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Case Report

Surinfection of the Renal Graft by a Strain of Klebsiella *pneumonia* Oxa 48 Producer and Therapeutic Impasse

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Abstract

The surinfection of the renal graft by multi-resistant germs constitutes a serious complication, which can engage the functional and vital prognosis in renal transplant patients. It is responsible for a problem of therapeutic management and of the benefit/risk ratio between antibiotic therapy at therapeutic doses and the contraindications linked to renal insufficiency and therapeutic impasse. This work reports the case of a kidney transplant recipient who died following complications of a superinfection of the graft by a strain of Klebsiella pneumoniae producing OXA 48. The purpose of this observation is to underline the nosocomial risk in kidney transplant patients and the difficulty of the therapeutic management of these multi-resistant infections.

Keywords: Klebsiella pneumonia-Oxa 48- therapeutic impasse- renal transplant – carbapenemase- superinfection.

INTRODUCTION

The emergence of carbapenem resistance in enterobacteria producing carbapenems OXA-48 has been proclaimed increasingly important in Morocco. It is currently considered a major clinical problem, especially in resuscitation cases. In fact, carbapenemase-producing strains are often multidrug resistant, as they create multiple resistance mechanisms that can lead to therapeutic impasse [1].

Solid organ transplant recipients, especially renal transplant recipients, are particularly at risk of infection with these multi-resistant bacteria.

Carbapenemase-producing Klebsiella pneumoniae is a widespread source of nosocomial infection worldwide. It represents a challenge for the control and treatment of these infections.

This work reports the case of a renal graft recipient who died following complications of a surinfection of the renal graft by a strain of Klebsiella pneumoniae producing OXA 48. The aim of this observation is to highlight the nosocomial risk in renal transplant patients and the difficulty of therapeutic management of these multi-resistant infections.

OBSERVATION

This observation reports the case of a 28-year-old female patient, who benefited from a renal transplantation at the department of nephrology at the Mohammed VI University Hospital of Marrakech. The complete pre-transplant work-up showed no particularities and the complete infectious work-up was negative. The cytobacteriological examination of the preserved fluid revealed the isolation of a Klebsiella pneumoniae resistant to C3G and sensitive to colistin, amikacin, imipenem and tigecycline. The patient had no clinical or biological signs of infection, and her infectious tests were all negative. Ten days later, the patient presented a complete thrombosis of the renal artery associated with a bacteremia with a urinary origin and an infection of the surgical site.

The Klebsiella pneumoniae strain isolated from the blood culture, urine, and surgical site had the same multidrug resistance profile as the one isolated 10 days earlier from the preservation fluid. This required a change in antibiotic therapy from C3G to Imipenem (500 mg/d) and Amikacin (15 mg/kg/d) with a good clinical and biological evolution: CRP went from 250 mg to 24 mg after 11 days of treatment.

At D12 after thrombectomy, there was a reappearance of the clinical and biological infectious syndrome with pus coming out through the surgical site and a re-ascension of the CRP to 112 mg/l. A reoperation was indicated again, with isolation of the same germ, which this time acquired more resistance. The strain developed resistance to imipenem with an imipenem MIC of 8 mg/l and resistance to tigecycline with a tigecycline MIC of 4 mg/l. The strain produced an OXA 48 carbapenemase and was only sensible to Amikacin and Colistin. Colistin was introduced at D29 post-transplant, in triple therapy with Amikacin and Imepeneme.

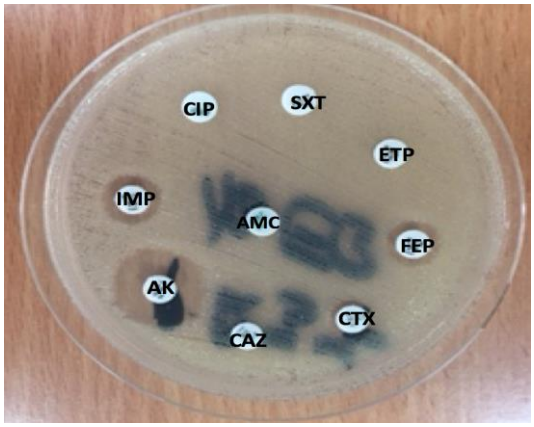

Figure 1: Antibiogram of Klebsiella pneumoniae strain (preserved sensibility only to Amikacin)

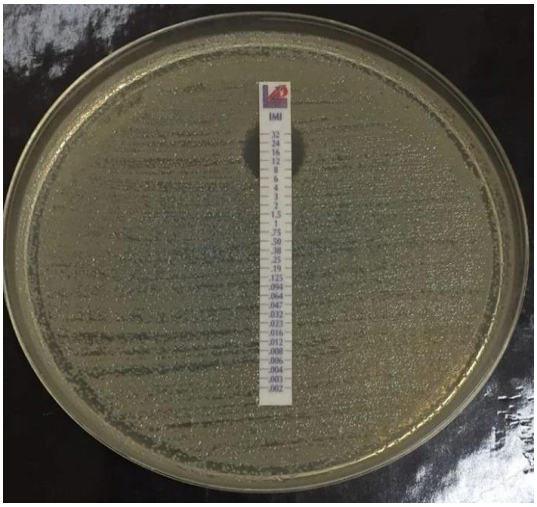

Figure 2: IMP MIC of Klebsiella pneumoniae OXA 48 carbapenemase-producing strain

The evolution was marked by three more uncontrollable infectious episodes leading to graft rejection and detransplantation of the patient, and her transfer to the ICU.

As treatment progressed, the strain continued to be isolated from urine and the surgical site and developed resistance to colistin with an MIC of 6 mg/l and high-level resistance to Imipenem with an MIC >32mg/l. The case ended with the death of the patient due to a therapeutic impasse.

DISCUSSION

In enterobacteria, two mechanisms of carbapenem resistance have been known since the 1980s. One combines the hyperproduction of a cephalosporinase with the loss of a porin as described in E. cloacae or E. aerogenes. The other consists in the production of a class A carbapenemase in a chromosomal position, thus not transferable between species. Fortunately, these enzymes have remained marginal [2]. In the last decade, the number of carbapenemases with the types IMP (Active on imipenem), VIM (Veronaintegron-encodedmetallo- b-lactamase), SME (Serratia marcescens enzyme), KPC (Klebsiella pneumoniae carbapenemase), OXA-48 (Oxacillinase) and NDM-1 (New Delhi metallo-b-lactamase) has exploded [3, 4]. The latest development identified recently is much more worrying as it is linked to the discovery of plasmid carbapenemases, allowing inter-species transfer and rapid dissemination.

Oxacillinases are penicillinases whose spectrum has been extended in some cases to C3G and in others to carbapenems. The first OXA-type carbapenemase was described in 1993, in a strain of multi-resistant A. baumannii isolated in 1985 in Scotland. This plasmid enzyme was named "Acinetobacter resistant to imipenem" (ARI-1), then renamed OXA-23 after sequencing.

There are nine subgroups of class D carbapenemases based on protein sequence homology (OXA-23, OXA-51, OXA-24, OXA-58, OXA-48, OXA-55, OXA-50, OXA-62, and OXA-60).OXA-48, first described in Turkey in K. pneumoniae, has a natural reservoir of environmental species of the genus Shewanella. Unlike the other OXA-type carbapenemases, which are mainly found in Acinetobacter spp, the OXA-48 group has only been described in enterobacteria.

The OXA carbapenemases show a great diversity of protein sequences, but have a fairly similar spectrum of activity.

The OXA-48 gene is located within a transposon. The Mediterranean region, especially Turkey, Tunisia, France and Lebanon, is the site of diffusion of Carbapenemases [6, 7]. These are responsible for the strong hydrolysis of carbapenems without third generation cephalosporins (C3G). Their activity is not inhibited by clavulanic acid, but their frequent association with other betalactamases (ESBL) contributes to the multidrug resistance of these strains [6, 8]. In addition, the gene coding for carbapenemase is bla (KPC), which spreads rapidly to Gram-negative bacilli. It is located on a Tn 3 transposon based on Tn

4401, which carries a polymorphic region giving rise to five isoforms (a, b, c, d, and e). It is located immediately upstream of the bla (KPC) gene and therefore probably involved in its expression [9].

Klebsiella pneumoniae is the most frequently found, expressing this resistance to carbapenems [6, 10, 11, 7, 12, 13]. However, the preferential diffusion of these carbapenemase genes in K. pneumoniae in the hospital setting is not known [6], especially since the emergence and important diffusion of these germs occur in hospitals but also in the community [6, 13]. pneumoniae isolated from clinical specimens should be suspected of producing carbapenemase if it is resistant or of decreased susceptibility to carbapenems and to combinations of penicillins with betalactamase inhibitors and to cephalosporins including cefepime and cefoxitin.

The risk factors are (I) prolonged hospitalization, (II) admission to an acute care unit, (III) placement of foreign material, (IV) immunosuppression, and (V) previous use of antibiotics (ß-lactams but also fluoroquinolones).

Infections caused by multidrug-resistant bacteria are a major emerging challenge. The problem is particularly acute with carbapenemase-producing Enterobacteriaceae (EPC), which typically exhibit a prolonged drug resistance phenotype and remain susceptible to only a few antibiotics [21, 22].

The detection of carbapenemase-producing bacteria in the laboratory is a problem of major importance for the selection of an appropriate treatment regimen and the implementation of dissemination control measures. However, this detection remains difficult, because in view of the multitude of phenotypes, it cannot be based solely on the resistance profile. Indeed, the MICs of carbapenemase-producing strains are highly variable and may remain in the zone of sensitivity according to the current limits of the CA-SFM, the EUCAST. Moreover, no specific test has yet been well standardized. Numerous algorithms have been proposed to test for carbapenemase production without any of them being satisfactory.

The modified Hodge test (MHT) (or clover leaf method) has been widely used as a general phenotypic method for detecting carbapenemase production, and is currently the only method recommended by CLSI. This test is sensitive for the detection of carbapenemases, but does not provide information on the type of carbapenemase involved. False positives have been described, particularly in CTX-M producing strains with altered porins. Difficulties in the interpretation of this test in weak carbapenemase producers have also been highlighted.

The enzymatic properties of class D carbapenemases have not allowed the development of specific phenotypic tests for their detection. Thus, the specific identification of such organisms requires molecular techniques (PCR specific to the genes of interest).

It is also important to note that phenotypic tests are non-contributory for strains co-producing different classes of carbapenemases.

Solid organ transplant recipients are at increased risk of acquiring an infection caused by multidrug-resistant bacteria. This is due to a number of risk factors inherent to these patients; including immunosuppression, invasive procedures, prolonged exposure to the hospital environment, and antibiotic treatment [25, 26]. These infections are usually caused by pathogens acquired in the hospital setting or already present as colonizers in the transplant recipient [25, 27, 28]. However, cross-transmission of multidrug-resistant bacteria is also possible from donors infected or colonized with the bacteria. Surveillance of these patients at high risk for carriage or infection with carbapenem-resistant strains should strictly adhere to standard precautions. If a hospitalized patient is infected with carbapenem-resistant Enterobacteriaceae, screening should be performed in all patients with an epidemiological link to the infected patient (i.e., patients hospitalized on the same unit) [29].

Carbapenems, the last antibiotics of the b-lactam class, have a very large antibacterial spectrum and are highly stable against almost all b-lactamases. Like other b-lactams, they exert their bactericidal activity by inhibiting bacterial wall synthesis through binding to penicillin binding proteins (PLPs).

Colistin and tigecycline are the most likely to be active in vitro against OXA-48 producing bacteria. However, resistance to these molecules has been reported among these isolates [23]. Fosfomycin may be useful as a last resort in combination because of the high potential for resistance emergence [24]. Because OXA-48-producing bacteria have variable resistance profiles, selection of appropriate therapy must be made on a case-by-case basis, as the progress thought to have been made in the control of the bacteria is being undone by this phenomenon, which has become alarming, and may lead to problems of management and therapeutic impasse in the treatment of patients. The World Health Organization (WHO) recently published a report on antimicrobial resistance, including antibiotic resistance. According to the WHO, this phenomenon is described as "a public health problem and a serious threat that affects all countries".

Proper use of antibiotics is also part of the fight against the prevalence of carbapenemases.

Decreasing the prescription of antibiotics has shown a complete reduction in the prevalence of resistant germs [30].

Surveillance and strict implementation of infection control measures are essential to prevent the rapid spread of outbreaks of these multidrug-resistant isolates in health care settings [31].

CONCLUSION

The surinfection of the renal graft by multi-resistant germs constitutes a serious complication, which can engage the functional and vital prognosis in renal transplant patients. It is responsible for a problem of therapeutic management and of the benefit/risk ratio between antibiotic therapy at therapeutic doses and the contraindications linked to renal insufficiency and therapeutic impasse.

The best treatment remains prevention through early detection of infections in patients with renal failure and compliance with good antibiotic prescription practices. Controlling bacterial resistance to antibiotics is a public health priority that requires concerted action in health care and research institutions. Prevention of cross-transmission and reduction of selection pressure through rational use of antibiotics are the two essential components.

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