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Lactococcus garvieae endocarditis in a patient with colonic diverticulosis: first case report in Italy and review of the literature

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SUMMARY

Lactococcus garvieae is a human opportunistic pathogen with low virulence, but it is a well-known pathogen in aquaculture. A total of 21 human infections have been reported in the literature, mostly endocarditis. Automated methods can wrongly identify this microorganism as *Enterococcus spp* with a non-standard phenotype, leading to an underestimation of the incidence of this infection. The route of infection could be the ingestion of raw fish, grilled fish or fresh dairy products. We describe the first case of *L. garvieae* mitral valve endocarditis in Italy, in a patient with mitral valve repair with autologous pericardium, mechanic prosthetic aortic valve and colonic diverticulosis.

KEY WORDS: Endocarditis, Lactococcus garvieae, Diverticulosis, Mitral valve.

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INTRODUCTION

Lactococcus genus was separated from *Streptococcus* genus in 1985 on the basis of genetic analysis (Schleifer *et al*., 1985), but it is still often misidentified as a variant of *Enterococcus spp* (Vinh *et al.,* 2006; Li *et al.,* 2008). *Lactococcus* genus is composed of eight species and subspecies, of which *Lactococcus lactis* and *Lactococcus garvieae* are mostly involved in human pathology (Boone *et al.,* 2001) and seem to behave like opportunistic agents with low virulence (Fihman *et al.,* 2006). *L. garvieae* is a catalase-negative, facultatively anaerobic, serogroup N, gram-positive coccus, originally described as *Streptococcus garvieae* and isolated from cases of bovine mastitis (Facklam *et al.,* 1995). *L. garvieae* is a major pathogen in aquaculture, with an endemic peak during the summer (Wang *et al.,* 2007). In 1991 it was identified as a pathogen in 21 human infections (Fefer *et al.,* 1998; James *et al.,* 2000; Mofredj *et al.,* 2000; Furutan *et al.,* 2001; Fihman *et al.,* 2006; Vinh *et al.,* 2006; Wang *et al.,* 2007; Yiu *et al.,* 2007; Li *et al.,* 2008; Aubin *et al.,* 2011; Chan *et al.,* 2011; Hirakawa *et al.,* 2011; Nadrah *et al.,* 2011; Watanabe *et al.,* 2011; Wilbring *et al.,* 2011; Zuily *et al.,* 2011). We describe the first case of *L. garvieae* infection in Italy involving a repaired mitral valve in a patient with aortic prosthetic valve and colonic diverticulosis.

CASE REPORT

A 63-year old man was admitted to our division for seven-day history of fever with chills, pharyngodynia, and generalized weakness. His medical history included a type A aortic dissection 15 years before, treated with replacement of the ascending aorta and aortic valve with a composite

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graft. At that time he started both anticoagulant treatment and therapy for severe arterial hypertension. Seven years later an abdominal aortic aneurysm was diagnosed. After three years, the patient developed aortic prosthetic valve endocarditis and severe mitral insufficiency: thus, aortic valve substitution with mechanical prosthesis and mitral valve plastic surgery with autologous-pericardium were performed. Few months later, the patient was again admitted to hospital for an aortic prosthetic valve endocarditis due to *Enterococcus faecalis*. A colonoscopy was performed showing diverticulosis. After two years, the patient underwent a deep dental tartar ablation without antibiotic prophylaxis and developed a new episode of aortic prosthetic valve endocarditis due to *E. faecalis*; at that time, a colonoscopy showed diverticulosis with signs of diverticulitis.

On the present admission, the patient was febrile (38.5°C), tachycardic (94 beats/minute), with arterial blood pressure of 100/60 mmHg. Physical examination revealed a grade III/VI mitral systolic murmur, and an aortic systolic click; moderate hepatomegaly and abdominal soft murmur over abdominal aorta; hypotrophy and hypotonia of the left leg as infantile poliomyelitis sequela. Laboratory data showed anaemia (Red Blood Cells count 3440000/mmc; haemoglobin 9.9 g/dl), moderate neutrophilia (81%) with normal leucocyte count (White Blood Cells count 8600/mmc), high reactive C-protein (RCP 9.1 mg/dl; normal value <0.5 mg/dl), lactate dehydrogenase (LDH 394 UI/L; normal value 40-480 UI/L), rheumatic factor within normal range; the pre-therapeutic creatinine clearance was 71 ml/min; microscopic examination of urine sediment showed haematuria.

Three blood cultures were taken from separate venipuncture at 30-minute intervals and a trans-oesophageal echocardiography (TOE) disclosed a vegetative mass on the mitral valve annulus. Considering the patient's cardiologic history and the lack of involvement of the mechanical prosthetic aortic valve, an empiric antibiotic treatment for infective endocarditis with vancomycin 500 mg every 6 h plus gentamicin 80 mg every 8 h was started. After 72 h of incubation, the three blood cultures showed the growth of *L. garvieae* and the empiric antibiotic therapy was continued. Creatinine clearance was 68 ml/min and 51 ml/min at the end of the 1st and 2nd week of treatment, respectively. After two weeks of treatment, gentamicin was stopped and vancomycin was replaced by ampicillin 3 g every 6 h, because of high pre- and post-administration serum vancomycin concentrations (40 pg/ml and 54 pg/ml respectively; normal range 5-10 pg/ml and 20-40 pg/ml respectively).

At the end of the 1st week of antibiotic treatment the patient was no longer febrile; a control TOE, performed at the end of the 4th week of antibiotic therapy, showed disappearance of the mass on the mitral valve annulus and RCP was normal. The patient was discharged with specific nutritional advice, and the prescription of intestinal disinfection in the first two weeks of each month alternating two different intestinal antibiotics (rifaximin or neomycin plus bacitracin). The patient remained clinically well after 6 months of follow-up, and monthly controls of inflammatory markers and serum creatinine, were persistently normal; the TOEs, performed every three months, did not show any sign suggestive for endocarditis.

Our isolate was a gram-positive, catalase-negative, non-haemolytic, non-mobile coccus, able to grow at 10°C but not at 45°C (unlike the genus *Enteroccocus*), positive at bile-esculin reaction, facultative anaerobic with similar biochemical characteristics to *Enterococus spp*, although it was Lancefield serogroup D-negative. It did not require particular growth conditions and it was detected in common culture media. Species identification was performed by both manual (API Rapid ID 32 Strep system, bio-Merieux) and automated (Vitek® 2 cards, bio-Merieux) biochemical methods.

The identification of *L. garvieae* was excellent (99.9%) through both techniques. Molecular methods based on the 16S rRNA gene sequences (1500 bases), confirmed the presence of *L. garvieae* with 100% identity with the corresponding sequences of the type strain of *L. garvieae* ATCC 49156 (Patel *et al.,* 1998). The antibiotic susceptibility pattern was performed by both the Vitek® 2 and the E-test method (Fihman *et al.,* 2006), but the results of the latter were considered more reliable.

Concerning the E-test, plates containing Brain Hearth Infusion agar (BHI agar-BD) were used, and antimicrobial agents were tested at concen-

TABLE 1 - *Pattern of antibiotic susceptibility of Lactococcus garvieae isolated in our patient (E-test method).*

Antibiotic	*MIC (mcg/ml)*	*Interpretation*
Erythromycin	0.125	S
Penicillin	2	I
Cefotaxime	0.5	S
Levofloxacin	0.5	S
Tetracycline	0.5	S
Imipenem	0.023	S
Ampicillin	0.25	S
Amoxicillin/Clavulanic Acid	0.5	S
Ciprofloxacin	0.75	S
Daptomycin	0.125	S
Rifampin	>64	R
Bacitracin	>64	R
Clindamycin*	>64	R
Vancomycin	2	S
Gentamicin	2	S
Teicoplanin	0.5	S

**Lactococcus garvieae*, unlike *L. lactis*, is resistant to clindamycin.

trations ranging from 0.016 to 256 mcg/ml. The agar plates were inoculated by confluent swabbing of the surface with the adjusted *inoculum* suspension.

The E-test strips were aseptically placed onto the dried surfaces of each inoculated agar plate. The minimal inhibitory concentrations (MICs) were read after 24 hours of incubation following manufacturer's instructions.

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for streptococci, our strain was considered resistant to clindamycin, bacitracin, rifampin and susceptible to the other antibiotics listed in the Table 1.

DISCUSSION

The case we report here is the 14th described case of *L. garvieae* infective endocarditis, the first in Italy, and the first involving a mitral valve repaired with autologous pericardium, affecting a patient with colonic diverticulosis. In our patient the present infective endocarditis was the 4th episode over a 6-year period. The first episode, which occurred in the absence of microbiological identification, involved prosthetic aortic valve leading to surgical replacement of the mechanical prosthesis. The second and third episodes of endocarditis, both involving aortic prosthetic mechanical valve, were due to *E. faecalis*. Biochemical identification of such strains was further revaluated and the hypothesis that they could belong to *Lactoccoccus* genus was excluded. Concerning the present endocarditis, which involved the mitral valve (previously repaired with autologous pericardium) and which was due to *L. garvieae*, the diagnosis was performed according to Duke's criteria (2 major criteria were met) (Durack *et al.,* 1994). The empiric antibiotic treatment administered after blood culture sampling did not include rifampin because of a major interaction with current oral anticoagulant treatment. Furthermore, the involvement of the prosthetic aortic valve was excluded with a TOE performed within 24 hours after hospital admission. Considering the recurrence of endocarditis and the colonic diverticulosis affecting our patient, a colectomy was recommended, but the patient refused the operation. For this reason, at discharge and in order to reduce the risk of diverticulitis and consequent bacteraemia, an intestinal disinfection in the first 2 weeks of each month, alternating rifaximin with neomycin plus bacitracin was prescribed.

L. garvieae is considered a rare human pathogen with low virulence but it is a well-known fish pathogen, especially in cultured marine and freshwater fish species, and it is also found as a contaminant in dairy products (Fortina *et al.*, 2007).

In the majority of the case reports, the ingestion of contaminated food is the most probable source of the infections due to *L. garvieae* (Table 2). Our strain was lactase negative and this phenotype is more frequent in the strains isolated from fish (Fortina *et al.*, 2007). Consequently the ingestion

TABLE 2 - *Clinical characteristics of the 21 cases of Lactococcus garvieae associated infections (published in literature since 1991).*

References	*Age/sex*	*Type of infection*	*Predisposing conditions*	*Risk factor*	*Comorbidities*	*Therapy (duration)*	*Outcome*
Aubin et al., 2011	71/F	Hip prosthesis infection	Hip prosthesis	Fishmonger	Obesity, AH, DM, alcohol abuse, ischemic cardiomyopathy, hemochromatosis	CTX & LEV (12 weeks)	Clinical improvement
Chan et al., 2011	70/M	Spondy-lodiscitis	Antacid therapy	/	/	AMP (6 weeks)	Clinical improvement
Hirakawa et al., 2011	58/F	PMV IE	Metallic PMV	Gingival perforation with a "fish bone"	AH, DM, Dyslipidemia	VAN (4 weeks)	Clinical improvement
Nadrah et al., 2011	81/M	Bacteremia	PMV, PAV, Tricuspid valve plastic, pacemaker	Diverticular disease	CHF, AH, CRF, anemia, reflux esophagitis, hypothyroidism	TZP. Then AMP (6weeks) & GEN (first 15 days)	Clinical improvement
Watanabe et al., 2011	55/F	NMV IE	/	/	/	PEN G & GEN. Then CTX & GEN (9 weeks)	Mycotic aneurysm, pneumonia, renal embolism
Wilbring et al., 2011	55/M	PTV IE	Mechanic PTV, chronic parodontitis	Fish farmer	Previous NTV IE	VAN & GEN. then AMC & LEV (8 weeks)	Clinical improvement
James et al., 2010	56/F	Osteomyelitis and possible endocarditis	Xenograph PAV	/	/	VAN. Then Teico (12 weeks)	Clinical improvement
Zuily et al., 2010	64/F	PMV IE	Metallic PMV, pacemaker, colon polyp	/	Pacemaker, paroxysmal atrial fibrillation, HCV cirrhosis	AMX & GEN (6 weeks)	Clinical improvement
Li et al., 2008	41/M	NMV IE		Chef by profession	/	PEN G & GEN (30 days)	Mitral valve replacement
Yiu et al., 2007	67/M	NMV IE	/	/	CAF, rheumatic heart disease, previous NMV IE	AMP (6 weeks) plastic	Mitral valve
Vinh et al., 2006	80/M	NAV IE	Polyp(s)?	/	DM, hypercho-lesterolemia, coronary artery disease, remote resection of malignant colonic polyps	AMP (6 weeks)	Aortic valve replacement with bioprosthesis

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→ *References*	*Age/sex*	*Type of infection*	*Predisposing conditions*	*Risk factor*	*Comorbidities*	*Therapy (duration)*	*Outcome*
Fihman et al., 2006	86/F	PAV IE	Aortic valve bioprosthesis	Duodenal ulcer		AMX & GEN (7 weeks)	Clinical improvement
Wang et al., 2007	72/M	NMV IE	Mitral valve prolapsed, gastric ulcer	Eating of raw fish	Kidney stones, intermittent epigastralgia	PEN G (4 weeks) & GEN (2 weeks)	Clinical improvement
	10/M	Sepsis	Oesophageal stenosis, subcutaneous colon interposition	Eating of grilled Tilapia fish	/	/	Death
	56/F	Bacteremia	Small bowel diverticulosis	/	Asthma, Hyperthyroidism, AH	CEF & GEN (2 days). Then SXT (5 days)	Clinical improvement
	47/M	Peritonitis	Car accident with intestinal perforation	Eating of raw fish	/	PIP & AMK (1 week)	Clinical improvement
Mofredj et al., 2000	68/F	Liver abscess	Steroid therapy Teflon biliary prosthesis	/ Carcinoma	Cholangio-	AMX, NET & MTZ	Death
Fefer et al., 1998	84/F	NMV IE	Pacemaker Aortic valve bioprosthesis Antacid therapy	/	Hypertrophic cardiomyopathy, complete hearth block, hypothyroidism, immune thrombocytopenic purpura	CTX	Mitral valve replacement, cerebral hemorrhage, death
Furutan et al., 1991	NA	Prosthetic valve infective endocarditis	NA	NA	NA	NA	NA
	NA	Prosthetic valve infective endocarditis	NA	NA	NA	NA	NA
	NA	Prosthetic valve infective endocarditis	NA	NA	NA	NA	NA

M, male; F, female; NA, not available; PMV IE, prosthetic mitral valve infective endocarditis; NMV IE, native mitral valve infective endocarditis; PTV IE, prosthetic tricuspid valve infective endocarditis; NTV IE, native tricuspid valve infective endocarditis; PAV IE, prosthetic aortic valve infective endocarditis; NAV IE, native aortic valve infective endocarditis; PMV, prosthetic mitral valve; PAV, prosthetic aortic valve; PTV, prosthetic tricuspid valve; AH, arterial hypertension; DM, Diabetes mellitus; CHF, congestive heart failure; CRF, chronic renal failure; CAF, chronic atrial fibrillation; VAN, vancomycin; PEN G, penicillin G; GEN, gentamicin; CTX, ceftriaxone; AMP, ampicillin; LEV, levofloxacin; AMC, amoxicillin clavulanic acid; AMX, amoxicillin CEF, cefazolin; SXT PIP, piperacillin; AMK, amikacin; NET, netilmicin; MTZ, metronidazole; Teico, teicoplanin; TZP, piperacillin and tazobactam.

of contaminated fish could be the source of infection. The exact incidence of such infection cannot be defined because of the difficulties in the distinction of *Lactococcus spp.* from *Enterococcus spp* using biochemical reactions only (Teixeira *et al.,* 1996). Automated phenotypic systems, such as Vitek® and MicroScan® (Dade Bhering, West Sacramento, CA), may not correctly identify *Lactococcus* genus without additional tests. As occurred in our case, a more precise identification of *Lactococcus spp.* can be achieved with molecular techniques, including 16S rRNA gene sequencing (Zlotkin *et al.,* 1998). Concerning antibiotic susceptibility testing, Vitek® 2 is an automated method but it is not the gold standard for *Lactococcus spp*. Based on a better pattern of antibiotic release, the most reliable method for antibiotic susceptibility testing for this microorganism is the E-test (Fihman *et al.,* 2006). The pattern of antibiotic susceptibility can help to discriminate among *Lactococcus* species: resistance to clindamycin is a feature of *L. garvieae* whereas *L. lactis* is always susceptible (Elliott *et al.,* 1996). An analysis of the case reports published over the last 20 years, showed 21 cases of *L. garvieae* related infections (Table 2): 13 infective endocarditis (6 native valves infections and 7 prosthetic valve infections) (Fefer *et al.,* 1998; Furutan *et al.,* 2001; Fihman *et al.,* 2006; Vinh *et al.,* 2006; Wang *et al.,* 2007; Yiu *et al.,* 2007; Li *et al.,* 2008; Hirakawa *et al.,* 2011; Watanabe *et al.,* 2011; Wilbring *et al.,* 2011; Zuily *et al.,* 2011), 3 cases of bacteremia, of which 2 without definite infective focus, the third associated with diverticulitis (Wang *et al.,* 2007; Nadrah *et al.,* 2011), one peritonitis (Wang *et al.,* 2007), one liver abscess (Mofredj *et al.,* 2000), one osteomyelitis with possible endocarditis (James *et al.,* 2000), one spondylodiscitis (Chan *et al.,* 2011), and one hip prosthesis infection (Aubin *et al.,* 2011). Most of patients were elderly, with underlying disease and predisposing factors, such as prosthetic heart valve, gastrointestinal tract lesions (ulcers, polyps), use of antacid drugs. Some patients had a history of consumption of raw or grilled fish, or were in close contact with raw fish because of their work. All patients were treated with antibiotic therapy, mainly β-lactam antibiotics, with clinical improvement. Only three cases of death are reported (Table 2).

L. garvieae seems to behave like an opportunistic pathogen in the elderly, in immunocompromised subjects, in individuals affected by malignancy or cardiovascular diseases and in carriers of prosthetic valves. In our patient we recognized 4 risk factors for *L. garvieae* endocarditis: age, cardiovascular disease, the presence of a prosthetic valve and surgically modified mitral valve. In the present case we can consider as further risk factors the chronic use of antacid drugs, the eating of Italian naturally fermented cheese and fish (James *et al.,* 2000, Fortina *et al.*, 2007) and the colonic diverticulosis with recurrence of diverticulitis.

In conclusion, *L. garvieae* is a human opportunistic pathogen which most common presentation is infective endocarditis (14/22 reported cases, including our patient), involving native (n=6), prosthetic (n=7) or repaired (n=1) valve. The route of infection can be the ingestion of contaminated raw fish, grilled fish or not matured cheese. Because of the increasing development of aquaculture in which *L. garvieae* can cause seasonal outbreaks, the number of human cases of *L. garvieae* infection is expected to arise. Moreover, the exact incidence of *L. garvieae* infection is unknown because of misidentification using automated systems. Consequently, *L. garvieae* should be taken into consideration in patients with endocarditis due to *Enterococcus spp.* with non-standard phenotype.

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