Rapid Diagnosis of Meningococcal Meningitis in a Patient With Familial Mediterranean Fever by the FilmArray Meningitis/Encephalitis Panel: A Case Report

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Abstract

Familial Mediterranean fever (FMF) is a rare autoinflammatory disorder of the innate immune system. Patients with innate immune system defects are at a high risk of meningococcal disease, although it is unclear if patients with FMF also have increased susceptibility to invasive infection. Herein, we present a diagnostically challenging case of a male adolescent with a past medical history of FMF stabilized on colchicine who presented with some of the early clinical features of community-acquired bacterial meningitis. To our knowledge, this is the first case of meningococcal meningitis in a patient with FMF diagnosed with the FilmArray Meningitis/Encephalitis (ME) Panel. This case report demonstrates that rapid detection of *Neisseria meningitidis* by the ME Panel can aid in the early diagnosis and prompt treatment of patients with suspected meningitis and may be the only positive test in patients with early presentation and/or prior antimicrobial therapy.

Keywords

neurology, Familial Mediterranean fever, meningitis, meningococcal, PCR

Introduction

Familial Mediterranean fever (FMF) is a rare inherited systemic autoinflammatory disease characterized by recurrent episodes of fever and polyserositis.^{1,2} Autoinflammatory episodes typically begin in childhood and adolescence, with use of colchicine for long-term, prophylactic management.¹ Familial Mediterranean fever disproportionately affects people of Eastern Mediterranean heritage and is most commonly inherited in an autosomal recessive pattern.¹

Neurological complications in FMF are rare, though there have been several reported cases of recurrent aseptic meningitis.³ Efforts to establish causal links between FMF and recurrent aseptic meningitis have been hampered by the rarity of such cases and the lack of diagnostic uniformity across reports.⁴ Herein, we describe a case of *Neisseria meningitidis* in a 19-year-old male with FMF. To our knowledge, this is the first reported case of *N meningitidis* infection in a patient with FMF. This case demonstrates the utility of the FilmArray Meningitis/Encephalitis (ME) polymerase chain reaction (PCR) panel (Biofire Diagnostics, Salt Lake City, Utah) in rapidly detecting meningococcal meningitis, an illness

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associated with high morbidity and mortality.⁵ Additionally, this case reflects the increased risk of exposure to *N meningitidis* in college students and raises the question of whether there may be defects in the innate immune system in FMF that result in enhanced susceptibility to *N meningitidis* infection.

Case Description

A 19-year-old Caucasian male college student with a 4-year medical history of FMF presented with 1 day of nausea, episodes of nonbloody vomiting, myalgias, arthralgias, diaphoresis, and chills. These symptoms were followed by a severe frontal headache accompanied by ocular pressure, mild neck pain, photophobia, phonophobia, and a sensation that the room was "tilted." He reported an episode of nonbloody diarrhea and denied subjective fevers or respiratory or urinary symptoms. He noted that his symptoms differed from his usual FMF flares, characterized by fever, severe abdominal pain, nausea, and rash. Recent travel history was notable for a hiking trip to Canada where he was bitten by several insects. He had a total of 4 to 5 sexual partners and had never been tested for sexually transmitted illnesses though he had unprotected sex. The patient's vaccine status was not known.

He presented to the emergency department (ED) after he began feeling dizzy on standing and walking. In the ED, he was afebrile and normotensive. Physical examination revealed photophobia, 1 to 2 mm petechiae on his eyelids, soft palate/buccal mucosa, trunk, back, and upper extremities, and a 2-cm tender, nonblanchable, erythematous macular rash on his right anterior thigh. Neurological examination was grossly intact and nonfocal according to ED documentation. Initial blood testing revealed leukocytosis with bandemia (Table 1). Basic metabolic panel, liver function, lipase, urinalysis, electrocardiogram, chest X-ray, and computed tomography of the abdomen/pelvis were normal. He was administered one 2-gram dose of intravenous ceftriaxone and 100 mg of oral doxycycline before being admitted for further workup and management. Lumbar puncture (LP) was deferred in the ED due to the absence of fever and the lack of meningismus, with the plan to pursue LP if his headache worsened or he developed meningismus.

The patient complained of neck stiffness upon transfer, and an LP was performed within 6 hours of empiric antimicrobial administration. Lumbar puncture was significant for cerebrospinal fluid (CSF) neutrophilic predominant pleocytosis. The CSF ME Panel was positive for *N meningitidis* within approximately 3 hours of CSF being received in the laboratory and approximately 24 hours after patient presented to the ED (Table 1). Of note, repeat ME panel testing of the same CSF specimen was negative. Cerebrospinal fluid Gram stain was significant for rare WBCs, but no organisms were seen, and CSF culture showed no growth after 5 days. Cerebrospinal fluid and whole blood specimens were sent to the New York State Department of Health (NYSDOH), where they were

Table 1. Summary Results of Laboratory Investigations Throughout Hospitalization.

Investigations	Results	Reference Values
Complete blood count with differential at admission		
White blood cell (WBC) count	30.34/ μ L	3.12-8.44 $\times$ 10(3)/ μ L
Polymorphonucleocytes (PMN)	70.0%	20.0%-50.0%
Lymphocytes	4.0%	20.0%-50.0%
Monocytes	2.0%	4.0%-8.0%
Bands	16%	0%-5%
Mean platelet volume	8.9 fL	9.0-12.1 fL
C-reactive protein	217.50	0.00-10.00 mg/L
Basic metabolic panel at admission		
Serum glucose	91	75-100 mg/dL
Blood urea nitrogen	21	7-20 mg/dL
Serum calcium	8.5	8.7-10.0 mg/dL
HIV	Nonreactive	Nonreactive
RPR	Negative	Negative
Lumbar puncture/CSF analysis at admission		
Appearance	Yellow	Clear
Opening pressure	31	7-18 cm H ₂ O
Closing pressure	19	
White blood cell (WBC) count	206	0-5/ μ L
Polymorphonucleocytes (PMN)	87	0%-0%
Lymphocytes	4	0%-0%
Monocytes/macrophages	7	0%-0%
Bands	2	0%-0%
Protein	50	15-45 mg/dL
Glucose	70	40-70 mg/dL
Biofire FilmArray Meningitis/Encephalitis (ME) PCR Panel	<i>Neisseria meningitidis</i> Detected Second run: Not Detected	Not detected
NYSDOH <i>Neisseria meningitidis</i> real-time PCR C _t values from CSF	ctrA: 35.3 porA: 36.1 ^a siaD: 37.8	Not detected
NYSDOH <i>Neisseria meningitidis</i> real-time PCR C _t values from blood	ctrA: 27.9 porA: 30.1 ^a siaD: 31.4	Not detected
Complement levels		
Total complement	1	60-144 CAE units
Complement component 1Q (C1Q)	165	109-242 μ g/mL
Complement component 2 (C2)	2.3	1.0-4.0 mg/dL

Abbreviations: CSF, cerebrospinal fluid; NYSDOH, New York State Department of Health; PCR, polymerase chain reaction.

^aSerogroup B specific.

both positive for *N meningitidis* by real-time PCR (Table 1). Notably, crossing threshold (C_t) values from the CSF specimen showed substantially lower DNA present in CSF than blood, although the blood specimen was drawn before empiric

Ceftriaxone, and CSF was drawn over 4 hours after the first dose was given. Lyme disease, babesiosis, Rocky Mountain spotted fever, and anaplasmosis serologies in the blood (and CSF for Lyme) were sent and later returned negative. Complement component 1Q and C2 complement levels were normal but total complement level was abnormally low (Table 1). There were no prior values for comparison. Neuroimaging and electrophysiology were not performed due to rapid improvement of his symptoms on the first day of admission. Ceftriaxone 2 g intravenously every 12 hours was continued given the ME panel result. Oral doxycycline 100 mg every 12 hours was continued to cover for tick-borne illness in the setting of negative cultures but was discontinued at discharge after confirmatory *N meningitidis* PCR results from NYSDOH became available. Day 3 of his hospital course was complicated by arthralgias progressing to right wrist arthritis consistent with disseminated meningococcal disease. Based on the semiology, initial positive CSF PCR for *N meningitidis*, and rapid clinical recovery with appropriate antibiotics, meningococcal meningitis was considered the most likely discharge diagnosis and was confirmed by subsequent sample testing by the NYSDOH. Direct contacts of the patient were administered chemoprophylaxis, and the patient was discharged after 4 days to complete his antibiotic course as an outpatient.

Discussion

Although the patient presented with early clinical features of community-acquired bacterial meningitis and had drastic improvement of symptoms after initiation of antimicrobial therapy, this case was diagnostically challenging due to the underlying history of flares associated with FMF. Differentiating an FMF flare from bacterial meningitis was particularly challenging given the lack of all the features of the classic triad (fever, headache, neck stiffness) and negative Gram stain and culture on initial presentation. Notably, normal CSF glucose and protein levels have been well described in early bacterial meningitis, especially in immunocompromised individuals.⁶ Fever may also be absent, and LP/empiric therapy should not be withheld if other clinical signs and symptoms are consistent with bacterial meningitis.

This case demonstrates the utility of rapid multiplex in vitro PCR assays for the diagnosis of community-acquired bacterial meningitis. Multiplex PCR assays such as the ME panel are capable of simultaneously testing for an array of bacterial, viral, and fungal pathogens that cause life-threatening central nervous system infections and complications. Early etiologic diagnosis ensures that patients with high likelihood of rapid clinical deterioration receive optimal and timely antimicrobial therapy, thus minimizing overall morbidity and mortality. Since meningococcal disease progresses rapidly, early diagnosis and intervention are critical to optimizing outcome.⁵ Although CSF culture remains gold standard for diagnosis of *N meningitis*, it can take several days for pathogen growth or may remain sterile as in our case in the

setting of empiric antimicrobial use. In such cases, comprehensive, rapid, high-sensitivity/specificity assays can contribute significantly to the clinical decision-making process, aid antimicrobial stewardship, and may improve individual patient health outcomes.^{7,8} Interestingly, repeat ME panel testing on the initial CSF specimen did not detect *N meningitidis*, which suggested that the amount of bacterial DNA was near the limit of detection, an impression later confirmed by reverse transcription polymerase chain reaction (RT-PCR) results from NYSDOH. Assay variability for specimens near the limit of detection has been previously described,^{7,8} and meningococcal disease should not be excluded in the context of significant clinical suspicion. The ME panel was run a second time at the discretion of the laboratory director given the absence of organisms seen on the CSF Gram stain and the clinical importance and urgency of the case. Positive ME results are not usually repeated at our institution, although in our experience repeat testing may be useful in certain cases to clarify ambiguous or uncertain findings, such as discordance with CSF Gram stain. Given the rapid progression and severe consequences of untreated meningococcal disease, the utility of repeat testing on the ME panel for *N meningitidis* is questionable; however, if the clinical suspicion is high, communication of positive results from the initial test should not be delayed during repeat panel testing. In culture-negative meningitis, PCR also serves as a valuable epidemiologic tool to allow contact tracing and potentially serve as the first indication of an outbreak. The lack of serotype specificity of the ME panel is a drawback, although serogroup information was ultimately obtainable from RT-PCR performed at NYSDOH.

With the NYSDOH confirmation that the etiology was indeed *N meningitidis*, this case raises an important question as to the possible connection between FMF, the complement system,^{9,10} and susceptibility to *Neisseria* infections. Deficiencies of the complement pathway, particularly terminal complement components, are associated with a substantially increased risk of invasive *Neisseria* infections.¹¹ Although the patient's total complement level was very low during this admission, a single measurement of the 50% hemolytic complement (CH50) activity can be affected by multiple preanalytic variables,¹¹ and repeat testing and evaluation of individual complement component levels are needed to evaluate this patient further. Virtually all cases of FMF are caused by mutations in the Mediterranean Fever gene, which encodes for the protein pyrin, and results in inflammasome activation and production of interleukin-1 β , which would suggest increased, and not deficient, activity of the innate immune system. Most studies have also shown increased, and not decreased, complement total hemolytic activity in patients with FMF.⁹

Conclusions

Clinicians have a very narrow window of opportunity to deliver the most appropriate treatment before patients

progress to fulminant meningococemia associated with high mortality.⁵ In such cases, rapid PCR assays such as the ME panel can be potentially lifesaving, although the full clinical picture must be considered, as even PCR results can be variable in the setting of early disease and/or prior antimicrobial therapy.

Authors' Note

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Declaration of Conflicting Interests

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