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**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 72726

**Manuscript Type:** CASE REPORT

**Treatment failure in a patient infected with *Listeria* sepsis combined with latent meningitis: A case report**

Wu GX *et al.* *Listeria monocytogenes*

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**Abstract**

**BACKGROUND**

*Listeria* is a food-borne disease, which is rarely prevalent in the normal population, but it mostly occurs in the pregnant women, newborns, immunodeficiency patients, and the elderly. The main manifestations of patients include sepsis, meningitis, *etc.*, and the mortality rate remains high, although the onset of meningitis is relatively insidious.

**CASE SUMMARY**

A 75-year-old man presented with a fever for 1 wk and was admitted to the hospital for diagnosis as well as management of the lung infection. His condition improved after receiving anti-infective treatment for 2 wk. However, soon after he was discharged from the hospital, he developed fever again, and gradually showed various neurological symptoms, impaired consciousness, and stiff neck. Thereafter, through the cerebrospinal fluid metagenomic testing and blood culture, the patient was diagnosed with *Listeria monocytogenes* meningitis and sepsis, but died after being given active treatment which included penicillin application and invasive respiratory support.

**CONCLUSION**

This case highlights the ultimate importance of early identification and timely application of the various sensitive antibiotics such as penicillin, vancomycin, meropenem, *etc.* Therefore, for high-risk populations with unknown causes of fever, multiple blood cultures, timely cerebrospinal fluid examination and metagenomic detection technology can assist in confirming the diagnosis as soon as possible, thereby guiding the proper application of antibiotics and improving the prognosis.

**Key Words:** *Listeria monocytogenes*; Encephalitis; Sepsis; Lung infection; Case report

Wu GX, Zhou JY, Hong WJ, Huang J, Yan SQ. Treatment failure in a patient infected with *Listeria* sepsis combined with latent meningitis: A case report. *World J Clin Cases* 2022; In press

**Core Tip:** *Listeria* is considered as a food-borne disease, but is rarely prevalent in the normal population. We present herein, a rare case of meningoencephalitis caused by *Listeria monocytogenes* (*L. monocytogenes*) that evolved in a previously healthy immunocompetent old male patient. Both the cerebrospinal fluid metagenomic test and bilateral blood culture test results suggested the occurrence of *L. monocytogenes*. This findings of this case highlight the ultimate importance of early identification and timely application of sensitive antibiotics. Therefore, for high-risk populations with unknown causes of fever, multiple blood cultures, timely cerebrospinal fluid examination and metagenomic detection technology can assist in confirming the diagnosis as soon as possible, which can facilitate the application of suitable antibiotics and significantly improve the prognosis.

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## INTRODUCTION

*Listeria monocytogenes* (*L. monocytogenes*) is a Gram-positive facultative intracellular bacteria. It can be spread to the humans through the ingestion of contaminated foods, especially ready-to-eat foods, products with a longer shelf life, cooked foods, and soft

cheeses<sup>[9,18,28]</sup>. It can predominantly affect pregnant women, newborns, the elderly, and immunocompromised patients<sup>[16,27,28]</sup>. The morbidity rate is estimated to be about 3-6 cases per million per year, and the mortality rate is approximately 27%<sup>[11]</sup>. The most common forms of infections include listeriosis of the nervous system, bacteremia, and the vertical transmission from the mother to child<sup>[18]</sup>. Moreover, infections caused during the pregnancy can contribute to the miscarriage, premature delivery, and amnionitis, while neonatal infections can lead to delayed meningitis, conjunctivitis, and pneumonia. Additionally, in immunodeficiency patients, *Listeria* can also easily cause central nervous system infection, endocarditis, and sepsis<sup>[13]</sup>. The clinical symptoms of *Listeria* meningitis have been found to be similar to meningoencephalitis caused by other bacterium, but it has been found that the prodromal period is relatively long, the repeated detection rate of the traditional tests is low, and the first-line treatment with the third-generation cephalosporins is often ineffective<sup>[23]</sup>. Therefore, it is especially important to diagnose the disease as early as possible so that an appropriate treatment can be initiated and the best clinical outcome can be achieved in the various infected patients especially immunocompetent elderly patients.

## **CASE PRESENTATION**

### ***Chief complaints***

A 75 years old male was suffering from fever for 1 wk, as a result of which the patient was admitted to the Department of Infectious Diseases on May the 18<sup>th</sup>, 2020

### ***History of present illness***

The highest body temperature recorded was 39.0 °C, and it was accompanied by chills, dizziness during the fever, and remission after fever. The patient suffered from no headache, abdominal pain, diarrhea, as well as no other obvious sputum, nasal congestion or runny nose.

### ***History of past illness***

He had a history of hypertension.

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### ***Personal and family history***

No special.

### ***Physical examination***

The patient's temperature was 39 °C, heart rate was 98 bpm, respiratory rate was 20 breaths per minute, blood pressure was 139/75 mmHg and oxygen saturation in room air was 98%. The breath sounds in both the lungs were clear, heart rhythm was uniform, and the neurological tests were negative.

### ***Laboratory examinations***

A number of routine blood and biochemical tests were conducted which showed the following values: white blood cell count  $7.1 \times 10^9/L$ , neutrophils 58.6%, monocytes 24.4%, hemoglobin 83 g/L, C-reactive protein (CRP) 111.20 mg/L, cell factor interleukin (IL)-6: 279.22 pg/mL↑, cell factor IL-10 3653.30 pg/mL↑, plasma procalcitonin 0.19 ng/mL, blood amyloid A 509.5 mg/L↑, erythrocyte sedimentation rate 71 mm/L, lactate dehydrogenase 694 U/L↑, creatine kinase 19 U/L↓, albumin 27 g/L↓,  $K^+$  2.99 mmol/L↓,  $Na^+$  135.1 mmol/L↓,  $Cl^-$  98.5 mmol/L↓, calcium 1.87 mmol/L↓, phosphorus 0.65 mmol/L↓, but creatinine level was found to be normal. The patient's anti-nuclear antibody, titer 1:100, anti-SSA-, and anti-SCL70 positive. The patient's TORCH test (Toxoplasma, rubella, cytomegalo and herpes viruses), Plasmodium test, fungal D-glucan test, coronavirus disease 2019, hemorrhagic fever IgM antibody, Widder test, and Weil Felix reaction results were all noted to be normal.

### ***Imaging examinations***

The chest computed tomography (CT) results of the patient revealed a small amount of effusion in the pleural cavities on both the sides, and nodules were distinctly visible in

the pleura and under the pleura (Figure 1A and B). However, no obvious abnormalities were found in cranial computed tomography.

### **FINAL DIAGNOSIS**

The patient's diagnosis was finally considered to be "sepsis, lung infection, respiratory failure, electrolyte imbalance: hyponatremia, hypokalemia, autoimmune disease and *Listeria monocytic meningoencephalitis*".

### **TREATMENT**

The patient was hospitalized in the emergency intensive care unit (ICU) and was given high-frequency oxygen inhalation. The patient was administered anti-infective and anti-inflammatory treatment with "piperacillin and tazobactam injection 4.5 g q8h intravenously, 40 mg methylprednisolone injection". The patient still suffered from the repeated fever, and his body temperature was above 38.3 °C. Considering that atypical bacterial infections were not covered, he was also given an intravenous infusion of levofloxacin 0.5 g qd as an anti-infective treatment, and thereafter his body temperature returned to the normal state and his consciousness became clear. The patient's CRP dropped to 76.4 mmol/L and was thereafter transferred to the general ward of the Department of Respiratory Medicine for further treatment.

On the day of the transfer to the Department of Respiratory Medicine, atrial fibrillation occurred suddenly, and he displayed unresponsiveness, slurred speech, and shortness of breath under nasal cannula oxygen inhalation. Upon the physical examination, there were slow light reflections, stiff neck, increased muscle tone, wet rales in both the lungs.

Considering that the patient's condition was critically severe, the patient suffered from the repeated fever, with the body temperature fluctuating around 38.7 °C, and also displayed sudden blood pressure drops, as well as the signs of "septic shock", active rehydration. Hence, "norepinephrine" micropump was used to maintain the blood pressure. For the bacterial encephalitis, antibiotics were adjusted to 1 million units of

vancomycin injection q12h and combined with "meropenem injection 1.0 g q8h" to fight the bacterial infection and he was again transferred to ICU for the continuous treatment. At the same time, the methylprednisolone needle was first reduced to "20 mg" and thereafter it was completely stopped. However, in the early morning of the 6<sup>th</sup> day after returning to the ICU, the patient suddenly became unconscious, the base of the tongue fell back, he suffered from the shortness of breath, stiff neck, tremor of the limbs, and heart rate dropped to 40 beats per minute. The patient's trachea was observed to be intubated, and ventilation was assisted by a ventilator. Since then, the patient's condition continued to deteriorate rapidly, with symptoms of repeated high fever, septic shock, and multiple organ failure, accompanied by a gradual decrease in consciousness. The patient was given active fluid resuscitation, administered norepinephrine injection to maintain the blood pressure, and was subjected to the tracheal intubation combined with ventilator-assisted ventilation.

#### **OUTCOME AND FOLLOW-UP**

The patient condition did not improve significantly, and his family decided to discontinue the further treatment.

#### **DISCUSSION**

*L. monocytogenes* exist as short, facultative anaerobic, non-spore forming, catalyst-positive, oxidase-negative gram-positive bacilli, and are often found to be arranged in pairs<sup>[8,15]</sup>. The *Listeria* genus includes several species including *Listeria gastronomy*, *Listeria innocuous*, *Listeria escherichia*, *L. monocytogenes*, *Listeria weisei*, and *Listeria moere*. Among them, only *L. monocytogenes* has been reported to be significantly pathogenic to the humans<sup>[15,31]</sup>. *Listeria* is an important food-borne disease<sup>[15,26]</sup>, which can result invasive ailment in the humans and animals, especially causing serious central nervous system infections<sup>[5,8]</sup>. It primarily causes gastroenteritis in healthy people, while it can also lead to a serious and life-threatening infections in newborns, the elderly, pregnant women, and especially those suffering with cellular immune

deficiency<sup>[4,26]</sup>. For instance, Mylonakis *et al*<sup>[20]</sup> investigated 41 different cases of *Listeria* meningitis (except in newborns or during pregnancy). They reported that the various predisposing factors were as following: 24% of malignant tumors, 21% of transplantation, 13% of alcoholism and liver function insufficiency, 11% of immunosuppressive therapy/steroid use, 8% of diabetes, 7% of HIV and AIDS, and for remaining 36% the exact risk factors could not be determined<sup>[2]</sup>. We have summarized the details of various patients with intracranial infection caused by *Listeria* infection in the past 3 years, and found that most of them were immunodeficient patients, and several of them had a history of intake of oral hormones or immunosuppressants (Table 1).

<sup>4</sup> Invasive *L. monocytogenes* infection usually manifests itself as bacteremia, accompanied with or without obvious foci of infection, as well as the central nervous system infection, including meningitis, meningoencephalitis, brainstem encephalitis (rhomboid encephalitis), and brain abscess<sup>[8,15,23,28]</sup>. It has been reported in the literature that <sup>2</sup> *monocytogenes* is the third most common cause of bacterial meningitis in the elderly, after *Streptococcus pneumoniae* and *Neisseria meningitidis*<sup>[20,24]</sup>. *L. monocytogenes* can potentially invade the central nervous system through at least three distinct mechanisms, including: (1) transport through the blood-brain or blood-vessel barrier in the parasitic white blood cells; (2) extracellular blood-derived bacteria can directly invade endothelial cells; or (3) retrograde (centripetal) migration through the brain axons into the brain<sup>[8,15]</sup>. Monocytic encephalitis is a typical biphasic disease that initially starts with prodromal symptoms lasting 4 d to 5 d, and then can suddenly display various neurological symptoms, including asymmetric cranial nerve palsy, cerebellum, and the long fascicular signs<sup>[22,23,28]</sup>. The typical manifestations of patients include fever, headache, nausea, vomiting, meningeal irritation, ataxia, *etc.*<sup>[22,23,28]</sup>. Encephalitis is rare and can serve as a focal infection of the cerebral cortex, or it can potentially progress to a brain abscess. The patient showed changes in the consciousness or cognitive dysfunction. The CSF of the patient displayed an increase of 75% of multinucleated cells, consisting mainly of the neutrophils, but monocytes can



also be seen<sup>[8,23,32]</sup>. In addition, about 40% of patients suffering from intracranial infection can display respiratory failure. At this time, the fatality rate is often high, and serious sequelae have been observed. Brain abscesses account for 10% of the central infections, and the thalamus, pons, and medulla often occur. Spinal cord infections are rarely observed in patients<sup>[8,23]</sup>.

During the diagnosis of *Listeria* monocytic meningoencephalitis (LMM), the positive rate of the blood and cerebrospinal fluid culture is often low due to the intervention of antibiotics<sup>[6,22]</sup>. In addition, the symptoms and signs of patients with monocytogenes meningitis have been found to be <sup>2</sup> similar to those of the general population of community-acquired bacterial meningitis, but the prodromal period is relatively longer, the pre-disease symptoms are not typical, and it is often easy to miss the exact diagnosis in the early stage. According to previously reported studies, LMM is sensitive to most antibiotics, including penicillin, Trimethoprim-sulfamethoxazole, vancomycin, meropenem, linezolid, levofloxacin, erythromycin, tetracycline, and rifampicin. It was found to be only resistant to fosfomycin and daptomycin, so the selection of the correct antibiotics does not seem to be a difficult choice<sup>[6,15,23,33]</sup>. However, in actual clinical practice, antibiotic treatment is not often observed to be effective, especially when combined with central nervous system infections, which can lead to an increase in the mortality rate to approximately 25%-30%<sup>[10,15]</sup>. This might be related to *Listeria*'s ability to effectively invade the host cells and proliferate (such as macrophages, hepatocytes, and neurons) to facilitate an escape from the cytotoxic actions of antibiotics. The prodromal period of *Listeria* meningitis is often longer, and the exacerbation of the meningitis symptoms can occur after the initial improvement of the patient's systemic symptoms, thereby leading to a significant delay in the diagnosis of meningitis, which may also be the reason for the higher mortality of patients with meningitis<sup>[33]</sup>. Therefore, an early identification of *Listeria* infections, especially the central infections, maybe more important than the choice of antibiotics used for the therapy. Moreover, after the analysis of the various cases of intracranial infection caused by *L. monocytogenes* in the past three years, we have found that most of the patients had

neuropsychiatric symptoms of varying degrees at the time of onset of the disease, and most of them were seriously ill and even required respiratory support in the intensive care unit, or during operation. With timely, combination and long-term treatment of the various sensitive antibiotics, some patients could recover and were discharged, but the condition of a certain proportion of patients eventually deteriorated and they ultimately died or were left neuropsychiatric sequelae (Table 1).

In summary, combined with the analysis of this treatment failure case, we have summarized the following experiences and lessons: (1) early symptoms of *Listeria* meningitis might be concealed or mild, but proper attention should be paid to careful identification and cerebrospinal fluid examination as soon as possible; (2) meningitis symptoms can suddenly aggravate even after the clinical symptoms show improvement following the treatment; (3) upon retrospective analysis of the patient's first chest CT (Figure 1 A and B), scattered nodules were seen in the pleura and under the pleura. At this time, it was necessary to consider the possibility of the blood-borne disseminated lesions. Moreover, in the second reexamination of chest CT (Figure 1 C-E), it was found that the number of nodules have increased significantly and developed into patchy shadows, which increased the possibility of blood infection. At this time, multiple blood cultures could be very important for exact diagnosis; (4) it may be necessary for patients with positive blood cultures to undergo cerebrospinal fluid examination simultaneously; (5) as the background bacterial interference of the cerebrospinal fluid is rather low, pathogenic microbial metagenomic sequencing (mNGS) can be used as a highly sensitive and effective method. Therefore, it can be very useful to accurately detect the etiology of cerebrospinal fluid by mNGS; and (6) early identification, adequate, and the relatively long course of treatment might be the key to significantly improve the cure rate of patients with *Listeria* infection.

## **CONCLUSION**

For elderly patients, and especially those with immunocompromised conditions who have sepsis or meningoencephalitis, it is necessary to be highly vigilant against the

possibility of acquiring *Listeria* infection. During the disease, the patient's history related to consuming unclean diet should be verified to confirm the exact diagnosis as soon as possible. Adequate treatment with the various sensitive antibiotics is a key factor affecting the prognosis of the disease. In addition, the pathogenic metagenomic detection PCR-NGS can potentially serve as a timely and effective detection method to facilitate an early management of the disease.

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