Pearls & Oy-sters: Diagnosis and Subtyping of Listeria Ventriculitis in an Immunocompetent Host

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Abstract

Listeria monocytogenes is a Gram-positive food-borne pathogen that causes gastrointestinal symptoms and CNS infection in susceptible hosts. Two lineages of *Listeria* cause the majority of neurolisteriosis in humans. In this report, we discuss a case of a 23-year-old previously healthy woman who presented with acute-onset rapidly progressive altered mental status after eating undercooked meats at a local restaurant. Given her age and lack of comorbidities, bacterial meningitis was suspected, and she was treated with ceftriaxone, vancomycin, and steroids. MRI of the brain was consistent with meningitis and ventriculitis; CSF analysis also suggested bacterial meningitis. Despite mechanical ventilation, pressors, and ventricular drain placement, she quickly decompensated and died 12 hours after arrival. CSF culture later returned positive for *Listeria monocytogenes*. We used whole-genome sequencing and near-source comparison to identify the *Listeria* subtype that led to her unexpected presentation. The results suggest that her CSF isolate was consistent with a lineage II *Listeria* serotype, which is known to exhibit greater genetic variation than the more commonly isolated lineage I serotypes. We conclude the discussion with diagnostic and treatment approaches to neurolisteriosis. In susceptible hosts, namely immunocompromised, pregnant, neonatal, or elderly patients, *Listeria* infection may result in CNS invasion, causing meningoencephalitis and, rarely, ventriculitis and rhombencephalitis. Although neurolisteriosis most commonly affects individuals with known risk factors, CNS infection is nevertheless possible in otherwise healthy young patients. Suspicion should be raised in patients with an exposure history who do not improve with empiric antibiotics.

Pearls

- Although neurolisteriosis most commonly affects immunocompromised, pregnant, neonatal, or elderly patients, CNS infection is nevertheless possible in otherwise healthy young patients.

Oysters

- In a patient with possible recent exposure, *Listeria* meningitis should be suspected if the patient does not improve with empiric antibiotics that do not cover for *Listeria*.
- CSF and clinical findings consistent with bacterial meningitis are less common in *Listeria* meningitis than other causes of bacterial meningitis.
- Ventriculitis is a rare complication of meningitis and can present with elevated intracranial pressure.

Case

A 23-year-old previously healthy woman presented with altered mental status. Three days prior, she began experiencing nausea and abdominal pain. Her symptoms progressed to headache, fever, and vomiting. Two hours before presentation, she became acutely delirious and confused, prompting her family to bring her to the emergency department (ED). She did not have any medical history, including any immunosuppression or chronic infections.

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In the ED, she had a temperature of 102.2°F (39°C), pulse 130 beats per minute, respiratory rate 30–38 breaths per minute, and blood pressure 100/53 mm Hg. She opened her eyes only to pain, her speech was incomprehensible, and she withdrew upper and lower extremities only to pain (Glasgow Coma Scale = 8). Pupils were symmetric but sluggish with a pupillary diameter of 4 mm in ambient light. Physical examination was also positive for meningeal signs (i.e., pain on passive neck flexion).

Laboratory values showed an elevated serum white cell count (13.49×10^9/L), C-reactive protein (144.14 mg/L), erythrocyte sedimentation rate (54 mm/hour), and lactate (5.59 mmol/L). CSF showed severe pleocytosis ($1,629 \times 10^6$ cells/L) with 90% mononuclear cells, decreased glucose (1.26 mmol/L, CSF:serum glucose ratio 0.09), elevated protein (2.47 g/L), and elevated lactate dehydrogenase (1218 IU/L). Her urine pregnancy test was negative.

Given high suspicion for bacterial meningitis and sepsis (qSOFA score 3/3, SIRS criteria 4/4), she was started on ceftriaxone (2 g, IV, q12h), vancomycin (20 mg/kg, IV, q12h), and dexamethasone (0.15 mg/kg, IV, q6h).

Twenty minutes after arrival, she became apneic and unresponsive and was emergently intubated. Pupils were symmetrically dilated at 6.5 mm with no pupillary reflexes. MRI of the brain showed lateral ventriculomegaly, intraventricular debris, periventricular hyperintensity, and ependymal enhancement, consistent with meningitis complicated by ventriculitis and obstructive hydrocephalus (Figure 1). A ventricular drain was placed by neurosurgery.

Unfortunately, she was persistently hypotensive despite fluid resuscitation and pressor support. The patient died 12 hours after arrival. One day later, *Listeria monocytogenes* was identified from the CSF via metagenomics and later confirmed by culture (Figure 2). Meanwhile, extensive rheumatology and infectious disease workup (including HIV serology) was found to be negative. On reexamination of her history, it was found that 3 days before presentation, she had lunch with a friend at a restaurant where she ate self-cooked pork, beef, and chicken. Her friend was asymptomatic.

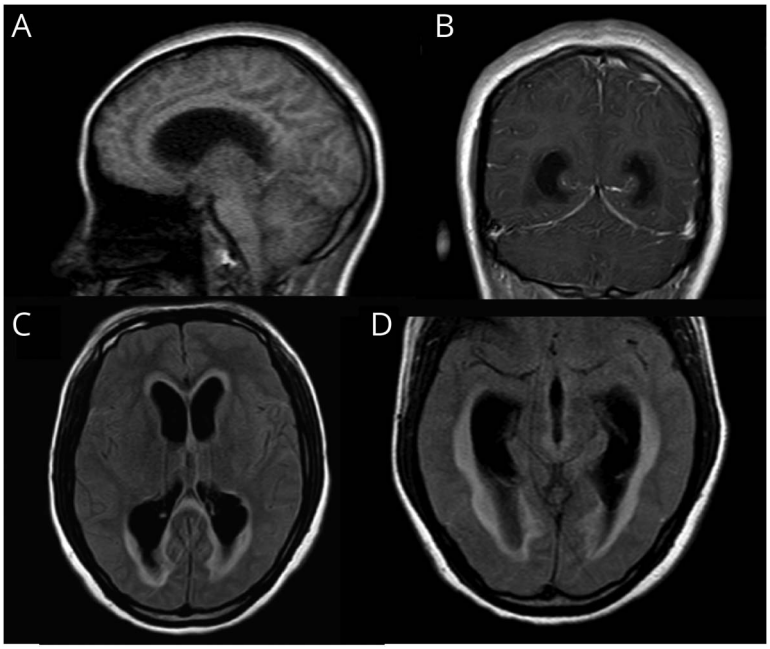
We subsequently performed genetic testing of the CSF isolate using next-generation whole genome sequencing and compared the results with near-source species using nucmer[1] (Bioyi Biotechnology, Wuhan, China). This identified the isolate as being closest to *Listeria monocytogenes* serotype 1/2c, strain NH1.

Discussion

L. monocytogenes is a Gram-positive, facultative anaerobic intracellular rod-shaped bacterium, classically described to exhibit tumbling motility on light microscopy.[2] There are 17 species of the genus *Listeria*,[2] of which *L. monocytogenes* most commonly infects humans. *Listeria* was recognized as a foodborne pathogen in the 1980s, and although outbreaks are rare, it causes significant morbidity and mortality in susceptible hosts.[3]

Demographically, our patient was a young woman without any of the traditional risk factors of neurolisteriosis.[4] In immunocompetent young patients, listeriosis typically manifests

Figure 1 MRIs Obtained at the Time of Admission

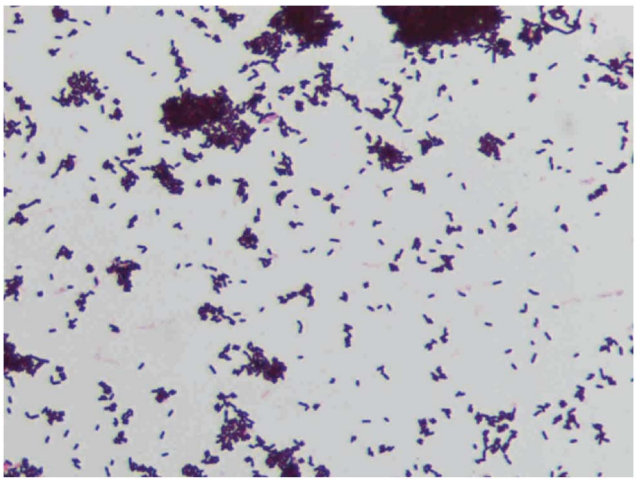


(A) T1-weighted image showing ventriculomegaly of the lateral ventricle. (B) Postcontrast T1-weighted image showing leptomeningeal enhancement. (C and D) FLAIR images showing periventricular hyperintensity and debris in the occipital horns of the lateral ventricles.

as a febrile gastroenteritis consisting mainly of self-limited diarrhea. Susceptible hosts consist of 3 groups: (1) those with immunosuppression, such as patients on medications that suppress cell-mediated immunity; (2) those at the extremes of age, including neonates and adults greater than 50 years old; and (3) pregnant women. In these individuals, *Listeria* infection can result in bacteremia and CNS infection. Because our patient was young, previously healthy, not immunosuppressed, and not pregnant, her recent exposure history to potentially undercooked meats was initially overlooked and was discovered only after the diagnosis of *Listeria* infection.

Clinically, CNS *Listeria* most commonly manifests as meningitis and meningoencephalitis and less commonly as rhombencephalitis (focal brainstem infection) and brain abscess.[5] Like other forms of bacterial meningitis, fever and altered mental status are the most common findings in CNS listeriosis. Although our patient exhibited signs of meningeal irritation, patients with *Listeria* meningitis often do not exhibit specific meningeal signs, unlike meningitis caused by other bacteria.[4] Ventriculitis, more commonly seen in postneurosurgery patients such as those with ventricular indwelling devices, may occur as a rare complication of meningitis. One case of *Listeria* ventriculitis has been reported in a 78-year-old immunocompetent patient[6] and other cases in pediatric patients or neonates. However, ventriculitis by itself is not specific or unique to neurolisteriosis; thus, our initial empiric antibiotic coverage consisted of IV vancomycin and a third-generation cephalosporin,[7,8] which does not cover *Listeria*. Because of the emergent nature of this patient's progression in the ED, it would not be unreasonable to broaden her antibiotic coverage to include *Listeria*. Given her normal fundoscopic examination and absence of specific signs at presentation, elevated intracranial pressure (ICP) was initially not suspected. Once florid ventriculitis and elevated ICP were established, the priority became lowering of ICP through neurosurgical intervention while simultaneously addressing the underlying cause.[9]

Figure 2 Gram Stain of CSF Culture Showing *Listeria* Organisms at 10x Magnification



Diagnosis of CNS listeriosis is typically performed using a combination of clinical, CSF, and MRI findings and confirmed using blood or CSF culture or PCR. Pleocytosis in the CSF indicates CNS inflammation and may be seen in a variety of infectious or autoimmune conditions.[10] Our patient had a severe neutrophil-predominant pleocytosis suggestive of bacterial or early viral meningitis. However, it should be noted that pleocytosis may be absent in 1%–12% of bacterial meningitis cases, and neutrophil predominance has poor discriminatory power for bacterial vs viral meningitis.[10] CSF glucose is related to the degree of pleocytosis[10] and a CSF: serum glucose ratio <0.5, as seen in our patient, along with a CSF protein >1.5g/L and elevated CSF lactate dehydrogenase, is consistent with bacterial rather than viral meningitis. Of note, these classic CSF chemistry findings of bacterial meningitis (i.e., high protein, low glucose) are present in only 77% of cases of *Listeria* meningitis,[11] and Gram staining for *Listeria* misses about two-third of cases,[4,11] suggesting the need to have a relatively low threshold to treat at-risk patients who have an atypical presentation for bacterial meningitis.

Treatment for *Listeria* meningitis is ampicillin or penicillin G, or alternatively trimethoprim-sulfamethoxazole or meropenem, for at least 21 days.[7] The addition of an aminoglycoside such as gentamicin may have a synergistic effect and could be considered, although the potential for renal failure limits its general use.[8] In a large prospective study, adjunctive dexamethasone was associated with increased mortality in CNS listeriosis[12]; thus, it is no longer recommended. Despite the relatively available antibiotic therapies, globally neurolisteriosis remains highly morbid, with a mortality rate of around 30%.[3] In our case, septic shock was the most likely cause of death.

The question remains as to why our patient, a healthy immunocompetent host, manifested with *Listeria* ventriculitis, whereas her friend was asymptomatic. Although genotyping *Listeria* subtypes is not typically performed in clinical practice because it has little implications for treatment or prognosis, we pursued genetic subtyping to further investigate pathogen factors that may contribute to the patient's presentation, which we briefly discuss below.

The mechanism by which *Listeria* infects the nervous system is unknown. One proposed mechanism involves hematogenous spread, whereby the bacteria invade intestinal mucosa and gain access to the bloodstream. From there, *Listeria* may use internalin (Inl) proteins InlA and InlB to interact with E-cadherins and Met proteins present on choroid plexus epithelial and brain endothelial cells to gain entry through the blood-brain barrier. An alternative hypothesis posits that bacterial cells are taken up by host phagocytes, escape from phagosomes using a pore-forming toxin listeriolysin O, and then move into the cell cytosol via actin assembly-inducing protein, thus gaining access to the CSF space through these phagocytes.[2,5]

Phylogenetic studies have identified 4 evolutionary lineage of *L. monocytogenes*, of which isolates from lineages I

(serotypes 1/2b, 3b, 4b, 4d, and 4e) and II (serotypes 1/2a, 1/2c, 3a, and 3c) are implicated in the majority of human outbreaks.[13] In our genetic analysis using whole-genome sequencing and near-source species comparison, the 3 strains with the highest similarity to the patient's isolate are lineage II serotypes (strain NH1, serotype 1/2c, similarity 0.978268; strain SLCC2479, serotype 3c, similarity 0.978242; strain 2018TE5305-1-4, serotype 1/2a, similarity 0.978107). Animal studies suggest that lineage I serotypes exhibit greater virulence, possibly because lineage II serotypes overexpress truncated InlA proteins,[14] whereas lineage II serotypes exhibit greater genomic plasticity.[15] One might hypothesize that lineage II subtypes of *Listeria* may have a higher propensity for CNS invasion in otherwise healthy adults, such as in our case, although more systematic studies are needed to elucidate the mechanism.

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Shujuan Dai, MD	Department of Neurology, Kunming Medical University, Yunnan, China	Major role in the acquisition of data and analysis or interpretation of data
Qian Wu, MD, PhD	Department of Neurology, Kunming Medical University, Yunnan, China	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and study concept or design

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