

# *Listeria monocytogenes* meningitis in an immunocompromised patient

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## SUMMARY

This report describes a case of meningitis caused by *Listeria monocytogenes* in a stem cell transplant recipient on immunosuppressive therapy for cutaneous chronic graft-versus host disease. A 59-year-old woman had undergone allogeneic stem cell transplantation (from a matched unrelated donor) 13 months previously for chronic lymphocytic leukemia. She was on regular hematologic follow-up. Though her previous malignancy has been in remission, she was immunosuppressed due to the pharmacological treatment. We describe a meningitis caused by a typical food-borne pathogen, dangerous in patients with impaired cell-mediated immunity. Moreover the bacterium had a multidrug resistance, a rare characteristic in clinical listeriosis. Rapid diagnosis and treatment are key factors in these cases. We chose ampicillin and rifampicin that allowed a complete resolution of the clinical manifestations.

**KEY WORDS:** *Listeria monocytogenes*, Meningitis, Chronic lymphocytic leukemia.

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*Listeria monocytogenes* is a facultative intracellular bacterium, the causative agent of a series of diseases from meningitis to gastroenteritis. It is one of the most virulent foodborne pathogens with a mean of 20% of clinical infections resulting in death (Ramaswamy *et al.*, 2007). The manifestations of listeriosis include septicemia, meningitis (or meningoenzephalitis) (Gray and Killinger, 1966), encephalitis (Armstrong and Fung, 1993), and intrauterine or cervical infections in pregnant women, which may result in spontaneous abortion or stillbirth. Gastrointestinal symptoms such as nausea, vomiting, and diarrhoea may an-

ticipate more serious forms of listeriosis or may be the only symptoms. During passage through the gastrointestinal tract *L. monocytogenes* encounters low pH. The low pH in the human stomach provides a significant barrier to *L. monocytogenes* infection and patients taking medications to reduce gastric acid (including proton pump inhibitors) are at increased risk of infection (Bavishi and Dupont, 2011). Arterial hypertension seems to be another important predisposing factor because it could impair the integrity and function of the blood/brain barrier and thus enable the invasion of *L. monocytogenes* into the subarachnoid space and/or brain tissue (Dzupova *et al.*, 2013). There are well-defined risk groups for human invasive listeriosis: pregnant women, the elderly, and cellular immunocompromised individuals such as those receiving corticosteroids or chemotherapy, haemodialysis, transplants, diabetic, HIV carriers, and drug

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abusers (Vazquez-Boland *et al.*, 2001; Mook *et al.*, 2011). Exposure and colonization may occur in any person, but patients without predisposing factors represent less than 20% of the cases (Di Maio, 2000). Unlike other foodborne diseases, the incubation period for listeriosis can be long. A study reported an overall median incubation period of invasive listeriosis of 8 days, ranging from 1 to 67 days (Goulet *et al.*, 2013). Therefore it is usually difficult to establish the source of infection. Listeriosis often requires antimicrobial therapy. The treatment of choice consists of a beta lactam antibiotic, normally ampicillin, alone or in combination with an aminoglycoside, classically gentamicin. Second line agents in case of allergy to beta lactams or in certain disease states include trimethoprim/sulfamethoxazole, erythromycin, vancomycin, and fluoroquinolones (Temple and Nahata, 2000). Resistance of *L. monocytogenes* clinical isolates to these antibiotics is low (Morvan *et al.*, 2010). However, since the isolation of the first multiresistant strain of *L. monocytogenes* in France in 1988 (Poyart-Salmeron *et al.*, 1990), strains resistant to one or more antibiotics have been recovered from food, the environment and sporadic cases of human listeriosis (Hadorn *et al.*, 1993; Franco Abuin *et al.*, 1994; Charpentier *et al.*, 1995). Early diagnosis and antibiotic administration increases the probability of a favourable outcome (Temple and Nahata, 2000). In order to enhance the rapidity of the diagnosis, in addition to the classical methods, we can now use PCR or real-time PCR (Le Monnier *et al.*, 2009). Rapid and accurate results are helpful for an empirical antibiotic treatment adoption, usually based on a high dose of expanded-spectrum cephalosporins inactive against *L. monocytogenes* or on adding or removing ampicillin (Stahl *et al.*, 2009).

## CASE REPORT

A 59-year-old woman with arterial hypertension was admitted to the Emergency Department of the General Hospital with a three-day history of high fever, headache, fluctuating mental status and altered consciousness. At the time of admission she was on immunosuppressive thera-

py (prednisone 25 mg daily and micophenolate 500 mg daily) and her medications included bisoprolol, omeprazole and valacyclovir prophylaxis; the patient was not on cotrimoxazole prophylaxis.

Physical examination confirmed the patient's fluctuating mental status and altered consciousness. Her body temperature was 39.6°C and blood pressure was 110/75 mmHg. The patient demonstrated significant nuchal rigidity and accentuated sweating.

Chest radiography and a non-contrast computed tomography (CT) scan of the head were unremarkable, as in a previous CT performed one year before, with the exception of a monolateral maxillary sinusitis.

Cerebrospinal fluid (CSF) examination indicated a strong suspicion of bacterial meningitis (cloudy aspect, WBC 2500/mm<sup>3</sup>, 90% neutrophils, 10% lymphocytes, RBC 4.6 M/mm<sup>3</sup>, total proteins 350 mg/dL, glucose 18% of blood glycaemia). Gram stain and antigen detection methods for *Streptococcus pneumoniae*, *Haemophilus influenzae* type b and *Neisseria meningitidis* were negative.

As the early administration of antibiotics correlates with reduced morbidity and mortality associated with bacterial meningitis, it was of crucial importance to initiate appropriate treatment as soon as possible. Soon after the results of the lumbar puncture, because of the strong suspicion of bacterial meningitis, the patient was empirically started on ceftriaxone (2 g iv) and ampicillin/sulbactam therapy (3 g iv). In view of the sinusitis detected by CT scan, the first etiologic hypothesis was pneumococcal meningitis.

To provide a rapid and reliable information about the therapy, CSF culture was supported by a PCR analysis (Barocci *et al.*, 2008) (Figure 1). Both confirmed the presence of *L. monocytogenes*. At the same time as the identification, an automatic antibacterial test was performed. The patient was subsequently admitted to the Infectious Diseases Department. On admission, the patient was in serious condition. She was disoriented with altered consciousness, and signs of serious meningeal irritation without focal neurologic signs. Her body temperature was 38.5°C, blood pressure 150/110 mm Hg, and heart rate 100 bpm. She had numerous

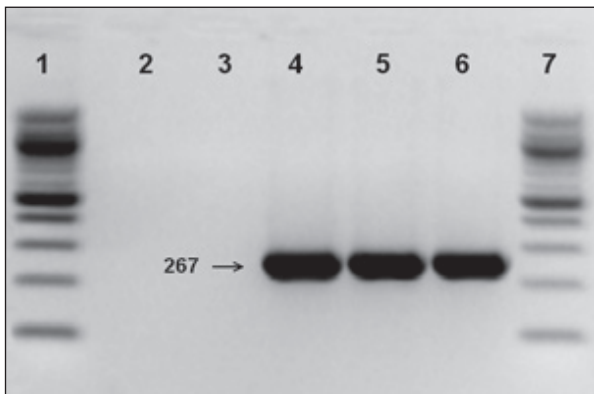


FIGURE 1 - PCR results for molecular identification. Lanes 1 and 7: ladder 100 bp; lane 2: negative amplification control (sterile distilled water); lane 3: negative extraction control (*E. coli* DNA); lane 4: patient sample; lane 5: positive extraction control (*L. monocytogenes* ATCC 7644); lane 6: positive amplification control (*L. monocytogenes* ATCC 7644), (negative image).

bruises on the abdomen, arms, and medial surface of the thighs; fine bilateral basal crackles were detected on chest auscultation. After laboratory tests, urine examination disclosed mild proteinuria. All other clinical parameters were within normal ranges. ECG and chest radiogram were unremarkable. All blood cultures were negative.

During her Hospital stay the patient received specific IV antibiotic therapy with ampicillin (12 g daily, in 4 separate doses every 6 h) and rifampicin (600 mg daily), after supportive therapy based on dexamethasone and paracetamol. Rifampicin was added to ampicillin in order to minimize the risk of relapse and treatment failure as the patient was immunocompromised.

In a few days, the patient's conditions improved and her fever disappeared. She was discharged after 14 days of in-patient intravenous treatment and was kept on oral antibiotics (amoxicillin/clavulanic acid 1 g 8 hourly plus rifampicin 600 mg 24 hourly) for two additional weeks.

#### Microbiological characterization and molecular identification

Automatic instruments carried out serum clinical chemistry and hemochromocytometric analyses. CSF examination and pathogen isolation were carried out following the Health

Protection Agency protocols (Health Protection Agency, 2008).

Antimicrobial susceptibility test was performed following the EUCAST disk diffusion method (EUCAST, 2009). Due to shortcomings in the interpretation of *L. monocytogenes* breakpoints, the zone diameters were interpreted referring to *Staphylococcus* spp breakpoint tables, as recommended by Clinical and Laboratory Standards Institute (CLSI, 2006) and suggested by some Authors (Conter *et al.*, 2009; Chen *et al.*, 2010). *Staphylococcus aureus* ATCC 29213 was used as control strain.

The PCR protocol used for *L. monocytogenes* confirmation followed the indications of Barocci *et al.* (Barocci *et al.*, 2008). Automatic antimicrobial susceptibility test were performed with an AST-580 card for VITEK®2 (Bio- Mérieux, Marcy l'Etoile, France), and successively confirmed by disk diffusion method.

The strain resulted sensitive to ampicillin (AMP10), ampicillin/sulbactam (SAM20), streptomycin (S10), imipenem (IPM10), levofloxacin (LEV1), tigecycline (TGC15), teicoplanin (TEC30), amoxicillin/clavulanic acid (AMC30), chloramphenicol (C30), gentamicin (G10), penicillin (P10), vancomycin (VA30), erythromycin (E15), linezolid (LZD30, according to CLSI breakpoints) and was resistant to cotrimoxazole, ceftriaxone, clindamycin and tetracycline.

#### DISCUSSION

According to the Centers for Disease Control and Prevention, *L. monocytogenes* is the fifth most frequent cause of bacterial meningitis (Wenger *et al.*, 1990).

Despite adequate antibiotic treatment, the overall mortality of central nervous system infection is still high (25 to 30%) and neurological sequelae are common (Le Monnier *et al.*, 2009). In this study, *L. monocytogenes* infection was confirmed as the cause of meningitis. Clinical presentation was that of typical acute bacterial meningitis, with fever, headache, fluctuating mental status and altered consciousness (CDC, 2014). The patient had several predisposing factors like immunodeficiency and arterial hypertension (Mook *et al.*, 2011; Dzupova *et al.*, 2013) She was on immunosuppressive medica-

tions after allogeneic stem cell transplant complicated by chronic graft versus host disease and bisoprolol for hypertension treatment.

It has been very difficult to determine the exact source of infection due to the long disease incubation period. Most authors comment that 99% of human *Listeria* infections have a food-borne origin (Wiedmann, 2003; Mena *et al.*, 2004; ILSI, 2005). *L. monocytogenes* has been recovered from several foods such as meat, milk, cheese, fish products, ice cream, vegetables and several ready-to-eat foods (Nightingale *et al.*, 2005; Garrido *et al.*, 2009). Our patient was well aware of the dietary recommendations for preventing foodborne infections, including listeriosis in high-risk patients, as she had been properly counseled by her haematologist. Nonetheless, the patient acknowledged that she was not always compliant with specific dietary restrictions, having eaten some soft cheese (blue-veined *gorgonzola* cheese) several weeks before the onset of her meningitis episode. Soft cheese is considered a high-risk product for listeriosis because the bacteria may grow to significant numbers during refrigeration and to date we have several reports that prove this thesis (CDC, 1985; Longhi *et al.*, 2003; Bille *et al.*, 2006).

As a concomitant risk factor for food-borne invasive listeriosis, the patient was on omeprazole treatment, which could promote infections due to food-borne pathogens by stomach alkalization (Bavishi and Dupont, 2011). In addition, she was not on trimethoprim/sulfamethoxazole prophylaxis, which is usually known to be effective in the prevention of invasive listeriosis in immunocompromised patients. However, the isolated strain had a resistance to cotrimoxazole.

Concerning antibiotic therapy, penicillin, ampicillin, tetracycline or erythromycin are often used as treatments of choice (Conter *et al.*, 2009). The combination of cotrimoxazole plus ampicillin was associated with lower failure rates and fewer neurologic sequelae than ampicillin with gentamicin. The same study found failure of ampicillin and gentamicin in 57% of patients (Merle-Melet *et al.*, 1996). Unfortunately, our strain was resistant to cotrimoxazole so we decided to use ampicillin and rifampicin that allowed a complete resolution of the clinical

manifestations and a good outcome.

Even if there had been no controlled trials to establish a drug of choice for *Listeria* infection, the beta-lactam antibiotics are reported as being bacteriostatic for *listeriae*. Aminoglycosides are known to poorly penetrate the blood-cerebrospinal fluid and blood-brain barrier (Hof, 2004), thus raising concerns about the efficacy of such "first-line" combination therapy for central nervous system infections due to *L. monocytogenes*. At least in the immunocompromised host, ampicillin in combination with rifampicin, which is effective against intracellular *listeriae* and penetrates the CSF, could be a good alternative regimen to minimize the risk of treatment failures.

After antimicrobial susceptibility test we found that the strain carried a rare four antibiotic multiresistance to cotrimoxazole, ceftriaxone, clindamycin and tetracycline. Usually resistance of *L. monocytogenes* to antibiotics is low and to date there are few reports of multiresistant *L. monocytogenes* strains from clinical cases. In a 10-year study, Walsh *et al.* found that the resistance to one or more antibiotics was exhibited in 0.6% of 1001 *L. monocytogenes* isolates and resistance to tetracycline was the most frequently observed (Walsh *et al.*, 2001). In a study in Italy on 98 *L. monocytogenes* isolates, two strains were resistant to streptomycin, sulfamethoxazole, and kanamycin, one strain was resistant to streptomycin, sulfamethoxazole, kanamycin, and rifampin, and one strain was resistant to the latter four antibiotics as well as to erythromycin and chloramphenicol (Facinelli *et al.*, 1991). A multiresistant strain of *L. monocytogenes* was isolated in Greece from a neonate who developed meningitis 21 days after birth. The strain was resistant to gentamicin, streptomycin, chloramphenicol, and clindamycin and was moderately susceptible to tobramycin (Tsakaris *et al.*, 1997).

Lastly, the definitive diagnosis of listeriosis was based exclusively on the isolation of *L. monocytogenes* in clinical samples. We used a PCR assay (Barocci *et al.*, 2008) to obtain a rapid and sensitive result but we are aware that molecular diagnostic testing must not replace culture, the only technique that allows antimicrobial susceptibility testing and epidemiological and microbiological surveillance of

emerging strains. However, together, PCR molecular tests and classical culture methods can give us a rapid and accurate result (Backman *et al.*, 1999; Gouws *et al.*, 2005; Welinder-Olsson *et al.*, 2007), helpful for a fast and specific antibiotic treatment adoption leading to a favourable outcome.

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