Donor-Derived *Candida dubliniensis* Resulting in Perigraft Abscesses in a Liver Transplant Recipient Proven by Whole Genome Sequencing: A Case Report

Y.E. Teh[a,*], M.L.T. Ang[b], M.V. La[c], V. Gunalan[d], C.K. Tan[e], A.L. Tan[f], R.T.P. Lin[b,i], T.T. Tan[a], P.R. Jeyaraj[g], S. Cumaraswamy[h], and B.H. Tan[a]

[a]Department of Infectious Diseases, Singapore General Hospital, [b]National Public Health Laboratory, Ministry of Health, Singapore; [c]Department of Laboratory Medicine, Changi General Hospital, [d]Bioinformatics Institute, Agency for Science, Technology and Research, [e]Department of Gastroenterology and Hepatology, Singapore General Hospital, [f]Department of Microbiology, Singapore General Hospital, [g]Department of Hepato-pancreato-biliary and Transplant Surgery, Singapore General Hospital, Singapore; [h]Heart and Lung Transplant Unit, Department of Cardiothoracic Surgery, National Heart Centre Singapore, Singapore; and [i]Department of Laboratory Medicine, National University Hospital, Singapore

ABSTRACT

Background. The transmission of fungi via transplant, although well-known, has not often been molecularly proven. We describe a case of donor-derived candidiasis verified by whole genome sequencing.

Case Description. The multiorgan donor was a 42-year-old woman with subdural hemorrhage. Procurement of the thoracic organs was performed followed by the abdominal organs. Tissue from the left bronchus grew *Candida dubliniensis*. The liver recipient was a 63-year-old woman with cryptogenic liver cirrhosis. She was noted to have worsening leukocytosis on postoperative day (POD) 9. Computed tomography of the abdomen and pelvis showed multiple rim-enhancing collections around the graft. Percutaneous drainage was performed. Fluid cultures grew *C dubliniensis*. *C dubliniensis* isolated from the donor's left bronchus and the liver recipient's abscesses were verified to be related by whole genome sequencing. We postulate that *C dubliniensis* colonizing the donor's transected trachea could have contaminated the inferior vena cava when the former was left open after explant of the donor's lungs. A portion of the donor's contaminated inferior vena cava was transplanted along with the liver graft, resulting in the infected collections in the recipient.

Conclusions. Our case report highlights the importance of maintaining a sterile field during organ procurement, especially in a multiorgan donor whose organs are explanted in succession.

DONOR-DERIVED fungal infections have been described in solid organ transplant recipients and are associated with significant morbidity and mortality [1,2]. Donor-derived candidiasis has been reported in kidney transplant recipients where contamination of the preservation fluid was a commonly proposed source [3,4]. In liver transplant recipients, fungal infections are not uncommon, but the source of donor-derived fungal infections is relatively less explored.

We describe a case of donor-derived Candidiasis proven by whole genome sequencing (WGS). The multiorgan donor had *Candida dubliniensis* isolated from tissue of the left bronchus with no evidence of invasive candidiasis. The liver recipient subsequently developed multiple abscesses at the vena cava anastomotic site and around the liver graft from

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

*Address correspondence to Yii Ean Teh, Department of Infectious Diseases, Singapore General Hospital, Singapore; Academia, Level 3, 20 College Road, Singapore 169856. E-mail: teh.yii.ean@singhealth.com.sg

0041-1345/18
https://doi.org/10.1016/j.transproceed.2018.01.017

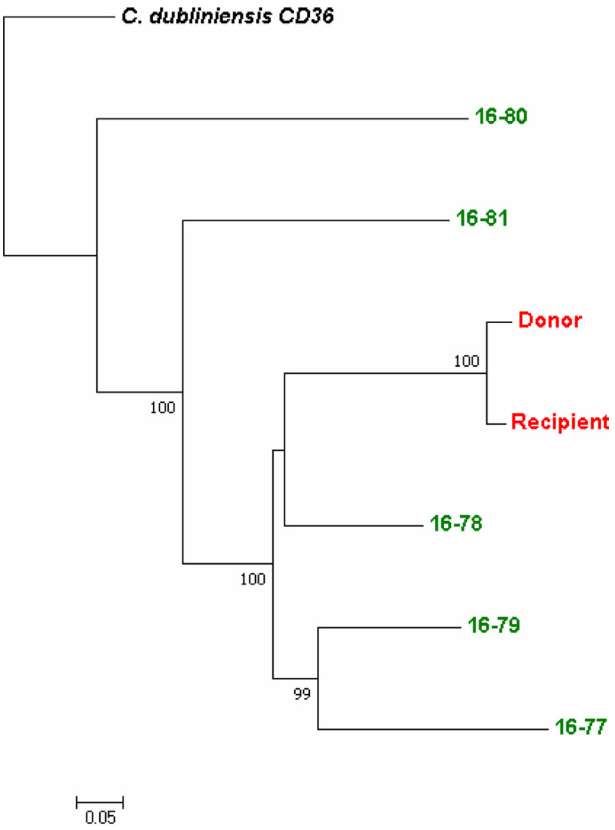

Fig 1. Genetic relations among 8 whole genome sequences of *Candida dubliniensis* inferred using the maximum likelihood method based on the general time reversible model. The publicly available *C dubliniensis* CD36 genome (Genbank assembly accession number GCA_000026945.1) was used as a reference to identify single nucleotide polymorphisms in sequenced isolates. The tree with the highest log likelihood (-77755.080) is shown. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. All positions containing gaps and missing data were eliminated. There were a total of 11,718 positions in the final dataset. Numbers next to branches show bootstrap values calculated using 1000 reiterations. Donor and recipient isolates are highlighted in red. Evolutionary analyses were conducted in MEGA7. Displayed tree is rooted at the reference genome, *C dubliniensis* CD36.

which *C dubliniensis* was isolated. The heart and the kidney recipients did not develop infective complications with *C dubliniensis*.

CASE REPORT

The Donor

A 42-year-old Chinese woman with asthma was admitted for left subdural hemorrhage and underwent craniectomy and clot evacuation. She was afebrile throughout the admission and did not receive antibiotics during her hospitalization. She was pronounced brain dead after being in the intensive care unit for 8 days. Blood cultures showed no bacterial or fungal growth. She was accepted for multiorgan donation and her organs, including the liver, lungs, kidneys, and heart, were procured. The thoracic organs were recovered first, followed by the abdominal organs. Bronchoalveolar lavage was performed as a part of the lung procurement protocol and this was negative for bacteria and mycobacteria culture. However, this later grew *Candida* species. A cuff of the left bronchus was also sent for culture and *C dubliniensis* was grown after 5 days.

The Liver Recipient

The liver recipient was a 63-year-old Chinese woman with Child's class C cryptogenic liver cirrhosis and a Model for End-stage Liver Disease score of 14, who was admitted to our center for elective liver transplantation. The donor and the liver recipient were admitted to different centers. Other medical history included hypertension, hyperlipidemia, and hypothyroidism secondary to pituitary adenoma and apoplexy. She required 12.4 L of blood products intraoperatively. Immunosuppressive treatment included basiliximab, corticosteroids, mycophenolate mofetil, and delayed initiation of tacrolimus.

She was extubated and weaned off inotropes on POD 1. She did not receive antifungal prophylaxis postoperatively. A routine Doppler ultrasound examination of the liver showed patent liver graft inflow and outflow vessels and an anechoic fluid collection, $4.1 \times 3.8 \times 1.2$ cm, around segment VI of the liver. She had a fever of 38.1°C on POD1 and was started on intravenous piperacillin-tazobactam and vancomycin. She was otherwise asymptomatic. Blood and urine cultures were negative for bacteria and fungi and she remained afebrile for the next 5 days. Antibiotics were switched to ciprofloxacin and she completed a 1-week course.

She was noted to have worsening leukocytosis with a white cell count of 17.24×10^9/L on POD 9. A computed tomography scan of the abdomen and pelvis showed multiple locules of fluid around the graft. Of significance, there were 2 rim-enhancing collections measuring $8.7 \times 5.2 \times 7.2$ cm and $6.7 \times 2.8 \times 5.2$ cm adjacent to the cava anastomosis and segments VI and VII of the liver, respectively. Both contained a small amount of gas. She was started on meropenem and anidulafungin, and percutaneous drainage of these collections was performed. Fluid cultures grew *C dubliniensis* with fluconazole minimal inhibitory concentration of 0.25 μg/mL and caspofungin minimal inhibitory concentration of 0.06 μg/mL. She received 17 days of anidulafungin and 9 days of meropenem. Repeat imaging showed an interval decrease in size of the collections. She was switched to oral fluconazole 400 mg in the morning and oral levofloxacin 500 mg in the morning, and was discharged on POD 30 with continuation of antimicrobials.

The *C dubliniensis* isolated from the donor bronchus and the recipient pericaval abscesses were verified to be related by WGS via 2 disparate single nucleotide polymorphism (SNP) calling pipelines. Phylogenetic analyses of both genome-wide concatenated SNP calls and individual chromosome-based alignment were performed using Maximum Likelihood in MEGA7. Maximum likelihood trees inferred from both pipelines suggest that both isolates are related in comparison to other epidemiologically unrelated *C dubliniensis* strains.

A check with our microbiology department and with the microbiology department of the donor hospital did not reveal an increase in *C dubliniensis* isolates around the time of the liver recipient's transplant.

Other Recipients

The lung recipient was started on oral voriconazole posttransplant because *Aspergillus nidulans* was isolated from culture of a cuff from bronchus from the explant. He did not develop invasive candidiasis.