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Eculizumab for Gemcitabine-Induced Hemolytic Uremic Syndrome: A Novel Therapy for an Emerging Condition
Raphael Karkowsky, MD and Kinjal Parikh, MD

INTRODUCTION
Atypical hemolytic uremic syndrome (aHUS), a thrombotic microangiopathy (TMA), is a disease characterized by hemolytic anemia, thrombocytopenia, and renal impairment. Gemcitabine, a commonly used chemotherapy, is emerging as a cause of aHUS. Although rare, the morbidity and mortality can be significant. Few studies have explored the use of eculizumab, an anti-C5 monoclonal antibody as a potential therapy for gemcitabine-induced aHUS.

CASE PRESENTATION
A 45 year old Caucasian male with metastatic urothelial carcinoma was started on weekly gemcitabine (1000 mg/m² per dose) to treat recurrent disease. During his seventh cycle, he was hospitalized for hypertension, acute kidney injury, and anemia. Laboratory data at that time revealed a hemoglobin of 6.2 g/dL (reference range 14.0-17.0 g/dL) and a platelet count of 70 x 10⁹/L (reference range 140-400 x 10⁹/L). Hemolysis was suggested by an elevated lactate dehydrogenase (LDH) of 420 IU/L (reference range 125-240 IU/L), undetectable haptoglobin, and the presence of schistocytes on the peripheral smear (see Figure 1). Creatinine was elevated to 2.8 mg/dL (reference range 0.7-1.4 mg/dL) and an ADAMTS-13 (A disintegrin and metalloproteinase with a thromboSpondin type 1 motif, member 13) returned as normal. The patient was diagnosed with gemcitabine-induced aHUS. Gemcitabine was discontinued, and the patient was started on steroids. Two weeks later, he presented with generalized tonic-clonic seizures, uncontrolled hypertension, and worsening renal failure. His labs on admission showed continued hemolysis and thrombocytopenia. In light of the patient’s poor response to steroids, the decision was made to start eculizumab.

DIFFERENTIAL DIAGNOSIS
Gemcitabine-induced aHUS is often a difficult diagnosis to make. In this case, it was distinguished from thrombotic thrombocytopenic purpura (TTP) by normal levels of ADAMTS-13. Furthermore, normal coagulation studies and the lack of bleeding made disseminated intravascular...
coagulation unlikely. Bone marrow biopsy showed trilineage, hypercellular hematopoiesis, suggesting peripheral destruction rather than myelosuppression from chemotherapy (see Figure 2). Idiopathic thrombocytopenic purpura was a less likely diagnosis, as the presence of schistocytes suggested microangiopathy.

OUTCOME AND FOLLOW-UP
The patient was started on eculizumab and received a course of six doses. His treatment was complicated by a multifocal pneumonia that developed four days after receiving his second dose. His labs two months after starting treatment showed an improved platelet count of 118 x 10^9/L. Although he remained anemic, his labs did not show evidence of further hemolysis (see figure 3). The patient’s creatinine remained elevated at 6.2 mg/dL, and he was started on renal replacement therapy (RRT). The patient died three months after initiation of eculizumab therapy secondary to complications of his underlying malignancy.

DISCUSSION
The vast majority of HUS are preceded by a bout of infectious diarrhea, usually due to Escheria coli; 90% of cases are not, and are therefore termed atypical. This atypical form of HUS is associated with factors such as human immunodeficiency virus infection, malignancy, organ transplantation, pregnancy, or medications, including anti-neoplastic drugs. Recently, gemcitabine, a 2',2'-difluorodeoxycytidine, has surfaced as a cause of atypical HUS. The incidence of gemcitabine-induced aHUS ranges from 0.015 to 1.4% per current case series reviews.

Pathologically, aHUS is identical to the typical form. Histology generally shows arteriole and capillary thickening, a swollen endothelium, and proteinaceous deposits in the subendothelium. A blood smear will typically show schistocytes. The kidneys are most commonly involved, but the brain, lung, pancreas, and gastrointestinal tract may be affected as well. Dysregulation of the alternative complement cascade leads to the formation of the final membrane-attack complex (MAC) and subsequent endothelial injury, which plays a pivotal role.

The most agreed upon treatment for gemcitabine-induced aHUS remains discontinuation of the drug. Other therapies, such as therapeutic plasma exchange (TPE), demonstrate less reliable effectiveness, as shown in a recent meta-analysis by Gore and colleagues, which concluded that the use of TPE is not associated with an improved rate of recovery. Recent case reports have also suggested a potential role for splenectomy or rituximab. Novel therapies such as Complement Factor H, a regulatory protein in the alternative complement
cascade, is currently being studied as a treatment for patients suffering from aHUS who are deficient in this protein.\textsuperscript{1}

The safety of eculizumab is still being determined. In this case, the patient developed multifocal pneumonia just days after receiving his second dose of eculizumab. Inhibition of MAC formation by eculizumab reduces defense against encapsulated organisms, specifically those that cause pneumonia.\textsuperscript{10} Therefore, it is reasonable to suspect, that eculizumab may have served as a risk factor in our patient’s development of this complication.

Only a few studies have investigated the treatment of gemcitabine-induced HUS with eculizumab. Similar to the studies by Starck and colleagues and Legendre and colleagues, this case study highlights eculizumab’s effectiveness in improving microangiopathy and the resultant thrombocytopenia and hemolysis in aHUS. Those studies, although promising, were somewhat confounded by prior use of TPE, which was not true in our case. Lohr and colleagues’ case series, seemed to suggest that eculizumab is an effective therapy for the kidney damage sustained in aHUS. In our case study, however, the patient did not demonstrate the same improvement in kidney function, and his kidney disease ultimately progressed to the point of needing RRT. The role of eculizumab in treating aHUS and its efficacy is still being defined.

**KEY POINTS**

The above case demonstrates eculizumab’s partial effectiveness in treating the microangiopathy in gemcitabine-induced aHUS. Although the patient demonstrated recovery in platelet count and resolution of his hemolysis, he showed only limited improvement in renal function. Moreover, the patient’s course of therapy was complicated by pneumonia, which along with infections from other encapsulated organisms, may represent a possible side effect of the medication. Further research, specifically, larger scale prospective studies, are needed to better assess the degree of efficacy and safety of eculizumab for gemcitabine-induced TMA.

**REFERENCES**