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Successful multiple organ donation after donor brain death due to *Actinomyces israelii* meningitis

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ABSTRACT

The increasing gap between availability of solid organs for transplantation and the demand has led to the inclusion of donors which according to current guidelines may be discarded, some of them because of the possibility for transmission of infection to their recipients. We present the first report, to the best of our knowledge, of a case of a brain-dead donor with a localized and treated *Actinomyces israelii* central nervous system infection who, after a thorough evaluation, led to successful transplant procedures in four recipients. There was no evidence of transmission of infection within a 6-month follow-up. Relative contraindications must be individualized in order to expand the number of real organ donors, emphasizing cautious measures in rare causes for brain death in which patients should be thoroughly evaluated for possible donation.

Keywords:

Actinomyces israelli, meningitis, multiple organ donation

1 INTRODUCTION

The shortage of suitable organ donors for transplantation has led the transplant community to look at more marginal candidates, including donors who could potentially transmit diseases to their recipients.[1] Infections without systemic spread such as acute meningitis are not an absolute contraindication for transplantation if three criteria are met: identified cause, appropriate antimicrobial therapy is administered to donors for 48 hours or more and infection is clinically controlled. [2,3]

Central nervous system (CNS) infection caused by *Actinomyces* species is a rare infection, generally presenting as brain abscesses. Reports exist of more uncommon forms of infection, such as meningitis or meningoencephalitis,[4-6] subdural empyema, or spinal abscess.

Actinomycosis of the CNS is usually secondary to hematogenous spread from a primary infection site, such as the lung, abdomen, or pelvis. However, infection may also directly extend from the ears, paranasal sinuses, or cervicofacial regions causing focal infection or diffused basilar meningitis. To date, no reports in the literature discuss the safety of procuring organs from patients progressing to brain-death due to CNS infection caused by this pathogen.

Here, we present a multi-organ brain-dead donor, with death caused by *Actinomyces israelii* CNS infection, to emphasize that relative contraindications should be individualized in order to increase the number of real organ donors.

2 CASE REPORTS

2.1 Donor

A 53-year-old woman, an active smoker, was admitted to her local hospital because of a 2 week moderate headache associated with dizziness, photophobia, and nausea. Symptomatic treatment was administered with poor clinical improvement. Five days later, she was referred to our institution; after full study and on the basis of the analysis of cerebrospinal fluid (CSF), empirical antibiotic treatment was initiated with ampicillin and acyclovir. Cranial computed tomography (CT) scan was normal, and blood and CSF cultures and polymerase chain reaction (PCR) for common viral and bacterial causes were negative.

In the following 5 days, the patient's clinical condition improved with attenuation of dizziness, and headache. Antibiotic and antiviral treatment was discontinued and she was discharged from hospital with the presumptive diagnosis of aseptic meningitis.

Three weeks after hospital discharge, she was readmitted because of fever (38.5°C), intense headache, and the appearance of diplopia. Cranial CT scan, and CSF analysis and culture were repeated with same results as at the first admission. Serological analysis for *Borrelia* and syphilis and nucleic acid testing for Epstein-Barr virus, cytomegalovirus, as well as antinuclear, anticytoplasmic and SSA/Ro60, SSB/La, Ro52, Sm, RNP, Scl 70, anti Jo1 autoantibodies were all negative. The oral cavity, including dentition and paranasal sinuses were evaluated by exam and imaging and were disease free. No antibiotic treatment was initiated owing to the lack of identification of an active infection.

On day 7 after readmission, her consciousness level deteriorated secondary to a generalized seizure. Intubation and mechanical ventilation were initiated, and the patient was admitted to the intensive care unit (ICU). A magnetic resonance image (MRI) showed a slight thickness and leptomeningeal enhancement at the brainstem, associated with purulent intraventricular material compatible with meningitis complicated with ventriculitis and hydrocephalus (Figure 1). An external ventricular drainage (EVD) was placed in order to monitor intracranial pressure and to evacuate purulent material. Despite no identification of microorganisms in blood or CSF cultures, antimicrobial therapy was initiated with carbapenem plus linezolid. Antituberculous treatment was initiated in the following 24 hours owing to persistence of fever, leukocytosis, and changes in CSF composition with increase in lymphocytes. Intracranial pressure remained high despite control measures.

A second MRI showed worsening of the leptomeningeal uptake and appearance of several bilateral cerebellar infarcts at posteroinferior and anteroinferior cerebellar artery territories. On day 13 after admission, intracranial hypertension became refractory to all control measures, finally evolving to brain death.

After brain-death certification, her family expressed the wish for organ donation, so a thorough clinical evaluation was performed to determine her eligibility. Microbiological cultures from CSF samples taken when EVD was placed became positive on day 13 with *Actinomyces israelii* and *Fusobacterium nucleatum* isolation. Thoracic and abdominal CT scan ruled out extra CNS involvement. Blood, respiratory, and urinary cultures were all reported as negative.

Multiple organ procurement and donation of the heart, liver, kidneys, and corneas was performed. Her lungs were discarded owing to the observation of a sub-segmental thromboembolism during the extraction procedure. Organs were allocated to three different transplantation centers around the country. A complete post-mortem study was performed after the retrieval process. No extracranial signs of actinomycosis were found. The brain presented edematous changes in convexity and a thick basal purulent exudate encompassing brainstem, cranial nerves, and basilar artery, extending into the basal surface of cerebellum (Figure 2A). A thick yellowish material occupied the subdural spinal space (with a maximal thickness of 0.8 cm), reaching cauda equina (Figure 2B and 2C). On coronal sections, ventricular lining and choroid plexus appeared friable. Microscopic study revealed a dense neutrophilic infiltrate occupying the subarachnoid space (spinal, infra-, and supratentorial), intraventricular space and choroid plexus, and focally invading brain parenchyma. Isolated branching, filamentous, basophilic microorganisms silver-methenamine positive, consistent with *Actinomyces* were found mixed with the inflammatory infiltrate (Figure 2D and E).

2.2 Recipients

2.2.1 Heart

A 67-year-old male underwent heart transplantation owing to end-stage ischemic cardiomyopathy. He presented in cardiorespiratory arrest 7 years ago requiring an automatic implantable cardioverter defibrillator and he had experienced progressive worsening of cardiac functional parameters. A decision was therefore made to list the patient for heart transplantation as the only life-saving option. The immediate

postoperative course was favorable, allowing extubation on postoperative day (POD) 2. Immunosuppression, antimicrobial prophylaxis, and outcome are listed on Table 1. The patient was discharged from hospital at day 15 post transplantation.

2.2.2 Right kidney

The right kidney recipient was a 36-year-old male diagnosed with chronic kidney failure owing to focal segmental glomerulosclerosis. He had already received two kidney transplantation (in 1995 and 2000), but had lost both grafts because of recurrence of his underlying disease. He received anti-thymocyte globulins pretransplantation protocol and nonetheless, being a hypersensitized recipient (>98% CPRA), he required hemodialysis as well as treatment with rituximab on two occasions and a total of 5 plasmapheresis sessions owing to the development of delayed graft function. Immunosuppression, antimicrobial prophylaxis and outcome are listed on Table 1.

On POD 20, the patient presented with a generalized seizure episode. A cranial CT scan revealed small hypodensities in the cortico-subcortical region and no occlusion in any of the extra or intracranial vascular territories. A posterior cranial MRI revealed findings compatible with a tacrolimus-induced posterior reversible encephalopathy syndrome. On POD 35, the patient returned to the operating room for perigraft hematoma drainage and cleaning of his surgical wound. He again received ceftriaxone (2 g every 24 hours) for 10 days. Blood, urine, and wound-drainage cultures were informed as sterile.

2.2.3 Left kidney

A 41-year-old male underwent left kidney transplantation because of end-stage kidney disease caused by nephroangiosclerosis. He had received hemodialysis for 3 years. Immunosuppression, antimicrobial prophylaxis, and outcome are listed in Table 1. Patient was discharged from hospital at POD 8.

2.3.4 Liver

The liver transplant recipient was a 64-year-old male diagnosed with alcoholic liver cirrhosis in 2014. Radiofrequency ablation of an uninodular hepatocarcinoma before transplantation was performed. Immunosuppression, antimicrobial prophylaxis, and outcome are listed on Table 1. An episode of acute leukopenia and low platelet count occurred, that normalized after the withdrawal of amoxicillin. The patient was discharged on POD 7 with no further complications.

All recipients were informed of donor infection, and were successfully discharged from hospital. After 6 months' follow-up, none of them had any sign of infection caused by *A. israelii* or graft dysfunction.

3 DISCUSSION

This is, to our knowledge, the first reported brain-death case of CNS infection caused by *A. israelii* that resulted in a multiple organ donor with successful outcome in all organ recipients. Several reports[1,7-10] conclude that patients dying from documented or presumed meningitis have become successful donors. Most of them had meningitis due to common pathogens such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, or *Haemophilus*

influenzae. Current recommendations on donation[2,3,15] and maintenance of the potential donor in the ICU[11] state that patients with bacterial meningitis are suitable organ donors, provided they have received appropriate therapy. No consensus exists on treatment duration before organ procurement, but several authors have suggested that 24-48 hours might be enough. The organ recipient should be treated with a similar antibiotic regimen for 5-10 days. [2,3] In such cases no transmission of infection has been reported. When assessed, no differences were seen in recipient or graft survival rates between patients receiving organs from meningitis donors vs non-infected ones, and no pathogens were observed in recipients.[1,9]

A different scenario may occur with CNS infection caused by highly virulent or intracellular organisms such as *Cryptococcus neoformans*, *Listeria monocytogenes*, and *Mycobacterium tuberculosis.* These pathogens require longer treatments and their presence has been associated with higher risk of transmission.[12,13] Most of the post-transplant conditions have been associated with pathogens with no known effective treatment, like lymphocytic choriomeningitis virus (LCMV), *Ballamuthia,* or rabies, so great caution should be exercised in accepting donors with meningoencephalitis of unknown cause. Meningitis caused by these microorganisms is still considered an absolute contraindication by many transplant centers.

A. israelii is a microaerophilic gram-positive microorganism that normally colonizes the mouth, colon, and vagina, causing infection by disruption of the mucosa. Actinomycosis of the CNS is infrequent.[14] In the present case, *A. israelii* meningitis was not considered an absolute contraindication for transplantation, although information on donor-derived

infection of this infectious pathogen is non-existent. First, *Actinomyces* species are usually extremely susceptible to beta-lactams, especially penicillin G or amoxicillin, and also to doxycycline, ceftriaxone, and clindamycin. Our donor received treatment with meropenem over 48 hours. Second, transmission is more likely in case of disseminated infection. In our donor, cranial, cervical, thoracic, and abdomino-pelvic CT scan revealed no signs of actinomycosis outside the brain. In our case, the origin of meningitis was suspected to be the upper respiratory tract, as *Fusobacterium nucleatum* was also isolated from CSF, thus confirming that most actinomycotic infections are polymicrobial in nature depending on the site of infection.[14] The autopsy confirmed that actinomycosis was confined to the CNS. Third, actinomycosis is usually an indolent and slowly progressive infection and prolonged antimicrobial therapy along with debridement of infected tissue (whenever feasible) are the cornerstones of treatment.[14] All recipients received an appropriate antibiotic against *A. israelii*. It is unclear whether other bacteria frequently co-isolated, *F. nucleatum* in our case, require treatment. The type of antibiotic and treatment duration was at the discretion of each transplant team. In all recipients, treatment was prolonged for >2 weeks, amply exceeding the recommendation suggested by current guidelines. [2,3] Although autopsy results are rarely available in a timeframe useful for making decisions regarding organ donation, efficient communication of donor disease to all transplant teams helps to ensure appropriate postoperative antibiotic use and to avoid ruling out possible donors.

In summary, we present the successful outcome of multi-organ donation from a donor with brain death caused by *A. israelii* bacterial meningitis. However, caution should prevail when using donors with CNS infection of unknown cause.

Conflicts of interest:

The authors state that they have no conflicts of interest.

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FIGURE LEGENDS

FIGURE 1 Brain magnetic resonance image shows light thickness and leptomeningeal enhancement at brainstem associated with purulent intraventricular material compatible with meningitis complicated with ventriculitis and hydrocephalus

FIGURE 2 A. Basal view of the brain with a thick yellowish exudate located over brainstem and cerebellum, and extending into the subdural spinal space (B, C). On hematoxylin-eosin staining, isolated basophilic branching microorganisms were found (D), highlighted with silver-methenamine (E), 400x.

[Both figures are only 96 dpi]

TABLE 1 Organ recipient's immunosuppression, antimicrobial prophylaxis for *Actinomyces israelli* infection and duration and outcome characteristics.

Organ	Immunosuppression	Antibiotic prophylaxis	Outcome	Delayed graft dysfunction
Heart	Induction: Basiliximab, methylprednisolone Regimen: Tacrolimus, mycophenolate mofetil, and prednisone.	Ceftriaxone on POD 3 for 12 days. Doxycycline for 2 months.	Discharged on POD 15.	No
Right kidney	Induction: Anti-thymocyte globulin Regimen: Steroids, mycophenolic acid, and tacrolimus.	Ceftriaxone for 14 days.	Discharge from hospital.	No
Left kidney	Induction: Basiliximab Regimen: Tacrolimus, prednisone, and mycophenalte mofetil.	Ceftriaxone for 8 days followed by amoxicillin during 6 weeks.	Discharged on POD 8.	No
Liver	Regimen : Methylprednisolone and tacrolimus	Amoxicilin followed by doxycycline for 8 weeks.	Discharged on POD 7.	No

POD, postoperative day.