Case report

Fatal case of donor-derived colistin-resistant carbapenemase-producing Klebsiella pneumoniae transmission in cardiac transplantation

Lisia Miglioli Galvão a, Anna Paula Romero de Oliveira a, Aline Santos Ibanês a, Jussimara Monteiro b, Fernanda Inoue b, Daniel Chagas Dantas c, Flavio Sanchez c, Daniel Wagner Santos d, Cely Saad Abboud a,∗

a Instituto Dante Pazzanese de Cardiologia, Divisão de Doenças Infecciosas, São Paulo, SP, Brazil
b Associação Fundo de Incentivo a Pesquisa – AFIP, Departamento de Pesquisa e Desenvolvimento, São Paulo, SP, Brazil
c Instituto Dante Pazzanese de Cardiologia, Divisão de Transplante de Coração, São Paulo, SP, Brazil
d Hospital do Rim – Universidade Federal de São Paulo, Divisão de Doenças Infecciosas, São Paulo, SP, Brazil

ARTICLE INFO

Article history:
Received 24 January 2018
Accepted 20 April 2018
Available online 26 May 2018

Keywords:
Cardiac transplantation
Klebsiella pneumoniae
Donor-derived infection
Carbapenem-resistant

ABSTRACT

Herein we report a fatal case of donor-derived transmission of XDR-resistant carbapenemase-producing Klebsiella pneumoniae (KPC-Kp) in cardiac transplantation. A 59-year-old male patient with non-obstructive hypertrophic cardiomyopathy underwent heart transplantation. On day 5 post-operation, blood cultures from the donor were positive for colistin-resistant carbapenemase-producing K. pneumoniae (ColR KPC-Kp) susceptible only to amikacin. Recipient blood cultures were also positive for ColR KPC-Kp with the same sensitivity profile as the donor isolate with an identical PFGE pattern. The patient was treated with double-carbapenems and amikacin. The patient evolved to pericarditis, osteomyelitis, and pulmonary necrosis, all fragment cultures positive for the same agent. The patient developed septic shock, multiple organ failure and died on day 50 post-transplantation. Based on current microbiological scenario worldwide the possibility of transmitting multidrug resistant (MDR) organisms should be considered.

© 2018 Sociedade Brasileira de Infectologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Multidrug-resistant Gram-negative bacterial infections in solid organ transplantation have been increasingly recognized in the past decade.1 Most recently, XDR-resistant carbapenemase-producing Klebsiella pneumoniae (KPC-Kp) infection has emerged as a significant healthcare challenge, especially considering that few antibiotics are effective to treat it.1 The incidence of donor-derived transmission of infections is <1% in solid organ transplants (SOTs), with morbidity and mortality rates of 40%.2 This case report aims to address the challenges involved in prevention, detection and management of donor-derived infection by MDR organisms.
Case report

A 59-year-old male patient with non-obstructive hypertrophic cardiomyopathy was hospitalized to manage cardiac insufficiency with inotropic therapy. The worsening of his clinical picture required the use of an intra-aortic balloon, and he was prioritized for cardiac transplantation. During the pre-transplant period, the patient did not develop any infectious complications. Blood cultures collected 24 and 48 h before transplantation were negative.

The patient underwent bivacal–bipulmonary heart transplantation, which required another surgery in the first 24 h to resolve hemostasis. He remained under mechanical ventilation with the use of vasoactive drugs and an intra-aortic balloon for 48 h, maintaining a good clinical condition. The immunosuppressive regimen included mycophenolate mofetil, cyclosporine and prednisone. On day 3 post-operation, a blood culture from the donor was positive for Gram-negative bacilli. As the donor was receiving piperacillin–tazobactam at the time of transplantation, the same drug was administered to the recipient. Although the recipient was clinically stable without signs of infection, blood cultures and surveillance cultures (from the groin and rectal areas) were collected. On day 5 post-operation, the final identification turned out CoR KPC-Kp.

Blood cultures from the recipient were positive for CoR KPC-Kp on day 7 post-operation with the same sensitivity profile as the donor isolate. The surveillance cultures were negative. At this time, the recipient was afebrile and hemodynamically stable, presenting with 26,000 cells/mm³ leukocyte count and 6.5 mg/dL C-reactive protein (CRP) levels. Double-carbapenems (meropenem 2 g/8 h in a 4-h infusion combined with ertapenem 1 g/day, 1 h before one of the meropenem doses) and amikacin (15 mg/kg once a day) was started. The patient developed pericarditis on day 9 post-operation and required the drainage of 1000 mL of exudate; his pericardial fluid cultures were positive for CoR KPC-Kp. The patient underwent a surgical approach to clean the pericardium, requiring a repeated surgery eight days later; a sternum bone fragment collected at this time was positive for CoR KPC-Kp. On day 37 post-operation, he presented with worsening respiratory signs with chest computed tomography exhibiting consolidation with lung fluid levels suggestive of pulmonary cavitation due to necrosis (Fig. 1). This diagnosis was confirmed by histopathology of lung fragments obtained from lobectomy, in which a pulmonary abscess with liquefactive necrosis and necrotizing arteritis were noted. The patient developed septic shock, and antibiotic coverage was extended to linezolid and fluconazole while maintaining the initial treatment regimen for CoR KPC-Kp (double-carbapenem and amikacin). The patient progressed to multiple organ failure and died on day 50 post-transplantation.

The donor and other recipients

The donor was a 17-year-old male who died from traumatic brain injury after being hospitalized in the intensive care unit (ICU) for seven days having received piperacillin/tazobactam and vancomycin for two days. His blood cultures and surveillance cultures were negative at the time of donation. The culture that was positive for CoR KPC-Kp was collected from the splenic artery at the time of organ removal. The recipients of other organs (two kidneys) did not present any infectious complications or positive cultures and did not receive specific antimicrobial treatment. The liver was not used for transplantation.

Microbiological aspects

Bacterial identification was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS) technology, using Vitek MS® system (bioMerieux, Marcy-l’Étoile, France), and the antimicrobial susceptibility profile was determined using the Vitek® 2 system (bioMerieux). The minimum inhibitory concentration (MIC) for polymyxin B was defined by broth microdilution (Probac, Brazil). The two strains evaluated (donor and recipient) exhibited high levels of resistance to cefepime, cefoxitin, ceftazidime, ceftriaxone (MIC ≥ 64 μg/mL), ertapenem (MIC ≥ 8 μg/mL), imipenem (MIC ≥ 8 μg/mL), meropenem (MIC ≥ 16 μg/mL), ciprofloxacin (MIC, ≥4 μg/mL), gentamicin (MIC ≥ 16 μg/mL), and tigecycline (MIC, 4 μg/mL) following the breakpoints established by CLSI, 2016. Resistance to polymyxin B (MIC, ≥64 μg/mL) was established using the EUCAST breakpoint, 2017. Ampicillin was the only susceptible drug (MIC, 4 μg/mL). The presence of the blaKPC resistance gene was detected in all strains evaluated, and the molecular gene identification using Sanger sequencing exhibited 100% homology with the enzyme KPC-2. The genetic similarity between strains was established by pulsed field gel electrophoresis (PFGE) using the SpeI restriction endonuclease, demonstrating an identical PFGE pattern (Pattern A) between the donor and recipient strain (Fig. 2). Multilocus sequence typing (MLST) analysis also identified the same sequence type (ST 437) from the donor and the recipient strains, and eBURST analysis (http://eburst.mlst.net) revealed that ST 437 belonged to clonal complex CC 258.
Discussion

To date, this is the first report of donor-derived transmission of XDR-resistant KPC-Kp in cardiac transplantation. Based on the categorization suggested by Garzoni and Ison, this case reports a proven transmission of infection by a donor with a fatal outcome. The strains isolated from the recipient and donor exhibited a unique PFGE pattern and the same sequence type (ST 437). Both strains were isolated and identified early in the post-transplant period without any clinical or microbiological evidence of infection in the recipient during the pre-transplant period. The agent was identified using traditional culturing methods following organ acceptance, with no possibilities for directed prophylaxis and adequate early treatment that could have contributed to a favorable outcome.

The incidence of donor-derived transmission of infections is <1% in solid organ transplants (SOTs), with morbidity and mortality rates of 40%. There are infection screening protocols for donors to reduce the risk of transmission. Requesting blood and urine cultures from donors hospitalized for more than 72 h is suggested. However, with the increased prevalence of multidrug-resistant organisms (MDROs) the transmission of MDROs has increased. The amount of time required by traditional sample collection methods to the final results, including the susceptibility profile, can range from 48 to 120 h, depending on detection time and the need for additional resistance testing. This delay is a matter of concern, affecting the time of introduction of proper antimicrobial therapy. Studies demonstrate that the mortality rate for KPC infections in SOTs is between 40 and 71%. Therefore, surveillance swab samples and cultures (blood cultures, urine cultures and tracheal secretions) are suggested for the rapid identification of resistance genes in hospitals with an epidemiological history of these agents. Communication delays are another contributing factor for the transmission of infection, fast and effective communication between Organ Procurement Organizations (OPOs) and transplant centers is highly important and should occur within 24 h.

Due to organ shortages, the use of donor organs known to be infected has been discussed. Accepting more borderline donors has been proposed, including those with bacteremia. Data indicate that 5% of donors have bacteremia at the time of donation; fever in the last 24 h is predictive of this situation. Studies have demonstrated that bacteremia due to Gram-negative bacilli has an increased risk of transmission and worse outcomes compared with Gram-positive bacteria. Ideally, the donor should already be on appropriate treatment for at least 24–48 h prior to donation with some degree of clinical response, and treatment for the recipient should be maintained for 7–14 days. However, the use of donor organs with multidrug resistant (MDR) bacterial infections is a major problem. Studies have proposed the donation of all organs from colonized donors and the use of prophylaxis directed at the recipient. These studies suggest that lungs and kidneys should be rejected if tracheal secretion and urinary cultures are positive, and all organs should be rejected if the blood cultures are positive. However, a risk-benefit analysis should always be performed that also considers the risk of death of those on the transplant waiting list. Ariza-Heredia et al. reported on four recipients from a donor with KPC-Kp meningitis but negative blood cultures. The recipients received adequate prophylaxis and exhibited good progression after transplantation. The authors demonstrated the possibility of using organs from donors with MDR infections with rapid communication between centers to allow for preventive measures and adequate treatment for the recipients.

It is intriguing that kidney recipients did not develop infection. Berenger et al. studied the risk factors for nosocomial bloodstream infections in SOT and found a reduced incidence in kidney compared to heart recipients (0.54 vs. 1.5/100 patient-years). However, Yeşilkaya et al. reported similar rates of bloodstream infections in heart and kidney transplantation patients. The reasons behind this finding are complex and not fully understood yet.

Our patient progressed with hematogenous dissemination of ColR KPC-Kp; he displayed pericardial and bone (sternal) involvement and necrotizing pneumonia. However, he did not initially exhibit signs and symptoms of infection, likely due to immunosuppression. Treatment with double-carbapenems and amikacin (the only susceptible drug in the antibiogram) was not effective in controlling the spread of infection probably because of the low effectiveness of the regimen and late treatment initiation, since the donor was not known to be infected. The choice of
antimicrobial regimen was based on the lack of therapeu-
tic options for the treatment of CoR KPC-Kp given that 
new therapeutic options, such as ceftazidime-avibactam 
and meropenem–vaborbactam, are not available in Brazil. 
This regimen was successfully used in one kidney transplantation 
despite meropenem MIC ≥ 16 μg/mL. Infection/colonization 
by CoR KPC-Kp susceptible only to amikacin should be a rele-
vant factor when considering organ acceptability. A 2015 study 
reported a 51% mortality rate at 30 days for CoR KPC-Kp blood-
stream infections.

Conclusion

Despite screening policies, the possibility of donor-derived 
infection exists. This case brings up many challenges that 
contributed to a fatal outcome such as gaps in screening 
tools, delay in laboratory identification by traditional culture 
methods, lack of therapeutic options and associated immuno-
suppression.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Simkins J, Muggia V, Cohen HW, Minamoto GY. 
Carbapenem-resistant Klebsiella pneumoniae infections in 
kidney transplant recipients: a case-control study. Transpl 
Infect Dis. 2014;16:775–82.
2. Ison MG, Hager J, Blumberg E, et al. Donor-derived disease 
transmission events in the United States: data reviewed by 
the OPTN/UNOS Disease Transmission Advisory Committee. 
3. Clinical and Laboratory Standards Institute. Performance 
standards for antimicrobial susceptibility testing: 
twenty-sixth informational supplement. Wayne (PA): CLSI; 
2016 [document M100-S26].
4. European Committee on Antimicrobial Susceptibility Testing. 
Breakpoint tables for interpretation of MICs and zone 
Rapid detection of carbapenemase genes by multiplex 
6. Garzoni C, Ison MG. Uniform definitions for donor-derived 
infectious disease transmissions in solid organ 
7. Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D, 
et al. Infection with Klebsiella pneumoniae carbapenemase 
(KPC)-producing K. pneumoniae in solid organ transplantation. 
transplantation using organs from donors infected or 
colonized with carbapenem-resistant Gram-negative 
donor; potential pitfalls. J Heart Lung Transplant. 
12. Len O, Garzoni C, Lumberas C, et al., ESCMID Study Group of 
Infection in Compromised Hosts. Recommendations for 
screening of donor and recipient prior to solid organ 
transplantation and to minimize transmission of 
7:10–8.
The utilization of solid organs for transplantation in the 
setting of infection with multidrug-resistant organisms: an 
transplantation using organs from a donor infected with 
Klebsiella pneumoniae carbapenemase (KPC)-producing K. 
15. Berenger BM, Doucette K, Smith SW. Epidemiology and risk 
factors for nosocomial bloodstream infections in solid organ 
transplants over a 10-year period. Transpl Infect Dis. 
2016;18:183–90.
16. Yeşilkaya A, Azap OK, Demirkaya MH, Ok MA, Arslan H, 
Akdur A. Bloodstream infections among solid organ 
transplant recipients: eight years’ experience from a Turkish 
17. Oliva A, Gizzi F, Mascellino MT, et al. Bactericidal and 
synergistic activity of double-carbapenem regimen for 
infections caused by carbapenemase-producing Klebsiella 
due to KPC-producer E. coli in a renal transplant recipient 
treated with the double-carbapenem regimen and analysis of 
2016;95:e2243.
(Italian Study Group on Resistant Infections of the Societa 
Italiana Terapia Antinfettiva). Risk factors for bloodstream 
infections due to colistin-resistant KPC-producing Klebsiella 
pneumoniae: results from a multicenter case-control-control 