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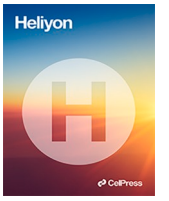

Clinical characteristics of 15 patients with listeria meningitis in adult

Haixia Qu [a], Yanhong Wang [b,*], Haiyan Diao [a], Gang Ren [b], Zhijun Wang [b], Jing Shang [b], Lijuan Shangguan [b], Hailong Wang [b]

[a] *Third Hospital of Shanxi Medical University, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Taiyuan, 030032, China*
[b] *Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, 030032, China*

A R T I C L E I N F O

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Case report

A B S T R A C T

Objective: To report and analyze the clinical characteristics of 15 patients with Listeria meningitis in adult.
Methods: We reviewed the medical records of 15 patients with Listeria meningitis who were admitted to Shanxi Bethune Hospital between January 2017 and January 2023.
Results: The clinical manifestations was primarily characterized by fever ， altered mental status, headache, neck stiffness, and vomiting. Blood or cerebrospinal fluid (CSF) cultures were performed in 15 cases, and pathogens were detected in 11 of them. Metagenomic next-generation sequencing (mNGS) detected pathogens in 10 cases, with four being negative by conventional methods and six being positive through traditional tests. The laboratory blood results presented leukocytosis. The CSF analysis upon admission showed elevated levels of white blood cells and proteins, as well as decreased chloride and glucose concentration. The brain computed tomography (CT) revealed ventricular enlargement in 3 patients. The brain magnetic resonance imaging (MRI) showed abnormalities in multiple areas of the brain. Despite 3 patients with decompensated hydrocephalus underwent lateral ventricle puncture and drainage ，their neurological deterioration were increasingly deteriorating.7 patients were treated by mechanical ventilation due to respiratory insufficiency. After 3 months, there were 9 cases with excellent outcomes （modified Rankin Scale score of 0–2 ）,2 cases with favorable outcomes (score of 3–5) , and 4 deaths (score of 6) .
Conclusions: This thesis found that the detection rate of *Listeria monocytogenes* has been on a rise over the past six years in our department, ranking second only to *Streptococcus pneumoniae*. Additionally, the detection rate achieved by mNGS surpasses that of other conventional methods. Among the patient cohort, 11 had underlying diseases such as systemic lupus erythematosus, tuberculosis, diabetes mellitus, pituitary neoplasms, leukemia and other related illnesses. Once listeriosis is early identified, the adequate antibiotic therapy should be promptly introduced in the course of empirical treatment.

* Corresponding author.
E-mail address: 13834676852@163.com (Y. Wang).

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1. Introduction

Listeria meningitis has been known as the common serious disease of central nervous system infections, with its role in adults becoming evident in recent years. It has been reported that *listeria* mainly affect special groups, including neonates, pregnant women, elderly person and immunocompromised patients. Different from other types of suppurative meningitis, *listeria* infection is characterized by a poor prognosis and high mortality rate, emphasizing the need to summarize and analyze the clinical characteristics of this disease. We retrospectively reviewed epidemiological characteristics, clinical symptoms, blood and cerebrospinal fluid examinations, imaging examinations, treatments and prognoses to draw attention from medical professionals.

2. Materials and methods

2.1. Participants and sample collection

We obtained the medical records of all patients who were diagnosed with Listeria meningitis by blood and/or cerebrospinal fluid examination admitted to Shanxi Bethune Hospital between January 2017 and January 2023. All patients had clinical, radiological and microbiological findings during hospitalization and underwent lumbar puncture. Blood or CSF cultures were performed in 15 cases, and metagenomic next-generation sequencing (mNGS) was performed in 10 cases.

2.2. Prognosis and follow-up

Patients were evaluated based on the modified Rankin Scale (mRS) at the time of hospital discharge. After 3 months, those with an excellent outcome had a score of $\leq$2; those with a favorable outcome scored between 3 and 5 points, while the dead was indicated by a score of 6 points, see Table 1.

2.3. Statistical analysis

The continuous variables were represented as medians with interquartile ranges and compared by the Mann-Whitney test. The categorical variables were expressed as the number of cases and percentage (n,%) and compared by McNemar-Bowkerχ^2 test. P value < 0.20 or variables considered clinically significant for death and odds ratios with 95 % confidence intervals (CIs) were calculated by logistic regression ($\alpha = 0.05$) .

3. Results

3.1. Epidemic features

Of all 76 participants who were diagnosed with purulent meningitis, definitive identification of pathogen was established in 43/76 (56.6 %). *Streptococcus pneumoniae* was identified as the causative bacteria in 20/43 (46.5 %), followed by *Listeria* in 15/43 (35.0 %). Among 15 Listeria meningitis, the median age of patients was 54 years old. The gender ratio was 3:2, with a higher proportion of males than females.

3.2. Clinical characteristics

11 patients presented with underlying conditions, including systemic lupus erythematosus, tuberculosis, diabetes mellitus, pituitary neoplasms and leukemia. Reported symptoms included fever in 15 patients , altered mental status in 12, headache in 11, neck stiffness in 11 out of the total of 15 patients , and vomiting in 10.

3.3. Laboratory tests

The median opening pressure was measured to be 220 mmH_2O.Blood or CSF cultures were performed in 15 cases, and pathogens were detected in 11 out of the 15 cases. Metagenomic next-generation sequencing (mNGS) was performed in 10 cases, with negative

Table 1
Modified rankin scale.

Outcome	Score	Description
Excellent outcome	0	No symptoms at all
	1	No significant disability despite symptoms; able to carry out all usual duties and activities
	2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
Favorable outcome	3	Moderate disability; requiring some help but able to walk without assistance
	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
Death	6	Dead

Table 2
Laboratory findings.

Laboratoryfindings	Case1	Case2	Case3	Case4	Case5	Case6	Case7	Case8	Case9	Case10	Case11	Case12	Case13	Case14	Case15
CSF															
WBC count/($\times 10^6$ L-1)	100	4000	1600	210	8900	960	90	530	610	260	2130	140	663	1850	260
Monocytes/%	40	20	30	80	30	30	90	85	40	80	85	30	80	90	70
Protein level/(g·L-1)	1.130	4.997	4.294	1.964	4.025	3.835	0.558	4.815	1.992	1.980	3.816	2.205	2.958	1.155	1.709
Chlorine/(mmol·L-1)	122.6	130.3	114.1	111.7	120.1	122.8	118.0	111.4	117.0	114.1	110.6	113.7	126.7	128.3	121.8
Glucose/(mmol·L-1)	1.29	4.78	0.87	4.07	5.92	3.21	2.86	2.59	0.69	1.50	1.93	0.92	2.84	3.78	2.27
CFP/(mmHg)	115	182	185	220	350	185	265	165	250	230	350	110	220	330	190
mNGS	No	Positive	Positive	Positive	Positive	No	Positive	Positive	No	No	Positive	No	Positive	Positive	Positive
culture result	Positive	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Positive	Positive	Negative	Positive	Positive
Blood															
culture result	Positive	Negative	Negative	Negative	Negative	Positive	Negative	Negative	Positive	Positive	Positive	Negative	Positive	Positive	Negative
WBC count/($\times 10^9$ L-1)	6.7	20.1	18.0	7.5	8.5	8.8	9.8	20.1	5.2	10.2	5.7	7.1	11.4	12.5	12.8
Neutrophils/%	71.8	90.9	93.0	71.6	88.9	82.4	70.2	93.6	78.9	88.8	79.0	91.8	88.7	93.2	83.2
Glucose/(mmol·L-1)	5.4	16.0	17.3	11.8	16.7	12.3	7.3	8.6	5.4	7.7	15.4	6.0	17.3	15.6	12.6

CSF: cerebrospinal fluid; WBC: white blood cell; CFP: cerebrospinal fluid pressure; mNGS：metagenomic next-generation sequencing.

results obtained by conventional methods in 4 cases and positive results shown through traditional tests in the remaining 6 cases. The presence of pathogens was detected in all 10 cases. The initial cerebrospinal fluid (CSF) showed leukocytosis, elevated protein levels, as well as decreased chloride and glucose concentration. In addition, the laboratory blood results presented leukocytosis, see Table 2.

3.4. Imaging examination

The brain computed tomography (CT) revealed ventricular enlargement. The brain magnetic resonance imaging (MRI) revealed abnormal signs in the frontal, parietal, temporal lobes as well as the brainstem, basal ganglia, and cerebellum, see Fig. 1.

3.5. Treatment and prognosis

Median time from clinical manifestations of the disease to the diagnosis of Listeria meningitis was 3 days (range 2–18 days). Listeria meningitis was initially suspected in all patients except one. Empirical antimicrobial therapy included penicillin, cephalosporins, vancomycin, or meropenem. Antibacterial coverage against *listeria* was not included in the treatment of the third patient before the definitive diagnosis. Case 7 was diagnosed viral meningitis and acyclovir was stopped until mNGS resulted positive. With clinical suspicion of nervous system infection, three patients was empirically treated with cephalosporin. Seven patients developed meningoencephalitis and was performed mechanical ventilation. Although three patients (case 2, case 3 and case 8) presented with decompensated hydrocephalus and underwent lateral ventricle puncture and drainage, they either died or had unfavorable outcomes. Eleven patients were discharged in good condition after receiving definitive antibiotics based on pathogen identification and undergoing a few days of hospital treatment, with no neurological sequelae observed, see appendix. The cure criteria for Listeria meningitis include the absence of clinical symptom recurrence, normal cerebrospinal fluid cytology, and negative cerebrospinal fluid bacterial culture after approximately one month of cessation of antibacterial therapy [1].

After 3 months, cases with an excellent outcome (defined as a modified Rankin Scale of 0–2) accounted for 9 out of 15 cases; cases with a favorable outcome (defined as a modified Rankin Scale of 3–5) accounted for 2 out of 15 cases; and deaths (defined as a modified Rankin Scale of 6) accounted for 4 out of 15 cases, see Fig. 2.

According to Table 3 , a p value of < 0.20 or variables considered clinically significant for death were analyzed by Logistic regression. Immune dysfunction, older age, hydrocephalus may increase the risk of death, see Tables 3 and 4. However, the number of cases in this article is sparse, and it can be further confirmed by increasing the sample size.

4. Discussion

Listeria is a facultative anaerobic gram-positive rod bacteria that is isolated from soil, water, sewage, and the feces of mammals. There are 17 species of *Listeria* have been recognized thus far [2]. *Listeria monocytogenes* can infect human beings [3] and cause symptoms of listeriosis including encephalitis, septicemia and meningitis [4]. Not only does *Listeria* survive at a wide range of temperature, but also reproduces in both acid and alkaline conditions. The main route of infection with listeriosis is by ingesting contaminated food [5]. In recent years, there has been an increase in the emergence of listeriosis, in part attributed to the ingestion of products that had been stored in long-term refrigeration. This study found that the detection rate of *Listeria* in our department ranked second only to *Streptococcus pneumoniae* over the past six years.

It is known to Listeria mainly affect special groups including neonates, pregnant women, the elderly, immunocompromised patients, as well as patients with occupational exposure [6]. Despite the widespread of listeria, human infections are not very frequent, especially in immunocompetent patients [7,8]. There were 11 patients with recognized underlying diseases, such as systemic lupus erythematosus , tuberculosis , diabetes mellitus , pituitary neoplasms, leukemia and others. Kim [9] reported a case of pneumonia with pleural effusion caused by Listeria from a patient diagnosed with acute lymphoblastic leukemia. In addition , pregnant women contract listeriosis at a rate that in 16-to 18-fold greater than the general population [10]. We have identified a case of pregnancy-related listeriosis by transplacental blood culture. Claudia [11] described a case of Listeria meningitis that occurred in a

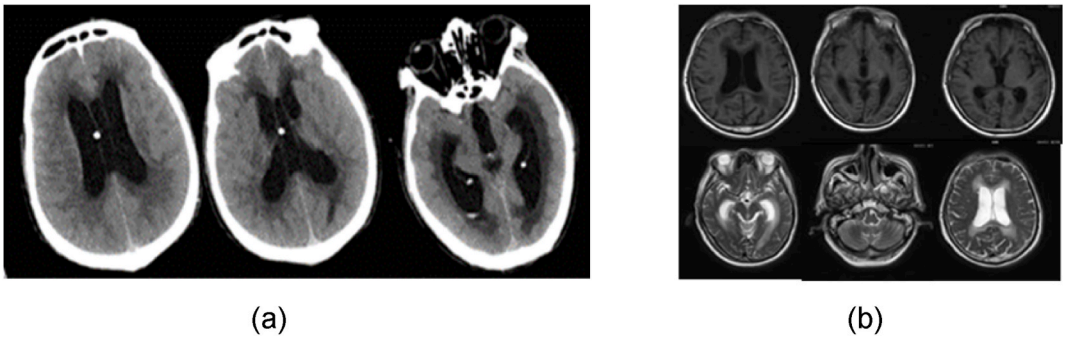

Fig. 1. Imaging studies of patient 3. (a) Non-contrast computed tomography showing enlarged ventricular. (b) MRI showing abnormal signs with enlargement of the lateral ventricles. MRI-magnetic resonance imaging.

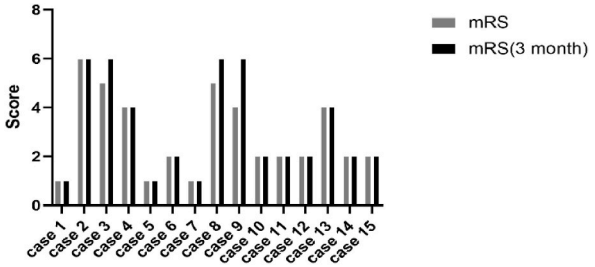

Fig. 2. The modified Rankin scale results of 15 patients.

Table 3
Data of patients who survived and died.

Clinical data	All patients	Survived patients	Dead patient	P
Male	9 (60.0)	6 (54.5)	3 (75.0)	0.604
Age (median)	54 (27.0 ~ 65.0)	53 (27.0 ~ 60.0)	68 (48.8 ~ 70.0)	0.050
Immune dysfunction [n (%)]	11 (73.3)	10 (90.9)	1 (25.0)	0.033
T_{max} (median)	40.0 (39.3 ~ 40.0)	40.0 (39.3 ~ 40.0)	40.0 (39.3 ~ 40.8)	0.543
Headache [n (%)]	11 (73.3)	8 (72.7)	3 (75.0)	1.000
Vomiting [n (%)]	10 (66.7)	7 (63.6)	3 (75.0)	1.000
Neck stiffness [n (%)]	10 (66.7)	7 (63.6)	3 (75.0)	1.000
Altered mental status [n (%)]	12 (80.0)	8 (72.7)	4 (100.0)	0.516
CFP ($>180mmH_2O$) [n (%)]	12 (80.0)	9 (81.8)	3 (75.0)	1.000
Hydrocephalus [n (%)]	3 (20.0)	0 (0.0)	3 (75.0)	0.009
Dyspnea [n (%)]	7 (46.7)	4 (36.3)	3 (75.0)	0.282
CSF WBC count (median)	610.0 (210.0 ~ 1850.0)	610.0 (210.0 ~ 1850.0)	1065.0 (200.0 ~ 3400.0)	0.896
CSF protein level (median)	2.2 (1.7 ~ 4.0)	2.0 (1.7 ~ 3.2)	4.6 (1.5 ~ 5.0)	0.151
CSF chlorine (median)	118.0 (113.7 ~ 122.8)	120.1 (113.7 ~ 122.8)	116.0 (112.1 ~ 127.2)	0.845
CSF glucose (median)	2.6 (1.3 ~ 3.8)	2.3 (1.3 ~ 3.8)	2.7 (1.3 ~ 4.3)	0.794
Blood WBC count (median)	9.8 (7.1 ~ 12.8)	8.5 (6.7 ~ 11.4)	19.1 (11.9 ~ 20.1)	0.019
Blood glucose (median)	12.3 (7.3 ~ 16.0)	12.3 (6.0 ~ 15.6)	12.3 (7.6 ~ 17.0)	0.556
CSF: blood glucose ratio (median)	0.24 (0.15 ~ 0.30)	0.19 (0.15 ~ 0.26)	0.30 (0.11 ~ 0.37)	0.359

CSF: cerebrospinal fluid; WBC: white blood cell; CFP: cerebrospinal fluid pressure; Tmax: maximum temperature recorded within 24 hours prior to admission; The measurement data were described by median.

Table 4
Univariate analysis of the dead.

Variables	P	OR (95 % CI)
Gender	0.482	2.500 (0.194–32.194)
Immune dysfunction	0.029	30 (1.410–638.150)
Age	0.311	0.955 (0.874–1.044)
Respiratory insufficiency	0.207	0.190 (0.015–2.501)
CSF: blood glucose ratio	0.428	194.464 (0–89012207.42)

CSF: cerebrospinal fluid.

young puerpera without any immunological disorders or other risk factors. It is worth noting that 2 patients with hematologic diseases in our cases had recovered well, and one of them eventually died from not listeriosis but form leukemia.

The clinical manifestations of Listeria meningitis are nonspecific, mainly characterized by fever, headache, vomiting and consciousness disorder, which are similar to those of other types of purulent meningitis. The main physical positive is neck stiffness. Detection of pathogens can be performed using both classical microbial culture methods and molecular-based methods. However, traditional methods are affected by many factors and the positive rate is low. It is difficult to distinguish differences based solely on clinical manifestations and traditional laboratory tests. Pathogen identification of Listeria is always difficult, as it can be often affected by a variety of factors including antibiotic exposure. Blood or CSF cultures were performed in 15 cases, and pathogens were detected only in 11 of them. In recent years, Metagenomic Next-Generation Sequencing (mNGS) could yield higher sensitivity and faster speed for pathogen identification [12–14], thereby emerging as a valuable technology capable of detecting pathogens from clinical samples. Metagenomic next-generation sequencing was performed in 10 cases, and pathogens were detected in 10 cases. Experts have developed this consensus that mNGS of cerebrospinal fluid could be used for pathogen identification in severe patients with unknown community-acquired encephalitis or meningitis for the first time. Therefore, mNGS could be firstly considered for patients suspected of having severe pathogen infections.

Listeria is sensitive to most antibiotics, but it is resistant to cephalosporins. Aminopenicillin alone or in combination with an

aminoglycoside is considered the gold standard for antibiotic treatment of Listeriosis, whereas there is little evidence addressing the clinical value of penicillin in combination with gentamicin for listeriosis [15,16]. Trimethoprim-sulfamethoxazole may be considered in cases of penicillin allergy [17]. Cephalosporin antibiotics were used to empiric treatment for suspected cases of purulent encephalitis or meningitis. The limited clinical experience of suppurative encephalitis or meningitis, particularly for fastidious pathogens, makes diagnosis challenging in most cases. If left untreated, it may develop into severe infections. Cephalosporin antibiotics were initially used to treat 7 cases, and only 4 of them were treated in combination with penicillin. The antibiotics used in the cure case included penicillin, ampicillin, gentamicin, moxifloxacin, meropenem or sulfamethoxazole. There were 11 patients receiving effective antibiotics that were sensitive to Listeria according to CSF or blood culture positive tests. The remaining patients promptly received treatment and all achieved recovery or cure upon presentation of positive mNGS results. 10 patients gradually recovered and were discharged in good conditions without abnormal CSF tests. Definitive treatments were administered for a median of 3 days.

Listeria may invade the brainstem through retrograding along the cranial nerves, resulting in Listeria encephalitis. However, the mechanisms of encephalitis remain poorly understood [18,19]. 7 patients were treated by mechanical ventilation because of respiratory insufficiency. In addition, *Listeria* causes meningitis and septicemia by hematogenous infection. Hydrocephalus is a severe complication [20] in adults with bacterial meningitis. The form of hydrocephalus in bacterial meningitis is associated with the failure of cerebrospinal resorption through arachnoid granulations due to severe infection [21]. Despite receiving definitive antibiotic therapy, three patients with hydrocephalus complicated by neurological deterioration died or had an unfavorable outcome within a few days.

In recent years, the incidence of adult Listeria meningitis has been increasing. Despite early identification of *Listeria* involvement and administration of definitive antibiotics, listeriosis remains a highly challenging disease. Neurologists should pay attention to the disease as it can lead to severe neurological symptoms. We emphasize the importance of mNGS for early diagnosis, especially in high-risk populations. A timely pathogen identification and an adequate treatment will have positive effects on prognosis of listeriosis to enhance the survival rates.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Haixia Qu: Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Investigation, Methodology, Software, Validation. **Yanhong Wang:** Writing – review & editing, Project administration, Supervision. **Haiyan Diao:** Investigation. **Gang Ren:** Resources. **Zhijun Wang:** Supervision. **Jing Shang:** Data curation. **Lijuan Shangguan:** Investigation. **Hailong Wang:** Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Ca
Presumptive diagnosis	SLE Purulent meningitis 32 weeks gestation	Purulent meningitis Hypertension 2-DM	Purulent meningitis	Intracranial infection 2-DM Hypertension	Purulent meningitis	Intracranial infection Hypertension Tuberculosis	Intracranial infection Pituitariectomy	Intracranial infection	Purulent meningitis	Purulent meningitis ALL	Purulent meningitis Hypertension 2-DM MDS	Purulent meningitis SLE	Hype
Antimicrobial therapy													
Empirical therapy	Penicillin+Ceftriaxone	Penicillin+Ceftriaxone/ Meropenem+Vancomycin	Penicillin+Ceftriaxone/ Meropenem+Vancomycin	Ceftriaxone+Acyclovir/ Meropenem+Vancomycin	Penicillin +Ceftriaxone/ Meropenem	Penicillin+Moxifloxacin/ Penicillin+Ceftriaxone+Moxifloxacin	Acyclovir	Ceftriaxone+ Arotinolol	Penicillin +Ceftriaxone	Ceftriaxone+Arotinol	Penicillin+Ceftriaxone	Meropenem	Peni +Cef ne
Definitive therapy	Ampicillin + Gentamicin	Penicillin + Meropenem +Gentamicin	Penicillin +Gentamicin	Penicillin	Penicillin +Gentamicin+Moxifloxacin+Sulfamethoxazole	Penicillin +Gentamicin+Moxifloxacin+Sulfamethoxazole	Penicillin+Sulfamethoxazole	Penicillin+Gentamicin	Penicillin + Meropenem	Penicillin + Meropenem	Ampicillin + Gentamicin	Ampicillin +Gentamicin+Sulfamethoxazole	Ampi +Gen n+Su hoxa
Diagnosis time	3d	18d	5d	7d	2d	2d	5d	3d	5d	2d	2d	3d	
Duration of antibiotic	27d	17d	49d	27d	35d	32d	13d	9d	29d	32d	15d	31d	
Mechanical ventilation	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	No	
Paraventriculostomy	No	Yes	Yes	No	No	No	No	Yes	No	No	No	No	
mRS	1	6	5	4	1	2	1	5	4	2	2	2	
mRS(3 month)	1	6	6	4	1	2	1	6	6	2	2	2	

SLE:systemic lupus erythmatosus;2-DM:type 2 diabetes mellitus;ALL:acute lymphoblastic leukemia;MDS:myelodysplastic syndromes

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