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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/mm^3 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

Salmonellae 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 non-typhoid *Salmonella* via the reticulo-endothelial 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.* 1956 [24]	18 years	Male	Competent	Lung abscess	*S. enterica* serotype Typhi	Rt. Pleural Empyema	Chloramphenicol + Thoracocentesis, open drainage, thoracoplasty	Improved
Rao & Sattar. 1967 [25]	30 years	Male	Competent	Enteric fever	*S. enterica* serotype Typhi	Lt. Pleural effusion	Chloramphenicol + Closed thoracic drainage	Improved
Annamalai *et al.* 1969 [26]	47 years	Male	Competent	Healthy plumber	*S. Paratyphi* B	Rt. Pleural Empyema	Chloramphenicol + Thoracocentesis	Improved
Galazka *et al.* 1972 [27]	Middle aged	female	compromised	mediastinal tumor	*S. enterica* serotype Typhi	Pleural Empyema		
Carel *et al.* 1977 [28]	60 years	Male	compromised	metastatic thyroid cancer	*S blockley*.	Unilateral malignant pleural effusion	Intrapleural administration of antibiotics	Improved
Buscaglia AJ. 1978 [29]	21 years	Female	Competent	splenic abscess	*S. enteritidis* serotype Newport	Empyema		
Reiss-Levy *et al.* 1980 [30]	51 years	Male	compromised	Previous rectal surgery	*Salmonella* Typhimurium	pulmonary cavitation and mycetoma	Antibiotic treatment	Chronic pulmonary infection
Saitoh *et al.* 1982 [31]	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 [32]	Adult	Male	Competent	Typhoid fever	*S. enterica* serotype Typhi	pleural effusion	Pleural drainage + Antibiotic treatment	Improved
Cistulli *et al.* 1991 [33]	Adult	Male	compromised	non-Hodgkin's lymphoma		Empyema	Antibiotics and surgery.	Improved
Sharma *et al.* 1992 [34]	19 years	Male	Competent	Associated typhoid fever	*Salmonella* Typhi	Rt. lower lobe pneumonia	Treatment with chloramphenicol	Improved
	43 years	Male	compromised	Previously treated from TB; Kabosi sarcoma associated typhoid fever	*Salmonella* Typhi	Bronchopneumonia		
Colebunders *et al.* 1995 [35]	20 years	Male	compromised	HIV and Kapoci Sarcoma	*Salmonella* Typhimurium	Bilateral Empyema	IV & oral ciprofloxacin	Improved
Yassine *et al.* 1995 [36]	25 years	Male	Competent	splenic abscess	*Salmonella* Typhi	left empyema	Antibiotic therapy with Cotrimoxazole, repeated pleural aspirates and physiotherapy,	Improved
Gill & Holden. 1996 [37]	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 [38]	28 years	Male	compromised	HIV-infection	*Salmonella* Typhimurium	Bilateral multiple cavitary lesions	ceftriaxone/ciprofloxacin	Improved
Ridha *et al.* 1996 [39]	49 years	Male	compromised	HIV-infected	*Salmonella* Tphimurium	Right upper lobe lung abscess	Ciprofloxacin treatment	Improved
Casado *et al.* 1997 [10]	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 3 cases had *Salmonella* Typhimurium	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 Nocradia asteroides
Wolday *et al.* 1997 [40]	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 [41]	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 [42]	70 years	Female	competent	Diabetes II	*Salmonella* group B	Empyema	Antimicrobial therapy and repeated therapeutic thoracocentesis	Improved
Ramanathan *et al.* 2000 [43]	50 years	Male	competent	Farmer	*S.* Senftenberg	Left Pleural Empyema	Antibiotic treatment + Intercostal tube drainage	Improved
	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.* 2003 [9]	72 years	Male	compromised	lung cancer	*Salmonella enterica* serotype Enteritidis	Pneumonia	Antibiotic treatment	Died
Mishra *et al*. 2004 [44]	35 years	Male	competent	No	*Salmonella* Typhi	Left hydropneumothorax		
Kömüs *et al.* 2005 [45]	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 [46]	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.* 2012 [19]	83 years	Male	compromised	Diabetes	*Salmonella enterica* serotype Typhi	Pleural Empyema	Antimicrobial treatment	Improved
Kam *et al.* 2012 [4]	66 years	Female	compromised	Diabetes + Smoking-induced Lung pathology	*Salmonella* group D	Pleural Empyema	Decortication + Antimicrobial treatment	Improved
Nale *et al*. 2013 [47]	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 [48]	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

Table 2. Reported studies in children with pulmonary salmonellosis

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		
Caksen *et al.* 2000 [53]	12 years	Male	competent	hepatosplenomegaly and severe anemia	S. typhi.	Pleural Empyema	Percutaneous drainage with ultrasonography and antibiotics	Improved
Eaton *et al.* 2002 [54]	4 years	Female	compromised	HIV-infected	S. typhimurium	Pneumonia		
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]		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 fluoro-quinolones [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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