A rare case of enteric and systemic *Yersinia enterocolitica* infection in a chronic, not iron-overloaded dialysis patient

Jari Intra, Sara Auricchio, Roberta M. Sala, Paolo Brambilla

Department of Laboratory Medicine, University of Milano Bicocca, Desio Hospital, Italy

Summary

We present herein a case of bacterial gastroenteritis due to *Yersinia enterocolitica,* occurred in a young woman undergoing haemodialysis with a previous history positive for prolonged (20 years) immunosuppressive therapy for glomerulonephritis before and for kidney transplant later. The patient's outcome was favourable after a third-generation cephalosporin treatment without complications. The possible pathophysiological association between patient clinical condition and *Yersinia* bacteraemia is discussed, along with the review of literature.

Introduction

Yersinia enterocolitica is a Gram-negative bacillus part of the Enterobacteriaceae family, non-lactose-fermenting,

urease-positive, oxidase negative, motile at temperatures between 22-29°C, non-motile at 37°C, and with a worldwide distribution in nature (6,16,30). This bacterium is the common cause of a zoonosis named yersiniosis that is transmitted from animals to humans with considerable impact on the public health. It implies several complications, such as appendicitis (24), small-bowel gangrene (31,32), peritonitis (3), enteric abscesses (5,14,27,34), and septicaemia (18,21,26,33). In 2014, 6839 confirmed cases of yersiniosis were reported in Europe (18 cases in Italy), with an overall rate of 1.8 cases per 100,000 population (15). Infection can arise from ingestion of contaminated foods, in particular pork and pork products (6,10,26,30), or infected water (16, 30). Moreover, in several cases of clinical sepsis, *Y. enterocolitica* infection was documented to be caused by using contaminated products in blood transfusions (18,20). Generally, *Y. enterocolitica* is primarily a gastrointestinal tract pathogen, typically limited in the normal host and usually antimicrobial therapy is not required. However, alcoholism, chronic liver disease, diabetes, immunosuppressive therapy, acute iron overload, malignancy, and malnutrition are conditions, which predispose to infection of *Yersinia* (6,22,25). In fact, in these particular situations, this bacterium has a strong propensity to circumvent the host defence, to transcend the gastrointestinal tract and cause systemic infections, reaching also the liver and the spleen, with a high mortality rate of about 50% (6,11,16,30). Elevated oral or intravenous iron supplementation and the possible consequent iron excess is a risk factor for infection of *Y. enterocolitica* in the host (1-3,23,24). Haemodialysis patients are chronically iron deficient and iron supplementation is routinely administered to maintain an iron appropriate level. Iron is an essential growth factor of bacteria for multiplication in the host, and, on the contrary, evidences showed that iron supplementation is harmful for the host defence mechanisms, oxygen transport, deoxy ribonucleotide synthesis, and redox reactions (6,28,35). In haemodialysis patients, various authors reported high incidence of iron-overload (8,13,26). *Y. enterocolitica* requires iron for growth and it is able to accelerate the proliferation using exogenous chelators as source of iron in patients showing an iron-overloaded state or receiving an iron-chelating therapy (6,13,26,28). *Y. enterocolitica* group is traditionally divided in 6 biogroups based on phenotypic features, and into more than 57 O serogroups based on their

O-lipopolysaccharide surface antigen. The most frequent strains considered as human pathogens belong to serogroups O:3, O:5,27, O:8 and O:9 (4). Serogroups O:3, O:9 and serogroup O:8 are the most frequent isolates detected in Europe and in United states, respectively (9).

We here present a case of enteric and systemic bacteraemia due to a *Yersinia enterocolitica* strain, in a 35-year-old woman on chronic haemodialysis, that acquired most probably the infection by uncooked meat, but she presented no other risk factors commonly associated with yersionisis.

Case report

We present a case of bacterial gastroenteritis due to *Yersinia enterocolitica,* occurred in a 35-year old Caucasian woman undergoing haemodialysis with a previous history of end-stage renal disease caused by glomerulonephritis, hypertension, malnutrition, and osteoporosis. From 2007 to 2010, she underwent thrice-weekly haemodialysis. On August 2010, the kidney transplant from a deceased donor was performed without complications, and anti-rejection regimen (steroids, mycophenolate and tacrolimus) was started. Recurrence of primitive glomerulonephritis occurred one year later leading to a progressive renal failure. Transplant period was complicated by the occurrence of vaginal intraepithelial neoplasia treated by imiquimod topical cream, and iron-deficiency anaemia with need for intravenous iron supplementation. She lost definitively her transplanted kidney in 2014, and she started haemodialysis 3 times a week again and continued intravenous iron supplementation one time per week. Iron-chelating therapy was not necessary, since ferritin, transferrin and iron levels were normal. Immunosuppressive treatment concluded 2 years ago. On admission to our hospital, on August 24, she had diarrheal and high-grade fever (38°C). Faecal and blood cultures taken were positive to a *Yersinia enterocolitica* strain, most probably acquired eating undercooked meat one week before. Laboratory tests showed haemoglobin value of 12.8 g/dL and haematocrit of 39.3%; white blood cell count of 6600/mm^3; mild platelet count of 133,000/mm^3. Leukocyte differential count revealed an increased value of neutrophils (74%) and a decreased value of lymphocytes (16%), compared to previous values of 47% of neutrophils and 40% of lymphocytes determined two months before. Absolute values of neutrophils and lymphocytes were 4880 and 1060/mm^3, respectively. Value of C-reactive protein was elevated, 44.58 mg/L (reference range: 0-5 mg/L). Faecal cultures were started two days later, due to a persisting a diarrheal condition, high fever, and an elevated value of C-reactive protein, about 40 mg/L. However, after other three days, no pathogens were identified. On September 1, the patient's clinical conditions were unchanged. Values of C-reactive protein and procalcitonin (reference range: 0-0.5 ng/mL) were elevated, 38.94 mg/L and 1.10 ng/mL, respectively. Percentage of neutrophils increased to 77 %, with an absolute value of 4110/ mm^3.

Faecal cultures were repeated, and blood cultures started. On the morning of September 2, cultures resulted positive, and initial Gram-staining disclosed gram-negative bacillus-shaped bacteria. Initial antimicrobial therapy with levofloxacin was administered. Identification of bacteria grown on the selective medium CIN (Cefsulodin-Irgasan-Novobiocin Agar) after over-night incubation and those grown on PolyViteX chocolate agar plates after only a 4-hour incubation of 5 drops of positive blood-broth medium (23) was carried out using Vitek® Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry system (bioMérieux, Marcy L'Etoile, France). The pathogen identified from both blood cultures than from faecal cultures was a *Yersinia enterocolitica* strain. As control, bacteria identification was confirmed by VITEK® GN (fermenting and non-fermenting Gram-negative bacilli) colorimetric identification cards, considered as the reference method. Vitek®2 GN-AST (Antimicrobial Susceptibility Testing) N202 cards were used to gain rapid, accurate susceptibility results and resistance detection. The antimicrobial susceptibility categorization was done accordingly to EUCAST 2016 clinical breakpoints. This isolated showed an antimicrobial profile of susceptibility to gentamicin, amikacin, cefepime, cefotaxime, ceftazidime, imipenem, meropenem, ertapenem, and colistin, intermediate to ciprofloxacin, and resistance to amoxicillin/clavulanic acid. After three days of antimicrobial treatment, C-reactive value decreased to 11.8 mg/L, and white blood cell count declined to 2600/mm^3. However, control faecal cultures revealed again the presence of a *Yersinia enterocolitica* strain. Antibiotic therapy was changed, and a treatment for 2 weeks with a third-generation cephalosporin, ceftazidime, started. Patient's clinical conditions improved rapidly. On September 23, surveillance faecal cultures were repeated, and pathogens were absent. On September 28, white blood cells count was low, about 2200/mm^3, and percentage values of neutrophils and lymphocytes were 42 and 41, respectively. Moreover, C-reactive protein value was negative (<1.0 mg/L).

The source of *Y. enterocolitica* was most probably due to the undercooked meat eaten one week before, since the patient denied any other risk factors, such as consumption of unpasteurized milk, tofu or bean sprouts, and she had no animals at home. Furthermore, she had no history of blood transfusion. In the same time, family members reported diarrheal and abdominal symptoms, but faecal cultures were not performed, since infection was short, limited to the gut and medical therapy was not required. It is important to note that our patient receives intravenous iron supplementation one time for week with dialysis to keep the haemoglobin level constant. However, laboratory tests revealed that iron, ferritin and transferrin levels were normal in the last year, ranging from 93 to 119 µg/dL, from 55 to 59 ng/mL, and from 180 to 182 mg/dL, respectively. Iron saturation was about 45%. A month later the lymphocytes subpopulations were analysed and the result was only a CD4 lymphocyte deficiency (22%, with normal range between 31 and 61%) showing an altered state of immune competence.

Discussion

Yersinia incubation lasts 4-7 days, and the patient affirmed that she has eaten undercooked meat one week before, confirming the possible source of yersiniosis. In fact, other family members showed the same symptoms, such as abdominal pain and diarrheal, but the infection was confined to the intestinal tract, not requiring then antimicrobial treatment. However, the patient's clinical history was negative for the other risk factors and conditions previously described associated to *Yersinia* bacteraemia.

Y. enterocolitica is primarily a gastrointestinal pathogen that under particular conditions of the host has a strong propensity to tropism for extra-intestinal sites (16). Septicaemia with *Y. enterocolitica* is rare, and it is most often seen in patients who have a predisposing disease, or receiving an iron-chelating therapy, or are in an acute iron-overloaded state (16). Iron has a critical role in bacteria for multiplication in the host, and iron overload impairs the phagocytic activity of neutrophils (6,8,30). *Y. enterocolitica* strains have the ability to increase their virulence using iron provided in the environment during iron supplementation therapy. In fact, the set of virulence genes named High-Pathogenicity Island (HPI) is involved in the biosynthesis, transport, and regulation of the siderophore yersiniabactin, known to be as an iron-capture island (6,16,30). In previous studies, the state of iron overload was determined using the concentration of serum ferritin (2). Iron in its non-protein bound state catalyses the formation of reactive oxygen species, and ferritin plays an important role in the transient storage, which is considered a detoxification mechanism (13). Our case is the first in which a normal serum ferritin level predisposed a chronic dialyzed patient with intravenous iron supplementation to *Y. enterocolitica* septicaemia. Clinical history of our patient revealed that ferritin level was elevated between years 2006 and 2008, and from 2009, it was normal. Furthermore, iron-chelating agents and blood transfusions were not administered. Conversely, different studies have reported sepsis caused by *Y. enterocolitica* in dialyzed patients with mild or high iron overload, iron-chelating treatment or multiple blood transfusions (1,8,12,26).

The altered immune competence of the host (showed by CD4 lymphocytopenia) was perhaps the primary cause of this infective episode and it is probably the consequence of her past treatment history characterized by 20 years of immunosuppressive therapy.

The mortality rate associated to *Y. enterocolitica* infection can reach as high as 50% in immunocompromised individuals (16,20). Antimicrobial treatment varies among serogroups, and the microorganism is usually susceptible *in vitro* to cotrimoxazole, aminoglycosides, tetracycline, and fluoroquinolones, but is resistant to penicillin, ampicillin and first-generation cephalosporins (16,29). Intrinsic resistance to beta-lactam antibiotics is mainly due to the presence of two chromosomal genes encoding beta-lactamase, *blaA* and *blaB*, which confer a broad-spectrum or first-generation cephalosporins resistance, respectively (7,29). The presence or absence of each β-lactamase enzyme discriminates the antimicrobial susceptibility between different *Yersinia* serotypes (29). In our case, the *Y. enterocolitica* isolate was only resistant *in vitro* to β-lactams, intermediate to fluoriquinolones, and susceptible to the other antibiotics tested. Initially, antimicrobial therapy started administering levofloxacin, a member of third-generation fluoriquinolones, and then, after a control faecal culture resulted again positive, successfully switched to a monotherapy with a member of third-generation cephalosporins, ceftazidime, for a short duration of 2 weeks. Our results agree with previous data in literature. A retrospective case series of 43 *Y. enterocolitica* bacteraemia reported the susceptibility *in vitro* to newer β-lactam antibiotic classes, including imipenem and third-generation cephalosporins, such as ceftazidime (19). Mergenhangen and Telesz (26) presented an unusual case of *Y. enterocolitica* septicaemia in a chronic, mildly iron-overloaded dialyzed patient successfully treated with another third-cephalosporin antibiotic, ceftriaxone. Fluoroquinolones have been used to treat *Yersinia* bacteraemia, and, in particular, ciprofloxacin is considered the first line agent for treating septicaemia due to *Y. enterocolitica* (16). However, resistance to fluoroquinolones are increasing, leading to clinical failures (16,17). In our case, the *in vitro* intermediate susceptibility to ciprofloxacin and the failure of initial antimicrobial therapy with levofloxacin showed that also this *Y. enterocolitica* isolate has mechanisms of resistance to quinolones.

Conclusions

In conclusion, *Yersinia* infection is responsible for enteritis, but it can be a sporadic cause of septicaemia in chronic dialysis patient without predisposing conditions, as described in this clinical case. It is important to keep in mind that a rapid identification of pathogen ensures early initiation of adequate antimicrobial agents in a disease with high mortality.

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