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Daptomycin, Methicillin Resistant *Staphylococcus hominis* Catheter-Related Bacteraemia in a Hemodialysis Patient

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ABSTRACT

We report a case of a haemodialysis patient that presented a catheter-related bacteraemia caused by a Coagulase negative *Staphylococcus*. With the utilization of molecular biology techniques the bacterial isolate recovered from catheter was surprisingly identified as *S. hominis* by sequencing of the 16S ribosomal gene. The *S. hominis* isolate, which is not often associated with infections in dialysis patients, was resistant to methicillin, being *mec*A positive, and to daptomycin. The patient was successfully treated with vancomycin together with the catheter retirement.

Keywords: Bacteraemia; Catheter; Daptomycin; Methicillin; *Staphylococcus hominis*

1. Introduction

Catheter-related bacteraemia (CRB) is a common major complication encountered in catheter dependent haemodialysis (HD) patients. It has significant impact on morbidity and mortality, which is likely to increase with the rising rate of indwelling catheters for vascular access (VA) in newly diagnosed dialysis patients [1]. Catheter-dependent HD patients have a two- to three-fold increased risk for hospitalization and death compared to patients who have either an AV fistula or graft [2]. There is a direct relationship between rate of infection and duration of use of indwelling catheter [3]. Most cases of CRB resolve without major complication, but there is high risk (up to 20%) for the infected catheter to seed bacteria to distant places**.** Besides, these infections are commonly caused by drug-resistant organisms that are more prevalent in the dialysis setting than in the general population, representing a diagnostic and therapeutic challenge [4,5]. In this setting, utilization of molecular biology diagnostic techniques reinforces the identification of infectious agents and their resistance and virulence traits [6].

We report an HD patient that presented a CRB episode caused by a Coagulase negative (CoN) *Staphylococcus* rarely associated with human infections in dialysis patients. This patient was intermittent nasal carrier of MRSA and had a previous episode of *Staphylococcus aureus*-CRB that was successfully treated. This time, bacterial isolate recovered from catheter was identified as *Staphylococcus hominis* by 16S ribosomal gene sequencing. The *S. hominis* isolate was methicillin resistant, being *mec*A positive, and to daptomycin (DMRSH). The patient was successfully treated and the catheter removed.

2. Case Report

A 56-year-old man diagnosed of Chronic Kidney Disease secondary to nephroangiosclerosis started HD one year ago through a tunneled internal jugular-vein catheter. He had a previous clinical history of alcoholism without liver insufficiency. The patient was nasal carrier of MRSA properly treated with mupirocin by the time he initiated HD. After six month on HD he presented a CRB episode caused by *Staphylococcus aureus*, that was treated with vancomycin and gentamycin. Due to associated sepsis the catheter was retired and the episode resolved. No bacterial metastatic lesions were detected. A second tunneled catheter was implanted and four month later a new CRB was observed. Based on the previous sepsis episode, the catheter was removed. Within 48h, aerobic plate culture from the entrance site of the catheter was positive for bacteria (see below). Antibiotic treatment with vancomycin and gentamicin was initiated. Intrave-

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nous treatment with vancomycin was started at initial dose of 20 mg/kg and following doses depending on its blood levels and maintained for 21 days together with gentamicin at 80 mg after each HD session. After this period, the patient showed clinical improvement and is currently stable with an AV fistula as permanent vascular access.

Molecular diagnostic protocols were used to complement the traditional microbiology methods for obtaining a precise, up-to-date species identification of the infecting bacterium and detection of its resistance and virulence arsenal [6].

2.1. Bacterial Isolates and Phenotypic Characterization

One bacterial isolate was recovered from the catheter entrance site, BacT/ALERT (bioMérieux Inc., Durham). Standard microbiological and biochemical methods for isolate identification were employed, concluding it was a CoN *Staphylococcus.*

2.2. Antimicrobial Susceptibility Testing

Antibiotyping was performed with the automatic Vitek 2 system (bioMérieux, Lyon, France). Nine antimicrobials were chosen to establish the antibiotype of each isolate: penicillin, clindamycin, erythromycin, gentamicin, daptomycin, oxacillin, teicoplanin, vancomycin and mupirocin. *S. aureus* ATCC 25923 was included as quality control.

Phenotypic oxacillin resistance was confirmed by a standard disk method on Mueller-Hinton agar plates with disks each containing 1 μg of oxacillin. Mupirocin and daptomycin resistance were screened by disk diffusion and Etest methods. Inhibition of growth was interpreted according to Laboratory of HealthCare Associated Infection (LHCAI). *Staphylococcus* Reference Unit (SRU), Health Protection Agency from UK.

2.3. Sequencing and Molecular Identification

Molecular-level identification was based on 16S ribosomal-DNA (rDNA) sequencing on an ABI-PRISM310 genetic analyzer (Applied Biosystems Japan Co. Ltd., Tokyo). The sequences were compared with those in the GenBank database. The isolate 16S rDNA sequence had 99.9% identity with the *Staphylococcus hominis* ATCC 27844 16S rRNA gene sequence (GenBank: L37601.1).

2.4. PCRs

In addition to the phenotypic determinations, a multiplex PCR assay for the simultaneous identification of *S. aureus* (*fem*B gene) and detection of the *mecA* (methicillin resistance) and the *ileS2* (high level mupirocin resistance) genes was performed [5]. Results indicated that the isolate did not belong to *S. aureus* species (*fem*B negative), was oxacillin resistant (*mec*A positive) and mupirocin susceptible (*ile*S2 negative and susceptible by Etest result). Besides, a highly sensitive specific PCR was assayed for identifying the isolate at the species level as *Staphylococcus hominis.*

Moreover, PCR-analysis to detect the Panton Valentine Leukocidin (*pvl*-gene), which could convert infection to severe, showed that the isolate was PVL negative.

3. Discussion

The present case illustrates a common clinical situation in a catheter-carrying HD patient where the employment of molecular biology tools allowed to detect and identify an uncommon infectious *Staphylococcus* in the HD patients. The risk of infections in hemodialysis is linked to several factors, being the type of vascular access (VA) a cornerstone in the morbidity and mortality of the infected subjects [7]. Major complications from VA-related infections in dialysis are severe sepsis, metastatic mainly endocarditis and osteoarticular infections, increasing the mortality rate of these conditions [8]. Our patient had a tunnelled jugular-vein catheter since his initiation of dialysis therapy conditioned by previous sepsis episode. As already referred, the presence of permanent catheters is the main factor for infections in these patients.

Interestingly, there are several conditions that affect the presence of antibiotic resistant bacteria in the environment. Humans are the main natural reservoir of *S. aureus* being an important host factor for CRB [9]. The presence of *Staphylococcus* in the nose elicits a subclinical immune response, which is ineffective to prevent further colonization once the germ has reached the anterior nares [9]. HD patients are at increased risk for intermittent or persistent carrying of *Staphylococcus* spp. from the onset of dialysis. Our patient was MRSA carrier by the time he initiated HD, although it was successfully solved with mupirocin treatment. This condition together with the use of vancomycin for the previous CRB could determine the emergence of ulterior antibiotic resistant infections.

Daptomycin is a cyclic lipopeptide that has received approval for the treatment of complicated skin and soft tissue infections and *Staphylococcus* bacteraemia. Prior vancomycin exposure potentiates the development of daptomycin non-susceptibility in *Staphylococcus in vitro* [10]. However, clinical outcomes have generally been more favorable, with relatively few publications of therapeutic failure to date regardless of whether daptomycin was used as first- or second-line therapy [11]. Yet referred, our patient was previously treated with vancomycin for *Staphyloccocus aureus* CRB what could con-

dition the emergence of a subsequent daptomycin resistant strain. At present, the exact mechanism underlying daptomycin resistance remains unclear and it is plausible that several possible pathways exist for different MRSA clones [10]. The development *in vivo* of resistance to both agents suggests that the resistance mechanisms may be associated. We suggest that the clinician managing MRSA infection should anticipate daptomycin resistance when reduced glycopeptide susceptibility is detected. Development of decreased susceptibility to daptomycin during long-term therapy has been previously reported in patients with MRSA bacteraemia [12]. Similar reports of daptomycin resistance and treatment failure during daptomycin therapy for MRSA bacteraemia and osteomyelitis have also been described [13]. Although our patient was a MRSA carrier and he did not receive daptomycin this circumstance could condition the development of the current resistance pattern. Development of daptomycin non-susceptible MRSA isolates in both hospital-associated and community-associated settings is a concern. Further studies are needed to provide better insights into the development of daptomycin non-susceptibility in *S. aureus* [14].

The case herein described exemplifies a clinical situation where a prompt identification of the staphylococcal infectious agent and precise detection of its antibiotic and virulence malignancies are crucial for its successful management. This knowledge should mandate the appropriate antibiotic therapy in dialysis patients together with pre-emptive measurements in VA management and policy.

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