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Reasonable drug analysis of *Listeria monocytogenes* meningitis related to mantle cell lymphoma

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ABSTRACT

We report a case of *Listeria* meningitis related to mantle cell lymphoma. A clinical pharmacist adjusted repeatedly the patient's anti-infective therapeutic regimen by analyzing the pharmacologic and pharmacokinetic characteristics of antibacterial drugs (such as cefotaxime, meropenem, etc.) due to the patient's repeated fever during hospitalization. To the best of our knowledge, this is the first case of *Listeria* meningitis related to mantle cell lymphoma treated successfully with meropenem reported in China. This case aims to optimize the anti-infection treatment regimen of *Listeria* meningitis and to provide a reference for clinicians and clinical pharmacists to use drugs rationally.

Introduction

Listeria monocytogenes meningitis is a purulent bacterial meningitis caused by *L. monocytogenes* infection, and it is a rare but severe disease that primarily affects immunocompromised patients such as the elderly, neonates, transplant patients, and HIV patients unable to fight the organism, however, the probability of *L. monocytogenes* meningitis in normal adults is very low [1–3].

In 2001, Vazquez-Boland et al. found 99% of human *Listeria* infections represent a serious foodborne infection acquired from contaminated foods that includes animal products, dairy products and vegetables, foods stored in the refrigerator for a long time [4].

In 2013, Feng et al. had reported about the overall mortality rates of listeriosis were as high as 26% in China [5]. Delay in treatment is an independent risk factor for deterioration of *L. monocytogenes* infection, therefore, early and appropriate use antibiotic is the key to the treatment of *L. monocytogenes* meningitis [6,7]. Therefore, these are important issues that how to diagnose *L. monocytogenes* meningitis timely and rational anti-infective treatment for neurologists and clinical pharmacists to solve urgently. This article discussed the diagnosis and treatment process of a patient whose diagnosis were severe *L. monocytogenes* meningitis complicated with mantle cell lymphoma. We analyzed the anti-infective treatment and the pharmaceutical care of this patient according to a systemic literature review, in order to improve the therapy of *L. monocytogenes* meningitis.

Case report

A 54-year-old male presented to the emergency room complaining of a 6-days history of fever of up to 40 °C, headache, vomiting, chills, and then confusion over 10 h. After he entered the emergency room, doctors considered the possibility of intracranial infection initially, and gave anti-infective and antiviral treatment, etc. Subsequently, the patient was submitted to the department of internal neurology. Vital signs on admission were as follows: temperature 38.8 °C, pulse 83 beats/minute, breathing 18 times/min and blood pressure121/71 mmHg. Neurological examination disclosed neck stiffness, Kernig's and Brudzinski's signs and bilateral pathology were all positive. Initial laboratory work up showed leukocytes 4.28×10^9/L, hemoglobin 69 g/L, blood platelet 165×10^9/L, red blood cell 2.99×10^{12}/L, neutrophils 87.7%. Biochemical and conventional indicators of CSF in the patient are shown in Table 1. His previous medical history showed that he was diagnosed as lymphoma and performed autologous hematopoietic stem cell transplantation in 2013, furthermore, he had been doing immunosuppressive therapy (rituximab 375 mg/m^2 BSA) prior to admission. On the 10th hospital day, blood test demonstrated leukocytes 2.71×10^9/L, N% 84%, HB 62 g/L. Bacterial culture of CSF suggested that there was *L. monocytogenes* in CSF. Ultimately, the

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Table 1
Biochemical and conventional indicators of CSF in the patient.

Biochemical indicators of CSF					Conventional indicators of CSF		
Frequency	Pressure (mmH_2O)	Protein (mg/L)	Chloride (mmol/L)	Glucose (mmol/L)	TCS (10^9/L)[a]	Leukocyte (10^9/L)	Pandy test
1st (9/5)	180	2290	95.5	1.9	260	190	Positive
2nd (12/5)	60	3162	96.5	3.81	540	250	Positive
3rd (15/5)	100	3298	102	5.91	450	55	Positive
4th (18/5)	60	3369	100.1	5.39	1170	90	Positive
5th (23/5)	75	3320	108	7.24	1126	126	Positive
6th (31/5)	40	3211	116.3	6.1	/	20	Positive
7th (11/6)	80	192	122	3.37	2400	2	Negative
8th (12/6)	80	110	126.3	3.54	340	4	Negative
9th (20/6)	/	126	129.6	3.75	75	3	Negative
10th (22/6)	/	112	127	4.09	40	2	Negative

[a] Total cellular score.

Table 2
Electrolytes change in patient.

Frequency	K (mmol/L)	Na (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Anion gap (mmol/L)	Carbon dioxide combining power (mmol/L)
1st (9/5)	3.14	121.6	93.5	1.6	10.14	21.1
2nd (10/5)	3.44	123.2	94.2	1.71	14.14	18.3
3rd (11/5)	3	120.9	91	1.67	10.7	22.2
4th (12/5)	3.56	123.6	94	1.62	12.36	20.8
5th (13/5)	3.4	124.6	93	1.68	12.14	22
6th (14/5)	3.86	129.8	94.4	1.81	14.06	25.2
7th (15/5)	4.2	126.1	91.9	1.78	10.2	24.8
8th (16/5)	4	128	97	1.71	8.69	25.5
9th (17/5)	4.24	129.7	95.5	1.74	10.04	28.4
10th (18/5)	4.27	126.3	91.4	1.86	8.83	29.8
11st (19/5)	4.13	128.2	93.1	1.98	8.23	31
12nd (20/5)	4.3	126.7	90.4	2.04	10.27	2.6
13rd (23/5)	3.74	136.7	101.4	2.04	12.74	26.3
14th (2/6)	3.8	137	107	2.02	13.8	20
15th (5/6)	3.58	143.7	112.9	1.82	13.08	21.3
16th (11/6)	3.56	141	107.1	1.93	11.06	26.4
17th (15/6)	3.52	140.6	102.7	2.1	13.02	28.4
18th (18/6)	3.43	142.2	102.5	2.14	14.13	29
19th (23/6)	3.34	130.1	105	2.25	22.81	22.5

patient suffered from *L. monocytogenes* meningitis cured basically with meropenem.

Discussion

Pharmaceutical care of clinical pharmacists

This patient had repeated fever and his anti-infective therapeutic regimen had been adjusted several times during hospitalization which can be seen in Supplemental digital content, which demonstrates main treatment process. The patient's intracranial infection has been cured, but unfortunately, the patient suffered from a secondary pulmonary infection and caused poor clinical condition because of mantle cell lymphoma, hence the family finally decided to give up other treatments (Table 2).

After 6 days of meropenem used, the patient's condition improved which indicated that the anti-infection was effective. Doctors considered to step-down the anti-infective treatment, and successively used anti-infective drugs such as cefodizime and amoxicillin–clavulanic acid, but the effects were not ideal. On the 34th hospital day the patient had repeated fevers suddenly, at the time of general consultation of the whole hospital, doctors and clinical pharmacists thought the antimicrobial susceptibility test showed the organism was only susceptible to gentamicin and piperacillin–tazobactam and resistant to cefodizime and amoxicillin–clavulanic acid, this is also the reason why cefodizime and amoxicillin–clavulanic acid were not effective. Clinical pharmacists and clinicians changed amoxicillin clavulanic-acid to meropenem 1 g IV every 8 h, but the patient's condition did not improve significantly. On the 39th hospital day, clinical pharmacists advised adding cefoperazone–sulbactam 1.5 g IV every 8 h due to Acinetobacter baumannii from sputum cultures. In the light of the patient's final results of anti-infective treatment and cultures of CSF, the patient with *L. monocytogenes* meningitis got improved in the case of meropenem used.

Rational analysis of anti-infective drugs

His previous medical history showed that he was diagnosed as lymphoma and performed autologous hematopoietic stem cell transplantation in 2013. Furthermore, he had been receiving immunosuppressive therapy prior to admission. As for acute purulent meningitis in patients whose immune function had impaired, most guidelines recommend that empiric treatment regimens should be included antibacterial drugs resistant to the activity of *L. monocytogenes* for enhancing empirical anti-infective treatment. Early studies had found that there were at least five penicillin-binding proteins (PBP) on the cell membrane of *L. monocytogenes*. Although a wide range of antibiotics have demonstrated in vitro activity against *L. monocytogenes*, penicillin, ampicillin, and amoxicillin bind with high affinity to PBP, thus significantly hamper the activity of *Listeria*. While cephalosporin antibiotics such as cefotaxime and cefmenoxime were bound to PBP, therefore *Listeria* had natural resistance to these antibiotics, and this may be one of the reasons for the in vain treatment of cefmenoxime during the stage of empirical anti-infective treatment [8]. Therefore, in this case, monotherapy of cephalosporins was not sufficient, and application of cefmenoxime was unreasonable on the 1–8th hospital day. The patient has been confirmed infection with *Listeria* meningitis and

Table 3
Guidelines at home and abroad for the treatment of *Listeria* meningitis.

Domestic or foreign guides or literature	Standard treatment	Alternatives	Remarks
The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) in 2008	Ampicillin plus gentamicin	Trimethoprim-sulfamethoxazole	–
EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults (EFNS) in 2008	Ampicillin/amoxicillin	–	2 g 4 hourly
ESCMID guideline: diagnosis and treatment of acute bacterial meningitis in 2016	Amoxicillin or ampicillin, penicillin G	Trimethoprim-sulfamethoxazole, moxifloxacin, meropenem, linezolid	Duration was at least 21 days
The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults in 2016	Amoxicillin, 2 g 4 hourly	Trimethoprim-sulfamethoxazole	Duration was at least 21 days
Chinese the guidelines for the clinical application of antibacterial drugs (2015)	(Amoxicillin or ampicillin) plus gentamicin (80,000IU, 8 h hourly)	Trimethoprim-sulfamethoxazole	Amoxicillin or ampicillin (2 g 4 hourly iv)
The Sanford guide to antimicrobial therapy 2015 45th Edition	Ampicillin	Trimethoprim-sulfamethoxazole	–

treatment with meropenem 1 IV 8 h hourly on the 8–12th hospital day. Meropenem had excellent activity against *Listeria* in vitro tests and may have an effect on the treatment of *Listeria* infection according to research reported [9]. According to guidelines of IDSA and ESCMID, meropenem had been listed as an alternative treatment for bacterial meningitis [10–12]. One has the fine penetrating ability and many cases have reported a successfully treatment of *Listeria* meningitis although it had not been approved for the treatment of *Listeria* infection. Clinical pharmacists advised adjusting the dose of meropenem to 2 g IV every 8 h on the basis of Chinese the guidelines for the clinical application of antibacterial drugs and the specification of meropenem [13]. When the clinical pharmacist consulted and learned that the patient's meningitis bacteria were *L. monocytogenes*, it was suggested to change the dose of meropenem to 2 g 8 h hourly, but the dose of meropenem was not changed and followed the consultation opinion in the follow-up treatment, and the blood concentration was below the limit of quantification, which implied that the dose of meropenem was not enough, thus this may also be one of the reasons why the patient's anti-infection treatment was not so effective. Amoxicillin plus trimethoprim–sulfamethoxazole were used to strengthen anti-infective treatment on the 16–29th hospital day, according to The UK guideline the patients who were older than 50 years could be treated with second-line drugs-sulfamethoxazole trimethoprim combined with anti-infective treatment [14]. Therefore, treatment with amoxicillin and sulfamethoxazole–trimethoprim to enhance anti-infective was rational during the anti-infective process.

Conclusion

The high predilection of *Listeria* in the central nervous system poses a problem because many antibiotics cannot penetrate into the brain in adequate concentrations [15]. By searching the literature, it is known that appropriate empirical antibiotic therapy can reduce mortality [10]. For the *L. monocytogenes*-susceptible population, the reason for its poor initial anti-infective efficacy was that the antibiotics covering *Listeria* were not selected for empiric therapy [16]. Domestic literature has reported that clinicians often treat common meningitis empirically by using third-generation cephalosporins, but *L. monocytogenes* is naturally resistant to third-generation cephalosporins. Therefore, domestic physicians and clinical pharmacists should choose antibiotics that can cover the anti-*Listeria* activity for the empirical treatment of meningitis patients with immunosuppression.

This article aims to improve the understanding of *L. monocytogenes* meningitis by summarizing the schemes recommended in domestic and international guidelines (as shown in Table 3) and analyzing the medication of this patient. It is recommended that ampicillin or penicillin G plus gentamicin to strengthen anti-infective therapy for patients who have impaired immune function and suffered from *L. monocytogenes* meningitis. Those patients who are allergic to penicillin but unable to desensitize ought to use cotrimoxazole 10–20 mg/kg IV every 6–12 h, or meropenem 2 g IV every 8 h. To our knowledge, this is the first reported case of *L. monocytogenes* meningitis related to mantle cell lymphoma [10,12,14,17,18]. However, *L. monocytogenes* meningitis is a rare but enormously severe disease, so this article emphasizes the necessity of clinical pharmacists and physicians' awareness regarding clinical manifestations of listeriosis in order to establish a prompt diagnosis and treatment.

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Competing interests

None declared.

Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2019.04.010.

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