We describe a case of invasive meningococcal disease due to a vaccine-preventable and penicillin-resistant strain in a fully immunized young adult on long-term complement inhibitor therapy and daily penicillin chemoprophylaxis. Eculizumab is a humanized monoclonal antibody that binds human complement C5 protein and inhibits the terminal complement pathway. It is currently recommended for the treatment of complement-mediated thrombotic microangiopathies. An unwanted complication of inhibiting complement, however, is an increased risk of invasive meningococcal disease. Here, we report the first case of meningococcal group B vaccine failure in a young adult receiving eculizumab for atypical hemolytic uremic syndrome. She developed invasive meningococcal disease due to a vaccine-preventable and penicillin-resistant meningococcal group B strain 4 months after receiving 2 doses of meningococcal group B vaccine while on oral penicillin prophylaxis against meningococcal infection.

Monoclonal antibodies are increasingly used to treat a range of medical conditions. Eculizumab (Soliris; Alexion, New Haven, CT) is a humanized monoclonal antibody that is a terminal complement inhibitor used to treat paroxysmal nocturnal hemoglobinuria,1 and atypical hemolytic uremic syndrome (aHUS),2 although its use is extending to treat other immune-mediated conditions.3–5 In aHUS, uncontrolled complement activation due to defects of complement regulation leads to platelet, leukocyte, and endothelial cell activation and thrombotic microangiopathy.2

Eculizumab binds with high affinity to human C5 complement and blocks the generation of complements C5a and C5b-9. This prevents the formation of membrane attack complexes and proinflammatory pathway activation, thus preventing end-organ damage.1 An unwanted complication of complement inhibition, however, is an increased risk of infection with encapsulated bacteria, especially Neisseria meningitidis.6 Consequently, patients on eculizumab are advised to receive meningococcal vaccination at least 14 days before initiating treatment.7

Until recently, licensed meningococcal vaccines protected against only 4 of the 12 known meningococcal serogroups (A, C, W, and Y). In Europe, serogroup B (MenB) is responsible for nearly all invasive meningococcal disease (IMD) cases.8 In 2013, a multicomponent, protein-based, broad-spectrum meningococcal vaccine (4CMenB, Bexsero; GSK Biologicals, Siena, Italy) was licensed for protection against MenB, although the vaccine antigens can be found on the surface of all meningococci and, therefore, offer
protection regardless of capsular group. In the United Kingdom, the quadrivalent ACWY meningococcal conjugate vaccine (MenACWY) and 4CMenB are recommended for at-risk individuals, including those receiving complement inhibitors. Here, we report the first case of 4CMenB vaccine failure in a fully immunized young adult on penicillin prophylaxis who developed IMD caused by a vaccine-preventable and penicillin-resistant MenB strain during treatment with eculizumab for aHUS.

**CASE DESCRIPTION**

A 22-year-old woman presented to the emergency department with fever, myalgia, lethargy, sore throat, and headache, but no rash, photophobia, or neck stiffness. Six months previously, she was diagnosed with aHUS associated with the CFH mutation c.3643C>G; p.Arg1215Gly identified through genetic testing, after presenting with vomiting and diarrhea, headache, oliguria, hemolytic anemia, severe thrombocytopenia with bruising, acute renal injury requiring dialysis, and raised lactate dehydrogenase, consistent with a thrombotic microangiopathy. At the time, she was started on long-term eculizumab and penicillin prophylaxis. She had no other significant medical history.

Clinical examination was unremarkable. Her blood counts revealed elevated white cell (17.0 × 10^9/L) and neutrophil (15.8 × 10^9/L) counts, with normal renal and liver function. The C-reactive protein was 5 mg/L initially but increased to 150 mg/L within 20 hours before falling gradually. Lumbar puncture revealed no evidence of meningitis. She was treated with intravenous ceftriaxone (2 g twice daily) for 7 days followed by 10 days of oral ciprofloxacin 500 mg twice daily. Gram-negative diplococci were identified in the blood culture after 24 hours. She was discharged within 24 hours and has remained well on oral penicillin prophylaxis.

**VACCINATION HISTORY**

She had received the group C meningococcal conjugate vaccine as part of the national program in 2000 and the MenACWY vaccine with 2 doses of 4CMenB given 1 month apart when she was diagnosed with aHUS. Two months after MenACWY vaccination, serum bactericidal antibody titers using rabbit complement were 1024, 8192, 1024, and 512 for serogroups A, C, W, and Y, respectively. MenB serum bactericidal antibody titers for patients on eculizumab therapy are difficult to interpret because this assay uses exogenous human complement, which is inactivated by eculizumab.

**MICROBIOLOGY**

The meningococcal blood culture isolate was sent to the national reference laboratory and confirmed as nonserogroupable with a minimum inhibitory concentration of 0.5 mg/L for penicillin, which was double the threshold (0.25 mg/L) for penicillin resistance. Genomic analysis identified the isolate as belonging to the ST-162 clonal complex, a strain with established pathogenic potential. The capular gene csh (siaDb), however, was interrupted by an IS1301-related sequence, making the isolate unlikely to cause disease in immunocompetent individuals. Its penA allele (neis1753 allele 23) contained 3 mutations associated with reduced penicillin sensitivity (F504L, A510V, I515V). Within the PubMLST Neisseria database (pubmlst.org/neisseria; accessed August 12, 2015), this allele was predominantly associated with Neisseria gonorrhoeae (82/1758 annotated genomes versus 2/5464 annotated meningococcal genomes). The allele was not observed among any annotated genomes for Neisseria lactamica (n = 127), Neisseria subflava (n = 20), Neisseria polysaccharea (n = 15), Neisseria mucosa (n = 14), or other Neisseria species. Comparison of the broader genomic region (neis1740 to neis1773) with other cc162 genomes by using the PubMLST genome comparator tool revealed an uncharacteristic region spanning from neis1750 to neis1756. As with neis1753, the neis1754, neis1755, and neis1756 alleles were highly associated with N gonorrhoeae, whereas neis1750 and neis1751 were novel variants. This suggested a recombination event in an ancestral strain involving DNA of putative gonococcal origin.

The isolate also possessed genes for PorA P1.22,14, factor H binding protein peptide 3.31, and neisserial heparin binding antigen peptide 20, and was Neisserial adhesion A (nadA) negative. Meningococcal Antigen Typing System analysis confirmed the strain as vaccine-preventable because of neisserial heparin binding antigen positivity.

**DISCUSSION**

This case highlights the difficulties in protecting patients on complement inhibitors against meningococcal disease, even with vaccination and antibiotic chemoprophylaxis. Individuals on long-term eculizumab who are not otherwise immunosuppressed can produce high serum bactericidal antibody titers after meningococcal vaccination. However, the critical functions of the terminal complement pathway and, therefore, the ability to attract proinflammatory cells and initiate cell destruction by triggering pore formation, are impaired (even though the proximal complement pathway remains intact). Inherited
deficiencies of the terminal complement pathway are rare (0.03% of the general population), but associated with a 7000 to 10 000-fold higher risk of IMD, with 50% to 60% experiencing ≥1 IMD episode. In those with C5 deficiency, meningococci are responsible for >95% of invasive infections, with meningitis being the most common presentation (77%), and 42% suffer from recurrent disease, both in terms of relapse and newly acquired infections. Recurrent infections occur despite an adequate antibody response against the infecting isolates; in vitro studies have shown that these antibodies will kill the homologous isolate, but only when complement is added to the assay.

Interestingly, individuals with complement deficiency often have mild disease with low case fatality. One possible explanation is a less intense inflammatory response to infection because of lower endotoxin release from the bacterial surface in the absence of an intact terminal complement pathway. We have recently shown that eculizumab inhibited complement-mediated serum bactericidal activity but did not impede opsonophagocytic activity in patients on long-term eculizumab therapy. Opsonophagocytic activity is triggered by binding of C3 complement without requirement of the terminal complement and may, therefore, help protect against severe infection.

The increased risk of IMD in patients receiving eculizumab is well-recognized, with clear recommendations for meningococcal vaccination of patients at least 2 weeks before commencing treatment. Many clinicians additionally advocate lifelong antibiotic chemoprophylaxis for added protection because of the continued high risk of IMD despite adequate postvaccination antibody responses. In a recent evaluation of 195 patients on eculizumab, 2 IMD cases were identified during 467 patient-years of eculizumab exposure (0.42 infections/100 patient-years). Both had received various meningococcal vaccines, but developed IMD due to a nonvaccine serogroup. In another report, a 19-year-old with known factor H mutation, 3 renal transplants, and receiving several immunosuppressives in addition to eculizumab developed meningococcal group W (MenW) septicemia. She had been immunized 18 months previously with a MenACWY polysaccharide vaccine, which is likely to be less protective than the equivalent conjugate vaccine.

Recently, a toddler with aHUS diagnosed in infancy and receiving long-term eculizumab developed MenW septicemia despite previous immunization with the MenACWY conjugate vaccine. He was also on amoxicillin prophylaxis at the time, and the responsible MenW strain had intermediate penicillin sensitivity, with a minimal inhibitory concentration of 0.13 mg/L (sensitive 0.06 mg/L, resistant >0.25 mg/L). This child, too, had mild disease without complications. After her illness, she had nonprotective antibody titers against serogroups C, W, and Y, but responded with high antibody titers after a further dose of the MenACWY conjugate vaccine.

The recent licensure of 4CMenB was heralded as a major breakthrough in the global fight against meningococcal disease because it aimed to provide broad protection against all capsular groups. Our patient had been immunized with the MenACWY conjugate vaccine and 4CMenB, and was on long-term penicillin prophylaxis when she developed MenB disease due to a penicillin-resistant and vaccine-preventable strain. Current guidelines recommend testing antibody responses in patients receiving eculizumab before and 4 to 6 weeks after meningococcal vaccination, and subsequently every 1 to 3 years with a view to reimmunize if antibody titers are below protective thresholds. More data are needed to support this recommendation, given that antibodies require a functional terminal complement pathway to kill the meningococci efficiently. The development of IMD due to a penicillin-resistant strain in our patient and the published pediatric case is also concerning, given that penicillin resistance is rare (<5%) among invasive meningococci. These 2 cases highlight the importance of raising awareness of meningococcal disease, including use of information cards to be carried by patients and their caregivers, and to seek medical attention early. The development and maintenance of national specialized centers will play a vital role in monitoring the risks and outcomes of adverse events, including IMD, in children and adults on long-term eculizumab.

**ABBREVIATIONS**

aHUS: atypical hemolytic uremic syndrome
IMD: invasive meningococcal disease
MenACWY: quadrivalent ACWY meningococcal conjugate vaccine
MenB: meningococcal group B
MenW: meningococcal group W
4CMenB: multicomponent, protein-based, broad-spectrum meningococcal vaccine
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Meningococcal B Vaccine Failure With a Penicillin-Resistant Strain in a Young Adult on Long-Term Eculizumab
Sydel R. Parikh, Jay Lucidarme, Coralie Bingham, Paul Warwicker, Tim Goodship, Ray Borrow and Shamez N. Ladhani
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