



Case report

Bacteremic renal stone-associated urinary tract infection caused by nontypable *Haemophilus influenzae*: A rare invasive disease in an immunocompetent patient



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ABSTRACT

Haemophilus species are known to colonize the upper respiratory tract and can cause infections. However *Haemophilus influenzae* has been rarely described as a cause of genitourinary tract infection. We report a 44-year-old nonimmunocompromised Japanese man with bacteremic pyelonephritis caused by a nontypable *H. influenzae* associated with a left ureteral calculus. The organism was isolated from both blood and urine cultures. Treatment consisted of 14 days of intravenous ceftriaxone and oral amoxicillin one after than other and insertion of a left ureteral stent. After discharge, he underwent extracorporeal shock wave lithotripsy for the left ureteral calculus. He had no recrudescence of the symptoms. *H. influenzae* should be considered as a genitourinary pathogen among patients with certain risk factors such as anatomical or functional abnormality of genitourinary tract. Collaboration between clinicians and microbiology laboratory personnel is essential for correct identification of the organism and appropriate therapy for genitourinary tract infections due to this organism.

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Introduction

Haemophilus spp. generally colonize the upper respiratory tract and can cause infections such as bronchitis, sinusitis, epiglottitis, pneumonia and meningitis. *H. influenzae* has been reported as a rare cause of genitourinary tract infection such as urinary tract infection [1–5], pyelonephritis [6,7], prostatitis, epididymitis [8], salpingitis and endometritis [9]. Cases with bacteremia is even less common, especially in men [1,6,7,9].

We report here an immunocompetent Japanese man with bacteremic pyelonephritis caused by nontypable *H. influenzae* associated with a left ureteral calculus.

Case report

A 44-year-old Japanese man with a history of left ureteral renal calculus presented to our hospital with a one-day history of left flank pain, fever and malaise without any respiratory symptoms. He had left flank pain caused by a left ureteral calculus over the

past two decades. Otherwise, his past history and family history were unremarkable.

On physical examination, his blood pressure was 153/91 mm Hg, pulse rate 112 beats/min, respiratory rate 20 breaths/min, oxygen saturation on ambient air 98% and body temperature 38.9 °C. His breath and heart sounds were normal and his abdomen was soft. There was tenderness at left hypochondriac region and left costovertebral angle (CVA). Laboratory tests showed an elevated white blood cell (WBC) count $12.2 \times 10^3/\mu\text{L}$ and creatinine level of 1.25 mg/dL. Serum HIV antigen and antibody test was negative. Microscopic examination of the urine sediment showed an elevated WBC and red blood cell (RBC) count of 50 and 99 per high power field, respectively. Two sets of blood cultures were obtained using Bactec Plus Aerobic/F and Anaerobic/F culture bottles (Becton, Dickinson and Company, Sparks, MD). Urine culture was performed using sheep blood agar and Drygalski improved medium (Eiken Chemical Co, LTD, Tokyo, Japan). Gram stain of urine showed Gram-negative bacilli. Abdominal ultrasound and computerized tomography (CT) scan of the abdomen and pelvis without contrast showed a left ureteral calculus ($17 \times 10 \times 19$ mm), left hydronephrosis and a normal-sized prostate gland. After admission, treatment with intravenous ceftriaxone 2 g every 24 h was initiated and the ureteral stent was inserted

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Table 1
Summary of previously reported 59 patients and our patient with genitourinary tract infection caused by *Haemophilus influenzae*.

	Sex	Age (y)	Risk factor	Bacteremia	nontypable/type b	Biologic type
Reported patients (N = 59)	male (N = 39)	55.3 (26–90)	anatomical or functional abnormality of genitourinary tract	7.6% (3 cases)	11 cases/26 cases	2 (13 patients) 3 (9 patients) 1, 4 (3 patients, respectively) 8 (1 patient)
	female (N = 20)	34.8 (18–89)	pregnancy	75% (15 cases)	18 cases/1 case	4 (5 patients) 3 (4 patients) 1, 2, 5, 6 (1 patient, respectively)
Current patient	male	44	renal calculus	y	nontypable	3

Table legend: This table was developed on the reported cases ([1–9]).

into his left ureter. His left flank pain and CVA tenderness were immediately improved.

After 32 h of incubation, Gram-negative bacilli were isolated from an aerobic blood bottle. Both blood and urine cultures using sheep blood agar and Drygalski improved medium showed no growth. Chocolate II agar (Nissui Pharmaceutical Co, LTD, Tokyo, Japan) for blood and urine based on candle jar method at 37 °C were used for culture. After 24 h of incubation, small colonies had formed on chocolate agar. The bacteria required both X factor (hemin) and V factor (nicotinamide adenine dinucleotide) for its growth. These requirements were consistent with biochemical properties of *H. influenzae*. Furthermore, MicroScan Walker Away 40SI (BECKMAN COULTER, Inc., the United States) automated identification and susceptibility testing showed 99.99% probability of β -lactamase-negative *H. influenzae* biotype 3. It was also identified as nontypable *H. influenzae* by Influenza bacillus immune serum kit (DENKA SEIKEN, Co., LTD, Niigata, Japan). This commercial rapid kit identifies *H. influenzae* type a to f or nontypable. This organism was susceptible to ampicillin (MIC = 0.25 μ g/mL), amoxicillin clavulanic acid (MIC \leq 1 μ g/mL), ampicillin sulbactam (MIC \leq 0.5 μ g/mL), ceftriaxone (MIC \leq 0.12 μ g/mL), meropenem (MIC \leq 0.12 μ g/mL), clarithromycin (MIC = 4 μ g/mL), levofloxacin (MIC \leq 0.12 μ g/mL) and rifampicin (MIC \leq 0.5 μ g/mL) and resistant to sulfamethoxazole–trimethoprim (MIC = 4 μ g/mL). Nasopharyngeal culture that was obtained after the initiation of antimicrobials was negative for *Haemophilus* spp. Follow up blood and urine cultures were negative.

On hospital day 4, he became afebrile. He was discharged home on hospital day 9 and treated with oral amoxicillin 1000 mg three times a day for 5 more days. Fifteen days after discharge, he underwent extracorporeal shock wave lithotripsy for the left ureteral calculus. He had no recrudescence of the symptoms.

Discussion

The non-typable strains generally are not invasive and only the type b strain is preventable by vaccine.

Haemophilus spp. generally colonize the upper respiratory tract and could cause its infections. *H. influenzae* has been reported as a rare cause of genitourinary tract infection and fewer case reports of genitourinary tract infections along with bacteremia due to *H. influenzae*.

The reported prevalence of *H. influenzae* in urine samples was 0.04% in women and 0.22% in men [10]. True prevalence of this organism in the genitourinary tract, may be underestimated, since culture media for this organism are not routinely used for urine specimens. When chocolate agar was used for routine urine cultures, it was reported that the rate of *Haemophilus* spp. from urine cultures was approximately 0.2% (25 of 14,684 isolates over a 3-year period) [8].

Albritton et al. showed that biotype 4 predominated in genitourinary isolates, while biotype 1 in respiratory isolates

[11]. Wallace et al. also reported that nontypable *H. influenzae* of biotype 4 may have been most common for genitourinary tract infection of women [9]. The results of these studies suggest that *H. influenzae* biotype 4 might have some mechanism related to the affinity to the genitourinary systems and/or direct invasion to the epithelium.

Genitourinary tract infection caused by *H. influenzae* has been documented more than 60 cases. Table 1 shows 59 patients reported previously and our current patient. The patients were stratified by gender due to differences in clinical features.

In women, 90% (18/20 cases) of the patients were associated with pregnancy and, notably, 75% (15/20) had bacteremia [1,9]. Non-bacteremic urinary tract infection was only a case reported by Morgan et al. [4]. In men, 25.6% (10 out of 39 cases) of past reported patients had anatomical or functional abnormality of genitourinary tract such as renal calculus, benign prostate hypertrophy, ureteral occlusion or post-operation. Approximately 50% of the patients did not have information on underlying diseases. There were only 3 cases of bacteremia among the infections in males (7.6%). Therefore the true proportion of the patients with underlying diseases was possibly underestimated.

Regarding the serotypes of *H. influenzae*, a total of 66.7% (26 out of 39) was type b and 28.2% (11 out of 39) was nontypable (2 cases was unknown). In 29 out of 39 patients, biologic type of *H. influenzae* was determined. Thirteen were type 2, 9 were type 3, type 1 or 4 for 3 patients respectively and type 8 was only from one patient. Blood culture was positive in three patients [1,3,4,6–8]. Our patient had left renal calculus and serologic/biologic type was nontypable/type 3.

Regardless gender and serologic type, *H. influenzae* were mostly biotype 1–4 (39 out of 42). *H. influenzae* of these types are urease positive. It is possible that this ability might facilitate colonization or infection in the genitourinary tract. Indeed, urease production in the urine will produce an alkaline pH which can predispose to stone formation.

Conclusion

We report an immunocompetent patient with a ureteral calculus associated with bacteremic urinary tract infection caused by nontypable *H. influenzae* (biotype 3).

H. influenzae is difficult to grow on urine culture and its isolation may be underestimated. Collaboration between clinicians and microbiology laboratory personnel is essential for correct identification of the organism and appropriate therapy for genitourinary tract infections due to this organism.

Conflict of interests

All authors do not have any conflict of interests.

Ethical approval

This study did not require ethical approval.

Acknowledgement

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