Diagnostic Microbiology and Infectious Disease 107 (2023) 116001

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Case Report

Haemophilus influenzae septicaemia and urinary tract infection associated with nefrocalcinosis: case report

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ARTICLE INFO

Article history:
Received 28 March 2023
Accepted 2 June 2023
Available online 5 June 2023

Keywords:
Haemophilus influenzae
Urinary Tract Infection
Septicaemia
Bacteremia
Nefrocalcinosis
Renal Stone Disease

ABSTRACT

Haemophilus influenzae is an uncommon uropathogen with fastidious growth requirements, which must be taken into consideration in the diagnostic process. We present a rare case of urosepsis with *H. influenzae* in a young patient with nefrocalcinosis.

1. Introduction

Haemophilus influenzae is a gram-negative coccobacillus with fastidious growth requirements. It frequently causes respiratory tract infections in children and adults, and more rarely urinary tract infections [1]. We present a case of urosepsis with *H. influenzae* in a young patient with nefrocalcinosis.

2. Case report

A 25-year-old man was admitted to Danish hospital due to bilateral flank pain and fever. The previous 3 months he reported episodes of dysuria, pollakisuria, cloudy urine, urethral discharge, hematuria and passing small stones. Although urine cultures had been negative, he had 3 times been treated with oral pivmecillinam 400 mg x 3 in 7 days with short relief on symptoms. Physical examination revealed suprapubic and flank tenderness, and temperature 38.2°C. Blood samples showed leukocytosis 10×10^9 /L, CRP 105 mg/L and creatinine 169 μmol/L. Normal hemoglobin and electrolytes. Urine sample was positive for leucocytes, erythrocytes, and nitrite. Dual Energy CT scan showed bilateral medullary nefrocalcinosis with Hounsfield Units of 415 to 475 and a Dual Energy Ratio of 1.94 (Figs. 1 and 2) suggesting calcium phosphate stones (brushite or apatite). He was discharged with oral ciprofloxacin 500 mg b.d. for 10 days.

After discharge, 2 out of 4 peripheral blood cultures revealed small gram-negative rods identified as *Haemophilus influenzae* (MALDI-TOF MS, Bruker, Germany). Isolate was susceptible to piperacillin/tazobactam (disc diffusion (dd) 32 mm), ciprofloxacin (dd 34 mm), cefotaxime (minimum inhibitory concentration (MIC) 0.06 mg/L), and ceftriaxone (MIC 0.03 mg/L), but resistant to penicillin G (dd 6 mm), ampicillin (dd 12 mm), and amoxicillin/clavulanate (dd 14 mm). Whole genome sequencing (WGS) confirmed species, showed a noncapsular, biotype II-strain, multilocus sequence typing (MLST) type 203 [2], and the strain was ornithine negative, urease positive and indole positive.

The patient was readmitted for intravenous ceftriaxone 2 g x 1. Since previous urine culture was negative and that *H. influenzae* is not a typical pathogen of UTIs, lumbar puncture was performed. It showed 1×10^6/L nucleated cell, normal protein, lactate, and glucose. Spinal fluid cultures were as expected negative. Suspected origin of infection was still UTI. Urine culture using UTI CHROM agar, and a 5% blood agar plate showed no growth. However, culturing on a chocolate agar plate resulted in >100.000 colony forming units/mL of *H.*

Abbreviations: dd, disc diffusion; MIC, minimum inhibitory concentration; WGS, whole genome sequencing; MLST, multilocus sequence typing

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https://doi.org/10.1016/j.diagmicrobio.2023.116001

Fig. 1. Noncontrast CT with bone window setting.

influenzae with equal susceptibility. After 2 days of intravenous treatment, the patient was again discharged with oral ciprofloxacin 500 mg b.d. for further 5 days.

Metabolic evaluation ruled out hypercalcemia, hyperparathyroidism, renal tubular acidosis and hyperoxaluria as the cause of nephrocalcinosis. 24-hour urine analysis revealed diuresis of 4200 ml. pH 7.5. Normal oxalate (428 μmol) and citrate (2.1 mmol) excretion. Slightly elevated calcium excretion 10.4 mmoL (0.12 mmoL/kg body weight). No stones had been obtained for stone analysis. It is most likely a case of medullary sponge kidney. An excretory CT urography which could have supported this diagnosis was not made since the patient emigrated and was lost for further follow-up.

3. Discussion

The latest epidemiological report made by European Centre for Disease Prevention and Control states that in 2018 3,982 confirmed cases of invasive *H. influenzae* disease were reported, and noncapsulated strains caused 78% of cases. Of these cases, septicemia was the most common clinical presentation (38%), followed by pneumonia (26%), meningitis or both septicemia and meningitis (8%), and other

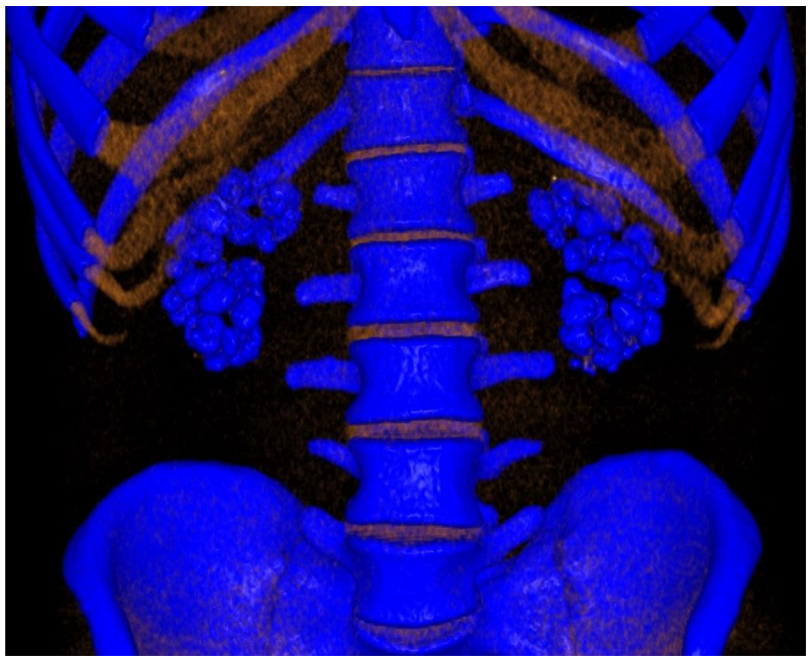

Fig. 2. DECT with 3D reconstruction. Blue color indicates it is not uric acid.

clinical presentations (epiglottitis, cellulitis, and septic arthritis/osteomyelitis) (1%) [3].

H. influenzae has been reported as a rare cause of genitourinary tract infection such as acute pyelonephritis [4,5], chronic prostatitis [6], endometritis [7] and urethritis [8]. Staerk *et al* in 2018 reported a similar case of a 32-year-old man with non-typable *H. influenzae* biotype II that was associated with renal stone disease [9].

Biotype II is the most common among invasive *H. influenzae* isolates in Denmark [2]. Albritton *et al.* showed that biotype II was found in both genitourinary and respiratory isolates, while biotype IV was predominated in genitourinary isolates [10]. In contrast to data reported by Albritton, Harper et al. [11] concluded that biotype IV was not a major urogenital pathogen .

Usually, urinary tract infections are caused by *Enterobacterales* such as *Escherichia coli, Klebsiella spp., Proteus spp.* [12]. UTIs caused by urease-producing bacteria may be accompanied by urolithiasis. *H. influenzae* of biotypes I-IV are urease positive. This enzyme catalyzes hydrolysis of urea to ammonia and carbon dioxide, thereby raising urinary pH. Due to alkalinization of urine, calcium and magnesium phosphates begin to precipitate out of solution, leading to formation of struvite and apatite crystals [13].

WGS characteristic of the *H. influenzae* isolate found in this case are the same as observed in previous cases both domestic and abroad. MLST type 203 isolates have in Denmark from 2014 to 2021 been observed in 3 bacteremia cases. The 3 isolates were all non-typable belonging to biotype II [2]. According to the MLST database, there has been registered 18 ST203 isolates, which all were found to be either nontypeable or not serotyped. They were furthermore found both as isolates from invasive and non-invasive cases [14].

Chocolate agar is an enriched general-purpose medium. It contains nicotinamide adenine dinucleotide (factor V) and hemin (factor X), which *H. influenzae* requires for growth [1]. In our laboratory from 2013-2022 *H. influenzae* have been founded in 30 urine samples. Probably we have underestimated incidence of *H. influenzae* UTIs as urine cultures were not routinely examined for not typical urinary pathogens.

4. Conclusion

We report an unusual case of nefrocalcinosis and UTIs caused by *H. influenzae*. The addition of chocolate agar to routine urine culture may help identify the cause of infection for patients with persistent UTI symptoms, but negative culture results.

Ethics approval

Informed consent was obtained from the patient for publication of this case report and accompanying images.

Author contribution statement

ASFM and VSA: designed manuscript and wrote original draft. LHB and KHA: collected patient data. HCS: performed WGS. DCAB performed supplementary radiological analyses and pictures. All authors revised, read, and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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