Case Report

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Acute Pyelonephritis with *Enterococcus hirae* and Literature Review

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To control for acute infectious disease, identification of the causative agent and determining the antibiotic susceptibility of the pathogen are crucial. If a particular organism is rare and relevant etiological information is scarce, it becomes difficult to determine appropriate antibiotic and therapy duration. *Enterococcus hirae* is a pathogen that infects animals, but rarely causes human infections. We present two cases of *E. hirae*-related pyelonephritis with successful treatment. Herein, our experience is discussed with relevant literature review.

Keywords: *Enterococcus*; Pyelonephritis; Sepsis

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Various bacterial organisms are known to cause urinary tract infections, such as acute pyelonephritis. *Enterobacteriaceae* are common pathogens and considered a significant cause of urogenital infections, with *Escherichia coli* being the typical infecting organism. In addition to *E. coli*, *Pseudomonas aeruginosa* and gram-positive cocci (*Staphylococcus* and *Enterococcus*) can also be critical pathogens, depending on the morbidity and source of infection (retrograde or hematogenous). Therefore, choosing an appropriate empirical antibiotic and antibiogram to treat urogenital infections is important. *Enterococcus hirae* are gram positive (GP) cocci, frequently associated with infections in animal species, particularly in birds, rats, and cats. However, since the pathogen rarely infects humans, little is known about the organism's biology and clinical mechanisms. The goal of this report is to promote awareness so that physicians can better handle this rare infection by presenting two cases of *E. hirae* pyelonephritis and a literature review.

CASE REPORT

1. Case 1

A 78-year-old man visited the hospital with the complaint of left flank pain and febrile sensation lasting for 2 days. His current medication consisted of treatment for diabetes mellitus, hypertension, and coronary arterial occlusive disease. Four weeks prior to admittance, he underwent endoscopic gastric mucosal resection for gastric adenoma. His blood pressure was 110/60 mmHg, pulse rate was 98 bpm, and body temperature was 38.6°C. The results from his blood test were as follows: white blood cell count, 14,450 cells/mm^3 (neutrophil, 78.4%); C-reactive protein, 12.96 mg/dl; blood urea nitrogen, 21.3 mg/dl; creatinine, 1.51 mg/dl; and procalcitonin, 0.23 ng/ml. Urinalysis revealed the following: microscopic red blood cell count, 11-20 cells/high power field; white blood cell count, 51-100 cells/high power field; and nitrite negativity. His left kidney was swollen, and a wedge-shaped, low attenuation area was detected on a contrast-enhanced abdomino-pelvic computed tomography scan (Fig. 1). Two grams of

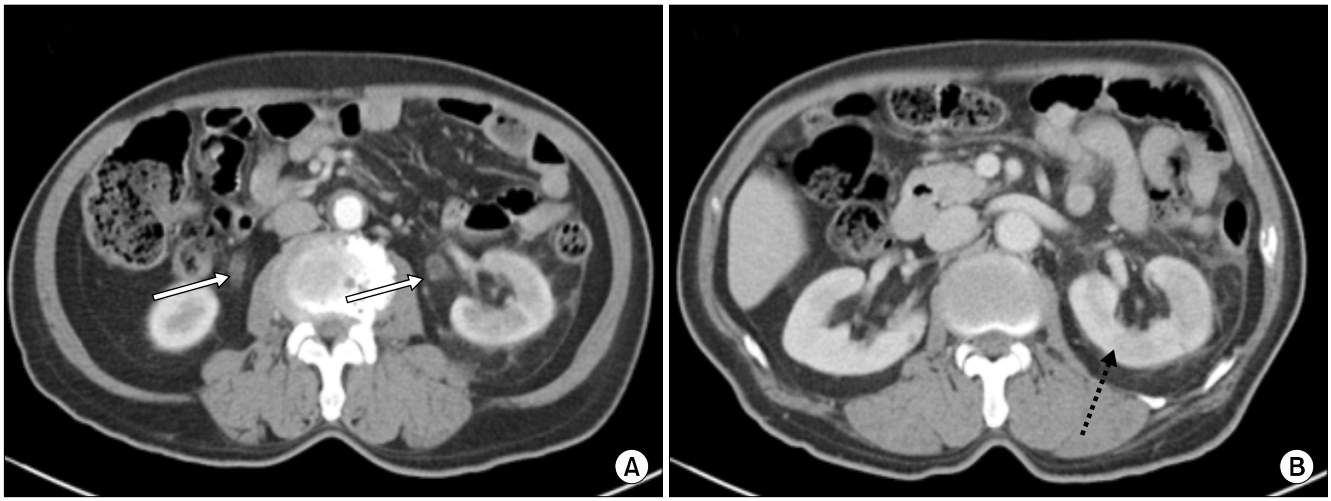

Fig. 1. Computed tomography scans of the first patient. (A) Contrast-enhanced phase; prominent wall thickening and enhancement in both ureters (line arrows). (B) Delayed phase; multifocal wedge shaped poor enhancing lesion in the left kidney (dotted line arrow).

Organism	Enterococcus hirae	
		RIS
Ampicillin	<=2	S
Ampicillin/sulbactam	<=2	S
Ciprofloxacin	<=0.5	S
Erythromycin	<=0.25	S
Gentamicin High Level Resistance	SYN-S	S
Imipenem	2	S
Levofloxacin	0.5	S
Linezolid	2	S
Nitrofurantoin	64	I
Norfloxacin	1	S
Penicillin - G	0.5	S
Quinupristin/Dafopristin	1	S
Streptomicin High Level Resistance	SYN-S	S
Teicoplanin	<=0.5	S
Tetracycline	<=1	S
Vancomycin	<=0.5	S
Tigecyline	<=0.12	S

Organism Growth rate	Enterococcus hirae Colony count : >= 100.000/ml	
		RIS
Ampicillin	<=2	S
Ampicillin/sulbactam	<=2	S
Ciprofloxacin	<=0.5	S
Erythromycin	<=0.25	S
Gentamicin High Level Resistance	SYN-S	S
Imipenem	2	S
Levofloxacin	0.5	S
Linezolid	2	S
Nitrofurantoin	64	I
Norfloxacin	1	S
Penicillin - G	0.5	S
Quinupristin/Dafopristin	1	S
Streptomicin High Level Resistance	SYN-S	S
Teicoplanin	<=0.5	S
Tetracycline	<=1	S
Vancomycin	<=0.5	S
Tigecyline	<=0.12	S

Fig. 2. Antibiogram of the first patient. Left column for blood culture result and right column for urine culture result.

ceftriaxone, the empirical antibiotic, was injected. Blood samples were collected from two different peripheral veins and used to inoculate a BacT/ALERT® FA Plus (bioMerieux Inc., Durham, NC, USA) culture and analyzed using the BacT/ALERT® 3D Microbial Detection System (bioMerieux Inc., Durham). Urine sample was cultured in blood agar plate and MacConkey agar plate. Biochemical tests for the cultured organism were completed by using the VITEK 2 system (bioMerieux Inc., Hazelwood, MO, USA). *E. hirae* was identified in the blood and urine cultures, and ceftriaxone was changed to ciprofloxacin in accordance with the antibiogram (Fig. 2). After 3 days, the patient was afebrile. He was treated successfully with antibiotics for 14 days, including an oral antibiotic period.

2. Case 2

A 74-year-old woman visited the hospital with a 5-day history of left flank pain, febrile sensation, and chills. The patient had diabetes mellitus, hypertension, and coronary arterial occlusive disease as underlying disease conditions. Upon admittance, she was in a state of shock, presenting a blood pressure of 62/40 mmHg, heart rate of 90 bpm, and a body temperature of 36.2°C. The blood test results were as follows: white blood cell count, 12,370 cells/mm^3 (neutrophil 80.2%); C-reactive protein, 12.10 mg/dl; blood urea nitrogen, 37.2 mg/dl; creatinine, 1.67 mg/dl; and procalcitonin, 1.24 ng/ml. Urinalysis revealed that the white blood cell count was 21-30 cells/high power field and nitrite was not detectable. Her left kidney showed diffuse enlargement, with a thickened left ureteral on the contrast-enhanced abdomino-pelvic computed tomography (Fig. 3). The shock was treated via intravenous hydration with 0.9% saline and infusion of vasopressor (norepinephrine) and empirical antibiotics (2 g of ceftriaxone). Two days after admission, she recovered from the shock; after 4 days, she recovered from febrile. *E. hirae* was identified

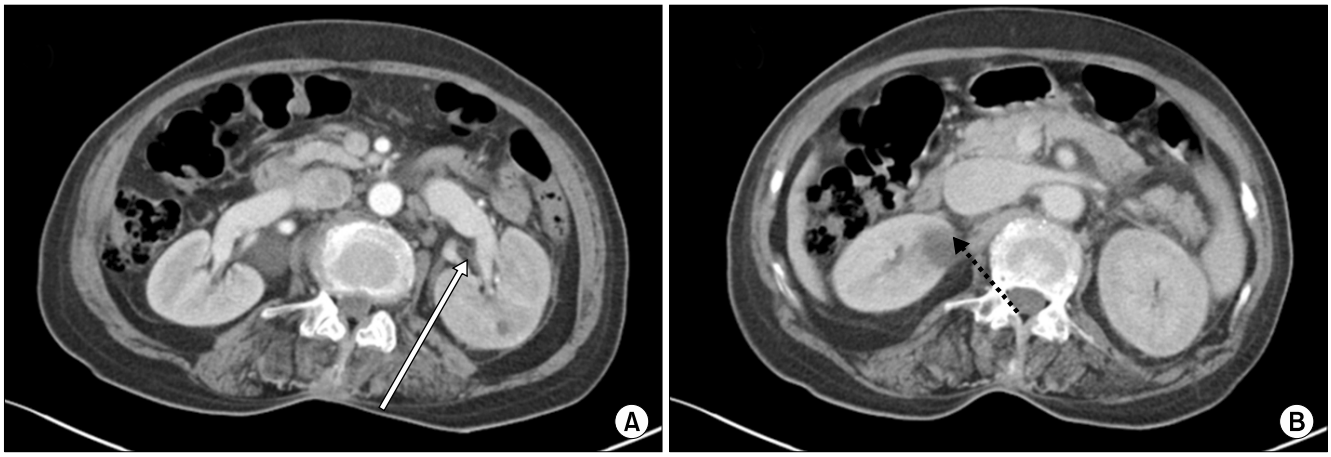

Fig. 3. Computed tomography scans of the second patient. (A) Contrast-enhanced (B) delayed phase show diffuse left renal swelling and left perinephric fat infiltration. Diffuse wall thickening of the left ureter (line arrow). Simple renal cyst (dotted line arrow).

Organism	Enterococcus hirae	
Growth rate	Colony count : >= 100.000/ml	
		RIS
Ampicillin	<=2	S
Ampicillin/sulbactam	<=2	S
Ciprofloxacin	<=0.5	S
Erythromycin	<=0.25	S
Gentamicin High Level Resistance	SYN-S	S
Imipenem	2	S
Levofloxacin	0.5	S
Linezolid	2	S
Nitrofurantoin	64	I
Norfloxacin	1	S
Penicillin - G	0.5	S
Quinupristin/Dafopristin	1	S
Streptomicin High Level Resistance	SYN-S	S
Teicoplanin	<=0.5	S
Tetracycline	<=1	S
Vancomycin	<=0.5	S
Tigecyline	<=0.12	S

Fig. 4. Antibiogram of the second patient. Urine culture.

as the pathogen only from the urine sample by catheterization, and her blood culture test was negative. According to the antibiogram (Fig. 4), the antibiotic was changed to ciprofloxacin. The treatment, which was administered for 14 days, was successful.

DISCUSSION

Acute pyelonephritis is frequent in young women. However, in the event of a delayed diagnosis or inadequate treatment, it often results, due to age or lack of symptoms, in severe complications, such as acute tubular necrosis and acute renal failure. Therefore, urine culture test used to identify the pathogen and antibiogram is very important. Moreover, the antibiogram is crucial for choosing the empirical antibiotic treatment, as well as the dosing and duration. *Enterococcus* species can cause urinary tract infections, endocarditis, and bacteremia; *E. faecalis* and *E. faecium* are reported to be the causative agents in 90% of these cases. Conversely, *E. hirae* is suspected in 1-3% of cases of enterococcal infections, making it a rare human pathogen [1]. Since there is limited information and experience in handling *E. hirae* infections, treatment for *E. hirae*-related pyelonephritis can be difficult.

In these two cases, we cannot confirm the risk factors for *E. hirae* infection, although both cases had the same underlying diseases. However, we conclude that the 14-day antibiotic treatment with ciprofloxacin has a relatively good clinical application. However, we frequently hesitate to choose ciprofloxacin as the empirical antibiotic due to its resistance rate being greater than 10% among *E. coli*, which is the most common pathogen for urinary tract infections [2]. Despite this limitation, there are many cases that demonstrate the clinical effectiveness of ciprofloxacin since the antibiotic is mostly secreted through the urine, with the urine concentration of the drug reaching 100-300 mg/L [2]. Antibiograms provide physicians with very important information, but the antibiogram for *E. hirae* is rare. According to the 1995 report, *E. hirae* showed a susceptibility to vancomycin and teicoplanin, and resistance to ampicillin, erythromycin, ciprofloxacin, high-dose streptomycin, and gentamicin, with resistance rates of 55%, 72%, 17%, 55%, and 34%, respectively [3]. Among the antibiograms reported within the country, one case demonstrated susceptibility to ampicillin and high-dose

Table 1. Reported cases of human infections (acute pyelonephritis) due to *Enterococcus hirae*

Origin	Reference	Year	Sex/age (y)	Morbidity	Culture	Treatment	Day
Domestic	Park et al. [10]	2000	F/21	Birth control pill	B	FLO+ISP→AMP+ISP	10
	Kim et al. [5]	2009	F/57	Rheumatoid arthritis	B, U	CIP→ CRO+AG→AM-SB	14
	Kim et al. [4]	2014	M/84	Horseshoe kidney	U	CIP→AM-SB	14
Overseas	Chan et al. [7]	2012	F/62	Constipation	U	CFZ+Gent→AMP→Amox	12
	Paosinho et al. [8][a)]	2016	F/78	Afib, CKD	U	AM-CL→PIP-TZ	14
	Brule et al. [9][b)]	2013	M/44	ALD, DCMP	B, U	CRO+Metro+AMK→Amox	25

F: female, B: blood, FLO: flomoxef sodium, ISP: isepamicin, AMP: ampicillin, U: urine, CIP: ciprofloxacin, CRO: ceftriaxone, AG: aminoglycoside, AM-SB: ampicillin-sulbactam, M: male, CFZ: cefazolin, Gent: gentamicin, Amox: amoxicillin, Afib: atrial fibrillation, CKD: chronic kidney disease, AM-CL: amoxicillin-clavulanic acid, PIP-TZ: piperacillin-tazobactam, ALD: alcoholic liver disease, DCMP: dilated cardiomyopathy, Metro: metronidazole, AMK: amikacin.
[a)]Co-infection with *Escherichia coli*, [b)]pyonephrosis.

gentamicin [4], and the other case demonstrated a susceptibility to ampicillin, with resistance to high-dose gentamicin and streptomycin [5]. Regarding the diagnostic tool, VITEK 2 is an automated identification and antimicrobial susceptibility testing system that is based on broth microdilution using reagent card for gram negative, GP, yeast, GP spore forming bacilli taxa. The substrates of reagents measure various metabolic activities, such as acidification, alkalinization, enzyme hydrolysis, and growth in the presence of inhibitory substances. This system allows kinetic analysis by reading each test every 15 minutes. The optical system combines the multichannel fluorimeter and photometer readings to record the fluorescence, turbidity, and colorimetric signals. This system aids clinicians for rapid and correct identification of the pathogens, despite having some limitations. Although there is a slight possibility for VITEK 2 to misidentify, we did not use 16S rRNA sequencing method for distinguishing *E. hirae* from *E. durans*, which has similar biochemical characters and about 98.8% of identical sequencing. Because reagent GP card in the VITEK 2 system has the ability to identify *E. avium*, *E. casseliflavus*, *E. cecorum*, *E. columbae*, *E. durans*, *E. faecalis*, *E. faecium*, *E. gallinarum*, *E. hirae*, *E. raffinosus*, and *E. saccharolyticus*, in theory, we did not use such sequencing. Moreover, Moore et al. [6] reported 100% accuracy for identifying *E. hirae* with supplemental test using manufacture's identification table. *E. hirae* is stated to produce acid from melibiose, and sucrose and *E. durans* is considered to be negative in both tests which can be done by the reagent card.

The majority of therapeutic plans for *Enterococcus* are focused on *E. faecalis* and *E. faecium*. According to the plans, ampicillin-based therapy with concomitant gentamicin or vancomycin is widely used as a treatment of choice for enterococcal infections. Other cases of *E. hirae*-related pyelonephritis (Table 1) [4,5,7-10], except for our case report, showed an antibiotic duration of 10 to 14 days, and the antibiotics of choice were ampicillin, ampicillin/sulbactam, or amoxicillin. In some areas, our report differed from that of previous cases, predominantly changing the antibiotics from ciprofloxacin to ampicillin/sulbactam. We changed ceftriaxone to ciprofloxacin, which is not an ampicillin-based regimen, and had the same successful outcome. Except in cases of urinary tract infections, *E. hirae* infections were treated using cefmetazole (bacteremia with cholangitis) [7]; ampicillin combination therapy comprising gentamicin and levofloxacin (spondylodiscitis) [1]; vancomycin (hemodialysis with bacteremia); three combination regimens with either vancomycin and gentamicin, amoxicillin and gentamicin, or ampicillin and rifampin (infective endocarditis); ampicillin combination therapy comprising piperacillin/tazobactam and levofloxacin (splenic abscess), and ampicillin (peritonitis). Each of the treatment had an average therapeutic duration of 2 weeks, with a maximum duration of 8 weeks [8]. Since *E. hirae* has low virulence, the pathogen can presumably be treated using antibiotic monotherapy in cases of non-invasive infections, such as urinary tract infections [9]. However, in cases of clinically unstable situations, such as septic shock or infective endocarditis, combination therapy may offer better outcome. In general, fluoroquinolone monotherapy is not recommended in cases of clinically unstable enterococcus infections, such as sepsis. This is so due to the low blood concentration that approaches the minimum inhibitory concentration. In the two cases shown in this

report, administering 400 mg of ciprofloxacin every 12 hours was not inferior to ampicillin treatment, as long as the *E. hirae* infection manifested only as pyelonephritis or mild bacteremia. Our cases suggest that monotherapy with ciprofloxacin in pyelonephritis with *E. hirae* is an effective antibiotic therapy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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