CASE REPORT

Extensively drug-resistant typhoid fever; it's not that simple: a case report

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Abstract

Multi-drug resistant strains of Salmonella typhi (S. typhi) has remained endemic in developing countries for the last two decades. With irrational use of antibiotics, an extensively drug-resistant (XDR) strain of S. typhi, sensitive only to Carbapenems and Azithromycin, has evolved which was first reported in Sindh, Pakistan, in 2018. Most of the cases of XDR *S. typhi* infection treated with antibiotics improve without any complications. Failure to respond to appropriate antibiotics should raise the suspicion of visceral abscesses. Splenic abscess is a rare complication of *S. typhi* infection. A patient with splenic abscess due to XDR *S. typhi* has been reported who responded to prolonged antibiotic treatment. We report the case of a young boy from Peshawar with multiple splenic abscesses due to XDR *S. typhi* which did not respond to percutaneous aspiration and culture-guided antibiotics for two weeks. Eventually, he had to undergo splenectomy. He has remained afebrile since then.

Keywords: Salmonella typhi, Antibiotic resistance, Abscess, Spleen, Typhoid fever.

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Introduction

In Pakistan, like in other developing countries, infectious diseases are a significant reason for morbidity and mortality. Typhoid, malaria, viral hepatitis, and dengue fever are endemic in Pakistan. Typhoid fever was once a major health concern globally. It is still a significant public health concern in developing countries, affecting 14.3 million individuals, and is responsible for 135,900 deaths every year.[1] In February 2018, an outbreak of *Salmonella typhi (S. typhi)* was reported in Pakistan. The strain responsible for the outbreak was resistant to Fluoroquinolones and third-generation Cephalosporins in addition to Chloramphenicol, Ampicillin, and Trimethoprim-sulfamethoxazole. This strain of *S. typhi* was labelled as Extensively Drug-Resistant (XDR) *S. typhi*.[2] The National Institute of Health, Islamabad, reported 14,360 cases of XDR *S. typhi* in Karachi till June 2021.[3] Patients with *Salmonella typhi* infection present with body aches, fever, abdominal pain, diarrhoea, and loss of appetite. Rarely, *S. typhi* infection may cause gastrointestinal bleeding, ileal perforation, peritonitis, abscesses, and encephalopathy. Leukopenia and raised alanine aminotransferase levels are the most common laboratory abnormalities.

Salmonella typhi-associated splenic abscess is rare with a prevalence of 0.14-2%. These are common in immunocompromised individuals and people with haemoglobinopathies, and have a mortality rate of 40%.[4] A case of XDR *S. typhi* causing multiple splenic abscesses has been reported from Pakistan which settled with prolonged antibiotic therapy.[5] We report a case of XDR *S. typhi* causing multifocal splenic abscesses which did not respond to prolonged antibiotic therapy and percutaneous drainage. The patient ultimately underwent splenectomy. The case has been reported after approval from the head of the institute and the consent of the patient's father.

Case Report

A 14-year-old boy presented to the emergency department of Hayatabad Medical Complex, Peshawar, Pakistan, on March 19, 2022, with a history of fever for two weeks, and pain in the left hypochondriac region for the last four days. He had been well two weeks back when he developed high-grade fever. He visited a general practitioner (GP) who prescribed him oral Ciprofloxacin and antipyretics. He completed the antibiotic course without any response. Thereafter, he developed left-sided abdominal pain. He revisited his GP who then prescribed oral Cefixime and Artemether/Lumefantrine. Before this illness, the boy had been in good health, with no previous significant medical or surgical history.

With no response to the above management, the patient was referred to Hayatabad Medical Complex, Peshawar. On presentation, he was pale, having a temperature of 101°F, pulse rate of 90 beats per minute, and blood pressure of 105/70 mmHg. He was 155 cm (between 10th and 25th centiles) tall and weighed 45 kg (approx. 25th centile). Examination of the abdomen revealed a tender spleen palpable 2cm below the costal margin. He was

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admitted for further management.

Blood culture, urine culture, chest X-ray, ultrasonogram of the abdomen and pelvis, special smear, thick and thin smears for malarial parasites, dengue serology, and other routine investigations were requested. Dengue fever, malaria, typhoid fever, infective endocarditis, Coronavirus disease-19, and brucellosis were considered in the differential diagnosis. Investigations performed at the hospital are tabulated in Table 1.

He was started empirically on Meropenem, considering the resistance patterns of the prevalent *S. typhi* strains, and Artemether-Lumefantrine. His ultrasonogram showed multiple anechoic areas in the spleen, the largest measuring 7.5cm x 5.0cm indicating multifocal collections. Transthoracic echocardiogram did not reveal any vegetations. He continued to have fever despite administration of empirical Meropenem for seven days. Blood culture did not reveal any growth till day 7. On day 8 of admission, ultrasound-guided aspiration of the largest collection was done. The purulent aspirate was sent for gram staining, and culture and sensitivity. He had a resurgence of fever up to 103°F after remaining afebrile for two days after the procedure. On day 13 of admission, the splenic aspirate culture grew XDR *S. typhi* sensitive only to Azithromycin and Carbapenems. Despite treatment with Meropenem for two weeks and percutaneous drainage, he remained febrile and toxic. A repeat ultrasonogram showed recollection of the splenic abscesses. Contrast-enhanced computed tomography scan showed multiple hypodense lesions with air foci in the spleen, suggestive of splenic abscesses with the largest measuring 70ml in volume (Figure 1). The case was discussed in a multidisciplinary team meeting with surgeons, interventional radiologist, infectious disease specialist, and microbiologist. Keeping in view the lack of guidelines for the management of splenic abscesses due to XDR *S. typhi*, the team decided that the patient should undergo splenectomy. He was vaccinated against streptococcus pneumonia, meningococcus, and haemophilus influenza, and was continued on antibiotics. He underwent splenectomy on day 18 of admission. He remained admitted for four days after splenectomy and continued to be afebrile during this period. He was discharged on day 22 of admission. He was asymptomatic when reviewed two weeks after splenectomy. Instructions were given on prevention against bacterial infections and malaria. A custom-made medical alert card

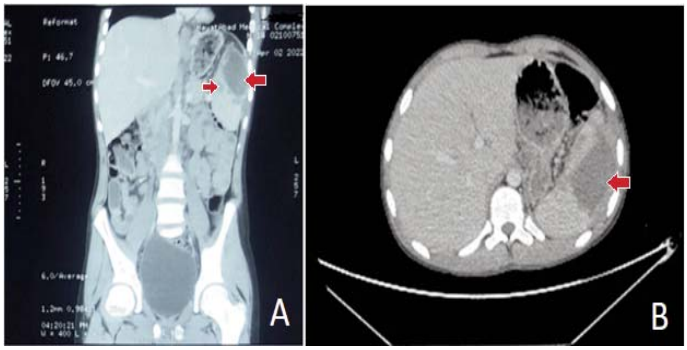

Figure-1: Contrast enhanced computed tomography of the abdomen showing multiple hypodense collections in the spleen (red arrows) suggestive of splenic abscesses [Coronal (A) and axial (B) views].

Table-1: Investigations carried out at tertiary care hospital

Investigations	Reference range	Results
Haemoglobin (g/dL)	13.5 – 17.5	10.6
Platelet count (x103/mcL)	150 – 450	325
White cell count (x103/mcL)	4.5 – 11	5.8
Blood smear	Hypochromic Microcytic picture	
Malarial Parasite	Not seen	
C-Reactive Protein (mg/dL)	< 0.5	4.5
Total Bilirubin (mg/dL)	0.2 – 1.2	0.2
Alanine aminotransferase (IU/L)	< 45	44
Alkaline phosphatase (IU/L)	< 350	209
Lactate dehydrogenase (U/L)	140 – 280	262
HBsAg (ELISA)	Non-Reactive	Non-Reactive
Anti-HCV (ELISA)	Non-Reactive	Non-Reactive
Anti-HIV (ELISA)	Non-Reactive	Non-Reactive
Dengue NS-1 antigen	Non-Reactive	Non-Reactive
Dengue IgM antibodies	Non-Reactive	Non-Reactive
SARS–CoV–2 PCR	Negative	Negative
Brucella IgM antibodies	Negative	Negative
Brucella IgG antibodies	Negative	Negative
Urinalysis	Normal	
Ultrasound Abdomen and pelvis	Enlarged spleen with multiple well-efined anechoic areas, largest 7.5cm x 5cm	
X-Ray Chest (PA) view	Normal	
Transthoracic Echocardiography	Normal study	
Blood culture	No growth	
Splenic aspirate analysis		
Aspirate total protein (g/dl)	3.53	
Aspirate LDH (U/l)	21894	
Aspirate Glucose (mg/dl)	< 2	
Aspirate WBC (x103/mcL)	97	
Aspirate RBC (x103/mcL)	1960	
Aspirate Neutrophils (%)	90	
Aspirate culture	*S. typhi* sensitive to Meropenem, Imipenem and Azithromycin. Resistant to Ciprofloxacin, Ceftriaxone, Cefixime, Cotrimoxazole and Ampicillin	

g/dL: Gram/deciliter; mcL: Microliter; U/L: Unit/liter; mg/dL: milligram/deciliter; IU/L: International unit/liter; ELISA: Enzyme-linked immunosorbent assay; NS: Non-structural Protein; PCR: Polymerase chain reaction' SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; IgM: Immunoglobulin M; IgG: Immunoglobulin G; PA: Posteroanterior; *S. typhi: Salmonella typhi*

was provided to him, and he was advised to report to his GP immediately if he got a fever.

Discussion

Splenic abscess is mostly seen as a complication of bacterial infections, splenic infarctions, abdominal trauma, haemoglobinopathies, and immune-compromised states, such as human immune deficiency virus infection, organ transplant, and neoplastic diseases. Infective causes of splenic abscess include typhoid fever, infective endocarditis, pneumonia, urogenital infections, and bacillary dysentery. Rarely, it may be caused by tuberculosis, and amoebic and fungal infections.[6]

Drug resistant typhoid fever not only poses a diagnostic dilemma but a therapeutic challenge as well.[7] It always keeps the internists on their toes. Achieving a defervescence status in XDR *S. typhi* is a daunting task. The continuous fever, the patient's toxic status, and the pessimistic queries of the patient and the relatives always compel the internist to add/change antibiotics and consider steroids. Failure to achieve a minimal inhibitory concentration of antibiotics and the development of the visceral abscess are possibilities that should cross the internists' minds in cases of an unusual course of the illness.

Splenic abscesses have been reported in typhoid fever. Chakraborthy et al have reported a case of a young boy from India with *S. typhi* infection complicated by splenic abscess and myocarditis.[8] Khan et al from Qatar have reported a multifocal splenic abscess due to *S. typhi*.[9] Bhongle et al have also documented a case of splenic abscess in a healthy immune-competent patient.[10] In contrast to our case, the splenic abscesses in all these case reports were caused by drug-sensitive strains of *S. typhi* which responded to conservative treatment.

A case of multifocal splenic abscesses due to XDR *S. typhi* has been reported from Quetta, Pakistan,[5] which had responded to prolonged antibiotic therapy. In contrast to this case, our patient underwent splenectomy because the abscesses were larger in size and recollected after percutaneous drainage. Moreover, our patient remained febrile and toxic despite two weeks of treatment with Meropenem. The growth of XDR *S. typhi* from splenic aspirate makes our case unique.

Percutaneous abscess drainage and antibiotics remain the treatment of first choice for solitary splenic abscess. However, splenectomy is a life-saving procedure for multifocal splenic abscesses and solitary abscess not responding to antibiotics and percutaneous drainage. Our patient, having multifocal splenic abscesses underwent successful splenectomy.

Conclusion

The documented cases of XDR *Tumour* in Pakistan represent the tip of an iceberg. Extensively drug-resistant S typhi has become a growing health catastrophe in a resource-limited country like Pakistan. With the onset of summer and monsoon season, XDR Tumour is going to spread at an exponential rate. Every practicing physician should be vigilant for a variety of presentations and complications of XDR *S. typhi*.

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