CASE REPORT

Eculizumab therapy in gemcitabine-induced thrombotic microangiopathy in a renal transplant recipient

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Abstract
A renal transplant recipient 7 years post-transplantation, diagnosed with locally advanced pancreatic adenocarcinoma developed thrombotic microangiopathy (TMA) after treatment with gemcitabine and nab-paclitaxel. Gemcitabine was the most likely cause for TMA and was ceased. He received methylprednisolone and plasma exchange with fresh frozen plasma and albumin. Despite plasma exchange, his renal allograft function worsened, and he had persistent haematological evidence of haemolysis. Eculizumab was commenced with resolution-significant improvement in his renal and haematological markers. This case highlights an unusual occurrence of progressive gemcitabine-induced TMA in a renal allograft that had an excellent response to eculizumab. The clinical response also demonstrates involvement of complement dysregulation in gemcitabine-induced TMA.

INTRODUCTION
Thrombotic microangiopathy (TMA) is a rare condition of uncontrolled complement activation with high mortality and morbidity characterized by microangiopathic haemolytic anaemia, thrombocytopenia and microvascular thrombosis. We present the case of a 56-year-old male 7 years post-replacement transplantation, diagnosed with TMA after treatment with gemcitabine for locally advanced pancreatic cancer. We highlight the importance of recognition of TMA and its triggers, and the use of eculizumab for progressive gemcitabine-induced TMA.

CASE REPORT
This report describes a 56-year-old male with a deceased-donor renal transplant for end-stage kidney disease secondary to autosomal dominant polycystic kidney disease 7 years post-transplantation, who was diagnosed with locally advanced pancreatic adenocarcinoma with no evidence of metastatic disease. The patient was on peritoneal dialysis for 2 years prior to transplantation. Maintenance immunosuppression was prednisolone and tacrolimus. Other immunosuppressive agents
(mycophenolate mofetil and azathioprine) were not tolerated due to cytopenias. His past history included hypertension, cluster headaches, Graves' disease managed with radio-iodine therapy and a prior cutaneous basal cell carcinoma. Medications were felodipine, atorvastatin, duloxetine, omeprazole and thyroxine. He lived at home with his wife, was independent and previously employed as a disability support worker. He never smoked, and he drank alcohol occasionally.

Treatment for the locally advanced pancreatic adenocarcinoma, consisted of gemcitabine (1000 mg/m², i.e. 1700 mg...
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Figure C: Temporal association with commencement of Gemcitabine and TMA.

Figure D: Serum creatinine (μmol/L) trend with treatment.

Over 5 cycles of gemcitabine, his serum creatinine climbed from baseline 80–90 μmol/L to 140–150 μmol/L (reference interval [RI], 64–104 μmol/L) associated with relative hypertension (140/80 mm Hg from a systolic blood pressure at baseline of 110–120 mm Hg), peripheral oedema, microscopic haematuria (RBC 200 × 10^6/L [RI], <10 × 10^6/L) and proteinuria (urine protein/creatinine ratio increased from 10 mg/mmol to 251 mg/mmol, [RI, <133 mg/mmol]). A percutaneous renal transplant biopsy demonstrated chronic TMA with extensive glomerular double contours and fibrin thrombi. C4d stain was negative (Fig. A and B). Haemoglobin was 90 g/L (RI, 130–180), and platelet count was 263 × 10^9/L [RI, 150–400]. Haptoglobin was 0.5 g/L [RI, 0.3–2.0 g/L], and lactate dehydrogenase was 683 U/L [RI, <250 U/L]. Blood film demonstrated fragmented red cells. Coagulation profile was normal, ADAMTS13 was 81% [RI, 40–130%] and faecal Shiga-toxin polymerase chain reaction was negative. His albumin was 28 [RI, 35–50 g/L] with normal liver function tests. His C4 was low, 0.13 [RI, 0.16–0.47], and C3 was low-normal, 0.91 [RI, 0.90–1.80]. See Table 1 for blood tests results.

Gemcitabine was the most likely trigger given the temporal association between drug exposure and onset of TMA (Fig. C). The other causes for TMA considered in this patient included calcineurin inhibitor use, antibody-mediated rejection and malignancy. The patient had been on tacrolimus since 2011 with stable therapeutic serum drug levels (trough levels 3 to 5 μg/L). The absence of donor specific anti-HLA antibodies reduced the likelihood of antibody mediated rejection as the direct cause of the TMA. Malignancy was not progressive on serial imaging.

He received three doses of 500 mg methylprednisolone and 2 weeks of alternate day plasma exchange with fresh frozen plasma and albumin. Despite plasma exchange, his creatinine rose to 170 μmol/L and blood film continued to demonstrate...
red cell fragmentation. Gemcitabine was ceased. Tacrolimus was continued.

Eculizumab induction was commenced at 900 mg weekly for 4 weeks, followed by 1200 mg of eculizumab at week 5. He was maintained on 1200 mg eculizumab fortnightly. He received prophylactic pneumococcus, meningococcal B and conjugate ACWY and haemophilus influenzae type B conjugate vaccinations and commenced lifelong amoxicillin for meningococcal prophylaxis.

Within 4 weeks, his renal function improved to creatinine 130–140 μmol/L, and there was no persistent red cell fragmentation on blood film (Fig. D and E). During the eculizumab treatment period, he received radiotherapy plus infused 5-fluorouracil for treatment of the pancreatic adenocarcinoma. Eculizumab therapy was continued for 4 months after discontinuation of gemcitabine. Two months after cessation of eculizumab, the patient maintains improved renal allograft function (serum creatinine 90–120 μmol/L [RI, 64–104 μmol/L]), a stable haemoglobin (∼120 g/L [RI, 130–180]), platelet count (∼120 \times 10^9/L [RI, 150–400]) with no evidence of haemolysis.

**DISCUSSION**

TMA is a rare condition of uninhibited complement activation with microvascular thrombosis, microangiopathic haemolytic anaemia and thrombocytopenia [1], classically described as three different entities with variable presentations [2]. Haemolytic uraemic syndrome (HUS) results from endothelial damage as a complication of Shiga toxin-producing Escherichia coli enteric infections. TTP is due to severe ADAMTS13 deficiency (activity, <10%) leading to uncleaved von Willebrand factor multimers. Atypical HUS is unregulated complement activity in the alternative pathway associated with a genetic or acquired factor [3, 4]. The latter entity was the diagnosis in this patient.

Gemcitabine is commonly used to treat lymphomas, bladder, ovarian, pancreatic and breast cancers [5]. TMA has been reported following gemcitabine with an incidence of 0.008–0.4%, a mean duration of 7.4 months between commencement of cyto-

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**Figure E:** Haemoglobin (g/L) and platelet count (×10^9/L) with treatment.

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toxic therapy and onset of TMA and a median cumulative dose of 20,000 mg/m² or 21.9 doses [6, 7]. It is suggested that gemcitabine has direct endothelial toxicity releasing large amounts of von Willebrand factor multimers with concomitant activation of the coagulation cascade [5].

Genetic and autoimmune factors can predispose to aHUS [8]. Genetic analysis for mutations associated with complement dysregulation in this patient was negative for any pathogenic sequence variation in complement factor H, factor I, factor B, complement regulatory protein and complement components 3 and 5 ex21, ADAMTS13, complement factor H-related protein 5, DGKE (encodes diacylglycerol kinase ε), ethylmalonic aciduria and homocystinuria type C protein and thrombomodulin.

Management of reported cases of gemcitabine-induced TMA has included drug-cessation, glucocorticoids, fresh frozen plasma infusions and plasma exchange. Eculizumab, a humanized IgG monoclonal antibody that binds to C5, is a novel therapy for drug-induced TMA that halts the terminal complement complex, effectively interrupting TMA [9, 10].

This case highlights an unusual occurrence of progressive gemcitabine-induced TMA in a renal allograft that responded to eculizumab, demonstrating involvement of complement dysregulation. Although the patient had an excellent response from the point of view of the TMA and renal allograft function, further studies are needed to clearly define the risks and benefits of eculizumab therapy for chemotherapy-induced TMA in the presence of malignancy.

**CONFLICT OF INTEREST STATEMENT**

None declared.

**FUNDING STATEMENT**

No funding was received for this study.
ETHICAL APPROVAL
Consent was obtained from the patient involved in the study.

CONSENT
Written informed consent was obtained from the patient for publication of this case report.

GUARANTOR
Francesco Ierino.

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