INTRODUCTION

Thrombotic microangiopathies (TMAs) are life-threatening clinical syndromes due to dysregulation of the complement and coagulation cascades. When a precipitant to endothelial injury persists (e.g., from infection, drug, autoimmunity, malignancy, or pregnancy), particularly in the setting of an acquired or genetic defect in complement and/or coagulation regulatory proteins, then alternative complement activity propagates abnormally without inhibition. Pathologically, this results in microvascular thrombosis with a predilection for glomeruli. Clinically, microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury ensue with the attendant risks of irreversible kidney damage, dialysis dependence, and death.

The chemotherapy drug gemcitabine has been implicated as one such precipitant to the development of TMA. Although anti-complement therapy is the approved treatment for complement-mediated TMA, the optimal therapy for drug-induced TMA (DITMA) is unknown. Progressive kidney injury has been observed in most patients with gemcitabine-induced TMA (GITMA) despite drug discontinuation and treatment with plasma exchange, plasma infusions, and/or glucocorticoids. However, the description of using the terminal complement blocker eculizumab for the treatment of GITMA has been mainly limited to case reports. Moreover, there are only scant data published on renal and hematologic outcomes of patients rechallenged with gemcitabine after prior GITMA.

Here, we report a case of a patient with GITMA with progressive TMA despite drug discontinuation, who was then successfully treated with eculizumab, and finally restarted on gemcitabine using concomitant eculizumab to prevent recurrent TMA; a strategy that, to our knowledge, has not been reported to date.

CASE PRESENTATION

A 29-year-old man with a history of cholangiocarcinoma presented to the hospital for evaluation of new-onset hypertension and edema. Six months before presentation, the patient began treatment for unresectable intrahepatic cholangiocarcinoma. He received gemcitabine 1000 mg/m² intravenously (IV) and cisplatin 25 mg/m² IV on days 1 and 8 of each 21-day cycle for a total of 9 cycles. This resulted in cumulative doses of 18,000 mg/m² and 450 mg/m² for gemcitabine and cisplatin, respectively.

On presentation, his blood pressure was 162/108 mm Hg. Laboratory testing revealed a serum creatinine (SCr) of 1.2 mg/dl (baseline 0.7 mg/dl 6 months prior with subsequent gradual uptrend), hemoglobin 7.5 g/dl (baseline 12.6 g/dl), platelet count 160 K/ml, lactate dehydrogenase (LDH) 635 U/l (normal range, 110 to 210 U/l), haptoglobin <10 mg/dl, and schistocytes (1+) on peripheral blood smear. Urinalysis was significant for blood (2+) and protein (2+). Examination of the urine sediment revealed the presence of non-dysmorphic red blood cells and granular casts. His spot urine total protein:creatinine ratio was 0.9 g/g. Testing for a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), antinuclear antibody, human immunodeficiency virus, and direct antiglobulin were negative. Testing for C3,
C4, fibrinogen, prothrombin time, and partial thromboplastin time were normal. The absence of diarrhea precluded testing for Shiga toxin. There was no known family history of a thrombotic microangiopathy. Functional and genetic complement studies were not pursued. A kidney biopsy was deferred. A clinical diagnosis of GITMA, or atypical hemolytic uremic syndrome, was made. In addition to discontinuation of gemcitabine and cisplatin, the patient was treated with furosemide, carvedilol, and amlodipine, and provided transfusion support with packed red blood cells. He was discharged home with a blood pressure of 130/80 mm Hg, SCr 1.1 mg/dl, hemoglobin 9.5 g/dl, and platelet count 180 K/µl.

Four weeks after hospital discharge and without intervening chemotherapy, laboratory testing showed SCr 2.1 mg/dl, LDH 698 U/l, hemoglobin 7.9 g/dl, and platelet count 77 K/µl. At this point, the patient was initiated on eculizumab at 900 mg IV weekly for 4 doses followed by 1200 mg every 2 weeks starting on week 5 for 2 doses (6 total doses). The LDH rapidly improved (Figure 1A), and the SCr level reached a nadir of 1.3 mg/dl (Figure 1B). The platelet count (Figure 1C) and haptoglobin level also normalized.

Over the subsequent 6 months after stopping gemcitabine, the patient’s malignancy progressed despite undergoing sequential treatment with fluorouracil, isocitrate dehydrogenase 1 inhibitor therapy, and folic acid, fluorouracil, and oxaliplatin. Gemcitabine and cisplatin were subsequently restarted. The patient received three infusions of gemcitabine at 800 mg/m², 700 mg/m², and 500 mg/m², respectively, over 25 days (Figure 1). One week before restarting gemcitabine, eculizumab was reinitiated as a measure to minimize the risk of recurrent TMA. He received eculizumab 900 mg IV weekly for 4 doses. After the first gemcitabine infusion, there was a transient decrease in the platelet count to 82 K/µl accompanied by leukopenia and worsening anemia that was attributed to myelosuppression from gemcitabine. The cell count levels immediately improved after the subsequent gemcitabine doses were reduced. In addition, he was hospitalized after his third gemcitabine infusion for evaluation of altered mental status. On admission, his SCr was 1.9 mg/dl. Evaluation revealed new ascites, splenomegaly, and left hydronephrosis with obstructive nephrolithiasis. The SCr level rapidly decreased to

Figure 1. Clinical course of patient treated with eculizumab (Ecu). Shown is the trend of the lactate dehydrogenase (LDH) (a), serum creatinine (b), and platelet count (c) throughout exposure to gemcitabine (Gem) (pink capped line), followed by treatment with eculizumab (blue arrows), and finally during gemcitabine rechallenge with concomitant eculizumab. Day 0 represents initiation of gemcitabine after cancer diagnosis. A rapid decline in LDH is noted after initiating eculizumab (a). The serum creatinine decreased to a nadir 1.3 mg/dl after eculizumab. The serum creatinine increased to 1.9 mg/dl during gemcitabine rechallenge. It rapidly (continued) improved with volume expansion and was attributed to pre-renal azotemia (b). The platelet count improved after eculizumab. There was a transient decrease in platelet count after the first gemcitabine rechallenge dose accompanied by leukopenia and worsening anemia that was attributed to myelosuppression from gemcitabine. The cell count levels improved after the subsequent gemcitabine doses were reduced (c).
1.3 mg/dl after volume expansion with intravenous crystalloids. The serum LDH, haptoglobin, and blood pressure remained normal throughout gemcitabine rechallenge. Because of continued cancer progression, the patient died 2 months later after his care was transitioned to comfort measures only.

**DISCUSSION**

This case report of a patient with GITMA shows several key features of the clinical presentation, management, and recurrence of GITMA. First, it adds to the growing body of literature on the association of TMA and gemcitabine (Table 1). Second, it emphasizes the typical presenting features of GITMA — a long duration of exposure, a high cumulative dose, a gradual increase in SCr over months before recognition of TMA, and new-onset hypertension and edema as the initial clinical finding. Third, it highlights that a mainstay of therapy for DITMA (drug discontinuation and supportive care) alone failed to control disease activity and delayed definitive therapy. Fourth, it adds to limited literature on the successful therapeutic use of terminal complement blockade with eculizumab for GITMA. Finally, it describes the clinical course — notably absent findings for recurrent TMA — after rechallenge with gemcitabine using concomitant eculizumab; a strategy which, to our knowledge, has not been reported to date.

Gemcitabine is a deoxycytidine analog that acts as a DNA polymerase inhibitor. It is a commonly used cytotoxic drug with a broad spectrum of activity against many malignancies. The results of its phase I first-in-human clinical trial were published in 1991. In 1994, Casper et al. first reported a case of hemolytic-uremic syndrome in a patient receiving gemcitabine. In 2015, Al-Nouri et al. conducted a large systematic review of DITMA and found 85 individual patients with GITMA reported in the literature. Lastly, in 2019, Daviet et al. retrospectively identified 120 patients with GITMA across France from 1998 to 2015, which is the largest cohort published to date. Current estimates of the incidence of TMA among patients treated with gemcitabine range between 0.3% and 2.2%. Although GITMA is uncommon, its risks of severe kidney damage and death warrant careful monitoring of renal and hemolytic parameters in all patients undergoing treatment with gemcitabine.

The mechanism of GITMA is unknown. Gemcitabine is speculated to directly disrupt the endothelium and expose the subendothelial extracellular matrix, which promotes complement fixation, platelet aggregation, and thrombosis. Furthermore, hyperactive complement activity on the platelet surface could further promote complement deposition and thrombosis. This mechanism of drug toxicity is believed to be dose- and/or duration-dependent, and thus expected to clinically present with gradual onset of disease (e.g., renal failure occurring over weeks to months), which is consistent with observational data showing a median duration of approximately 6 to 7 months of gemcitabine exposure, a median cumulative dose of 18 to 22 g/m², and an incremental increase in SCr over months before establishing a diagnosis of TMA. In contrast to direct drug toxicity, one report postulated immune complex formation with a drug antigen, which deposits in tissue and triggers local inflammation and coagulation. This purported immune-mediated mechanism is expected to clinically present with sudden onset of disease (e.g., rapid acute kidney injury after recent initiation of drug), which has not been observed in most cases.

The treatment of certain clinical subsets of TMA are supported by strong evidence, such as plasma exchange for ADAMTS13 deficiency–mediated TMA (also called thrombotic thrombocytopenic purpura) or eculizumab for complement-mediated TMA (also called atypical hemolytic uremic syndrome). However, the optimal treatment strategy for DITMA, and specifically GITMA, is still unknown. In the study by Daviet et al. of 120 patients with GITMA, approximately 60% of patients did not attain complete remission (defined by improvement in renal function, hemolysis, and thrombocytopenia) in a cohort of patients mostly treated with plasma exchange, fresh frozen plasma infusion, and/or glucocorticoids. Moreover, the study found no difference in the survival of patients treated with or without plasma exchange. While these observations are limited by incomplete data from a retrospective study, they nonetheless highlight an unmet need in a significant proportion of patients.

In contrast to plasma-based therapies, the use of eculizumab has shown consistent promise as an effective therapy for GITMA. Eculizumab is a recombinant humanized immunoglobulin G2/4 kappa anti-C5 monoclonal antibody. It prevents the cleavage of C5 into C5a and C5b, which inhibits the downstream prothrombotic and proinflammatory sequelae of the pathway.
Complement system. To date, including the present report, 12 publications have described 20 patients with GITMA treated with eculizumab (Table 2). Of these 20 patients, 19 (95%) documented resolution of hemolysis and thrombocytopenia and 16 (80%) documented improvement in renal function. The interpretation of these findings is limited by potential reporting bias; however, there remains a mechanistic rationale for its use given the growing understanding of the role of complement activation and dysregulation in various forms of TMA. Furthermore, eculizumab was used as second-line therapy for most of the reported patients after their TMA failed to remit with drug cessation, supportive care, and plasma exchange. It is likely that delayed initiation of eculizumab in these cases blunted its efficacy due to onset of irreversible kidney damage. Lastly, as in our patient, the reports did not observe significant complications related to eculizumab.

Patients with GITMA may require restarting therapy with gemcitabine for progressive cancer without viable alternative therapeutic options. However, published details on renal and hematologic outcomes after restarting gemcitabine are sparse. To our knowledge, only five patients have been mentioned in prior reports as having been restarted on gemcitabine after prior GITMA (Table 3). Of these five patients, two developed recurrent TMA, two did not develop recurrent TMA, and one outcome was not reported. For our patient, we elected to use concomitant eculizumab as a measure to minimize the risk of recurrent TMA. We observed no significant evidence suggesting recurrent TMA after a cumulative 2000 mg/m² of gemcitabine re-exposure. Notably, another report observed recurrent TMA with the same gemcitabine re-exposure dose that our patient received. However, without a control group, it is difficult to determine the efficacy of eculizumab to prevent recurrent GITMA in these circumstances.

Table 2. Published experience of eculizumab treatment for GITMA

| Study                  | Year | No. of patients | Treatments failed before eculizumab | Eculizumab doses | Outcome after eculizumab |
|------------------------|------|-----------------|------------------------------------|------------------|-------------------------|
| Al Ustwani et al.⁹      | 2013 | 4               | Drug cessation                      | 8                | Improved Improved       |
|                        |      |                 | Drug cessation                      | 6                | Improved Improved       |
|                        |      |                 | Drug cessation                      | 6                | Improved Improved       |
|                        |      |                 | Drug cessation                      | 5                | Improved Improved       |
| Starok et al.⁴,¹¹       | 2013 | 1               | Glucocorticoids, PLEX, RTX         | 4                | Improved Improved       |
| Rogier et al.²⁻⁸        | 2016 | 1               | PLEX                               | 7                | Improved Improved       |
| Tumoh et al.²⁻⁷         | 2017 | 2               | Drug cessation                      | NR               | Improved Improved       |
|                        |      |                 | Drug cessation                      | NR               | Improved Improved       |
| Faccini et al.⁸         | 2017 | 1               | RTX, PLEX, IVIG                    | 7                | Improved Improved       |
| Rubio et al.²⁻¹³        | 2017 | 1               | PLEX                               | 7                | Improved Improved       |
| Gosain et al.²⁻¹⁵       | 2017 | 1               | PLEX                               | NR               | Improved Improved       |
| Krishnappa et al.²⁻¹⁶   | 2018 | 1               | PLEX                               | 18⁶             | Improved Improved       |
| Martin et al.²⁻¹⁵       | 2019 | 1               | Glucocorticoids, PLEX              | 10²             | Improved Improved       |
| Daviet et al.⁸          | 2019 | 5               | PLEX (n = 4)                       | NR               | Improved Improved       |
|                        |      |                 | Drug cessation (n = 1)              |                 | Improved Improved       |
| Burns et al.²⁻¹⁴        | 2020 | 1               | Drug cessation                     | 1                | Improved Improved       |
| Efe et al. [present study] | 2021 | 1               | Drug cessation                     | 6                | Improved Improved       |

GITMA, gemcitabine-induced thrombotic microangiopathy; IVIG, intravenous immunoglobulin; NR, not reported; PLEX, plasma exchange; RTX, rituximab.

Table 3. Published experience of gemcitabine rechallenge after GITMA

| Study                  | Year | No. of Patients | Cumulative dose of gemcitabine rechallenge | Outcome | Additional details |
|------------------------|------|-----------------|---------------------------------------------|---------|--------------------|
| Flombaum et al.²⁻¹⁶    | 1999 | 1               | 3000 mg/m²                                   | No recurrent TMA | Fatal acute myocardial infarction after second dose. Hemoglobin and platelet count were normal at time of cardiac event. |
| Walter et al.²⁻¹¹       | 2002 | 1               | 2000 mg/m²                                   | Recurrent TMA | Developed hematuria, increase in Scr and LDH, and a decrease in platelet count. No schistocytes noted. |
| Glazerman et al.²⁻¹⁹    | 2009 | 1               | NR                                           | NR      | NR                 |
| Tumoh et al.²⁻¹²        | 2017 | 1               | NR                                           | No recurrent TMA | Received 2 additional months of gemcitabine. |
| Daviet et al.²⁻¹⁸       | 2019 | 1               | NR                                           | Recurrent TMA | Recurrent TMA remitted after second discontinuation of gemcitabine. |
| Efe et al. [present study] | 2021 | 1               | 2000 mg/m²                                   | No recurrent TMA | Received concomitant eculizumab. |

GITMA, gemcitabine-induced thrombotic microangiopathy; LDH, lactate dehydrogenase; NR, not reported; Scr, serum creatinine; TMA, thrombotic microangiopathy.
we cannot exclude the possibility that a longer duration or higher cumulative re-exposure dose of gemcitabine would lead to breakthrough TMA on eculizumab.

**CONCLUSION**
Blockade of the terminal complement cascade has the potential to significantly advance the treatment of DITMA. Our case highlights the successful use of eculizumab in the treatment of GITMA, as well as the use of eculizumab to lower the potential risk of recurrent GITMA after gemcitabine rechallenge.

**DISCLOSURES**
All the authors declared no competing interests.

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**PATIENT CONSENT STATEMENT**
The patient’s next of kin provided informed consent for publication of this report.

**SUPPLEMENTARY MATERIAL**
Supplementary File (PDF)
Supplementary References

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