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CASE REPORT

A challenging case of carbapenemase-producing *Klebsiella pneumoniae* septic thrombophlebitis and right mural endocarditis successfully treated with ceftazidime/avibactam

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Abstract

Introduction The emergence of carbapenemase-producing Klebsiella pneumonia (KPC-Kp) has become a significant problem in terms of public health and clinical outcome in many hospitals in Southern Europe. Treatment options are usually limited and effective treatment of infections caused by these pathogens is a considerable challenge for clinicians. Ceftazidime–avibactam has been recently approved for the treatment of difficult-to-treat infections due to aerobic Gram-negative organisms in patients with limited treatment options.

Case report We reported the first case of KPC-Kp septic thrombophlebitis and right atrial endocarditis associated with metastatic lung abscesses successfully treated with a prolonged ceftazidime/avibactam plus ertapenem treatment course, suggesting that this combination therapy could be safe and effective for serious Gram-negative infections. Interestingly, we also observed an apparent discrepancy between clinical and microbiological courses: the patient became rapidly afebrile; hemodynamically stable and his procalcitonin levels showed a prompt decreasing trend. Nevertheless, blood cultures remained persistently positive for a prolonged period.

Conclusion In conclusion, ceftazidime–avibactam plus ertapenem was a safe and effective therapy of serious endovascular infection due to KPC-Kp. Moreover, in this setting, follow-up blood cultures might represent an irreplaceable tool to guide the therapy.

Keywords *Klebsiella pneumoniae* · Thrombophlebitis · Endocarditis · Ceftazidime–avibactam · Procalcitonin

Introduction

Gram-negative bacteria are an infrequent cause of infective endocarditis, accounting for the 1–3% of the etiologies according to the International Collaboration on Endocarditis Prospective Cohort Study and the Italian Endocarditis Study [1–3]. During the 1970s and 1980s, these infections were mostly community-acquired since that intravenous drug addiction represented the main risk factor for Gram-negative endocarditis (GNE) [3].

Currently GNE has been observed mainly among patients hospitalized or with healthcare contacts who undergo invasive procedures, implant of endovascular devices or are affected by comorbidities that are likely to increase the risk for Gram-negative bacteremia [3].

According to the ICE-PCS the overall in-hospital mortality rate for patients with non-HACEK GNB endocarditis is around 25%. However, recent reports describe trends towards multidrug resistance (MDR) among isolates of GNE with associated higher mortality rates [3, 4].

We here report a unique case of a trauma-patient with right mural endocarditis and central veins thrombophlebitis caused by *Klebsiella pneumoniae* carbapenemase producing *Klebsiella* (KPC-Kp) that was successfully treated with adoption of a prolonged ceftazidime-avibactam (CAZ/AVI) plus ertapenem treatment course.

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Case report

A 49-year-old man was admitted to intensive care unit (ICU) for chest trauma (he had been trampled by a bull). His medical history showed no previous infections and no comorbidities. On admission, he was neither conscious nor hemodynamically stable, and required vasopressors and mechanical ventilation. Lung high resolution computed tomography (HRTC) revealed the presence of multiple lung contusions, rib fractures and bilateral pneumothorax with hemothorax, so three pleural drainage tubes were positioned. On day 7, he developed fever (up to 38.7°C) and respiratory and hemodynamic failure. Lung HRTC revealed new parenchymal infilatrates, meanwhile bronchial aspirate cultures revealed growth of a KPC-Kp strain susceptible only to colistin (MIC < 0.5 µg/ml) according to Vitek 2 (Biomérieux) test. The presence of the *Klebsiella pneumoniae* carbapenemase gene was confirmed using the GeneXpert System (Cepheid) nucleic acid test. A diagnosis of KPC-Kp ventilator associated pneumonia (VAP) was made and the patient was started on a colistin (9 MU i.v. loading dose, followed by 4.5 MU i.v. q12h and 2MU aerosol q8h), tigecycline (150 mg i.v. loading dose, followed by 100 mg i.v. q12h) and meropenem (2 g extended infusion i.v. q8h) regimen. On day 10, he developed a severe *Clostridium difficile* infection, unresponsive to topical vancomycin (125 mg po q6h), that resolved with a 10-day fidaxomicin (200 mg po q12h) treatment course. On day 13, KPC-Kp breakthrough bacteremia developed and fosfomycin (8 g i.v. q8h) was added to therapy. As shown in Fig. 2, at the beginning of KPC-Kp bacteremia procalcitonin increased up to 4.6 ng/ml. On day 21 (10th day of treatment course), the patient was afebrile, hemodynamically stable without vasopressors with a significant clinical improvement, and procalcitonin levels decreased below 0.5 ng/ml. However, his blood cultures remained still positive. On day 28, CT scan detected new cavitary lung lesions. A transesophageal echocardiogram (TEE)

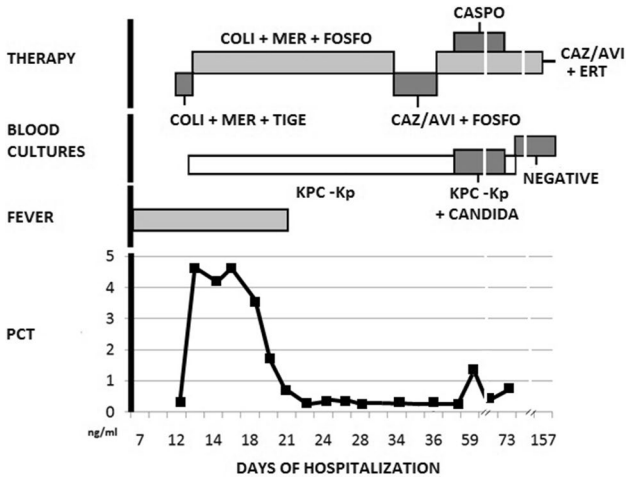

Fig. 2 Relationship between clinical and microbiological course. *COLI* colistin, *TIGE* tigecycline, MER meropenem, *FOSFO* fosfomycin *CAZ/AVI* ceftazidime/avibactam, *ERT* ertapenem, *CASPO* caspofungin

displayed 0.8 mm vegetation on the superior wall of the right atrium. There was no vegetation at any of the valves and no obvious abscess. CT angiography revealed jugular and superior cava veins thrombosis. Based on these data, a diagnosis of septic thrombophlebitis and right atrial mural endocarditis with secondary septic pulmonary embolism and abscesses was been established (Fig. 1).

Surgical debridement was not recommended and the patient was started on enoxaparin treatment. On day 33, blood cultures still yielded KPC-Kp. Disc diffusion susceptibility test revealed in vitro susceptibility of the KPC isolate to CAZ/AVI and a possible synergy effect of CAZ/AVI with ertapenem [5]. Thus, initial combination of CAZ/AVI (provided for compassionate use) and fosfomycin was modified to a combination of CAZ/AVI (2 g/500 mg i.v. q8h) and ertapenem (1 g i.v. q24h) since day 38 (Fig. 2). No adverse events developed during therapy and clinical conditions continued to improve. Except for a candidemia episode

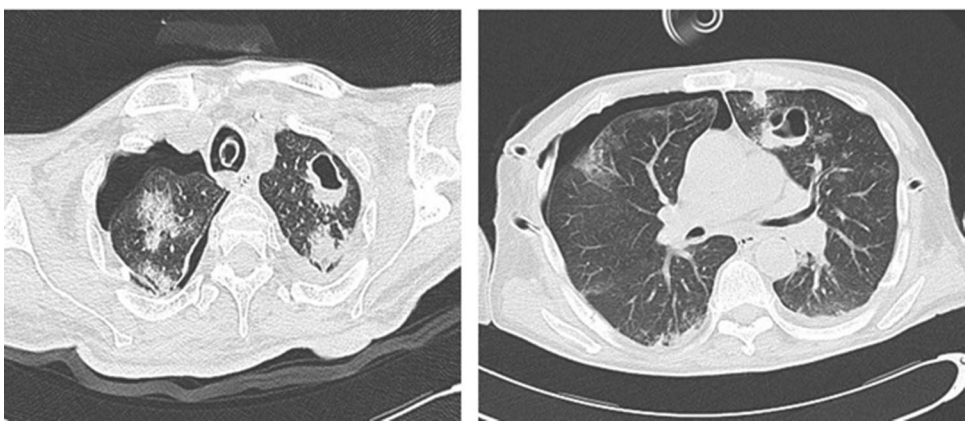

Fig. 1 Lung HRTC showing septic pulmonary embolism and pulmonary abscesses

successfully treated with a 14-day caspofungin treatment course, the patient remained afebrile with low procalcitonin levels. Nevertheless, blood cultures continued to be persistently positive until day 80. Subsequently, CT angiography and serial TEEs documented disappearance of both veins and atrial lesions. On day 157, the patient was discharged in good clinical conditions.

The patient resulted no sick at three follow up visits during a 5-month period of clinical observation. Eventually, the patient had a sudden death 6 months after hospital discharge. Close relatives denied any sign or symptom attributable to infection relapse.

Discussion

Nowadays, infections due to hospital-acquired MDR organisms are a major matter of concern for clinicians worldwide [6] being associated with increased short- and long-term mortality rates [7]. In particular, the emergence of KPC-Kp has become a significant problem in terms of public health and clinical outcome since these organism have been not only able to cause numerous infection outbreaks worldwide, but are now considered endemic in many hospitals in southern Europe.

Effective treatment of infections caused by these pathogens is thus a considerable challenge for clinicians [8, 9], and microbial stewardship is a crucial tool in limiting the spreading of the current epidemic [10, 11].

Treatment options are usually limited to colistin, gentamicin and/or tigecycline in association with a carbapenem [12], but the optimal regimen for infections caused by KPC-Kp has yet to defined.

CAZ/AVI consists of a combination of ceftazidime, a widely used expanded-spectrum anti-pseudomonal cephalosporin, and avibactam, a novel non-suicide non-β-lactam β-lactamase inhibitor that restore in vitro activity of ceftazidime against MDR Enterobacteriaceae and *P aeruginosa* by inhibiting class A (such as ESBLs, *Klebsiella pneumonia* carbapenemases), class C (AmpC), and some class D (eg, OXA 48) β-lactamases enzymes [13].

CAZ–AVI has been recently approved by European Medicines Agency (EMA) for the treatment of complicated urinary tract infections, nosocomial pneumonia including ventilator-associated pneumonia (VAP), complicated intra-abdominal infections and infections due to aerobic Gram-negative organisms in patients with limited treatment options. In clinical practice, it has been used with encouraging results in small series of patients with CR-Kp bacteremia and pneumonia [13, 14]. Recently, in a large series of 138 cases of KPC-Kp infections in adults who received CAZ/AVI in compassionate-use programs in Italy it appearred to be a promising drug for treatment of as severe infections as bacteremias [15].

To our knowledge, here we describe the first case of septic thrombophlebitis associated to right atrial endocarditis complicated by multiple lung abscesses due to Kp-KPC successfully treated with long-term CAZ/AVI plus ertapenem therapy. Persistent bacteremia and the possible erratic susceptibility to colistin according to Vitek 2 [16, 17] prompted us to change therapy with a CAZ/AVI based regimen. We decided to use CAZ/AVI in combination with a carbapenem hoping to a possible synergistic interaction [5, 18] either able to result in an enhanced antibacterial effect and to prevent the recently reported emergence of resistance during therapy with this agent [19]. In our case, the synergy between both antimicrobials was not clearly demonstrated by adequate "in vitro" studies as time-kill curves or checkerboard assays: therefore, it cannot be definitively ruled out that the beneficial effect of the antimicrobial treatment could be assigned exclusively to CAZ/AVI alone. Moreover, CAZ/AVI plus ertapenem was started on day 38 of evolution and the patient remained with persistent bacteremia until day 80. Thus, it cannot be definitively ruled out that having continued with the initial antimicrobial regimen that the patient received could have been as effective as the combination of antimicrobials used in the final phase of evolution.

Another interesting aspect of our case is the apparent discrepancy between clinical and microbiological course. Indeed, our patient clinically responded to the antibiotic therapy: he became rapidly afebrile, hemodynamically stable and his procalcitonin levels showed a prompt decreasing trend. Nevertheless, blood cultures remained persistently positive for a prolonged period (approximately 8 weeks), despite appropriate antibiotic therapy. This finding not only confirms our recent observation in a small series of GN bacillary thrombophlebitis [20], but is also corroborated by recent observations demonstrating significantly lower PCT levels in endovascular infections as endocarditis or catheter-related infections (0.21 and 0.76 ng/ml, respectively) compared to deep-seated infections (e.g. urinary tract infection, median PCT levels 5.05 or abdominal infection 3.36 ng/ml) [21].

Based on these studies, clinicians should be aware that PCT studies might not be a reliable marker neither for suspicion of infection nor to monitor the clinical outcome of Gram negative bacillary endovascular infections. Under these circumstances, follow up blood cultures remain an irreplaceable tool to guide the therapy.

In conclusion, even if further study is required to confirm this preliminary favourable observation, CAZ/AVI plus ertapenem was safe and effective therapy of a serious infection as septic thrombophlebitis and right atrial endocarditis with secondary septic pulmonary embolism caused by a KPC-Kp. This case report could constitute an argument for

initiating the new β-lactamase-inhibitor containing combination at an early time point in the course of a complicated infection due to MDR *Klebsiella*.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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