Interdisciplinary Neurosurgery: Advanced Techniques and Case Management 7 (2017) 12–16

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery: Advanced Techniques and Case Management

journal homepage: www.inat-journal.com

Technical Notes & Surgical Techniques

Vancomycin resistant *Enterococcus faecium* (VRE) vertebral osteomyelitis after uneventful spinal surgery: A case report and literature review☆

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ARTICLE INFO

Article history:
Received 1 August 2016
Revised 9 October 2016
Accepted 13 November 2016
Available online xxxx

Keywords:
Spinal surgery
Vertebral osteomyelitis
Enterococcus faecium
Transforaminal Lumbar Interbody Fusion (TLIF)

ABSTRACT

Objective: Case report and literature review.
Background: Enterococcus faecium is an emerging pathogen responsible for post procedural infections in patients who have undergone spinal decompression surgery. In this case report, the authors discuss and review recent literature on approaches to post-operative spinal infection.
Case report: We herein report the case of a 55-year-old HIV-negative Caucasian Italian woman who showed vertebral osteomyelitis with abscesses around the interbody cage caused by an Enterococcus faecium vancomycin resistant gen-Van A, following a Transforaminal Lumbar Interbody Fusion (TLIF). The same strain was detected in disc biopsy, urine culture and rectal swab. After the implant (screws, bars and cage) was removed and a suitable medical therapy administered, the infection resolved completely. The strain was identified and its susceptibility profile was characterized; biofilm-associated genes and biofilm-induced antimicrobial resistance is highlighted.
Conclusions: In any case, the management of infections complicating spinal surgery is controversial, and various mono or combined surgical and/or anti-infective timing approaches to remove infected implants have been proposed. The authors suggest a multidisciplinary approach taking into account virulence, microbiological features of causative pathogens and patient's risk factors. More efforts should be directed towards the early identification of pathogens in surgical specimens.

1. Background

Surgical site infection (SSI) after spinal surgery is a challenging medical problem that results in increased rates of morbidity, length of hospital stay and health care costs [1]. The reported incidence of infection following posterior spinal instrumentation surgery is between 2.6% and 3.8% [2–6]. Bacteria isolated from disc material are more frequent in patients with disc herniation than ones with other spinal disorders [7,8]. *Staphylococcus aureus* is the most common cause of SSI, although infections due to *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Pseudomonas* spp., *Enterobacter cloacae*, and *Proteus mirabilis* have also been reported [9,10]. The surgical procedure seems to be the most significant variable affecting rate of infection. The risk of infection following a simple lumbar discectomy is <1% due to shorter operative times, less muscle trauma, and generally healthier patients than those requiring more extensive spinal procedures. When more extensive decompression is performed, without fusion, the risk of infection rises to 2%. When fusion is added to the procedure, operative time is longer and blood loss is greater. In this case, the infection rate rises to 6%. Other factors include extended pre-hospitalization, high blood loss (>1000 mL), and prolonged operative time (>3 h) [11]. (Although rates of infection are clearly lower in younger patients because of fewer comorbidities, other significant risk factors are: diabetes mellitus, obesity, and a history of an SSI [2].) Accurate diagnosis is essential in order to effectively eradicate the infecting organisms, but this is often difficult to achieve. Specific clinical signs, laboratory and radiographic investigations that aid diagnosis of infection may be absent. Inflammatory markers together with the clinical symptoms (low back and radicular pain) should alert the physician to the possibility of infection [12]. *Enterococcus* spp. is an emerging opportunistic pathogen that causes implant-related SSI. Treatment of enterococcal prosthetic joint infection is difficult, in part due to biofilm-associated antimicrobial resistance. The antibiotic resistance properties of *E. faecium* strains have recently been associated

☆ Declaration of interest: The authors report no declarations of interest. No funds were received in support of this work.

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http://dx.doi.org/10.1016/j.inat.2016.11.002

with biofilm formation which leads to resistance to environmental stress, and adhesion to eukaryotic cells, such as those of the urinary tract [9–11,13]. We report the clinical and surgical management of a case of disc infection due to Vancomycin Resistant *Enterococcus faecium* (VRE) after surgical decompression.

2. Case report

A 55-year-old HIV-negative Caucasian Italian woman with fever and low back pain lasting one month was admitted to our Emergency Surgical Department in April 2015. Her medical history was remarkable for hypertension and coronary artery disease. Before treatment, the patient had had several episodes of urinary tract infection, and a urine culture resulted in the isolation of *Enterococcus* spp. susceptible to vancomicin, gentamicin and ampicillin (minimal inhibitory concentration, MIC for ampicillin <64 g/ml). Surgical history revealed that the patient had undergone L3–L5 open decompression and a 360° fusion with pedicle screws in L3–L4–L5 as well as a Peek interbody cage by TLIF in L4–L5 since 8 months prior the admission to our surgical setting, for a severe low back pain due to L3–L4, L4–L5 instability and diffuse spondyloarthrosis (Figs. 1–2). A physical examination of the patient at admission showed fever (temperature, 38.9 °C [102 °F]) and left L3–L4–L5 radicular hypoesthesia. Initial laboratory studies revealed the following values: white blood cell (WBC) count, 27.3×10^4 cells/mm^3 (74% neutrophils, 10% bands, 10% lymphocytes, and 3% eosinophils); hemoglobin level, 12.7 g/dL; platelet count, 2.7×10^5 platelets/mm^3; serum creatinine level, 0.9 mg/dL; aspartate aminotransferase level, 29 U/L; alanine aminotransferase level, 27 U/L; total bilirubin level, 1.5 mg/dL; indirect bilirubin level, 0.5 mg/dL; and lactate dehydrogenase level, 2900 U/L. A lumbar puncture was performed. The opening pressure was 15 mm Hg, and analysis of cerebrospinal fluid (CSF) revealed the following values: WBC count, 28 cells/mm^3; glucose level, 58 mg/dL; and protein level, 19 mg/dL. Microscopic examinations, aerobic and anaerobic bacterial cultures as well as acid-fast bacillus test (AFB) and fungal cultures to identify pathogens in the CSF were negative; polymerase chain reaction (PCR) tests for relevant viral and bacterial infectious agents such as Mycobacterium tuberculosis were negative. Moreover, bacterial cultures and other analyses for other pathogens which are epidemiologically relevant in our geographic area (e.g. *Rickettsia conorii*, *Brucella* spp.) were negative, as previously reported in another case of suspected infection involving the CNS [14]. A Lumbar CT scan showed areas of bone remodeling with sclerotic margins at both L4 and L5, somatic cortical profiles consistent with an inflammatory process (Fig. 3A–B). A Magnetic Resonance Imaging (MRI) of the lumbar sacral tract confirmed osteomyelitis of the L3–L4–L5 bodies, especially around the cage at the L4–L5 interbody level. The infection seemed to reach the screws in the L4–L5 body and the left paravertebral region; there was another quota of pathological tissue both in the prevertebral L5 and in the subcutaneous space, with 8 cm extended fluid collection (Fig. 3C–D). The results of blood, urine and fluid sample cultures were negative. Therefore, a medical therapy with intravenous cefuroxime (140 mg/kg per day) and vancomycin (2 g/day) for suspected vertebral osteomyelitis, was administered. On day 18 of hospitalization, the patient became febrile (temperature, 39.4 °C [103 °F]) without clinical manifestations of sepsis or other suspected focus of infection. A transthoracic echocardiogram showed no valvular abnormality or vegetation. A head CT scan without contrast was unremarkable. Culture of blood and urine were performed. *Enterococcus faecium* strain was isolated from the urine culture. It was resistant to ampicillin (MIC ≥ 64 μg/ml) and vancomycin (MIC of minimum inhibitory concentration ≥ 256 μg/ml), and exhibited high-level resistance to aminoglycosides (high-level resistance to gentamicin was tested for using the 120 μg gentamicin disc) and susceptibility to rifampin, daptomycin, tygeciclyne and linezolid [15,16]. The patient was given rifampicin and daptomycin for possible systemic *Enterococcus faecium* infection. The same resistant strain was isolated from the patient's rectal swab. A persistent fever over the following days prompted our multidisciplinary neurosurgical and infection team to develop a surgical strategy. Therefore, a surgical lumbar wound exploration was performed; instrumentation was all removed and a wound debridement was carried out. Once completed, fibrin sealant (Vivostat®) was sprayed on the operative field, in order to prevent CSF leakage [17–23]. Disc biopsy culture identified *Enterococcus faecium*. The isolate showed the same susceptibility profile as the strain isolated from the urine culture. At discharge, 6 months of oral antibiotic therapy with Linezolid plus Rifampicin plus Doxycyclin was prescribed. After six months of *anti*-infective treatment, MRI investigations showed that the inflammatory disease had progressively resolved (Fig. 4). At the final follow up the neurologic examination was unremarkable. No motor or sensory deficit was evident. Patient referred just low back pain which was significantly lower than pre operatory status. Analysis of *E. faecium* strains isolated from disc biopsy, rectal swab and urine culture by PCR amplification revealed the presence of the vanA gene [15]. A new posterior transpedicle fixation to correct lumbar segmental instability has been proposed to the patient but she has actually refused.

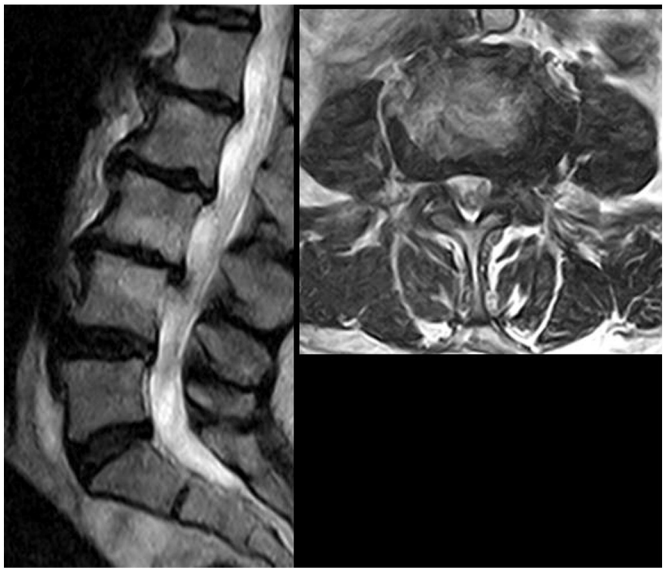

Fig. 1. Pre-operative lumbar MRI. A. Sagittal view. A diffuse spondyloarthrosis, with herniated discs in L3–L4 and microinstability at L4–L5 is documented. B Axial view. The L3–L4 level is depicted.

3. Discussion

In 2014, scientific literature addressed the issue of instrumentation removal or retention in the attempt to reduce infection following spinal surgical procedures, especially after Posterior/Transforaminal Lumbar Interbody Fusion [16,24,25]. The management of infections is currently under debate because, as reported by Wei-Hua et al., it is likely that the implants do not interfere with the body's attempt to fight infection, especially precocious infection [25]. The more complicated procedures and more reconstruction levels involved in fusion surgery with instrumentation may explain the higher revision and mortality rates [26,27]. In this manuscript the authors describe and discuss the role of *Enterococcus faecium* as an emerging pathogen responsible for vertebral osteomyelitis after spinal surgery. Enterococci occur naturally among the normal flora in the human gastrointestinal tract. Initially thought to be harmless commensal organisms in hospitalized patients, enterococci have emerged as significant nosocomial pathogens. At present, Enterococci are known to be the cause of important nosocomial infections such as endocarditis, bacteremia and urinary tract infections, especially in elderly female patients [28]. Enterococci are intrinsically resistant to several antibiotics and possess the ability to acquire resistance through the exchange of genetic material [29]. As a result, they have become more

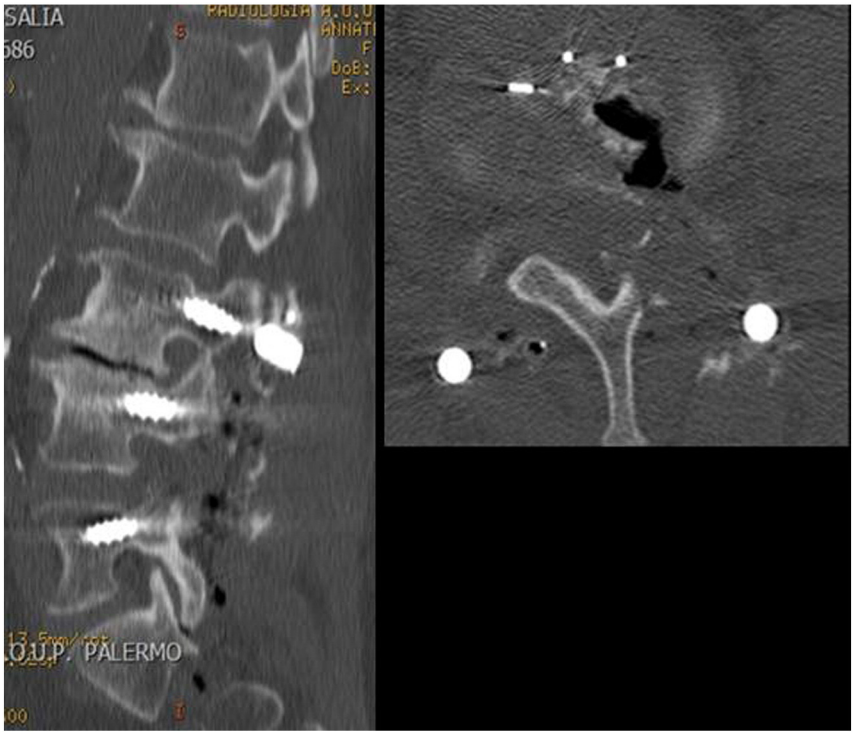

Fig. 2. Post-operative lumbar CT scan. Pedicle screws in L3, L4 and L5 bilaterally and intersomatic L4–L5 cage by TLIF.

resistant to multiple antibiotics [13,29]. According to the European Antibiotic Resistance Surveillance System, an international network that collects data on antibiotic resistance of bloodstream-infecting isolates in 28 European countries (http://www.earss.rivm.nl/), in Italy the proportion of VRE was higher than 10% in 2001 and 2015. Colonization and infection with vancomycin-resistant enterococci are associated with prolonged hospitalization, exposure to cephalosporins and vancomycin, and the use of antianaerobic agents [30]. Compared to *Enterococcus faecalis*, *E. faecium* isolates are more resistant to penicillin, and large molecules such as nafcillin, oxacillin, ticarcillin, ertapenem, most cephalosporins, and aztreonam. Moreover E. faecium is more impermeable to aminoglycosides, and the serum concentrations of aminoglycosides required for bactericidal activity are much higher than other pathogens [29–32]. Two hospital outbreaks have been reported in Italy in the last decade; one was due to VRE belonging to the species *Enterococcus faecalis* (VRE) in a neurosurgical ICU [29]. Management of post-operative spinal infection is controversial, and various treatment options have been proposed: some advocate medical therapy only, some suggest irrigation and serial wound debridement plus antibiotic therapy, while others report that infection can be eradicated only by removing implants [25–27]. Chaichana et al. retrospectively reviewed 817 consecutive adult patients who underwent instrumented posterior lumbar

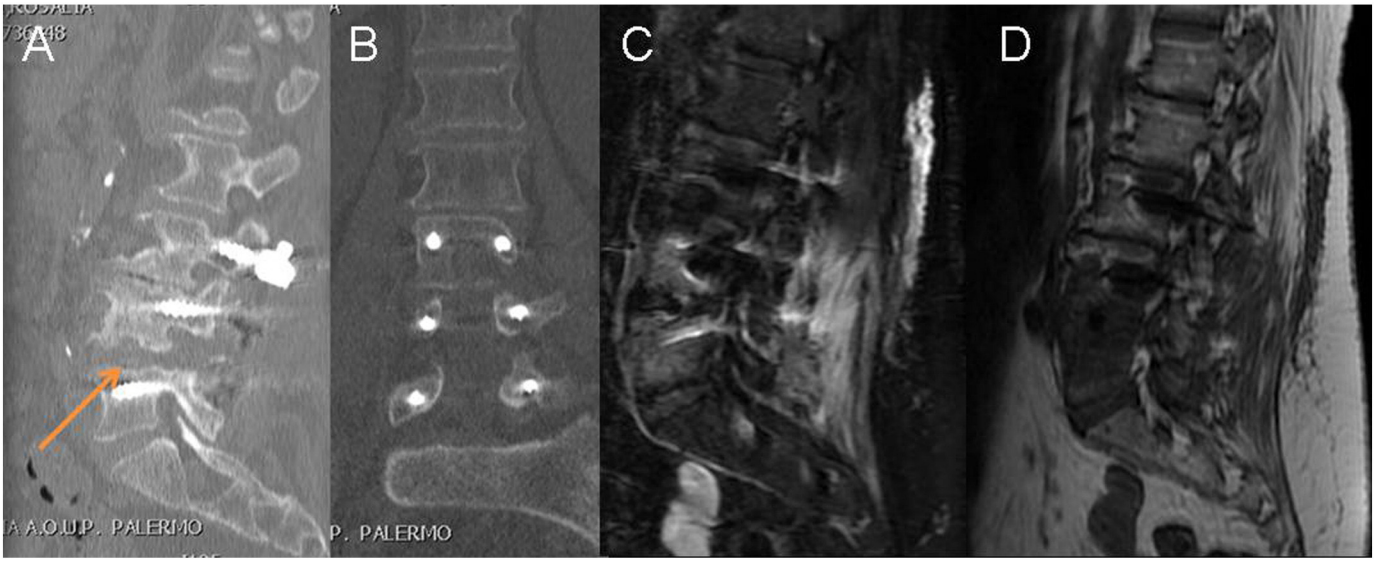

Fig. 3. A–B: Post operative CT scan (8 months). An area of bone remodeling in both L4 and L5 somatic cortical profiles (orange arrow) is depicted C–D Post operative lumbar MRI scan. C. T2 weighted sagittal images. D. T1 weighted, post contrast MRI. Lumbar enhanced MRI scan revealed a pathological enhancement in vertebral bodies of L4, L5, vertebral canal and paravertebral L3–L5 region. All these findings were suggestive of surgical site infection. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

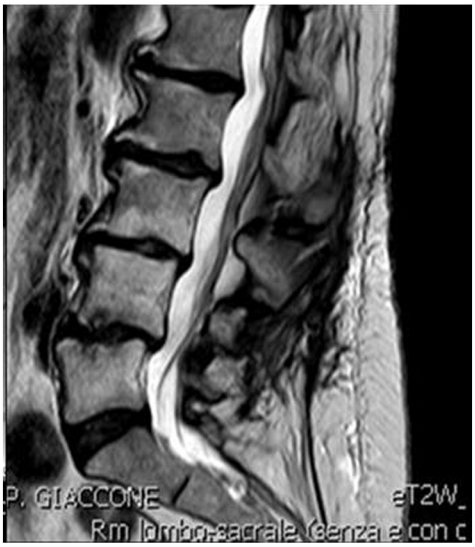

Fig. 4. Post-medical treatment lumbar MRI. Six months after anti-infective treatment, MRI showed a progressive resolution of infection.

fusion for degenerative spine disease between 1993 and 2010; among 817 pts, 37 (4.5%) developed postoperative spine infection [12].

Because patterns of infection acquired in patients undergoing operation are ever changing, it is an essential part of nosocomial infection surveillance programs to periodically document the epidemiologic features of infection in these patients [33]. Table 1 reassume old and new risk factor for infection following neurosurgery procedure [2,34–38].

Biofilm formation is a crucial step in the pathogenesis of many subacute and chronic bacterial infections, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *S. aureus* (MSSA), *Candida* species, and *Enterococcus* species foreign body-related infections.

There is general consensus that the adhesion of microbes to a surface influences bacterial metabolism, like microorganisms involved in device-related infection: they are in a dormant, that is a stationary phase of growth, and the analysis of their growth reports increased biofilm growth rates in comparison to the effects of effluents on planktonic growth activity (1). Parsek and Singh (2) were the first to attempt to define the significance of biofilm infection. Like other scholars, they recognized the consequences of biofilm formation by bacteria, especially in surgery (3, 4). Today the main problem for the microbiologist remains biofilm identification, which requires particularly sophisticated morphological techniques such as microscopy or fluorescence in situ hybridization (FISH), as often neither culture nor biomolecular investigations are helpful (5, 6). Obviously antibiotics have limited efficacy on implant-associated infection because not all antibiotics can overcome the biofilm in sufficient quantities to clear the microorganism, hence some studies have looked at combined treatment options (infectious and surgical management) to avoid infection [39–45]. Recent research has shown how some bacterial species, such as enterococcus, are able to enter bone cells and induce osteoblast apoptosis, osteoclast recruitment, and highly destructive osteomyelitis [46]. Biofilm formation in the pathogenesis of enterococcal infections is now widely recognized and underscores the importance of taking the pathogenesis of biofilm infections into consideration when comparing the management of postoperative infection due to strain biofilm-associated genes and biofilm-induced antimicrobial resistance after spinal instrumentation [47].

This controversial aspect, especially in enterococal infection, should be solved with appropriate controlled studies. In our case report, the decision to remove instrumentation led to the resolution of the infection. Information on the strain, its susceptibility profile, vancomycin genotype and clonal relationship were collected for our clinical information, and represent the goal of biofilm associated pathogens causative of implant-related infections. Cost-effective analysis should be conducted in subsequent studies to determine the costs involved in the prevention of invasive VRE infections in the surgical setting: implementation of active surveillance culture, VRE decolonization and probiotics should be studied further.

Table 1
Risk factors for *Enterococcus* spp. infection in adult patients in a neurosurgery setting.

Increased risk	Emerging risk factors
Age (≥70 years)	History of urinary tract infection
Sex, female	Emergence of regional clones of *Enterococcus faecium*
Diabetes	Vancomycin-resistant *Enterococcus* (VRE) colonization
Hematologic malignancy	Number of VRE-colonized patients on the unit
Solid tumor	Transferred from rehabilitation facilities and long-term care facilities
Steroid therapy	Polymicrobial infection
Previous hospitalization	Type of surgery: genitoperineal surgeries
Length of stay in hospital	Admission for other surgical pathology (wound infection, enteric peritonitis)
Urinary catheter	Heart disease
Management of implant retention	Diverticulosis
Exchange (one or two stage)	Overweight (BMI between 25.0 and 29.9)
Median (IQR) of antibiotic treatment	
Obesity (BMI of 30 or higher)	

4. Conclusion

A delayed infection after instrumented spine surgery can be difficult to diagnose. We report a very rare surgical site infection due to *Enterococcus faecium* following a urinary tract infection. Effective treatment usually includes irrigation and wound debridement, followed by prolonged administration of antibiotics and, in severe cases, by the removal of the implants. However, if the infection is not deep, probably the instrumentation can be left in place. Bacterial biofilm formation is central in the pathogenesis of infections related to foreign material, and *E. faecalis* and *E. faecium* can form biofilm. Therefore, considering that there is no clear consensus on how to manage patients with postoperative instrumented spinal infection, currently the best choice of treatment should be made case-by-case.

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