CASE REPORT

Ciprofloxacin-Resistant *Salmonella Enterica* Serotype Typhi in a Patient with Osteomyelitis of the Rib

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Summary

Salmonella osteomyelitis of the rib is a rare clinical entity. In our case, a multidrug resistant *Salmonella enterica* serotype Typhi was isolated from an immuno-competent patient with osteomyelitis of the ribs, who was treated earlier with ciprofloxacin for typhoid fever. The patient was successfully treated for osteomyelitis with intravenous ceftriaxone.

Key Words: Ciprofloxacin, Multidrug resistance, Osteomyelitis, Rib, *Salmonella typhi*

Introduction

Salmonella enterica serotype Typhi is endemic in developing continents like Africa, South and Central America, and Indian subcontinent, with an estimated incidence of eighty-eight million cases of enteric fever each year. For patients with typhoid fever, chloramphenicol was the first-line drug of choice from 1948 to the mid-1970s[1]. The incidence of multidrug resistance (MDR) to chloramphenicol, ampicillin and trimethoprim started increasing in UK as well as in the Indian subcontinent from 1990 onwards. Fluroroquinolones became active drugs against isolates of *Salmonella* species. However, in recent years, there are several reports of treatment failures with these antibiotics against *Salmonella* infections caused by strains with reduced fluoroquinolones susceptibility[2].

The most common sites for *Salmonella* infection in bone are the metaphyseal ends of long bones and the lumbar spine. *Salmonella* osteomyelitis in children is often seen in association with sickle cell disease or other haemoglobinopathies, systemic lupus erythematosus, neoplasms, or in individuals with immuno- suppression.

We describe a case of osteomyelitis of rib with MDR *Salmonella enterica* serotype Typhi strain that had developed resistance against ciprofloxacin during treatment for typhoid fever in an adult immuno-competent patient.

Case History

A twenty-eight-year-old male was admitted to Manipal Teaching hospital, Pokhara, Nepal with a seven day history of high fever (>38°C), headache, malaise and vomiting. He had rose spots over the trunk and a soft, palpable spleen. Widal test showed a titre of 320 against '0' and 'H' antigens of *Salmonella enterica* serovar Typhi. He was HIV negative.

Blood and bone marrow cultures yielded the growth of non-lactose fermenting gram-negative rod shaped bacilli, which was biochemically and serologically confirmed as *Salmonella enterica* serovar Typhi. The isolate was found to be resistant to most of the conventional anti typhoid drugs like chloramphenicol, ampicillin, cotrimoxazole, nalidixic acid, gentamicin and amikacin by Kirby-Bauer disk diffusion method according to the criteria of the National Committee of Clinical Laboratory Standards (NCCLS). The isolate was sensitive to ciprofloxacin and ceftriaxone; with zone size 22mm (sensitive) and 26 mm (sensitive)

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respectively. The sensitivity was again tested by micro broth dilution according to the NCCLS guidelines (2001) for enterobacteriaceae using cation-adjusted Mueller-Hinton. The MIC_{50} for chloramphenicol, ampicillin, cotrimoxazole, nalidixic acid, gentamicin and amikacin were 32µg/ml, 32µg/ml, 4/76µg/ml, 32µg/ml, 32µg/ml and 64µg/ml respectively and for ciprofloxacin and ceftriaxone, 0.5 µg/ml (break point: 1 µg/ml) and 2µg/ml (break point: 8µg/ml) respectively.

The patient was given ciprofloxacin empirically, 500 mg every twelve hours, orally, which was continued as intravenous ciprofloxacin, 200 mg every twelve hours, after the sensitivity pattern was reported. The patient was afebrile only after sixth day and was discharged on eighth day was advised to take ciprofloxacin (500 mg every twelve hours) orally for another one week.

He was readmitted after three months with pain and swelling of the right lower costal margin. He was afebrile with no nausea, vomiting or diarrhoea. On examination, there was pain, swelling, redness and tenderness in the right lower costal margin over the 5th and 6th ribs at the costochondral junction. CT scan showed increased soft tissue density at the costochondral junction of the right 5th and 6th ribs with destruction of the underlying ribs (Figure 1).

A CT-guided wide bore needle aspiration was done and the aspirated pus was submitted in the microbiology laboratory for bacterial, fungal and mycobacterial staining and culture. Blood was drawn for routine blood test, culture and Widal test. Urine and stool were sent for microscopy and culture.

Gram staining of the aspirated pus revealed many polymorphonuclear leukocytes (10-15/oil immersion field) and gram-negative rod-shaped bacilli, both intra and extracellularly. Culture grew non-lactose fermenting, rod-shaped gram-negative bacilli, which was identified as *Salmonella enterica* serovar Typhi by standard biochemical and serological tests. The isolate was resistant to chloramphenicol, ampicillin, cotrimoxazole, nalidixic acid, gentamicin, amikacin and ciprofloxacin by Kirby-Bauer disk diffusion and by micro broth dilution method. The isolate was sensitive to ceftriaxone only. The MIC_{50} for ciprofloxacin was 8 µg/ml, and for ceftriaxone 2µg/ml.

Three blood cultures and urine and stool culture after admission were sterile. Widal test showed a titer of 1280 for 'O' and for 'H' antigens of *Salmonella enterica* serovar Typhi.

The patient was treated with ceftriaxone (2g intravenous infusion daily) for two weeks. Pain and swelling subsided dramatically within five days of initiation of therapy. A repeat CT scan showed marked decrease in swelling as well as soft tissue density at the costochonchal junction of the right 5th and 6th ribs after two weeks (Figure 2). The patient recovered uneventfully.

Discussion

This case of *Salmonella* osteomyelitis is unique in two important aspects: the emergence of ciprofloxacin-resistant strain during the treatment of typhoid fever, and osteomyelitis of the rib, a rare but serious complication, caused by the resistant mutants of *Salmonella enterica* serovar Typhi.

The emergence of resistance can be explained on molecular grounds, because in these species, a single point mutation in the quinolones-resistance-determining-region (QRDR), which raise the MIC of

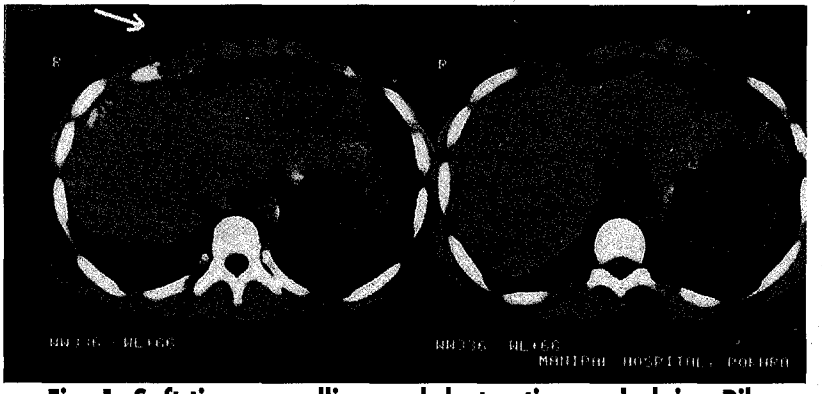

Fig. 1: Soft tissue swelling and destruction underlying Rib

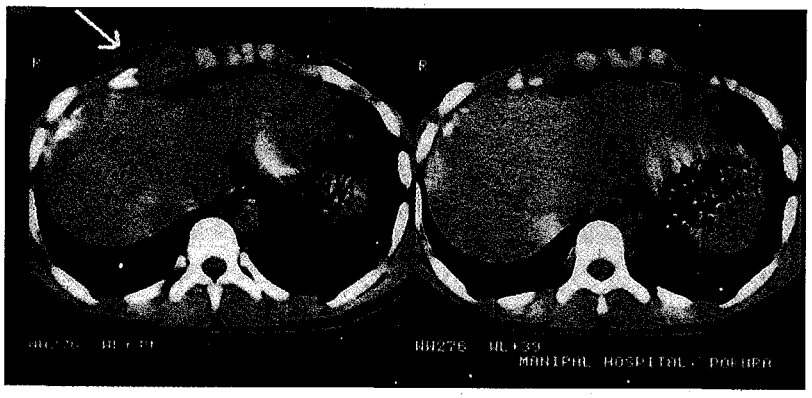

Fig. 2: Decrease in the soft tissue swelling after treatment

ciprofloxacin of these organisms 4 to 16 fold, and produce a level of resistance at or above peak drug concentrations achievable in serum, providing an opportunity for spontaneous first-step mutants (an amino acid change in the primary enzyme targets, like DNA gyrase genes *gyr* A and *gyr* B and topoisomerase IV genes *par* C and *par* E) to survive and emerge when a patient is exposed to fluoroquinolones. Selective pressure on the bacterial population by uncontrolled use of antimicrobial drugs is responsible for the emergence of this resistance. However, other mechanisms such as decreased permeability and active efflux of the anitimicrobial agent may also be involved[3].

Our case is an eye-opener as it demonstrates the development of osteomyelitis rib with a multi drug resistant as well as ciprofloxacin resistant *Salmonella enterica* serovar Typhi in a patient who was previously treated successfully for typhoid fever with ciprofloxacin. As it was hypothesized that the spontaneous first-step mutants during the treatment of typhoid fever gave rise to the complication, it points out the inadequacy of the current in-vitro antimicrobial susceptibility testing for detecting fluoroquinolone treatment failure in typhoid fever, which fails to detect the spontaneous first-step mutants and to prevent serious complications. Disk diffusion as well as broth dilution methods are inadequate and the detection of point mutation in the QRDR of *gyr* A gene by polymerase chain reaction (PCR) for routine laboratory purpose is not at all practical and cost effective. Routine testing of resistance to nalidixic acid with disk diffusion method (30 µg) as a useful screening test for fluoroquinolone resistance, is not sufficient in detecting mutation. No definite method to date is available for the routine laboratory detection of mutation to ciprofloxacin (fluoroquinolone) in *Salmonella enterica* serovar Typhi and thereby clinical response with ciprofloxacin in typhoid fever is the only way to detect probable mutants and treatment failure.

Conclusion

The ciprofloxacin-resistant strain was responsible for the osteomyelitis of the rib, a rare and serious complication. More effective routine laboratory diagnostic methods for regular detection of these isolates are to be developed; otherwise these isolates will remain undetected. It is reassuring that these isolates are so far sensitive to third generation cephalosporins like ceftriaxone.

References

1. Threlfall EJ, Ward LR. Decreased susceptibility to ciprofloxacin in *Salmonella enterica* serotype Typhi, United Kingdom. Emerg Infect Dis 2001; 7: 448-50.
2. Le Lostec Z, Fegueux S, Jouve P, Cheron M, Mornet P, Bolsivon A. A reduced susceptibility to quinolones in *Salmonella typhi* acquired in Europe: a clinical failure of treatment. Clin Microbiol Infect 1997: 3: 576-7.
3. Hooper DC. Emerging mechanism of fluoroquinolone resistance. Emerg Infect Dis 2001; 7: 337-41