J Infect Chemother 22 (2016) 180–183

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Case report

Implantable cardioverter defibrillator infection due to *Mycobacterium mageritense*

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ARTICLE INFO

Article history:
Received 7 July 2015
Received in revised form
27 August 2015
Accepted 14 September 2015
Available online 21 December 2015

Keywords:
Mycobacterium mageritense
Rapidly growing non-tuberculous mycobacteria
CIED infection
16S rRNA gene sequencing

ABSTRACT

Rapidly growing non-tuberculous mycobacteria (RGM) are usually detected in blood cultures after 4–5 days of incubation, so it is important to differentiate RGM from contamination of commensal organisms on human skin. We report an unusual case of *Mycobacterium mageritense* bacteremia and infection of an implantable cardioverter defibrillator originally misidentified as *Corynebacterium* spp. or *Nocardia* spp. in gram-stained smears. 16S rRNA gene sequencing had utility in the definitive identification of isolates. We should be aware that RGM infection may exist in repeated implantable device infections.

1. Introduction

Cardiac implantable electronic device (CIED) infection has been mostly due to staphylococcal organisms, and non-staphylococcal organism has been less. Mycobacterium infection was detected very rarely in CIED infection and culture negative infection were up to 7–21% [1,2]. However, rapidly growing non-tuberculous mycobacteria (RGM) may be underestimated as gram-positive bacilli and can be mistaken for *Corynebacterium* species, diphtheroids, or *Nocardia* spp., if further testing is not performed [3]. Here we report a case of *Mycobacterium mageritense* bacteremia and infection of an implantable cardioverter defibrillator (ICD). The isolation was identified with 16S rRNA gene sequencing. We should be aware that RGM infection may exist in a part of culture negative infection or in gram stain positive rod infection.

2. Case report

A 59-year-old female was admitted to our hospital because of repeated, treatment-resistant surgical site infections. The patient had a subcutaneous ICD in the left chest wall placed for the management of Brugada syndrome 8 years previously. The ICD generator had been exchanged 2 years previously due to a loss of energy. On postsurgical day 14, the patient noted spontaneous disunion of the ICD insertion site with pus present. A 14-day course of vancomycin was prescribed following debridement of the pocket tissue without extraction of the ICD leads. Further, purulent discharge and blood cultures revealed no evidence of infection. Following administration of an antimicrobial agent, a new ICD was inserted into the sub-muscular pocket. Following this procedure, the patient suffered repeated surgical site dissociation. Tests for allergy to the metal of the ICD and surgical sutures, performed to exclude this as a cause of the repeated surgical site dissociation, were negative. All the other non-infectious disease was carefully excluded. Finally, further new ICD and leads were implanted in the right chest wall and the old leads were buried in the left chest wall. The left surgical site then healed successfully.

One and half years later, the patient reported pain and noted that the left surgical site, where the previous ICD leads was buried, was erythematous. Subsequently, the skin color of right chest became purple and the patient reported pain at the new ICD insertion site. On admission to our hospital, the ICD was exposed with pus observed in the right chest pocket (Fig. 1). Skin erythema was observed involving a 4 × 5-cm area on the left chest wall at the

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http://dx.doi.org/10.1016/j.jiac.2015.09.010
1341-321X/

subcutaneous ICD insertion site. The area was warm to touch and minimally tender on palpation. The patient appeared nontoxic and afebrile with stable vital signs. Physical examination was normal, except for the changes to the chest area described above. Laboratory investigations were unremarkable. Two sets of blood cultures and wound tissue were submitted to the microbiology laboratory for bacterial culture. Direct Gram-stained smears of the wound cultures demonstrated few polymorphonuclear leukocytes with no organisms observed. To target *Staphylococcus* spp., the commonest organism isolated from CIED infections, empirical administration of vancomycin was initiated.

After 4 days of incubation, growth was detected in one of the two blood cultures. On the 5th day of hospital admission, gram-positive rods with characteristic *Corynebacterium* spp. morphology, were observed on gram-stained smears of wound broth cultures. Additional acid-fast bacillus cultures revealed that the isolated nonpigmented strain was present in both blood cultures and wound broths. DNA–DNA hybridization failed to identify the isolate. 16S rRNA gene PCR and restriction fragment length polymorphism (RFLP) assays of PCR amplicons from a partial heat-shock protein 65 gene revealed the following information: the isolate was *Mycobacterium* spp., as determined by the presence of a 1-kbp band specific to *Mycobacterium* spp. (Fig. 2A), and three isolates collected from different sites, the pocket site (I), lead tip (II), and the blood cultures (III) demonstrated identical restriction patterns (Fig. 2B) indicating that the same species was isolated from all sites. Despite these findings, the isolate remained unidentified. We tried to identify the isolate with 16S rRNA gene sequencing. The method was as follows: DNA was extracted from the isolate and the PCR product was amplified with AmpliTaq Gold DNA polymerase (Applied Biosystems, Foster City, CA), low DNA, and a primer set (E27F primer, 5′-AGAGTTTGATCMTGGCTCAG-3′; E1492R primer, 5′-TACGGYTACCTTGTTACGACTT-3′) [4]. After the primers and deoxyribonucleotide triphosphate were removed from the PCR with ExoSAP-IT (GE Healthcare UK Ltd., Buckinghamshrine, England), 1 μl was used as a template for the sequencing reaction. The sequencing reactions were performed with primer sets (E27F, E1492R, E907R; 5′-CCGTCAATTCMTTTRAGTTT-3′, E530F; 5′-GTGCCAGCMGCCGCGG-3′) [4] and BigDye Terminator Cycle Sequencing Kit version 3.1 (Applied Biosystems). A homology search of the assembled sequences was performed using the National Center for Biotechnology Information basic local alignment search tool (http://blast.ncbi.nlm.nih.gov/Blast.cgi) [5]. Finally, 16S rRNA gene sequencing identified the isolated mycobacterium as *Mycobacterium mageritense* with 99% (1393/1394 base) homology.

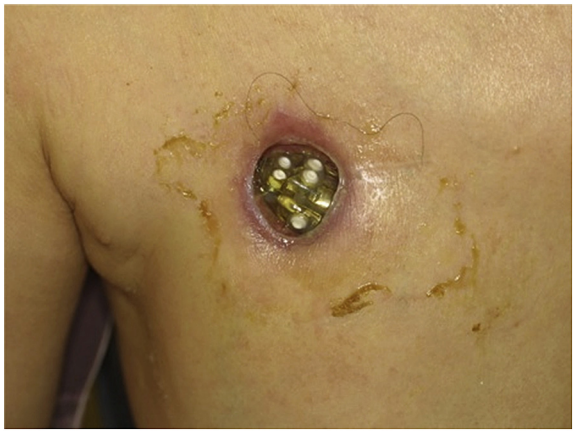

Fig. 1. Skin erosion with exposure of an implantable cardioverter defibrillator.

Susceptibility testing using the broth microdilution method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) was undertaken revealing sensitivity to levofloxacin (MIC = 0.25 μg/ml), amikacin (MIC = 16 μg/ml), clarithromycin (MIC = 16 μg/ml), rifampicin (MIC = 32 μg/ml), and isoniazid (MIC > 32 μg/ml). Following successful extraction of the percutaneous leads, a combination of levofloxacin (500 mg once daily), amikacin (10 mg/kg once daily, under monitoring), and rifampicin (450 mg once daily) were initiated according to the results of susceptibility testing and previous reports [6,7]. Consequently, antibiotic therapy had to be modified to ciprofloxacin (200 mg twice daily) and clarithromycin (400 mg twice daily) due to drug-induced severe thrombocytopenia. A new ICD was implanted 3 months after complete lead extraction with a further 12 months of dual antibiotic therapy prescribed. There have been no episodes of recurrence at 3 years since discharge.

3. Discussion

CIED infection is most commonly caused by staphylococci. Non-tuberculous mycobacterium infection is rarely detected in CIED infection with culture-negative infection reported in 7%–21% of cases [1,2]. Rapidly growing non-tuberculous mycobacteria (RGM) are typically detected in blood cultures after a 4–5-day incubation. Therefore, differentiating RGM infection from contamination by human skin commensals is important. Moreover, RGM are likely to misidentified as gram-positive bacilli, such as *Corynebacterium* spp., diphtheroids, or *Nocardia* spp., without additional testing [3].

The presented case provides three important findings: First, repeated surgical site infection associated with CIED implantation should be treated as CIED infection, even in cases of negative pocket site swab and tissue cultures. Klug et al. reported that 79.3% of intravascular lead cultures were positive in patients presenting with clinical pocket infections without signs of systemic infection [8]. In an AHA (American Heart Association) statement, complete removal of all hardware was recommended as a class I indication, even in localized CIED infections without signs of systemic infection [9]. We also mention that careful differential diagnosis of metal allergy and non-infectious disease such as pyoderma gangrenosum and Behçet's disease should be made before the extraction of device and leads.

Second, methods for the reliable identification of causative organisms in cases of CIED infection are yet to be established. The majority of CIED infections are reportedly caused by skin flora, with *Staphylococcus aureus* and coagulase-negative staphylococci accounting for 63%–75% of all cases [10,11]. Furthermore, 27% of conventional generator pocket swab cultures have been reported to be positive in cardiac devices explanted without clinical signs of infection [12]. The concordance between bacterial isolates from leads are relatively high, approximately 70%, whereas concordance between isolates from the pocket and the lead are relatively low, approximately 45% [13]. Therefore, we are uncertain regarding the non-pathogenic nature of culture-negative CIED infections that account for 7%–21% of all cases [1,2]. Improvements in blood culture methods and the implementation of automated blood culture systems, such as BacT/ALERT (bioMRT RT, Durham, NC) or BACTEC (BD Diagnostic Systems, Sparks, MD), may reduce required blood culture incubation times [14]. RGM can be detected in blood cultures after 4–5 days incubation. As in the present case, the discrimination between RGM infections and normal skin flora is challenging; conventional methods are typically inconclusive and occasionally result in misidentification. Runyon group IV RGM produce visible growth on solid media within 7 days. The misidentification of RGM as gram-positive bacilli has previously been reported [6]. *Mycobacterium* spp. may be misidentified as