Superficial Thrombophlebitis caused by Extensively Drug-resistant Salmonella Enterica Serovar Typhi

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ABSTRACT

Salmonella enterica serovar typhi causes one of the most common blood stream infections, the typhoid fever. However, it can cause pyogenic infections involving different sites as well. Extensively drug resistant (XDR) strains of *Salmonella* typhi are resistant to all first line anti-typhoidal drugs (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) as well as ciprofloxacin and ceftriaxone. XDR-strains were first reported from Pakistan in 2016, and since then the strains have been spreading. These XDR *Salmonella* cases not only pose a therapeutic challenge but also predispose to complications as a result of prolonged illness and delayed treatment. Here, we report a case of superficial thrombophlebitis at intravenous cannula site in a 49-year male, who was being treated for XDR-typhoid fever. To the best of our knowledge, thrombophlebitis of a superficial vein is an unusual complication of *Salmonella* typhi, not previously reported in literature.

Key Words: *Bacteremia, Thrombophlebitis, Extensively drug-resistant, Typhoid fever, Salmonella typhi.*

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INTRODUCTION

Salmonella enetrica serovar typhi causes one of the most common blood stream infections, the typhoid fever. However, it can cause pyogenic infections as well. Soft tissue abscesses, wound infections, genital and hepatobiliary tract as well as vascular infections have all been reported.[1] In the antibiotic era, complications related to typhoid fever became less frequent because of early institution of effective antibiotic therapy. But with the emergence of extensively drug-resistant (XDR) strains that are resistant to all first line anti-typhoidal drugs (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) as well as ciprofloxacin and ceftriaxone, the complications may again become prevalent. All recommended treatments are ineffective against these strains. A delayed treatment predisposes the patients of XDR-typhoid to prolonged illness and complications.[2,3]

Here, we report a case of superficial thrombophlebitis at intravenous cannula site in a patient of XDR-typhoid fever.

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CASE REPORT

A 49-year male, known diabetic, reported to the medical outpatient department (OPD) with history of high grade intermittent fever for the past one week. At presentation, the patient had a fever of 101°F. Baseline investigations were done and a paired blood culture sample was taken for culture and sensitivity testing (Table I).

The patient was admitted in the medical ward. Intravenous ceftriaxone at a dose of 2 g daily was started as empirical antibiotic. Patient continued to have fever spikes despite starting the antibiotic therapy. The blood culture yielded the growth of XDR *Salmonella enterica subspecies enterica* serovar typhi (resistant to ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol, ciprofloxacin and ceftriaxone). The culture and antimicrobial susceptibility report was conveyed to the treating physician. The antibiotic was changed to injection meropenem, 1 g, thrice daily and oral azithromycin, 500 mg, once daily. On the 4th day of admission, redness and swelling were noted at the intravenous cannula site over left forearm. The cannula was removed and re-sited on the right forearm. By 7th day, the swelling and pain increased over left forearm, a thickened venous cord was palpable at the area. Patient again had fever spikes. Doppler ultrasound of left upper limb showed subcutaneous fluid collection with thrombophlebitis involving basilic vein and venae comitantes of brachial artery along with cellulitis of the surrounding skin. The infected thrombosed vein was surgically removed along with debridement of the surrounding skin. The pus collection was drained intraoperatively and sent to microbiology department for culture and sensi-

tivity testing. The pus was reddish brown in color and thick in consistency. Gram staining of the specimen showed numerous pus cells and gram negative bacilli. The specimen was inoculated on Sheep blood agar and MacConkey agar (Oxoid, UK). On next day, there was growth of flat, spreading colonies that were non-lactose fermenting and were oxidase negative. The isolate identification was done on the basis of biochemical reactions on API 20 E (bioMerieux, France) and antimicrobial susceptibility testing was performed by Kirby Bauer disk diffusion method using the Clinical and Laboratory Standards Institute (CLSI) guidelines.[4] The isolate was identified as *Salmonella enterica* serovar typhi, that was XDR and only susceptible to meropenem (MIC 0.64) and azithromycin (MIC 0.25). The patient's antibiotics were continued for 12 more days in-hospital. His fever and swelling over the arm settled with treatment. He was advised oral azithromycin, 500 mg, once daily for 10 days on discharge. On follow-up visit after two weeks, the patient did not report any fever or swelling at the site.

Table I: Antimicrobial susceptibility pattern of the *Salmonella* typhi isolated from paired blood culture.

Blood culture: *Salmonella enterica* serovar typhi		
Antimicrobial susceptibility testing (AST)	Ampicillin (10 ug)	Resistant
	Chloramphenicol (10 ug)	Resistant
	Trimethoprim-sulfamethoxazole (25 ug)	Resistant
	Ciprofloxacin	Resistant
	Ceftriaxone (5ug)	Resistant
	Azithromycin (15 ug)	Sensitive (MIC=0.25)
	Meropenem (10 ug)	Sensitive (MIC=0.64)

DISCUSSION

Pakistan is currently facing the largest epidemic of drug resistant typhoid fever. Cases of XDR-*Salmonella* typhi were first reported from Hyderabad, Pakistan in 2016; and since then, there have been reports of similar cases throughout the country.[5] The authors report an unusual complication of typhoid fever that was noted during the ongoing outbreak of XDR *Salmonella* typhi in Pakistan. The patient developed thrombophlebitis of basilic vein along with cellulitis of the surrounding tissue where the intravenous cannula was placed for administration of antibiotics.

The clinical spectrum of *Salmonella* infections may at times vary from the usual blood stream infection and gastroenteritis to different extra-intestinal focal forms. Various complications can occur that involve central nervous system, pulmonary system, musculoskeletal, hepatobiliary and genitourinary systems.[6] *Salmonella* infections cause bacteremia associated with a widespread inflammatory response. Thrombus development in *Salmonella* infections may be related to tissue inflammation triggered by the innate, TLR4-dependent inflammatory cascade.[7] Cases of infections of arterial aneurysms, grafts and deep veins due to non-typhoidal *Salmonella* species have been reported in literature; however, to the best of our knowledge, no case of thrombophlebitis involving superficial veins secondary to typhoidal *Salmonellae* has been reported earliar in literature. In the cases of vascular infections previously reported, associated bacteremia was established in only few cases.[8-10] The *Salmonella* species identified in these cases were *S. typhimurium* and *S. enteritidis*. One case of cutaneous vasculitis with pancreatitis and splenic abscess, secondary to *Salmonella* typhi bacteremia, has been previously reported. Diabetes mellitus has been reported as a risk factor for extra-intestinal dissemination.[6] The patient in this case was a known type-2 diabetic for the past 12 years.

The isolate in the present case was XDR. There is one previously reported case of extra-intestinal infection by XDR-*Salmonella* in literature, which was a case of breast abscess in a pregnant lady reported from Karachi, Pakistan. The infection was treated with a combination of meropenem and azithromycin as was our patient. Meropenem is not a recommended treatment for typhoid fever. It was, however, used successfully for the treatment of XDR-typhoid cases in the outbreak in Pakistan.[11]

The extra-intestinal manifestations of *Salmonellae* infections should be kept in mind, especially in areas where the disease is endemic. The bacterium can disseminate to virtually all internal organ systems once the bacteremia is established. Vigilance in early identification of these extra-intestinal foci is, therefore, imperative. It is also emphasised that there is an urgent need to look for newer treatment options for typhoidal *Salmonellae* and breakpoints for susceptibility testing of meropenem against *Salmonellae* should be introduced in guidelines.

PATIENT'S CONSENT:

Informed consent was obtained from the patient to publish the data concerning this case.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

AI, IAM, QF, NS: Identification and follow-up of case, drafting manuscript and its revision.

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