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1. Title

Solid organ donation after death from listeria encephalitis: A case-report.

2. Running title

Organ procurement after Listeria infection.

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5. Acknowledgements

None

6. Abstract and keywords

Despite organ shortage, organs from donors with listeria infections have been discarded for transplantation. We present the first reported case of liver transplantation following listeria encephalitis.

The patient was admitted with progressing neurological symptoms after an episode of gastroenteritis. Rhombo-encephalitis was diagnosed and *Listeria monocytogenes* was found to be the causative pathogen. Despite proper antibiotic treatment and rapid clearance of bacteremia, he continued to deteriorate and became brain dead, after which organ donation was performed. At procurement, he had been treated with amoxicillin for 9 days. The recipient was treated with piperacillin/tazobactam for 21 days. Besides an anastomotic biliary stricture, necessitating endoscopic dilatation and stenting, further clinical course was uneventful and she is doing well eleven months post-transplant.

Our case suggest that listeria encephalitis is not an absolute contra-indication to solid organ donation. We suggest that donors should be treated with adequate antibiotics for at least 48h prior to procurement and advocate confirmation of sterile blood cultures as a prerequisite for donation. According to listeriosis guidelines we suggest that the recipient should be treated with targeted antibiotics for at least 2 weeks. The risk of transmission should, however, always be balanced carefully against the suspected waiting list mortality.

Key Words

Listeria monocytogenes, Solid organ transplantation, Liver transplantation, Kidney transplantation, Invasive listeriosis, meningitis, Sepsis, Bacteremia, Donor, Organ procurement

7. Main Text

Introduction:

Inadvertent transmission of infectious diseases is a continuous concern in organ transplantation. Although solid organ donation after bacterial meningitis caused by *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* has become common practice; organ donation after *Listeria monocytogenes* infection is generally disadvised.^{1,2} The current European Committee on Organ Transplantation guidelines state: “*Meningitis caused by Listeria may disseminate systemically. Treatment by targeted antibiotics is possible, but management of immuno-suppressed patients with Listeria infection is troublesome and can lead to non-acceptance of such donors by recipient centers.*”³ Although the guideline does not formally exclude these donors, to date, there is no report of solid organ donation following invasive listeriosis. We present a case of liver transplantation from a donor who died of listeria encephalitis. The kidneys were transplanted in two other patients.

Case-report:

A 56 years old male with a history of alcohol abuse and a recent gastroenteritis was admitted to a regional hospital with progressive agitation, headache, singultus, dizziness, and ataxia. Computed tomography of the brain and spine were negative. A lumbar puncture showed lymphocytic pleiocytosis with negative culture and a low plasma C-reactive protein level (16mg/L). Subsequent magnetic resonance imaging revealed high signal intensities on T2-weighted images in the brainstem and upper cervical cord, and tentative diagnosis of transverse myelitis was made for which treatment with corticosteroids was initiated. Five days later, the patient developed spiking fever with rapid neurological deterioration necessitating intubation and mechanical ventilation. Blood cultures were taken and empirical antimicrobial treatment with ceftriaxone and acyclovir was initiated. The day after (12th day of admission), blood cultures revealed growth of *L. monocytogenes*.

Amoxicillin (2000 mg i.v., 6x/day) was added to the empirical antimicrobial therapy and the patient was referred to our hospital. New blood cultures in our hospital remained negative. Despite the rapid clearance of bacteremia and maximal supportive care, the patient deteriorated to brain death on the 21st day of admission. The patient did not object to organ donation before death and the family agreed.

The lungs, liver and both kidneys were procured but the lungs were declined in situ because of the presence of bullae. The liver and kidneys were transplanted in 3 patients in different centers.

The liver was transplanted in our center to a 65-year old women suffering from decompensated cirrhosis due to primary sclerosing cholangitis with a MELD score of 29. The transplant procedure was uneventful. The immunosuppressive protocol consisted of induction basiliximab followed by methylprednisolone, tacrolimus and mycophenolate mofetil. She was treated with piperacillin/tazobactam (4000/500mg IV, 4x/day) for 3 weeks due to a concomitant positive culture of preservation solution with *Enterobacter cloacae* and a rather high MIC (0.75 mg/L) of the *Listeria* strain for fluoroquinolones (levofloxacin/ciprofloxacin). The postoperative course was complicated by elevated cholestatic parameters due to an anastomotic biliary stricture treated with endoscopic dilatation and stenting. She had no symptoms of *Listeria* infection. Further clinical course was uneventful and the patient is doing well eleven months post-transplant.

The patient was informed that she received an organ from a donor with a potential transmittable pathogen requiring a post-transplant course of antibiotics. Additional informed consent was not acquired as our ethics committee requested that all our listed candidate organ recipients, are thoroughly informed about the risk of transmittable infectious diseases and the possible need for additional postoperative treatment. Patients agree to rely on our expert multidisciplinary team to balance an infectious risk against the risks of not timely receiving an allograft.

Both kidneys were transplanted at other centers. One of the kidney recipients left the hospital on postoperative day 9 with a good kidney function. This patient was treated for an unknown duration with sulfamethoxazole-trimethoprim because of penicillin allergy. The second patient had an uneventful postoperative course, but unfortunately we were unable to attain any information on postoperative antibiotic administration.

Discussion:

Listeriosis is a rare foodborne infection caused by *L. monocytogenes*, a gram-positive, rod-shaped bacterium.⁴ Most patients present with mild to febrile gastro-enteritis which typically resolves within 2 days of onset without treatment. However, in more susceptible patients (such as children, elderly, pregnant women, alcoholics and immunocompromised individuals) *L. monocytogenes* may traverse the intestinal barrier and replicate intracellularly in liver, spleen and lymphocytes resulting in a general dissemination of the pathogen.⁵⁻⁷ This invasive listeriosis has three major clinical presentations which include sepsis, meningoencephalitis and abortion, and carries a 30-

day fatality rate up to 40%.^{8–10} We presume it is the combination of the unique intracellular life cycle of *Listeria* and the traditionally reported high mortality that explains the overall reluctance of transplant professionals to accept organs from *Listeria* infected donors.⁴ Moreover, *L. monocytogenes* is very resistant to environmental stresses, such as low temperature, making it more likely to survive cold storage in comparison with more classical pathogens of meningitis.⁴ However, because listeriosis is a rather uncommon infection, this poor outcome can be largely explained by a delayed diagnosis and delayed initiation of adequate treatment, as empirical coverage of listeriosis is usually not considered before the organism is identified in blood or cerebrospinal fluid.¹¹ Indeed, patients receiving adequate empirical antibiotic therapy have a significant lower 30-day mortality of 13%.¹⁰

In 2010, the annual worldwide incidence of invasive listeriosis was estimated at 23.150 cases of which 5.463 (= 23.5%) presumably died.¹² Whereas the incidence of invasive listeriosis remained stable in the United States between 2008–2016, there was a significant annual increase since 2008 in Europe with a notification rate of 0.48 cases per 100,000 population and overall reported mortality of 13,8% in 2017.^{13,14} Although the numbers of potential donors related to listeriosis are not overwhelming, every potential donor should be considered in order to reduce the disparity between organ demand and supply.

The gold standard in antibiotic treatment for listeriosis is high dosed ampicillin or amoxicillin (2000 mg IV, 6x/day). Some authors recommend the addition of gentamycin (5 mg/kg/d IV) because of an in vitro synergistic effect. Clinical evidence for increased efficacy is however scant, and gentamycin is nephrotoxic, does not cross the blood-brain-barrier sufficiently well and does not penetrate into the intracellular compartment.^{10,15–17} Second-line therapy consists of trimethoprim-sulphamethoxazole (3–5mg/kg, 4x/d IV).^{15,16} Vancomycin may be an alternative if meningitis is excluded, as it barely crosses the blood-brain barrier, but clinical failure have been reported despite proven in vitro activity.^{15,16,18} Although broad-spectrum antibiotics such as piperacillin/tazobactam or high dose carbapenems are widely used as empiric therapy for sepsis in vulnerable and immunocompromised patients, they are not considered as optimal empirical therapy for patients at risk of listeriosis since the central nervous system penetration of piperacillin/tazobactam is not reliable and both clinical failure and increased mortality has been reported in invasive listeriosis patients treated with meropenem.^(7,9–14) Fluoroquinolones have been highly recommended by some authors.^{15,19}

We are rather reluctant for their use since reduced fluoroquinolone susceptibility (30-67%)^{20,21} or resistance (17%)²² is not infrequent, and the absence of official susceptibility breakpoint values.²³ Never forget, that in contrast with most other meningitis pathogens, *Listeria* is naturally resistant to cephalosporins.

Although piperacillin is not the first-choice antilisterial antibiotic, the presented recipient was post-transplant treated with piperacillin/tazobactam (4000/500mg IV, 4x/day) because this dosing regimen has a high probability of obtaining piperacillin plasma levels sufficient to treat *L. monocytogenes* bacteremia and concomitantly covers the *E. cloacae* isolated from the preservation solution. In addition, the risk of *Listeria* transmission was considered low due to the fast documented clearance of bacteremia in the donor and invasive listeriosis has been successfully treated with piperacillin/tazobactam.^{10,17} A switch to fluoroquinolones was considered, but was eventually avoided because of relative high MIC values for fluoroquinolones in the *Listeria* strain. In concordance with international guidelines on the management of bacteremic donors, we would advise to treat a *Listeria* infected donor with high dosed amoxicillin (+/- gentamycin) for at least 48h prior to procurement, combined with evidence of 'clinical improvement' of the donor (improved white blood cell count, improved hemodynamics, ...) and the confirmation of sterile blood cultures at time of organ recovery.^{1,3} Only when all these criteria are fulfilled, we would advise donation. In our case, the patient was even treated for 9 days before procurement due to the time gap between the diagnosis of invasive listeriosis and the confirmation of brain death. In our opinion, the presence of abscesses or persistence of active bloodstream infection are absolute contra-indications for transplantation.

For the recipient, we recommend high dosed amoxicillin (2000 mg IV, 6x/day) for at least 14 days following the current clinical guidelines on *Listeria* bacteremia.¹⁵ After extensive consultation with colleagues, our recipient received a 21-day of antibiotics, out of precaution, which is the median duration of antibiotic therapy for the treatment of listeriosis in solid organ transplant recipients reported in the literature.^{9,24}

In contrast to the liver, *L. monocytogenes* is not known to accumulate and to replicate in kidneys, making the risk of transmission via transplantation theoretically much lower.²⁵ Both kidneys were accepted and were transplanted at two other centres. Both organs resumed normal renal function and the recipients displayed no signs of *Listeria* infection. This report suggests that transplantation of solid organs from donors who died of *Listeria* encephalitis might be considered under favorable conditions. However, we would still advocate caution in accepting *Listeria* infected donors and the

risk of transmission should always be balanced carefully, on case-by-case basis, against the suspected waiting list mortality. In the presented case the risk to transmit listeria was deemed low since fast clearance of bacteremia under adequately antibiotic treatment was documented in the donor. To further diminish the transmission risk, the recipient received a prolonged post-transplant antibiotic course. The recipient is doing well eleven months post-transplant. We would like to encourage other teams to report their experience with this type of donors.

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9. Tables

None

10. Figures legends

None

11. Appendices

None

12. Authors contribution

All authors were involved in the clinical care of the donor and/or recipient. TD and YD drafted the manuscript. KL, IJ, MSB, DM and JP critically revised the manuscript. All authors approved the final version of the manuscript.