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The Brief Case: Meningococcemia Leading to a Diagnosis of Complement Deficiency in a 23-Month-Old

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CASE

A 23-month-old female presented to the emergency department (ED) in Philadelphia, PA, in February of 2018 with acute-onset seizures and 3 days of fever. She was previously healthy and up to date on vaccinations. The morning of presentation, she was taken to a primary care physician where she was clinically diagnosed with influenza. Her condition worsened and her family was en route to the ED when she was noted to have tonic contraction of her extremities and right eye deviation. On physical exam, the patient was found to be febrile to 38.4°C, tachycardic, tachypnic, hypotensive, and hypoglycemic. A nonblanchable purpuric rash was noted on the patient's lower legs, arms, and abdomen. A chest X-ray and computed tomography of her brain were both unrevealing. She was urgently admitted to the intensive care unit for septic shock and intubated due to concerns of respiratory and neurologic failure. She was started on epinephrine for shock, levetiracetam and lorazepam to control seizures, oseltamivir for suspected influenza virus infection, and ceftriaxone and vancomycin for broad antibacterial coverage. A battery of tests were ordered, including blood cultures and a complete blood cell count (CBC). CBC showed a low white blood cell count of 3,600 cells/μl (reference range, 6,500 to 13,000 cells/μl) and thrombocytopenia (84,000 cells/μl; reference range, 150,000 to 400,000 cells/μl). A lumbar puncture was not attempted due to thrombocytopenia and clinical instability.

One day postcollection, on hospital day 2 (HD2), the blood culture became positive for Gram-negative diplococci (Fig. 1). After subculture and incubation in 5% CO_2, growth of smooth glistening gray colonies was observed on both sheep blood and chocolate agars. *Neisseria meningitidis* was identified via matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) and confirmed via an automated biochemical-based identification instrument (Vitek 2 NH card; bioMérieux), as well as Rapid NH (Remel) and cysteine tryptic agar (CTA) sugar fermentation tests performed at the Pennsylvania State Public Health Laboratory. Molecular testing for influenza virus on HD2 was negative, and oseltamivir was discontinued. The patient was continued on ceftriaxone at a meningitic dosage for presumed meningococcal meningitis and treated for 7 days from her first negative blood culture. Her family and close contacts received prophylaxis for possible *N. meningitidis* exposure. Health care workers had taken the appropriate respiratory precautions based on the purpuric rash and thus did not require prophylaxis. Typing results from the state public health laboratory showed a nongroupable meningococcus. The diagnosis of meningococcal sepsis and meningitis in a 23-month-old prompted consultation with immunology for evaluation of a potential immunodeficiency. On HD3, testing was sent to a reference laboratory to screen for classical complement pathway activity (CH50), with very low levels of CH50 detected at 6 units/ml (reference range, 60 to 144 units/ml). Testing for immunoglobulin isotype levels was normal. CH50 levels were repeated on HD9, as well as screening

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For answers to the self-assessment questions and take-home points, see https://doi.org/10.1128/JCM.01516-18 in this issue.

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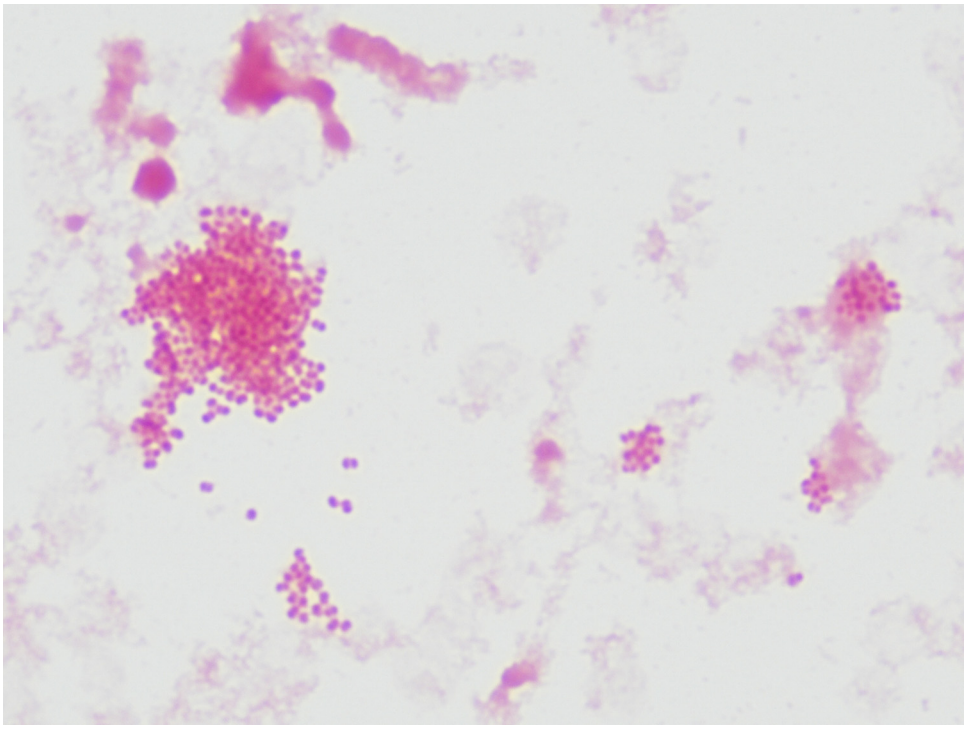

FIG 1 Gram stain showing Gram-negative diplococci suggestive of *Neisseria* species in the blood culture collected from the case presented.

for alternative complement pathway activity (AH50). CH50 levels were still low, and AH50 was undetectable (reference range, 77 to 159 units/ml), suggesting a terminal complement deficiency (Fig. 2). Subsequent testing of the individual terminal complement proteins was sent to a reference laboratory, which identified low levels of C6 (3 μg/ml; reference range, 28 to 69 μg/ml, respectively) and normal levels of C5 and C7 to C9 (Fig. 2).

On HD13, the patient was transferred to the inpatient rehabilitation unit for intensive physical, occupational, and speech therapies. She showed significant improvement after 4 weeks of therapy and was discharged to home, still requiring nasogastric tube feeding. The patient's family was given a prescription for amoxicillin and was counseled to administer a single dose (562.5 mg) and seek emergent medical attention, with blood culture collection, for any fever of >38.5°C. She also received vaccination for *N. meningitidis* serotypes A, C, Y, W-135, and B prior to discharge. At 4 months postpresentation, the patient had almost completely returned to baseline, with only slight residual left leg motor weakness.

DISCUSSION

An accurate and timely laboratory diagnosis of meningococcemia is critical to ensure adequate treatment for a disease associated with high mortality and to prevent secondary exposure. In the case presented, the purpuric rash was the first clue to the diagnosis and, as a result, meningococcemia was highest on the differential. There are several methods for rapid presumptive identification of *N. meningitidis*, including Gram stain examination of cerebrospinal fluid (CSF) or positive blood cultures, with characteristic Gram-negative diplococci (Fig. 1). One manufacturer produces 2 FDA-approved molecular panels that can detect *N. meningitidis* in CSF or positive blood cultures in just over 1 h. As these assays detect nonviable and low levels of organisms, the CSF panel may be more sensitive than CSF Gram stain for *N. meningitidis*, but currently, there are insufficient data for generalizations to be made (1).

N. meningitidis can grow on sheep blood agar, and colonies typically appear gray,

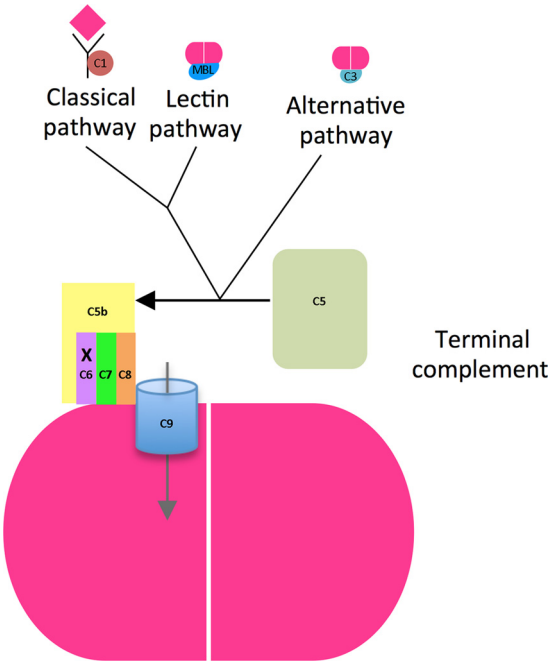

FIG 2 Complement pathways. The classical, lectin, and complement pathways are shown with the associated activation triggers from meningococcus (pink shapes). For the classical pathway, antigen antibody complexes are recognized by C1 to trigger the cascade. The lectin pathway is activated via mannose binding lectins (MBL) interacting directly with the bacterial surface. The alternative pathway is also activated by direct interaction between the bacterial surface and C3. All pathways lead to the conversion of C5 into C5b and accumulation of C6 to C9 on the bacterial cell surface forming the membrane attack complex (MAC), which lyses the cell. In the case presented, C6 is deficient, marked with "X"; as a result, the MAC cannot form.

nonhemolytic, glistening, and smooth. The organism is oxidase positive and oxidizes glucose and maltose, though other nonpathogenic *Neisseria* spp. can produce the same reactions (2). Identification of *N. meningitidis* is FDA cleared on the two current commercially available MALDI-TOF MS systems in the United States, as well as several of the manual and automated biochemical systems; however, no system is 100% specific, and results should be interpreted with caution. Several groups have reported cases of misidentification of nonpathogenic *Neisseria* spp., particularly *N. polysaccharea* as *N. meningitidis* and vice versa via MALDI-TOF MS (2). Similar misidentifications or inability to identify pathogenic *Neisseria* spp. have been reported for some rapid biochemical assays (2). For definitive identification, a mix of rapid acid detection, enzyme production, and colistin resistance tests, as well as observation of pigment, may be needed (Table 1). Ultimately, 16S ribosomal sequencing may be necessary for some select cases with unusual phenotypic test results (2). Results should always be

TABLE 1 Laboratory methods to differentiate several pathogenic and nonpathogenic species of *Neisseria* that may be misidentified as *N. meningitidis*[a]

Neisseria sp.	Growth on sheep blood	Yellow pigment	Acid from glucose	Acid from maltose	Colistin resistance	Enzyme production[b]
N. meningitidis	+	−	+	+	+	GGT[c]
N. gonorrhoeae	w	−	+	−	+	PAP
N. polysaccharea	+	−	+	+	+/−	PAP
N. lactamica	+	+	+	+	+	B-Gal
N. sicca	+	−	+	+	−	PAP
N. subflava	+	+	+	+	−[d]	GGT or PAP

[a]+, yes; w, weak or slow growth; +/−, a minority of strains exhibit this phenotype; −, no.
[b]GGT, gamma-glutamyl aminopeptidase; PAP, hydroxyl-prolyl aminopeptidase; B-Gal, beta-galactosidase.
[c]GGT-negative strain reported in reference 2.
[d]*N. subflava* bv. perflava may exhibit resistance.

interpreted in the clinical context and questioned as appropriate. Questionable isolates can and should be sent to state public health laboratories for confirmation, and all isolates from sterile sites should be sent for serotyping. Although there are CLSI clinical breakpoints, susceptibility testing is not routinely performed, as resistance to the standard treatment for meningococcal disease, third-generation cephalosporins, had not been described. However, resistance has been reported to rifampin and ciprofloxacin, which are routinely used for prophylaxis.

Any manipulations of *N. meningitidis* colonies should be performed with appropriate safety practices, as untreated laboratory-acquired meningococcal infections can be fatal. Suspect cultures should only be opened and manipulated inside a biosafety cabinet to avoid aerosolization of organisms. In a study employing volunteer reporting of suspected laboratory-acquired *N. meningitidis* infections between 1985 and 2001, the authors identified 16 cases worldwide, with a 50% fatality rate (3). Importantly, in 15 of the cases, isolate manipulation was noted to have been performed outside a biosafety cabinet with no respiratory precautions.

N. meningitidis can produce a capsule as a virulence factor to resist antibody- and complement-mediated killing. While encapsulated strains are more likely to cause invasive disease, unencapsulated (nongroupable) strains also have the potential, particularly in hosts with immunodeficiencies, like the case presented here. There are 13 capsule serogroups described, with B, C, and Y being the most common in the United States (4). In 2005, a vaccine targeting the A, C, Y, and W-135 serogroups was licensed in the United States for use in 11- to 55-year-olds. More recently, a vaccine targeting just the B serogroup has been licensed for use in the 10- to 25-year-old age group. Overall, cases have declined since the introduction of the vaccine, with approximately 370 cases reported in the United States in 2016 (4). Cases are reported most frequently in the 0- to 4-year-old and adolescent (15 to 24 years) age groups, concomitant with higher rates of nasopharyngeal colonization (4). While 5 to 10% of adolescents are reported to asymptomatically carry the organism, the mechanisms that lead to invasive disease are still unclear. Given that there are peaks of invasive disease in the winter months, many postulate that preceding respiratory viral infection plays a role in dissemination (3).

Special populations are at increased risk for meningococcal disease at any age, including individuals with a primary or acquired immunodeficiency and asplenic individuals. In particular, individuals with terminal complement deficiencies (C5 through C9, Fig. 2) have a 7,000- to 10,000-fold-higher risk of developing meningococcal disease than does the general population, and it is estimated that 39% of these individuals will develop invasive disease (5). This unique association is due to the role of terminal complement proteins C5b to C8 fusing to form the membrane attack complex and subsequent C9 pore formation that leads to bacterial lysis (Fig. 2). For reasons that are still not completely clear, this mechanism of immune clearance is critical for the control of *Neisseria* infection.

Since meningococcemia may be the first presenting sign in a child or young adult with complement deficiency, it is recommended that any child/young adult with a diagnosis of meningococcemia be considered for an immunodeficiency workup, including, at a minimum, a CH50 screen (5). It is important to note that CH50 levels may be artificially low during the septic period in a normal immune response to overwhelming infection. Thus, a low level should be confirmed, like the case presented, after sepsis has resolved. A low CH50 level indicates that some component in C1 to C9 is deficient. Subsequent screening for deficiency in the alternative pathway (AH50) should be performed to further pinpoint the specific component. A low or absent AH50 result points to a deficiency of a shared component between the pathways, C5 to C9 (Fig. 2). Testing of the individual component levels can then be pursued for prognostic value. The genetic mechanisms of terminal complement deficiency are well defined, and genetic testing is available at specialized laboratories for family planning.

There are no specific treatments available for terminal complement deficiencies. Rather, prevention and early treatment of *Neisseria* infections are the standard of care.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends the primary *N. meningitidis* series (one of the 2 available vaccines can be given as early as 2 months of age), followed by boosters every 3 to 5 years (6). Specific vaccination for serogroup B is also recommended. It is important to note that the available vaccines do not protect against non-A/C/Y/W-135/B or nongroupable meningococci, like the case presented here. In addition to vaccination, administration of antibiotics effective against *N. meningitidis* should be considered in the setting of fever in individuals with terminal complement deficiencies. These patients and their parents should be counseled on the importance of seeking emergent medical care and early treatment for a fever, as the risk of meningococcemia is so high in this population (6).

SELF-ASSESSMENT QUESTIONS

1. What is the estimated rate of nasopharyngeal carriage of *N. meningitidis* in adolescents?
    a. 5% to 10%
    b. 20% to 25%
    c. 35% to 40%
    d. 50% to 55%
2. What 3 serogroups of *N. meningitidis* are most commonly seen in the United States?
    a. A, B, C
    b. B, C, X
    c. B, C, Y
    d. C, Y, W-135
3. Which *Neisseria* species has been mistakenly reported as *N. meningitidis* by MALDI-TOF MS systems, and what test could be used to differentiate the two species?
    a. *N. sicca*, observation of pigment
    b. *N. lactamica*, colistin resistance
    c. *N. polysaccharea*, 16S sequencing
    d. *N. subflava*, gamma-glutamyltransferase (enzyme) detection

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