Case Report

Salmonella pneumonia complicated with encysted empyema in an immunocompromised youth: Case report and literature Review

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Abstract

In this case report we described a Bahraini male patient of twenty years of age, a smoker and diagnosed with stage IV B Hodgkin lymphoma. He presented with fever, nonproductive cough, upper back pain and shortness of breath due to right upper lobe pneumonia with right encysted pleural effusion. Salmonella enterica serotype Enteritidis was isolated from the sputum. He was successfully treated with 2 weeks of ceftriaxone followed by 2 weeks of oral cefixime. This was the first case of encysted empyema caused by Salmonella enterica serotype Enteritidis reported in the Kingdom of Bahrain. The different aspects of pulmonary Salmonella infections were discussed and the literature was reviewed.

Key words: Salmonella; pulmonary, Bahrain; Hodgkin lymphoma; Pneumonia.

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Introduction

Salmonella is a common enteric pathogen; causing various types of gastroenteritis, typhoid fever and enteric fever. Extra-intestinal infections were recorded such as bacteremia, or localized infections, such as septic arthritis, osteomyelitis, nephritis, endocarditis, cholecystitis, and meningitis. Rare pulmonary involvement occurs in the form of bronchopneumonia, lung abscess, and empyema. It was long ago in 1885 when Artaud noticed typhoid like bacilli in lungs of two dying typhoidal patients with pulmonary apoplexy [1]. Pulmonary Salmonella infections were never reported before in the Kingdom of Bahrain. We described a case of pneumonia caused by Salmonella enterica serotype Enteritidis in an immunocompromised patient and short review the pertinent literature.

Case Presentation

A male Bahraini smoker of twenty years of age known to have stage IV B Hodgkin lymphoma and on the 5th cycle of ABVD regimen (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) presented with a history of fever, non-productive cough, upper back pain and shortness of breath of a 2-day duration. There was no history of nasal discharge, earache, and no gastrointestinal symptoms such as vomiting, diarrhea or bleeding. He was diagnosed 5 months earlier as having a syncytial variant of nodular sclerosing Hodgkin lymphoma, stage IVB. He had also reduced glucose-6-phosphate dehydrogenase (G6PD) activity; past history of excisional biopsy of left inguinal lymph node; and frequent blood transfusions. Examination showed pallor, fever, tachypnea and tachycardia but no cyanosis or jaundice. Chest examination showed bilateral basilar crackles and expiratory wheezes over the left chest. The rest of the examination was unremarkable except for a palpable right axillary lymph node (2 cm by 1.5 cm). Chest X-ray showed widened mediastinum, and the computerized tomography (CT) scan of the chest without contrast showed right apical upper lobe consolidation with atelectasis. There were also right encysted pleural effusion; multiple axillary, hilar and mediastinal lymphadenopathy. The white blood cell count was 16,000/mm³ with 63% polymorphonuclear cells, 33% lymphocytes, and 4% monocytes.

Three sets of blood and one set of urine culture specimens were taken on admission and were negative. Expectorated sputum stained with gram stain showed few squamous epithelial cells, abundant white blood cells and Gram-negative bacilli. Specimen was inoculated on blood agar, chocolate agar and MacConkey agar. Twenty-four hours later, sputum sample cultures yielded a Gram-negative aerobic rod. Identification was done by the standard conventional biochemical methods through glucose fermentation, urease reaction, lysine decarboxylase, indole test, and H2S production. Serotyping was done using polyvalent antisera for flagellar (H) and somatic (O) antigens and
revealed *Salmonella enterica* serotype Enteritidis. Antimicrobial susceptibility testing was performed with an automated system using Phoenix automated microbiology system (BD Diagnostics, Sparks, USA) showed sensitivity to cotrimoxazole, ceftriaxone, meropenem, chloramphenicol, and ciprofloxacin but resistant to nalidixic acid and ampicillin. Stool specimen cultured for enteric pathogens also identified the same organism with the same serotype. On the basis of antibiotic sensitivity, the patient was treated with ceftriaxone for a period of 14 days after which the patient was successfully discharged, followed by another 14 days of oral cefixime.

**Discussion**

*Salmonella* are worldwide non-spore-forming Gram-negative facultative anaerobic motile bacilli of the *Enterobacteriaceae* family. There are only two species of *Salmonella*, *Salmonella bongori* and *Salmonella enterica*. *Salmonella enterica* serotype Enteritidis is one of the most common serotypes; frequently reported as a cause of human illness due to salmonellosis in most industrialized countries despite ongoing implementation of targeted control and prevention strategies [2,3]. The genus *Salmonella* is named after Daniel E. Salmon who first isolated *Salmonella enterica* Serotype Choleraesuis from pigs in 1884. *Salmonella* infections typically manifest as gastroenteritis, bacteremia, or septicemia. Extraintestinal complications, such as pleuropulmonary infections, secondary to nontyphoid serotypes of *Salmonella* are extremely rare, with only a few cases reported in the last century [4]. One of the mechanisms by which *Salmonella* can induce lung injury is through the activation of the contact system, which leads to massive infiltration of red blood cells and fibrin deposition in the infected lungs [5]. Our case was the first reported case of pulmonary *Salmonella* infection described in the Kingdom of Bahrain.

Immunity to *Salmonella* is complex and involves both local and systemic antibody and cell-mediated immunity components. Serum antibodies to *Salmonella* antigens are likely to play an important role in the defense against *Salmonella*, when they are extracellular. However, *Salmonella* can persist intracellularly in the human host, thereby avoiding destruction by antibodies and complement; cell-mediated immunity is expected to be essential in eliminating *Salmonella* infection. T-cells contribute to the control of intracellular replication in macrophages [6,7].

Systemic dissemination of the organism is most likely to occur through hematogenous spread of nontyphoid *Salmonella* via the reticuloendothelial system [8]. Despite being generally rare; pulmonary infection due to non-typhoidal *Salmonella* should be considered among the possible pathogens associated with Gram-negative bacillary pneumonia in immunosuppressed patients. The most common serotypes isolated from *Salmonella* pulmonary infections are *S. enterica* serotype Typhimurium and *S. enterica* serotype Choleraesuis. *S. enterica* serotype Enteritidis is much less frequently encountered as a causative agent of respiratory infection than the previous two serotypes according to the available literature. Two important factors could precipitate for pulmonary infections with *S. enterica* serotype Enteritidis; systemic factors such as impaired cell-mediated immunity, impaired B-cell function, prior use of antibiotics, a diminished gastric acidity, or low socioeconomic status with poor hygienic conditions; and local factors such as prior lung or pleural disease or abnormalities. Other conditions such as diabetes mellitus, uremia, hypochlorhydria, and gastrectomy may play a role. However; the real pathophysiological mechanisms remain unclear [9,10].

Impaired cell-mediated immunity is an important factor in the pathogenesis of extra-intestinal salmonellosis. Macrophage phagocytosis is important in clearing *Salmonella* infections. Patients with lymphoma have induced phagocyte blockade, impairing the intracellular killing in the spleen [11]. Impaired cell-mediated immunity can occur with prolonged corticosteroid therapy, alcohol abuse, some types of chemotherapy, and some types of malignancies, mainly leukemias and lymphomas. Patients with impaired cell-mediated immunity have impaired eradication of the intracellular organisms including *Salmonella* [12]. Patients with Hodgkin's disease have persistent defects in cellular immunity; either at presentation or in remission. The untreated patients have depressed natural killer cell mediated cytotoxicity and their humoral immune function becomes transiently reduced following treatment. The cellular immune defects result from enhanced sensitivity to suppressor monocytes and T-suppressor cells, in addition to abnormal interleukin-2 production. Patients with advanced disease have an inherent T-lymphocyte defect. Reed-Sternberg cells function as antigen-presenting cells for mitogen-induced and mixed lymphocyte T-cell proliferation. All these factors increase their susceptibility to opportunistic and recurrent infections [13].
## Table 1. Reported studies in adults with pulmonary salmonellosis

| Author(s)          | Age of the patient(s) | Sex       | Immune status | Medical & Social Status | Organism detected | Type of pulmonary involvement | Treatment                                                                 | Outcome       |
|--------------------|-----------------------|-----------|---------------|-------------------------|-------------------|-------------------------------|----------------------------------------------------------------------------|---------------|
| Gopinath et al.    | 18 years Male         | Competent | Lung abscess  | S. enterica serotype Typhi | Rt. Pleural Empyema | Chloramphenicol + Thoracocentesis, open drainage, thoracoplasty | Improved       |                           |
| Rao & Sattar, 1967 | 30 years Male         | Competent | Enteric fever | S. enterica serotype Typhi | Lt. Pleural effusion | Chloramphenicol + Closed thoracic drainage | Improved       |                           |
| Annamalai et al.   | 47 years Male         | Competent | Healthy plumber | S. Paratyphi B       | Rt. Pleural Empyema | Chloramphenicol + Thoracocentesis | Improved       |                           |
| Galazka et al.     | Middle aged female    | compromised | mediastinal tumor | S. enterica serotype Typhi | Pleural Empyema   |                                                                               |                |
| Carel et al.       | 60 years Male         | compromised | metastatic thyroid cancer | S blockley. | Unilateral malignant pleural effusion | Intrapleural administration of antibiotics | Improved       |
| Buscaglia AJ. 1978 | 21 years Female       | Competent | splenic abscess | Salmonella serotype Newport | Empyema          |                                                                               |                |
| Reiss-Levy et al.  | 51 years Male         | compromised | Previous rectal surgery | Salmonella Typhimurium | pulmonary cavitation and mycetoma | Antibiotic treatment | Chronic pulmonary infection |                           |
| Saitoh et al. 1982 | 47 years Male         | compromised | hereditary spherocytosis, HSM, chronically ill | Salmonella Oranienburg, mucoid and non-mucoid strains | Pleural effusion | Pleural drainage + cefazolin and gamma-globulin | Improved       |
| Devi et al. 1982   | Adult Male            | Competent | Typhoid fever | S. enterica serotype Typhi | pleural effusion | Pleural drainage + Antibiotic treatment | Improved       |
| Cistulli et al. 1991 | Adult Male            | compromised | non-Hodgkin's lymphoma | Salmonella Typhi | Rt. lower lobe pneumonia | Treatment with chloramphenicol | Improved       |
| Sharma et al. 1992 | 43 years Male         | compromised | Associated typhoid fever | Salmonella Typhi | Bronchopneumonia |                                                                               |                |
| Colebunders et al. | 20 years Male         | compromised | HIV and Kapoci Sarcoma | Salmonella Typhimurium | Bilateral Empyema | IV & oral ciprofloxacin | Improved       |
| Yassine et al. 1995 | 25 years Male         | Competent | splenic abscess | Salmonella Typhi | left empyema | Antibiotic therapy with Cotrimoxazole, repeated pleural aspirates and physiotherapy, | Improved       |
| Gill & Holden, 1996| 70 years Male         | compromised | ischaemic heart disease, atrial fibrillation, CHF, small cell bronchogenic carcinoma | Salmonella Enteritidis | left malignant pleural effusion | Ciprofloxacin for 4 weeks + oral etoposide | Remained well for 12 months follow up |
| Riantawan et al. 1996 | 28 years Male       | compromised | HIV-infection | Salmonella Typhimurium | Bilateral multiple cavitary lesions | Ceftriaxone/ciprofloxacin | Improved       |
| Ridsa et al. 1996  | 49 years Male         | compromised | HIV-infected | Salmonella Typhimurium | Right upper lobe lung abscess | Ciprofloxacin treatment | Improved       |
| Casado et al. 1997 | 10 subjects (26-40 years with mean age 31.3 years) | All are male | compromised | HIV-infected individuals with Salmonella bacteremia, previous lung lesion | 7 cases had Salmonella Enteritidis | 6 cases had lung abscesses and 4 cases had pneumonia | antibiotic therapy according to culture and sensitivity | 9 cases survived & one died; he had co infection with Noeradria asteroides |
| Wolday et al. 1997 | 25 years Male         | compromised | HIV infection | Salmonella Paratyphi | left-sided pleural effusion | Antibiotic therapy coupled with pleural drainage | Improved       |
Table 1 (continued). Reported studies in adults with pulmonary salmonellosis

| Author(s)         | Age of the patient(s) | Sex    | Immune status | Medical & Social Status | Organism detected          | Type of pulmonary involvement | Treatment                                                                 | Outcome       |
|-------------------|-----------------------|--------|---------------|-------------------------|-----------------------------|------------------------------|--------------------------------------------------------------------------------|---------------|
| Nair et al. 1999  | Adult                 | Male   | competent     | attempt at suicide by the intake of corrosive acid, which caused an esophageal stricture with leak of gastric contents into the mediastinum | Salmonella group E (S. senftenberg) | left-sided pneumonia with Empyema | Antibiotics therapy                                                  | Improved      |
| Rim et al. 2000   | 70 years              | Female | competent     | Diabetes II             | Salmonella group B          | Empyema                      | Antimicrobial therapy and repeated therapeutic thoracocentesis           | Improved      |
|                   | 50 years              | Male   | competent     | Farmar                  | S. Senftenberg             | Left Pleural Empyema         | Antibiotic treatment + Intercostal tube drainage                            | Improved      |
| Ramanathan et al. | 51 years              | Female | compromised   | Diabetes & Adenocarcinoma of gall bladder | S. Senftenberg             | Left Pleural Empyema         | Pig-tail catheter drainage + treatment with IV imipenem & amikacin, and oral doxycyclin, Initial resistance to antibiotics then Improved |               |
| Samonis et al.    | 72 years              | Male   | compromised   | lung cancer             | Salmonella enterica serotype Enteritidis | Pneumonia                    | Antibiotic treatment                                                      | Died          |
| Mishra et al.     | 35 years              | Male   | competent     | No                      | Salmonella Typhi            | Left hydro pneumothorax      |                                                                                |               |
| Kömüs et al. 2005 | 65 years              | Female | compromised   | Hepatic cirrhosis secondary to autoimmune hepatitis and hepatocellular carcinoma | Salmonella Typhi            | Right Pleural Empyema         | Right tube thoracostomy was performed and sulbactam-ampicillin 6 g/day therapy | Improved      |
| Genzen et al. 2008| 55 years              | Male   | competent     | alcoholism, bronchitis, and esophageal dysmotility | Salmonella Typhimurium      | Right upper lobe pneumonia with areas of cavitation | Antibiotic therapy                                                       | Improved      |
| Afridi et al.     | 83 years              | Male   | compromised   | Diabetes                 | Salmonella enterica serotype Typhi | Pleural Empyema              | Antimicrobial treatment                                                    | Improved      |
| Kam et al. 2012   | 66 years              | Female | compromised   | Diabetes + Smoking-induced Lung pathology | Salmonella group D          | Pleural Empyema              | Decortication + Antimicrobial treatment                                      | Improved      |
| Nale et al. 2013  | 30 years              | Male   | compromised   | Chronic alcoholic and Diabetes type II, HSM | Salmonella Typhi            | left sided pleural effusion with subdiaphragmatic collection.             | Antibiotic ceftriaxone for 30 days along with intercostal drainage, Initial failure then Improved |               |
| Chao CT 2014      | 61 years              | Male   | compromised   | intravenous drug abuse, major depression, suicide attempt & mycotic saccular abdominal aortic aneurysm | Salmonella enterica serotype Enteritidis | Left Pleural Empyema          | video-assisted thoracoscopic surgery and endovascular repair of the abdominal aortic aneurysm & 6 weeks of ciprofloxacin | Improved      |
In this case, the patient had nodular sclerosing Hodgkin lymphoma; treated with ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) regimen. He developed pneumonia caused by *S. enterica* serotype Enteritidis while he was on the 5th cycle of treatment. ABVD regimen can induce significant immunity and pulmonary side effects. Adriamycin inhibits DNA replication and thus can induce severe lymphocytopenic syndrome and can suppress CD8+ T-cell immune responses during the treatment protocol [14]. Bleomycin can induce pulmonary fibrosis (fibrosing alveolitis), organizing pneumonia (presence of granulation tissue progressing from fibrin exudates to loose collagen containing fibroblasts in the distal air spaces of buds), hypersensitivity pneumonitis and impaired lung functions in up to 10% of patients receiving the drug [15]. Development of infection during the 5th cycle may be explained through the time needed by the drug to induce lung injury. Our patient also had the potential of smoking-related lung injury, as he was a smoker for the previous 3 years. Vinblastine is anti-mitotic drug and can suppress 3H-thymidine inclusion into lymphoid cells; it is accompanied with complete elimination of humoral response of the

| Author(s)                  | Age of the patient(s) | Sex | Immune status          | Medical & Social Status | Organism detected | Type of pulmonary involvement | Treatment                                      | Outcome |
|---------------------------|-----------------------|-----|------------------------|-------------------------|-------------------|------------------------------|-----------------------------------------------|---------|
| Martinez-Vazquez *et al.* 1977 [49] | 13 years            | Female | competent             | Splenomegaly with abscess | *S. typhi*       | Left Pleural Empyema         | Repeated pleural taps, antibiotic treatment with chloramphenicol, splenectomy | Improved |
| Chaturvedi *et al.* 1978 [50] | 5 years              | Male | compromised            | Sickle cell anaemia     | *S. typhi*       | Pleural Empyema              | Antimicrobial treatment                       | Improved |
| Rahman & Sinclair. 1980 [51] | 9 years              | Male | competent             | Protein energy malnutrition, anaemia, septicaemic typhoid infection | *S. typhi*       | frank empyema                | chloramphenicol and drainage of the pus via an intercostal drain. | Improved |
| Fonollosa *et al.* 1980 [52] | 11 years             | Male | compromised            | Haemolytic anaemia, splenic abscess | *S. typhi*       | Left Pleural Empyema         |                                        |         |
| Eaton *et al.* 2002 [54] | 4 years              | Female | compromised           | hepatosplenomegaly and severe anemia | *S. typhi.*      | Pleural Empyema              | Percutaneous drainage with ultrasonography and antibiotics | Improved |
| Mankhambo *et al.* 2006 [55] | 16 months           | Female | compromised           | From malaria-endemic area | Nontyphoidal Salmonella | Lt lobar pneumonia          | treatment with ceftriaxone                    | Improved |
| Aslam *et al.* 2006 [23] | 5 years              | Female | competent             | hemoptysis, fever and weight loss | *Salmonella typhi* | Infected hydatid cyst        | Surgical removal and antibiotic treatment     | Improved |
| Adhisivam *et al.* 2006 [56] | 5 years              | Female | competent             |                                 |                   | Right lower zone lung abscess |                                              |         |
| Thapa *et al.* 2009 [21] | 11 years             | Female | competent             | Associated thrombocytopenia & loose stools, septicemia | *S. group B spp* | Left lower lobe lung abscess | 2 weeks of IV ceftriaxone followed by 2 weeks of oral cefixime | Resolution of the abscess within 6 weeks |
| Mohanty *et al.* 2010 [57] | 10 years             | Female | competent             | Healthy girl had typhoid fever | *S. enterica serotype Typhi* | pleural effusions          | parenteral ceftriaxone and intercostal chest tube drainage | Improved |
| Nandan *et al.* 2012 [58] | 18 months            | Male | competent             | low socioeconomic class     | *Salmonella typhi* | left-sided Pleural Empyema   | Antimicrobial treatment                      | Improved |
draining lymph node; and a five-fold decrease of the number of antibody-forming cells in the spleen [16]. Dacarbazine is an alkylating agent that may inhibit DNA and RNA synthesis. It can induce immune suppression in some case [17].

In this patient, Salmonella enterica serotype Enteritidis was detected from the sputum but no growth was detected from the blood culture, which decreases the possibility of the hematogenous dissemination, or probably due to prior treatment with antibiotics before admission. Aspiration of infected gastric secretions could be a source of infection. However, the fact that Salmonella was isolated from his stools does not necessarily mean that he was a carrier. The patient most likely swallowed infected respiratory secretions, and this could account for the positive stool cultures. In our case; pneumonia was complicated with encysted empyema. Therefore, antibiotic therapy should be initiated immediately with sufficient duration of treatment and in accordance to antibiotic resistance. Recommended antibiotics are third generation cephalosporins, trimethoprim-sulfamethoxazole, ampicillin or fluoroquinolones [18]. Pleural empyema or abscess usually requires surgical drainage in addition to the antimicrobial therapy. In our case, after completing a course of antimicrobial therapy, the patient improved without the need for surgical drainage [19]. Multidrug resistance does not represent a serious problem among non-typhoidal Salmonella serotypes [20].

When reviewing similar cases of pulmonary Salmonellosis, we did not find any previously reported case from the kingdom of Bahrain. There were few cases reported during the last century. Table 1 summarizes adult cases while table 2 summarizes pediatric cases. Although most of the reported cases were associated with immune suppression; however, some cases were immunocompetent. Thapa et al. described an 11-year-old immunocompetent girl with Salmonella group B spp with lung abscess and thrombocytopenia [21] while Adhisivam et al. described Salmonella spp. as the primary cause of lung abscess in an immunocompetent, five-year-old otherwise-healthy girl, who had a cough associated with respiratory distress of five months’ duration and finger clubbing secondary to a solitary lung abscess in the right lower zone [22]. Yet, previous lung abnormalities may be a reason for Salmonella pulmonary involvement. Aslam et al. described a 12-year-old girl with a pulmonary hydatid cyst infected with S. typhi. She presented with hemoptysis, fever and weight loss. She was initially diagnosed and treated for presumed tuberculosis and lung abscess. Salmonella typhi was isolated from the abscess. The hydatid cyst was diagnosed at the time of surgery [23].

Conclusion

Despite pulmonary salmonellosis being a rare infection; it should be considered in any immunocompromised patient with symptoms of pneumonia. Such patients should be treated aggressively because of high morbidity and mortality rate. Increased awareness about this atypical presentation of Salmonella enterica is crucial to start timely laboratory diagnosis and treatment.

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