Risk factors matter: case report of *Yersinia pseudotuberculosis* in obese patient

Lara Scoppapietra[1], Giuseppina Amarù[1], Cristina Crocillà[2], Mara Finotti[2], Marika Salafia[2], Alessandra Canevaro[3], Valentino Granero[2]

[1]S.C. Laboratorio Analisi Unificato Rivoli-Pinerolo ASL TO3, Rivoli (TO); [2]S.C. Banca del Sangue e Immunoematologia, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin; [3]S.C. Laboratorio Analisi Chimico-Cliniche e Microbiologia. Azienda Ospedaliera Ordine Mauriziano, Turin, Italy

Correspondence: Valentino Granero, S.C. Banca del Sangue e Immunoematologia, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Corso Bramante 88, Turin (TO), Italy.
Tel: +39 011 6334107. Fax: +39 011 6334090.
E-mail: vgranero@cittadellasalute.to.it.

Key words: Risk factor; *Yersinia pseudotuberculosis*; infection; prevention; diagnosis.

Authors' contributions: LS: first author and responsible for data acquisition, microbiologist during the work; GA: author and designer, microbiologist during the work; CC: author, designer and responsible for coordination between the various laboratories, microbiologist during the work; MF: author and reviewer, microbiologist in formation during the work; MS: author, biologist during the work; AC: author and reviewer, medical lab technologist during the work; VG: author, reviewer and responsible of all questions related to integrity and accuracy of work, microbiologist during the work. LS, GA, CC and VG conceived the idea; LS and GA carried out the diagnostic investigations; CC, LS, and GA sent the samples for confirmatory analysis; based on the results CC, LS, GA and VG organized and planned the drafting of the manuscript with MS; VG, MF and AC contributed to supervising the work. All authors discussed the case and contributed to the final manuscript.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: None.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Received for publication: 8 August 2022.
Accepted for publication: 23 September 2022.

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Licensee PAGEPress, Italy
Microbiologia Medica 2022; 37:10784
doi:10.4081/mm.2022.10784

Summary

Yersinia pseudotuberculosis is a Gram-negative bacillus that can occasionally cause zoonosis. Infections of this bacterium typically present as self-limiting ileitis, often accompanied by diarrhea, but, especially in the case of immunocompromised patients, can also lead to serious secondary complications which, if not treated properly, can progress with a poor prognosis. Here, we present a case of successfully treated bacteremia due to *Y. pseudotuberculosis* in a multipathological obese patient. The diagnosis was possible through blood culture and this highlights the importance of the search for unconventional pathogens, especially in certain categories of patients whose risk factors are strongly indicative and suggestive.

Introduction

Yersinia pseudotuberculosis (*Y. pseudotuberculosis)* is a Gram-negative rod bacterium belonging to Enterobacteriaceae that causes zoonotic infections in domestic and wild animals, such as rodents, rabbits, deer, farm animals and birds (2). There are different serotypes of *Y. pseudotuberculosis* and, in Europe, most isolates belong to serotypes 1 and 3, which can be acquired from contaminated food or water (1).

Y. pseudotuberculosis infections typically present as self-limiting ileitis, often accompanied by diarrhea, but can also lead to secondary complications, such as subacute obstruction syndrome, intussusceptions, perforation and, in few cases, acute kidney failure (3). Although rare, *Y. pseudotuberculosis* infection may progress to bacteremia, which can lead to a very high mortality rate (>75%) (4). In literature, most of the cases have usually been reported in patients with underlying illnesses including liver cirrhosis, diabetes, hemochromatosis, thalassemia, malignancy and immune suppression (6).

Here, we describe a case of *Y. pseudotuberculosis* bacteremia, analysed and treated in Rivoli Hospital, in an obese multi-pathological patient.

Case description

A 66-years-old ex-smoker woman presented to the emergency room with fever lasting 4 days complaining of chills, watery diarrhea and odontalgia.

The lady was an obese patient (BMI>36) with renal insufficiency (eGFR<10 mL/min) and type II diabetes, recently vaccinated with 3 doses of anti-SARS-Cov-2 (Comirnaty, Pfizer, New York, USA) and a significant clinical history (uterine adenocarcinoma, various recurrent urinary tract infections and acute myocardial infarction in 2020).

She took as therapy β-blocker 1.25 mg (1 cp/*die*), sevelamer carbonate (3 cps/*die*), 26 UL insulin glargine (1/*die*, h22), calcium carbonate (2 cp/*die*), pantoprazol 40 mg (1 cp/*die*), allopurinol 300 mg (½ cp/die), rapid insulin 6+16+14 UL, cholecalciferol (8 drop/*die*), acetylsalicylic acid (1 cp/*die*), atorvastatin calcium trihydrate 40 mg (1 cp/*die*).

Four days before admission, during a dialysis session, she had a feverish episode (39.5°C), with diarrhea and a spontaneous resolution after a few hours. Two days before admission, during a dialysis session, she had another feverish episode (39.2°C) and was swabbed for Sars-CoV-2 infection, with negative molecular result on LIAISON® MDX (DiaSorin, Saluggia, Italy), and two sets of blood cultures were done. The aerobic blood culture was detected as positive on the BD BACTEC™ FX Blood (Becton Dickinson, Milan, Italy) after 36 hours of incubation, but with doubtful positivity for a Gram-negative bacterium (probably related to the quality of the Gram stain). Blood sample was sown on MacConkey Agar and on Blood Agar.

The day of admission, after a dialysis session, another feverish episode (39°C) led to recovery.

Serum parameters were investigated, and demonstrated a net increase in inflammation indices four days before admission, C-reactive protein level of 53.2 mg/L increased to 179.8 mg/L and to 291.1 mg/L on the day of recovery; procalcitonin level of $6.27x10^6$ pg/L indicated a severe systemic inflammatory reaction. She was negative for *C. difficile* infection.

Imaging revealed nothing of significance except a "steatotic liver" and a marked reduction in renal parenchyma with a 25 mm cyst in the lower right third.

Three days after admission to the emergency room, she was transferred to the medical ward where, as a dialysis patient, she was initially treated empirically with ceftriaxone (2 g/die) and vancomycin (1/week, during dialysis), and a low-glucose diet without milk and derivatives was set up.

She was alert and oriented to time, person, and place. Two sets of blood cultures were re-performed. During the dialysis session, the patient got started on paracetamol 1 g for feverish peak (38.5°C).

On day 3, two stools of feces were collected for the search of *Yersinia spp*. with standard coprocultures (direct seeding on Salmonella-Shigella Agar and Hektoen Agar with incubation at 37°C for 24 hours and CIN Agar at RT for 48 hours) with a negative result, and the aerobic and anaerobic bottle of the second blood culture done were positives.

For the identification and antibacterial susceptibility testing, we applied the MicroScan WalkAway (Beckman Coulter, Cassina de'Pecchi, Italy) with N83 panel on colonies isolated after 24 hours from MacConkey agar and the Gram-negative rod bacteria were identified as *Y. pseudotuberculosis* serotype 1.

The isolated microorganism was then transplanted on CIN Agar Yersinia Supplement and subsequently sent to Piedmont Reference Center for confirmation with MALDI-TOF mass spectrometry.

The strain was sensitive to several antibiotic molecules (see Table 1).

The patient, that was empirically treated with vancomycin and ceftriaxone, according to the sensibility test, underwent de-escalation for vancomycin, while successfully continued therapy with ceftriaxone for 17 days in hospital.

Once discharged and with no more fever, the patient continued home antibiotic therapy with integrated home care, completely resolving the symptoms.

Discussion

Y. pseudotuberculosis is a motile, facultative anaerobic Gram-negative coccobacillus that has a broad range of animal reservoirs, including both domestic and wild animals. Following the ingestion of contaminated water or food, *Y. pseudotuberculosis* can reach the gastrointestinal system, by binding to the wall of the intestine, and can pass into the bloodstream through the spleen and liver. Symptoms of the infection are abdominal pain, diarrhea and fever (2). Since most *Y. pseudotuberculosis* infections are mild and self-limiting and the isolation of the microorganism is difficult, the spread of the bacterium may be underestimated.

Studies have shown that obesity is associated with an increase in infection and greater severity: obesity seems to dysregulate the balance between adipocytes and cells of the immune system leading to an alteration of the immune surveillance system (6). In addition to obesity, our patient was a smoker, a known risk factor that contributes to the destruction of the protective function of the colon and small intestine by inducing cellular apoptosis and reducing the flow of mucosal blood (6). Type 2 diabetes is linked with altered microbiota composition: upon disturbance of the microbiota, colonization resistance can be transiently disrupted, and pathogens can gain the opportunity to grow to high levels. One consequence of pathogen expansion is the triggering of the inflammatory host

Table 1. Antibacterial susceptibility testing results from blood culture isolate in according to EUCAST Breakpoints (version 12.0 – released 2022.01.01).

Drug	MIC (mg/L)	Interpretation*
Amikacin	≤8	S
Amoxicillin/Clavulanic Acid	<2/1	R*
Ampicillin	<2	R*
Aztreonam	>4	R
Cefepime	≤1	S
Cefotaxime	≤1	S
Cefoxitin	<8	R*
Ceftazidime	<1	S
Ciprofloxacin	≤8	R*
Chloramphenicol	≤8	S
Colistin	>4	R
Ertapenem	≤0.5	S
Fosfomycin	<32	S
Gentamicin	≤2	S
Imipenem	≤1	S
Levofloxacin	≤0.5	R*
Meropenem	≤0.12	S
Piperacillin	<4	S
Piperacillin/Tazobactam	≤4	S
Tetracycline	≤8	R*
Tigecycline	≤1	S
Tobramycin	≤2	S
Trimethoprim/Sulfamethoxazole	<2/38	S

*Interpretation performed with the support of the Expert System; S, sensible; R, resistant.

responses and pathogen-mediated disease: human enteric pathogens, including *Yersinia spp.*, can begin to proliferate if normal health conditions change (9).

The source of the infection in this patient remains unknown: she denies having taken foods or drinks other than usual and having had contact with animals; considering then that the incubation period varies from 4 to 10 days after ingestion (8) and stool culture did not detect *Y. pseudotuberculosis* in our case, blood-stream infection could originate from the intestinal one, improving the identification of what may have cause the first infection.

The patient was presented to the emergency room with fever and diarrhea and subjected to stool and blood culture before starting antibiotics, but only the blood culture was positive, proving to be more sensitive than the traditional method of detecting *Yersinia spp.* in the stool sample.

According to a report in 2010 (5), a high proportion of *Y. pseudotuberculosis* cases have been diagnosed by blood culture, suggesting that underdiagnoses of less invasive *Y. pseudotuberculosis* infections may explain the rarity of its incidence. Furthermore, the fact that this bacterium and its natural history are very unfamiliar to physicians makes the clinical diagnosis more difficult (7).

*Lee et al. (*2021*)* reviewed literature, between 2000 and 2021, and found that were reported only a few cases of bacteraemia caused by *Y. pseudotuberculosis*[7]. In 4 of the 12 reported cases, the patients had no underlying diseases; in the remaining cases, people presented comorbidity and risk factors such as smoke, obesity and diabetes. Fever with gastrointestinal symptoms was the most common, three cases only presented extraintestinal symptoms (7).

Although it was not possible to understand the origin of the infection and despite the clinical complexity of patient management, in this case report a *Y. pseudotuberculosis* infection was diagnosed in an obese patient with suggestive risk factors and symptoms.

In conclusion, this report will help in the future to make a differential diagnosis when multi-pathological patients with fever and diarrhea, who have possibly many risk factors, will go to the hospital saying they have gastrointestinal symptoms and fever. In addition, it emphasizes the need to pay diagnostic attention also to non-conventional pathogens in order to promptly help clinicians in the best therapeutic approach.

References

1. Delchier JC, Constantini D., Soule JC. Presence of anti-Yersinia pseudotuberculosis agglutinins during a flare-up of ileal Crohn's disease. Apropos of 3 cases. Gastroenterol Clin Biol 1983;7:580-4.
2. Fukushima H, Gomyoda M, Ishikura S, et al. Cat-contaminated environmental substances lead to Yersinia pseudotuberculosis infection in children. J Clin Microbiol 1989;27:2706–09.
3. Galindo CL, Rosenzweig JA, Kirtley ML, et al. Pathogenesis of Y. enterocolitica and Y. pseudotuberculosis in Human Yersiniosis. J Pathogens 2011;2011:182051.
4. Hashimoto T, Takenaka R, Fukuda H, et al. Septic shock due to Yersinia pseudotuberculosis infection in an adult immunocompetent patient: a case report and literature review. BMC Infect Dis. 2021;7;21:36.
5. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes (Lond) 2013;37:333-40.
6. Jiang C, Chen Q, Xie M. Smoking increases the risk of infectious diseases: A narrative review. Tob Induc Dis. 2020;14:18-60.
7. Lee YJ, Kim J, Jeon JH, et al. Extraintestinal Manifestation of Yersinia pseudotuberculosis Bacteremia as Acute Hepatitis: Case Report and Review of the Literature. Pathogens 2021;28;10:1255.
8. Mead PS. "231-Yersinia Species (Including Plague)", in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed.", Elsevier, 2015.
9. Stecher B. The Roles of Inflammation, Nutrient Availability and the Commensal Microbiota in Enteric Pathogen Infection. Microbiol Spectr. 2015;3.