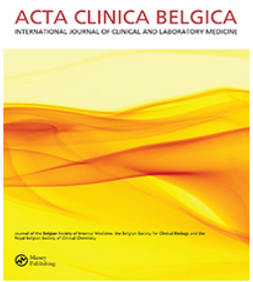

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Case Report

ACUTE CHOLECYSTITIS WITH *LISTERIA MONOCYTOGENES*

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ABSTRACT

Listeriosis, an opportunistic food-borne disease caused by *Listeria monocytogenes*, is infrequent and occurs preferentially in patients at the extremes of age, during pregnancy or in immunocompromised hosts. Most common manifestations are maternofoetal and neonatal infections, severe invasive presentations such as bacteraemia with or without central nervous system symptoms occuring preferentially in immunosuppressed patients and self-limited gastro-enteritis affecting healthy individuals. Exceptionally, focal infections such as cholecystitis are described. We report here a case of acute cholecystitis caused by *Listeria monocytogenes* in an 82-year-old woman. Thanks to a successful treatment: cholecystectomy and antimicrobial therapy (amoxicillin plus clavulanic acid), the patient soon recovered. This case-report provides an opportunity to review the current literature concerning the association of *Listeria monocytogenes* and cholecystitis.

Key words: *Listeria monocytogenes* – cholecystitis – gastrointestinal tract

INTRODUCTION

Listeriosis is caused by a Gram positive, intracellular motile bacillus, *Listeria monocytogenes* (LM). This microorganism is ubiquitously found in various environments such as soil, water, vegetation, various food products and even in the faecal flora of mammals. LM can survive in a variety of adverse environmental conditions and thus can contaminate many food products even at refrigeration temperatures, such as cheese made with raw milk, raw vegetables, delicatessen products, meat, poultry, smoked fishes and "ready-to-eat" meals (1). Except in some cases, LM is the only human pathogen among the six described species of the genus *Listeria*. Listeriosis occurs primarily in groups at-risks: newborn infants, patients older than 60 years, pregnant women and patients with impaired cell-mediated immunity (AIDS, haematologic malignancy, organ transplantation, corticosteroid therapy, haemodialysis, diabetes mellitus …) (1). The annual incidence in Europe is 3 reported cases per million inhabitants; 30% of cases happen during pregnancy, probably related to a mild immunosuppression during gestation. This pathogen causes infrequent but severe food-borne diseases, with a high case-fatality rate (20-30%) (2, 3). Most common invasive disease manifestations in adults are bacteraemia with or without central nervous system (CNS) infection, such as meningitis, meningoencephalitis and rhombencephalitis, but symptoms of self-limited febrile gastro-enteritis can also occur in immunocompetent hosts. Infants acquire the infection in two ways: (i) maternofoetal infection during pregnancy resulting in chorioamnionitis and delivery of septic infant or fetus, (ii) perinatal contamination leading to bacterial meningitis in newborn up to 3 weeks after exposure to infected birth canal. More rarely, localized forms are described: endocarditis, osteomyelitis, arthritis, conjunctivitis, endophtalmitis, peritonitis, splenic abscess, pleuropulmonary infections and skin infections (1).

We report here the case of a patient with acute cholecystitis, where LM was the only isolated pathogen. We also review the current literature concerning some recent progress in the knowledge of infection and colonization of the human gastrointestinal tract by *Listeria monocytogenes*.

CASE REPORT

An 82-year-old woman, with a past medical history of hysterectomy and hypertension, was admitted to Emergency Department for evaluation of abdominal pain, nausea without vomiting and diarrhoea. No fever was reported. On admission, the patient presented a supple abdomen but with a diffuse tenderness, no hepatosplenomegaly, no perturbation of liver enzymes but a light inflammatory syndrome with

elevated leukocyte count and slightly elevated C-reactive protein (CRP). She was hospitalized for clinical surveillance and gastroenterological assessment.

On day 2, worsening of the inflammatory syndrome was observed with increasing fibrinogen and CRP. She also had biological signs of hepatic cytolysis and cholestasis. Hepatomegaly was noticed. Echography showed a cholecystitis with sludge and microlithisasis in the gallbladder, a bile duct dilatation and Murphy's sign. An abdominal scanner confirmed a diagnosis of cholecystitis and showed a light ectasia of intrahepatic bile tracts and bile duct. An antibiotherapy by amoxicillin plus clavulanic acid (AUGMENTIN®) was initiated. A cholecystectomy was performed by laparoscopy on day 3. During surgery, the gallbladder showed signs of inflammation and peri-hepatic adhesions. Peroperative cholangiography was normal. Histological examination of the biliary mucosa brought to light inflammatory infiltrates and presence of necrotic tissue. Post operative follow up was favourable, as was the biological evolution. The patient was discharged from hospital on the eighth post-operative day.

Unfortunately, no blood culture was performed during her hospital stay. Only one bile sample was collected during intervention: the Gram stain did not show any leukocyte or bacteria but the bile culture yielded a few colony forming units (CFU) of LM that were susceptible *in vitro* to penicillin, ampicillin, gentamicin, ciprofloxacin, vancomycin, erythromycin and trimethoprim-sulfamethoxazole. The Belgian reference laboratory identified the strains as serotype 4b.

DISCUSSION

Listeria monocytogenes is a Gram-positive rod, able to survive and replicate in extreme environmental conditions (drought, high salinity and a wide range of pH levels and temperatures). After ingestion, LM translocates through the intestine to reach the mesenteric gland. LM then replicates in the spleen and in the liver. In patients with impaired cell-mediated immunity, LM is discharged into the blood flow and afterwards replicates preferentially in the CNS or in the placenta of pregnant women.

To reach, colonize and subsequently infect the gastrointestinal (GI) tract, LM encounters numerous microenvironmental conditions, including stomach acidity followed by elevated osmolarity and exposure to bile salts in the upper small intestine. Sigma-B (σ^B) is a key factor involved in adaptation to GI environments: σ^B regulon is required for rapid induction of expression of LM genes most likely to be important for survival of GI stresses, including reduced pH, elevated osmolarity and bile salts (4). Given that *sigB* is transcriptionnally upregulated at elevated osmolarity, the osmotic stress appears to be at the top of hierarchy of LM stress responses during GI transit. Furthermore, σ^B has recently been shown to modulate PrfA (positive regulatory factor A), the master regulator of virulence gene cluster which coordinates the intracellular phase of LM infection (4).

Ability to tolerate high levels of bile stress is also a key challenge for LM. In addition to their role in digestion, bile salts have a cytotoxic effect by degrading the lipid-containing bacterial and viral membranes. Two major virulence factors discovered recently seem to be involved in the intestinal and hepatic phases of listeriosis: a bile salt hydrolase (BSH) and a bile exclusion system (BilE). *Bsh* is a LM-specific putative gene encoding a protein able to hydrolyse conjugated bile salts (5). Several Gram-positive bacteria of the enteric microflora produce this enzyme, which protects them from bile salt toxicity and contributes to intestinal colonization. BilE is more likely to be an exclusion system, close to multidrug efflux pumps, known to play an important role in bile resistance in Gram-negative microbes (6). Both *bsh* and *bilE* genes are preceded by σ^B-dependent promoter sites and are transcriptionnally downregulated in a *sigB* mutant (4).

Some studies have investigated the replication of LM in gallbladder bile of murine and porcine models. Dowd, et al. (7) showed that when the pH of porcine gallbladder bile is reduced to pH 5.5, in order to mimic the release of bile within the small intestine, specific resistance mechanisms (BSH, BilE, and Sigma-B) are essential for survival of the pathogen under these conditions. Hardy, et al. (8) reported that LM can replicate in the murine gallbladder and demonstrated that its replication is extracellular and intraluminal. While many bacteria infect and cause disease in the gallbladder tissue, LM belongs to the rare pathogenic bacteria capable of growing in the asymptomatic gallbladder in an animal model. This finding makes it difficult to prove that LM really was the pathogen responsible for cholecystitis in the reported case, as LM could have grown harmlessly in the gallbladder without illness. A positive blood culture, which wasn't performed, would have provided direct evidence to the involvement of LM in the infection. At best, the absence of other pathogen isolated from the bile sample provides indirect evidence to the role of LM in the development of cholecystitis, which would have been strengthened if more samples had been collected and shown positive with LM.

Only a few cases of listerial cholecystitis have been reported in literature during the last thirty years (9-13). In most cases, cholecystitis occurs in patients older than 60-year-old, more often female than male, with or without an underlying disease such as diabetes or some form of immunosuppression. The first case, reported in 1971 (9), was a 60-year-old woman, with no underlying disease, where infection of the gallbladder was not suspected until the patient underwent surgery for chronic cholecystitis. Unexpectedly, LM was grown from a culture of the gallbladder. Our reported case has an antecedent of hysterectomy and hypertension, like another patient in a previous case (10) who underwent cholecystectomy by laparotomy. In that report, the Gram stain of the bile sample showed Gram-positive rods and the culture yielded only LM. A paper (11) reported two cases of localized infections of the gallbladder in patients (a man and a woman) where cholecystitis was diagnosed and bile samples positive with LM. In all these oldest cases (1971 to 1989), no blood culture was performed and, as LM was only found in bile samples, his pathogenic role in the development of cholecystitis is debatable. In more recent reports (12, 13), LM was isolated both from blood culture and bile samples or swab culture of the gallbladder. The three patients – one man and two women- were all receiving immunosuppressive therapy. Two of them developed systemic listeriosis, including cholecystitis and CNS infection, shortly after initiation of a TNF-blocking therapy (12). In most cases, fever, abdominal pain, nausea and diarrhoea were described before disease occurrence. Serovar 4b, isolated from our patient's bile sample, appears to be the most virulent of

the three major serovars (1/2a, 1/2b and 4b) responsible for human listeriosis: indeed, all major outbreaks of invasive disease have been caused by LM serotype 4b. As for the treatment, cholecystectomy and antibiotherapy with amoxicillin plus clavulanic acid was successful. *In vitro* data and *in vivo* clinical experience suggest that ampicillin is the most effective therapeutic agent, in combination with an aminoglycoside for the treatment of invasive listeriosis. For those intolerant to penicillins, trimethoprim-sulfamethoxazole appears to be the best alternative (1). All strains of LM are uniformly resistant to cephalosporins: consequently, as third-generation cephalosporins are commonly used in empirical treatment of bacterial meningitis, combination with ampicillin must be used when listerial meningitis is suspected.

In conclusion, we present here the case of an acute cholecystis probably caused by LM in an 82-year-old woman who soon recovered thanks to a treatment by cholecystectomy and antibiotics (amoxicillin plus clavulanic acid). The recent discoveries about infection and colonization of the GI tract by LM stress the need for specimen collection (especially blood culture) to prove the pathogenic role of LM in gallbladder infection.

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CONFLICT OF INTEREST: None declared.

REFERENCES

1. Lorber B. *Listeria monocytogenes*. *In*: GL Mandell, JE Bennett, R Dolin, eds. Mandell, Douglas, & Bennett's principles and practice of infectious diseases, 6th ed. Elsevier Churchill Livingstone. 2005: 2478-2483.
2. Denny J, McLauchlin J. Human *Listeria monocytogenes* infections in Europe – an opportunity for improved European surveillance. *Eurosurveillance* 2008; 13: 1-3.
3. Swaminathan B, Gerner-Smidt P. The epidemiology of human listeriosis. *Microbes Infect* 2007; 9: 1236-1243.
4. Sleator RD, Watson D, Hill C, Gahan CG. The interaction between *Listeria monocytogenes* and the host gastrointestinal tract. *Microbiology* 2009; 155(8): 2463-2475.
5. Dussurget O, Cabanes D, Dehoux P, Lecuit P, Buchrieser C, Glaser P, Cossart P. *Listeria monocytogenes* bile salt hydrolase is a PrfA-regulated virulence factor involved in the intestinal and hepatic phases of listeriosis. *Mol Microbiol* 2002; 45(4): 1095-1106.
6. Sleator RD, Wemekamp-Kamphuis HH, Gahan CG, Abee T, Hill C. A PrfA-regulated bile exclusion system (BilE) is a novel virulence factor in *Listeria monocytogenes*. *Mol Microbiol* 2005; 55(4): 1183-1195.
7. Dowd GC, Joyce SA, Hill C, Gahan CG. Investigation of the mechanisms by which *Listeria monocytogenes* grows in porcine gallbladder bile. *Infect Immun* 2011; 79(1): 369-379.
8. Hardy J, Francis KP, DeBoer M, Chu P, Gibbs K, Contag CH. Extracellular replication of *Listeria monocytogenes* in the murine gall bladder. *Science* 2004; 303: 851-853.
9. Medoff G, Kunz LJ, Weinberg AN. Listeriosis in humans: an evaluation. *J Infect Dis* 1971; 123: 247-250.
10. Gordon S, Singer C. *Listeria monocytogenes* cholecystitis. *J Infect Dis* 1986; 154(5): 918-919.
11. Alleberger F, Langer B, Hirsch O, Dierich MP, Seeliger HP. *Listeria monocytogenes* cholecystitis. *Z Gastroenterol* 1989; 27(3): 145-147.
12. Glück T, Linde HJ, Schölmerich J, Müller-Ladner U, Fiehn C, Bohland P. Anti-tumor necrosis factor therapy and *Listeria monocytogenes* infection: report of two cases. *Art. and Rheum* 2002; 46(8): 2255-2257.
13. Loupa CV, Kouppar G, Kosionis N, Zouberi Koliomichali M, Lelekis MI. Biliary tract infection caused by *Listeria monocytogenes*. *Clin Microbiol Newsl* 2007; 29(1): 6-8.