Case Report

Eggerthella lenta bacteraemia in a patient with Caroli disease

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Introduction: *Eggerthella lenta* is an obligate anaerobic, non-spore-forming, Gram-positive rod found as a normal commensal of the human intestinal flora, which is capable of reducing digoxin into several metabolites. Disease caused by this micro-organism is unusual, although more frequent than reported.

Case presentation: A 74-year-old man presented to the emergency room and was admitted with a mild acute cholangitis syndrome. One anaerobic blood culture became positive after 5 days of incubation. After an additional 5 days, the usual aerobic subcultures were negative, whereas anaerobically incubated Columbia blood agar presented tiny smooth colonies. The isolate was capable of reducing digoxin and was identified as *Eggerthella lenta*. Adequate antibiotic treatment with meropenem had been started and the patient recovered fully.

Conclusion: We have described a patient with a potentially fatal bacteraemia with *E. lenta* that may have gone unnoticed. More case reports are necessary, not only to understand the pathogenicity and clinical course of infections by this neglected bacterium, but also to investigate its digoxin degradation and antimicrobial susceptibility variability.

Introduction

Eggerthella lenta (formerly *Eubacterium lentum*) is an obligate anaerobic, non-spore-forming, Gram-positive rod found as a normal commensal of the human intestinal flora. Of note, these bacteria are capable of reducing digoxin into several metabolites (Robertson *et al.*, 1986), which could affect patients taking this drug. Disease due to this micro-organism is unusual, but central nervous system (Arias *et al.*, 2006), articular (Pardo Sánchez *et al.*, 2008; Bok & Ng, 2009), blood (Thota *et al.*, 2011; Venugopal *et al.*, 2012) and disseminated infections (Salameh *et al.*, 2012) have been reported. In this case report, we describe bacteraemia in a patient with Caroli disease and attempt to add some insight to our understanding of this neglected pathogen.

Case report

A 74-year-old man presented to the emergency room with 24 h of epigastric pain, nausea, post-prandial vomiting, chills and

fever up to 40 °C. Four years earlier, he had undergone cholecystectomy with choledochoduodenostomy due to several episodes of choledocholithiasis, cholangitis and pancreatitis, and had remained asymptomatic since. On presentation, he was on paracetamol and had taken 500 mg cefuroxime as prescribed by his general practitioner. Physical examination and routine laboratory testing did not reveal any abnormalities, except for a neutrophilic leukocytosis with a white cell count of 31900 leukocytes μl^{-1} (93.6 % neutrophils, 1.8 % lymphocytes, 4.4 % monocytes, 0.1 % eosinophils, 0.1 % basophils) and elevation of liver enzymes: aspartate aminotransferase of 110 U l^{-1} , alanine aminotransferase of 90 U l^{-1} , bilirubin of 2.14 mg dl^{-1} and C-reactive protein of 182 mg l^{-1} . An abdominal ultrasound was performed at the emergency room and showed intrahepatic pneumobilia. Although current guidelines recommend obtaining three sets of blood cultures to increase the chances of microbial identification, only two sets were drawn before intravenous antimicrobial treatment with 1 g meropenem every 12 h was started.

The patient was admitted with a mild acute cholangitis syndrome. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography were performed, which demonstrated diffuse cholangiopathy consistent with acute cholangitis. The patient's fever and symptoms subsided after 3 days of meropenem treatment, and after 7 days on meropenem, the patient recovered fully and was discharged.

Blood cultures were incubated in BacT/ALERT 3D (bioMérieux) and one anaerobic bottle became positive after 5 days of incubation. A Gram-stain revealed slender, pleomorphic, Gram-positive rods that even formed small chains mimicking a *Streptococcus*-like appearance. The usual aerobic subcultures were negative after 5 days, whereas anaerobically incubated Columbia blood agar presented tiny smooth colonies. This isolate was identified as *E. lenta* by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Microflex LT; Bruker Daltonics) and Vitek 2 ANC ID card (bioMérieux). Antimicrobial susceptibility testing was performed by the E-test method on supplemented *Brucella* blood agar. The isolate was susceptible to imipenem, meropenem, metronidazole and clindamycin but resistant to cefuroxime, ceftriaxone and cefotaxime.

At the time of this episode, all bile duct abnormalities were attributed to cholangitis, and Caroli disease was not considered. A year later, the patient presented a new episode of acute cholangitis and an abdominal ultrasound showed pneumobilia and dilated bile ducts, chiefly in the left lobe of the liver, whilst magnetic resonance imaging showed multiple segmented cystic and fusiform dilatations of the left intrahepatic biliary tract. Thus, the patient was diagnosed with Caroli disease.

Investigations

In order to add evidence to our identification, we conducted an experiment to test the ability of the isolate to reduce digoxin by incubating it at an approximate concentration of 1.5×10^6 bacteria ml^{-1} in tryptic soy broth (TSB) supplemented with approximately 2 ng digoxin ml^{-1} . TSB without the micro-organism was used as negative control, and both *E. lenta* and the control were incubated in an anaerobic atmosphere at 36 °C. After 4 days, a 10 % reduction in the level of digoxin was detected in the medium with *E. lenta* but not in the control. This reduction was 21 % after 7 days. Digoxin levels were measured with a micro-particle enzyme immunoassay (AxSYM Digoxin II; Abbott Laboratories).

Discussion

Bacteraemia by *E. lenta* occurs chiefly as a secondary translocation into blood from the gut in patients with underlying malignancies and gastrointestinal disorders such as inflammatory bowel disease or hepatobiliary disorders as discussed by Brook & Frazier (1993). Bacterial translocation is a physiological process through which indigenous enteric bacteria or their products cross the intestinal barrier and reach the

mesenteric lymph nodes, establishing a crosstalk between the gut microbiota and the immune system in order to achieve a healthy equilibrium by means of an adequate T-cell response. A pathological bacterial translocation occurs when bacteria get to normally sterile tissues; bacterial overgrowth, increased intestinal permeability and immunological alterations are the principal factors involved in this process.

Bacterial translocation from the biliary tract to the bloodstream and lymphatic system may occur due to cholestasis, resulting in increased biliary pressure. Both bile stagnation and increased pressure have a deleterious effect on defensive barrier mechanisms, i.e. intercellular junctions controlling the blood–biliary barrier, Kupffer cells, the resident liver macrophages, and antibacterial products such as Ig A and mucus excreted into the biliary tract. In addition, the continuous flushing that prevents bacterial colonization by micro-organisms that grow in the presence of bile salts such as *E. lenta* is lost (Karsten *et al.*, 1998; Sung *et al.*, 1992).

Our patient had Caroli disease, a rare congenital disorder characterized by unilobular or bilobular segmental cystic dilatation of the intrahepatic bile ducts, predisposing to cholestasis, biliary lithiasis and recurrent cholangitis that can be complicated by liver abscesses and sepsis. Therefore, this congenital condition set the perfect scenario for bacterial translocation from the biliary tract. In addition, empirical treatment with cefuroxime favoured bacteraemia by *E. lenta* in this patient, as the isolate was resistant to this antimicrobial.

Monomicrobial bacteraemia by this micro-organism is also associated with clinically significant infections (Thota *et al.*, 2011). Prior studies have demonstrated that infection by *E. lenta* is more frequent than reported (Lau *et al.*, 2004a, b; Rodríguez-Cavallini *et al.*, 2011; Shinagawa *et al.*, 2011) and that bacteraemia is associated with significant mortality and morbidity, especially when there is no fever at presentation (Brook & Frazier, 1993; Venugopal *et al.*, 2012). Our patient presented with cholangitis, bacteraemia by this micro-organism and a systemic inflammatory response syndrome that did not develop into a full-blown blood infection, most likely due to early treatment with meropenem. Thus, the prevalence and clinical features of *E. lenta* bacteraemia are probably underestimated and remain imprecise, chiefly due to culture difficulties, i.e. nutritional requirements, prior antimicrobial treatments or established incubation times, all of which can give rise to false-negative results.

Besides these ambiguities, studies have shown great variability in the antimicrobial susceptibility profile of *E. lenta*, leading to uncertainty regarding the most appropriate therapy (Lau *et al.*, 2004a; Lee *et al.*, 2012; Mosca *et al.*, 1998). Mosca *et al.* (1998) described two antimicrobial susceptibility patterns in *E. lenta*: type A was resistant to cephalosporins, intermediate to clindamycin and susceptible to imipenem, piperacillin, metronidazole and ampicillin, but presented high MICs; type B was susceptible to all antimicrobials tested but presented high MICs to metronidazole.

Lee *et al.* (2012) presented different results; most of their isolates were susceptible to cefamandole but had high MICs, and 63 % were resistant to clindamycin. Our isolate was different from these three patterns although closely related to type A of Mosca *et al.* (1998). This variability could be due to clonal geographical differences. In addition, although more research is needed, the high cephalosporin MICs observed could be explained by the presence of low-affinity penicillin-binding proteins to these antimicrobials.

All things considered, two issues should be emphasized in this case report: first, that the only positive blood culture grew after the recommended incubation time for automated blood cultures, i.e. 5 days (Lamy & Seifert, 2012); and secondly, that the digoxin degradation rate was very different from prior studies, i.e. a 21 % reduction versus about 100 % after 7 days (Robertson *et al.*, 1986), possibly due to metabolic variability among *E. lenta* isolates, or to substrate competition caused by amino acids from the culture medium (Lu *et al.*, 2014). Both circumstances pose questions about false-negative blood cultures, especially regarding fastidious, anaerobic bacteria, and about how much *E. lenta* digoxin reduction variability could affect patients under digoxin regimes.

A full-genome sequence of *E. lenta* has been described (Saunders *et al.*, 2009; Yokoyama *et al.*, 2011) and may be a means to better understand: (i) its virulence factors, such as antimicrobial resistance mechanisms; (ii) its metabolic pathways, as well as their regulation, bringing some light to the observed digoxin degradation variability; and (iii) the cell wall biogenesis, especially the properties of its penicillin-binding proteins and its affinity to β -lactams.

In conclusion, we have described a patient with potentially fatal *E. lenta* bacteraemia secondary to acute cholangitis and underlying Caroli disease who responded to treatment with a carbapenem but could have passed unidentified. It is worth mentioning that a final identification was achieved 3 days after the patient was discharged. Finally, to the best of our knowledge, this is the first published case report of *E. lenta* bacteraemia associated with Caroli disease, indicating that more case reports are necessary, not only to understand the pathogenicity and clinical course of infections by *E. lenta* but also to investigate its digoxin degradation and antimicrobial susceptibility variability.

References

- Arias, M., Sesar, A. & Requena, I. (2006). [Recurrent meningoencephalitis caused by *Eubacterium lentum*]. *Med Clin (Barc)* **127**, 599 (in Spanish).
- Bok, C. W. & Ng, Y. S. (2009). *Eggerthella lenta* as a cause of anaerobic spondylodiscitis. *Singapore Med J* **50**, e393–e396.
- Brook, I. & Frazier, E. H. (1993). Significant recovery of nonsporulating anaerobic rods from clinical specimens. *Clin Infect Dis* **16**, 476–480.
- Karsten, T. M., van Gulik, T. M., Spanjaard, L., Bosma, A., van der Bergh Weerman, M. A., Dingemans, K. P., Dankert, J. & Gouma, D. J. (1998). Bacterial translocation from the biliary tract to blood and lymph in rats with obstructive jaundice. *J Surg Res* **74**, 125–130.
- Lamy, B. & Seifert, H. (2012). Septicemia. In *European Manual of Clinical Microbiology*, pp. 101–110. Edited by G. Cornaglia, R. Courcol, J.-L. Hermann, G. Kahlmeter, H. Pelgue-Lafeuille & J. Villa. Paris: Société Française de Microbiologie.
- Lau, S. K., Woo, P. C., Fung, A. M., Chan, K. M., Woo, G. K. & Yuen, K. Y. (2004a). Anaerobic, non-sporulating, Gram-positive bacilli bacteraemia characterized by 16S rRNA gene sequencing. *J Med Microbiol* **53**, 1247–1253.
- Lau, S. K., Woo, P. C., Woo, G. K., Fung, A. M., Wong, M. K., Chan, K. M., Tam, D. M. & Yuen, K. Y. (2004b). *Eggerthella hongkongensis* sp. nov. and *eggerthella sinensis* sp. nov., two novel *Eggerthella* species, account for half of the cases of *Eggerthella* bacteremia. *Diagn Microbiol Infect Dis* **49**, 255–263.
- Lee, M. R., Huang, Y. T., Liao, C. H., Chuang, T. Y., Wang, W. J., Lee, S. W., Lee, L. N. & Hsueh, P. R. (2012). Clinical and microbiological characteristics of bacteremia caused by *Eggerthella*, *Paraeggerthella*, and *Eubacterium* species at a university hospital in Taiwan from 2001 to 2010. *J Clin Microbiol* **50**, 2053–2055.
- Lu, L., Wu, Y., Zuo, L., Luo, X. & Large, P. J. (2014). Intestinal microbiome and digoxin inactivation: meal plan for digoxin users? *World J Microbiol Biotechnol* **30**, 791–799.
- Mosca, A., Summanen, P., Finegold, S. M., De Michele, G. & Miragliotta, G. (1998). Cellular fatty acid composition, soluble-protein profile, and antimicrobial resistance pattern of *Eubacterium lentum*. *J Clin Microbiol* **36**, 752–755.
- Pardo Sánchez, F., Romero Jung, P. A., Martínez Lamas, L. & Arca Barca, B. (2008). [Septic bursitis due to *Eggerthella lenta*]. *Reumatol Clin* **4**, 82–84 (in Spanish).
- Robertson, L. W., Chandrasekaran, A., Reuning, R. H., Hui, J. & Rawal, B. D. (1986). Reduction of digoxin to 20R-dihydrodigoxin by cultures of *Eubacterium lentum*. *Appl Environ Microbiol* **51**, 1300–1303.
- Rodríguez-Cavallini, E., Vargas, P., Rodríguez, C., Quesada-Gómez, C. & Gamboa-Coronado, M. M. (2011). Phenotypic identification of over 1000 isolates of anaerobic bacteria recovered between 1999 and 2008 in a major Costa Rican hospital. *Clin Microbiol Infect* **17**, 1043–1047.
- Salameh, A., Klotz, S. A. & Zangeneh, T. T. (2012). Disseminated infection caused by *Eggerthella lenta* in a previously healthy young man: a case report. *Case Rep Infect Dis* **2012**, 517637.
- Saunders, E., Pukall, R., Abt, B., Lapidus, A., Glavina Del Rio, T., Copeland, A., Tice, H., Cheng, J. F., Lucas, S. & other authors (2009). Complete genome sequence of *Eggerthella lenta* type strain (IPP VPI 0255). *Stand Genomic Sci* **1**, 174–182.
- Shinagawa, N., Osanai, H., Hirata, K., Furuhashi, T., Mizukuchi, T., Yanai, Y., Hata, F., Taniguchi, M., Sasaki, K. & other authors (2011). [Bacteria isolated from surgical infections and its susceptibilities to antimicrobial agents – special references to bacteria isolated between April 2009 and March 2010]. *Jpn J Antibiot* **64**, 125–169.
- Sung, J. Y., Costerton, J. W. & Shaffer, E. A. (1992). Defense system in the biliary tract against bacterial infection. *Dig Dis Sci* **37**, 689–696.
- Thota, V. R., Dacha, S., Natarajan, A. & Nerad, J. (2011). *Eggerthella lenta* bacteremia in a Crohn's disease patient after ileocecal resection. *Future Microbiol* **6**, 595–597.
- Venugopal, A. A., Szpunar, S. & Johnson, L. B. (2012). Risk and prognostic factors among patients with bacteremia due to *Eggerthella lenta*. *Anaerobe* **18**, 475–478.
- Yokoyama, S., Oshima, K., Nomura, I., Hattori, M. & Suzuki, T. (2011). Complete genomic sequence of the equol-producing bacterium *Eggerthella* sp. strain YY7918, isolated from adult human intestine. *J Bacteriol* **193**, 5570–5571.