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CASE REPORT

A rare Danish case of *Yersinia pseudotuberculosis* pyogenic liver abscess

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Abstract

Yersinia pseudotuberculosis is a rare Gram-negative bacillus that cause enterocolitis and terminal ileitis. We report the first Danish case with *Y. pseudotuberculosis* multiple pyogenic liver abscess presenting with 6 weeks intermittently fever, fatigue, and weight loss. The patient was successfully treated with percutaneous drainage and intravenous piperacillin/tazobactam and oral ciprofloxacin.

KEYWORDS

hepatic abscess, pyogenic liver abscess, treatment, *Yersinia pseudotuberculosis*

1 | INTRODUCTION

Yersinia pseudotuberculosis is a facultative anaerobic, Gram-negative, motile, non-spore-forming bacillus, belonging to the family *Yersiniaceae*. *Y. pseudotuberculosis* is a rare zoonotic infection, which may be transmitted to humans through contact with infected animals or after ingestion of contaminated food or water.¹ The most common manifestations of infection with *Y. pseudotuberculosis* in humans are enterocolitis, terminal ileitis and/or mesenteric lymphadenitis, initially often interpreted as acute appendicitis, therefore sometimes characterized as pseudoappendicitis.²

A pyogenic liver abscess (PLA) is pus-filled cavity within the liver due to a bacterial infection.³ The annual

incidence of PLA has been reported between 1 and 7 cases per 100,000 in some Western Countries and higher among men than women,^{4–6} while higher rates have been reported in Taiwan (17.6 per 100,000) with *Klebsiella pneumoniae* as the primary pathogen.⁷ The majority of PLA occurs in patients with pre-existing gastrointestinal or biliary disease and originates from hematogenous spread through the portal vein. The most common pathogens include *Klebsiella pneumoniae*, *Escherichia coli*, *Streptococcus anginosus*-group, *Enterococcus* species and anaerobic bacteria such as *Bacteroides* species or *Fusobacterium* species.³ But, in some cases, the etiologic microorganisms remain unidentified. This is particularly common, when abscess drainage is difficult and antibiotics are initiated before abscess puncture resulting in culture-negative PLA.⁸

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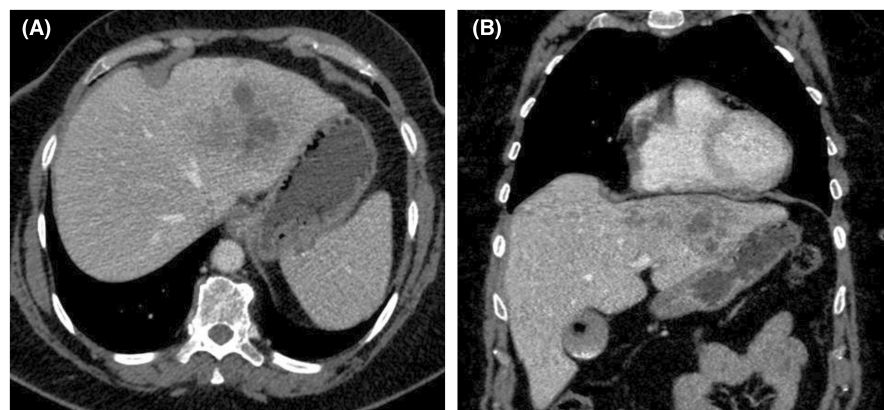


FIGURE 1 The hepatic abscesses by contrast-enhanced computed tomography scan in the axial plane (A) and coronal plane (B). An multiloculated abscess of total 8 cm diameter was depicted in the left liver lobe.

Sepsis with *Y. pseudotuberculosis* is rare, but have been described in patients with underlying medical conditions such as diabetes mellitus, malignancy, iron overload, and liver disease.^{1,2} Though uncommon, infections with *Y. pseudotuberculosis* disseminated through the blood stream have been described, including hepatic,^{9–14} splenic^{13,15} and pulmonary abscesses,¹⁶ peritonitis,² myocarditis,² osteomyelitis,¹⁷ septic shock,¹⁸ and meningitis.² Here, we describe the first Danish case of *Y. pseudotuberculosis* PLA in a patient with newly diagnosed diabetes mellitus.

2 | CASE HISTORY

A 59-year-old female patient was referred from her General Practitioner (GP) to the Department of Gastroenterology, Aalborg University Hospital upon suspicion of a PLA. The diagnose was made based on outpatient contrast-enhanced computed tomography (CT) scan ordered by GP, see below. The patient presented with intermittent high fever 1–2 times a week during the previous 6 weeks, fatigue, and had an unintended weight loss of 6–7 kg. She was recently diagnosed with type 2 diabetes mellitus as a part of general examination but was otherwise immunocompetent. Treatment for Diabetes had not been started yet. She had no close contacts to animals or recent travel history. There were no signs of infection among her relatives or close contacts. At admission, the patient was afebrile, vital parameters were normal, and she was otherwise unaffected with no diarrhea, abdominal tenderness, or jaundice.

3 | INVESTIGATIONS AND TREATMENT

Blood tests taken at admission showed elevated C-reactive protein (CRP) (137 mg/L, normal value <8 mg/L), alkaline phosphatase (174 U/L, normal range 35–105 U/L), and plasma ferritin (311 µg/L, normal range 15–290 µg/L), whereas the white blood cell count, alanine transaminase,

lactate dehydrogenase, and bilirubin were within the normal range.

A standard blood culture set (two BD BACTEC™ Plus Aerobic medium and one BD BACTEC™ Lytic Anaerobic medium glass culture vials) incubated in the BACTEC FX Top instrument (Becton Dickinson AB, Stockholm, Sweden) obtained upon admission and at day three, seven, and 11 were all negative after 6 days of incubation. Moreover, a stool sample obtained at day nine was culture-negative for enteric pathogenic bacteria, including *Yersinia* species.

The abovementioned CT-scan of abdomen and pelvis performed before hospital admission had revealed three liver lesions suggestive for abscesses: one in the left lobe, and two in the right lobe segment five and six, with sizes of 8, 3.6 and 1.8 cm in diameter, respectively, see Figure 1. Moreover, cholecystolithiasis with multiple small gallstones was diagnosed, but with no signs of cholecystitis or cholestasis. Ultrasound-guided percutaneous drainage of the largest abscess was performed before initiation of antibiotic therapy, and small amounts of brown-reddish pus was obtained and sent to the microbiology laboratory. Microscopy (Gram stain and wet smear) did not detect any microorganisms; however, bacterial growth was observed on both chromogenic and blood agar plates after 2 days incubation, and the preliminary identification of *Y. pseudotuberculosis* was performed by use of the matrix-assisted laser desorption ionization–time of flight (MALDI Biotyper 3.1, Bruker Daltonics Microflex LT, MBT 6903 MSP Library) with a score of 2.480. Antibiotic susceptibility testing was performed by use of McFarland standard 0.5 on Mueller-Hinton agar and ETEST (BioMérieux, Marcy l'Etoile, France) using EUCAST clinical breakpoint table for *Enterobacterales*, version 11.0. The isolate was sensitive to ampicillin (Minimum inhibitory concentration [MIC]: 0.19 mg/L); cefotaxime (MIC: 0.016 mg/L); ceftriaxone (MIC: 0.016 mg/L); meropenem (MIC: 0.016 mg/L); ciprofloxacin (MIC: 0.023 mg/L); and gentamycin (MIC: 0.19 mg/L). No ETEST was available for piperacillin-tazobactam, but the isolate was interpreted susceptible with a disk diffusion zone diameter of 40 mm.

Next, the isolate was sent to the national reference laboratory at Statens Serum Institut (SSI) and whole-genome sequencing was performed on the Illumina NextSeq instrument using the Nextera XT DNA Library Preparation Kit (Illumina, San Diego, USA) to produce paired-end reads (2×150bp). Raw reads were submitted to the SSI in-house QC pipeline (<https://github.com/ssi-dk/bifrost>), confirming the isolate as *Y. pseudotuberculosis* and performing genome assembly into 477 contigs representing a genome size of 4,768,263 bp and a GC content of 47.78%. No acquired resistance genes were detected in the isolate by the QC pipeline.

By use of the MLST 2.0 webtool (available at: <http://www.genomicepidemiology.org>), the sequence type ST-43 was assigned using the *Y. pseudotuberculosis* scheme. In addition, the finding of monomicrobial infection with *Yersinia* species was confirmed using standard 16S/18S microbiome sequencing directly from the pus aspirate, and subsequently speciated as *Y. pseudotuberculosis* by a species-specific PCR (data not shown) to distinguish from the close *Yersinia pestis*, the causative agent of plague, and previously proven to be a recently emerged clone from *Y. pseudotuberculosis*.

4 | OUTCOME AND FOLLOW-UP

After abscess drainage, empiric intravenous piperacillin-tazobactam 4.5 g q6h was administered. However, 3 days later the patient's condition deteriorated with fever of 39.0°C and CRP increased to 332 mg/L. Piperacillin-tazobactam was continued for a total of 19 days, combined with intravenous ciprofloxacin 400 mg q12h for the last 10 days. The patient was discharged after 20 days of hospitalization with oral ciprofloxacin 500 mg q12h as monotherapy with a treatment regime for a total of 8 weeks. The patient fully recovered, and all blood parameters were normal 1 week after discharge. Seven months after the index admission, the patient was seen in an outpatient setting due a slight discomfort from the upper right abdominal quadrant. The physical examination and all blood parameters were normal. However, a follow-up CT-scan showed slight scarring and small abscess residue at the site of the primary infection. Therefore, a second follow-up CT-scan was made 1 year after index admission, which showed significant regression of the changes, that was seen on the first follow-up CT-scan.

5 | DISCUSSION

To our knowledge, this is the first reported case of multiple PLA caused by *Y. pseudotuberculosis* in Denmark using

MEDLINE, Embase, Web of Science, Google Scholar, and Danish Medical Journal for literature review. Our patient presented with 6 weeks of intermittently fever, fatigue, and unattended weight loss. A CT-scan performed in the General Practitioner setting had revealed the diagnosis of multiple hepatic abscesses. She was successfully treated with percutaneous drainage combined with antibiotic therapy with piperacillin/tazobactam and ciprofloxacin for a total of 8 weeks.

In general, approximately half of PLA patients have secondary bacteremia.⁸ While there are only a few case-reports of *Y. pseudotuberculosis* PLA,^{9–14} it seems this also applies to *Y. pseudotuberculosis* PLA (in four cases the bacteria was cultured from blood).^{9–11,13} In one case, the diagnosis was based on antibody titers for *Y. pseudotuberculosis* only.¹² In our case, blood culture and stool were culture negative, but only the first blood culture set was taken prior to antibiotic therapy. Overall, cryptogenic liver abscesses are most often monomicrobial.⁸ Prior case reports of *Y. pseudotuberculosis* PLA^{9–14} and ours, suggest that *Y. pseudotuberculosis* PLA are also monomicrobial.

The majority of PLA occurs in patients with underlying hepatobiliary or pancreatic disease through ascending cholangitis or hematogenous spread through the portal vein,⁸ others may be induced by trauma (e.g., post-surgical), and a substantial part remains cryptogenic. While our patient had choledocholithiasis, she had no signs of cholecystitis or cholestasis. Diabetes mellitus is associated with an increased risk of PLA,¹⁹ and also a risk factor for systemic *Y. pseudotuberculosis* infection, including bacteremia.² Our patient had a newly diagnosis of type 2 diabetes mellitus, which also was reported in three of six prior cases of *Y. pseudotuberculosis* PLA,^{9,11,13} and in a patient with a splenic abscess.¹³ Iron overload has been suggested to predispose for *Y. enterocolitica* liver abscesses and systemic *Y. pseudotuberculosis* infection (owing to lack of sophisticated iron metabolism pathways).²⁰ One of six prior cases of *Y. pseudotuberculosis* PLA had a diagnosis of genetic hemochromatosis.¹⁰ While our patient had a slightly elevated level of plasma ferritin at admission, this was interpreted as an acute-phase reactant, as she had no other signs of hemochromatosis.

Yersinia pseudotuberculosis is hosted by various animals with main reservoir in rodents, deer, and wild birds.² Multiple *Y. pseudotuberculosis* outbreaks have been reported from contaminated food such as carrots and lettuce,^{21,22} but no Danish outbreaks have yet been identified. We were not able to confirm the source of infection in our patient, and she had no close contacts to animals.

Treatment of PLA includes drainage (either percutaneous or surgical) and antibiotic therapy. The usual regime includes 2 weeks of parental antibiotic treatment followed by 4 to 6 weeks of oral antibiotics.⁵ The optimal

antibiotic treatment and duration of antimicrobial treatment for *Y. pseudotuberculosis* PLA is unknown, and was heterogeneously reported in the published cases.^{9–14} *Y. pseudotuberculosis* is usually in vitro susceptible to ampicillin, cephalosporins, tetracycline, ciprofloxacin, and aminoglycosides,^{1,2} and the recommended antibiotic therapy in case of bacteremia or systemic infection includes a third-generation cephalosporin such as ceftriaxone 2 g per day (or alternatively ciprofloxacin) combined with a daily dose of gentamycin 5 mg/kg.^{2,23,24} The treatment regimens of the prior cases of *Y. pseudotuberculosis* PLA all differed, but included ampicillin, amoxicillin-clavulanic acid, ceftriaxone, quinolones (ciprofloxacin and ofloxacin), gentamicin, and, in one case, troleandomycin.^{9–14}

Our isolate of *Y. pseudotuberculosis* was susceptible for all tested antibiotics including ampicillin, but owing to worsening on the clinical condition after drainage, the empiric piperacillin-tazobactam treatment was supplemented with ciprofloxacin. After ribosomal 16S PCR analysis confirmed monomicrobial finding of *Y. pseudotuberculosis*, oral treatment was finalized with ciprofloxacin alone.

In conclusion, this is the first Danish case of *Y. pseudotuberculosis* PLA. *Y. pseudotuberculosis* was identified in pus after liver abscess drainage but not in blood cultures, highlighting the need for drainage for both treatment and for identification of the etiology. Of note, our patient had diabetes mellitus, which was also reported in prior cases of *Y. pseudotuberculosis* PLA.

AUTHOR CONTRIBUTIONS

M. Dudina and H. L. Nielsen conceived the idea for the case report, did the microbial analysis and contributed to the writing and editing of the manuscript. K. K. Søgaard contributed to the literature review, writing, and editing of the manuscript. T. Deleuran was responsible for treating the patient obtained informed consent and editing of the manuscript. K. G. Joensen did the reference bacterial DNA sequencing and editing of the manuscript. J. B. Frøkjær was responsible for the imaging diagnostics and editing the manuscript. All authors read and approved the final manuscript.

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FUNDING INFORMATION

None.

CONFLICT OF INTEREST

All authors declare no conflict of interest in relation to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

Personal data have been respected.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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