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Rapid Improvement in Gemcitabine-associated Thrombotic Microangiopathy After a Single Dose of Eculizumab: Case Report and Review of the Literature

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Abstract. *We present here the case of a 39-year-old man with metastatic pancreatic carcinoma receiving chemotherapy with the combination of gemcitabine and nab-paclitaxel as part of a clinical trial. Despite an impressive response to therapy, he ultimately developed profound anasarca, renal insufficiency, progressive cytopenias, and malignant hypertension 6 months into his treatment course. The diagnosis of gemcitabine-associated thrombotic microangiopathy (G-TMA) was made based on renal biopsy, and receipt of the anti-C5 monoclonal antibody eculizumab proved successful at reversing his deteriorating clinical course and improving his laboratory parameters. This case illustrates the importance of recognizing this rare but serious complication, and highlights one potential therapeutic option that can be used in the appropriate clinical context.*

The nucleoside analogue gemcitabine, originally approved by the Food and Drug Administration in 1996 for the treatment of advanced pancreatic cancer, is now used extensively as part of combination chemotherapy regimens for a variety of solid tumor indications, including not only carcinomas of the pancreas but also those of the breast, ovary, lung, and biliary tract (1-5). While stereotypical side effects of gemcitabine (most commonly cytopenias, nausea, flu-like symptoms, myalgias, and rash) are well-recognized and generally manageable with appropriate supportive care measures, other less common toxicities associated with this cytotoxic agent can also contribute to significant morbidity and even mortality (6). However, these rare events may often go unrecognized by treating medical providers and have less well-defined algorithms for appropriate management and treatment. One of the more serious complications, thrombotic microangiopathy (TMA), can be associated with severe kidney injury, dialysis dependence, and death. We present here the case of a patient with metastatic pancreatic cancer receiving gemcitabine-based chemotherapy as part of a clinical trial who developed florid TMA 6 months into treatment. After progressively worsening symptoms, his disease course was successfully reversed with administration of a single dose of the terminal complement inhibitor eculizumab.

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Case Presentation

The patient was a previously healthy 39 year-old man who presented with progressive left calf pain and swelling which extended proximally up to the knee over the next several months. A Doppler ultrasound showed an extensive deep venous thrombosis involving the proximal to distal left lower extremity including the femoral vein, popliteal vein and peroneal vein, extending into the inferior vena cava and right common femoral vein, for which he was started on low molecular weight heparin (enoxaparin, 1 mg/kg BID dosing).

Further diagnostic evaluation included computed tomographic (CT) scans of the chest, abdomen, and pelvis which revealed a 6.9 cm pancreatic tail hypoattenuating mass, innumerable hepatic lesions measuring up to 4.7 cm, and multiple retroperitoneal and peripancreatic lymph nodes up to 1.5 cm in size, along with bilateral lower lobe subsegmental pulmonary emboli. Fine needle aspiration of one of the liver lesions showed poorly differentiated carcinoma, with immunostains positive for cytokeratin 7 and deleted in pancreatic cancer (DPC)-4 and negative for cytokeratin 20, chromogranin and synaptophysin, trypsin, as well as caudal type homeobox (CDX)-2. Baseline laboratory

studies were notable for an elevated alkaline phosphatase (326 IU/l; normal range, 31-95 U/l) and cancer antigen (CA) 19-9 level (73,870 U/ml, normal range 0-37 U/ml).

The patient's past medical history included gastroesophageal reflux disease, asthma, and a history of tonsillectomy and undescended testicle repair. His family history was notable for a maternal grandmother diagnosed with colon cancer at the age of 60. He did report light cigarette use as well as alcohol consumption in moderation.

After considering standard-of-care and experimental treatment options, he enrolled on a clinical trial evaluating chemotherapy with gemcitabine plus nab-paclitaxel at standard dosing (gemcitabine 1,000 mg/m^2 and nab-paclitaxel 125 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) together with a combination immunotherapy regimen which included an immune checkpoint inhibitor [anti-programmed cell death protein-1 (PD-1) monoclonal antibody]. Treatment was associated with an excellent clinical, radiographic, and biochemical response; CT scans after his initial 2 cycles demonstrated a partial response [-33% reduction by response evaluation criteria in solid tumors (RECIST)], and after completion of 6 cycles his measurable disease had decreased by 62% (Figure 1). Meanwhile, his CA19-9 levels decreased from 83,000 U/ml at the start of therapy to 10 U/ml over that same period of time.

Following his 7th cycle of treatment, he began experiencing progressive fatigue, nausea, abdominal distention, lower extremity and scrotal edema, and total-body anasarca with a 38 lb weight gain over a one-month period for which he was initiated on furosemide 40 mg PO daily. This conferred minimal benefit and study treatment ultimately had to be held midway through cycle 8. Transthoracic echocardiogram was performed showing normal left ventricular function (ejection fraction of 55-60%). Urinalysis was notable for a protein level of 100 mg/dl, large hemoglobin, white blood cells <5 per high power fields (hpf), red blood cells 11-20 per hpf, and 6-10 hyaline casts.

One month later, he was admitted to the hospital due to worsening symptoms and for expedited diagnostic workup. Laboratory studies at the time of admission were notable for a serum creatinine of 1.9 mg/dl (baseline: 0.8 mg/dl), hemoglobin of 8.8 g/dl (baseline: 15 g/dl), and platelet count of 146,000/μl (stable). Hemolysis workup showed a haptoglobin level at <6 mg/dl (normal range=36-195 mg/dl) and an elevated lactate dehydrogenase level at 405 U/l (normal range=102-119 U/l); blood smear was notable for rare schistocytes (0 to 1 per hpf) and tear drop cells (2 to 5 per hpf). Serum complement levels (C3 and C4) were within normal range.

A kidney biopsy was performed next as part of his further diagnostic evaluation. This showed mesangial expansion with occasional schistocytes, thickened capillary walls with narrowed lumens, extensive reduplication of glomerular basement membranes, and fibrinoid necrosis of arterioles with intraluminal thrombi (Figure 2). Immunofluorescence staining was positive for IgM (2+ arteriolar), C3 (2+ arteriolar), and C1q (2+ arteriolar). These findings were indicative of thrombotic microangiopathy (TMA). ADAMTS13 activity was also measured and found to be normal at 100% (reference range, 40-130%), ruling out the likelihood of immune-mediated or familial TTP (thrombotic thrombocytopenic purpura). Therefore, the development of the patient's TMA was felt to be most likely attributable to gemcitabine (G-TMA).

During the patient's hospital course, he was diuresed aggressively with intravenous furosemide, with his serum creatinine rising to 2.8 mg/dl by the time of discharge. Hematologic parameters remained stable throughout admission. He was discharged with plans for short-term outpatient follow-up with both Nephrology and Medical Oncology. However, he subsequently re-presented to the hospital less than two weeks later for blurry vision in his left eye and an elevated blood pressure of 199/113 (baseline: 130/70). Ophthalmologic exam showed retinal hemorrhages and retinal disc edema with concern for impending central/branch retinal vein occlusion. Brain MRI demonstrated scattered subcortical and periventricular T2/FLAIR hyperintense white matter, likely representing the sequelae of chronic microangiopathic ischemia.

The patient declined admission and was discharged on carvedilol; however, five days later he returned to the hospital with worsening headaches, dizziness, lightheadedness, persistent blurry vision, chest pressure, and shortness of breath, at which time his blood pressure was markedly elevated at 213/121. He agreed to re-admission and was started on aggressive anti-hypertensive and fluid management. Laboratory studies early during his hospital course showed elevated creatinine levels (3.14 mg/dl) as well as worsening thrombocytopenia (49,000/μl) and anemia (6.7 g/dl).

At this point, due to his florid symptoms together with progressive renal dysfunction and cytopenias, consultative hematology services recommended the use of eculizumab (anti-C5 monoclonal antibody) therapy for treatment of his G-TMA. He received his first dose of eculizumab at 900 mg intravenously, with gradual improvement of his symptoms and laboratory parameters over the succeeding several days. He was eventually discharged to home 5 days later in stable clinical condition on bumetanide, carvedilol, and amlodipine. Although original plans for additional outpatient doses of eculizumab had to be cancelled due to financial concerns (approximate per-dose cost of eculizumab=$18,000 USD), within one month his anasarca had fully resolved; his serum creatinine had plateaued at 1.73 mg/dl, and his cytopenias had improved (hemoglobin 11.4 g/dl, platelets 103,000/μl).

Repeat CT scans following this 3-month period off anti-cancer therapy showed that his pancreatic cancer had progressed modestly. He resumed chemotherapy with FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) and completed a total of 7

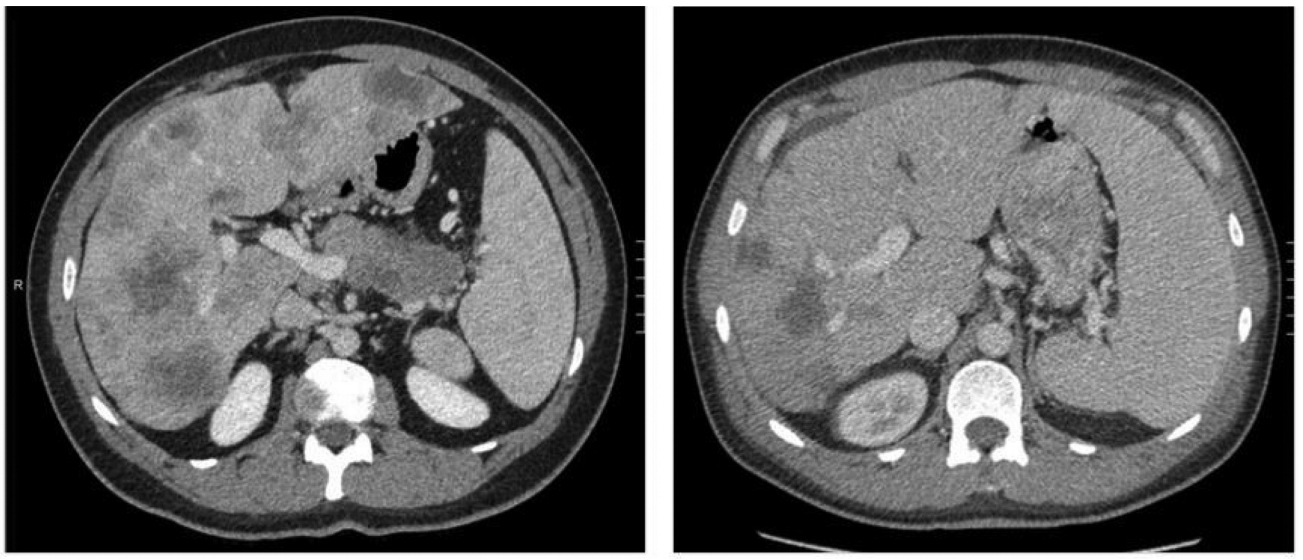

Figure 1. *Abdominal CT scans at baseline (L) and after 6 months of treatment (R).*

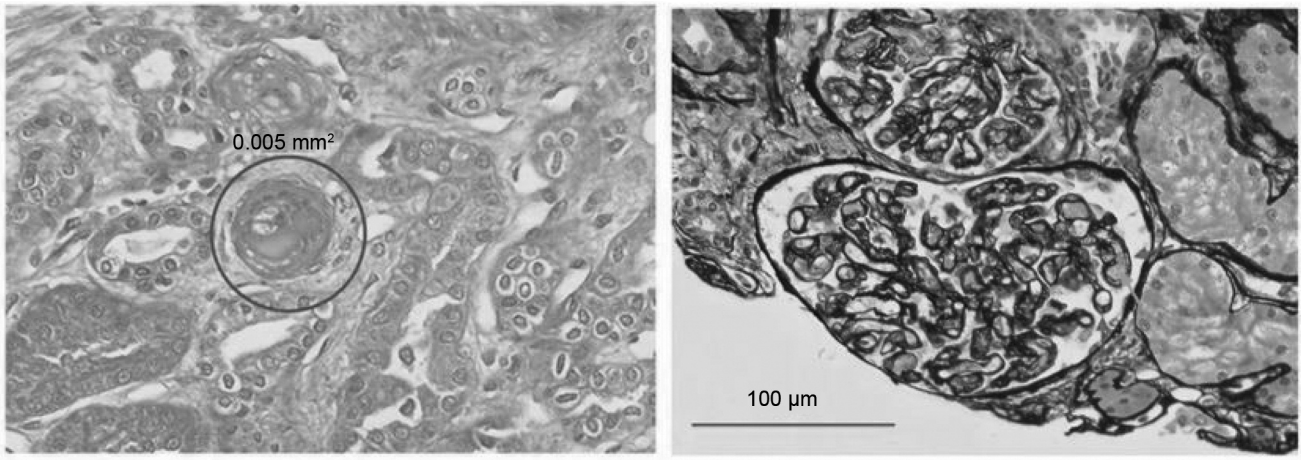

Figure 2. *Trichrome stain, 40× (L) and PAS-Jones stain, 40× (R). Trichrome stain shows fibrinoid necrosis in an arteriolar wall (circle). PAS-Jones stain shows fibrin thrombi in glomerular capillaries (middle arrow) as well as focal basement membrane reduplication (outer arrows).*

cycles before electing to discontinue treatment due to cumulative asthenia, peripheral sensory neuropathy, and anorexia. He ultimately expired two months later secondary to disease progression.

Discussion

Thrombotic microangiopathies represent a group of disorders, the most common of which include TTP and hemolytic uremic syndrome (HUS), that are characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end organ damage (especially renal failure) resulting from the formation of microscopic thrombi within small blood vessels (7). A number of pharmacologic agents have been implicated in the development of TMA at varying incidences, including chemotherapeutic and targeted cancer therapies (7-9). The initial case reports of gemcitabine-induced TMA (G-TMA) included one patient enrolled on a phase II trial of gemcitabine in advanced pancreatic cancer while this drug was still in clinical development (10); and subsequently, following its FDA approval, in a patient with non-small cell lung cancer who ultimately developed dialysis-dependent chronic renal failure despite early initiation of steroids and plasmapheresis (11). A subsequent publication in 1999, including both interrogation of

the manufacturer's safety database and literature review, found 12 cases meeting either clinical or pathologic criteria for HUS out of a total of 78,800 patient exposures, for an overall incidence rate of 0.015% (12). Later studies suggested a slightly higher incidence of G-TMA ranging from 0.3 to 1.4% (13-17). The true incidence may be difficult to establish due to the overlap of symptoms associated with cytotoxic chemotherapy, including anemia and thrombocytopenia, as well as an underreporting of mild disease symptoms and lack of familiarity regarding this phenomenon (18). While the exact pathophysiology of G-TMA remains unknown, direct endothelial damage by the drug may play a role, causing release of large amounts of von Willebrand factor (vWF) multimers that leads to platelet aggregation and fibrin deposition (19). An immunological explanation also represents a plausible alternative or additional mechanism, given pathological findings of complement and immunoglobin deposition as well as the presence of circulating immune complexes in patients with this diagnosis (20).

Descriptions of the natural course of, and treatment outcomes for, G-TMA have largely been derived from published case reports and single-institution experiences (13, 14, 16-18, 20-26). The largest and most comprehensive study to date consists of a retrospective cohort analysis by Daviet and colleagues (6), detailing 120 cases that were reported to the French Pharmacovigilance Network and the French TMA Reference Center between 1998 and 2015. Patients were identified by either a renal biopsy or a combination of two symptoms from the classical TMA triad (hemolytic anemia, thrombocytopenia, and/or acute kidney injury). In this cohort, G-TMA was diagnosed after a median of 210 days on treatment, with the most common clinical symptoms being hypertension (62.7%) and edema (56.7%). Almost all patients had laboratory evidence of hemolytic anemia (95.6%) and acute kidney injury (97.4%), while thrombocytopenia was observed in 74.6% of subjects. Treatment approaches varied widely, with the most common being plasma exchange, fresh frozen plasma (FFP), and steroid administration. In total, the reported complete remission rate was 42.1%; however, not surprisingly, there was considerable morbidity and mortality associated with G-TMA, including more than a quarter of patients (27.8%) who required hemodialysis. Additionally, of the 52 patients in whom the survival status was known, 19 deaths (36.5%) were directly attributable to G-TMA.

Suspicion or confirmation of a diagnosis of G-TMA should prompt immediate discontinuation of gemcitabine and implementation of supportive care measures, including rigorous blood pressure management. For more severe cases, such as the case of our patient, therapeutic considerations in addition to plasma exchange, FFP, and corticosteroids may include immunomodulatory monoclonal antibodies such as rituximab (anti-CD20) (27-29) and eculizumab (anti-C5). Eculizumab, which was originally approved by the FDA in 2007 for treatment of paroxysmal nocturnal hemoglobinuria and subsequently for treatment of atypical hemolytic uremic syndrome (aHUS) in 2011, inhibits complement-mediated intravascular hemolysis by preventing formation of C5a and membrane attack complex (C5b-C9) in the alternate pathway of the complement system. The first successful case report of this agent in G-TMA was described in 2013 in a patient with hemodialysis-dependent renal insufficiency refractory to steroids, plasma exchange, and rituximab (30). However, data remain very limited overall in terms of the safety and efficacy of this approach and its optimal timing relative to other interventions (19, 30-34). The largest reported series comes from the French retrospective cohort study, in which a total of 5 patients with G-TMA received eculizumab, 4 in whom plasma exchange had previously been tried (6). Clinical outcomes in this group varied; one patient achieved a complete remission of TMA, and while 3 others reached hematologic remission, 2 remained dialysis-dependent until death.

Specific to our patient, the onset of signs and symptoms suggestive of TMA occurred approximately 6 months into his treatment course. While these findings could have potentially been directly attributable to his underlying malignancy, cancer-associated TTP typically occurs in the setting of poorly controlled carcinomas, whereas chemotherapy-associated TMA is more common when individuals have well-controlled disease (35), such as in this patient's case. Moreover, as he was concurrently receiving immunotherapy with an anti-PD-1 monoclonal antibody as part of a clinical trial, the possibility of immune-related or allergic interstitial nephritis (AIN), which can be seen in up to 2.2 percent of individual treated with immune checkpoint inhibitors (36), was originally considered on the differential diagnosis. Urine findings can be quite variable in AIN, with only half of patients demonstrating pyuria and one-quarter with hematuria; therefore, a kidney biopsy was ultimately required to establish the diagnosis of TMA. Whereas in AIN, renal biopsy typically shows CD3+ T lymphocytes in the interstitium of the kidney associated with tubular inflammation, pathologic hallmarks of TMA include edematous intimal thickening of the arteries, endothelial cell swelling, microvascular obstruction, and luminal thrombi and fibrinoid necrosis affecting both the glomeruli and vessels. Ongoing endothelial damage can lead to reduplication of glomerular basement membranes. These distinct features, present in our patient's kidney biopsy, allowed us to rule out an autoimmune etiology and make a more definitive diagnosis of TMA.

As his clinical picture worsened, the decision was made to try eculizumab first rather than either immunosuppressive medications or plasmapheresis. Dosing was adapted from the aHUS protocol, which consists of weekly intravenous infusions of eculizumab at 900 mg for 4 weeks, 1200 mg *i.v.*

on week 5, then 1200 mg *i.v.* every other week thereafter. The patient received meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB) vaccines as prophylaxis before initiating treatment due to the increased risk of *Neisseria meningitidis* infection associated with this agent. Quite remarkably, his clinical picture and laboratory parameters began improving almost immediately after receipt of his first dose, and based on this improvement, along with financial considerations (high co-pays associated with his insurance plan coupled with the expense of eculizumab), he did not receive subsequent doses as originally planned. It is difficult to ascertain whether eculizumab was solely or primarily responsible for reversing the course of his G-TMA; the time elapsed since discontinuation of the offending chemotherapy agent (2 months) may certainly also have contributed to its resolution. While he ultimately improved sufficiently to be able to resume chemotherapy safely, we felt that rechallenging with gemcitabine-based chemotherapy represented too great a risk despite the excellent tumor response he had achieved earlier and rare reports describing safe rechallenge (31). He was instead treated with a fluoropyrimidine-based regimen commonly used in the second-line setting, and eventually succumbed to cancer-related complications unrelated to G-TMA.

In summary, while TMA remains a fairly rare complication in cancer patients receiving gemcitabine-based chemotherapy, it should be considered on the differential diagnosis for individuals who develop new-onset hypertension during the course of treatment, unexplained renal insufficiency (independent of volume depletion from dehydration), along with the more common and expected adverse events of gemcitabine including edema and cytopenias. Heightened awareness of G-TMA and screening for such signs and symptoms of this entity may allow for earlier diagnosis and discontinuation of gemcitabine, resulting in a higher likelihood of resolution and less associated morbidity and mortality such as end stage renal disease (21). While clinical experience to date does not allow for clear recommendations regarding the appropriate selection and sequence of interventions for G-TMA, our patient's case demonstrates the utility of eculizumab as one potentially effective, if costly, therapeutic approach.

Conflicts of Interest

AHK has received research funding (paid directly to his institution) from Celgene, Roche/Genentech, Bristol-Myers-Squibb, and Merck. None of the other Authors have any conflicts of interest to disclose.

Authors' Contributions

STB: Manuscript writing. LD: Patient care, manuscript review and editing. NA: Patient care, manuscript review and editing. ZL: Patient care, manuscript review and editing. AHK: Conceptualization, patient care, manuscript writing.

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