

Salmonella enteritidis Concurrent Spinal Epidural Abscess, Urinary Tract Infection and Endocarditis in an Immunocompetent Host: Case Report and a Review of the Literature

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Abstract

We present a discussion of a rare case of *Salmonella* non-typhi epidural abscess in an immunocompetent patient without any risk factors with the finding of concurrent mitral valve endocarditis and urinary tract infection. Non-typhoidal salmonella is a reportable food-borne illness which typically presents as a gastrointestinal infection. In immunocompetent individuals, *Salmonella* infections are often subclinical and almost always self-limited. 5% of non-typhoidal infections progress to a systemic infection from a nonspecific febrile illness often associated with a disseminated bacteremia and metastatic foci of infection with the development of a *Salmonella* arthritis, urinary tract infection, infection of the central nervous system, bone infection, soft tissue infection. Our case illustrates that *Salmonella enteritidis* can cause a significant disseminated infection even in the absence of any predisposing factor (if the host is overwhelmed with a high bacterial load).

Keywords: *Salmonella enteritidis*; Immunocompetent host; Food borne infection; Disseminated infection

Introduction

A 54-year-old African American woman with a no medical history, presented with confusion and progressive weakness for 5 days. Her initial symptom was lower back pain which radiated down her right leg, associated with paresthesias and progressive difficulty standing. She presented to an outpatient clinic where she was given oral and intramuscular pain medications, cyclobenzaprine and a steroid taper for 'acute' worsening of pain that was thought to be related to a motor vehicle accident 10 years prior. With continued and rapid worsening of the pain (only after one dose of prednisone), and the development of confusion with a loss of bowel and bladder control the next day, she was brought into the emergency room. She was noted to be febrile (fever of 102 F). She was normotensive but tachycardic. Notable laboratory results included a white blood cell count of 9.9 K/microliter with 3% bands, a urine analysis with 51-100 white blood cells, mild kidney injury (creatinine of 1.4), the procalcitonin was significantly elevated (10.7 ng/ml) and she had a mild elevation of her transaminases (AST 61 and ALS 68). After she was started on empiric antibiotics (ceftriaxone and vancomycin) a CT head was performed which was unremarkable. She was then sent to interventional radiology for a lumbar puncture after an unsuccessful bedside attempt was made. After several additional attempts were made at obtaining

cerebrospinal fluid without success (described as a dry tap), contrast was injected into the thecal sac and it was noted that the epidural space had collapsed. An urgent MRI of the lumbar spine revealed a heterogeneously T2 hyper intense dorsal epidural collection from the inferior T12-L3 levels, measuring 6 mm in AP thickness at the L2-L3 level associated with constriction of the thecal sac and complete effacement of CSF at the L1-L3 levels. Linear peripheral enhancement and dural enhancement was also noted (Figure 1 and 2).



Figure 1: Sagittal T1 weighted image.



Figure 2: T2 weighted image.

At the time the MRI results were made available, all the blood cultures were reported a positive for gram negative rods. She urgently underwent right L1-2, L2-3, and L3-4 hemilaminotomies with an evacuation of the epidural collection with a significant pocket of purulent material was also found at the L3-L4 facet joint with concerns for a septic arthritis (Figure 3).

A heterogeneously T2 hyper intense dorsal epidural collection with linear rim enhancement is present from the inferior T12-L3 levels, measuring roughly 6 mm in AP thickness at the L2-L3 level. Associated constriction of the thecal sac with complete effacement of CSF at the L1-L3 levels.

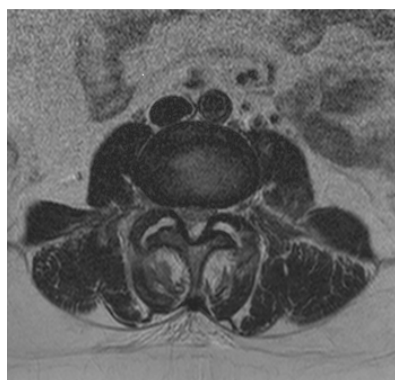


Figure 3: Axial T2 image showing increased T2 signal in the facet joints at L3-L4 compatible with septic facet arthritis. This demonstrates that the epidural abscess possibly started as septic facet arthritis.

Intra-op gram staining also revealed gram-negative rods. The blood, epidural fluid and urine cultures subsequently revealed a pan-sensitive *Salmonella enteritidis* non-typhi confirming a *Salmonella enteritidis* epidural abscess. The patient had a negative screen for sickle cell and other possible rheumatologic. HIV was negative. Due to the significant

bacteremia and seeding, concern was voiced for an endovascular infection. A transesophageal echocardiogram was performed (after a negative transthoracic study) and a 3 mm sessile lesion was seen on the anterior mitral leaflet suggestive of vegetation without valve damage or leak (Figure 4).

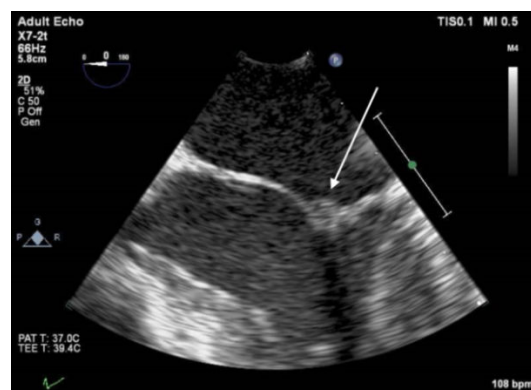


Figure 4: Sessile lesion on the anterior leaflet of the mitral valve. No mitral regurgitation or leaflet perforation was noted.

Given that the blood cultures cleared on antibiotics and the patient improved significantly with resolution of her altered mental status and regained strength in her lower extremities, a decision was made to proceed with medical management, in the absence of any valve abnormality. The antibiotic regimen was modified to ceftriaxone 2 gm q12 for 6 weeks (from the last negative blood culture) followed by the initiation of ciprofloxacin 500 mg p.o. twice a day for an unspecified subsequent duration.

Discussion

Non-typhoidal salmonella is a reportable food-borne illness which typically presents as a gastrointestinal infection, most often self-limiting. It is second only to campylobacter for the most commonly isolated bacteria in diarrheal illness [1]. In the late 1990s, *S. typhimurium* serogroup B and *Salmonella enteritidis* serogroup D were the most frequently isolated serotypes, accounting for approximately 50% of isolates from patients in the United States [1]. Nontyphoidal *Salmonella* serovars cause five clinical patterns: gastrointestinal tract infection, enteric fever, bacteremia, local infection, and the chronic reservoir state. Transmitted most commonly by contaminated foods, the most noteworthy recent outbreaks of *Salmonella* infection have been linked to eggs, cheese, dry cereal, ice cream premix, a variety of fresh sprouts, juice, cantaloupes, and other fresh vegetables. 5% of non-typhoidal infections progress to a systemic infection from a nonspecific febrile illness often associated with a disseminated bacteremia and metastatic foci of infection with the development of a *Salmonella* arthritis, urinary tract infection, infection of the central nervous system, bone infection, soft tissue infection [1]. Bacteremia is more likely to occur in immunologically compromised patients (those patients with malignancy, HIV, diabetes, those receiving corticosteroids, or immunotherapy agents,) and these hosts are also more likely to develop focal infection [2]. To our knowledge, the incidence of nontyphoidal salmonella bacteremia is rare in the immunocompetent host. In immunocompetent individuals, *Salmonella* infections are often subclinical and almost always self-

limited. In the immunocompromised hosts, nontyphoidal *Salmonella* infections are associated with suppurative foci and primary bacteremic disease, which may be recurrent, up to 43%, and more severe on presentation [3,4]. A meta-analysis from 2010 reported an overall incidence of 49 cases per 100,000 population with the greatest incidence in Africa, which included patients with HIV, malaria, and children under the age of 5 years old [5]. A study from Japan which included 35 patients over a nine year period found that extremes of ages <6 years old and >60 years old may be an additional risk factor for non-typhoidal salmonella infections [6]. Our case is unique in that our patient was neither immunocompromised, nor extreme of age. In addition, our patient did not report any notable gastrointestinal symptoms. In retrospect, the patient recalled that, as part of a new diet, she was eating large amounts of spinach for several weeks prior to her illness. The presumed increased bacterial load from ingesting large amounts of contaminated spinach, which otherwise would have been destroyed by the bodies innate defenses, typically intact and effective in an immunocompetent host, may have been overwhelmed and hence leading to a systemic infection.

Salmonella Epidural Abscess

Central nervous system involvement with *Salmonella* infection occurs in 3–35% of patients. Encephalopathy, seizures, meningitis (12%) [7,8] transient Parkinsonism, ataxia [9] motor neuron disorders, cerebral abscesses [10] cerebral edema [11] are all central nervous system manifestations of this infection. Guillain-Barre syndrome has also been described in association with *Salmonella* [12] Endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, ventriculitis, trauma and surgery have been described as risk factors for the involvement of the central nervous system although several cases of CNS involvement without any reported risk factors [13]. These patients often present with fever, followed by headache, vomiting, seizures, altered mentation, papilledema, and focal neurological deficits [14,15]. Neuroimaging with magnetic resonance imaging (MRI), computed tomography (CT), angiography, and/or radionuclide scans may be helpful, especially with focal central nervous system lesions such as subdural and epidural empyemas [16] and brain abscesses [16]. Electroencephalogram and cerebrospinal fluid studies, although usually abnormal, are often not diagnostic [17]. Spinal epidural abscesses are exceedingly rare, reported in 0.2 and 2 cases per 100,000 admitted to the hospital [18] and are often difficult to recognize early. More common causative organisms include *Staphylococcus aureus* amongst the gram positives, and less commonly *Escherichia coli* and *Pseudomonas aeruginosa* amongst the most common gram-negative organisms. In a prominent review, *Salmonella* vertebral osteomyelitis carried a bimodal age distribution, with one peak occurring at ages 10–19 years and the other peak occurring at ages 60–69 years. There was a male preponderance, with a 1.7:1 distribution. Diabetes, alcoholism, intravenous drug abuse, a history of spinal anesthesia and other causes of immunosuppression predispose to the development of an epidural abscess. 54% of cases in this review carried a predisposing condition for the development of the focal infection; however 46% did not have any risk factor. Back pain was the most common presenting symptom. The lumbar vertebrae were involved in 50% of time while the thoracic vertebrae were involved in 20% of cases [19]. Vertebral osteomyelitis primarily occurs via hematogenous seeding, either from transient bacteremia or from a distant focus of infection, and most commonly infects the lumbar spine as just described [20–22]. This predisposition may be a consequence of the lymphatic and venous drainage of the lower

intestine. Imaging of the spine almost always reveals disease involving the intervertebral disc and its contiguous vertebrae; hence arterial passage of the bacteria is also plausible as the segmental arteries divide to supply the adjacent vertebrae.

Symptoms of an epidural abscess include focal lower back pain, often out of proportion to exam findings, sensory deficits, lower extremity weakness, and bowel/bladder incontinence, although may not be present on initial presentation, can evolve later on depending on the degree of involvement and severity and location of compression. In our case, the unusual finding of multiple unsuccessful lumbar puncture attempt resulting only in 'dry taps' despite visualization of the needed in the epidural space, lead to the realization that the thecal sac had collapsed due to a dorsal epidural collection, which was causing a disruption in flow of the cerebrospinal fluid. This has been reported before during a dry spinal anesthesia procedure [23]. Imaging plays an important role in the diagnosis of an abscess. MRI is more sensitive than CT as an imaging modality for infective spondylitis. Low signal intensity on T1WI and high signal intensity on T2WI are shown as the typical pattern on MRI. Nevertheless, negative MRI findings during the initial period of disease have been reported such a case reported a patient with positive *Salmonella enteritidis* blood cultures and a normal initial MRI who underwent a subsequent MRI to work up recurrent fevers and positive blood cultures with *Salmonella* after completing a course of ceftriaxone. There was an increase in signal in the L5-S1 area however with a negative needle biopsy of L5. A third MRI was performed when he developed bowel and urinary incontinence with worsening in the back pain which showed a small epidural collection which was subsequently drained. Although the cultures were negative from the fluid collection, but the patient improved clinically, with resolution of his fever. A high index of suspicion is needed to repeat an initially negative MRI, but in the setting of persistent focal symptoms and fevers should warrant repeat imaging [23]. The role of a repeat MRI after diagnosing and treating the epidural abscess however in minimal as subsequent MRI findings do not concur with the improvement of clinical symptoms. Hence, MRI's usefulness is low for following the recovery and is not recommended.

Drainage of the abscess, a surgical emergency in the setting of progressive neurologic symptoms, is the cornerstone of treatment along with antibiotic therapy (details below). Only one case of salmonella typhi epidural abscess has been reported to have been managed conservatively with antibiotics (ciprofloxacin 500 mg twice daily for 5 weeks) [24]. This case involved no neurologic deficits however.

Salmonella Endocarditis

Salmonellae have the unique propensity to adhere to damaged endothelium, which may explain why *Salmonella* species are the gram-negative bacteria most likely to produce valvular infection and endarteritis in patients with preexisting atherosclerotic aneurysms [25,26]. A classic study from 1978 found that 25% of adults over 50 years of age with salmonella bacteremia, developed arteritis or endocarditis [27]. *Salmonella* valvular disease has been reported to be aggressive and destructive to the valve, frequently requiring replacement. In a review of non typhoidal salmonella endocarditis, previously existing structural valvular disease predisposes to infection and often with involvement of two sites (the second site often being endocardial) [28]. *Salmonella choleraesuis*, frequently associated with bacteremia and also considered to be the most virulent of the

Salmonella subtypes, is found to have a particularly poor prognosis due to its propensity to cause significant destruction of the endovascular tissue often leading to rapid cardiac decompensation. It is also the most common serotype associated with a salmonella endovascular infection. *Salmonella typhimurium* and enteritidis endocarditis have also been described [29]. In almost all cases however, either a preexisting valvular or endocardial abnormality was noted or an immunocompromised state, such as HIV. *Salmonella* endocarditis but can be occasionally treated medically in the absence of significant damage to the valve. In one such case, the patient was also fortunate to have a sensitive salmonella species as resistant strains are being reported more frequently since the 1990's [1]. Our patient presented with largely neurologic symptoms, without hemodynamic compromise or abnormality on cardiac examination or on the transthoracic echocardiogram. Further investigation was pursued due to the knowledge that *Salmonella* species carries a propensity of causing endocarditis and we knew that the patient had developed positive blood cultures very early (within 24 hours) with additional seeding the urinary tract (positive *Salmonella enteritidis* urinary cultures). The transesophageal echocardiogram performed soon after the initial negative transthoracic image revealed the sessile lesion which otherwise would have been missed. The frequently destructive course of *Salmonella* endocarditis requires valve replacement. Medical therapy alone for both native and prosthetic-valve involvement has been reported with successful long-term outcomes and survival and hence arguably may be offered in select cases in which there is no hemodynamic instability and for whom surgery is not otherwise possible [29].

Other Rare Sites of *Salmonella* Infection

Salmonella has also been reported in the literature to infect several other sites. The incidence of pulmonary infections with *Salmonella enteritidis* has been also rarely reported. Xaplanteri et al. [30] reported an unusual case of an immunocompetent 81 year old woman who developed a *Salmonella* bacteremia, without gastrointestinal symptoms, with presumed seeding of a pleural effusion, thought to be present secondary to congestive heart failure, and the subsequent development of a culture proven *Salmonella enteritidis* empyema. The empyema was treated by draining the infected fluid with a chest tube, and antibiotics (ceftriaxone followed by ciprofloxacin) for 10 days. Bastin et al. [31] reported also a case of an immunocompetent 33-year-old male with septic shock and acute renal failure secondary to broncho alveolar lavage culture proven *S. enteritidis* pneumonia. A computed tomography (CT) of his abdomen revealed diffuse edema in the rectum, colon, and small bowel prior to the onset of respiratory distress, blood cultures were negative, and the ensuing pneumonia was likely a result of seeding of the lungs secondary to aspiration. Only four other cases of *S. enteritidis* pneumonia in an immunocompetent host have been reported, all from the development of *S. enteritidis* bacteremia from the consumption of contaminated food [32-34]. *Salmonella enteritidis* bacteremia leading to pulmonary infection is rare (Mandell et al.) [35] especially in an immunocompetent host and is regarded to be less than 1% with a presumed tropism for abnormal tissues once in the blood stream, as was likely the case reported by Xaplanteri et al. [30] (pleural effusion secondary to congestive heart failure) and Samons et al. [34] (lung cancer). In our case, the development of an epidural abscess may have been due to a seeding after the development of a *Salmonella enteritidis* bacteremia to an unrecognized back injury as a result of the remote motor vehicle accident.

Treatment

The primary treatment of *Salmonella enteritidis* epidural abscess is antibiotics and drainage of the fluid. Surgical interventions are particularly important in cases where there is osseous instability, neurological deficits, and clinical unresponsiveness to antibiotics, refractory infection and the failure of biopsy to provide a firm diagnosis in the presence of suspicious MRI findings. Antibiotics that have been used for *Salmonella* epidural infections include fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMZ), ampicillin, and third-generation cephalosporins. Since resistance to TMP-SMZ and ampicillin is now common, the use of a third-generation cephalosporin or quinolone is preferred. In the 1990s, clinical isolates studied at the CDC showed increasing resistance to ampicillin, chloramphenicol, and TMP-SMZ. This may possibly due to the changing sensitivities of the offending organism secondary to transferred antimicrobial resistance [36]. Antimicrobial resistances have been increasing among *Salmonella* worldwide and are likely associated with the agricultural use of antimicrobial agents [37]. Useful alternative antibiotics that may be considered include azithromycin and aztreonam, primarily if there is a concern for drug resistance or a known allergy to the first line antibiotics. Treatment of *Salmonella* bacteremia is generally undertaken with a single bactericidal drug, however, given the resistance trends, life-threatening infections should initially be treated with dual therapy, both a third-generation cephalosporin and a fluoroquinolone until the susceptibilities of antimicrobial agents become available [1]. Generally, a minimum of 4 weeks of antibiotics should be used however, the exact length of therapy is still debatable and should also take into consideration the extent of the infection and also possibly implement improvement of the clinical symptoms and reduction of the C-reactive protein values to gauge treatment response.

When dealing with an endocarditis or an endovascular *Salmonella* infection, antimicrobial therapy should be continued for a minimum of 6 weeks if surgical intervention was included as part of the treatment plan. There may however also be a role for short versus long term suppressive therapy. Lifelong suppressive antimicrobial therapy should be a serious consideration in cases where residual organisms are an expectation (e.g., infected grafts or devices that have not been removed, when surgery for an abscess or endocarditis is not possible, and for *Salmonella* osteomyelitis and joint involvement). For any suggestion of meningitic or deep CNS involvement, high-dose ceftriaxone, as used with other CNS infections, would be the best choice for optimal penetration of the blood-brain barrier.

The National Committee for Clinical Laboratory Standards defines "sensitive" *Salmonella* species as those for which MICs of fluoroquinolone are <1-2 mg/mL and those for which MICs of ceftriaxone are <8 mg/mL. When looking at average serum levels of fluoroquinolones (4-6 mg/mL), and meningitis doses of ceftriaxone (200-250 mg/mL) although most susceptible *Salmonella* species have MICs that are low (usually 20-100-fold lower than what has been defined) the higher serum levels to minimum bacterial concentrations ratios achieved by cephalosporins may favor the use of cephalosporins for the elimination of infection within vegetation's or devitalized tissue. Fluoroquinolones however have been shown to result in quick clinical responses and possibly more long lasting responses than cephalosporins. This may be due to its greater penetration of the host's phagocytic cells from which the organism disseminates the infection into the blood stream from the gastrointestinal tract [38,39]. The daily or twice-daily oral dosing of the fluoroquinolones and their safety/

tolerability make them ideal for suppressive therapy in many instances. The individual advantages held by both these antibiotics may advocate the preferred use of b-lactams when initially treating a salmonella species infection, followed by a longer term, or as previously discussed, lifelong therapy with an oral fluoroquinolone. Of note, there are no published clinical data that suggest that combination therapy, once susceptibilities are established, is more effective than either single agent.

One needs to note also that ceftriaxone treatment may be associated with neutropenia. Current literature has reported ceftriaxone-associated agranulocytosis with standard doses during parenteral antibiotic therapy [40-43]. Becq-Giraudon et al. described a case of a 75-year-old man being treated for pneumococcal septicemia who developed an acute transient agranulocytosis after he had received 36 g ceftriaxone which resolved following discontinuation of the cefalosporin. The pathogenesis of ceftriaxone-induced agranulocytosis remains uncertain, and it is suggested to occur either by an immunologic mechanism or as a result of toxicity. One review of the literature in which the clinical findings and bone marrow histology in the 14 cases were investigated, favored an immunologic mechanism over drug toxicity in many instances [43]. In the same review, the mean time to recognition of neutropenia was 23 days (standard deviation \pm 14; median, 21 days; range, 5-49 days). In view of these data, blood counts should be monitored in patients receiving prolonged courses of ceftriaxone.

Conclusion

Our case illustrates that *Salmonella enteritidis* can cause a significant disseminated infection even in the absence of any predisposing factor (if the host is overwhelmed with a high bacterial load) and with the lack of gastrointestinal symptoms. When evaluating and treating a case with salmonella bacteremia, it is reasonable to look for multiple foci of local infection, as concurrent spinal epidural abscess, urinary tract infection and endocarditis has been demonstrated here with a recommendation to proceed to a transesophageal echocardiogram if initial evaluation is negative is significant bacteremia. Endocarditis may be especially important to rule out due to its destructive nature and the propensity of this organism to adhere to damaged endovascular tissue (and possibly healthy tissue) and cause infection. Imaging of the spine should be pursued and repeated if there are the presence or development of neurologic symptoms. Treatment should initially include a third generation cephalosporin (especially if the infection is endovascular or involving the CNS), with dual therapy (addition of a fluoroquinolone) if the patient is critically ill, pending susceptibilities of the organism. Although optimal length of treatment is debatable (4-6 weeks), decisions may be made based on clinical improvement with longer, possibly lifelong suppressive therapies (with a fluoroquinolone) advocated for patients that are likely to harbor persistent organisms due to the presence of devitalized tissue or in cases where only non-surgical therapies could be offered.

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