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Salmonella–Salmonellosis–Rare presentations of a common pathogen

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ABSTRACT

Salmonella are most commonly associated with gastroenteritis and enteric fever in humans. Occasionally, dissemination of bacilli throughout the body results in establishment of localized foci of persistent infection especially in patients with debilitating diseases and immunosuppressive states. Infection at various aberrant sites due to *Salmonella* has been reported relatively seldom. It has perfected the art of intracellular survival in niches from where they can cause myriad of effects. Six cases with *Salmonella* infection at unusual sites without any preexisting or underlying disease diagnosed over a period of two years are presented here. *Salmonella* etiology was not suspected in these patients and the diagnosis was made microbiologically only after culture isolation.

1. Introduction

Salmonella are enteropathogenic gram negative bacilli causing about 1.3 billion cases of human diseases ranging from systemic to localized infections each year^[1]. Infections caused by *Salmonella* remain an important public health problem, particularly in developing countries. Morbidity and mortality attributable to these infections are increasing with the emergence and worldwide spread of *Salmonella* strains that are resistant to most commonly used antibiotics^[2]. *Salmonella enterica* serovar Typhi and Paratyphi usually cause typhoid in humans, characterized by systemic infection, fever and often gastrointestinal symptoms such as diarrhea. Bacteremia is a constant feature of enteric fever and occasionally, dissemination of bacilli throughout the body results in establishment of one or more localized foci of persisting infection especially in patients where a preexisting abnormality has made a tissue or organ vulnerable including haemoglobinopathies, previous joint trauma, surgery, connective tissue diseases, lymphoma or immunosuppressive state^[2,3]. Isolation of *Salmonella* species, with variety of clinical syndromes from aberrant sites, where they are hardly expected has been reported^[4,5]. We present here a series of case reports of aberrant site *Salmonella* infections observed during the last two years (May 2008– July 2010) at our tertiary care centre.

2. Case report

All the cases of salmonellosis were followed up from the data collected in the Department of Microbiology over a period of two years (May 2008–July 2010). The case files of the patients were studied for extra intestinal presentations, treatment and follow up. Those who fitted in the criterion were included and the brief history of the six cases is as follows:

2.1. Case 1

A 36-year-old multiparous female patient presented in the outpatient department with a history of fever, of and on, and congestive dysmenorrhoea since the preceding 7 months. On physical examination, the patient was febrile, chest was clear; abdomen was soft and non tender. Bowel sounds were normal, and there was no organomegaly or free fluid. Per vaginal examination revealed bilateral adnexal masses and the cervix was tender. Laboratory analysis revealed a hemoglobin level of 10.8 g/dL, total leukocyte count (TLC) 12 600/μ L with 85% neutrophils, and platelet count was 2.83 × 10⁵/μ L. Erythrocyte sedimentation rate was increased (100 mm/h). A differential diagnosis of genital tuberculosis, endometriosis, and pelvic inflammatory disease was made. Pelvic ultrasonography revealed a large complex multiloculated cystic mass approximately 8.5 cm × 6.0 cm in the right adnexal site. A calcified focus was also seen. Another thick-walled round-to-oval cystic mass 4 cm ×

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4 cm was visualized in the left side of adnexa. Papanicolaou smear tests of uterine cervix and endometrial were negative. To rule out genital tuberculosis, Mantoux skin test and enzyme-linked immunosorbent assay test to determine IgG and IgM antibodies in the sera of the patient against *Mycobacterium tuberculosis* were carried out, both of which were found to be negative. Tumor markers were significantly elevated (CA-125, 295.05 U/mL).

Ultrasound-guided fine-needle aspiration was done under all aseptic precautions. Dirty thin pus was aspirated and sent for histopathological and microbiological examination. Histopathological examination revealed dense neutrophilic infiltrate, macrophages, and foreign body giant cells in a necrotic background with no malignant cells. Ziehl-Neelsen stain for acid-fast bacilli was negative. The pus was inoculated onto plates of blood agar, MacConkey agar, and Lowenstein-Jensen medium and also passed in brain-heart infusion broth. Non-lactose-fermenting colonies were obtained on MacConkey agar after overnight incubation at 37 °C. Brain-heart infusion broth was subcultured onto solid media that showed the similar growth after 24 h of incubation. On the basis of the colony characteristics, gram staining, motility, biochemical reactions, and agglutination with specific antisera, the isolate was identified as *Salmonella* Paratyphi A which was sensitive to chloramphenicol, ampicillin, cotrimoxazole, ciprofloxacin, and ceftriaxone. Blood and stool cultures were negative. Widal test revealed titers of 1:320 both for *Salmonella* Paratyphi O (somatic) and AH (flagellar) antigens. Polymerase chain reaction and BACTEC (Becton-Dickinson, Franklin Lakes, and NJ) for tuberculosis was negative. No growth was obtained on Lowenstein-Jensen medium after 6 weeks of incubation.

Exploratory laparotomy was performed and the pus was drained by inserting the needle into the abscess. Infected tube and ovary were not removed because patient wanted fertility sparing. Patient was given a full course of third-generation cephalosporin (ceftriaxone) intravenously. Patient responded favorably and was discharged in good condition after 2 weeks of hospitalization and showed improvement on follow-up.

2.2. Case 2

A five year old male child was admitted at our tertiary care hospital with complaints of fever and pain in the right hip for the last seven days. There was a decreased range of motion and flexion abduction deformity at the right hip. Laboratory investigations revealed normal haemoglobin of 11.2 g/dL, TLC was 9 000/ μ L and the CRP was 19.8 μ g/ml. Blood culture was sterile. Widal test was done and titres of 1:320 for both *Salmonella* Typhi O (somatic) and H (Flagellar) antigens. Radiologically there was abduction deformity suggestive of effusion in the hip. MRI revealed oedema of the proximal femoral head. A serosanguinous fluid was aspirated from the infected site which was sent for microbiological examination. Gram stain of the fluid revealed polymorphonuclear cells and gram negative bacilli. The fluid was inoculated on blood agar and MacConkey agar and passed in brain heart infusion broth. Lactose nonfermenting colonies were obtained on MacConkey agar after overnight incubation at 37 °C. Brain heart infusion broth was sub cultured on solid media and similar growth

was obtained after 24 h of incubation. On the basis of colony characteristics, gram staining, motility, biochemical reactions and agglutination with antisera, the isolate was identified as *Salmonella* Typhi. The isolate was sensitive to chloramphenicol, ampicillin, cotrimoxazole, ciprofloxacin, ceftriaxone and resistant to nalidixic acid.

An orthopedic diagnosis of proximal femoral osteomyelitis was made. Surgical drainage was done and the patient was given a full course of parenteral ceftriaxone. On follow-up there was no fever or discharge from the affected site and patient showed improvement in signs and symptoms.

2.3. Case 3

An eleven year old male child presented with pain in the right lower limb for the last 25 d. There was no significant past history of fever, loss of appetite or weight. Family history of tuberculosis was present. On clinical examination there was tenderness at the right hip and movements at the hip joint were restricted. Hemoglobin was 10.8 g/dL, TLC 7 200/ μ L with 56% of neutrophils and 40% of lymphocytes. Radiological examination revealed decreased joint space. Biopsy was taken from the right hip and sent for microbiological examination. Meanwhile a provisional diagnosis of tuberculosis of the right hip was made and patient was put on antitubercular therapy (ATT) and discharged. The biopsy specimen was processed as per standard protocol. Ziehl-Neelsen stain for AFB was negative. The biopsy specimen was inoculated on BHIB, blood agar MacConkey agar and LJ medium. Lactose nonfermenting colonies were obtained after 24 h of incubation at 37 °C. On the basis of colony characteristics, gram staining, motility, biochemical reactions and agglutination with antisera, the isolate was identified as *Salmonella* Typhi. The isolate was sensitive to chloramphenicol, ampicillin, cotrimoxazole, ciprofloxacin, ceftriaxone and nalidixic acid. No growth was obtained on LJ medium after 8 weeks of incubation at 37 °C. No clinical improvement was seen on the subsequent visits of the patient and hence ATT was withdrawn. The patient was put on oral ciprofloxacin to which he responded well within 21 d.

2.4. Case 4

A 17 year male patient presented with fever and left side flank pain of 15 d duration. He denied history of vomiting, jaundice, dysuria, bladder or bowel disturbance, prior valvular heart disease and substance abuse. General physical and systemic examination was unremarkable except for fever and mild tenderness over the left lumbar region. Investigations revealed haemoglobin 11 g/dL, TLC of 3 600/ μ L (polymorphs 55%, lymphocytes 43%, Monocytes 0.1% and eosinophils 0.1%), with normal platelet count, liver and renal functions and normal fasting blood sugar. Urine examination was normal except for 20 pus cells/high power field with traces of albumin. No acid fast bacilli were seen in three consecutive early morning samples. Serology for HIV was negative. Cultures of blood and urine were negative. A hypoechoic lesion measuring 2.5 cm \times 2.6 cm suggestive of an abscess was seen in the postero-medial cortex of the left kidney in the midpolar region on ultrasound abdomen and confirmed on contrast enhanced computed tomogram. No abnormality was detected on chest X-ray and

echocardiography.

Ultrasound guided needle aspirate was sent for culture and sensitivity, meanwhile patient was started empirically on intravenous cloxacillin. Lactose nonfermenting colonies grew on MacConkey agar. These were confirmed to *Salmonella* Paratyphi biochemically and serologically. The strain was sensitive to ceftriaxone, cefoperazone–sulbactam, ofloxacin, amikacin and gentamicin. Repeat aspirate showed the same growth and antimicrobial sensitivity pattern. Patient was started on amikacin and gentamycin to which he responded by fifth day. Amikacin was discontinued after 14 d and ofloxacin continued till 4 weeks. Review ultrasound done at 4 weeks revealed marked reduction in size of the abscess.

2.5. Case 5

A 55 year old male patient presented with history of swelling and pus discharge from the perianal region for the last 5–7 d. Patient was febrile. On local examination there were multiple sinuses with foul smelling discharge. Incision and drainage was done and pus sent for microbiological examination. The specimen was inoculated on blood agar MacConkey agar. Lactose fermenting and Lactose nonfermenting colonies were obtained after 24 h of incubation at 37 °C. On the basis of colony characteristics, gram staining, motility, biochemical reactions and agglutination with antisera, the isolate was identified as *Escherichia coli* and *Salmonella* Paratyphi A. *Salmonella* Paratyphi A was sensitive to ceftriaxone and amoxycyclavulanic acid intermediate sensitive to ciprofloxacin and resistant to amoxicillin. Blood cultures and Widal test was negative. Stool culture was positive for *Salmonella* Paratyphi A.

2.6. Case 6

An 11 year old male child was admitted to the orthopedics ward with chief complaints of pain and inability to move and to bear weight on the right leg following an injury on the right hip 15 d back. He also developed high grade fever from the last 7 d which was sudden in onset and was relieved on medication. Local examination showed tenderness with increased local temperature, flexion deformity and restricted movements of the right hip joint. Laboratory findings included a hemogram level of 7.3 g/dL, total leukocyte count of 8 900/mm³, platelets 3.8 × 10⁵/mm³ and C–reactive protein was 17.4 μg/mL. Ultrasonography revealed mild bulkiness at the site of pain. Altered signal intensity and edema of proximal femoral head was seen on MRI. Radiologically, there was no fracture/dislocation of hip joint however abduction deformity suggestive of joint effusion was seen. Clinical diagnosis of septic arthritis of right hip joint was made and arthrotomy was subsequently performed.

Serosanguineous fluid was aspirated from the infected site and sent for microbiological examination which was processed as per standard protocol. Gram stained smear showed polymorphonuclear cells and gram negative bacilli and culture yielded non lactose fermenting colonies on MacConkey agar medium and showed typical biochemical reactions of *Salmonella* Typhi which was further confirmed by agglutination reaction with specific antisera. The isolate was found to be susceptible to gentamicin, cotrimoxazole,

chloramphenicol, cefotaxime, ceftriaxone and resistant to ampicillin and nalidixic acid. A retrospective blood culture was found to be negative and the widal test showed titres of 1:160 for TO (somatic antigen) and 1:320 for TH (flagellar antigen). Surgical intervention was done as an initial mode of management followed by ceftriaxone (100 mg/kg) therapy for 21 d subsequent to which patient showed signs of recovery.

3. Discussion

Salmonella are gram negative bacteria which usually cause gastroenteritis and enteric fever in human. Being entrepreneurial and ubiquitous in nature, it exists in a multiplicity of habitats, is highly adaptable and has the propensity for intracellular survival. For this purpose, *Salmonella* are very ably equipped with a number of pathogenic mechanisms in their armature. They proliferate within macrophages and escape phagocytosis by neutrophils to establish a systemic infection, thus providing a means of extraintestinal dissemination[6]. This ability of *Salmonella* to invade and survive in a variety of host cells is vital to its success as a pathogen. New reports, however, demonstrate that pathogens such as *Salmonella* or *Citrobacter* exploit inflammation to establish a competitive advantage against the normal microflora[7]. Irrespective of dose or infection route, more than 80% of *Salmonella* within tissues are inside of professional phagocytes. An intracellular location may allow bacteria to avoid immune system components (i.e. complement and antibodies), replicate or manipulate the host immune response. Haemophagocytosis, the phenomenon of activated macrophage consumption of red and white blood cells, including professional phagocytes and lymphocytes, may also be important for the establishment and maintenance of chronic *Salmonella* infections because they can provide the bacteria with a survival niche[8].

Salmonella is often considered to affect primarily the gastrointestinal tract, however infection at other sites where they are hardly expected may also occur, producing characteristic clinical syndromes[9]. Increased host susceptibility to infection secondary to lowered resistance due to debilitating diseases is an important determinant of *Salmonella* infection[10]. However, many cases have not had any precipitating factors and can occur as a complication of previous clinical or sub clinical bacteremia in an apparently otherwise healthy host[11]. Much less frequent but much more severe presentations are focal infections which may affect different sites in the body causing different disorders which frequently occur during or after *Salmonella* bacteremia but can also occur concomitantly with other syndromes.

Localization of infection may occur at any site after *Salmonella* bacteremia irrespective of the associated clinical syndrome. Local abscess formation is uncommon with an overall incidence of up to 1.7% which may occur as a complication of any *Salmonella* infection by either hematogenous or lymphatic spread or direct contact with the inflamed bowel wall[12]. There are anecdotal case reports in world literature of abscesses (liver, subphrenic space, ovary, inguinal region, thyroid, psoas muscle and spleen) being caused by this organism[13]. Renal abscess although commonly caused by *Staphylococcus* species but infrequently, *Salmonella* like *Salmonella* enteritidis and

Salmonella Typhimurium and *Salmonella* Paratyphi A have been documented in few case studies^[14]. The resistance of kidneys to the invasion by this fastidious organism is still a matter of speculation. *Salmonella* have also been reported worldwide as an important causative agent of ovarian abscesses and mostly by *Salmonella* Typhi and non typhoidal *Salmonella*. It is a sequel of pelvic inflammatory disease that is composed of an infectious inflammatory complex encompassing the fallopian tube and ovary, develops following ascending infection, direct extension from the abdominal cavity and hematogenous and lymphatic routes^[15].

Osteomyelitis and septic arthritis are reported, but relatively uncommon, manifestations of *Salmonella* infection in less than 1% of cases^[16]. It is likely to occur in patients with haemoglobinopathies, previous joint disease, trauma, surgery, connective tissue disorders and immunosuppressive states^[5,17]. In another review of 142 extraintestinal *Salmonella* infection cases in a United Kingdom hospital, 5 were found to have osteomyelitis (3.5%). No clinical or radiographic hallmarks aid the diagnosis of osteomyelitis, but most patients presented with pain and variable swelling^[18]. The most commonly isolated serotypes in septic arthritis are *Salmonella* Typhimurium and *Salmonella* Cholerasuis but *Salmonella* Typhi and *Salmonella* Paratyphi A have also been emerged as an important cause of osteomyelitis^[19].

Salmonella infection at various sites requires timely intervention, correct diagnosis and appropriate treatment. The antibiotic therapy in *Salmonella* infections must be given for an extended period of time, for up to 4–6 weeks depending upon the site of infection and serotype of *Salmonella*. Specific surgical intervention is often necessary in conjunction with antibiotic management. Antibiotic resistance in *Salmonella* is a global concern that includes multi-drug resistant strains. With emergence of multidrug resistant (MDR) *Salmonella* Typhi, either quinolones or third generation cephalosporins are currently recommended for empirical antibiotic treatment. Fluoroquinolone resistance is an important emerging factor and was reported by the CDC to be 41.8%^[20]. Ceftriaxone, a third generation cephalosporin is the best choice for *Salmonella* as no other drug has been found as rapidly acting or as effective as ceftriaxone and the relapse rate is also low with this antibiotic.

In conclusion, *Salmonella* is a unique pathogen that has mastered the ability to persist in the body by means of exquisite molecular sophistication and that for long periods of time. As evident from these case reports clinicians should keep *Salmonella*, an eminently treatable pathogen as a differential diagnosis while managing such patients because there is a possibility of *Salmonella* infection at aberrant sites, especially in patients with history of persistent fever or gastroenteritis or any underlying disorders.

Conflict of interest statement

We declare that we have no conflict of interest.

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