

Listeria Meningoencephalitis: Two Cases and a Review of the Literature

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Abstract

Introduction: Although presently uncommon locally, *Listeria* is increasing an important cause of central nervous system (CNS) infection worldwide. It differs from the common meningitis pathogens in its clinical features and treatment. **Clinical Picture:** We present 2 recently encountered cases of *Listeria* meningoencephalitis. In case 1, a previously healthy 42-year-old man presented with clinical features of meningoencephalitis. In case 2, a 64-year-old woman had clinical features of pneumonia and meningoencephalitis. Both had a predominantly lymphocytic picture in their cerebrospinal fluid (CSF) samples. *Listeria* grew in blood cultures of both patients and the CSF culture of the first. **Treatment:** In both cases, *Listeria* was resistant to the empirical antibiotics used. Intravenous ampicillin was eventually used in both patients, with gentamicin added for synergistic action in the first. **Outcome:** The first patient developed complications of hydrocephalus, subdural collection and extensive cerebritis and ventriculitis. The second patient had focal seizures and a pontine infarct. Both did not survive. **Conclusion:** These 2 recent cases with different presentations of intracranial listeriosis highlight the increasing importance of listerial infections in Singapore. Clinicians need to be familiar with the features of this lethal disease in order to recognize and manage it successfully.

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Introduction

The general experience of local physicians and available data suggest that listerial infections of the central nervous system (CNS) are uncommon among adults in Singapore.¹ This situation may change. With increased use of pneumococcal and meningococcal vaccines and, in particular, the conjugate *Haemophilus influenzae* vaccine, the incidence of adult meningitis due to traditional pathogens is likely to decline. In the United States, *Listeria monocytogenes* is presently one of the leading causes of community-acquired acute meningitis among adults.^{2,3}

L. monocytogenes CNS infection differs from conventional bacterial infections in its epidemiology, clinical presentation, cerebrospinal fluid (CSF) profile and drug treatment. It carries a higher mortality than most other cause of bacterial meningitis, approaching more than 30% in large series.⁴ Especially significant is the fact that

L. monocytogenes is intrinsically resistant to antibiotic classes that are often empirically used as first-line treatment of bacterial meningitis. Delay in treatment with appropriate antibiotics correlates with poor outcome.⁵ It is thus necessary for clinicians to be familiar with the features of *L. monocytogenes* CNS infection and to consider the diagnosis early in the course of presentation. We report 2 cases of *L. monocytogenes* meningoencephalitis treated at our medical centre over the last year. One case had radiological evidence of diffuse cerebral and brainstem meningoencephalitis, while the other had meningoencephalitis complicated by brainstem infarction.

Case Reports

Case 1

A previously healthy 42-year-old Norwegian of Vietnamese extraction was visiting Vietnam when he was

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hospitalised for a 4-day history of fever, headache and decreased mental status. He was diagnosed to have meningitis and treated with intravenous ceftriaxone, chloramphenicol and hydrocortisone. Initial examination of the cerebrospinal fluid (CSF) showed an increased white cell count (3500 cells/mm³), raised protein levels (3.5 g/L) and low glucose levels (0.65 g/dL). His mental status deteriorated despite treatment and he had to be intubated 2 days after admission. A repeat CSF examination showed increased white cell counts from the baseline (8000 cells/mm³). The initial blood and CSF cultures were negative. He was then air-evacuated to Singapore where he was admitted to the medical intensive care unit (MICU) and maintained on mechanical ventilatory support.

The patient's haemodynamic parameters were normal on admission. He was deeply comatose, with no response to pain. No skin rash was visible. There was neck stiffness. The pupils were 4 mm and non-reactive to light bilaterally and the gag reflex was present. Clonus could be elicited in the lower limb and was more prominent on the left side. The plantar responses were equivocal.

A computed tomographic (CT) scan of the head done on admission showed gross hydrocephalus. An external ventricular drain (EVD) was inserted into the left lateral ventricle the same night and a further sample of CSF was sent for analysis and culture.

The CSF appearance was turbid, with cell counts showing red cells 100/mm³ and white cells 136/mm³ (69% lymphocytes, 24% polymorphs). Biochemical analysis showed a CSF sugar of <0.6 mmol/L (blood sugar 6.4 mmol/L), chloride 98 mg/dL and total protein 1.92 g/dL. A smear for acid-fast bacilli and the CSF cryptococcal antigen were both negative.

Initial antimicrobial treatment consisted of intravenous ceftriaxone, vancomycin, and ampicillin. Acyclovir and anti-tuberculous agents (isoniazid, pyrazinamide, rifampicin) were also given.

Cultures for neurotropic viruses (herpes simplex viruses, mumps, measles, enteroviruses) and a polymerase chain reaction test for tuberculosis were negative. *L. monocytogenes* was identified on blood and CSF cultures on the fifth admission day. Vancomycin, acyclovir, and anti-tuberculous agents were then stopped and ampicillin and gentamicin were given.

A second EVD was inserted on the right side on the third day of admission because of persistent right ventricular dilatation. This resulted in good resolution of hydrocephalus, and on day 5 of admission, the patient was noted to be spontaneously moving his eyes and his right arm. However, he remained unresponsive to commands, and despite continued treatment with antibiotics, there was no further improvement in his neurological status. Instead, serial CT

head scans subsequently showed development of a subdural collection deemed too small for surgical intervention overlying the right frontal lobe. A magnetic resonance imaging (MRI) of the brain (Fig. 1) on day 15 showed extensive ventriculitis and cerebritis. CT brain on day 19 showed mild to moderate generalised cerebral oedema and mildly dilated lateral ventricles. Clinically, the patient's condition remained in *status quo* till day 24 when he developed bradycardia, hypotension and loss of brainstem reflexes. An urgent CT brain did not show any significant change compared to that done on day 19. He died the following day.

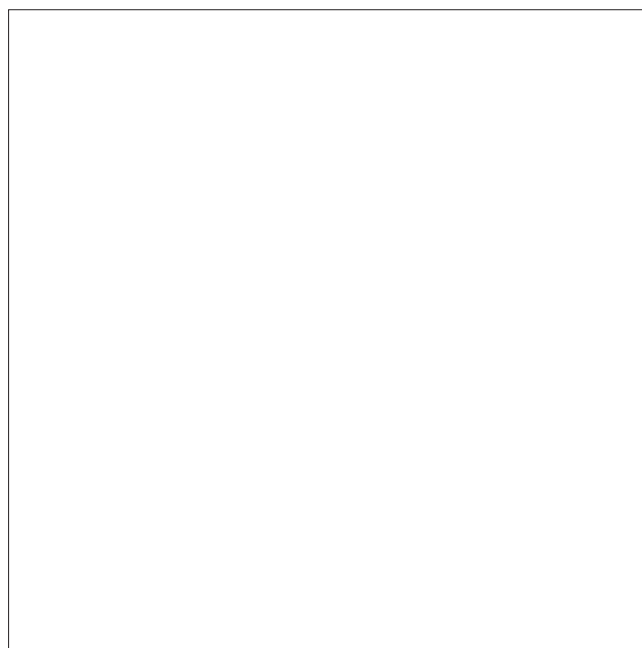


Fig. 1. MRI brain showing periventricular as well as cerebellar hyperintensities that enhances after gadolinium, indicating extensive ventriculitis and cerebritis.

Case 2

Our second patient was a 64-year-old Singaporean Chinese female who had a history of post tuberculous bronchiectasis as well as a nephrectomy for renal cell carcinoma 30 years prior to admission. She was admitted with fever, chills, rigors and drowsiness for two days. At presentation, she was febrile (40.8°C), drowsy (Glasgow Coma Scale = 6), dehydrated and pale. Examination of the chest showed decreased excursion, dullness to percussion and diminished breath sounds on the left as well as coarse crepitations on the right side. There was neck stiffness, and both plantar responses were extensor. No focal neurological deficits were noted at that time. The cardiovascular and abdominal examination was unremarkable. She was intubated in the emergency department and ventilated in the intensive care unit (ICU). Initial blood investigations showed an increased white cell count of $19.12 \times 10^9/L$ with

83.5% polymorphs. There was mild renal dysfunction (urea, 22.8 mmol/L; creatinine, 126 mmol/L). The chest X-ray showed diffuse opacification of the left lung field and infiltrates in the right upper lung field. She was given intravenous ceftazidime (1 g bd) and cloxacillin (1 g qds, later 500 mg qds).

Two days later, blood cultures grew *L. monocytogenes* and ampicillin 2 g tds was added. Lumbar puncture was then performed. The opening pressure was elevated at 42 cmH₂O and there were raised cell counts (white blood count of 300/mm³, red blood count of 40/mm³, 38% polymorphs, 44% lymphocytes, 18% monocytes). Biochemical analysis of the CSF showed a raised protein level (3.87 g/dL), with glucose level of 5.3 mmol/L (blood glucose was 16.8 mmol/L) and chloride level of 126 mmol/L. Gram stain of the CSF was negative for organisms and no acid-fast bacilli were seen. Her antibiotics were changed to ampicillin, ceftriaxone, and vancomycin.

On the third day of admission, the patient had a focal seizure involving the left side of the body. She remained febrile and required inotropic support as well as haemodialysis for worsening renal failure. Thrombocytopaenia was noted and attributed to sepsis. Neurological examination on day 6 of admission, after sedation was stopped, showed bilaterally reactive 2 mm pupils, no response to pain and bilateral extensor plantar responses with preservation of the brainstem reflexes. A repeat CT scan of the head a week after admission did not show new abnormalities, but MRI scan of the head done one week after the CT scan demonstrated changes compatible with diffuse meningitis involving the cerebral cortex and brainstem as well as an acute pontine infarct. There was no cerebritis.

Her neurological status did not improve, and she expired on day 16 from pneumonia and septic shock.

Discussion

In the United States, a 1990 Centers for Disease Control and Prevention (CDC) surveillance study showed *L. monocytogenes* to be a less common cause of meningitis than *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis* or Group B *Streptococci*, but being the organism responsible for the highest mortality rates.⁶ After the widespread introduction of *H. influenzae* vaccination, a later survey in 1995 showed that the incidence of *L. monocytogenes* meningitis had overtaken that due to *H. influenzae*.² Our impression is that *L. monocytogenes* meningitis is presently rare in our adult population.¹ This situation may change with the growing incidence of HIV infection, the advent of organ transplantation and ageing of the Singapore population. Certain groups are more susceptible to *L. monocytogenes* meningitis. These include

those at the extremes of age (neonates, people aged above 50 years) and the immunocompromised.^{4,7} Nevertheless, healthy individuals at any age are at risk of this lethal disease.⁴

Mode of Transmission

Human listerial infection can occur sporadically or in outbreaks.⁴ Infections are mainly food-borne, and previous outbreaks have been attributed to contaminated coleslaw, milk, cheese, pate, ready-to-eat pork products, gravad or cold smoked trout.⁷ Dietary recommendations for prevention of food-borne listeriosis were developed by CDC in 1992.⁸ These include thoroughly cooking raw food from animal sources, thoroughly washing raw vegetables, keeping uncooked meats separate from ready-to-eat food, avoiding consumption of raw milk and washing of hands and utensils after handling uncooked foods.

To the best of our knowledge, our first patient was healthy prior to this fatal illness. Both our patients did not have an apparent food-related source for their infections. Indeed, the food products commonly associated with *L. monocytogenes* infection do not form a major part of the Southeast Asian diet. Our second patient was more elderly, in poorer health and more susceptible to sepsis than our first. It is relevant to note that initial empirical treatment for bacterial meningitis in patients above 50 years of age should include coverage for *L. monocytogenes*.^{4,7,9}

Meningitis/Meningoencephalitis

Listeria meningitis presents much like other bacteria meningitides, but some clinical differences may be present (Table I).

TABLE I: COMPARISON OF CLINICAL FEATURES BETWEEN *LISTERIA* MENINGITIS AND MENINGITIS DUE TO OTHER PATHOGENS

	<i>Listeria</i> meningitis	Meningitis due to other pathogens
Neck stiffness	Less common (present in 71%)	More common (present in 90%)
Movement disorders	More common	Less common
Seizures	More common (39%)	Less common (23%)
CSF gram stain	Low sensitivity (<40%)	Higher sensitivity (>60%)
CSF glucose level	Not low in most	Usually low
CSF white cells differentials	Lymphocyte predominance in 30%	Neutrophil predominance in most
Blood culture	Higher positive rates (75%)	Lower positive rates

CSF: cerebrospinal fluid

Adapted from Lorber B.⁷

Mylonakis et al⁴ have reviewed 776 episodes of CNS listeriosis from the literature and 44 cases treated at Massachusetts General Hospital over a period of 33 years. In their series, there was a non-significant trend for fever and altered sensorium to be less common on presentation in patients with *L. monocytogenes* meningitis compared with other bacterial meningitides. Patients with *L. monocytogenes* meningitis were found to be significantly less likely to have headache (46% versus 90%) and meningeal signs (71% versus 90%). The CSF profile may also be atypical for bacterial meningitis. There is a trend towards lower leukocyte counts, and mononuclear cell predominance is present in about 30%. The CSF glucose level is often not low, and the CSF protein levels may also be normal or only modestly elevated.

Due to the pleomorphism of *L. monocytogenes*, its resemblance to diphtheroids or pneumococci, and its tendency to become over-decolourised, the organism is difficult to identify with precision by gram stain. Gram stain of the CSF is negative in two-thirds of cases, and may be misleading in many of the remaining cases. This is in contrast to the aetiologic agent being identified on CSF gram staining in 60% to 75% of all cases of acute meningitis with other bacteria. The blood culture, however, is positive up to 75% of the time.⁶

Our first patient had typical symptoms of meningitis and the initial CSF examination revealed a fairly typical picture of bacterial meningitis, but with a predominance of lymphocytes. As in many instances, the CSF gram stain was unhelpful in identification of the bacteria. It was unfortunate that the initial CSF and blood cultures were negative, as this further delayed the use of effective antibiotics.

Rhombencephalitis

Other causes of bacterial meningitis rarely involve the brain parenchyma. In contrast, *L. monocytogenes* has tropism for the brain and often causes meningoencephalitis rather than meningitis alone.⁷ Encephalitis involving the brain stem (rhombencephalitis) is therefore an uncommon but classical presentation of CNS listerial involvement. *L. monocytogenes* rhombencephalitis was first described by Eck¹⁰ in a case from East Germany in 1957, and a review by Armstrong and Fung⁵ in 1992 found a total of 62 reported cases in the literature. Patients were noted to be predominantly healthy non-immunocompromised people. They presented with variable combinations of asymmetric cranial nerve deficits, cerebellar signs, hemiparesis or hemisensory deficits after a prodrome of fever, headache, nausea and vomiting lasting a few days. Forty-six per cent had both cranial nerve palsies and long-tract or cerebellar signs at presentation, 44% had cranial nerve palsies alone

while 10% has long-tract or cerebellar signs only. These symptoms tended to progress until 80% had combined cranial nerve and long-tract signs while 19% had isolated cranial nerve deficits in the course of the disease. CSF abnormalities in rhombencephalitis tend to be mild: 58% of patients had a lymphocytic predominance and CSF cultures were positive in about 40%. Ten patients had repeated CSF examinations. In 9 of these, the second examination demonstrated more leukocytes than the first. Blood cultures were positive in about 60%. There was a high incidence of concurrent respiratory infection. Listerial rhombencephalitis is associated with high mortality and serious neurological sequelae in survivors. Timely use of appropriate antibiotics correlates strongly with chances of survival. Of the 22 patients that were initially treated with ampicillin or penicillin, 76% survived; in contrast to only 40% of 10 patients initially treated with other agents.

Our first patient had extensive cerebritis involving the cerebral cortex, cerebellum and brainstem. His presenting neurological deficits in Vietnam are unknown, but he had literalising long-tract signs when he presented to us. The high mortality of the infection, extensive involvement of the CNS and the delay in use of ampicillin all pointed to a grim prognosis early in his presentation.

Other clinical syndromes of *Listeria* infections are listed in Table II.

TABLE II: CLINICAL SYNDROMES OF *LISTERIA* INFECTIONS IN HUMAN ADULTS

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|---|
| <ul style="list-style-type: none"> • Bacteraemia without an evident focus • CNS infections: meningitis/encephalitis/rhombencephalitis/cerebral abscess • Endocarditis • Febrile gastroenteritis • Localised infections • Infection in pregnancy |
|---|

Our patient in case 2 presented with pneumonia. *Listeria* bacteraemia has been known to lead to pneumonia as well as cholecystitis, peritonitis, splenic abscess, hepatitis and hepatic abscess, joint infection, osteomyelitis, pericarditis, myocarditis, arteritis and endophthalmitis.⁷ Bacteraemia without an evident focus is a common manifestation of listeriosis in compromised hosts. Pregnant women have a mild impairment of cell-mediated immunity and are prone to develop listerial bacteraemia. For unknown reasons, CNS infection is not common in this group. Listerial infection can also cause endocarditis and gastroenteritis.

Treatment

CNS *Listeria* infections are not responsive to the cephalosporins commonly used as empirical treatment for

bacteria meningitis.^{4,7} Chloramphenicol is also associated with unacceptable failure and relapse rates in treatment.^{4,7} Ampicillin is considered the preferred agent while trimethoprim-sulfamethoxazole seems to be the best alternative when penicillin is contraindicated.^{4,5,7} Addition of an aminoglycoside for possible synergistic activity has been recommended.^{4,5,7}

Treatment should be prolonged beyond the usual 2 weeks for bacterial meningitis to between 2 and 3 weeks.^{4,7} Patients with rhombencephalitis or brain abscess should be treated for at least 6 weeks and followed with serial MRIs.^{4,7}

Listeria was not initially suspected in our first patient as he was young, previously healthy and initial CSF cultures were negative. In retrospect, early treatment with ampicillin might have altered his outcome. The second patient's presentation was dominated by the presence of pneumonia. Meningitis was noted only after the blood culture grew *L. monocytogenes* and patient threw a seizure. Thus, there was again a delay in the use of ampicillin.

Conclusion

The number of listerial infections seems likely to increase with the increasing prevalence of HIV infection and organ transplantation. Familiarity with the clinical and investigational characteristics of CNS listerial infection is therefore important if we are to manage the condition successfully. The diagnosis should be considered in previously healthy non-immunocompromised patients with meningitis presenting with neurological deficits. Neonates,

those above 50 years of age and immunocompromised patients presenting with CNS infection should receive ampicillin as part of their initial empirical antibiotic therapy.

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