Case Report

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간경변 환자에서 발생한 *Hafnia alvei*에 의한 자발성 복막염 1예

정상경 · 이준성 · 김경아 · 김영두 · 좌윤정 · 김나경 · 곽이경
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Spontaneous Bacterial Peritonitis Caused by *Hafnia alvei* in a Patient with Liver Cirrhosis

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Hafnia alvei is a gram-negative bacillus that is rarely isolated from human clinical specimens and is rarely pathogenic. This organism is an extremely uncommon cause of spontaneous bacterial peritonitis (SBP). We report a case of an 83-year-old male with hepatitis C-associated liver cirrhosis and hepatocellular carcinoma who was diagnosed with SBP caused by *H. alvei*. He was admitted to an university-affiliated hospital with fever and abdominal pain. There were 2 episodes of SBP during 2 months. Although isolates of *H. alvei from* ascitic fluid were shown to be susceptible to cefotaxime, responses for cefotaxime treatment were inadequate in both episodes. Therefore, cefotaxime was switched to imipenem in the first episode and to ciprofloxacin in the second, according to the results of antimicrobial susceptibility. After the antibiotics was changed, SBP was resolved.

Key Words: Spontaneous bacterial peritonitis, *Hafnia alvei*, Liver cirrhosis

Introduction

Hafnia alvei, a member of the family Enterobacteriaceae, is a member of normal human gastrointestinal flora and is found in environmental habitats such as sewage, water, and food. These bacteria are rarely isolated from human clinical specimens and are rarely considered to be pathogenic [1, 2]. Extra-intestinal invasive infections caused by this organism usually develop in patients with chronic debilitating disorders and are often hospital-acquired that occur after antibiotic treatment [2, 3]. Cases of septicemia, endocarditis, endophthalmitis, meningitis, pneumonia, abscesses, and surgical wound infections constitute representative examples of invasive infections caused by *H. alvei* [1, 4]. Herein, we describe a case of a patient with spontaneous bacterial peritonitis (SBP) in whom *H. alvei* was identified from the ascitic fluid culture.

Case report

An 83-year-old male patient with hepatitis C-associated liver cirrhosis of

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27 years' duration was admitted to our hospital with fever and abdominal pain. He was diagnosed with type II diabetes mellitus 17 years ago and usual interstitial pneumonia (UIP) 5 months ago, for which he had been receiving subcutaneous insulin and prednisolone 7.5 mg, respectively. Three years prior to this admission, he was diagnosed with hepatocellular carcinoma and had been treated 7 times with transarterial chemoembolization. One month prior to admission, his hepatocellular carcinoma recurred and percutaneous ethanol injection (PEIT) was performed 3 times as an inpatient, and he was discharged 9 days prior to this admission. On admission, his blood pressure was 130/70 mmHg, pulse rate was 80/min, and body temperature was 37.9℃. The patient appeared chronically ill and initial physical examination was positive for ascites and right-sided abdominal tenderness, but his chest and heart examinations were all normal. His initial laboratory results were as follows: hemoglobin, 11.5 g/dL; platelet count, 49,000/mm^3; white blood cell count, 5,550/mm^3 (segmented neutrophils 74.2% and lymphocyte 13.9%); total bilirubin, 2.2 mg/dL; alanine transaminase, 132 U/L; aspartate transaminase, 117 U/L; alkaline phosphatase, 132 U/L; total protein, 6.3 g/dL; albumin, 2.4 g/dL; blood urea nitrogen, 23 mg/dL; creatinine, 1.0 mg/dL; sodium, 133 mmol/L; potassium, 4.8 mmol/L; prothrombin time, 14.9 seconds (international normalized ratio, 1.21); and C-reactive protein, 5.7 mg/dL. His chest radiograph was normal and abdominal radiograph showed focal ileus. Since SBP was suspected, diagnostic paracentesis was performed. The result of the initial ascitic fluid analysis showed a leukocyte count of 1,200/mm^3 (polymorphonuclear cell [PMN] 93%) and red blood cell count of 11,750/mm^3. Ascitic fluid chemistry demonstrated total protein of 0.83 g/dL, albumin of 0.8 g/dL, glucose of 330 mg/dL, and lactate dehydrogenase (LDH) of 81 U/L. Cytology of ascites revealed negative findings for malignant cells. Because clinical and laboratory findings were compatible with SBP, we started empirical antibiotic therapy with intravenous cefotaxime 2 g every 8 hours, after which fever and abdominal pain subsided. No organisms were isolated from the blood and ascitic fluid culture, and a follow-up analysis of ascitic fluid showed decrease in leukocyte count to 470/mm^3 (PMN 87%). However, on the ninth hospital day, fever and abdominal pain developed again. Ascitic fluid analysis was performed and it showed increase in leukocyte count to 3,250/mm^3 (PMN 67%) and this time *H. alvei* was isolated from the ascitic fluid culture. Susceptibility testing performed using the Vitek 2 system GN card and the antimicrobial susceptibility test-N056 card (bioMerieux, Hazelwood, MO, U.S.A.) showed that the isolate was susceptible to third-generation cephalosporin, cefepime, ciprofloxacin, amikacin, gentamicin, piperacillin/tazobactam, tetracycline, trimethoprim/sulfamethoxazole, imipenem, and meropenem, but resistant to ampicillin, amoxicillin/clavulanic acid, and cefazolin. Although *H. alvei* was reported to be susceptible to third-generation cephalosporins, the antibiotic was switched to imipenem because SBP recurred while the patient was receiving cefotaxime. Fever and abdominal pain resolved over the next 2 days, and since he showed clinical improvement after treatment with imipenem, follow-up paracentesis was not performed. After continuing antibiotic therapy with imipenem for a total of 10 days, he was discharged.

Two months later, the patient was admitted again because of abdominal pain. This time, he did not have fever (37℃) and abdominal tenderness was negative on physical examination, but the patient appeared to have a distended abdomen. Since SBP could not be ruled out, diagnostic paracentesis was repeated and the ascitic fluid analysis showed a leukocyte count of 3,300/mm^3 (PMN 84%), red blood cell count of 80/mm^3, albumin concentration of 0.8 g/dL, protein of 1.8 g/dL, LDH of 55 U/L, and glucose of 193 mg/dL. The serum-ascites albumin gradient was 1.3 and thus, cefotaxime was initiated to treat SBP. Subsequently, *H. alvei* was isolated again from the ascitic fluid and the pattern of antimicrobial susceptibility was almost the same as that of the previous isolate except for the susceptibility to tetracycline, which was intermediate. On the fourth hospital day, the antibiotic was changed from cefotaxime to oral ciprofloxacin (500 mg every 12 hours) because ascitic fluid leukocyte count increased from 3,300/mm^3 (PMN 84%) to 5,900/mm^3 (PMN 76%). After the antibiotic was changed, the patient no longer complained of abdominal pain throughout his remaining hospital stay. Follow-up ascitic fluid analysis performed on the eighth hospital day showed that the leukocyte count has decreased to 475/mm^3 (PMN 82%). Therefore, the patient was discharged with oral ciprofloxacin to be taken for 5 more days.

Discussion

SBP is a potentially fatal but a reversible cause of deterioration in patients with advanced cirrhosis [5]. It is defined as a bacterial infection of the ascitic fluid in the absence of a focal contiguous source that almost universally occurs in the background of severe liver disease [5]. Microorganisms, presumably of enteric origin, account for up to 75% of the pathogens in SBP. *Escherichia coli* is the most frequently recovered pathogen followed by *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, and other

Streptococcus species including enterococci [6, 7].

SBP caused by *H. alvei* is extremely uncommon [8, 9]. Akcam et al. reported a case of peritonitis caused by *H. alvei* in a 60-year-old man with underlying mesothelioma [8]; and Song et al. reported a case of SBP in a 50-year-old man with hepatocellular carcinoma [9]. The clinical presentation in our patient was similar to that of SBP caused by other organisms: fever, abdominal pain, and abdominal tenderness. The diagnosis of SBP is made when there is a positive bacterial culture from the ascitic fluid and an elevated absolute PMN cell count over 250/mm^3 in the ascitic fluid without an evident intra-abdominal, surgically treatable source of infection.

H. alvei has been recognized as an infrequent cause of human infection. This organism has been identified as an etiologic agent of the infection in the urogenital tract, lower respiratory tract, and intra-abdominal organs as well as a cause of endophthalmitis and bacteremia without definite focus [1]. It is important to note that extra-intestinal *H. alvei* infections are usually nosocomial and are associated with underlying diseases or predisposing factors [1]. Previous case reports have shown human immunodeficiency virus (HIV) infection, liver disease, solid organ transplants, and underlying malignancy to be associated with extra-intestinal infection by *H. alvei* [1, 10, 11]. In our case, *H. alvei* infection was hospital-acquired and occurred in a patient with underlying illness who was suffering from liver cirrhosis, hepatocellular carcinoma, UIP, and diabetes.

In a study by Stock et al., 76 *H. alvei* isolates were investigated for their susceptibility to 69 antibiotics or drugs [12]. The general pattern that emerges from this study is that *H. alvei* are typically susceptible to carbapenems, monobactams, chloramphenicol, quinolones, aminoglycosides, and antifolates, but resistant to penicillin, oxacillin, and amoxicillin plus clavulanic acid. Susceptibility to tetracyclines and cephalosporins is variable, with most *H. alvei* strains being susceptible to broad-spectrum and fourth-generation cephalosporins such as cefepime, but often resistant to narrow- and extended-spectrum compounds [12]. *H. alvei* is known to encode an inducible or constitutive AmpC-type beta-lactamase that is distinct from that of many other Enterobacteriaceae and results in resistance to third-generation cephalosporins [13, 14]. Although optimal treatment of *H. alvei* infections is not known, treatment of *H. alvei* infection based on antimicrobial susceptibility testing results has been reported to be effective [15]. In severe cases, treatment with imipenem or a third-generation cephalosporin in combination with an aminoglycoside was recommended [4, 15]. In our case, *H. alvei* from ascitic fluid was shown to be susceptible to cefotaxime, but the response for cefotaxime treatment was inadequate. Although the reason for the inadequate response is unclear, there is a possibility that inducible β-lactam resistance in *H. alvei* was undetected by automated Vitek 2 system [16].

In our case, the patient developed two episodes of SBP caused by *H. alvei*. Since the ascitic fluid culture was not taken after a 10-day imipenem treatment in the first episode, we cannot be certain whether the occurrence of the second episode had been due to the treatment failure with imipenem or a relapse of *H. alvei* SBP. However, because the abdominal pain and tenderness improved after treatment with imipenem, the possibility of relapse seems more likely. In patients who have recovered from an episode of SBP, recurrence of SBP is common, with its rate estimated to be 43% at 6 months and 69 % at 1 year [17]. In general, 10-14 days of intravenous antibiotics is considered to be the standard duration of treatment for SBP, but a shorter duration of 5-day treatment appears to be as effective as that of a 10-day treatment [5, 18]. However, the optimal duration of antibiotic therapy for SBP caused by *H. alvei* has not been determined.

In conclusion, *H. alvei* is an extremely uncommon cause of SBP. Although treatment of *H. alvei* infection based on antimicrobial susceptibility testing results is effective in most of the cases, it should always be kept in mind that some strains have inducible β-lactamase. Considering the small number of cases reported thus far, further study is needed to expand our understanding on the significance of the infections caused by *H. alvei*.

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