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Short Communication

Biliary Infection and Bacteremia Caused by β-Lactamase-Positive, Ampicillin-Resistant *Haemophilus influenzae* in a Diabetic Patient

Şukru Oksuz*, Elif Ozturk, Idris Sahin, Osman Ertor[1] and Demet Kaya

Department of Microbiology and Clinical Microbiology and
[1]Department of Clinical Microbiology and Infectious Disease, Faculty of Medicine,
Abant Izzet Baysal University, Duzce 81100, Turkey

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SUMMARY: We report the case of a 73-year-old female patient with diabetic nephropathy and cholelithiasis. She was admitted to our hospital with right upper abdominal pain, nausea, and vomiting. The patient had visited an outpatient clinic with the same complaints 2 days earlier, and had been prescribed antibiotics empirically (two doses ofloxacin orally). Blood cultures taken before the start of antibiotic treatment in our hospital were negative. The patient was treated with parenteral ampicillin/sulbactam + ciprofloxacin empirically. The empiric antibiotic treatment was discontinued after 7 days. Elective cholecystectomy was performed after her general condition improved. An aerobic chocolate agar culture of the cholecystectomy material yielded *Haemophilus influenzae* type b. On postoperative day 3 the patient developed fever again. The fluids collected after cholecystectomy were evaluated microbiologically. *H. influenzae* type b was isolated from the samples and blood cultures. The patient was diagnosed with *H. influenzae* cholecystitis, and recovered after10-day treatment with ampicillin/sulbactam + ciprofloxacin. The findings are discussed together with references for differential diagnosis. *H. influenzae* cholecystitis due to cholelithiasis, although rare, should be considered in elderly patients with a history of chronic diseases such as diabetes mellitus or nephropathy.

Haemophilus influenzae is a member of the family of normal upper respiratory flora of humans. It may cause meningitis, otitis media, upper respiratory infections and pneumonia, especially in children, and rarely, bacteremia, endocarditis, pericarditis, arthritis and hepatobiliary tract infections. *H. influenzae* is a small Gram-negative rod (coccobacillus). Growth of the organism on laboratory media requires the addition of two components, heme (factor X) and NAD (factor V), for adequate energy production. Of the six serotypes, type b causes most of the severe, invasive diseases, such as meningitis and sepsis. *H. influenzae* type b causes epiglottitis, pneumonia, empyema, bacteremia, meningitis, pericarditis, abscess, osteomyelitis, arthritis, and cellulitis. Unencapsulated strains cause conjunctivitis, sinusitis, bronchitis, otitis media, and urinary tract infections. In rare cases, *H. influenzae* can cause infections such as cholecystitis and gallbladder empyema (1,2). This paper reports a case of cholecystitis caused by cholelithiasis due to *H. influenzae* infection with diabetes mellitus and nephropathy.

A 73-year-old woman was admitted to our hospital with right upper abdominal pain, nausea, and vomiting. The patient had visited an outpatient clinic with the same complaints 2 days earlier, and had been prescribed antibiotics empirically (two doses of ofloxacin orally) (Fig. 1). Clinical examination revealed fever (38.3°C), a blood pressure of 130/90 mmHg, pulse of 99/min, respiratory rate of 19/min, right upper quadrant abdominal pain, Murphy's sign positivity and right upper quadrant tenderness with percussion. Abnormal laboratory findings included hemoglobin of 10.5 mg/dl, total white blood cell count of 11,600/mm^3 with 75% neutrophils, fasting blood glucose of 184 mg/dl, blood urea nitrogen (BUN) of 119 mg/dl, plasma creatinine of 2.63 mg/dL, γ-glutamyl transferase of 87 U/L, lactate dehydrogenase of 982 U/L, plasma cholesterol of l80 mg/dl, and triglyceride of 228 mg/dl. Ultrasonography showed a stone/multiple stones in the gallbladder, diffuse gallbladder wall thickening and pericholecystic fluid. These sonographic findings were interpreted as cholecystitis. Antral gastritis and grade 3 duodenitis were observed by gastroscopic examination.

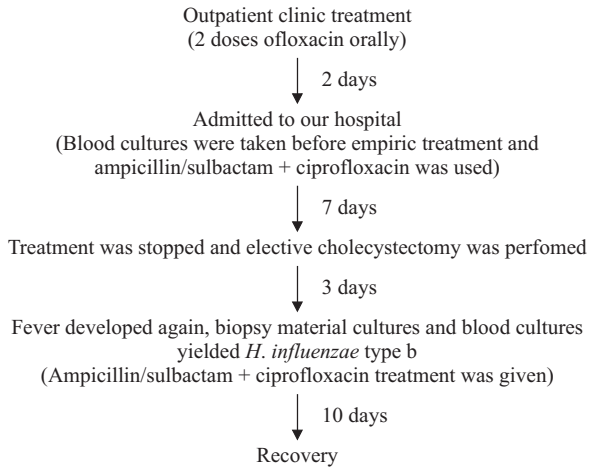

Fig. 1. Summary of clinical course.

The patient was admitted to the intensive care unit with calculous cholecystitis, type 2 diabetes mellitus, diabetic nephropathy, and hypertension. Blood cultures taken before antibiotic treatment in our hospital yielded negative results. The patient was treated with parenteral ampicillin/sulbactam

*Corresponding author: Mailing address: Department of Microbiology and Clinical Microbiology, Abant Izzet Baysal University Duzce Medical School, 81100 Duzce, Turkiye. Tel: +90-380-5414107-2014, Fax: +90-380-5414105, E-mail: sukruoksuz@hotmail.com, sukruoksuz81@mynet.com

+ ciprofloxacin empirically. The patient's fever improved on the 4th day of the antibiotic treatment, her hyperglycemia was regulated by insulin treatment, and her serum BUN and creatinine levels decreased. The empiric antibiotic treatment was discontinued on the 7th day. Elective cholecystectomy was performed after her general condition improved. No further antibiotic treatment was given to the patient. Histopathological results of the operational material showed gangreneous cholecystitis. An aerobic chocolate agar (Becton Dickinson, San Jose, Calif., USA) culture of the material yielded *H. influenzae*. The organism was identified as *H. influenzae* using an API NH system (bioMérieux, Etoile, France) and the latex agglutination test (Slidex Meningite Kit5; bioMérieux) results showed that the organism was type b. The organism was found to be susceptible to ampicillin/sulbactam, trimethoprim/sulfamethoxazole, azithromycin, cefaclor, cefuroxim, ceftriaxon, chloramphenicol and tetracyclin by the Kirby-Bauer disk diffusion method. The strain was resistant to ampicillin (MIC $\geq$ 8 μg/L), and the organism was positive for productivity of β-lactamase (Oxoid, Hampshire, England). She did not receive antibiotics after the operation. On the 3rd postoperative day she developed fever again. Blood cultures were taken. A hyperemia and a mass were noticed over the incision area. Ultrasonographic investigation revealed fluid collection in the perihepatic and right subdiaphragmatic spaces. Giemsa staining of ultrasonographic punction material showed leukocytes consisting of 95% neutrophils. Blood cultures (Bactec 9050; Becton Dickinson) and aerobic chocolate agar (Becton Dickinson) culture of the material indicated that it was *H. influenzae*. The organism was identified as *H. influenzae*, and a latex agglutination test (bioMérieux) revealed that it was type b. Susceptibility test results were the same as for the first isolate. The strain was resistant to ampicillin (MIC $\geq$ 8 μg/L). The organism tested positive for the production of β-lactamase (Oxoid). The patient recovered after 10-day treatment with ampicillin/sulbactam + ciprofloxacin.

Chronic diseases such as diabetes mellitus and nephropathy may predispose patients to *H. influenzae* cholecystitis. In the present case, clinical findings (fever and pain) and postoperative bacterial cultures revealed the presence of *H. influenzae* type b. The reason that the blood culture taken before the operation was negative may have been related to the fact that the patient had been prescribed antibiotics empirically. In cases similar to the present one, Garces et al. (3) reported biliary system infection and bacteremia caused by *H. influenzae* in 1996. Gomez et al. (4) reported a case of cholecystitis caused by *H. influenzae* type e in 1982. Crowe et al. (5) and Norden et al. (6) reported cholecystitis cases caused by invasive *H. influenzae* infections. Sigwart et al. (7) reported cholecystitis caused by *H. influenzae* in 1972. Common features among all these cases were that the patients were elderly and had chronic diseases such as diabetes, nephropathy and hypertension. Farley et al. (8) defined the incidence of and possible risk factors for invasive *H. influenzae* disease in adults. Underlying conditions were noted in 92% of the patients. Chronic lung disease was the most common risk factor, but pregnancy, HIV infection, and malignancy were also important. *H. influenzae* was reported as an important cause of bacteremia in the compromised adults. Bachrach (9) reported an outbreak of *H. influenzae* type b bacteremia in the infant unit of a pediatric intermediate care hospital. A high attack rate of 36% (4 of 11 patients) was found, which was of concern in a population already compromised by chronic illness. In the present case, of course, the patient had diabetes mellitus, nephropathy, and hypertension.

In conclusion, encapsulated *H. influenzae* spp. can cause severe invasive infections in older adults with chronic diseases such as diabetes mellitus and nephropathy. *H. influenzae* cholecystitis and bacteremia due to cholelithiasis, although rare, should be considered in elderly patients with chronic diseases such as diabetes mellitus and nephropathy.

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