Relapse of *Enterococcus hirae* Prosthetic Valve Endocarditis[▽]

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***Enterococcus hirae*, a Gram-positive bacterium, is a rare isolate in clinical specimens. We report an unusual case of a relapse of prosthetic valve endocarditis due to *E. hirae* 6 months after the initial episode. Clonal relationship was proven by genomic analysis.**

CASE REPORT

In April 2008, a 78 year-old woman presented with a 5-month history of fever, generalized weakness, and a 7-kg weight loss. She had a history of diabetes mellitus and hypertension and had undergone in 2001 an aortic valve replacement with a bioprosthetic valve. On admission, her temperature was 38°C, and cardiac examination revealed a 3/6 systolic murmur. Transthoracic and transesophageal echocardiographies showed no evidence of endocarditis.

Five blood cultures yielded colonies of Gram-positive cocci with a morphology typical of *Streptococcus*. On blood agar culture, colonies were circular and smooth and reached 0.2 to 0.5 mm after 24 to 48 h of incubation in the presence of 5% CO_2. The strain was identified by phenotypic determination and genetic analysis. The phenotypic identification was based upon colony and Gram stain morphologies and a negative catalase reaction. The cocci reacted with both Lancefield group F and D antisera (Streptex; Diamondial, Sees, France). The biochemical identification remained difficult even by a semiautomated system. Accurate identification to the species level was not possible with the IDGP N052 card (bioMérieux, Marcy l'Etoile, France) due to low discrimination (50.52% for *Enterococcus durans* and 49.48% for *Enterococcus faecium*). The Rapid ID 32 Strep identification system (bioMérieux) failed, producing an unacceptable profile for *Enterococcus gallinarum* with the current database.

The strain was correctly identified to the species level as *Enterococcus hirae* by genetic methods using 16S rRNA and $sodA_{int}$ gene sequencing (where "int" represents "internal") as previously described (5, 12). Sequence analysis of this strain yielded 99.81% and 99.76% identities with the sequences of the 16S rRNA gene (GenBank accession no. AB362598) of type strain of *E. hirae* and the *sodA* gene (GenBank accession no. AJ387916) of *E. hirae*, respectively. As the growth was deficient, antibiotic susceptibility testing was performed with an agar diffusion technique using a Mueller-Hinton agar supplemented with 5% horse blood (bioMérieux). The strain was susceptible to amoxicillin (MIC, 0.032 μg/ml, as measured by the Etest technique), moxifloxacin, vancomycin, teicoplanin, erythromycin, and rifampin but resistant to clindamycin, tetracycline, and fosfomycin and exhibited low-level resistance to streptomycin, kanamycin, and gentamicin.

Despite our patient's normal echocardiography, a diagnosis of possible infective endocarditis was established (Table 1), and intravenous amoxicillin (200 mg per kg of body weight per day) and gentamicin (3 mg per kg per day) were initiated. After 2 weeks, gentamicin was discontinued and rifampin (20 mg per kg per day) was initiated. Antimicrobial treatment was administered for 6 weeks. The patient improved clinically and became afebrile 48 h after antibiotic initiation, and blood cultures became negative. Colonoscopy investigation revealed multiple colonic polyps, which were endoscopically removed. Histological examination showed no evidence of cancer.

Four months after discontinuation of antimicrobial therapy, the patient was readmitted for fever. Echocardiography showed a vegetation involving the aortic prosthetic valve, and antimicrobial therapy with amoxicillin and gentamicin was initiated. Two days later, the two blood cultures obtained before initiation of antimicrobial therapy yielded a Gram-positive coccus with the same cultural characteristics and the same antibiotic susceptibility pattern as described above, which was identified as *Enterococcus hirae*. A diagnosis of definite endocarditis was made according to the modified Duke criteria (7) (Table 1), and the patient received the same antimicrobial therapy as for the initial episode, i.e., intravenous amoxicillin for 6 weeks, intravenous gentamicin for 2 weeks, and oral rifampin for 4 weeks. Her poor general condition contraindicated surgery.

The evolution was quickly favorable; the patient became afebrile, and blood cultures remained negative. Echocardiography performed 1 month later did not reveal any vegetation or dysfunction of the aortic bioprosthesis. Control by colonoscopy showed a 20-mm colonic polyp, which was removed; histological examination revealed an adenoma without evidence of neoplasia.

Both *E. hirae* isolates were then genetically compared in order to distinguish relapse from reinfection of the endocarditis. Analysis of the genomic patterns of both isolates after pulsed-field gel electrophoresis after restriction with SmaI showed that they were clonally related (Fig. 1), according to the criteria of Tenover et al. (16).

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TABLE 1. List of modified Duke criteria for each episode of endocarditis in our patient[a]

Category	Duke criterion from:	
	First episode	Second episode
Major criteria	5 separate blood cultures yielded *Enterococcus hirae*	Echocardiography was positive for infective endocarditis, with demonstration of aortic vegetation 2 separate blood cultures yielded *E. hirae*
Minor criteria	Bioprosthetic aortic valve Fever	Bioprosthetic aortic valve Fever

[a] Note that the sensitivity of the modified Duke criteria is diminished when infection affects a prosthetic valve.

The patient remained clinically well 1 year after completion of therapy.

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Enterococci are frequently identified as important causes of infections in humans, such as bacteremia, endocarditis, and urinary tract infections. Most enterococcal strains isolated from clinical samples belong to two species, *Enterococcus faecalis* and *Enterococcus faecium*. *Enterococcus hirae* causes infections mainly in various animal species (2, 3), and only three cases of human infection have been reported to date (1, 4, 11). In these three reports, *E. hirae* was responsible for septicemia, spondylodiscitis, and native valve endocarditis.

We describe a case of *E. hirae* prosthetic valve endocarditis, which relapsed despite adequate antibiotic therapy according to the European guidelines (14). The patient initially presented with *E. hirae* bacteremia, and a diagnosis of possible endocarditis was established, as she met one major and two minor criteria of the modified Duke criteria for the diagnosis of endocarditis (7). When bacteremia relapsed, a diagnosis of definite endocarditis was made, as the patient met two major criteria. To the best of our knowledge, our case constitutes the first description of prosthetic valve endocarditis due to *E. hirae* and the fourth report of human infection caused by this bacterium. The source of infection in our patient was probably the digestive tract, as colonoscopy showed multiple colonic polyps. Currently, there is no demonstrated relationship between *E. hirae* infection and colonic pathology, but very few cases of infections due to this particular bacterium have been reported; however, enterococci are commensal species of the human intestinal tract, and *E. hirae* has been involved in colonic pathology in animals (6, 9). Therefore, we decided to perform a colonoscopy in order to seek intestinal disease, as is recommended for other bacteria colonizing the gastrointestinal tract.

The only other reported case of *E. hirae* endocarditis, by Poyart et al. in 2002, was a 72-year-old man with native valve endocarditis who was treated with ampicillin, gentamicin, and rifampin (11). Despite the *in vitro* susceptibility of the strain, this regimen was not able to sterilize the vegetation, and endocarditis recurred 3 months after discontinuation of antimicrobial treatment. The same phenomenon occurred in our patient, although adequate antimicrobial therapy was administered for 6 weeks, suggesting that *E. hirae* is a difficult-to-treat bacterium that causes relapsing infections (8). Moreover, we hypothesize that the particularly low virulence of this strain living likely in a dormant state may explain the delayed relapse. The treatment of infections due to this particular bacterium may necessitate prolonged antimicrobial therapy and a closer surveillance of clinical parameters (echocardiography and blood cultures after discontinuation of antibiotics) in order to detect a relapse. For our patient, we chose to add rifampin to the amoxicillin-gentamicin combination which is recommended for treatment of enterococcal prosthetic valve endocarditis (14). Rifampin has shown good activity against *Staphylococcus aureus* biofilm (13) and is recommended for treatment of staphylococcal prosthetic valve endocarditis (14). However, it has not been extensively studied for *Enterococcus* species infections, although some promising results have been reported (10, 18). As optimal therapy for the treatment of *E. hirae* infection remains unknown and valve replacement was contraindicated for our patient, we hypothesized that the addition of rifampin might optimize antibiotic therapy and reduce the risk of relapse.

Finally, identification of enterococci other than *Enterococcus faecalis* and *Enterococcus faecium*, in the absence of additional tests (11), remains difficult, with potentially serious implications for clinical management. As reported previously, the Vitek2 automated system may experience difficulties in properly identifying *E. hirae* and *Lactococcus garvieae*, another Gram-positive coccus involved in endocarditis. Accurate identification of enterococci can be achieved with molecular techniques (17).

Thus, misidentification of unusual *Enterococcus* species by the different semiautomated commercial identification methods might occur, and accurate molecular identification is required, as this species remains rare (8, 15).
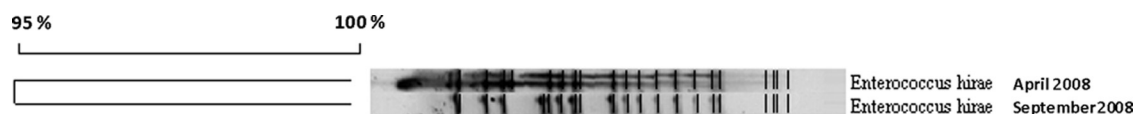

FIG. 1. Pulsed-field gel electrophoresis banding patterns after SmaI digestion of both clinical isolates of *E. hirae*. Percentages of similarity are shown above the dendrogram. Isolate dates are on the right.

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