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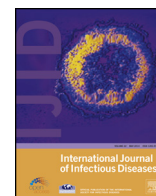
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Case Report

Spontaneous ascitic fluid infection and bacteremia due to *Yersinia pseudotuberculosis* in a liver transplant patient

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ABSTRACT

We report herein a case of bacteremic ascitic fluid infection in a liver transplant patient caused by a strain of *Yersinia pseudotuberculosis* serogroup I that lost the yersiniabactin core. The patient's outcome was favorable after a combined therapy with a third-generation cephalosporin and gentamicin.

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1. Case Report

A 49-year-old man was admitted to our hepatology intensive care unit on January 2013 for confusion, hyperthermia, and headaches with no stiff neck, persisting for four days. Three years earlier, the patient underwent liver transplantation because of alcohol and hepatitis C virus (HCV) cirrhosis. Following transplantation, he had a recurrence of HCV infection. He had travelled in Algeria and in Guadeloupe in 2011 and 2012, respectively. He reported no animal exposure except to his domestic cat. The patient had not benefited from prolonged antibiotic prophylaxis upon admission. On admission, physical examination revealed no specific

abnormalities. Blood analysis recovered a low white blood cell count of 3 G/L (N: 4–10 G/L), elevated liver enzymes (aspartate aminotransferase 240 U/L (N: 10–45 U/L), alkaline phosphatase 323 U/L (N: 35–120 U/L), gamma glutamyl transferase 861 U/L (7–55 U/L)), ferritinemia = 4111 µg/L, and triglyceridemia = 4.36 mmol/L. Blood (7 samples), cerebrospinal fluid and urine collected upon admission were culture-negative during the first three days of hospitalization, and the patient was not receiving any antibiotic (Table 1). On day (D) 5, a brain magnetic resonance imaging found a filled maxillary sinus, and a treatment with amoxicillin/clavulanic acid was initiated (Table 1). On D6, the whole body scan recovered an important ascitic fluid, which had not been detected upon clinical examination, and later explained by transjugular biopsy showing recurrence of cirrhosis. A simultaneous puncture of the ascitic fluid showed 600/mm³ leukocytes with 20% of polymorphonuclear neutrophils, but both cultures incubated at 37 °C and ascitic fluid sample seeded into blood culture bottles were negative. However, ciprofloxacin was added to amoxicillin/clavulanic acid since

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Table 1

Schematic chronological representation of antibiotic treatment, outcome, and bacteriological samples

	Treatment						Bacteriological diagnosis			
	AMC	CIP	CRO	CTX	TZP	GEN	Three positive samples			Negative samples
							BC	BC	AF	
D1										7 BC
D2										
D3										
D4							Sampled			2 BC
D5								Sampled		
D6								Positive		1 BC & 1 AF
D7								DST available	Sampled	2 BC
D8							Positive			
D9							DST available			1 BC & 1 AF
D10								Positive		1 BC
D11								DST available		1 BC
D12										
D13										
D14										
D15										
D16										
D17										

AMC: amoxicillin/clavulanic acid 3 g tid, CIP: ciprofloxacin 500 mg bid, CRO: ceftriaxone 1 g, CTX: cefotaxime 1 g qid, TZP: piperacillin/tazobactam 4 g tid, GEN: gentamicin 300 mg, BC: blood culture, AF: ascitic fluid, DST: drug susceptibility testing.

polymorphonuclear neutrophils count was higher than 250/mm³ which met the criteria for an ascitic fluid infection (Table 1). On D7, i.e. 24 hours after the initiation of ciprofloxacin treatment, a second puncture of the ascitic fluid showed a decrease of leukocytes count to 280/mm³ with 27% of polymorphonuclear neutrophils; this ascitic fluid seeded into blood culture bottles and also two blood samples seeded in anaerobic blood culture bottles (sampled on D4 and D5), grew Gram negative rods at 37 °C (Table 1). The identification of the strain using API[®] 20E and 32GN systems (Biomérieux, Marcy l'Etoile, France) was unambiguously *Yersinia pseudotuberculosis*. Bacterial identification of the strain was performed by 16S rRNA sequencing as previously described;¹ we obtained a 470 bp sequence, which was found to differ at only 1 nucleotide position from that of *Y. pseudotuberculosis* and *Y. pestis* (GenBank CP002956 and CP001048, respectively), consisting of 99.8% similarity. We used protein profiling through the use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Autoflex I MALDI TOF mass spectrometer) to identify the strain, as described.² We obtained a spectrum with no reliable identification: scores were higher than 2 (up to 2.22) for both *Y. pseudotuberculosis* and *Y. pestis*. Finally, a positive urease test (different from the one present in API[®] systems) yielded a definitive identification of *Y. pseudotuberculosis*, which was further confirmed by the French national reference center, and the isolate was

assigned as *Y. pseudotuberculosis* serotype I using a serotyping scheme based on O-antigen.

To evaluate the pathogenicity of this isolate, the presence of the three key virulence factors (the T3SS encoding virulence plasmid pCD1 (70 kb), the High Pathogenicity Island (HPI), and YPM superantigens) were investigated. The pCD1 plasmid required for pathogenicity was detected by DNA amplification of both the entire *lcrV* and *yopH* genes using the sets of primers [5'-TCACCGCGAAAATTATTGC (forward) and 5'-TTGTCTGCGA-TAAGCTCTG (reverse)] and [5'-TTGGTGCAGCAAGAGAGCG (forward) and 5'-CCAGTGAAGCGAGTGCCTTG (reverse)], respectively. The presence of HPI carrying the yersiniabactin (Ybt) system is correlated with the level of pathogenicity³ and was determined by PCR with primers located in 3 distinct genes: *ybtA* [5'-CACCG-CAAACGCAATCTGAAA (forward) and 5'-AAATGGCTGGCGTTGGCA-TAG (reverse)], *ybtX* [5'-GGGGTTTCCGCTCTGGAGA (forward) and 5'-ATGTCGCTGCGTCCGTCG (reverse)] and *fyuA* [5'-ATCAG-GATGGCCTGCTG (forward) and 5'-GACGATTAACGAACCGGA (reverse)], encoding AraC-transcriptional activator, a protein with unknown function and the outer membrane receptor of the Yersiniabactin, respectively. All three genes were absent from this strain, thus suggesting a spontaneous excision of HPI.⁴ Therefore, the possible presence of endogenous plasmid pGDT4 (~ 100 kb) involved in the autoexcision of the HPI was screened by PCR⁵ in

addition to a large plasmid extraction. The endogenous plasmid pGDT4 was not detected. The Ybt system appeared not to be essential for the *Y. pseudotuberculosis* strain isolated from our patient, partly because there are multiple additional iron capture systems operating in *Yersinia* capable of giving a similar phenotype.⁵ However, the iron-overload diagnosed in our patient may provide a better explanation for the absence of Ybt since iron-overloaded is known to restore or increase the virulence of Ybt-negative *Yersinia*.⁷ Then, the three variants of Ypm superantigens (*ypmA*, *ypmB* and *ypmC*) were searched directly in the strain using PCR technique with the following primers: *ypmA1*:C1/*ypmA2*:C2, ACACCTTCTCTGGAGTA(GCG/ACA)GGACATTTCTGCA, and *ypmB1*/*ypmB2*, CTAATCCCCGAGGATAA(GTT/GGC)GATTCGACGACATA-TAAC.⁸ As expected according to clinical symptoms, this strain of *Y. pseudotuberculosis* did not produce the superantigenic toxin YPM which seems to be involved in microvascular disease such as Kawasaki syndrome⁹ rather than bacteremia. Lastly, detection of type IV pilus locus that has been described in some strains of *Y. pseudotuberculosis* as a possible virulence factor associated with bacterial colonization of the intestinal mucosa was screened by PCR with 3 primers amplifying *pilN*, *pilS* and *pilQ*.¹⁰ No amplification products were obtained with the three primer sets. These results indicated that this strain did not harbour the type IV pilus gene cluster.

Antibiotic susceptibility testing by disk diffusion method¹¹ was characterized by a full susceptibility to beta-lactams, quinolones and aminoglycosides. The results of antimicrobial susceptibility testing were transmitted to clinicians on D7 (Table 1). Considering the lack of clinical improvement, amoxicillin/clavulanic acid was changed to third-generation cephalosporin. However, clinical evolution was unfavorable under conditions of treatment with ciprofloxacin and third-generation cephalosporin. Thus, the patient received two once-daily dose of gentamicin. Ciprofloxacin therapy was stopped on D12 because of favorable clinical outcome, while third-generation cephalosporin was pursued until D18 for a total of nine days of treatment (Table 1).

2. Discussion

Y. pseudotuberculosis is a Gram negative coccobacillus that grows optimally at cooler temperatures, and a zoonotic organism of worldwide distribution with reservoirs in rodents, birds and mammals that causes formation of purulent, caseous abscesses of the lymph nodes, liver and spleen.^{12–16} Transmission to humans is uncommon and occurs through ingestion of contaminated food, water or milk, or direct contact with an infected animal.^{16,17}

Y. pseudotuberculosis infections typically manifest within a mesenteric lymphadenitis accompanied by abdominal pain and fever and less often vomiting and diarrhea; it is most often detected in children and adolescents and may be indistinguishable from acute appendicitis.¹⁶ Bacteremia due to *Y. pseudotuberculosis* rarely occurs,¹³ but they have been described in patients with an underlying disorder such as hepatic cirrhosis, hemochromatosis, hepatitis or diabetes; in particular, iron overload has been suggested to be a predisposing factor for systemic *Y. pseudotuberculosis* infection,^{13,16} such as was the case for our cirrhotic patient who presented with hemophagocytic syndrome. Isolation of *Y. pseudotuberculosis* from ascitic fluid samples or from peritoneal fluid samples has been rarely reported, since only four cases were recovered in the literature.^{18–21} *Y. pseudotuberculosis* can be recovered in the ascitic or peritoneal fluids or cause bacteremia in cirrhotic patients because bowel bacteria are likely to escape the bacterial filter in the liver, since (i) a high proportion of the portal flow may bypass the liver sinusoids and (ii) the local and systemic immune functions are altered in cirrhotic patients.

Delayed diagnosis was likely consecutive to difficulty associated with culturing *Yersinia* on standard media. The patient began to recover 24 hours after the initiation of an antimicrobial chemotherapy with a third-generation cephalosporin combined with gentamicin while a treatment by fluoroquinolone alone failed to cure the *Y. pseudotuberculosis* infection (Table 1), thus contrasting with results obtained in murine model of yersiniosis. Indeed, fluoroquinolone therapy has shown to be particularly effective in a murine model of yersiniosis and has been used successfully for *Yersinia* infections in several cases while beta lactams therapy is associated with lower survival in mice or poor clinical response.^{22,23} A poor clinical response to fluoroquinolone alone and favorable issue after introduction of an aminoglycoside to quickly control infection in immunocompromised patients has been previously described in a diabetic patient.¹³ Mortality rate associated with *Y. pseudotuberculosis* bacteremia has been reported as high as 75% despite antibiotic treatment in patients with underlying conditions, thus emphasizing the need for rapid bactericidal antimicrobial chemotherapy in immunocompromised patients with comorbidities.¹³ Finally, a rapid synergistic bactericidal antimicrobial chemotherapy against Gram negative bacillary infection may be better obtained with a combination of third-generation cephalosporin and aminoglycoside than fluoroquinolone alone in such patients. It is therefore questioned which molecules or antibiotic combinations are the most effective treatment of lethal invasive *Y. pseudotuberculosis* infections.

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