Salmonella Induced Aortic Aneurysm, A Case Study

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Abstract

Salmonella are Gram-negative, rod-shaped bacteria that are common in warm-blooded animals and can cause disease in humans. Non-typhoidal Salmonellae are a leading cause of bacterial diarrhea worldwide. Non-typhoidal Salmonella infections are usually restricted to the gastrointestinal tract and spontaneously resolve but can develop into invasive infections like bacteremia. The clinical course of non-typhoidal Salmonella bacteremia may be affected by age, immunosuppression and other factors. Serious disease can result, especially in debilitated, elderly patients and neonates. This is a case study of a 76-year-old female who arrived in the emergency department of a large acute care hospital with fever, diarrhea, vomiting and signs of dehydration. Blood cultures were positive for Gram-negative rods identified as non-typhoidal Salmonella Group D and the patient was treated with antibiotic therapy. Low-grade fever continued, and, over a period of two weeks in the hospital, an abdominal aortic aneurysm developed and ruptured causing the patient's death. The purpose of this case study is to alert medical professionals to the possibility of mycotic or infectious aortitis as a rare but lifethreatening result of Salmonella bacteremia that can lead to aortic aneurysm. If not properly treated with a combination of intensive antibiotic therapy and surgical debridement, with aneurysm repair if necessary, it has a high rate of aortic rupture and death. In this case of Salmonella induced aortic aneurysm, the possibilty of aortic aneurysm was not anticipated, and when found, not treated surgically leading to a ortic rupture and death of the patient.

Index Terms

Abdominal aortic aneurysm, aortitis, bacteremia, mycotic (infected) aneurysm, Salmonella

Abbreviations

bmp = beats per minute; CBC = complete blood count; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CVA = costovertebral angle; ED = emergency department; EKG = electrocardiogram; EVAR = endovascular aneurysm repair; °F = degrees Fahrenheit; g/dL = grams per deciliter; HCT = hematocrit; HGB = hemoglobin; ICU = Intensive Care Unit; IV = intravenous; /L = per liter; MDS = myelodysplastic syndromes; mEq/L = milliequivalents per liter; N = normal; NG = nasogastric; NTS = non-typhoidal *Salmonella*; S1 = first heart sound; S2 = second heart sound; μ L = microliter; US = ultrasound; WBC = white blood cell count

Introduction

Overview

A 76-year-old female with a history of myelodysplastic syndrome (MDS) arrived in the emergency department (ED) of a large acute care hospital complaining of diarrhea, vomiting and fever of 2-day duration. The patient was admitted with presumed dehydration. Subsequent blood cultures revealed non-typhoidal *Salmonella* Group D which was treated with intravenous (IV) antibiotics. Fever persisted, and back pain developed. On day 12, a computed tomography (CT) scan revealed a very large sacular abdominal aortic aneurysm without evidence of leakage. This contrasted with an abdominal X-ray on admission that found the abdominal aorta calcified but not aneurysmal. The patient had an event of syncope on day 16 and hemoglobin and hematocrit were found to be low. The patient was transferred to the medical intensive care unit due to hypotension and apparent blood loss. She was transfused with three units of packed red cells. The patient expired the next morning following presumed rupture of the abdominal aortic aneurysm.

Salmonella are Gram-negative, rod-shaped bacteria that are common in warm-blooded animals and can cause disease in humans. Non-typhoidal Salmonella usually causes mild gastrointestinal disease that resolves spontaneously, but it can cause invasive infection, especially in debilitated, older patients. In these patients, bacteremia can lead to aortitis with mycotic aortic aneurysm. Mycotic aneurysm is rare but severe and develops rapidly. Aortic rupture frequently follows

unless disease is recognized early and treated properly. The incidence of mycotic aneurysm rupture is greater than arteriosclerotic aneurysm and has a higher mortality rate. Early diagnosis and proper treatment (antibiotic and surgical treatment with adequate dosage and duration) improve survival. In western countries, about 0.5 - 1.3% of aneurysms are of bacterial origin with *Salmonella* infection second only to *Staphylococcus aureus*. The average age of 53 reported cases in the literature was 65.13 years; 79.2% of the patients were males. Most patients have other co-morbidities such as hypertension, diabetes, atherosclerosis, immunodeficiency, chronic kidney disease and smoking. They present with recurrent fever, diarrhea for 2 days to a month prior to aneurysm diagnosis, back and/or chest pain, and/or shock with rupture. Lab exam usually shows an increased white blood cell count with neutrophilia and an increase in inflammatory markers such as C-reactive protein or erythrocyte sedimentation rate. Most patients have at least one blood culture positive for *Salmonella* and most aneurysms are in the abdominal aorta below the level of the renal artery.

If targeted antibiotic therapy occurs before an aneurysm forms, mortality may be as low as 25%. If aneurysmal rupture occurs, mortality can exceed 65%. Historically, with medical treatment alone, mortality may reach 100%; therefore, treatment should involve targeted antibiotic therapy and surgical replacement of the infected aorta. While conventional open surgery, with resection of the infectious aneurysm, extensive local debridement and revascularization was regarded as the gold standard, there has recently been a shift towards endovascular aneurysm repair (EVAR) as an alternative to open surgery, but persistent infection requiring prolonged antibiotic therapy remains a problem with EVAR.

This case presentation will track the patient's progress over 17 days from entrance into the ED with fever, diarrhea and vomiting to the development of a *Salmonella* induced aortic aneurysm that was not surgically treated and resulted in aortic rupture and death of the patient. Had surgical intervention taken place when the aneurysm was discovered, perhaps the outcome would have been favorable. The case highlights the crucial role the laboratory plays in the diagnosis and treatment of *Salmonella* bacteremia induced aortic aneurysm.

Salmonella

Salmonella infection is still a major problem in public health. Salmonella are Gram-negative, rod-shaped bacteria that are common in warm-blooded animals and can cause illness in humans. Excluding S. typhi and S. paratyphi, Salmonella infections are usually restricted to the gastrointestinal tract and resolve spontaneously, but infections at other sites may occur. Acute gastroenteritis commonly produces fever, diarrhea, vomiting, crampy abdominal pain, and lethargy. Gastroenteritis due to non-typhoidal Salmonella effects approximately 30 persons per one million annually and transient bacteremia may be present in about 10% of these patients. The clinical course, however, may be affected by age, immunosuppression, and other factors creating a more severe presentation in debilitated, elderly patients and neonates. In one study, researchers found two peaks for bacteremia: between 0 and 3 months of age (23.8%) and greater than 65 years of age (29.6%). The bacteremia may cause localized extravascular infections such as septic arthritis, osteomyelitis, meningitis, and pleuropulmonary, renal, splenic or cardiovascular infections. Although the cardiovascular system is a typical, yet rare, site for non-

typhoidal *Salmonella* infection, it is one of the most common causes of primary mycotic aneurysm. ^{4,6}

Non-typhoidal *Salmonella* (NTS) bacteremia is caused by particularly virulent organisms that, in adults, should be considered life-threatening as an increased mortality has been reported. Affected patients usually have underlying diseases. A study in Taiwan reported solid organ malignancy, age, and extraintestinal infection as independent predictors for in-hospital death due to NTS bacteremia. A retrospective study was conducted in a large university-based hospital over a 10-year period with a total of 204 patients with NTS bacteremia. Of these patients, 36.2% had underlying medical illnesses (solid organ malignancy or hematologic malignancy). The inhospital mortality rate was 26.0% with 13.2% not surviving for 14 days. A study in Malaysia of 55 cases of NTS bacteremia found serogroup D to be the most common cause and to demonstrate the highest degree of blood invasiveness.

Salmonella Associated Aortic Aneurysm

Aortitis is a general term denoting inflammation of the aorta most commonly associated with rheumatologic diseases. Mycotic or infectious aortitis is a rare but potentially life-threatening disorder. Infectious causes include tuberculosis, syphilis, and other bacteria, most commonly the *Salmonella* and *Staphylococcal* species, along with *Streptococcus pneumonia*. The main risk factors are older age (over 65 years), diabetes mellitus, liver cirrhosis and advanced atherosclerosis. Most cases of bacterial aortitis present in older individuals with a preexisting aortic pathology, such as atherosclerotic plaque or aneurysmal sac. *Salmonella* organisms are

particularly virulent pathogens with a predilection for diseased arterial walls and rarely infect healthy arterial intima, but they do have the ability to invade both undamaged intima and preexisting atherosclerotic lesions. ^{4,6} While the abdominal aorta is the most frequent site of vascular infection by *Salmonella*, peripheral and visceral arteries may also be affected. ⁴

The clinical presentation of aortitis varies, ranging from back or abdominal pain with fever to acute severe aortic insufficiency to an incidentally identified large thoracic aortic aneurysm. Bacteremia may or may not be present. Aortitis should be suspected in an older individual with atherosclerosis and bacteremia with sepsis due to a typical organism such as the Salmonella species. Infectious aortitis leading to mycotic aortic aneurysm is a fulminant infectious process frequently resulting in aortic rupture and subsequent death unless diagnosed early and treated properly. ^{4,9} In 1948, the first case of a fatal rupture of a *Salmonella* abdominal aortic aneurism was reported in a 69-year-old man by Dehlinger. The diagnosis is generally based on the classic features of fever, pain, pulsatile mass and positive blood cultures.⁴ The best diagnostic imaging techniques are Computed tomography (CT) and ultrasound (US) which are widely available in most medical centers and have been shown to be effective, non-invasive methods for the detection of established mycotic aneurysms. 4,8 CT allows for the rapid exclusion of aortic pathologies that may mimic acute aortitis and accurate assessment of stenotic lesions of the aorta and the presence and extent of aortic aneurysm or thrombus. Although diagnosis is generally based on clinical presentation and aortic imaging, laboratory testing plays a key role. Initial testing for suspected aortitis should include markers for inflammation, such as erythrocyte sedimentation rate and C-reactive protein, a complete blood count (CBC), kidney and liver functions tests, and blood cultures to exclude the rare but critical diagnosis of infectious aortitis.8

Infectious aortitis requires rapid diagnosis, antibiotic therapy and consultation with a vascular surgeon.8 Unexplained fever, back pain, pulsatile abdominal mass, and persistent bacteremia suggests the presence of an infectious abdominal aortic aneurysm. However, only 53% of patients with infected aortic aneurysm have a palpable abdominal mass, about 30% have back pain, and blood cultures are negative in about 30% of patients. Patients with suspected mycotic aneurysm should be treated with antibiotics immediately after blood samples for culture have been drawn.⁴ Initial treatment is intravenous antibiotics with broad antimicrobial coverage for the most likely organisms, particularly the *Staphylococcus* species and Gram-negative rods.⁸ Salmonella is one of the most common causes of infected aortic aneurysm. In Taiwan, 76% of patients with infected aortic aneurysms are infected with Salmonella. In Salmonella infections, the antibiotics of choice include third generation cephalosporins or new generation fluoroquinolones. It is important to note that fluoroquinolone-resistant Salmonella infections may be increasing.⁶ A combination of intensive antibiotic therapy and surgical debridement, with aneurysm repair if necessary, is generally recommended. 4,6,8,9 No studies have reported long-term survival in patients treated otherwise. 9 A very high mortality rate has been reported in patients treated with medical therapy alone because of the frequent presence of aneurysm rupture. 4,8,9 Three reports describe patients treated with antibiotics only and all three patients died. Only a small number of cases have been reported, and despite aggressive combined medical and endovascular management of mycotic aneurysm, mortality remains high, largely due to a high rate of aortic rupture.8

Myelodysplastic Syndromes (MDS)

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell diseases characterized by dysplasia, cytopenias, bone marrow hypercellularity, and ineffective hematopoiesis in one or more major myeloid cell lines. Between 50-70% of chromosome aberrations in MDS are monoclonal. Some are well characterized while some new recurrent aberrations are showing up with unique clinical and genetic features. Structural rearrangements of chromosome Xq are infrequent but non-random and include translocations, deletions and isodicentrics. Two cases of isolated deletion of Xq24 have been reported in the literature. 10

Acute leukemia and myelodysplastic syndrome can have life-threatening complications such as bleeding and sepsis frequently due to associated pancytopenia. Although mortality for these patients seems to have declined over the past twenty years, it is still very high. These patients, especially those requiring critical care, have an increased risk of bleeding and thrombosis. This risk increases in patients with sepsis. Lower platelet values appear to be a risk factor for bleeding.¹²

Case History

A 76-year-old female arrived in the Emergency Department of a 400-bed acute care hospital. Her daughter relayed that her mother was living alone and when she had spoken with her the previous evening, the patient complained of vomiting undigested food. When her daughter arrived the next morning, she found the patient speaking incoherently, lethargic and unable to walk without assistance. The patient had two bowel movements with non-bloody diarrhea. The

patient's history was significant for myelodysplasia being followed on an outpatient basis, hypothyroidism treated with levothyroxine, hypertension in the past but not on medication, chronic pulmonary obstructive disease (COPD) due to chronic smoking, and a benign meningioma. Surgical history included cholecystectomy and hernia repair. Temperature on arrival was 102.8 degrees Fahrenheit (°F), blood pressure 120/70 supine; 110/70 seated. Pulse was 82/beats per minute (bpm) supine; 86/bpm seated. Mucus membranes and tongue were dry. Chest exam showed good air entry bilaterally, no wheezing, and no evidence of consolidation. Heart exam showed first heart sound (S1) and second heart sound (S2), regular rate and rhythm, without murmur, rub or gallop present. Abdomen was soft with no costovertebral angle (CVA) tenderness observed. Fullness in the periumbilical area was palpated but ill defined. Neurological exam revealed the patient was fully conscious, responsive, alert, not agitated, and oriented to time, place and person. Her speech was not totally fluid but not dysarthric and had no focal abnormalities. The patient was admitted to the hospital for presumed dehydration with a fever and intravenous hydration was given. Stool was sent out for culture; blood cultures were ordered times three; and a CT scan of the head was ordered. Lab results showed a white blood cell count (WBC) of 6.1 X 10⁹ per liter (/L) with a left shift; hemoglobin (HGB) 12.9 grams per deciliter (g/dL); hematocrit (HCT) 36.8 %; and platelets were 57.0 X 10⁹/L. Potassium was 3.1 milliequivalents per liter (mEq/L) (3.7-5.1 mEq/L) on admission. An electrocardiogram (EKG) showed an unusual P-wave axis, possible ectopic atrial rhythm, and inferior infarct, age undetermined. When compared to a previous tracing three months prior, there was no significant change observed. Chest X-ray showed no acute disease, and lung fields were clear. There were compression abnormalities and multiple dorsal vertebral bodies. The compression abnormality in the upper vertebral body appeared to be sclerotic. Abdominal X-ray on admission revealed an

unremarkable gas pattern with no free intraperitoneal air or obstruction seen. The abdominal aorta was calcified and dilated but did not appear frankly aneurysmal. Compression abnormalities in the lower dorsal spine were seen. CT scan of the brain revealed a parenchymal loss and a 1.5 cm left parietal meningioma. On day 3, three out of three blood cultures grew Gram-negative rods and the patient was started on gentamicin and ceftazidime. The patient had no genitourinary symptoms, abdominal pain, or previous history of infection. She did report a penicillin allergy. Her treatment was changed to IV sulfamethoxazole/trimethoprim when the Gram-negative rods were determined to be Salmonella Group D. A radiological work-up was done to determine the source of the infection. Abdominal ultrasound, obtained on day 4, revealed an abdominal aorta that was heavily calcified and ectatic, but no aneurysmal dilatation was found. CT scan of the pelvis was negative. On day 11, the patient complained of back pain, continued to have a low-grade fever, and antibiotic therapy was continued. Treatment was switched to Ciprofloxacin intravenously because blood cultures continued to show Gramnegative rods, which proved to be Salmonella Group D sensitive to Ciprofloxacin. The patient had a CT scan of the abdomen on day 12, which revealed a very large sacular abdominal aortic aneurysm, not clearly infrarenal, which was displacing retroperitoneal structures but without evidence of leakage. There was no evidence of abdominal abscess. On day 12, the patient also had an echocardiogram performed. This did not reveal any vegetation but revealed a small, possible mildly hypertrophied, left ventricle with hyperdynamic local systolic function and probable abnormal diastolic function. The left ventricular filling pressure was increased, and this was suggestive of increased left ventricular compliance. The patient continued to have a fluctuating mental status, being vague and at times confused and disoriented, however, this tended to improve over her hospitalization. Thyroid function tests were within normal limits

when checked on day 12. Blood cultures obtained on day 14 were negative for Salmonella Group D. The patient had an event of syncope on day 16. Hemoglobin and hematocrit were ordered and found to be low (HGB 4.7 g/dL, HCT 14.5 g/dL). The patient was transferred to the medical intensive care unit (ICU) on the evening of day 16 due to hypotension and apparent blood loss. The patient was transfused with 3 units of packed red cells and the Ciprofloxacin was changed to cefotaxime. A hemolytic reaction, gastrointestinal bleeding and leakage of the abdominal aortic aneurysm were considered. The patient had an evaluation by the medical ICU resident, which revealed a negative rectal examination for occult blood as well as a nasogastric (NG) tube negative for blood in the intestinal tract. The patient had been started on ibuprofen several days prior to the episode of syncope and hypotension, and decrease in hemoglobin and hematocrit, which suggested a possible hemolytic reaction. The patient continued to be hemodynamically unstable during the night. By morning, she was unresponsive and underwent multiple intravenous pressor medications, but she remained hemodynamically unstable and went into cardiopulmonary arrest. The patient was intubated and suffered a final cardiopulmonary arrest 3 hours later. Respirations and heart rhythm ceased at 11:50 AM and the patient was pronounced dead at 12:05 PM. No postmortem examination was performed.

Discussion

Clinical laboratory testing played a critical role in the diagnosis and treatment of *Salmonella* Group D induced aortic aneurysm in this patient. Blood cultures on admission revealed Gramnegative rods and the patient was started on gentamycin and ceftazidime. When they were further identified as *Salmonella* Group D and sensitivities were reported, the antibiotic was

changed to IV sulfamethoxazole/trimethoprim. When blood cultures continued to grow Salmonella Group D organisms, the antibiotic was switched again to IV Ciprofloxin. On admission, lab results (Table 1) showed a WBC of 6.1 X 10⁹/L with a left shift; hemoglobin 12.9 g/dL; hematocrit 36.8 %; and platelets were 57.0 X 10⁹/L. These values were compared with a complete blood count one month earlier (Table 2) and with myelodysplasia, when the WBC was 2.5 X 10⁹/L, HGB 11.8 g/dL, HCT 35% and platelets 74.0 X 10⁹/L. The increase in WBC, HGB and HCT could be explained by dehydration due to vomiting and diarrhea. The increased WBC (though in the normal range was increased for this patient) could be further explained by infection. Thrombocytopenia was more pronounced and is known to be associated with severe bacterial infections. 13 Potassium was 3.1 mEq/L (N=3.7-5.1 mEq/L) on admission. Hypokalemia can also be explained by vomiting and diarrhea. Red blood cell counts demonstrated a steady decrease since admission, and hemoglobin and hematocrit levels dropped steadily also (see Table 1). This led doctors to look for bleeding and/or a hemolytic process. Normal thyroid function testing, Vitamin B12, and folic acid testing helped rule out other causes for anemia. Absolute neutrophilia developed over her hospital stay suggesting the infection was not under control. Erythrocyte sedimentation rate on day 14 was 70 (N=0-21) indicating inflammation was still apparent.

This patient had a classic case of Salmonella induced aortic aneurysm. In this patient's case, abdominal ultrasound, obtained on day 4 of hospitalization, revealed an abdominal aorta that was heavily calcified and ectatic, but no aneurysmal dilatation was found. The patient had a CT scan of the abdomen on day 12 to determine the focus of the infection because multiple blood cultures throughout her hospital stay revealed *Salmonella* Group D. The CT scan revealed a very large

sacular abdominal aortic aneurysm, which was displacing retroperitoneal structures but without evidence of leakage. The patient complained of back pain on day 11, a symptom which commonly presents in patients with mycotic aortic aneurysm. The rapid development of an aneurysm during the course of hospitalization, suggests that the aneurysm was formed by direct *Salmonella* infection of the artery. The patient case deteriorated quickly presenting with hypotension, syncope and apparent blood loss. Transfer to the medical intensive care unit, transfusion with 3 units of packed red cells, and reevaluation left the cause unknown.

Gastrointestinal bleeding, hemolytic reaction and leakage of the abdominal aortic aneurysm were considered. No aortic surgical repair was considered. The patient expired before the cause was determined.

This patient's case was complicated by myelodysplastic syndrome. Chromosome studies on the patient in this case revealed 14% of cells to be 46, X, del (X) (q24) and 86% normal 46, XX. This patient's MDS resulted in leukopenia (WBC 2.5 X 10^9 /L, normal (N) = 4.8-10.8 X 10^9 /L), anemia (HGB 11.8 g/dL, N = 12.0-16.0 g/dL, HCT 35.0%, N = 37.0-47.0 %), thrombocytopenia (74.0 X 10^9 /L, N = 120-450 X 10^9 /L) and neutropenia (780 per microliter (/ μ L), N = 2250-7500/ μ L), which was being followed on an outpatient basis (Table 2). Leukopenia, especially with neutropenia, creates an immunocompromised state that can lead to increased risk for serious infection. This patient presented with *Salmonella* Group D septicemia. Thrombocytopenia is associated with increased risk of excessive bleeding, possibly contributing to this patient's development of an aneurysm that began leaking with ultimate rupture and death of the patient.

In children, as well as elderly and immunocompromised patients, *Salmonella* would be phagocytized by macrophages but not killed. In the elderly, the macrophages carrying *Salmonella* are eventually located in the atheroma and lead to infection, followed by aortic aneurysm. When the focus of the infection is located inside the atheroma, it can cause a negative blood culture. This may explain why this patient's blood culture became negative on day 14 and escaped destruction by the antibiotic.

Mortality rate in patients treated with medical therapy alone is very high due to frequent aneurysm rupture. A combination of intensive antibiotic therapy and aneurysm repair are generally recommended. Despite aggressive treatment, mortality remains high; and in many cases, diagnosis is only made at autopsy. In summation, patients greater than 60 years of age with positive blood cultures for *Salmonella* presenting with fever and back, abdominal or chest pain should have an extensive work-up for mycotic aortic aneurysm.

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Table 2. Complete Blood Count (CBC) (1 month prior to hospital admission)

	Normal Range		
White Blood Cell	(4.8-10.8 x 10 ⁹ /L)	2.5(L)	
Red Blood Cell	$(4.2-5.4 \times 10^{12}/L)$	3.46(L)	
Hemoglobin	(12.0-16.0 g/dL)	11.8(L)	
Hematocrit	(37.0-47.0%)	35.0(L)	
Mean Corpuscular Volume	(81-99 fl)	97.0	
Mean Corpuscular Hemoglobin	(27-31 pg)	32.7(H)	
Mean Corpuscular Hemoglobin Concentration	(33-37%)	33.2	
Platelets	(120-450 x 10 ⁹ /L)	74.0(L)	
Reticulocytes	(0.5-1.5%)	1.1	
Red Cell Distribution Width	(11.8-15.6)	15.0	
Lymphocytes	(10-50%)	60.2(H)	
Mixed Cell	(1-15%)	9.4	
Neutrophils	(45-90%)	30.4(L)	
Absolute Lymphocytes	$(0.5-3.7 \times 10^9/L)$	1.6	
Absolute Mixed Cell	$(0.1-1.1 \times 10^9/L)$	0.2	
Absolute Neutrophils	(2.2-7.2 x 10 ⁹ /L)	0.8(L)	
Manual Differential			
Segmented Neutrophils		30	
Bands		1	
Lymphocytes		59	
Monocytes		9	
Basophils		1	

g/dL = grams per deciliter, fl = femtoliters, pg = picograms, /L = per liter(H) = high, (L) = low