

***Listeria monocytogenes* following orthotopic liver transplantation: Central nervous system involvement and review of the literature**

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Received: 2007-04-26 Accepted: 2007-05-12

Abstract

Listeria monocytogene is a well-recognized cause of bacteremia in immunocompromised individuals, including solid organ transplant recipients, but has been rarely reported following orthotopic liver transplantation. We describe a case of *listeria meningitis* that occurred within a week after liver transplantation. The patient developed a severe headache that mimicked tacrolimus encephalopathy, and was subsequently diagnosed with *listeria meningitis* by cerebrospinal fluid culture. The infection was successfully treated with three-week course of intravenous ampicillin. Recurrent hepatitis C followed and was successfully treated with interferon alfa and ribavirin. Fourteen cases of *listeriosis* after orthotopic liver transplantation have been reported in the English literature. Most reported cases were successfully treated with intravenous ampicillin. There were four cases of *listeria meningitis*, and the mortality of them was 50%. Early detection and treatment of *listeria meningitis* are the key to obtaining a better prognosis.

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Key words: *Listeria monocytogene*; Meningitis; Liver transplantation

Mizuno S, Zendejas IR, Reed AI, Kim RD, Howard RJ, Hemming AW, Schain DC, Soldevila-Pico C, Firpi RJ, Fujita S. *Listeria monocytogenes* following orthotopic liver

transplantation: Central nervous system involvement and review of the literature. *World J Gastroenterol* 2007; 13(32): 4391-4393

<http://www.wjgnet.com/1007-9327/13/4391.asp>

INTRODUCTION

Listeria monocytogene (*L. monocytogene*) is a well-known environmental organism that is most often transmitted to humans via contaminated foods such as milk and cheese, undercooked meat, or uncooked vegetables. Although *L. monocytogene* has been isolated from the stool of approximately 5% of healthy adults, disease caused by the microorganism occurs primarily in neonates, pregnant women, and immunocompromised individuals^[1]. Immunosuppression following organ transplantation has been described as a risk factor for *listeriosis* and there are several reports in the literature of occurrence following renal and bone marrow transplantation^[2,3]. Occurrence of *listeriosis* following liver transplantation (LT) has not been widely documented, especially *listeria meningitis*. We describe a case of *listeria meningitis* occurring in the early post-orthotopic liver transplant period and review the English literature on *listeriosis* following LT.

CASE REPORT

A 53-year-old Caucasian male underwent orthotopic LT due to hepatitis C virus (HCV)-induced liver cirrhosis with associated hepatocellular carcinoma. He was doing well and afebrile before transplantation. White blood cell count (WBC), total bilirubin, creatinine, and prothrombin time international normalized ratio (PT INR) were 4500/mL, 0.8 mg/dL, 1.1 mg/dL, 1.1, respectively. The model for end-stage liver disease (MELD) score was 8. Cefazolin (6 g/d) was used for postoperative antimicrobial prophylaxis for two days. Posttransplant immunosuppression included oral tacrolimus and prednisone, and his early postoperative course was uncomplicated. On postoperative day five, he developed a severe, throbbing headache. His body temperature was normal, WBC was 6200/mL and a CT scan of the head revealed no abnormal findings. On the following day, his mental status gradually declined.

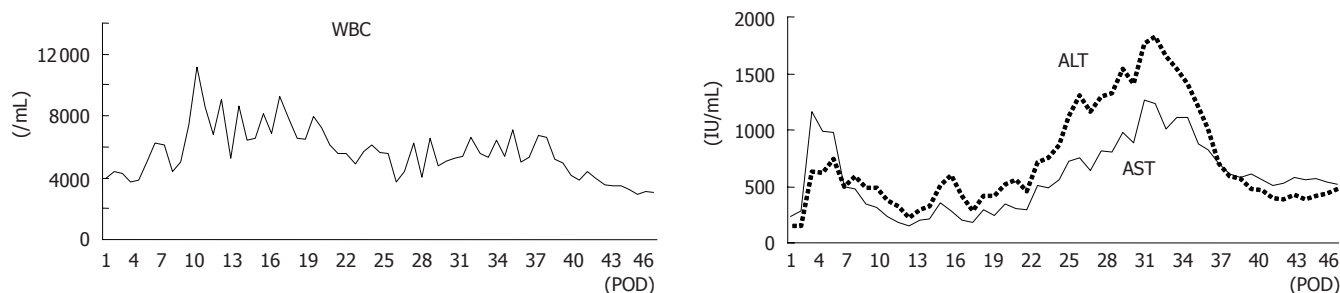


Figure 1 Laboratory profiles of this patient following liver transplantation. WBC: white blood cells; AST: aspartate aminotransferase; ALT: alanine aminotransferase; POD: postoperative day.

Table 1 Cases of listeria infection following liver transplantation

Age (yr)	Sex	Time postTx	Clinical presentation	Clinical syndrome	Treatment	Outcome	Ref
66	F	32 mo	Fever, right flank pain, anorexia	Bacteremia	Ampicillin	Survived	7
39	F	7 d	Fever, abdominal pain	Bacteremia	Ampicillin	Survived	8
63	F	62 d	Fever, abdominal pain	Bacteremia	Ampicillin	Survived	9
66	M	50 d	Fever, abdominal pain	Bacteremia	Ampicillin	Survived	9
46	F	3 yr	Fever, diarrhea, recurrent	Bacteremia	Ampicillin Gentamicin	Survived	10
55	F	4 mo	Fever, confusion, diarrhea	Bacteremia	TMP/SMZ Gentamicin	Survived	11
57	F	20 mo	Fever with chill	Bacteremia and hepatitis	Ampicillin	Survived	12
56	M	8 mo	Fever, jaundice	Bacteremia and hepatitis	Ampicillin Gentamicin	Survived	13
41	F	Unknown	Fever, malaise	Endocarditis and septic pulmonary emboli	Ampicillin	Survived	14
47	F	Unknown	Fever, malaise	Peritonitis and bacteremia	Ampicillin Amikacin	Survived	15
8 M	M	10 d	Fever, rash, irritability, dyspnea	Meningitis, peritonitis, epididymitis and orchitis	Ampicillin	Survived	16
UNK	UNK	14 d	Unknown	Meningitis	Unknown	Survived	17
67	F	21 d	Unknown	Meningitis	Unknown	Died	18
13	F	4 mo	Fever, headache	Meningitis	Ampicillin	Died	19

Tacrolimus encephalopathy was suspected due to a high tacrolimus trough level (22.9 ng/mL), and administration of tacrolimus was temporarily discontinued. On the seventh postoperative day, the serum tacrolimus level decreased to 8.9 ng/mL, but his headache remained and he became unresponsive. A CT scan showed extensive acute hydrocephalus with no evidence of bleeding or herniation. His body temperature increased to 39.1°C. and his WBC elevated to 13 000/mL. The patient underwent lumbar puncture and analysis of cerebrospinal fluid (CSF) revealed a white blood cell count of 100/mL (69% segmented neutrophils and 18% lymphocytes), protein level of 39 mg/dL, and glucose level of 69 mg/dL. *L. monocytogene* was grown in culture from the CSF. Blood culture also yielded the growth of *L. monocytogenes*. The diagnosis of listeria meningitis was made and the patient was treated with a three-week course of ampicillin. The patient became afebrile and WBC decreased to 7600/mL on the following day. The patient's neurological findings gradually improved but had persistent ventriculomegaly. Due to labile mental status and persistent hydrocephalus of a CT finding, a VP shunt was placed operatively on postoperative day (POD) 28. He had been stable since and his mental status became baseline. On POD 20, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) gradually increased (Figure 1), HCV RNA-b DNA level was markedly elevated to > 7961 230 IU/mL, and the recurrence of HCV was diagnosed by liver biopsy. The patient was started on interferon alfa and ribavirin, and AST and ALT levels

gradually decreased. He was discharged on the 48th d following operation.

DISCUSSION

Immunosuppression following organ transplantation has been described as a risk factor for listeriosis and several cases have been described following bone marrow and renal transplantation^[2,3]. Nolla-Salas *et al*^[4] recently reported that liver cirrhosis should also be considered a predisposing factor for listeriosis. Fourteen cases of listeriosis following LT have been reported^[5-17], in which, only four occurrences of meningitis were reported, three within three weeks and one within four months following transplantation (Table 1). The patient age ranged from eight months to 67 years (age not reported in one case). Clinical symptoms included fever, headache, and irritability. All patients with meningitis were treated with intravenous ampicillin with a 50% mortality, though all of the other listeriosis patients without meningitis survived after antibiotic treatment including either ampicillin or trimethoprim-sulfamethoxazole.

According to the centers for disease control and prevention (CDC), *L. monocytogene* is the fifth most frequent cause of bacterial meningitis^[18]. It was reported that listeriosis of the central nervous system is characterized by a high mortality rate (20%-50%). A recent prospective cohort study showed that the mortality rate even now is 17%^[19]. Stamm *et al*^[20] reported that, in patients with

listeriosis after kidney transplantation, meningitis is also associated with a significantly higher mortality (37%) than listeriosis without meningitis (11%).

In our patient, the correct diagnosis was delayed because of the appropriate initial thought that the patient's CNS symptoms were secondary to tacrolimus toxicity. It is well known that tacrolimus-associated encephalopathy demonstrates various symptoms, such as tremor, convulsions, drowsiness, headache, nausea, and cortical blindness. The risk of tacrolimus-associated encephalopathy is significantly correlated with the tacrolimus blood level.

The mode of transmission of *L. monocytogene* is not clearly understood. It is well known that *L. monocytogene* is widespread in nature, being found commonly in soil, decaying vegetation, and as part of the fecal flora in many mammals. Elsner *et al.*^[10], however, studied nosocomial infections with *L. monocytogenes* in immunocompromised patients and suggested that nosocomial food-borne and person-to-person transmission could not be proven. While this patient stayed at our hospital, there were no additional cases of listeria infection among patients or hospital staff. Transmission from the donor organ was also excluded because the donor blood culture was negative for listeria infection, and according to the information of the united network for organ sharing (UNOS), the recipients who received other organs from the same donor did not develop listeriosis. We speculate that enteric previous colonization is the rule in patients with listeriosis.

Vander *et al.*^[21] reported that inherent T cell dysfunction caused by HCV infection may increase the susceptibility to listeria infection. In our case, the patient underwent liver transplantation because of chronic HCV infection and hepatocellular carcinoma. He developed recurrent HCV infection as demonstrated by a very high HCV-RNA level in the early postoperative period (HCV RNA-b DNA > 7 961 230 IU/mL, HCV RNA-b DNA log > 6.89 log IU/mL). This situation might have caused the patient to have increased susceptibility to listeria infection.

Though our patient was successfully treated with ampicillin, it is important to diagnose and treat as early as possible because the prognosis of listeria meningitis is not favorable.

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S- Editor Zhu LH L- Editor Wang XL E- Editor Ma WH