A case of Lactobacillus casei bacteraemia associated with aortic dissection: is there a link?

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SUMMARY

We describe an unusual case of *Lactobacillus casei* bacteraemia in a heavy dairy consumer woman, with a one month history of low grade fever and admitted to our hospital for sudden onset of severe thoracic pain due to dissection of the aortic arch and ascending aorta. The patient underwent four weeks of intravenous ampicillin (2 g every 4 hours) followed by 2 weeks of oral amoxicillin (1 g every 8 hours) with resolution of fever, thoracic pain and progression of aortic disease. On the basis of the patient's symptoms, a possible penetration of *L. casei* in an aortic wall defect with development of aortic dissection is hypothesized.

KEY WORDS: Lactobacillus casei bacteraemia; Aortic dissection, Heavy dairy consumption, Intravascular infection, Low grade fever, Aortic wall defect

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INTRODUCTION

Lactobacillus is a gram-positive, rod-shaped, anaerobic facultative bacterium that varies from long and slender forms to short coccobacilli, occasionally forming short chains (Koneman *et al.,* 1992). It is a common inhabitant of the human mouth, gastrointestinal tract and female genital tract (Sussman *et al.,* 1986; Bayer *et al.,* 1978). Some species of *Lactobacillus* are utilized as probiotic bacteria and have been shown to be effective in the treatment of diarrhea, antibiotic-associated diarrhea, and candidal vaginitis (Alvarez-Olms *et al.,* 2001).

These micro-organisms are rarely infectious and their presence as commensals in the gastrointestinal tract is associated with protection against pathogens, stimulation of the immune system and positive effects on health and host nutrition (De Champs *et al.,* 2003). They are also found in vegetable matter, in milk products and other chilled food products.

Although lactobacilli are usually considered contaminants in blood cultures, they have been identified in some clinical reports as agents of dental caries, infectious endocarditis, bacteraemia, urinary tract infections, corioamniotitis, endometritis, meningitis and intra-abdominal, liver and spleen abscesses. Commonly, these infections can be correlated with previous illnesses (recent surgery, transplants, valvulopathy, diabetes mellitus, AIDS and cancer) and with either immunosuppressive therapy or antibiotic treatment. A recent review in the literature show that about two-thirds of the patients with *Lactobacillus casei* bacteraemia have an underlying structural heart disease or the presence of valvular or aortic prosthesis, and may develop intravascular infection (Cannon *et al.,* 2005). In some cases "heavy dairy consumption" was noted as a possible risk factor. We report here the unusual case of a woman with aortic prosthesis in the thoracic and abdominal tracts and a one month history of low grade fever, eventually found to be caused by *Lactobacillus*

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casei, who was admitted to our hospital for the sudden onset of severe thoracic pain due to dissection of aortic arch and ascending aorta.

Case presentation

A 75-year-old woman was admitted to hospital in September 2008 for the occurrence of retrosternal pain, lasting about 2 days, radiating to the armpit and to the back. For about 1 month before hospitalization, the patient reported low grade fever in the absence of other symptoms, refractory to oral macrolide therapy.

The patient was suffering from hypertension, which was treated with thiazide diuretic and ACE-inhibitors, previous placement of a prosthesis in the thoracic aorta, about 8 years before, and an abdominal prosthesis, about 3 years before, for aortic dissection. The patient's medical history was negative for atherosclerotic disease of the aorta, previous dental procedures, gastrointestinal, hepatic or genitourinary diseases.

On admission, clinical examination was negative, except for the presence of fever (37.5°C) and reduced pressure of the radial artery in the left wrist with a pressure gradient of 60 mmHg to the left. CT scans showed dissection of the aortic arch and ascending aorta. Results from blood tests showed anaemia (Hb 11.2 g/dl) with a progressive haemoglobin decrease (nadir 8 g/dl), WBC 11540 mm^3 with neutrophils 85%, raised erythrocyte sedimentation rate (82 mm/h) and CRP (10.3 mg/dl) levels. Urine analyses showed microhematuria. Urine culture was performed but yielded no microbial growth.

Due to persistence of fever a central venous catheter (CVC), inserted on admission, was removed and 6 blood cultures sets were performed over a 10 day period: 4 blood cultures were performed in the presence of fever and 2 in the absence of fever after the start of targeted intravenous antibiotic therapy with ampicillin.

Cultures of the CVC yielded no microbial growth, but a gram-positive bacillus was isolated from all blood cultures.

The patient also presented an episode, resolved spontaneously, of monolateral loss of vision which was interpreted as a possible consequence of cerebral microembolization. MR brain scans did not show any alteration.

No endocardial vegetation was seen on transesophageal echocardiography examination.

Bacterial strain identification was performed by 16S rDNA amplification with primers 27f and 907 R followed by direct double strand sequencing of PCR product. After overnight culture, bacterial cells were subjected to freeze-thawing four times and heated at 95°C for 20' to obtain cell homogenates. By centrifugation at 3000 rpm for 10', supernatants were collected and used for PCR reaction. Sequences were analyzed by the Blast software of the National Center for Biotechnology Information (NCBI) (Johnson *et al.,* 1994). By 16S rDNA sequencing and Blast analysis bacterial strain identification was possible. 16S rDNA sequence matched with *Lactobacillus casei* and *paracasei* strains with sequence homology of 98%.

The antibiotics susceptibilities were evaluated by the automated Phoenix system (Becton Dickinson), and with E test (AB Biodisk). MIC obtained with Phoenix system were as follows: penicillin G <2 mg/L; ampicillin <1 mg/L; cefazolin 16 mg/L; quinupristin/dalfopristin 2 mg/L; teicoplanin >16 mg/L; vancomycin >16 mg/L; linezolid 2 mg/L. Susceptibilities to tigecyclin (MIC 0,25 mg/L) and daptomycin (MIC 0,064 mg/L) were obtained with E test.

The patient underwent four weeks of intravenous ampicillin (2 g every 4 hours), treatment followed by 2 weeks of oral amoxicillin (1 g every 8 hours), with a prompt resolution of fever and thoracic pain, and progressive decrease to normal values of ESR and CRP.

Blood cultures performed under antibiotic therapy, and one and six months after antibiotics discontinuation yielded no microbial growth. CT scans performed one month after discharge did not show any progression of aortic dissection.

DISCUSSION

The clinical significance of *Lactobacillus* isolated from normally sterile sites is a subject of ongoing debate. Some believe this organism should never be dismissed as a contaminant (Antony *et al.,* 1998). Others comment that "not all positive blood cultures for lactobacilli are clinically significant, and lactobacilli are occasional contaminants" (Husni *et al.,* 1997). Lactobacilli are ubiquitous and inhabit a wide variety of habitats, including the gastrointestinal tract, oral cavity and vagina. Furthermore, these bacteria are tradi-

tionally used in the manufacture of fermented foods and as probiotics. They are also found in vegetable matter, in milk products and other chilled food products. Debate also surrounds the safety of *Lactobacillus* used as a probiotic and its link to infections, specifically in immunocompromised patients (Salminen *et al.,* 2004). Despite these opposing views, *Lactobacillus* has been implicated in various types of infection. Among pathogenic species in humans, *Lactobacillus casei* appears to be the most frequently isolated *Lactobacillus spp.*, although *L. paracasei* and *L. rhamnosus* are also encountered in clinical situations (Antony *et al.*, 1998; Elting *et al.,* 1997).

Bacteraemia results in significant morbidity and mortality, especially among immunocompromised patients, but it is uncommon among immunocompetent people without risk factors for bloodstream infections.

Several studies have demonstrated that specific *Lactobacillus* species, isolated from patients with endocarditis, possess pathogenic traits, such as platelet aggregation, binding to fibronectin, fibrogen and collagen, and production of enzymes enabling the breakdown of human glycoproteins and the synthesis of human fibrin clots. All of these characteristics allow the organism to survive and to colonize vascular surfaces, with the possible formation of biofilm (Harty *et al.,* 1993). Moreover, lactobacilli were examined for the production of glycosidases and proteases (arylamidases) that could be associated with the ability to grow in vivo and/or be a factor in the pathogenesis of endocarditis; the combined production of beta-N-acetyl-D-glucosaminidase and alpha-D-galactosidase was a feature of the endocarditis isolates, with activation of protein C-like, activated factor X-like and Hageman factor-like followed by kallikrein-like and chymotrypsin-like enzymes (Oakey *et al.,* 1995).

The data reported in the literature on *Lactobacillus casei* bacteraemia and endocarditis show that about two-thirds of the patients had an underlying structural heart disease and 12% reported a previous episode of endocarditis. A dental procedure or a dental condition was a possible predisposing cause in 47% of the cases. Of interest, in our patient (a farmer who lived in the countryside with a substantial consumption of cheese), as in three of 73 cases described in a recent review, "heavy dairy consumption" was noted as a possible risk factor (Cannon *et al.,* 2005; Zé-Zé *et al.,* 2004).

In the present case transesophageal echocardiography did not disclose typical endocardial lesions. In any case, multiple positive blood cultures, also in the absence of fever, for the same organism over a 10 day period, associated with persistent fever, microhematuria and a probable cerebral microembolization, strongly suggest an intravascular infection (The Task Force, 2004). Isolation of the organism from the 2 blood cultures performed in the absence of fever is probably due to the ability of the organism to survive and to colonize vascular surfaces, with the possible formation of biofilm.

Of interest, a striking feature of this case was the suggestive association between the persistent low grade fever, caused by an indolent continuous *L. casei* bacteraemia, and the development of aortic arch and ascending aorta dissection. These events lend support to the hypothesis of penetration of *L. casei* in an aortic wall defect that may have triggered the development of aortic dissection. Moreover, targeted intravenous antibiotic therapy resulted not only in the clearance of bacteraemia, with resolution of fever, but also in the disappearance of thoracic pain without progression of the aortic dissection.

Lactobacillus can go unrecognized by clinical laboratories, since growth of some strains requires special media and extended incubation (Salminen *et al.*, 2006). However, isolates are often only identified by genus and the most automated identification systems are not capable of accurate differentiation of *Lactobacillus* species (Wallet *et al.,* 2002). Even after recovery and isolation, *Lactobacillus* can be problematic to identify correctly by most commercial identification systems (Elting *et al.,* 1997; Murray *et al.,* 2003).

Other factors may also make the identification of lactobacilli difficult. Microscopy reveals that *Lactobacillus* morphology resembles members of other genera, including *Corynebacterium*, *Clostridium*, *Nocardia*, and *Streptococcus*. In addition, it may be confused with diphtheroids on Gram stain and dismissed as a contaminant.

Most experts agree that the treatment of choice for serious *Lactobacillus* infections should consist of high-dose intravenous penicillin or ampicillin plus an aminoglycoside (typically gentamicin) for synergy. The sensitivity data from these

cases suggest that ampicillin plus gentamicin may be a better empiric option than penicillin and gentamicin (Bayer *et al.,* 1980). In *vitro* preliminary studies suggest that linezolid or daptomycin may offer alternative treatment options (Goldstein *et al.,* 2004). More important, a peculiar feature of *Lactobacillus spp*. (except *L. acidophilus*) is the resistance to vancomycin (Salminene *et al.,* 2004; Swenson *et al.,* 1990). In the setting of bacteraemia caused by gram-positive organisms, in a patient with health-care contacts and intravascular prosthesis, empiric vancomycin may appear a reasonable option.

In summary, *Lactobacillus* can cause a variety of infections but it is most commonly associated with bacteraemia and endocarditis. The case here reported suggest that aortic dissection secondary to hematogenous penetration in aortic wall defects may represent an additional complication of *Lactobacillus casei* bacteraemia.

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