

[CASE REPORT]

***Salmonella enterica* Subspecies *arizonae* Detected from Bilateral Pleural Fluid in a Patient with Systemic Lupus Erythematosus and Malignant Lymphoma**

Natsuki Shima¹, Jun Nakamura¹, Keisuke Saito¹, Yasuyuki Kamata¹, Katsuya Nagatani¹, Takao Nagashima¹, Masahiro Iwamoto¹, Dai Akine^{2,3}, Tatsuya Saito⁴, Kojiro Sato¹ and Seiji Minota¹

Abstract:

A 72-year-old woman was admitted to our hospital with bilateral pleural effusions. She had a 31-year history of systemic lupus erythematosus and had been treated with prednisolone and azathioprine. Pleural fluid culture revealed *Salmonella enterica* subsp. *arizonae* infection. This pathogen rarely infects humans but is commonly found in the gut flora of reptiles, especially snakes. Our patient had not come in contact with reptiles. Despite antibiotic therapies and negative pleural cultures, the pleural effusion persisted. Colon cancer was detected concomitantly, and she finally died. The autopsy revealed that the pleuritis was due to underlying diffuse large B cell lymphoma.

Key words: bacteremia, malignancy, pleural effusion, pleuritis, *Salmonella enterica* subspecies *arizonae*

(Intern Med 59: 1223-1226, 2020)

(DOI: 10.2169/internalmedicine.3982-19)

Introduction

Salmonella is a Gram-negative facultative anaerobic bacterium that belongs to the family *Enterobacteriaceae*. This genus has two species, *S. bongori* and *S. enterica*, and the latter is further divided into six different subspecies: *S. enterica* subsp. *enterica*, *S. enterica* subsp. *salamae*, *S. enterica* subsp. *arizonae*, *S. enterica* subsp. *diarizonae*, *S. enterica* subsp. *houtenae* and *S. enterica* subsp. *indica* (1, 2). The *S. enterica* subsp. *arizonae* (represented here as *S. arizonae*) is an uncommon human pathogen. Rarely, serious infections by *S. arizonae* may occur in people in contact with reptiles for long periods of time and immunocompromised people (e.g. those with connective tissue diseases, malignancy, organ transplantation and acquired immunodeficiency syndrome) (3). It causes different types of infections, such as gastritis, gastroenteritis, bacteremia, septic arthritis, osteo-

myelitis, empyema, peritonitis and endocarditis (1).

Most reported cases of infection due to *S. arizonae* are related to contact with reptiles; indeed, about 70% of patients have a history of exposure to reptiles, especially snakes (3). Infections due to *S. arizonae* are well described in the southwestern part of the United States and Mexico, where rattlesnake-derived products (meat, capsules and powders) are used as traditional folk remedies (4). However, in Japan, *S. arizonae* infection has rarely been reported (5, 6).

We herein report a woman with systemic lupus erythematosus (SLE) who developed *S. arizonae* infection in the bilateral pleural fluid. We discuss her course of treatment, the complications involved and inferences withdrawn.

Case Report

A 72-year-old woman was admitted to our hospital with dyspnea and myalgia. She had a 31-year history of SLE and

¹Division of Rheumatology and Clinical Immunology, Department of Medicine, Jichi Medical University, Japan, ²Health Service Center, Jichi Medical University, Japan, ³Division of Clinical Infectious Diseases, Department of Infection and Immunity, Jichi Medical University, Japan and ⁴Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, Japan

Received: September 28, 2019; Accepted: November 21, 2019; Advance Publication by J-STAGE: February 12, 2020

Correspondence to Dr. Natsuki Shima, shimanatsuki@jichi.ac.jp

had been treated with prednisolone 8 mg and azathioprine 50 mg daily. Her vital signs on arrival were as follows: body temperature was 36.7°C, pulse rate was 117 beats/min, respiratory rate was 22 breaths/min, blood pressure was 131/85 mmHg, and percutaneous oxygen saturation was 88% (on an ambient air). Lung auscultation revealed reduced respiratory sounds at both lung bases.

Laboratory findings revealed that the leukocyte count was 7,000/ μ L (neutrophils, 88.4%; monocytes, 9.3%; basophils, 0.4%; lymphocytes, 1.9%), hemoglobin was 8.2 g/dL, and the platelet count was 43.1×10^3 / μ L. Serum albumin was 2.9 g/dL, lactate dehydrogenase was 241 U/L, and the liver and renal function test findings were within the respective normal ranges. The blood glucose was 150 mg/dL, and HbA1c was 7.2%. Investigations showed the levels of C-reactive protein to be 11.01 mg/dL, IgG 570 mg/dL and complement components C3 and C4 117 mg/dL (normal 73-138 mg/dL) and 37 mg/dL (normal 11-31 mg/dL), respectively. Antinuclear antibody was 1:40 with a homogeneous pattern, while anti-dsDNA antibody and anti-Sm antibody were negative. Urinary protein excretion was 0.17 g/day, and the urinary

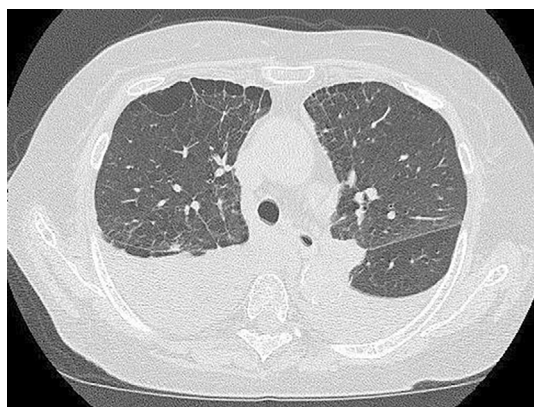


Figure. Chest computed tomography scan on admission. Bilateral pleural effusion and emphysema were found.

sediment contained no erythrocytes or casts. Chest radiography showed bilateral pleural effusion. Plain thoracic computed tomography (CT) revealed bilateral pleural effusion and emphysema without pleural thickening or massive consolidation (Figure). Transthoracic echocardiography showed a normal cardiac function.

Thoracentesis of the right-side pleural fluid revealed a neutrophilic exudate. It contained 91.5% neutrophils (cell count 5,970/ mm^3), 2.2 g/dL albumin and 110 mg/dL glucose (Table 1); the pH was 8.0, and cytology was negative. Three days after admission, thoracentesis of both sides was performed again. Cultures of the pleural fluids from the right side on admission and the left side collected three days after admission were positive. Both an automated instrument for infectious disease testing (VITEK[®]-2; bioMérieux SA., Marcy L'etoile, France) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; MALDI Biotyper, Bruker Daltonics, Bremen, Germany) identified these organisms as *S. arizonae* (MALDI Biotyper score: 2.2282). Further investigations confirmed the presence of *S. arizonae* serovar 18: z4, z32: -, which indicated that this serotype carried the "18" O antigen and "z4 and z32" H antigen and was negative for the Vi antigen. The bacteria were susceptible to ampicillin (Table 2). However, blood and sputum cultures taken before the initiation of antibiotics were negative for *S. arizonae*.

Chest tubes were placed into bilateral thoraxes for fluid drainage. Despite repeated interviews, the patient denied keeping any pets, had never had contact with any animals such as reptiles, had no history of consuming snake products and had never travelled abroad.

Treatment with intravenous sulbactam/ampicillin (SBT/ABPC) (12 g daily) was started for the tentative diagnosis of pleural empyema. One week after antibiotic treatment, stool culture was performed, and no bacteria of the *Salmonella* group grew. After she completed a 32-day course of antibiotic treatment, a further course of intravenous levoflox-

Table 1. The Results of the Pleural Fluids.

Variable	On admission	Three days after admission	
	Right-side	Right-side	Left-side
Total cell count (/ mm^3)	5,970	1,880	1,400
Differential cell count (%)			
Neutrophils	91.5	75.0	30.5
Macrophages	4.5	5.0	19.0
Lymphocytes	3.0	18.5	36.5
Mesothelial cells	1.0	0	1.0
Monocyte-like cells	0	1.5	9.0
Plasma cells	0	0	4.0
Glucose (mg/dL)	110	130	130
Total protein (g/dL)	3.5	3.4	3.3
Albumin (g/dL)	2.2	2.1	1.9
Lactate dehydrogenase (U/L)	423	505	317
Adenosine deaminase (U/L)	51.8	63.3	N/A

N/A: not available

acin (500 mg daily) was administered. She required oxygen via a mask on admission, but after antibiotic therapy, oxygen was not required. However, her fever did not subside after completion of the antibiotic course. The cytological evaluation of the pleural effusion was performed five times, and the results were class I twice, class II once and class III twice. Since subsequent cultures of pleural effusions were negative, we considered that she might have had concomitant lupus pleuritis. Therefore, the prednisolone dose was increased to 45 mg (1 mg/kg) daily. However, the pleural effusion did not respond to the glucocorticoid treatment. Colonoscopy was also performed, which revealed advanced colon cancer in the ascending colon. Adenocarcinoma was demonstrated histologically. About four months after admission, respiratory failure recurred due to recalcitrant bilateral pleural effusion, and she ultimately died of septicemia due to *Enterococcus faecium* infection.

The autopsy revealed that, in addition to advanced colon cancer, the patient had also suffered from multiple lymph node swelling in the abdominal cavity. Diffuse large B cell lymphoma was histologically demonstrated. Invasion of lymphoma cells into the pleural cavity was also discovered and determined as the main cause of her pleuritis.

Discussion

Our patient with SLE developed *S. arizonae* infection detected in the bilateral pleural fluid. She had never had any

contact with any animals or had previously travelled abroad. During her treatment, advanced colon cancer was detected concomitantly. Although she completed a course of antibiotics with known efficacy against *S. arizonae*, her bilateral pleuritis persisted. An autopsy revealed the pleuritis to have been caused by the invasion of malignant lymphoma.

Cases of *S. arizonae* infection in the pleural fluid are rare. Only a few cases of empyema caused by *S. arizonae* have been reported (3, 4). Pleuropulmonary infection may occur via several routes: direct extension from a nearby infection, aspiration of gastric secretions in patients with gastrointestinal infections and hematogenous dissemination (7). Although blood cultures were negative in the present case, hematogenous dissemination from the gastrointestinal tract may have been the source of bilateral pleural infection. Advanced colon cancer might have been the portal of entry.

Patients with *S. arizonae* infection tend to have various underlying conditions that can compromise their cell-mediated immunity, such as connective tissue diseases, malignancy and acquired immunodeficiency syndrome (3). *Salmonella* is an intracellular pathogen that infects various host cells (8). In the present patient, an impaired or suppressed adaptive immunity caused by SLE, immunosuppressive therapy or malignant lymphoma may also have contributed to the development of *S. arizonae* infection.

The choice of SBT/ABPC was reasonable because it can generally be used for the treatment of pneumonia or empyema until the causative microorganism is detected. Treatment with SBT/ABPC improved her respiratory condition. Third-generation cephalosporins might have been another suitable choice for the present patient based on drug susceptibility. A previous case series suggested that 72% of patients with *S. arizonae* infection were treated with third-generation cephalosporins (3).

S. arizonae infection is rare in Japan. We searched the literature related to Japanese cases of *S. arizonae* infection (both Japanese and English, including abstracts) in the PubMed database as well as Ichu-shi and Shorei-kun databases (from regional meetings held by chapters of the Japanese Society of Internal Medicine). Since 2000, we found a total of six cases of *S. arizonae* infection in Japan, including the present case (Table 3) (5, 6, 9-11). Of these, two patients were treated with glucocorticoids. Two-thirds of the patients

Table 2. Antibacterial Minimum Inhibitory Concentration Results for *Salmonella enterica* Subsp. *arizonae*.

Antibacterial agent	Minimum inhibitory concentration* (mg/mL)
Ampicillin	≤ 2 Susceptible
Ampicillin/Sulbactam	≤ 2 Susceptible
Ceftriaxone	≤ 2 Susceptible
Levofloxacin	≤ 0.12 Susceptible
Meropenem	≤ 0.25 Susceptible

*Drug susceptibility testing was carried out as per M100 Performance Standards for Antimicrobial by Clinical and Laboratory Standards Institute and VITEK[®]-2 system.

Table 3. Cases of Infection Caused by *Salmonella enterica* Subsp. *arizonae* Reported from Japan.

Case	Age/Sex	Infection site	History of contact	Sample of culture	Underlying disease	Outcome	Ref
1	64/F	Renal pelvis	No	Urine	Grave's disease	Cure	5
2	36/M	Pericardium	Yes	Pericardial fluid	Type 2 diabetes mellitus	Cure	6
3	78/F	Iliopsoas, vertebral disc	Yes	Blood	None	N/A	9
4	59/M	Lung	No	Sputum	Peptic ulcer	Cure	10
5	65/F	Iliopsoas, spine	No	Blood, abscess	Autoimmune hepatitis	Cure	11
Present case	72/F	Pleural fluid	No	Pleural fluid	SLE, colon cancer, and malignant lymphoma	Died	-

F: female, M: male, N/A: not available, Ref: reference, SLE: systemic lupus erythematosus

had no history of contact with reptiles, suggesting that there might be other as-yet-unknown sources of infection by *S. arizonae*.

Patients with no history of contact with reptiles might have contracted the infection through the consumption of contaminated food. Italian pasta was reported as one of the sources of *S. arizonae* infection in the United Kingdom (12). Even in the modern era, *S. arizonae* has been identified in fresh vegetables, pork and traditional Italian cheeses (13-15). One epidemiological study conducted in Japan showed that several *Salmonella sp.*, including *S. arizonae*, were isolated from 12.3% (7 out of 57 specimens) of chicken meat samples sold by domestic supermarkets, and *S. arizonae* was isolated from 1 of these 7 products (16). The patient discussed here might thus have contracted her infection by consuming contaminated chicken.

In the present case, bilateral pleuritis did not respond to the treatment, although the pathogen was found to be susceptible to SBT/ABPC. While we assumed that the infection had been successfully resolved after the initial antibiotic treatment, it persisted. An autopsy revealed that the bilateral pleuritis had been caused by the invasion of malignant lymphoma. Pleural effusion is relatively common in patients with non-Hodgkin lymphoma. In lymphomatous effusion, positive cytology is reported in 14% to 88% of cases (17). In cases of negative cytology and negative cultures, a thoracoscopic pleural biopsy may be needed to make a definite diagnosis (18).

The identification of the infectious agent is important for treatment. Conventional culturing often takes days, whereas multiplex polymerase chain reaction (PCR) panels offer fast and sensitive alternatives (19). In the present case, *S. arizonae* was not identified in the stool culture. The use of a multiplex real-time PCR assay for fecal specimens has not been approved in Japan. If approved, it might be another choice for detecting such pathogens.

In conclusion, the present patient who presented to our hospital with bilateral pleural infection by *S. arizonae* had several underlying immunocompromised conditions, such as SLE, advanced colon cancer and malignant lymphoma. Since the source of *S. arizonae* infection is unclear in more than half of such cases in Japan, we suspect that contaminated food might have been the cause. Therefore, a large-scale investigation to check the contamination levels of harmful pathogens, including *Salmonella sp.*, in food being sold in local markets should be carried out. It is imperative to identify the source of *S. arizonae* infection in order to establish effective preventive measures.

The family of the patient gave their written informed consent.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank Hidemasa Izumiya, MD, PhD (National Institute of Infectious Diseases, Tokyo, Japan), for the analysis of *S. arizonae*.

References

- Lamas A, Miranda JM, Regal P, Vazquez B, Franco CM, Cepeda A. A comprehensive review of non-enterica subspecies of *Salmonella enterica*. *Microbiol Res* **206**: 60-73, 2018.
- Gavrilovici C, Panzaru CV, Cozma S, et al. "Message from a turtle": otitis with *Salmonella arizonae* in children: case report. *Medicine (Baltimore)* **96**: e8455, 2017.
- Lee YC, Hung MC, Hung SC, et al. *Salmonella enterica* subspecies *arizonae* infection of adult patients in Southern Taiwan: a case series in a non-endemic area and literature review. *BMC Infect Dis* **16**: 746, 2016.
- Riley KB, Antoniskis D, Maris R, Leedom JM. Rattlesnake capsule-associated *Salmonella arizonae* infections. *Arch Intern Med* **148**: 1207-1210, 1988.
- Nishioka H, Doi A, Takegawa H. Pyelonephritis in Japan caused by *Salmonella enterica* subspecies *arizonae*. *J Infect Chemother* **23**: 841-843, 2017.
- Suzuki A, Tanaka T, Ohba K, et al. Purulent pericarditis with *Salmonella enterica* Subspecies *arizonae* in a patient with type 2 diabetes mellitus. *Intern Med* **56**: 2171-2174, 2017.
- Crum NF. Non-typhi *Salmonella* empyema: case report and review of the literature. *Scand J Infect Dis* **37**: 852-857, 2005.
- Gogoi M, Chandra K, Sarikhani M, Ramani R, Sundaresan NR, Chakravorty D. *Salmonella* escapes adaptive immune response via SIRT2 mediated modulation of innate immune response in dendritic cells. *PLoS Pathog* **14**: e1007437, 2018.
- Amano H, Kobayashi S, Hoshina T, et al. Spondylitis and iliopsoas abscess associated with *Salmonella enterica ssp. arizonae* in a 78-year-old woman. *Nihon Naika Gakkai Zasshi (J Jpn Soc Intern Med)* **106**: 84-89, 2017 (in Japanese).
- Katori N, Tanaka T, Kanno H. Pneumonia caused by *S. arizonae* with peptic ulcer. *Nihon Kagakuryouhou Gakkai Zasshi* **61**: 113, 2013 (in Japanese).
- Wakuda R, Takagi Y, Saito T, Niikawa J, Imawari M. Purulent spondylitis caused by *S. arizonae*. *Nihon Rinshou Biseibutugaku Zasshi* **13**: 100, 2003 (in Japanese).
- Hall ML, Rowe B. *Salmonella arizonae* in the United Kingdom from 1966 to 1990. *Epidemiol Infect* **108**: 59-65, 1992.
- Reddy SP, Wang H, Adams JK, Feng PC. Prevalence and characteristics of *Salmonella* serotypes isolated from fresh produce marketed in the United States. *J Food Prot* **79**: 6-16, 2016.
- Chaves-Lopez C, De Angelis M, Martuscelli M, Serio A, Paparella A, Suzzi G. Characterization of the *Enterobacteriaceae* isolated from an artisanal Italian ewe's cheese (Pecorino Abruzzese). *J Appl Microbiol* **101**: 353-360, 2006.
- Evangelopoulou G, Kritas S, Govaris A, Burriel AR. Pork meat as a potential source of *Salmonella enterica* subsp. *arizonae* infection in humans. *J Clin Microbiol* **52**: 741-744, 2014.
- Nakajima T, Arai M, Ogawa Y, Kato N, Nagasaka Y, Nomura Y. Prevalence of *Salmonella spp.* in ground chicken Samples in Japan. *Igaku to Seibutsugaku* **150**: 229-233, 2006 (in Japanese).
- Alexandrakis MG, Passam FH, Kyriakou DS, Bouros D. Pleural effusions in hematologic malignancies. *Chest* **125**: 1546-1555, 2004.
- Wang Z, Wu YB, Xu LL, et al. Diagnostic value of medical thoracoscopy in malignant pleural effusion induced by non-Hodgkin's lymphoma. *Oncol Lett* **14**: 8092-8099, 2017.
- Hannet I, Engsbro AL, Pareja J, et al. Multicenter evaluation of the new QIAstat Gastrointestinal Panel for the rapid syndromic testing of acute gastroenteritis. *Eur J Clin Microbiol Infect Dis* **38**: 2103-2112, 2019.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).