Eculizumab-Associated *Moraxella lacunata* Bacteremia and Systemic Inflammatory Response Syndrome in a Toddler with Atypical Hemolytic Uremic Syndrome

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ABSTRACT: *Moraxella lacunata*, a low-virulence Gram-negative coccobacillus, is classically associated with conjunctivitis and upper respiratory tract infections; systemic infections such as sepsis have rarely been reported, especially in children. We describe a 28-month-old girl with atypical hemolytic uremic syndrome and stage II chronic kidney disease on long-term eculizumab therapy who presented with systemic inflammatory response syndrome and was found to have *Moraxella lacunata* bloodstream infection. Eculizumab, a humanized monoclonal anti-C5 antibody, has been associated with susceptibility to infections with encapsulated bacteria, especially *Neisseria meningitidis*. This is the first report of an invasive bacterial infection with *Moraxella lacunata* in a pediatric eculizumab recipient.

KEYWORDS: *Moraxella lacunata*, eculizumab, atypical hemolytic uremic syndrome, meningococcal infections, anti-complement therapy

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Introduction

Moraxella lacunata, a Gram-negative coccobacillus, is a commensal organism of the conjunctiva and upper respiratory tract of humans typically encountered in individuals with conjunctivitis, blepharitis, and keratitis.[1,2] Rarely has this organism been identified as the cause of more serious illnesses, with only 4 prior case reports of bacteremic *Moraxella lacunata* infections in children (Table 1), none involving the use of immune-modulating agents as a predisposing risk factor.[3-6]

Atypical hemolytic uremic syndrome (aHUS) is characterized by dysregulation of the alternative complement pathway with excess production of the terminal complement complex C5b-9, leading to endothelial cell injury and thrombotic microangiopathy.[7] Eculizumab, a humanized chimeric anti-C5 monoclonal IgG-kappa immunoglobulin with a hybrid IgG_2 and IgG_4 Fc component, significantly reduces complement activation.[8] It has been shown to significantly reduce mortality and morbidity in aHUS.[9] Eculizumab is currently indicated in the United States for the treatment of paroxysmal nocturnal hemoglobinuria, aHUS, adults with generalized myasthenia gravis who are anti-acetylcholine receptor positive, and adults with neuromyelitis optica spectrum disorder who are anti-aquaphorin-4 antibody positive.

Eculizumab has been shown to increase the incidence of invasive meningococcal disease by up 1000 to 2000-fold.[10] Serious infections by non-groupable *Neisseria meningitidis, Neisseria gonorrhoeae*, and non-meningococcal, non-gonococcal *Neisseria* species have also been described.[10-12] *Moraxella lacunata* bacteremia was reported as an adverse event in 1 adult who received eculizumab as a participant in a study of anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis.[13] We present the first report of bacteremia and systemic inflammatory response syndrome (SIRS) caused by *M. lacunata* in a toddler who had been receiving eculizumab infusions for treatment of aHUS.

Case Description

A 28-month-old Caucasian girl on long-term intravenous eculizumab infusions through an anterior chest wall MediPort for aHUS and stage II chronic kidney disease presented with fever (39.1°C), tachycardia (heart rate 167 beats per minute), and respiratory rate 24 breaths per minute 20 days after her last eculizumab infusion, thereby fulfilling ⩾2 of the clinical criteria needed for diagnosis of age-appropriate systemic inflammatory response syndrome (temperature >38.5°C, heart rate >140 beats per minute, respiratory rate >22 breaths per minute, and abnormal leukocyte count).[14] There was a single episode of nonbilious emesis and diarrhea 4 days earlier, after which she improved. Her white blood cell count was 9.5 bil/L (neutrophils 7.5 bil/L, lymphocytes 1.2 bil/L, monocytes 0.8 bil/L), hemoglobin 12.3 g/dL, hematocrit 34.9%, MCV 84 fL, MCHC 35 g/dL, and platelets 177 bil/L (decreased from 250 bil/L 3 weeks earlier). Serum creatinine was 0.68 mg/dL, mildly elevated in comparison to her baseline of 0.5 mg/dL. Albumin was 4.1 g/dL, globulin 1.7 g/dL, aspartate aminotransferase 47 U/L, and alanine aminotransferase 22 U/L. C3, C4, and CH50 were not measured at the time of hospital admission. She had microscopic hematuria and proteinuria on urinalysis, which was similar to pre-illness findings. A rapid molecular test for influenza and respiratory syncytial virus RNA on a nasopharyngeal swab was negative. A MediPort blood culture was collected and she was started on intravenous vancomycin and ceftriaxone, along with a fluid bolus of normal saline.

Table 1. *Moraxella lacunata* bacteremia in children.

REFERENCE	AGE/SEX	DIAGNOSIS	SOURCE OF ISOLATE	UNDERLYING CONDITION	TREATMENT/DURATION	COMPLICATIONS	OUTCOME
Pavlatou and Athanasiades[3]	4 mo/male	Meningitis	Blood, bone marrow, cerebrospinal fluid	None	Penicillin + sulfamethazine/10 d	None	Recovered
Sanyal et al[4]	4 y/male	Infective endocarditis	Blood	Turner's syndrome, coarctation of the aorta, bicuspid aortic valve with recent cardiac catheterization	Penicillin + sulfamethazine/6 wk	Aortic valve vegetation	Recovered
Nagano et al[5]	15 mo/male	Infective endocarditis	Blood	Tetralogy of Fallot and dextrocardia, with prior shunt surgeries	Penicillin + sulfamethazine/6 wk	Mitral valve insufficiency	Recovered
Sawada et al[6]	12 y/male	Acute glomerulonephritis	Blood	None	Ampicillin/sulbactam, switched to cefotaxime on day 8 (total antibiotic duration 15 d)	None	Recovered
Present case	28 mo/female	Bacteremia with systemic inflammatory response syndrome	Blood	Atypical hemolytic uremic syndrome, stage II chronic kidney disease, and eculizumab therapy	Ceftriaxone for 3 d + oral cefdinir for 7 d	None	Recovered

The blood culture grew *Moraxella lacunata* after 19 hours of incubation, and its identity confirmed by MALDI-TOF (matrix-assisted laser desorption ionization-time of flight) mass spectroscopy. She improved quickly and was discharged after 3 days on an oral 7-day course of cefdinir. Her bacteremia was not considered catheter related. Blood cultures collected 6 and 10 weeks after this illness for intercurrent febrile illnesses were sterile.

The child had been diagnosed with aHUS at 14 months of age and was immediately started on intravenous eculizumab (600 mg at diagnosis and a week later, and then 300 mg every 2 weeks) because of illness severity. Hemodialysis was needed for 6 weeks. She was administered 1 dose each of a meningococcal conjugate quadrivalent vaccine (MenACWY) and serogroup B meningococcal vaccine (MenB) on the same day as the first dose of eculizumab. Amoxicillin prophylaxis was continued for 6 weeks. After a year of therapy, the interval between eculizumab infusions was extended to 3 weeks.

Prior to initiation of eculizumab, her C3, C4, and CH50 levels were 79 mg/dL (reference range, 83-240), 11 (reference range, 13-60), and 52 U/mL (reference range, 41-95), respectively. After 2 months of eculizumab therapy, C3 was 103 mg/dL, C4 30 mg/dL, and CH50 <16 U/mL when measured 10 days after an eculizumab infusion.

Functional complement testing at diagnosis was performed at the University of Iowa Molecular Otolaryngology and Renal Research Laboratories (MORL). The alternate complement pathway functional assay was 41% (reference range, 50-130), factor H level 43.7 (reference range, 45-80), and soluble C5b-9 was elevated at 0.5 (reference range, <0.3). Analysis of 11 genes implicated in thrombotic microangiopathies (*CFH, CFI, MCP(CD46), CFB, CFHR5, C3, THBD, DGKE, PLG, ADAMTS13*, and *MMACHC*) did not identify any pathogenic mutations. Copy number variation screening across the *CHFR3-CHFR1* region using Multiplex Ligation-Dependent Probe Amplification (MLPA) found homozygous deletions, del(*CHFR3-CHFR1*). This deletion is found in homozygous form in about 5% of Caucasians but is 3 times as common in the aHUS population and is associated with formation of anti-factor H antibodies and aHUS.

A few months after this illness, eculizumab infusions were extended to once every 6 weeks. CH50 was 57.2 U/mL just before an infusion but dropped to 20.8 U/mL 3 weeks later. This interval was similar to the timing of events surroundings her *Moraxella lacunata* bacteremia and SIRS.

Discussion

Moraxella lacunata is mostly associated with external eye and upper respiratory tract infections. The bacterium infrequently causes invasive or systemic disease, with just over 20 cases in adults reported in the medical literature. Of 5 children previously reported with invasive *Moraxella lacunata* infections, 4 had bacteremia and in 1 the organism was recovered from a patellar osteolytic lesion.[3-6,15] Of the 4 children with bacteremia, 2 had cardiac anomalies and developed infective endocarditis, 1 was

previously well but developed meningitis, and the fourth was healthy but developed acute glomerulonephritis (Table 1). One child with infective endocarditis developed aortic valve vegetation while the other had mitral valve insufficiency. Like the toddler described in this report, the infant with meningitis and the 12-year-old with acute glomerulonephritis recovered without complications. Several of the adults with invasive *Moraxella lacunata* infections were immunocompromised, but none were among children until this report.[13,16]

Eculizumab binds with high affinity and specificity to C5, inhibiting its cleavage to C5a and C5b. It thus blocks the terminal complement cascade, without affecting the generation of C3b which is needed for opsonophagocytosis and shaping adaptive immune responses.[6,7] C5a is needed for upregulation of phagocytosis.[17] C5b binds to damaged or foreign surfaces which leads to the joining of C5b to C6-C9, thereby forming the membrane attack complex whose function is to form transmembrane channels that disrupt the cell membranes of target cells leading to their lysis and death. Inhibition of C5 cleavage thus protects the kidney in aHUS but at the cost of diminished capacity to protect against invading bacteria. In vitro and in vivo studies demonstrate that the presence of eculizumab in the blood of vaccinated adults resulted in inhibition of killing of meningococci despite the deposition of serotype-specific IgG and C3b on the surfaces of bacteria.[17,18] *Moraxella lacunata* bacteremia, independent of eculizumab use, was noted to be associated with transient decreased concentrations of C3 and CH50 in a previously healthy 12-year-old boy with acute glomerulonephritis.[6]

The increased risk of invasive meningococcal infections resulted in the recommendation for universal immunization against these bacteria for eculizumab recipients. However, a survey of 10 selected jurisdictions in the United States between 2008 and 2016 identified 16 invasive meningococcal infections (including 6 with meningitis) among those treated with eculizumab, most of whom were immunized. The youngest was 16 years old, and the median age was 30 years. Non-groupable *Neisseria meningitidis* accounted for 11 (73%) of 15 that could be further characterized.[10] Other reports described serious infections caused by other species of *Neisseria* (eg, *Neisseria cineria*), gonococci, *Pseudomonas aeruginosa, Streptococcus pneumoniae, Haemophilus influenzae* type b, *Aspergillus niger*, and *Cryptococcus neoformans*.[11] Eculizumab recipients are therefore at risk for infection with a myriad of pathogens.

Amoxicillin prophylaxis for 2 weeks is recommended for those who receive eculizumab ⩽2 weeks from meningococcal vaccine administration, although the Centers for Disease Control and Prevention has suggested antimicrobial prophylaxis for the duration of eculizumab therapy.[10,12] The efficacy and safety of this approach has not been studied. Limited data suggest that eculizumab-treated individuals on antibiotic prophylaxis fared better than those not on antibiotics in terms of longer duration to their first episode of invasive meningococcal disease and no associated mortality. However, intermediate penicillin susceptibility and even resistance was considerably more common among those taking penicillin or amoxicillin prophylaxis.[10,12] We did not resume antimicrobial prophylaxis on this child, and she remained free of invasive bacterial infections for >2 years now.

Conclusions

Eculizumab recipients are at higher of invasive infections by a broad spectrum of bacteria, including some of low virulence. While *Moraxella lacunata* is generally regarded as a commensal bacterium colonizing the upper respiratory tract with a low-virulence potential, emerging reports indicate that it can act as an opportunistic pathogen, especially in an immunodeficient host. Our report represents the first description of *Moraxella lacunata* bacteremia and SIRS in an immune compromised child by virtue of her treatment with eculizumab.

Author Contributions

Bicoll, Goyal, Blatt, and Freij designed the study, reviewed the medical literature, participated in writing earlier drafts of the paper, and approve the final manuscript.

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