 4 g/m² for a small duration (1.1 months) can also induce HUS.^{11–16}

One of the problems with GiHUS is in its delay in manifestation and difficulty in its diagnosis, as typical features of HUS are not always seen in GiHUS.^{7,13,16–19} Thus, treatment is occasionally delayed, often resulting in the unsuccessful management of this condition.^{7,11,13,18–22} If inadequately

managed, persistent HUS can proceed to further complications such as end-stage renal disease and long-term neurological sequelae (including coma or seizures).^{4,8,9} The purpose of this case report is to present a patient with pancreatic adenocarcinoma who has developed GiHUS. Additionally, we will be describing our management to GiHUS, as well as reviewing the current literature regarding treatment options for this serious complication.

CASE PRESENTATION

A Caucasian woman in her mid-70s with stage IV metastatic pancreatic adenocarcinoma, presented with fatigue, nausea and bilateral leg swelling, 4 days after her chemotherapy infusion. She had a history of hypothyroidism, with a thyroidectomy undergone 25 years ago and is currently taking thyroxine. She had just begun her fourth cycle of chemotherapy, which included the regimen of intravenous nab-paclitaxel and gemcitabine. All agents were given as a weekly infusion for 3 weeks at the following doses: nab-paclitaxel at 100 mg/m² and gemcitabine at 790 g/m².

A thorough physical examination at presentation was conducted. Vital signs revealed a blood pressure of 161/77 mm Hg, heart rate 85 beats/min, respiratory rate of 16 beats/min and oxygen saturation of 99% on room air. Cardiac examination revealed pale conjunctiva, multiple ecchymoses throughout the trunk and upper limb, and bilateral lower limb oedema to the knees. Respiratory, neurological and abdominal examination showed no abnormalities.

INVESTIGATIONS

Laboratory tests on admission showed a haemoglobin of 68 g/L (120–150 g/L), platelet count $27 \times 10^9/L$ ($150\text{--}400 \times 10^9/L$), serum creatinine 103 $\mu\text{mol/L}$ ($50\text{--}90 \mu\text{mol/L}$), lactate dehydrogenase 360 U/L ($50\text{--}150 \text{U/L}$), haptoglobin 0.12 g/L ($0.47\text{--}2.1 \text{g/L}$) and a reticulocyte count of 5.1% ($0.5\%\text{--}1.5\%$). Schistocytes were also present on her peripheral blood smear. Her disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) level was normal. CT and ultrasound of the kidneys revealed no renal abnormalities. A diagnosis of HUS was determined after the criteria of microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure were met. Although a renal biopsy can also confirm the diagnosis of HUS to show arteriolar microvascular damage and thrombi occluding arteries, this

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procedure has a high bleeding risk and was unnecessarily invasive for severely ill patients such as herself.

DIFFERENTIAL DIAGNOSIS

Gemcitabine myelotoxicity.

TREATMENT

Transfusion of two units of fixed frozen platelets and 3 units of packed red blood cells did not resolve the anaemia and thrombocytopenia. Supportive therapy such as antihypertensives (amlodipine 10 mg) and diuretic (frusemide 20 mg) medication was administered but did not improve her lower extremity oedema nor her hypertension. After HUS was diagnosed, gemcitabine was immediately discontinued and intravenous methylprednisolone was administered; 1 g for 1 day, then 500 mg for the next 4 days.

OUTCOME AND FOLLOW-UP

A few days after the patient's initial dose of methylprednisolone, her platelet level and blood pressure normalised, with her haemoglobin level showing signs of improvement and her lactate dehydrogenase levels tending downwards. After a 10-day hospital stay, she was discharged without any further evidence of HUS.

A 4-month follow-up showed she was tolerating her new chemotherapeutic regimen of only nab-paclitaxel, with a normal blood count and renal function.

DISCUSSION

GiHUS is characterised by the triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury. However, early recognition of this condition is often delayed, as the first two signs can mimic the myelotoxicity of gemcitabine. Clinical cues such as new onset peripheral oedema and hypertension should alert the clinician of the likely diagnosis being HUS. New-onset hypertension and peripheral oedema are features that have been mentioned in previous case reports as the early signs of GiHUS before an official diagnosis was made.^{7 11 14–18 22–26}

Clinicians should be encouraged to perform a full investigation and workup at the slightest suspicion for HUS, which includes lactate dehydrogenase, reticulocyte count and a peripheral blood smear for schistocytes.²⁷ An ADAMTS-13 test could help differentiate between HUS and thrombotic thrombocytopenic purpura if there is any diagnostic uncertainty.^{27 28} Management is different between these two conditions, as plasmapheresis is indicated in the treatment of thrombotic thrombocytopenic purpura, but its use to treat atypical HUS (such as GiHUS) is still controversial.^{11 21 29 30}

The pathophysiology of GiHUS is unclear, with some authors suggesting that a dysregulation of the alternative complement pathway could be linked in causing endothelial damage to glomerular capillaries and the formation of thrombi.^{12 14 31} It has been proposed that gemcitabine could cause the alternative pathway to become uncontrolled, leading to the formation of the membrane attack complex and other immunological factors that could lead to endothelial cell damage, platelet activation and renal failure, features that are characteristic of HUS.^{11 12 31} Pathological findings of complement and immunoglobulin G deposition in the endothelium further support the possibility of an immunological role in endothelial damage and of GiHUS.^{12 31}

There is currently no consensus on the gold-standard treatment for GiHUS in patients with pancreatic adenocarcinoma. The most important step after diagnosing that the patient has

HUS is to immediately discontinue gemcitabine in treated patients.^{12 28 31 32} Following this, a range of treatment modalities can be given, such as plasmapheresis, corticosteroids, haemodialysis and monoclonal antibodies, to reverse the condition in patients.^{28–32} Further complications of HUS can be avoided such as seizures, comas and end-stage renal disease, with adequate management of GiHUS.^{4 8 9} GiHUS is not to be confused with the paraneoplastic manifestation of HUS that is associated with pancreatic cancer, which can occur in patients who have not undergone gemcitabine treatment.³³

In our patient, termination of gemcitabine treatment and administration of intravenous methylprednisolone helped reverse their GiHUS. However, this does not always hold true, as many case reports discuss the inefficacy of plasmapheresis, corticosteroids and/or plasma exchange therapy in improving renal function and thrombotic microangiopathic process in many of the patients.^{5 14 16 17 29} There have been emerging therapies to salvage patients from GiHUS, which target the immune system and hope to correct the underlying pathology and complement dysregulation involved in GiHUS. For pancreatic adenocarcinoma patients, administering rituximab (anti-CD20 monoclonal antibody) has shown promising signs, with none of the treated patients dying subsequently from HUS-related injuries.^{11 26} More recently, eculizumab (anti-complement C5 monoclonal antibody) has been trialled successfully for the treatment of GiHUS for patients with proven complement dysregulation.¹⁶ Atypical HUS (such as GiHUS) secondary to defective complement regulation should be considered if the following is present: previous personal or family history of HUS, unexplained anaemia and insidious onset.^{34 35} Appropriate workup to prove the involvement of complement dysregulation should include: measurement of component 3 (C3), component 4 (C4), complement factor H (CFH), CFH autoantibodies, complement factor I (CFI) and complement factor B (CFB) levels, and surface expression of membrane co-factor protein (MCP) on mononuclear leucocytes via flow cytometry.³⁴ However, due to its costs and its specialised use in patients with proven complement dysregulation, only a few patients diagnosed with pancreatic cancer (4) with GiHUS have been documented for treatment with eculizumab.^{16 32 34}

Learning points

- Haemolytic uraemic syndrome is a rare but serious complication of gemcitabine therapy in patients with pancreatic adenocarcinoma.
- Early signs of gemcitabine-induced haemolytic uraemic syndrome (GiHUS) include new-onset persistent hypertension and peripheral oedema.
- Investigations such as a full blood picture with a lactate dehydrogenase level, peripheral blood smear and reticulocyte count are essential in diagnosing GiHUS.
- Recognising the condition early is important, as prompt discontinuation of gemcitabine and administering salvage therapy such as corticosteroids is the best way to treat GiHUS and to avoid long-term complications such as end-stage renal disease and neurological sequelae.
- Emerging targeted immunotherapies such as rituximab have proven to be useful alternatives to treat GiHUS, if other modalities fail.

Contributors AnD: performed the renal function tests and subsequent blood tests. Add: wrote the background and the discussion. AnD: wrote the case presentation and investigations. TC wrote the treatment, differential diagnosis, treatment and follow-up. Add and AnD: made attempts to contact the patient's family. Add, AnD

and TC: analysed and interpreted the patient's data and blood results; were major contributors in writing the manuscript; read and approved the final manuscript; drafted the work for important intellectual content; approved the final version to be published; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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