



Case report

Nontyphoidal *Salmonella* purulent pericarditis presenting with pericardial tamponade in a patient on infliximab therapy

Kimberly Saddler^a, Miriams T Castro-Lainez^{b,*}, Rafael Deliz-Aguirre^c, Julieta Muñoz^d, Jorge Augusto Aguilar Espinal^d, Miguel Sierra-Hoffman^e, Harish Chandna^f, Alan Howel^g, John Midduri^g, Richard Winn^h

^a DeTar Healthcare System, 506 E San Antonio St, Victoria, TX, 77901, United States

^b Universidad Nacional Autónoma de Honduras, Facultad de Ciencias Médicas, Hospital Escuela Universitario, Boulevard Suyapa, Tegucigalpa, Honduras

^c Department of Biology & Chemistry, Texas A&M International University, 5201 University Blvd, Laredo, TX, 78045, United States

^d Loyola Medicine MacNeal Hospital, 3249 S Oak Park Ave Berwyn, IL, 60402, United States

^e Department of Infectious Disease, Citizens Medical Center, 2701 Hospital Dr, Victoria, TX 77901, United States

^f Department of Cardiology, DeTar Healthcare System, 506 E. San Antonio, Victoria, TX, 77901, United States

^g Baylor Scott & White Health- Temple, 2401 South 31st Street, Temple, TX, 76508, United States

^h Department of Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, 79430, United States

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ABSTRACT

Infection with nontyphoidal *Salmonella* is traditionally characterized by intestinal manifestations. However, extra-intestinal infections are known to occur, with purulent pericarditis associated with cardiac tamponade being rare. This case report is of a 57-year-old male with Crohn's disease initiated on infliximab therapy two months prior to presentation. He presented with recurrent chest pain and a single occurrence of fever. A Computed Tomography (CT) scan of the chest revealed a pericardial effusion. An echocardiogram confirmed the presence of the fluid with tamponade physiology, requiring immediate surgical decompression. The pericardial fluid culture grew *Salmonella enterica*, despite the patient having only a single episode of fever, disproportionate to the severity of the infection. Conceivably, the lack of systemic symptoms may be attributed to recent infliximab therapy. Upon conducting a literature review, immunosuppressive factors seem to play a significant role in nontyphoid *Salmonella enterica* pericardial effusion presenting with cardiac tamponade.

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Introduction

Nontyphoidal Salmonellosis is a common food-borne illness worldwide, usually presenting with acute diarrhea which typically resolves without treatment. We present a case of purulent pericarditis manifesting with pericardial tamponade due to nontyphoidal *Salmonella*. The pericardial fluid and stool cultures revealed nontyphoid *Salmonella*, despite no growth on blood cultures. Risk factor for development of *Salmonella* infection was Crohn's disease with a recent initiation of infliximab therapy.

Case Report

A 57-year-old Caucasian male with a past medical history of hypertension, hepatitis C, Crohn's disease, and Prinzmetal angina,

presented with recurrent chest pain, single episode of fever, general malaise, and diarrhea. The patient attributed his symptoms to his Crohn's disease. His immune status was compromised by his Crohn's disease treatments, infliximab that was recently started and azathioprine. The patient lives in a rural community, actively involved in poultry farming with significant exposure to several animals known to harbor *Salmonella* species, as well as ongoing alcohol and tobacco abuse. The patient also reported a remote history of cocaine abuse. Three weeks prior to admission, he presented with substernal chest pain meriting a coronary angiography revealing Prinzmetal angina without need for coronary angioplasty. His substernal chest pain recurred, prompting presentation to a rural hospital where a CT scan of the chest identified a large pericardial effusion, and he was transferred to our facility.

Upon initial physical exam, vitals revealed blood pressure of 90/60 mmHg, temperature of 36.8 °C (98.2 °F), tachycardia, respiratory rate of 26 breaths per minute and noted finding of dehydration upon oral mucosal examination. Laboratory data upon admission

* Corresponding author.

E-mail address: mtcastrolainez@gmail.com (M.T. Castro-Lainez).

revealed leukocytosis with left shift and negative troponin level. A transthoracic echocardiogram (Fig. 1) revealed cardiac tamponade physiology; therefore, a cardiothoracic consultation was obtained. A pericardial window was performed with drainage of 500 mL purulent fluid. The pericardial fluid and stool specimen grew nontyphoid *Salmonella enterica*, without further serotype. Blood cultures were collected on admission, and no growth was detected after five days of incubation. Vancomycin and piperacillin/tazobactam were initiated as empiric therapy and then de-escalated to ceftriaxone 2 g intravenously every 12 hours. His hospital course required ten days of care in an intensive care unit with subsequent transfer to the general medical ward on telemetry. He then developed recurrence of fevers up to 40 °C (104 °F) without hemodynamic instability. A comprehensive investigation for other causes of fever or nosocomial infection returned negative, and his fever eventually resolved with no change in therapy. The late fevers were believed to be a result of clearance of infliximab and a reconstitution of the immune system. Upon further interview, his last dose of infliximab was two weeks prior to admission. The patient completed four weeks of ceftriaxone 2 g IV every 12 hours, and at eight-week follow-up, the patient was completely asymptomatic.

Discussion

Salmonella is a leading water/food-borne fecal-oral zoonosis worldwide [1,2]. This Gram-negative genus is of the family Enterobacteriaceae related to *Escherichia* and *Shigella* [3]. Salmonellosis is classified as typhoid or nontyphoid. Typhoid fever is a non-zoonotic febrile systemic infection [4]. Vaccines and improved sanitation have reduced cases of typhoid fever [5]. Our focus, however, is the nontyphoidal *Salmonella*, a zoonotic pathogen present worldwide, and the leading cause of gastroenteritis although extra-intestinal manifestations have been reported, including septicemia, acute endocarditis, osteomyelitis, meningitis, vascular infection, and rarely pericarditis [6]. Gastrointestinal forms typically resolve without treatment. However, nontyphoid salmonellosis still represents the most common, most expensive, and deadliest foodborne illness in the United States [7]. The global burden of invasive nontyphoidal *Salmonella* is estimated to be 49

cases per 100,000 population [8]. Compared to other foodborne illnesses, ingestion of high concentrations of the organism are generally required to cause overt infection [9]. Weaponization of *Salmonella* makes it a bio-threat and increasingly the organism has become more antimicrobial resistant [6,10–12].

While 44 species of *Salmonella* (Lignières, 1900) existed in 1934, molecular biologists identified one species and seven serovars within *Salmonella* by 1987 [13–14]. In 2005, *Salmonella enterica* became the official name with six subspecies, the remainder became *Salmonella bongori* [15–16]. Of 2600 sub-groups, the most clinically relevant nontyphoidal serovars are Enteritidis (43.5% cases), Typhimurium (17.1%) and Newport (3.5%) [17]. Serovar Typhi causes typhoid fever occurring four times more frequently than Paratyphi, causing paratyphoid fever [18,19]. In addition to many serotypes, the relationship between host genetics and clinical manifestation remains poorly understood [20,21].

Infliximab is a monoclonal antibody approved in 1998 and indicated for Crohn's disease and ulcerative colitis, as well as other autoimmune diseases. Infectious complications due to immune suppression are well documented in the literature [22]. In one large study, infliximab was found to have a slightly higher risk of infection as compared to other Tumor necrosis factor alpha (TNF- α) inhibitors in rheumatoid arthritis patients [23]. TNF- α inhibitors have been associated with numerous opportunistic infections [24,25]. Although the risk of opportunistic infections was low (152 cases per 100 000 patient years), the severity of illness tend to be significant [25]. The risk of infection was higher when TNF- α inhibitors were combined with steroids; doses of greater than prednisone 10 mg per day [25].

Pericarditis, or inflammation of the pericardial lining, has multiple etiologies; among infectious causes, viral infections are by far the leading causative agents. While viral etiology is usually benign, purulent or bacterial pericarditis can be a potentially catastrophic infection. Patients commonly present with chest pain, pericardial rub, and fever. The presence of pericardial effusion on the echocardiogram is also considered a criterion for diagnosis. In developing countries, *Mycobacterium tuberculosis* must be high in the differential. Prior to the antimicrobial era, extension from bacterial pneumonia was the most common cause. Hence, it is not surprising that the leading causes cited in the literature include

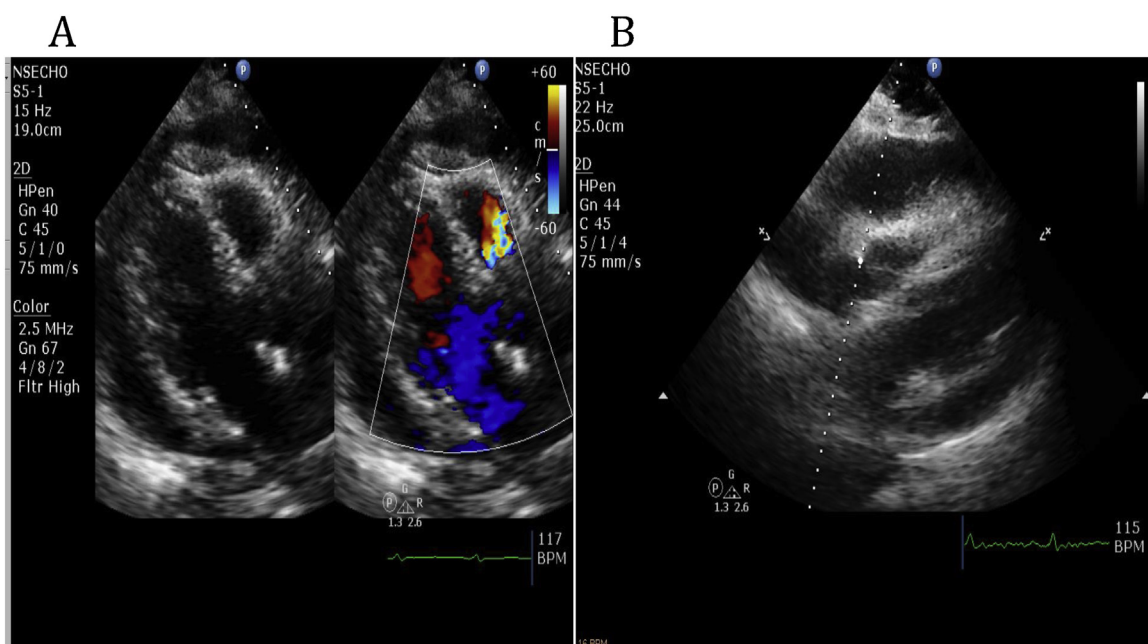


Fig. 1. Transthoracic echocardiogram with parasternal long axis (A) and subcostal (B) views with moderate to large pericardial effusion and impending cardiac tamponade.

Streptococcus pneumoniae, *Staphylococcus aureus*, and Group A streptococcus. Purulent pericarditis could occur from bacteremia, therefore additional bacterial pathogens to consider in the differential include enteric Gram-negative bacilli, *Pseudomonas aeruginosa*, *Salmonella*, *Neisseria meningitidis*, anaerobes and fungi. Prompt diagnosis is imperative since purulent pericarditis could present with life threatening manifestations. Echocardiography should be performed as soon as possible for diagnosis; this tool assesses for signs of cardiac tamponade and can assist in guided pericardiocentesis, if needed. Laboratory diagnosis is made based on purulent material with characteristics of exudate, predominance of polymorphonuclear leucocytes and lactate dehydrogenase, as well as low glucose from the pericardial effusion. Gram stain and culture, hematocrit, biochemistry, and cytology should also be performed.

We are reporting a patient presenting with nontyphoid *Salmonella* purulent pericarditis with cardiac tamponade while on infliximab treatment. We believe the suppressive effect of infliximab masked the expected systemic symptoms of a significant bacterial infection. Paradoxically, the patient did develop a robust inflammatory response ten days after the procedure that slowly resolved over three weeks upon completion of treatment.

We conducted a literature review using the Medline and PubMed databases of articles published between 1992 and March 2018. We found twelve relevant articles in English and Spanish of nontyphoid *Salmonella* purulent pericarditis complicated with cardiac tamponade (Table 1). The disease was found exclusively in adults, (age range 23- 67 years), with a mean age of 55 years. Using the human development index (HDI), most cases (11/12, 92%) were reported from countries with very high human development (HDI \geq 0.80), which represent 16% of the world population. The remaining case (1/12, 8%) came from a high human development country (0.80 > HDI \geq 0.70), which represents 14% of the world population, if we distinguish the Republic of China from the People's Republic of China. At first glance, the data leads us to believe that nontyphoid *Salmonella* purulent pericarditis complicated with cardiac tamponade is limited to developed countries. However, nontyphoid *Salmonella* is present worldwide, and presumably cases of nontyphoid *Salmonella* purulent pericarditis complicated with cardiac tamponade are underreported. Using the data from the countries with very high human development, at least 73 cases should have been reported worldwide. The majority of patients in this series had documented immunosuppressive factors, either iatrogenic or a preexisting medical condition. The

Table 1
Cases of Nontyphoidal *Salmonella* pericardial effusion with cardiac tamponade.

| Case No. | First Author (Reference) | Year | Age/Sex (yr) | Location | Medical Conditions & Risk Factors | Presenting Symptom | Treatments | Outcome |
|----------------|--------------------------|-----------|---|---|---|--|---|-------------------------|
| 1 | Canut Blasco | 1992 | 53/M | Zamora, Castile, Spain | Myocardial infarction, thrombophlebitis (lower extremities) | Fever | Ciprofloxacin, chloramphenicol (Failed) | Survived |
| 2 | Clesham | 1993 | 45/M | London, England, United Kingdom | - | Cough, dyspnea, chest pain, fever | - | Survived |
| 3 | Kiuchi | 1998 | 39/M | Tokyo, Japan | Alcoholic hepatitis, idiopathic thrombocytopenic purpura, malignant lymphoma, pneumonectomy, prior steroid use | Dyspnea, fever, night sweats | Ampicillin, surgical drainage | Survived |
| 4 | Salavert | 2002 | 61/M | Alicante, Valencia, Spain | Irritable bowel syndrome | Dyspnea, fever | Cefuroxime, amikacin | Survived |
| 5 | Fernández Guerrero | 2004 | 23/F | Madrid, Castile, Spain | Systemic lupus erythematosus, prior steroid use, immunosuppressant exposure | Dyspnea, chest pain, fever, night sweats | Cefotaxime, then ciprofloxacin | Survived |
| 6 | Arruvito | 2004 | 75/M | Buenos Aires, Argentina | Gastric cancer sp gastrectomy, candida, herpetic esophagitis, arthritis, prior steroid use | Weight loss | Ampicillin, gentamicin, fluconazole, acyclovir | Died |
| 7 | Hoag | 2005 | 47/F | Baltimore, Maryland, United States | Morbid obesity (Body-mass index of 49.7 kg/m ²), human immunodeficiency virus | Dyspnea, fever, night sweats, weight loss | Ceftazidime, levofloxacin | Survived |
| 8 | Tseng | 2010 | 66/M | Taoyuan, Taiwan, Republic of China | End-stage renal disease, chronic glomerulonephritis, congestive heart failure, invasive medical device | Dyspnea | - | Survived |
| 9 | Ortiz | 2014 | 62/M | Milwaukee, Wisconsin, United States | Hypertension, intermittent atrial fibrillation, drug-induced systemic lupus erythematosus, prior steroid use, immunosuppressant exposure, invasive medical device | Fever | Ceftriaxone, then levofloxacin. Right atrial and RV pericardiectomy | Survived |
| 10 | Pulido-Arenas | 2016 | 67/M | Bogotá, Colombia | Rheumatoid arthritis, prior steroid use, former smoker | Chest pain, weight loss | Ceftriaxone | Survived |
| 11 | Chand | 2016 | 67/M | St Leonards-on-Sea, England, United Kingdom | Hypertension, diabetes mellitus, hyperlipidemia, hepatitis B, previous stroke | Cough, dyspnea, fever | Ceftriaxone, ciprofloxacin | Survived |
| 12 | Saddler (This study) | 2018 | 57/M | Victoria, Texas, United States | Hypertension, hepatitis C, Crohn's disease, coronary spasm, ongoing alcohol and tobacco abuse, distant history of cocaine abuse, immunosuppressant exposure | Cough, dyspnea, chest pain, fever | Ceftriaxone, surgical drainage | Survived |
| Summary | | 1992-2018 | Mean, 55; (range, 23-75) M: 10/12 (83%) | Americas = 4 Asia = 3 Europe = 5 | Immunosuppressed = 5/11 (45%) Prior steroid use = 2/11 (18%) | Cough = 25% Dyspnea = 58% Chest pain = 33% Fever = 75% Night sweats = 25% Weight loss = 25% | Antimicrobials = 7/10 (70%) Antimicrobial & surgery = 3/10 (30%) | 11/12 (92%) survived |

most commonly reported symptoms among the study population were fever (75%), dyspnea (58%), and chest pain (33%). A third-generation cephalosporin was the most commonly prescribed antimicrobial therapy, with 92% surviving with antimicrobials alone or in addition to surgical intervention.

Nontyphoidal *Salmonella* pericarditis presenting with pericardial tamponade is rare; only twelve cases have been reported since 1992. Most patients are immunosuppressed, and an index of high suspicion is recommended in order to diagnose early, and implement appropriate surgical and medical treatments. With appropriate antimicrobials and surgical intervention there is a high probability of achieving a positive outcome.

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