Sepsis and Meningitis due to *Listeria Monocytogenes*

Orhan Yildiz,[1] Bilgehan Aygen,[1] Duygu Esel,[2] Uner Kayabas,[1] Emine Alp,[1] Bulent Sumerkan,[2] and Mehmet Doganay[1]

Departments of [1]Infectious Diseases and [2]Microbiology, Faculty of Medicine, Erciyes University, Kayseri, Turkey.

Purpose: This study focused on the effect of immuno-compromising conditions on the clinical presentation of severe listerial infection. **Patients and Methods:** Nine human listeriosis cases seen from 1991-2002 were reviewed. All adult patients, from whose blood, peritoneal fluid or cerebrospinal fluid (CSF) the *L. monocytogenes* was isolated, were included in this retrospective study. **Results:** Listeriosis presented as primary sepsis with positive blood cultures in 5 cases and meningitis with positive CSF cultures in 4 cases. All of these patients had at least one underlying disease, most commonly, hematologic malignancy, diabetes mellitus, amyloidosis and hepatic cirrhosis; 55.6% had received immunosuppressive or corticosteroid therapy within a week before the onset of listeriosis. The patients were adults with a mean age of 60 years. Fever, night sweats, chills and lethargy were the most common symptoms; high temperature (> 38℃), tachycardia, meningeal signs and poor conditions in general were the most common findings on admission. The mortality rate was 33.3% and was strictly associated with the severity of the underlying disease. Mortality differences were significant between sepsis (20%) and meningitis (50%) patients. **Conclusion:** Listeriosis as an uncommon infection in our region and that immunosuppressive therapy is an important pre-disposing factor of listeriosis. Sepsis and meningitis were more common in this group of patients and had the highest case-fatality rate for food-borne illnesses.

Key Words: *Listeria monocytogenes*, sepsis, meningitis, listeriosis, immunosuppressive

INTRODUCTION

Listeria monocytogenes is a gram-positive, motile,

rod-shaped bacterium that is ubiquitous in the environment and the principal route of acquisition of *Listeria* is through the ingestion of contaminated food products. *L. monocytogenes* is an uncommon cause of disease in humans. It occurs in sporadic and epidemic forms throughout the world.[1-3] Clinical manifestations of *L. monocytogenes* infection range from mild flu-like illnesses to life-threatening meningoencephalitis and sepsis. Pregnant women, newborn infants, the elderly, immunocompromised individuals and patients with malign diseases are susceptible to listeriosis.[4-6] Even with appropriate antibiotic therapy, listeriosis is fatal in about 1 out of 3 cases.[7] The aim of this study was evaluate the effect of immuno-compromising conditions on the clinical presentation of severe listerial infection.

PATIENTS AND METHODS

All adult (age > 17 years-old) patients, from whose blood, peritoneal fluid or cerebrospinal fluid (CSF) the *L. monocytogenes* was isolated, were included in this retrospective study (Department of Bacteriology, University of Erciyes from 1 January, 1991 to 30 June, 2002).

From 1991 to 2002, there were 9 cases of listeriosis; 4 cases had meningitis/meningoencephalitis and 5 cases had sepsis. An infection in the central nervous system (CNS) was defined by a clinical presentation of CNS symptoms and by the growth of *L. monocytogenes* in cultures of blood and/or CSF. Sepsis was defined as positive in the blood culture sample and febrile illness without a clinical or bacteriologic evidence of a localized infection. Listeriosis is defined as the growth of *L.*

monocytogenes from any physiological site. *L. monocytogenes* isolates were identified by standard methods, and serotyping was made using Bacto-Listeria O Antisera (Difco Laboratories, Detroit, MI, USA).

Pre-disposing factors, clinical features, laboratory data, treatment and outcome of the patients were recorded. The patients were considered to be immunosuppressed if systemic corticosteroids, cytotoxic agents or radiotherapy had been used within a month before the onset of listeriosis.

Clinical presentation

Patient 1

A 42-year-old man was admitted to the dermatology unit because of pemphigus vulgaris. He was being treated with methylprednisolone, ranitidine and hydrotalcid. On day 43 of admission, meningoencephalitis occurred, characterized by a sudden onset of fever (temperature 39.2℃), meningeal signs and disturbances of consciousness. The meningeal syndrome was associated with purulent CSF pleocytosis with a predominance of polymorphonuclear leukocytes (PMNs). He was transferred into the infectious diseases unit. The CSF culture was positive for serotype 1 of the *L. monocytogenes*. Blood cultures were negative. A combination of penicillin G (20 MU/d) and amikacin (1 g/d) was administered to the patient. The patient's condition began to deteriorate despite intensive supportive therapy and he died on the fourth day of the antibiotic therapy.

Patient 2

A 36-year-old man with epistaxis, dyspnea, headaches, sore throat, fever (temperature 39.8 ° C), meningeal signs and lethargy was admitted to the infectious diseases unit. One month before admission, he had undergone a renal transplantation due to amiloidosis. At the time of admission, he received prednisolone, cyclosporine and ranitidine. Examination of CSF revealed pleocytosis with a predominance of PMNs. The CSF culture yielded serotype 4 of the *L. monocytogenes*. Despite treatment with ampicillin (12 g/d) and netilmicin (300 mg/d), the patient's condition detoriated rapidly, and he died after four days of therapy.

Patient 3

A 70-year-old man was hospitalized in the hematology unit, showing symptoms of fever (temperature 38℃) and night sweats. The patient, who was treated for acute myeloid leukemia and with his last chemotherapy having been 6 weeks ago, had pancytopenia (a WBC count of 400/mm^3 with 20% PMNs). On day 3 of hospitalization, *L. monocytogenes* was cultured in blood samples. The therapy began with ampicillin (8 g/d) and amikacin (1 g/d). On day 9, his condition continued to detoriate. He developed orofaringeal candidiasis and laboratory findings revealed deep neutropenia (a WBC count of 100/mm^3). Antibiotic therapy was continued and I.V. amphotericin B (1 mg/kg/d) was added. Despite these therapies, he died on the 13th day of hospitalization.

Patient 4

A 28-year-old woman was admitted to the gynecology unit diagnosed with a recurrence of disgerminoma. Six months earlier, she had undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy and cyto-reductive surgery for disgerminoma. After the surgery, she received radiotherapy and 4 sessions of chemotherapy. The last session of chemotherapy had ended 2 weeks ago. On day 4, the patient developed a fever (temperature 39.2℃), chills and sweats and was in poor condition in general. Two sets of blood cultures were positive for serotype 1 *L. monocytogenes*. The patient started receiving penicillin G (20 MU/d). On day 6 of hospitalization, she became afebrile and her symptoms and findings progressively improved. Blood cultures that were taken within 3 days of therapy gave negative results for *L. monocytogenes*. She was discharged from the hospital on the 18th day and subsequently received ampicillin (4 g/d) perorally for 7 days.

Patient 5

A 64-year-old man with fever, nausea, vomiting, diarrhea and altered mental status was admitted to the infectious diseases unit. On physical examination, he had lethargy and acutely ill with a high fever (temperature 38℃), tachycardia and meningeal signs. The analysis of the CSF

revealed a meningeal syndrome with increased levels of protein, pleocytosis with a predominance of PMNs. He had a history of chronic obstructive pulmonary disease. The CSF culture yielded serotype 4 *L. monocytogenes*. Two sets of blood cultures came out negative. He was treated with penicillin G (24 MU/d for 14 days), and his condition transiently improved after administering the antibiotic treatment. The patient became afebrile and was discharged with a prescription for po ampicillin (4 g/d) to complete a 21-day course of antibiotic therapy.

Patient 6

A 59-year-old man was admitted to the infectious diseases unit with a 2-day history of fever, altered mental status and headaches. He had a coronary heart disease. On admission to hospital the patient was afebrile. On day 2 of hospitalization, he developed a high fever (temperature 38.5℃) and meningeal signs. Examination of the CSF revealed a meningeal syndrome. The CSF culture yielded serotype 4 *L. monocytogenes*. The patient received penicillin G (24 MU/d) and amikacin (1 g/d) intravenously for 14-day. On day 6 of hospitalization, he became afebrile and his symptoms and findings gradually improved after administering of the therapy. The patient was diagnosed with diabetes mellitus. Antibiotic therapy continued with po ampicillin (4 g/d) for 4 days, and then he was discharged.

Patient 7

A 62-year-old man with a history of diabetes mellitus, hepatic cirrhosis and congestive heart failure was admitted to the hospital. He was taking gliclazide, furosemide and digoxin He was admitted to the gastro-enterology unit with abdominal distention, ascites and edema on his feet. On day 12, he developed a fever, night sweats, chills, dyspnea and general malaise. His physical examination revealed a high fever (temperature 38.3℃) and tachycardia; blood and peritoneal fluid cultures were positive for serotype 4 *L. monocytogenes*. He underwent a course of treatment with intravenous penicillin G (24 MU/d) and amikacin (1 g/d) for 14 days. The patient's fever diminished after 3 days of therapy and he was discharged with a prescription of po ampi-

cillin (4 g/d) for 7 days.

Patient 8

A 57-year-old man with a history of chronic lymphocytic leukemia and hepatic cirrhosis with a positive serology for the hepatitis C virus was brought to the hospital with a fever (temperature 38.5℃), chills, night sweats, headaches, cough and anorexia. He was empirically treated with I.V. ampicillin/sulbactam (6 g/d) and amikacine (1 g/d). Two separate blood specimen cultures, drawn over 72 hours, yielded serotype 4 *L. monocytogenes*. The antibiotic therapy continued for 14 days. The patient's condition gradually improved with antibiotic therapy. When discharged, he was advised to take oral ampicillin/sulbactam (1,5 g/d) for an additional 5 days.

Patient 9

A 63-year-old man was admitted to the infectious diseases unit with diarrhea, fever (temperature 39℃), chills, sweats and a poor condition in general. He had chronic renal failure due to amyloidosis and multiple myeloma (stage 2b). Ten days before admission, he had taken the last session of immunosuppressive therapy and ranitidine. Laboratory tests revealed a WBC count of $500/mm^3$ with 34% PMNs. His condition had been diagnosed as febril neutropenia. He was immediately admitted to the hematology unit and started receiving imipenem (1 g/d; dose adjusted to his renal function). Blood cultures were positive for serotype 4 *L. monocytogenes*. The initial antibiotic therapy was continued, and amikacin (500 mg/d) was added second days of therapy. Four days after the administration of imipenem, the patient became afebrile, and the laboratory tests showed an abatement of his neutropenia. On day 14, he was discharged with a 7-day prescription for po ampicillin/sulbactam (1250 mg/d).

RESULTS AND DISCUSSION

Clinical and demographic characteristics of these cases are shown in Table 1. The mean age of the patients was 53.7 ± 14.2 years and 8 of the 9 cases (88.9%) were male.

Table 1. Clinical and Demographic Characteristics of Listeriosis Patients

Patient No.	Age (yrs)	Sex	Underlying diseases	Immunosup- ressive therapy	Additional underlying conditions	Infection	Sero- type	Out- come
1	42	Male	Pemphigus vulgaris	Steroid	Use of ranitidine	Meningo- encephal.	1	Died
2	38	Male	Renal transplantation	Steroid, cyclosporine, azathioprine	Amiloidosis use of ranitidine	Meningo- encephal.	4	Died
3	70	Male	Acute myeloid leukemia	Cytosine arabinoside		Sepsis	4	Died
4	28	Female	Dysgerminoma	Cisplatin, etoposid, bleomycin	Radiotherapy	Sepsis	1	Cured
5	64	Male	Chronic obst. pulm.disease			Meningitis	4	Cured
6	59	Male	Coronary heart disease		Diabetes mellitus	Meningitis	4	Cured
7	62	Male	Hepatic cirrhosis		Diabetes mellitus	Sepsis peritonitis	4	Cured
8	57	Male	Hepatic cirrhosis		Chronic lymphocytic leukemia	Sepsis	4	Cured
9	63	Male	Multiple myeloma	Steroid, adriamycin etoposid, vincristin cyclofospha.	Chronic renal failure amiloidosis use of ranitidine	Sepsis	4	Cured

Pre-disposing factors

Eight of the 9 patients (88.9%) had 1 or more immuno-compromising conditions and/or underlying diseases. Four patients had malignant diseases and 5 had received chemotherapy, steroid therapy, or both, shortly before the onset of the *L. monocytogenes* infection. Other immuno-compromising conditions were hepatic cirrhosis (2 cases), renal transplantation (1 case) and diabetes mellitus (2 cases). Two patients had amyloidosis diagnosed by renal biopsy speci-mens, but we did not determine intestinal involvement in these patients. Only 1 patient had no immuno-compromising conditions and/or underlying diseases, except for a mild chronic obstructive pulmonary disease. The symptoms and findings at the time of diagnosis are summarized in Table 2. The main symptoms were a fever, chills, night sweats and meningeal signs.

Laboratory data

The diagnosis was based on the isolation of *L. monocytogenes* from the peritoneal fluid, blood and cerebrospinal fluid (CSF). The isolates were identified to the species level by conventional methods.[2,3] A total of 4 cases (44.4%) had men-ingitis; *L. monocytogenes* was isolated in the CSF cultures, and *L. monocytogenes* was also isolated in the blood culture in 1 of the cases. Laboratory findings of CSF in these patients are shown in Table 3. Five cases (55.6%) had sepsis; 4 of which only had the blood culture as positive. However, in a patient with hepatic cirrhosis, *L. monocyto-genes* grew in both the blood and peritoneal fluid cultures.

Serotyping was done using specific antisera. Two isolates (22.2%) belonged to serotype 1; seven isolates (77.8%) belonged to serotype 4. Serotype 1 *L. monocytogenes* was isolated from blood and CSF cultures in a patient with meningoence-phalitis, but in another case, serotype 1 *L.*

monocytogenes was isolated only from the blood culture. In 3 cases with meningitis/meningoencephalitis, serotype 4 *L. monocytogenes* was isolated from only the CSF cultures. In the 4 sepsis

Table 2. Presenting Symptoms and Findings of Nine Listeriosis Patients

	Cases (n)	%
Symptoms		
Fever	9	100
Night sweats	7	77.8
Altered mental status	4	44.4
Chills	4	44.4
Headache	2	22.2
Nausea	2	22.2
Vomiting	2	22.2
Diarrhea	2	22.2
Sore throat	1	11.1
Epistaxis	1	11.1
Dispnea	1	11.1
Cough	1	11.1
Findings		
Temperature (> 38℃)	9	100
Tachicardia	6	66.7
Poor general condition	5	55.6
Meningeal signs	4	44.4
Depressed consciousness	2	22.2
Hyperventilation	2	22.2
Periferic edema	2	22.2
Hepatomegaly	1	11.1
Splenomegaly	1	11.1

cases, blood cultures were positive, and in 1 of these cases, both the blood and peritoneal fluid cultures were positive for serotype 4 *L. monocytogenes*.

The *in vitro* susceptibilities of the strains to penicillin G, gentamicin, amikacin, trimethoprim-sulfamethoxazole (TMP/SMX), rifampicin, ciprofloxacin, teicoplanin, and vancomycin were determined using the E test on the Mueller-Hinton sheep blood agar. These organisms, which were isolated from the blood, peritoneal or CSF cultures were susceptible to penicillin G, amikacin, gentamicin and ciprofloxacin, and were resistant to a third generation of cephalosporins.

Treatment and outcome

In treating sepsis and meningitis patients, first penicillin or ampicillin combined with amikacin or netilmicin were given intravenously for 14 days (see clinical presentation). Then the treatment continued with oral ampicillin/sulbactam or ampicillin for an additional one-week period. In two sepsis patients, the initial therapy began with ampicillin/sulbactam or imipenem alone, but in the febrile neutropenia patient treated with imipenem, amikacin was added to the therapy. The average time from when the fever began to the onset of treatment with these antibiotics was 1.9 days (1-4 days). There was no difference in the efficacy of the initiation time of the antibiotics and different antibiotic regimens on mortality.

The crude mortality rate in patients with *L. monocytogenes* infection was 33.3% (3 of 9). Median time until death was 7 days (4-13 days). The mortality rates in patients with sepsis were 20% (1 of 5) and with meningitis were 50% (2 of 4). The prognosis of the sepsis patients was better than that of the meningitis patients.

Table 3. CSF Analysis of Patients with Meningitis/Meningoencephalitis due to *L. monocytogenes*

Patient No.	Leukocyte counts (/mm^3)	Glucose levels (mg/dL)	Protein levels (mg/dL)	Gram stains
1	1,400 (96% PMNs)	48	128	Gram-positive diplococcus
2	1,500 (36% PMNs)	20	280	No microorganisms
5	380 (24% PMNs)	58	208	No microorganisms
6	3,400 (94% PMNs)	79	350	Short gram-positive rods

We described nine patients with systemic *L. monocytogenes* infections as proven by positive blood, peritoneal or CSF cultures. The mean ages in the different series ranged from 50 to 67 years; more than 60% were male.[8,9] In this study, the mean age of the patients was 53.7 ± 14.2 years; 8 of the 9 cases (88.9%) were male. Because the elderly population rates are very high in developed countries, the incidence of adult *L. monocytogenes* infection has increased in these countries. Listeriosis is found to be the disease of an immuno-compromised host, and underlying diseases have been described in more than 70% of the cases.[4,6,7]

Listeria are facultative intracellular bacteria. The intracellular location protects the bacteria from humoral immune response. In addition, immuno-compromised patients are unlikely to produce an adequate supply of specific antibodies. In this study, 88.9% of the patients had 1 or more immuno-compromising conditions and/or underlying diseases. All immuno-compromised patients had a new onset of malignant diseases, were receiving immunosuppressive treatment or showed a deterioration in their clinical conditions just before the *L. monocytogenes* infection. Patients were known to be at the greatest risk for listeriosis shortly after renal transplantation. In two of the studies, listeriosis was diagnosed within a month after renal transplantation.[4,10] We observed that a patient with renal transplantation developed listerial meningitis and died. He received prednisolone, cyclosporine and ranitidine at the onset of the *L. monocytogenes* infection.

Sepsis and meningitis are the 2 most common clinical forms of listeriosis.[11,12] In our study, bacteremia without the known foci was described in 4 patients. In a patient with hepatic cirrhosis, both blood and peritoneal fluid cultures were positive for serotype 4 *L. monocytogenes*. Meningitis/meningoencephalitis was determined in 4 patients (44.4%).

Most cases of listeriosis are sporadic and the route of infection remains unknown. The epidemics associated with contaminated food drew attention to the possibility of a gastrointestinal origin.[3,13] It is estimated that 5-10% of the healthy population are fecal carriers of *L. monocytogenes*.[1,14] The transition from asymptomatic carriage to become an invasive disease may then be facilitated by some gastroenterologic disease, such as amyloidosis of the intestines, diarrhea, colorectal surgery or immunosuppressive therapy-related mucosal damage. In our study, 3 of the patients were taking ranitidine, 2 had amyloidosis, 2 had hepatic cirrhosis, 2 developed diarrhea shortly before the onset of listerial infection. However, we did not determine the involvement of the intestines in the patients with amyloidosis. Hospital transmission of *L. monocytogenes* among neonates in nurseries was described by several investigators.[15,16] In adult patients, 5 studies on hospital-acquired listeriosis are available. The presumed hospital acquisition occurred on day 3-67 of hospital stay in 16% of the patients.[16-18] Our study showed 1 case developing hospital-acquired listeriosis on day 43 of hospitalization. He received prednisolone, ranitidine and hydrotalcid.

In our study, all the *L. monocytogenes* isolates were susceptible to practically all common antibiotics *in vitro*, except to third generation cephalosporins; this is quite similar to the case reported by Espaze et al.[19] The optimal antimicrobial therapy for listeriosis has not been established in controlled clinical trials. Ampicillin or amoxicillin exhibit synergistic action with aminoglycoside antibiotics.[12] We treated most patients with either a penicillin or ampicillin, plus an aminoglycoside combination. Comparing the efficacy of ampicillin and aminoglycoside therapy with that of other therapies should be evaluated in a larger group of patients, but as a consequence of the rarity of listeriosis, there have been no controlled trials establishing the optimal antibiotic treatment.

Different percentages of patients with underlying conditions might explain the variation in mortality rates in previous studies, ranging from 19% to 44%.[7,20] In this study, the crude mortality rate was found to be 33.3% (50% for patients with meningitis; 20% for patients with sepsis).

In conclusion, we observed that listeriosis as an uncommon infection in our region and that immuno-suppressive therapy is an important Predisposing factor of listeriosis. Sepsis and meningitis were more common in this group of patients and had the highest case-fatality rate for food-borne illnesses.

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