Multidrug-resistant Combined Infections in a Liver Transplanted Patient: Case Report

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Abstract

We report a case of successfully treated multiple liver abscesses in a liver-transplanted patient, sustained by combined multidrug-resistant infections. Two months after a liver transplant, a computed tomography scan revealed the presence of multiple abscesses in the liver graft. Blood cultures and abscessual liver fluid were both positive for acquired colistin- and carbapenem-resistant Klebsiella pneumoniae and an extended-spectrum of beta-lactamases–producing Enterobacter aerogenes. The treatment strategy consisted of different prolonged antimicrobial combinations and draining of the abscesses with complete recovery of the liver lesions.

Key words: Liver abscess, Carbapenem-resistant infection, Beta-lactamases-producing Enterobacter aerogenes, Klebsiella pneumonia, Liver transplant

Introduction

Multidrug-resistant (MDR) organisms have important clinical implications and are major problems in liver transplant recipients. Options for treating patients with these infections are often extremely limited with poor clinical outcomes. In the field of solid-organ transplant, gram-negative rods have always represented important pathogens for hospital-acquired infections. These conditions usually are associated with increased mortality, length of hospital stay, admission to the internal care unit, surgical procedures, and costs, when compared with a matched hospital population. The expression of MDR (or pandrug resistance) constitutes an additional concern regarding those bacteria.1,2 Therefore, the risk of combined MDR-infection may become a further serious and life-threatening problem with poor outcomes.

In the absence of a standardized treatment protocol, we report the case of multiple liver abscesses sustained by simultaneous MDR gram-negative infections sustained by a colistin- and carbapenem-resistant Klebsiella pneumoniae and an extended-spectrum of β-lactamase (ESBL)-producing Enterobacter aerogenes. Carbapenem-resistant Klebsiella pneumonia (KP) represents a worrisome cause of nosocomial infection with reported bloodstream infections accounting for 19% to 30% of all major infections after liver transplant and a mortality rate approaching 36% for these patients.3,4 Also, the prevalence of ESBL Enterobacter aerogenes has been steadily increasing during the past 10 to 15 years as part of a global pandemic. Extended-spectrum of β-lactamase producers frequently express coresistance to other important antimicrobial drug classes, limiting therapeutic options. Only a few detailed studies regarding combined MDR infection have been conducted for the liver transplanted population.5,6 The coexistence of different MDR infections represents a rare and unfortunate event. We report the case of successfully treated multiple liver abscesses in a liver-transplanted patient, sustained by different MDR infections, with the final complete recovery.

Case Report

A 65-year-old woman was referred to our transplant center for alcohol-related cirrhosis. The patient had no significant medical background, except for
chronic renal failure; pretransplant standard cultures from intranasal and rectal swab were negative. No infections resulted in the surveillance cultures collected from the donor. The early postoperative course after the liver transplant was characterized by a biliary anastomotic fistula and consequent choleperitoneum. For this reason, on postoperative course day 16, the patient underwent surgery, and a hepaticojjunostomy was performed. Peritoneal fluid, collected during surgery, tested positive for Enterobacter aerogenes and KP, both producing ESBL, and an ampicillin- and gentamicin-resistant Enterococcus faecium. The last one also was isolated from blood cultures and surgical wound swabs. The antibiotic therapy was modified from penicillin to a combination of teicoplanin and meropenem. The postoperative course was uneventful and the patient gradually improved.

Surveillance cultures collected from rectal swabs confirmed an ESBL-producing Enterobacter aerogenes (day 13); a resistant colistin- and carbapenem-resistant Klebsiella pneumoniae (intermediate sensitivity to gentamycin and tigecycline, but resistant to quinolones, phosphomycin, carbapenem, cephalosporin, and colistin) was also isolated from the rectal swab. The patient was getting better, judged to be colonized by a carbapenem-resistant Klebsiella pneumoniae in the gastrointestinal tract, and placed on contact and droplet precautions. Despite this colonization, she was doing well and then discharged home.

Two months later, the patient presented for the abrupt onset of chills and fever with increased serum creatinine (322 mmol/L) and elevated C reactive protein (162 mg/L) and procalcitonin (2.6 ng/dL). A computed tomography scan revealed the presence of multiple liver abscesses in the liver graft at both lobes, the bigger one at segment 8 (maximum diameter 3.5 cm) (Figure 1 A, B). Teicoplanin, anidulafungin, and meropenem were initially started as empiric therapy with a weaning of the immunosuppressive therapy. Blood cultures and fluid samples of the liver abscesses collected after admission were positive for ESBL Enterobacter aerogenes and colistin- and carbapenem-resistant Klebsiella pneumoniae. The antimicrobial therapy then was adjusted by starting tigecycline and gentamicin with a high dose of meropenem.

A control computed tomography scan performed on day 17 showed an enlargement and confluence of the lesions. The lack of clinical improvement and the radiologic worsening, imposed to proceed with the drainage of the liver lesions by a percutaneous route. After the drainage, the patient started improving and became apyretic on day 21. An additional computed tomography scan (day 32) revealed a reduction of the liver lesions. A week later, a positron emission tomography–computed tomography scan confirmed the reduction of the abscesses. Our concern about the risk of a progressive renal impairment made us modify the antimicrobial therapy by stopping gentamicin, adding ertapenem (1000 mg) to meropenem, and increasing the dosage of tigecycline (100 mg every 12 hours). The new treatment was well tolerated, and no adverse events were noted. Further positron emission tomography–computed tomography scan revealed a progressive response with only residual activity (Figure 2 A, B). The therapy for
carbapenem-resistant *Klebsiella pneumoniae* was stopped (84 overall days), and the patient was discharged. The patient’s hospital stay was without any other complications; an abdominal ultrasound 1 month later showed the complete recovery of the liver lesions. At the moment the patient is still in good condition; we keep monitoring the patient with rectal and throat swabs that are still negative.

### Discussion

In the field of solid-organ transplant, gram-negative rods always have represented an important pathogen for hospital-acquired infections. These conditions usually are associated with increased mortality, length of hospital stay, admission to the internal care unit, surgical procedures, and costs when compared with a matched hospital population. In particular, KP represents one of the major causes of nosocomial bacterial infection, with reported bloodstream infections accounting for about 33% of all major infections in solid-organ transplant. Among liver transplant patients, the infection rate has even lead to a higher incidence, with 89% of colonized patients. Patel and associates confirmed in their series that an incidence of 41 out of 99 cases (41%) of carbapenem-resistant *Klebsiella pneumoniae* infection occurred in solid-organ transplant recipients, and Bergamasco and associates identified 35% of carbapenem-resistant *Klebsiella pneumoniae* infection cases in solid-organ transplant recipients.

Published data report a variable mortality rate, ranging from 44% to about 70%. Clinical data are available from only a limited number of case studies and reports, underscoring that the best approach for carbapenem-resistant *Klebsiella pneumoniae* antibiotic treatment has not been established. Our case was further complicated by the presence of a pandrug resistance due to colistin- and carbapenem-resistance of KP, associated with an ESBL-producing *Enterobacter aerogenes* infection. Bacteria-producing ESBL should be considered resistant to all generations of cephalosporins, all penicillins, and to the monobactams such as aztreonam, even if the in vitro susceptibilities are in the sensitive range according to the Clinical and Laboratory Standards Institute breakpoints.

Experience demonstrated that the efficacy of currently available antibacterial agents is poor for MDR agents. The risk associated with the use of a single antibiotic potentially active against MDR infection is the development of resistance; their use is even limited by pharmacokinetics and toxicity profiles, which might lead to treatment discontinuation or failure. At the moment, the association of a combined antibiotic therapy represents an optimistic choice, because it may be related to a better outcome. In solid-organ transplant, the use of aminoglycosides is usually avoided because of renal toxicity; therefore, colistin alone or in combination with carbapenem or tigecycline represents the drug chosen to treat such patients. Only preliminary data exist suggesting that the combination therapy with colistin and tigecycline could be effective. Some clinical reports suggested reasonable success rates with double-carbapenem combinations, even though resistant. The concomitant use of ertapenem and another carbapenem is based on the higher affinity of
carbapenemases for ertapenem, which could consume the enzymes, leaving a higher concentration of the other carbapenem to exert its antimicrobial activity. Fosfomycin also could have a place in the therapy: in a multicentre study of all consecutive patients (not solid-organ transplant) with extensive MDR.

Development of resistance during therapy did not occur frequently; however, the necessity of combination with other antibiotics requires further investigation. In our case, the treatment was predominately based on tigecycline and double-carbapenem combination therapy. Although not indicated specifically for Enterobacter or bloodstream infections, tigecycline has excellent in vitro activity against these gram-negative bacilli.16,17

To the best of our knowledge, this is the first study specifically describing a case of a multiple liver abscesses caused by a multiple MDR infection sustained by colistin-and carbapenem-resistant-Klebsiella pneumoniae and ESBL Enterobacter aerogenes in a liver transplant recipient who was successfully treated with a combination of surgical and medical treatment. Based on our experience, a well-designed, prospective cohort study would be valuable in determining surveillance strategies and exploring effective strategies for treating carbapenem-resistant Klebsiella pneumoniae infections. This report emphasizes the need to tailor the treatment in the setting of solid-organ transplant with therapeutic strategies based on synergy lab-tests, which characterized the mechanism of carbapenem resistance. This approach might permit to test early the effect of different combination therapy and to obtain a rationale drug association in the setting of a targeted therapy.

References