CASE REPORT

FEVER OF UNKNOWN ORIGIN OWING TO SALMONELLOSIS WITH NALIDIXIC ACID RESISTANT SALMONELLA SCHOTTMUELLERI: A CASE REPORT

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ABSTRACT
Resistance to fluoroquinolones is a rare situation in Salmonella strains. We report here a case of fluoroquinolone-resistant Salmonella schottmuelleri which caused a confusion in the diagnosis. Forty years-old female was admitted to our clinic with a 19 day-history of fever. The patient had applied to another hospital five days ago and had been given ciprofloxacin. In our hospital, her blood Gruber-Widal test showed a titer of 1/200 against BO and BH antigens. However, because the patient was unresponsive to ciprofloxacin, this result was ignored and specific antibiotic therapy was not started. Later, Salmonella schottmuelleri was isolated in bone marrow culture, but blood cultures were negative. The isolate was resistant nalidixic acid, susceptible to ciprofloxacin and ceftriaxone. Ceftriaxone was begun. After three days, fever disappeared. The purpose of this report is to emphasize the probability of quinolone resistant salmonella strains in the differential diagnosis of fever of unknown origin and to call attention to ineffectiveness of ciprofloxacin even tough seems to be susceptible in vitro.
Key Words: Salmonella schottmuelleri; Nalidixic Acid Resistant Fever; Fever of Unknown Origin

Introduction

Enteric fever is still a major health concern and one of the reasons for fever of unknown origin in the developing world. Quinolones and third generation Cephalosporins are used as a current treatment of choice. Although resistance to quinolones is known a rare situation in Salmonella strains, recently being reported with increasing frequency from all over the world.[1,2] We now report here a case of salmonellosis with quinolone-resistant Salmonella schottmuelleri which caused a confusion in the diagnosis of a patient unresponsiveness to ciprofloxacin.

Case Report

A previously healthy 40 years-old female was admitted to our clinic with a 19-day history of fever and severe headache. The patient had applied to hospital five days ago with complaints of fever, night sweats, arthralgia, diarrhoea, nausea and vomiting. The laboratory tests had not revealed any diagnosis and she had been given ciprofloxacin 2x750 mg for five days empirically. Due to the persistence of fever, the patient transferred to our hospital for further investigation. On admission, her fever was 40.1°C and pulse rate 113/min. Other systemic examinations were normal. Laboratory values were revealed as WBC count 6940/µl, ESR 36 mm/h and CRP 28 mg/dl (0-5 mg/dl). The AST and ALT had been elevated to 202 and 181 U/L, respectively. Blood, stool and urine cultures were negative. The results of urinalysis, chest radiography, abdominal ultrasound and cranial magnetic resonance (MR) were normal. Brucella standard tube agglutination test was negative. A blood Gruber-Widal test showed a titre of 1/200 against BO and BH antigens of Salmonella. However, because of the ineffectiveness of ciprofloxacin, this result was ignored and specific antibiotic therapy was not started. On follow-ups, fever was continued and invasive diagnostic methods were used. Granulomatosus inflammation was detected in the bone marrow biopsy samples. On the 27th days of fever Salmonella schottmuelleri was isolated in bone marrow culture.

We have identified the isolate firstly according to colony morphology (non-lactose fermenting colony) on Salmonella-Shigella agar, Gram stain (Gram negative rod shaped organism), motility (motil) and biochemical characteristics (oxidase, catalase, indole, Voges Proskauer (VP), methyl red, Simmons citrate, H2S and urea) and then confirmed the isolate by slide agglutination with Salmonella antisera (Remel, ÜLKE) in accordance with the Kauffman White scheme (1). A polyclonal monospecific serum against Vi antigen was negative. Antimicrobial susceptibility testing was performed by the disc diffusion test for ciprofloxacin (5 µg), ampicillin (10 µg), cotrimoxazole (1.25/23.75 µg), chloramphenicol (30 µg), nalidixic acid (30 µg), and

ceftriaxone (30 µg) as per Clinical Laboratory and Standard Institute guidelines of 2012 (2). The isolate was susceptible to all antibiotics tested except nalidixic acid by disc diffusion test. The antimicrobial susceptibility was also performed using VITEK 2 automated system (bioMerieux/France). The organism was reported to be sensitive to amoxicillin-clavulanic acid, cefotaxime, ceftriaxone, aztreonam, piperacillin-tazobactam, meropenem, tetracycline and tigecycline, but resistant to nalidixic acid. The minimum inhibitory concentration (MIC) of ciprofloxacin was 0,25 µg/ml and the isolate was accepted as having a reduced susceptibility to ciprofloxacin according to Clinical and Laboratory Standards Institute guidelines of 2012.

According to the antimicrobial susceptibility test result, ceftriaxone 2x1 gr intravenous was began. Fever disappeared in the third days of ceftriaxone and the patient was discharged in the seventh days without any complication.

Discussion

Enteric fever is one of the reasons for fever of unknown origin and still a major global health problem which is a severe illness characterized by fever and abdominal pain caused by dissemination of S. typhi and S. paratyphi. An estimated 200.000 to 600.000 death occur annually worldwide from this infection.[1]

Due to emerging and spreading of multidrug resistance against the conventional antityphoid drugs (chloramphenicol, co-trimoxazole, and ampicillin) among salmonella isolates, Flouroquinolones became a choose of major antimicrobial agent.[3] These are the most effective agents with high cure rate and low relaps and fecal carriage rates.[1,2,4] However, the widespread use of Flouroquinolones caused emerging of resistant isolates.[2,5] Ciprofloxacin-resistant typhoid fever was reported firstly in 1992 in the United Kingdom.[6] Now, it is being reported with increasing frequency from all over the world, especially from the countries such as Vietnam, Nepal, India and Bangladesh.[2,7-10] In the 1990s there was no resistance against the Flouroquinolones in Turkey.[11] Ciprofloxacin resistance or decreased susceptibility (MIC ≥ 0.125 µg/mL) had been detected in the beginning of 2000s and in 2006, resistance and decreased susceptibility to Flouroquinolones was detected in 12.3% of human Salmonella enterica strains in a study from Turkey.[12,13] In the United States, 42% of recent S. typhi isolates and 87% of S. paratyphi isolates were founded resistant to nalidixic acid and had a reduced susceptibility to ciprofloxacin.[14,15]

In infections of nalidixic acid resistant Salmonella isolates, even they were susceptible to ciprofloxacin, the patients may not be treated with ciprofloxacin. A correlation between resistance to nalidixic acid and reduced susceptibility to ciprofloxacin and other Flouroquinolones have been reported by several authors.[2,5,16] In a case unresponsive to Flouroquinolones therapy, a probability of nalidixic acid resistant Salmonella isolates should be considered. For determination of Flouroquinolones resistance, disc diffusion test is used usually. But the decreased susceptibility to quinolone is detected only with MIC test. While ciprofloxacin MIC ≤ 1 µg/mL and MIC ≥ 4 µg/mL are interpreted as susceptible and resistant respectively, MIC 0.125 - 1.0 µg/mL is interpreted as decreased ciprofloxacin susceptibility according to CLSI 2012 guidelines.[17] In our case, the isolate had a decreased susceptibility to ciprofloxacin (MIC 0.25 µg/mL) and this antibiotic was ineffective in the therapy of the patient. However, the determination of MIC may not be practicable in routine laboratory practice. For this reason, nalidixic acid screening test may be used. Routine testing of resistance to nalidixic acid is performed by a disk content of 30 µg.[15] The test has high sensitivity and specificity for detecting decreased susceptibility to Flouroquinolones (sensitivity 98.6-100%, specificity 98.8%).[9,10,18]

The most common mechanism leading to decreased susceptibility to Flouroquinolones is a chromosomal point mutation in the quinolone resistance-determination region (QRDR) of bacterial DNA gyrase and/or DNA topoisomerase IV.[2,3,19] Recently, there have been reported a decreasing trend in identified MDR S. typhi isolates while Flouroquinolones resistance have been rising. May be, in the future the classic anti-typhoid drugs can be used again for the treatment of enteric fever.[3]

Enteric fever is the only bacterial infection of human for which bone marrow examination is recommended routinely. The sensitivity is variable (55% to 90%).[1] Bone marrow culture, although more sensitive, is infrequently performed.[20] Bacteria in the bone marrow of typhoid patients are less affected by antibiotic treatment than bacteria in the blood.[21,22] Higher colony counts are present in the bone marrow compared with blood and, not reduced by up to five days of prior

antimicrobial therapy unlike blood culture.[1] In patient suspected of enteric fever, bone marrow culture must be taken in addition to blood culture, especially in patient given antibiotics empirically.

Conclusion

This case highlights two important points. The first, although Flouroquinolones are major drugs in Salmonella infections, resistant strains may mislead us and cause a delay in the diagnosis of the patients given Flouroquinolones previously. Secondly, the nalidixic acid disc diffusion assay can be used an indicator for detecting S. typhi isolates with decreased ciprofloxacin susceptibility in clinical practice. For infections of nalidixic acid resistant Salmonella isolates, ciprofloxacin may be ineffective in vivo even if it was seen susceptible to in vitro.

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