**Enterococcus raffinosus endocarditis. First case and literature review**

Prima segnalazione di endocardite da Enterococcus raffinosus e rassegna della letteratura

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**INTRODUCTION**

*Enterococcus raffinosus* is a non-*faecalis* and non-*faecium* enterococcus that has rarely been proven a human pathogen. Indeed, infections in humans are rare. We report the first reported case in the literature of primary bacterial endocarditis caused by *E. raffinosus*, an unusual manifestation of *E. raffinosus* infections, in an 85-year-old man who was admitted to our hospital with a clinical picture suggestive of an indolent febrile illness.

**CASE REPORT**

An 85-year-old male was admitted to the hospital with a six-month history of low fever with sweating. He reported weakness in his legs that compromised his walking ability. The patient had no history of heart disease or right heart catheterization, or a history of periodontal disease or dental work. He had essential hypertension and dyslipidaemia. Laboratory examinations revealed inflammation.

WBC 9.150 x 10^9/L (neutrophils 69.6%, lymphocytes 213.1%), haemoglobin 11.3 g/dL, haematocrit 34.5%, MCV 81.9 fl, platelets 236 x 10^9/L, ESR 102 mm/h, fibrinogen 586 mg/dL, C-Reactive Protein 49.7 mg/L, d-dimer 437 ug/L.

Blood cultures yielded Gram-positive cocci on Gram stain. These cocci were identified at the species level as non-*faecalis* and non-*faecium* enterococcus *E. raffinosus*.

The microorganism was resistant to clindamycin (MIC >8 mg/L), erythromycin (>8 mg/L), and tetracycline (>16 mg/L), and susceptible to glycopeptides (vancomycin <1 mg/L; teicoplanin <0.5 mg/L), quinolones (ciprofloxacin <1 mg/L; levofloxacin <0.5 mg/L; moxifloxacin <0.25 mg/L), G penicillin (<0.12 mg/L), ampicillin (<2 mg/L), cefuroxime (<1 mg/L), cotrimoxazole (<1 mg/L), linezolid (<1 mg/L, quinupristin/dalfopristin (<1 mg/L), and imipenem (<1 mg/L).

Further examinations such as X-rays of the thorax and the oral cavity, and an ultrasonogram of the abdomen were carried out. A transthoracic echocardiogram demonstrated a mobile vegetation attached to mitro-aortic valves. Transesophageal echocardiography confirmed the presence of small vegetations on the native mitral and aortic valves, 1.1 cm² and 2 mm, respectively, and a mild mitral insufficiency (Figures 1, 2). Taking into account the patient’s age (no screening), and the association between enterococcal bacteraemia and colon neoplasia, a colonoscopy was performed. It revealed a tubular adenoma of the colon with moderate dysplasia without evidence of colorectal cancer.

He was treated with appropriate intravenous antibiotics (ampicillin, 12 g daily + levofloxacin 1 g daily) for 3 weeks and subsequently at home with oral antibiotic therapy (amoxicillin/clavulanate 4.5 g daily) for 3 weeks with a good clinical recovery at the six-month follow-up. During the follow-up the patient was in a stable condition and the main laboratory parameters remained normal.

Fever gradually decreased, and disappeared after the first ten days of therapy. Initial elevated flogosis indexes fell to the normal range within the fourth week of therapy. Follow-up
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was carried on for six months, with monthly controls, and neither clinical nor laboratory disorders were observed. Transthoracic echocardiography, performed after six months, resulted negative.

DISCUSSION

In the last few decades, enterococci, usually regarded as indigenous flora of the intestinal tract, oral cavity and the genitourinary tract of humans and animals, have emerged as major opportunistic pathogens and as the cause of serious infections, especially in hospitalized patients, including endocarditis, bacteraemia, intra-abdominal and urinary tract infection. The *Enterococcus* genus comprises more than 21 species and enterococci have also emerged as major important pathogens because of their increasing resistance to many antibiotics. Although the majority of the isolates are members of *E. faecalis* or *E. faecium*, other *Enterococcus* species have been implicated in human infections as well. In recent years, there has been increasing interest in unusual non-*faecalis* and non-*faecium* enterococci not only because of their ability to cause serious infections like septicaemia (with or without endocarditis), more frequently associated with peripheral or central catheters, urinary-tract infections, surgical and non-surgical wound infections and peritonitis, but also due to their increasing resistance to several antimicrobial agents, including β-lactams and glycopeptides. The first ampicillin-resistant enterococcal isolates, described in 1986-1988, were *E. faecalis*, while ampicillin-resistant *E. faecium*, *E. raffinosus* and *E. gallinarum* were reported subsequently [1]. Enterococcal strains resistant to high levels of gentamicin have been found among *E. faecalis*.
and *E. faecium*, and in unusual enterococci, including *E. raffinosus*, a genetic diversity of high-level resistance to gentamicin in enterococci has also been demonstrated [2, 3].

Sahm et al. investigated the reliability of several screening methods for testing aminoglycoside resistance in different enterococcal species. The 85 strains used included five *E. raffinosus* and their profile was as follows: two strains were resistant to gentamicin alone, two others were resistant to both gentamicin and streptomycin, and one isolate was resistant to streptomycin [3].

*E. raffinosus* was described as a new enterococcal species in 1989; it was distinguished from the phenotypically similar species *E. avium* by the ability of the former to metabolize raffinose, a feature not recognizable unless detailed biochemical examination is undertaken [4].

Phenotypic characteristics used for the identification of *E. raffinosus* include acid formation in different carbohydrate broths, such as mannitol, sorbose, arabinose, raffinose, sucrose and sorbitol; utilization of pyruvate; acid production from MGP broth; resistance to erythromycin, but non-hydrolysis of arginine.

The natural habitat of *E. raffinosus* is unknown, but this organism has been described as occurring among the oropharyngeal flora of domestic cats [5].

*E. raffinosus* is occasionally isolated from human clinical specimens [6-7].

There have only been scattered case reports of *E. raffinosus*-related infection in humans in the past 20 years. Reviewing their clinical experience with the increasing occurrence of penicillin and ampicillin resistance among clinical isolates of enterococci from 1981 to 1987, Sapico et al. founded 16 isolates of ampicillin-resistant enterococci; four of the 16 isolates were identified as *E. raffinosus* [8]. Clinical features of the four patients with *E. raffinosus* isolates were females, age 45-86, with underlying illnesses (venous stasis, lower extremities [1 pt]; alcoholic liver disease with ascites [2 pts]; rheumatoid arthritis [1 pt]). Sources of the isolates were: stasis dermatitis ulcer (1), clean-catch urine (1), Bartholini’s gland abscess and rectal swab (1), and clean-catch urine, rectal swab (1). Three patients had received at least one antimicrobial agent within three weeks prior to enterococcal isolation: one patient was treated with dicloxacillin, ampicillin and oxacillin; another patient was treated with oxacillin, and the third patient received neomycin p.o.

In a survey on the incidence of various enterococcal species by Ruoff et al., only one isolate of *E. raffinosus* was reported out of 302 consecutive isolates of enterococci [9]. This isolate was obtained from urine; it was β-lactamase-producer negative and resistant to methicillin and clindamycin as all the other strains, but data on its profile of sensitivity to other antibiotics were not obtained [9].

A prospective review of all enterococcal isolates for 13 months by Oster et al. identified nine (31.6%) isolates of *E. raffinosus*; all isolates were found β-lactamase negative, resistant to ampicillin, and susceptible to vancomycin, teicoplanin and daptomycin [1]. Several isolates exhibited intermediate susceptibility to ciprofloxacin. The majority of the patients concerned were male with a mean age of 66.5 years, and underlying disease included chronic urological abnormalities, wounds and cancer.

Two patients each had a mix of ampicillin-resistant *E. raffinosus* and high-level gentamicin-resistant *E. faecalis*.

A prospective study identified 9 isolates of *E. raffinosus* from hospitalized patients [10]. Clinical characteristics of these patients include: age 50-91, 8 males/1 female, underlying illness in 8 cases, 4 patients underwent surgical procedures and 9 patients underwent urinary tract instrumentation, 1-291 days of hospitalization before isolation, and use of penicillins in 4 patients, cephalosporins in 5 patients and other antibiotics in 8 patients.

Four of the nine patients were infected by *E. raffinosus*: 1 was isolated from blood, 2 from urine, and 1 from bile. Three of these patients had severe underlying diseases and the fourth patient had recurrent urinary-tract infections. Five of the nine patients were colonized with *E. raffinosus*: 2 isolates were from urine, 2 from wounds, and 1 from peritoneal fluid. Seven of the nine *E. raffinosus* isolates were hospital-acquired.

The *E. raffinosus* isolates were β-lactamase negative and resistant to ampicillin-sulbactam, clindamycin, and fosfomycin, but susceptible to vancomycin, daptomycin and ciprofloxacin; no isolates exhibited high-level gentamicin or streptomycin resistance. Prior antibiotic treatment and prolonged hospitalization were considered more frequently associated with patients with ampicillin-resistant *E. raffinosus* [10].

Analysis of the emergence of ampicillin-resistant enterococci was conducted from April 1986
to December 1988 at Miriam Hospital, Providence [11]. During the study period, the number of enterococcal isolates identified remained relatively stable. However, the proportion of ampicillin-resistant enterococci increased. Ampicillin-resistant enterococci isolates were detected from 47 patients, and 9 out of the 47 isolates were *E. raffinosus*. Four patients developed wound infections that yielded the same strain of *E. raffinosus*. Indeed, all these four isolates had identical restriction endonuclease digestion patterns of plasmid DNA, suggesting nosocomial transmission. One patient who had persistent growth of *E. raffinosus* from an intra-abdominal infection developed septic shock and died despite therapy with imipenem. Post-mortem examination showed findings consistent with sepsis and a myocardial abscess that contained ampicillin and imipenem-resistant *E. raffinosus*. Three patients admitted from nursing homes or long-term care facilities with decubitus or foot ulcers yielded *E. raffinosus*. All strains were found resistant to penicillin, ampicillin, and imipenem, and susceptible to vancomycin. Increasing imipenem use appeared to have contributed to the emergence of genetically unrelated strains of ampicillin-resistant enterococci in this institution [11].

A case of vertebral osteomyelitis caused by *E. raffinosus* in an elderly patient as well as microbiological and diagnostic features was described in 2001 [12]. This patient was elderly, had underlying medical problems, and may have been immunosuppressed following steroid therapy.

The case of a haematoma infected by *E. raffinosus* in a 72-year-old patient undergoing immunosuppressive therapy reported in 2005 confirmed the pathogenic potential of this bacterium, although it rarely occurs in humans [13].

The first case of vaginal infection caused by *E. raffinosus* was recently reported; the same authors also reported the first case of a wound ulcer infected with multidrug-resistant *E. raffinosus* [14, 15].

The present report is believed to be the first to report a case of *E. raffinosus* endocarditis.

In various reports *E. raffinosus* constitutes a relatively large proportion of enterococcal isolates resistant to ampicillin (1, 10, 11). *E. raffinosus* is usually represented by a few isolates in vancomycin-resistant enterococci (VRE) survey studies or collections [16]. The only description of clonal spread of vancomycin-resistant *E. raffinosus* concerned a US hospital between December 1995 and February 1996, and affected four patients; in this study the isolates of *E. raffinosus* were initially misidentified as *E. avium* [17]. Indeed, in this report, bacteraemias caused by *E. avium* were observed to be *E. raffinosus* infections (6 of 8 cases, 1.1% of all cases) when biochemical identification methods were applied.

Four vancomycin-resistant *E. raffinosus* strains (van A by PCR) from a single institution had the same phenotypic and molecular pattern, indicating clonal dissemination among four patients over a 66-day period [17]. Since *E. avium* has been more often associated with human infections, and reported as vancomycin-resistant more frequently than *E. raffinosus*, there was a possibility of misidentification of these two species, given the difficulties identifying *E. raffinosus* using broader identification systems [16]. Indeed, Kowalec et al., investigating the genetic background of a VRE outbreak in a large medical centre in Poland, reported the predominance of a single *E. raffinosus* clone, initially identified as *E. avium* with the classical methods, using the VITEK 2 system and the MLSA molecular approach [16]. Grayson et al. were unable to identify any increasing resistance to penicillin among their collection of strains of *E. raffinosus* isolated during the past 14 years [18].

A recent study conducted in southern India reveals the emergence of multi-drug resistance among unusual species of enterococci [7]. In this study, all six strains of *E. raffinosus* showed resistance to ciprofloxacin, while 33.3% were susceptible to penicillin and ampicillin, and 66.6% were susceptible to gentamycin and streptomycin.

None of the isolates was positive for β-lactamase, and all the isolates were susceptible to vancomycin and teicoplanin [7].

In a recent survey performed to detect the prevalence of faecal vancomycin-resistant enterococci in hospitalized patients in Turkey, *Enterococcus* spp was isolated from 81 patient samples and 2.5% were identified as *E. raffinosus* [19]. No vancomycin resistance was detected, and none of the enterococci had β-lactamase activity. A long hospitalization period, antibiotic usage and experience of intra-abdominal operation were found to be significant risk factors for colonization of the resistant bacteria.
Calculating in five hospitals during 1996-1997 in Porto Alegre, Brazil, among a collection of 455 enterococci isolates, *E. raffinosus* was identified in 0.2% (one isolate); this single *E. raffinosus* isolate showed a high-level resistance to ampicillin but was susceptible to gentamicin, streptomycin and vancomycin [20]. The first VanD-type *E. raffinosus* strain was reported in 2006 [21].

*E. raffinosus* strains exhibiting resistance to a variety of antimicrobial agents were isolated from an aquatic environment in Greece; bathing water may contribute to the dissemination of uncommon enterococcal species with resistance to several antibiotics [22]. A considerable percentage of *E. raffinosus* isolates was found to exhibit resistance to erythromycin, rifampicin, ciprofloxacin and streptomycin. Resistance to ampicillin, amoxicillin-clavulanate, vancomycin and gentamicin at high level was not detected in any of the isolates examined in this study. We suggest monitoring the incidence and the degree of resistance of unusual enterococci to β-lactam agents.

This case illustrates the importance of identifying unusual enterococci at the species level. *E. raffinosus* may initially be dismissed as a contaminant in clinical cultures. Improved bacteriologic techniques have allowed detection of cases of infective endocarditis caused by unusual organisms such as *E. raffinosus*.

In addition, accurate identification of *E. raffinosus* would further help investigations defining its pathogenic role in human infections. Isolation of *E. raffinosus* from blood suggests that, in addition to producing bacteraemia or septicaemia, the organism may inhabit heart valves like other *E. faecalis* and *E. faecium* species. Therefore, whenever this non-*faecalis* and non-*faecium* enterococcal organism is found in a patient with endocarditis, early treatment should be considered and close monitoring is essential.

This case reminds the clinician to maintain a high index of suspicion for endocarditis in any patient with persistent low fever, even in the absence of a certain source of infection, and to pursue blood culture results even for rare and unexpected organisms.

**Key words:** *Enterococcus raffinosus*, bacterial endocarditis

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**SUMMARY**

*Enterococcus raffinosus*, a non-*faecalis* and non-*faecium* enterococcus, rarely causes infections in humans.

We describe the first reported case of primary bacterial endocarditis caused by *E. raffinosus*, with a review of the literature.

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**RIASSUNTO**

*Enterococcus raffinosus*, è un enterococco di tipo non-*faecalis* e non-*faecium*, il cui ruolo patogeno dell’uomo è stato dimostrato solo raramente. Nel presente articolo descriviamo il primo caso di endocardite batterica causata da *E. raffinosus* e riportiamo con una rassegna completa la letteratura sull’argomento.

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**REFERENCES**


