An Unusual cause of Atypical Hemolytic Uremic Syndrome Relapse

Dear Editor,

Atypical hemolytic uremic syndrome (aHUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment and is a rare variant of thrombotic microangiopathies (TMAs). This disease is caused by hyperactivation of the alternative complement pathway due to overactivation of C3 convertases and loss of complement regulatory mechanisms, and abnormalities of the complement pathway may be in the form of mutations in key complement genes or autoantibodies against specific complement factors. The disease has been triggered by pregnancy, viral illness, and sepsis among other causes; approximately 30% of aHUS results from unknown mechanisms. Regardless of the cause, aHUS is a rare disorder with poor clinical outcomes, and higher morbidity and mortality than infection-associated typical HUS.[1] We herein present a case of aHUS relapsing after oral contraceptive (OC) usage in patient who discontinued eculizumab therapy.

A 21-year-old female patient presented with the complaints of nausea, vomiting, and icterus 4 years ago. The kidney biopsy of the patient, who had acute kidney injury (AKI), oliguria, hematuria, and proteinuria, was compatible with TMA. ADAMTS13 activity was normal and shiga toxin-producing *escherichia coli* (STEC) was not detected in fecal culture. Complement factor H (CFH) p.Arg1215Gly (c.3643C>G) and p.Glu936Asp (c. 2808G>T) heterozygous, and CFHR5 p.Lys144Asn (c.432A>T) heterozygous gene mutations were detected in the patient, who was considered as aHUS. Treatment of 900 mg eculizumab was given once a week for 4 weeks, and hemodialysis was required twice a week for the first 3 weeks. The clinical and laboratory values of the patient then returned to normal and 1200 mg eculizumab treatment was continued every 2 weeks. However, the patient discontinued eculizumab treatment approximately 2 years ago and then presented with nausea, vomiting, and oliguria at our hospital 4 years after the first diagnosis and treatment. The physical examination was normal, with the exception of blood pressure of 150/90 mmHg. The laboratory test values are shown in Table 1. The C3-C4, ANA, and ANCA values were normal. The patient had proteinuria and hematuria, and in the peripheral blood smear, several schistocytes were observed in each area. The patient was evaluated as aHUS recurrence. Hemodialysis support was given as the patient was symptomatic and oliguric, and eculizumab treatment was started at 900 mg/week for 4 weeks at the same time. Treatment was then continued at 1200 mg every 2 weeks. The patient was questioned about her drugs to be able to understand the cause of relapse. It was learned that she had been using OCs for the last 15 days because of menstrual irregularities. Apart from OC usage, no drug use, focus of infection, or stress status could be detected. Clinical and laboratory improvement was achieved with eculizumab treatment. The laboratory values of the patient, who did not need hemodialysis before discharge, are shown in Table 1. Hematuria and proteinuria were completely resolved. The patient was evaluated as aHUS relapse due to the use of OC and remission was achieved again with eculizumab treatment, and the patient was discharged without any problems.

Table 1: The course of blood samples

Laboratory tests	Before treatment	After treatment
Creatinine	7.3 mg/dL	0.85 mg/dL
Blood urea nitrogen	55 mg/dL	15 mg/dL
Lactate dehydrogenase	2148 U/L	186 U/L
Hemoglobin	6.9 g/dL	12.8 g/dL
Platelets	52,000/mm^3	435,000/mm^3

Eculizumab treatment has been reported to significantly decrease the risk of end-stage renal disease (ESRD) from 60–70% to 15–20% in patients with aHUS.[2] The optimal treatment strategy is unknown. There is no evidence to support the need for lifelong therapy. Limiting the initial treatment period to 3 months in carefully evaluated patients with native kidney aHUS and withholding prophylactic therapy in patients with aHUS at transplantation is the first step toward restrictive use of eculizumab.[3] However, there is a risk of aHUS relapse after eculizumab discontinuation, and relapse may lead to AKI, irreversible chronic kidney disease (CKD), ESRD, and potentially neurological and cardiovascular manifestations.[4] In the current case, a 2-year disease-free period was achieved with successful eculizumab treatment. After this period, the patient discontinued the medication voluntarily and stopped follow-up. aHUS presentation can be idiopathic or associated with triggers. Approximately 50% of cases are triggered by infections, primarily upper respiratory tract infection or diarrhea. Pregnancy is another frequent trigger for women and most will present in the postpartum period.[4] The recurrence of aHUS occurred in this patient following the use of OCs for the last 15 days due to menstrual irregularity. However, no other reason for the relapse could be identified. The duration of onset of TMA in patients with OCs varies from 3 weeks to 10 years.[5] In the current case, recurrence was observed 15 days after the use of OCs. The reason for the earlier TMA in this case compared to other cases may have been the presence of CFH and CFHR5 heterozygous gene mutations.

Fakhouri *et al*. analyzed the risk of relapse associated with complement gene variants after eculizumab discontinuation

in 38 patients. The 3-year risk of aHUS relapse after eculizumab discontinuation was found to be significantly higher in patients with pathogenic variants in CFH genes compared to patients with no identified variants.[4] In the current case, there was also CFH Arg1215Gly heterozygous gene mutation, which can be considered to have had an effect on the relapse.

The relationship between drugs and aHUS is unclear. There are a few case reports of aHUS relapse with the usage of some drugs (calcineurin inhibitors, quinine, mitomycin C, cisplatin, etc.).[6] OCs are also thought to trigger aHUS, and reports have described an increased frequency of thromboembolic events and strong evidence for the presence of an abnormal state of hypercoagulability in women using OCs.[7] However, there are also several case reports of aHUS relapse due to pregnancy.[8] OCs and other drugs which raise estrogen levels induce TTP/aHUS by a mechanism similar to that leading to the condition during pregnancy or postpartum, possibly by reducing prostacyclin production.[9]

In conclusion, aHUS patients with FH mutation are at greater risk of recurrence and should be closely monitored. OCs are also thought to trigger aHUS, and recurrence of aHUS due to OC use was considered in the present case. Therefore, to minimize the risk of disease relapse, the use of OCs in aHUS patients should be avoided, especially those who are FH mutation-positive. In addition, decision to reduce eculizumab should be approached on an individual basis. In all cases of discontinuation eculizumab, close monitoring of patients with blood tests and urine analysis is required to allow for early detection of aHUS relapse.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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