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Case Report

Meningococcemia in a vaccinated child receiving eculizumab and review of the literature

Diana Üçkardeş[1], Nilüfer Göknar[1], Nurhan Kasap[2], Emre Keleşoğlu[1], Mustafa Arga[2], Cengiz Candan[1]

[1]Department of Pediatric Nephrology, İstanbul Medeniyet University Faculty of Medicine, İstanbul; [2]Department of Pediatric Allergy and Immunology, İstanbul Medeniyet University Faculty of Medicine İstanbul, Türkiye.

ABSTRACT

Background. Atypical hemolytic uremic syndrome (aHUS) is a rare and severe disease characterized by uncontrolled activation and dysregulation of the alternative complement pathway and development of thrombotic microangiopathy. Eculizumab, which is used as a first-line therapy in aHUS, blocks the formation of C5 convertase and inhibits the formation of the terminal membrane attack complex. It is known that treatment with eculizumab increases the risk of meningococcal disease by 1000-2000-fold. Meningococcal vaccines should be administered to all eculizumab recipients.

Case. We describe a girl with aHUS who was receiving eculizumab treatment and experienced meningococcemia with non-groupable meningococcal strains which rarely cause disease in healthy people. She recovered with antibiotic treatment and we discontinued eculizumab.

Conclusions. In this case report and review, we discussed similar pediatric case reports in terms of meningococcal serotypes, vaccination history, antibiotic prophylaxis and prognosis of patients who experienced meningococcemia under eculizumab treatment. This case report highlights the importance of a high index of suspicion for invasive meningococcal disease.

Key words: meningococcemia, eculizumab, atypical hemolytic uremic syndrome, child, vaccine.

Atypical hemolytic uremic syndrome (aHUS) is a rare and severe disease that develops due to dysregulation in the alternative complement pathway by way of mutations in the complement gene or acquired autoantibodies against complement regulatory proteins.[1] This thrombotic microangiopathy is characterized by non-immune hemolytic anemia, thrombocytopenia and acute kidney injury.[2] Uncontrolled activation of the alternative complement system causes overproduction of the membrane attack complex in children with aHUS. Eculizumab (Soliris®; Alexion Pharmaceuticals, New Haven, CT, USA), which is used as a first-line therapy in aHUS, is a humanized, chimeric monoclonal antibody.[3] Eculizumab prevents the formation of the membrane attack complex that is important for meningococcal serum bactericidal activity. Therefore, eculizumab treatment is a well-known risk factor for meningococcal disease.[1,4,5] Meningococcal vaccines must be administered at least 14 days before initiating treatment or antibiotic prophylaxis should be given if eculizumab is to be administered earlier due to the urgent condition of the patient.[4] However, meningococcal disease can occur in eculizumab recipients despite vaccinations and antibiotic prophylaxis.[5-7] In this case report and review, we present a 19-month-old girl who developed meningococcemia under treatment with eculizumab and discuss related *Neisseria meningitidis* serotypes and vaccination history

✉ Diana Üçkardeş
dianauckardes@gmail.com

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and prognosis of similar cases presented in the literature.

Case Report

A 19-month-old girl, who was receiving eculizumab for aHUS, was admitted to our pediatric emergency department with fever and low appetite; but no vomiting, rash, or neck stiffness. She was diagnosed as having aHUS when she was eight months old, after presenting with anemia, thrombocytopenia, and acute kidney injury. After obtaining consent from the family and performing meningococcal ACWY (Menveo; GSK Biologicals) and B serotype (Bexsero; GSK Biologicals) vaccinations, eculizumab was initiated with antibiotic prophylaxis (40 mg/kg/day amoxicillin and clavulanic acid). After two weeks, antibiotic prophylaxis was stopped. Hematological and renal improvement was achieved and eculizumab 300 mg was given every two weeks during the follow-up. She had two doses of meningococcal ACWY and three doses of B serotype vaccine. Family history revealed consanguineous marriage. Genetic analysis revealed complement factor I homozygous missense mutation on exon 11; c.1421G>A (p.R474Q).

On admission, her physical examination was unremarkable except a body temperature of 38°C and hyperemia of the right tympanic membrane on otoscopic examination. She had received the 22nd dose of eculizumab six days prior. Laboratory examination showed leukocyte count 20,200/mm^3 (<10,000/mm^3), CRP 2.9 mg/dl (<0.5mg/dl), and procalcitonin level 15.9 ng/ml (<0.5 ng/ml, >10ng/ml: septic shock). Treatment with empirical ceftriaxone at a dose of 75 mg/kg was started after obtaining blood culture. On follow up, vital signs were normal and she was free of fever after the first 12 hours. *N. meningitidis* was detected in the blood culture and serotyping revealed non-groupable *N. meningitidis.* The patient completed 10 days of intravenous ceftriaxone treatment. Eculizumab was stopped and fresh frozen plasma (FFP) in two-week intervals was scheduled as a replacement.

Primary immunodeficiency was also investigated, due to the presence of consanguinity, and meningococcemia with a meningococcal strain which is unusual to be pathogenic in healthy individuals. Laboratory evaluations showed normal complete blood count and immunoglobulin levels. Extended lymphocyte phenotyping also revealed normal percentages of T and B lymphocyte subsets and natural killer cells. Immune dysregulation clinical exome sequencing analysis was conducted and no pathogenic or possibly pathogenic variant was detected, consistent with the patient's clinical findings and inheritance pattern. In the 'variant of unknown significance (VUS)' variant list, a homozygous missense variant, causing a mutation of *TET2*, c.4832 with a C>A amino acid substitution was found which is associated with 'Immunodeficiency-75 (IMF75), OMIM #619126' phenotype. Sanger sequencing analysis confirmed the variant.

She was followed up closely by the pediatric nephrology unit with intermittent FFP infusions and eculizumab was not reintroduced. At the fifteenth month of follow-up, she was free of aHUS attack with normal hemoglobin values, renal functions, and without proteinuria.

Written informed consent was received from the parents for publication.

Discussion

Herein, we present a patient with aHUS due to complement factor I mutation; she was receiving eculizumab treatment and developed meningococcemia with non-groupable *N. meningitidis* strains despite meningococcal vaccinations. Interestingly, she had very mild symptoms on presentation. This observation highlights the importance of having high clinical suspicions for invasive meningococcal disease in children receiving eculizumab treatment even if vaccinations have been administered appropriately. *N. meningitidis*

serotype was non-groupable in our case and the vaccines administered to the patient provided protection only for meningococcus ACWY and B serotypes. In Turkey, antibiotic chemoprophylaxis is officially in use in the first two weeks of eculizumab treatment; chemoprophylaxis can be stopped thereafter. However, many countries including the USA, France and the United Kingdom recommend prolonged chemoprophylaxis during eculizumab treatment.[7-9] Chemoprophylaxis may help to reduce the risk of meningococcemia in eculizumab recipients. Our case had received antibiotic prophylaxis only for 2 weeks and this may have facilitated the development of meningococcemia.

Our patient also had a VUS in *TET2* gene shown in the immunodeficiency genetic panel. Individuals with *TET2* mutation reported so far in the literature usually presented with severe and recurrent infections in infancy with lymphoproliferation and various types of hypo- or hypergammaglobulinemia and T- or B-cell deficiencies.[10] Sanger sequencing analysis results confirmed the variant; however, the clinical findings, family history, and laboratory results were not found to be clinically related to the patient's condition.

Cases of meningococcemia in eculizumab recipients have been reported in the literature.[5-7] In a study published by the Centers for Disease Control and Prevention in 2017, meningococcal disease was reported in 16 patients (age interval 16-83 years) who used eculizumab between 2008 and 2016. Findings on admission were nonspecific and included fever, chills, diarrhea, vomiting, muscle pain and joint pain. Fourteen patients were vaccinated against MenACWY serotypes and 3 were vaccinated against MenB before the onset of the disease. The majority of cases were caused by non-groupable *N. meningitidis* (n= 11). The others included serogroup Y in four patients (three were vaccinated for ACWY) and undetermined in one patient. Antimicrobial susceptibility test showed that one patient was resistant to penicillin. One patient died.[5] The reason for meningococcal disease in vaccinated children could be the fact that eculizumab therapy inhibits development of meningococcal antibodies against vaccine serotypes and antibodies developing against vaccine serotypes do not provide cross-protection against non-groupable serotypes.

Socié et al.[11] showed that the overall meningococcal infection rate was 0.25 per 100 patients per year for eculizumab recipients. They presented 76 cases of meningococcemia between March 2007 and October 2016, and eight patients were under the age of 16 years. The majority of the patients were aged between 16 and 44 years and most common serotypes were non-groupable and B. They reported eight fatal cases. Gäckler et al.[12] evaluated antibody titers after meningococcal vaccination in 25 patients diagnosed with aHUS who received eculizumab treatment. Only 20% of the patients had antibody responses to all serotypes, and 28% did not develop an antibody response to any serotype. An increase in bactericidal antibody titer was observed against all serotypes with repeated vaccinations. The authors advised evaluation of antibody titers and booster doses. Also, even if booster doses were performed, vaccinations were not 100% protective against meningococcemia and the authors advised antibiotic prophylaxis to all eculizumab recipients.

Review of the literature reveals a limited number of pediatric case reports that describe patients who were on eculizumab treatment and experienced meningococcemia despite vaccinations or chemoprophylaxis plus vaccinations (Table I). Findings on admission were nonspecific and included fever, chills, headache, macular rash and/or myalgia. Fatal cases were also reported. Polat et al.[6] described an 11-year-old boy who developed meningococcemia due to *N. meningitidis* serotype Y. He had two doses of MenACWY-D (*Neisseria meningitidis* serogroup A, C, W, Y vaccine, Menactra; Sanofi Pasteur, Inc, Swiftwater, PA, USA) vaccine and antibiotic prophylaxis. He died within hours in pediatric intensive care unit despite antibiotic treatment,

Table I. Pediatric patients who experienced meningococcemia under eculizumab treatment.

Study	Age at admission for meningococcemia/ Gender	Diagnosis/ Genetic defect	Microbiology-Antibiotic susceptibility	Eculizumab duration before meningococcemia	Antibiotic prophylaxis	Men B vaccination	Men ACWY vaccination	Prognosis	Eculizumab continued/ discontinued
Polat M et al. 2018[6]	11 years, boy	aHUS N/A	Serogroup Y-intermediate penicillin susceptibility, with minimal inhibitory concentration of 0.19 mg/L *	16 months	Yes	No	Yes (2 doses)	Fatal	-
Cullinan N et al. 2015[13]	4 years, girl	aHUS Hybrid CFH/ CFHR3 mutation	Serogroup W135-intermediate penicillin sensitivity, with minimal inhibitory concentration of 0.13 mg/L *	30 months	Yes	No	Yes (1 dose)	Survived	Revaccinated, eculizumab continued
Menne J et al. 2019[14]	13-19 age category, N/A	aHUS C3 mutation	Blood culture is negative	N/A	Yes	No	Yes	Survived	Eculizumab continued
Rondaeu E et al. 2019[15]	15 years, N/A	aHUS N/A	Serogroup B	21 months	No	Yes	No	Survived	Eculizumab continued
Nolfi-Donegan D et al. 2018[7]	16 years, girl	PNH	ST-2578 and non-groupable, penicillin susceptible	<1 month	N/A	Yes	Yes	Fatal	-

N/A: not available, aHUShus: atypical hemolytic uremic syndrome, CFH: complement factor H, CFHR3: complement factor H receptor 3, PNH: paroxysmal nocturnal hemoglobinuria, * sensitive, 0.06 mg/L, resistant 0.25 mg/L

aggressive fluid resuscitation and inotropic and ventilatory support. Nolfi-Donegan et al.[7] reported a 16-year-old-girl who had fatal meningococcemia only twenty-four hours after the second eculizumab dose. They showed that neither Men B-4C vaccination (*Neisseria meningitidis* serogroup B vaccine; Bexsero; Glaxo Smith Kline, Bellaria Rosia, Sovicille, Italy) which matched 2 antigens in the strain, nor the high serum antibody titers prevented the rapidly fatal disease.

Annual measurement of meningococcal vaccine responses was advised in eculizumab recipients.[13] Cullinan et al.[13] presented a patient with meningococcemia due to *N. meningitidis* W135 after 30 months of treatment. They showed that vaccine responses were suboptimal and they performed revaccination. After successful treatment of meningococcemia, they continued eculizumab treatment and they experienced neither relapse of aHUS, nor meningococcemia.

Some clinicians did not interrupt eculizumab treatment after meningococcemia. Menne et al.[14] described a boy with C3 mutation and renal transplantation and clinically diagnosed meningococcemia. Blood cultures were negative and they continued eculizumab treatment. Rondeau et al.[15] released a five-year safety report of eculizumab. They presented a pediatric patient who experienced meningococcemia with meningococcus B serotype despite vaccination for that serotype. They did not discontinue eculizumab treatment.

In conclusion, eculizumab treatment increases the risk of meningococcemia, and neither vaccination nor antibiotic prophylaxis provide 100% protection from meningococcemia. Vaccination should be performed against both A, C, W, Y and B serotypes to reduce the risk, and antibiotic prophylaxis should be considered due to possible fatal course of the disease. Repeated doses of vaccines may be needed for adequate antibody titers. The presentation of meningococcal disease under eculizumab treatment might be vague. Initial symptoms are often mild and nonspecific. However, the disease can progress to shock and death within hours. In patients who present with fever under eculizumab treatment, the risk of meningococcemia should be carefully evaluated and early treatment should be performed regardless of prophylaxis and vaccination status.

Ethical approval

Written informed consent was received from the parents for publication.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: DÜ, NG, EK, NK, MA, CC; data collection: DÜ, NG, CC; analysis and interpretation of results: DÜ, NG, CC; draft manuscript preparation; DÜ, NG, NK, EK, MA, CC. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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