

RESEARCH ARTICLE

Beyond the gut - Atypical presentation of *Salmonella* spp. infection

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Salmonella is a Gram-negative, non-spore-forming, motile, facultative anaerobic rod. The most studied species are *Salmonella typhi* and *paratyphi* (causing typhoid fever) and non-typhi *Salmonella* species (which can cause different clinical syndromes - gastroenteritis, disseminated infections, etc.). A 61-year-old male patient with multiple comorbidities (including myelofibrosis) presented to the Pulmonology outpatient department, Clinical County Hospital of Târgu Mureş, with a mucopurulent nocturnal cough. Paraclinical examinations showed the presence of a pleural empyema, which was evacuated in local anesthesia. The pleural fluid was sent to the Microbiology Department for bacteriological testing, where a fluoroquinolone-resistant strain of *Salmonella* spp. was detected. The patient received antibiotic treatment according to the antibiotic susceptibility testing. Due to the persistence of the symptoms, the patient returned two weeks later, when another puncture was performed. *Salmonella* was isolated again, but the strain showed a higher resistance to antibiotics. The two strains were compared using molecular methods of diagnosis (Enterobacterial Repetitive Intergenic Consensus Polymerase Chain Reaction - ERIC-PCR), the results showing a similarity of 92%. The occurrence of an extra amplicon band in ERIC-PCR suggests an important change in the bacterial genetic material, potentially related to acquisition of antibiotic resistance factors.

Keywords: pleural empyema, *Salmonella*, extraintestinal salmonellosis

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Introduction

Genus *Salmonella* is part of the *Enterobacteriaceae* family, being named after Daniel E. Salmon who first isolated *Salmonella cholerae suis* in 1884 from pigs [1]. *Salmonella* is a Gram-negative, non-spore-forming, motile, facultative anaerobic rod [2]. Among this genus, the most studied species are *Salmonella typhi* and *paratyphi*, which due to their increased pathogenicity can invade the body, thus becoming the causative agents of typhoid fever [1]. Non-typhi *Salmonella* species are usually related to a few clinical syndromes such as enterocolitis (gastroenteritis – usually self-limited), enteric fever, bacteriemia, endocarditis, urinary tract infections and septic arthritis [3,4]. Following bacteriemia, the localization of the infection can occur at any site in the organism, unrelated to the associated initial symptoms. Infections with *Salmonella* spp. outside of the gastrointestinal tract remain uncommon, and even more, pleural effusions or empyema with this genus are extremely rare [3].

Pleural empyema with *Salmonella* spp. is associated with different types of immunosuppression or underlying diseases such as diabetes mellitus, malignancy or pulmonary disease, especially in older patients [3]. In these cases, *Salmonella* is able to penetrate the intestinal mucosa and reach the blood stream, thus being transported in remote areas, including the pleural space [3]. In rare cases intestinal-pleural fistulas can be a cause of empyema [5].

To our knowledge, this is the first case of pleural empyema with *Salmonella* spp. described in Romania.

The study was approved by the Ethics Committee of Mureş County Clinical Hospital, decision no. 6076/07.04.2023.

Case presentation and isolation of the *Salmonella* spp. strains

A 61-year-old male patient presented to the Pulmonology outpatient department, Clinical County Hospital of Târgu Mureş, with a mucopurulent nocturnal cough.

The patient has a history of multiple comorbidities, including acute myeloblastic leukemia with secondary myelofibrosis, secondary immune system dysfunction and anemia, aortic insufficiency due to atherosclerosis (grade I), tricuspid and mitral regurgitation and pericarditis. The patient was undergoing treatment with Ruxolitinib (Jakavi) for myelofibrosis.

Other important information from the patient's history include: the presence of a splenic abscess, accidentally discovered during a surgery consult and further confirmed by the paraclinical investigations (computed tomography scan – CT scan); his family medical history which revealed the presence of a tuberculosis case in the family in the past (therefore, infection with *Mycobacterium tuberculosis* was also taken into consideration); clinical examinations, which revealed bilateral lower limb oedema, more severe on the right side and diminished respiratory sounds on the left side.

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The paraclinical examinations showed the following results:

- Spirometry:
 - Forced vital capacity (FVC): 53%;
 - Forced expiratory volume in one second (FEV1): 50%;
 - Tiffneau index (FEV1/FVC): 74.34;
 - Maximal expiratory flow at 50% of the forced vital capacity (MEF50): 42%.
- Thoracic ultrasound: pleural fluid with a viscous consistency, encysted, on the left side;
- Thoracic radiography (X-ray): pleural fluid on the left side (Figure 1);
- Fibro bronchoscopy: purulent secretions in the left bronchial tree;
- CT scan of the thorax (native and using contrast substance) - Figure 2: focal consolidation with air bronchogram of the left lower lobe, extended into

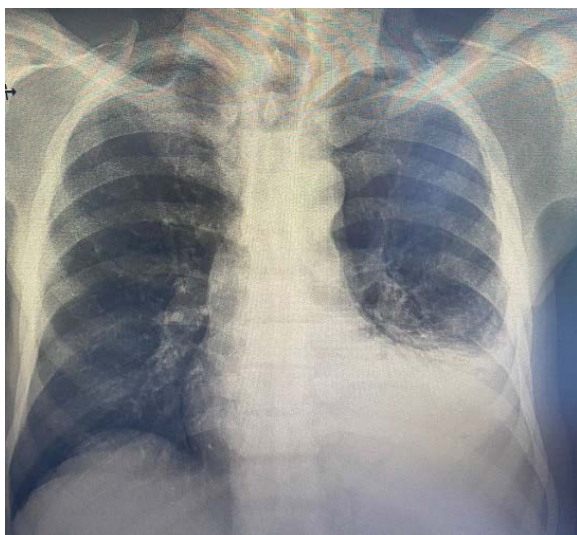


Fig. 1. Thoracic X-ray of the chest showing fluid accumulation in the left pleural space

the lower segments as well as in the hilar and lingular regions, associated with a bilocular encysted posterior-basal pleural collection, with air inclusions and a thick iodophilic wall, having dimensions of approximately 61/73 mm (suggestive aspect for pleural empyema); focal inferior lingular congestion; thickening of the interlobular septa and centrilobular nodules of the upper segment of the lower lobe and upper lingular segment (suggestive of endobronchial infectious dissemination);

- CT scan of the abdomen: collection with several dense areas, multiloculated, with air inclusions, having dimensions of 115/90/94 mm, starting in the superior pole of the spleen (suggestive aspect for a spleen abscess), splenomegaly, hepatomegaly.

The pleural collection was punctured and drained in local anesthesia with 1% Lidocaine. Approximately 300 ml of pleural fluid were evacuated and sent to the Medical Laboratory Department of the Clinical County Hospital of Târgu Mureș for biochemical and microbiological testing.

Macroscopically, the pleural fluid had a cloudy, turbid appearance and was yellowish-brown in color. Biochemical tests of the pleural fluid revealed: decreased levels of amylase: 17 U/l (reference values: 138-144 U/l) and glucose: 8 mg/dl (reference values: 70-100 mg/dl); increased levels of lactate dehydrogenase - LDH: >3325 U/l (the specific value could not be detected, even after dilution); proteins: 4.86 g/dl (reference values: 0.3-4.1 g/dl).

All tests for tuberculosis were negative, including microscopic examination in Ziehl-Neelsen staining and cultivation on Lowenstein-Jensen. The pleural fluid was also inoculated on all the specific culture media for this type of pathological sample: blood agar (one in aerobiosis and one in anaerobiosis), lactose agar, Mannitol salt agar, chocolate agar and Sabouraud dextrose agar. Following incubation at 35°C for 24 hours in normal conditions, respectively in a CO₂ atmosphere for chocolate agar, grey, S type colonies

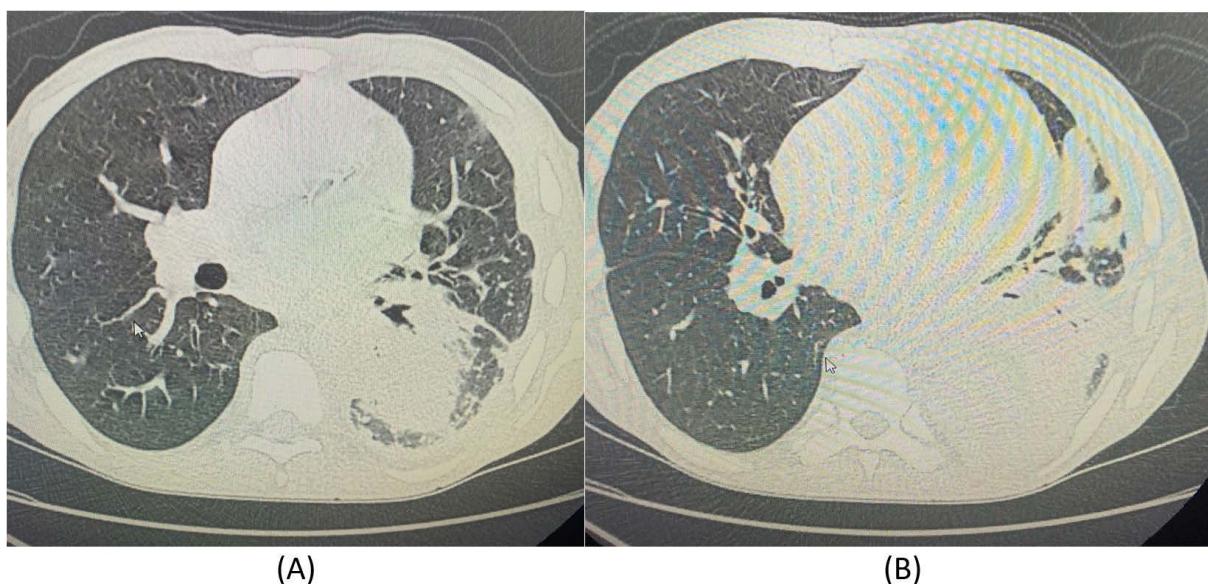


Fig. 2. CT scan of the thorax showing the pleural collection on the left side

specific for *Enterobacteriaceae* grew on all culture media (Figure 3), except for Sabouraud agar which was negative for all fungal pathogens.

For identification, the colonies were further isolated on lactose agar, followed by the study of their biochemical traits, which revealed a typical aspect for *Salmonella* spp. As a confirmation test to prove that the bacteria were lactose-negative, the o-nitrophenyl- β -D-galactopyranoside test (ONPG test) was also performed (Figure 4).

Conventional methods of identification were followed by automatic identification using Vitek 2 Compact (Biomérieux, France), which confirmed the *Salmonella* genus. To detect the serogroup, agglutination was performed with pooled O antisera (SSI Diagnostica). The result was negative, but it was negative only for the tested groups that were available: OMA, OMB, OMC, OMD, OME, OMF, OMG – Figure 5.

Antibiotic susceptibility testing (AST) was further performed (Figure 6), showing susceptibility to most antibiotic classes both by disk diffusion (Table 1), and minimum

inhibitory concentration (MIC) (Table 2). The results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standard. Initially, the patient received empirical antibiotic treatment with Clindamycin associated with Metronidazole and Levofloxacin. After antibiotic susceptibility testing was available, the antibiotic used was according to the AST.

After two weeks of treatment, the patient was asked to return for a routine check-up, and he reported that the symptoms (mucopurulent nocturnal cough and thoracic constriction) persisted. Ultrasound further showed the presence of condensation areas. Another aspiration of the pleural fluid was performed, evacuating 20 ml of pleural fluid. The turbid, brown liquid was sent once more for bacteriological and mycological testing.

Direct microscopy using the Gram staining from the pleural fluid showed frequent neutrophils, rare lymphocytes, frequent red blood cells (some of them dysmorphic), free nuclei and rare Gram-negative bacilli, some of them phagocytized. The sample was further cultivated on all the

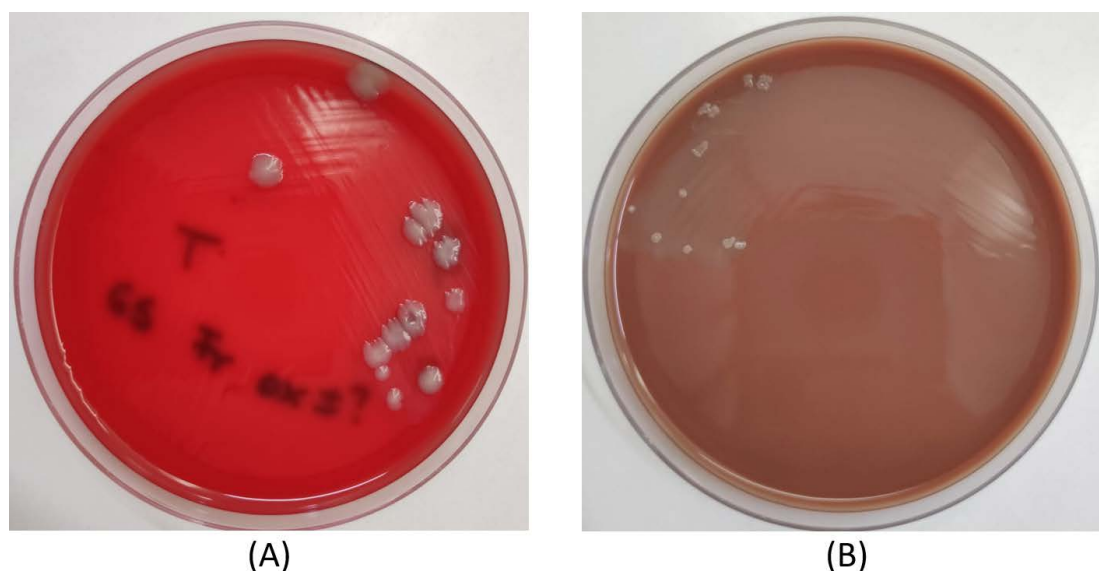


Fig. 3. Direct culture aspect after the inoculation of the pleural fluid on (A) Sheep blood agar and (B) Chocolate agar

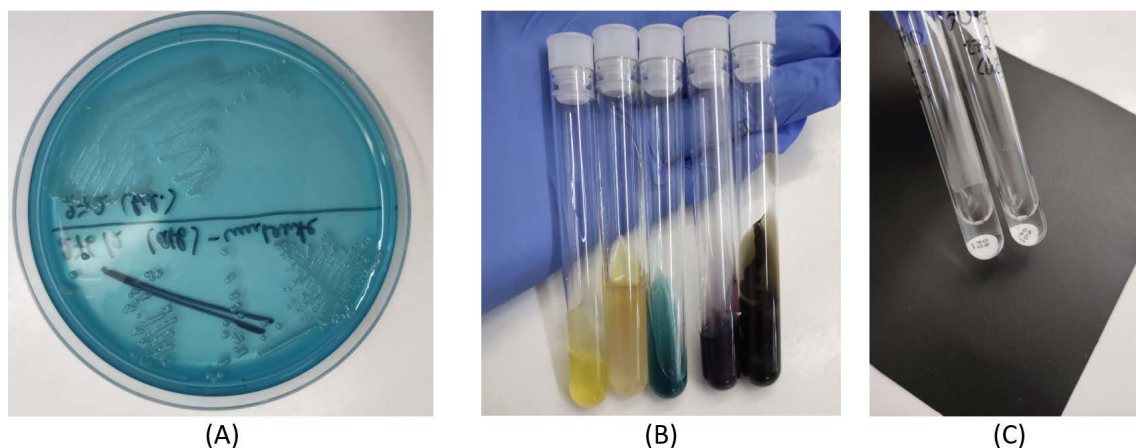


Fig. 4. (A) Isolation of the non-lactose fermenting strain on lactose agar; (B) Biochemical traits characteristic for *Salmonella* spp. (in order from left to right): urease negative; SIM agar – hydrogen sulphite positive, indole negative, motility positive; citrate negative; lysin decarboxylase and lysin deaminase positive, hydrogen sulphite positive; triple sugar iron: glucose positive, lactose and sucrose negative, hydrogen sulphite positive. (C) ONPG test – negative (lactose non-fermenting bacteria)



(A)

(B)

Fig. 5. Agglutination test to detect the serogroup of *Salmonella* spp. The tests were negative (no agglutination present) for all the tested sera

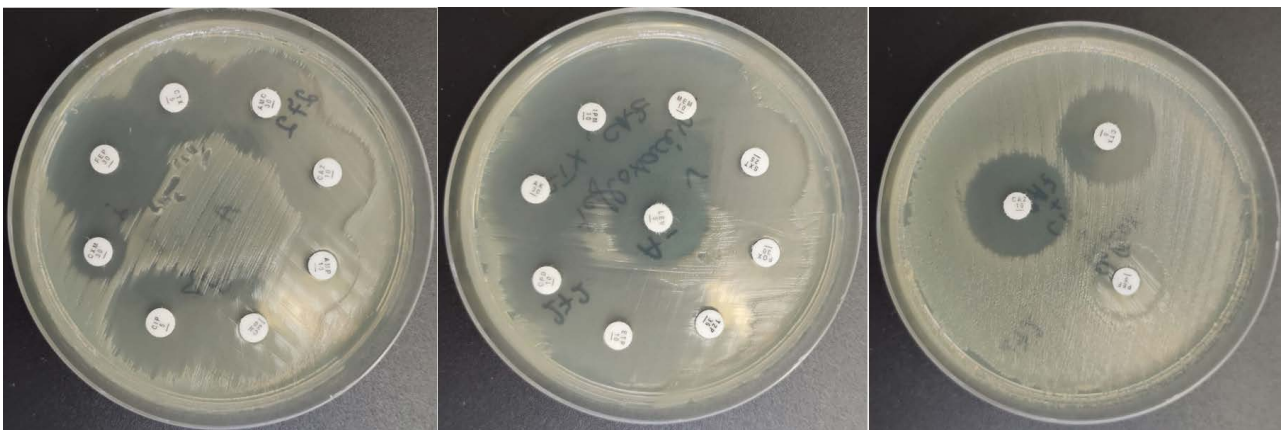


Fig. 6. Antibiotic susceptibility testing of the first isolated strain of *Salmonella* spp.

Table 1. Comparison of the antibiotic susceptibility testing for the strains of *Salmonella* spp. before and after receiving antibiotic treatment

Antibiotic	AST before antibiotic treatment (1 st strain)	AST after two weeks of antibiotic treatment (2 nd strain)
Ampicillin (iv)	Susceptible	Resistant
Cefotaxime	Susceptible	Susceptible
Ceftazidime	Susceptible	Intermediate*
Ciprofloxacin	Resistant	Resistant
Trimethoprim/sulfamethoxazole	Susceptible	Susceptible

*Susceptible, with increased dosage

Table 2. Minimum inhibitory concentrations for several antibiotics tested against *Salmonella* spp. using Vitek 2C

Antibiotic	MIC before antibiotic treatment (1 st strain)	MIC after two weeks of antibiotic treatment (2 nd strain)
Amikacin	Susceptible (<=1 µg/ml)	Susceptible (<=2 µg/ml)
Amoxicillin/clavulanic acid	Susceptible (4 µg/ml)	Susceptible (16 µg/ml)
Ampicillin	-	Resistant (>=32 µg/ml)
Cefepime	Susceptible (<=0.12 µg/ml)	Susceptible (<=1 µg/ml)
Cefotaxime	Susceptible (1 µg/ml)	Susceptible (<=1 µg/ml)
Ceftazidime	Susceptible (1 µg/ml)	Intermediate* (4 µg/ml)
Cefuroxime	-	Resistant (1 µg/ml)
Ciprofloxacin	Resistant (1 µg/ml)	Resistant (1 µg/ml)
Colistin	Susceptible (<=0.5 µg/ml)	-
Gentamicin	Susceptible (<=1 µg/ml)	Susceptible (<=1 µg/ml)
Ertapenem	Susceptible (<=0.12 µg/ml)	Susceptible (<=0.5 µg/ml)
Imipenem	-	Susceptible (<=0.25 µg/ml)
Meropenem	Susceptible (<=25 µg/ml)	Susceptible (<=25 µg/ml)
Piperacillin	-	Resistant (1 µg/ml)
Piperacillin/tazobactam	Resistant (16 µg/ml)	Resistant (16 µg/ml)
Tigecycline	Susceptible (<=0.5 µg/ml)	-
Trimethoprim/sulfamethoxazole	Susceptible (<=20 µg/ml)	Susceptible (<=20 µg/ml)

*Susceptible, with increased dosage

usual culture media, revealing a more abundant culture of *Salmonella* spp. (Figure 7).

The bacteria was identified based on the classical method of identification described before, followed by automatic identification with the same results. The antibiotic susceptibility testing showed a surprising phenomenon: the second isolated strain was more resistant to antibiotics than the first one. The results for the disk diffusion method (Figure 8) and the MIC, as well as a comparison between the two strains can be seen in Table 1 and Table 2. The treatment of the patient was changed according to the new AST.

Since the *Salmonella* spp. strain found in the pleural fluid was suspected to be a secondary dissemination from an intestinal carriage, a stool exam was also performed, but the results were negative (Figure 9).

Following the targeted antibiotic treatment according to the second AST, the evolution of the patient was favorable, with complete remission of the symptoms. Even more, he was able to restart his treatment with Ruxolitinib.

Intrigued by the shift in *Salmonella* susceptibility to antibiotics, molecular methods were used to investigate the genetic similarity of the strains. This aimed to determine if the resistance arose from a new infecting strain or if the initial strain adapted during the antibiotic treatment.

DNA extraction and molecular methods of differentiating between the two strains

The two strains were compared using a molecular method of diagnostic, commonly used for bacteria part of the *Enterobacteriaceae* family – Enterobacterial Repetitive Intergenic Consensus Polymerase Chain Reaction (ERIC-PCR).

To be able to perform ERIC-PCR, DNA was first extracted from the two strains, using a DNA extraction kit (IndiSpin Pathogen Kit, INDICAL BIOSCIENCE GmbH, Leipzig, Germany) and following the instructions of the producer.

ERIC-PCR was performed in a mix that contained 12.5 μ L DreamTaq Green PCR Master Mix (Thermo Fisher Sci-

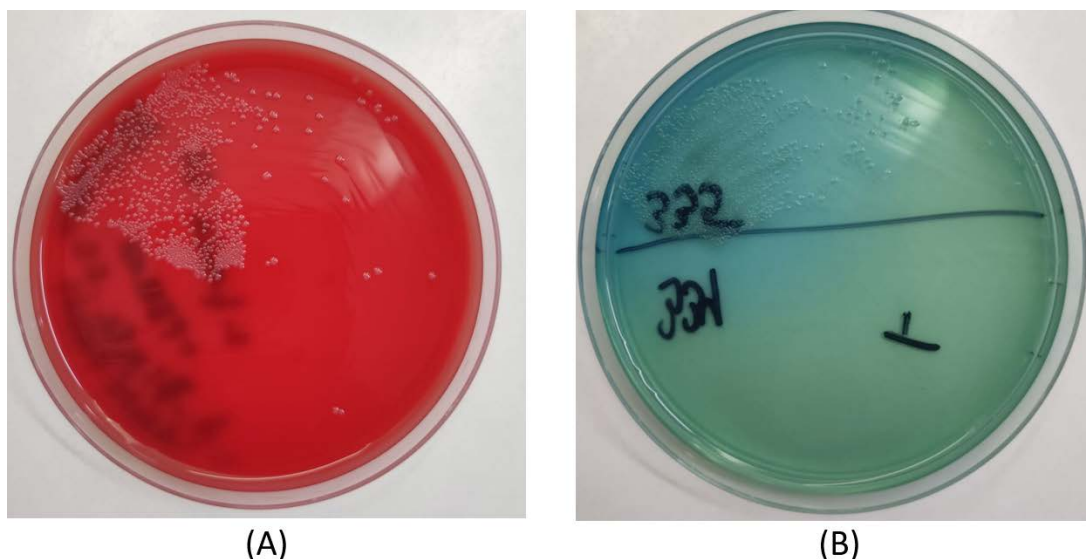


Fig. 7. Cultivation of the second sample of pleural fluid on (A) Sheep blood agar; (B) Lactose agar (lactose negative colonies)

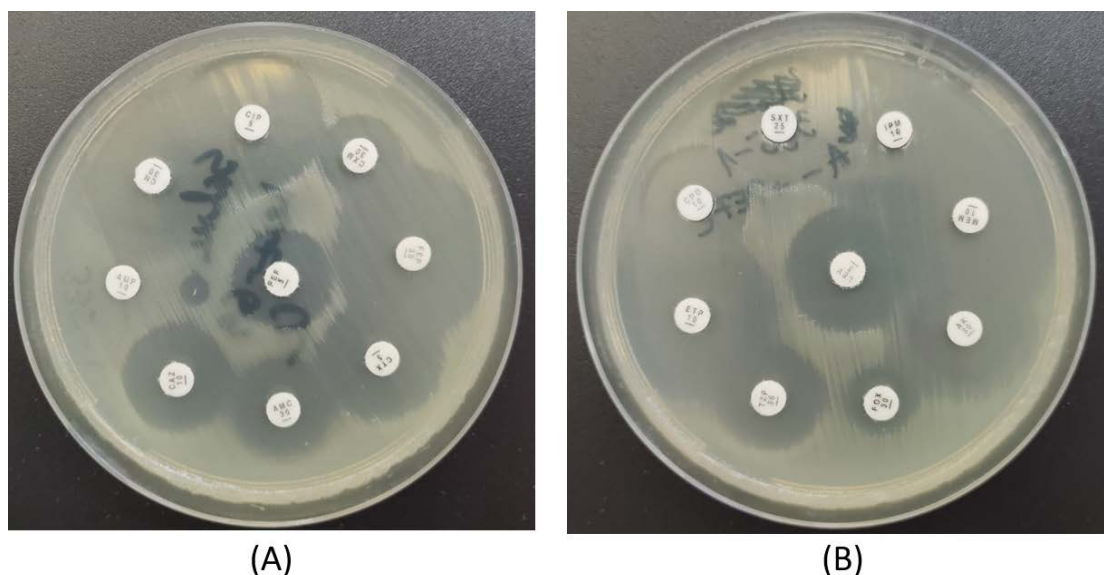


Fig. 8. Antibiotic susceptibility testing using the disk diffusion method for the second strain of *Salmonella* spp.

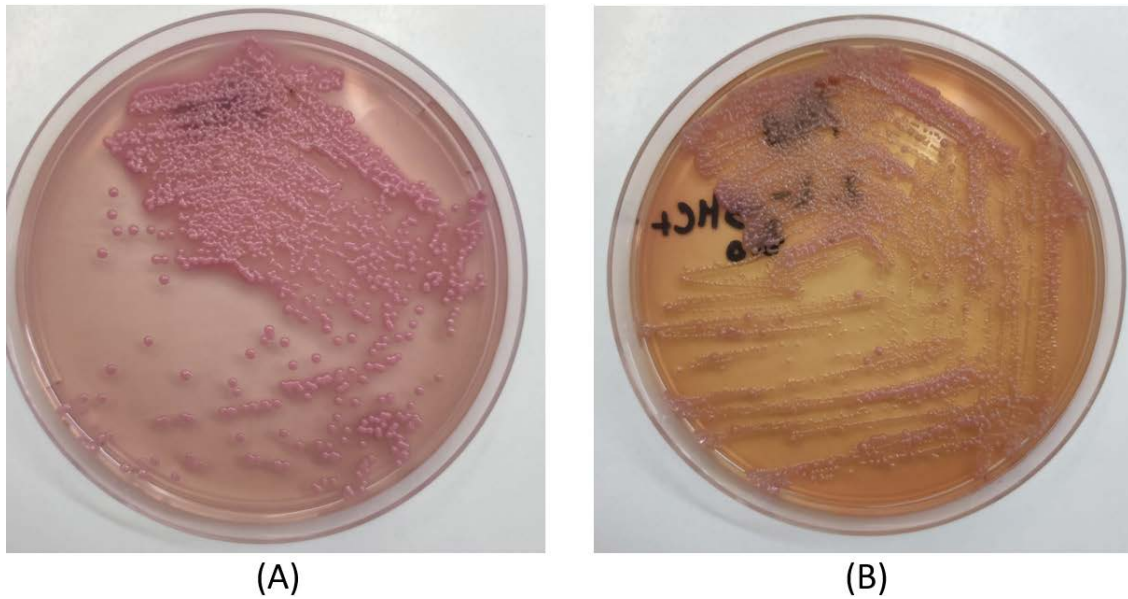


Fig. 9. Screening for carriage of *Salmonella* spp. in the stool sample of the patient; the sample was inoculated on: (A) MacConkey agar, where the presence of only lactose positive colonies can be seen and (B) Salmonella-Shigella agar (SS) – where some lactose negative colonies were present; the colonies were further isolated on SS agar followed by the study of their biochemical traits, but they were finally negative for the presence of *Salmonella* spp.

entific, Waltham, MA, USA), 0.5 µL of forward ERIC1 (5'-ATGTAAGCTCCTGGGGATTAC-3') and reverse ERIC2 (3'-AAGTAAGTGACTGGGGTGAGCG-5') primers (Thermo Fisher Scientific, Waltham, MA, USA), 1.5 µL of bacterial DNA and 10 µL water, to reach a final reaction volume of 25 µL.

The PCR protocol was adapted from Nath et al. [6], as follows: initial denaturation at 95°C for 5 minutes; 30 amplification cycles: 95°C for 30 seconds; annealing at 49°C for 1 minute; elongation at 72°C for 2 minutes; followed by final elongation at 72°C for 8 minutes.

The PCR products were resolved by gel electrophoresis in a 2% agarose gel (TopVision Agarose, Thermo Fisher Scientific, Waltham, MA, USA) containing GelRed (Biotium Inc., Fremont, CA, USA) for 2 hours at 80V. A molecular ladder (GeneRuler 1 kb, Thermo Fisher Scientific, Waltham, MA, USA) was loaded in the first lane of both

gels. The image of the results was captured using MiniBIS Pro (Bio-Imaging Systems, Neve Yamin, Israel).

The amplification of the PCR products can be seen in Figure 10. The amplicons had molecular weights between 250 base pairs (bp) and 1000 bp; a major difference between the two strains can be noted, as an amplification band in the case of the second strain was visible at approximately 200 bp.

The ERIC-PCR dendrogram was generated using GelJ Software (UPGMA method, with the band matching tolerance set at 1). The dendrogram showed a similarity of about 92% (Figure 11).

Discussions

Acute gastroenteritis is the most common clinical manifestation of *Salmonella* spp., but it can also cause fever and sustained bacteriemia without manifestations of enteric fe-

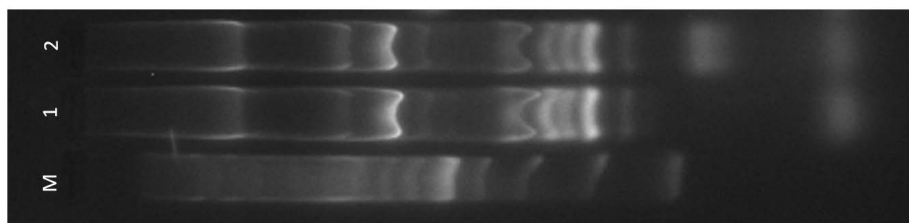


Fig. 10. The electrophoresis gel aspect after the migration of the PCR products: M – 1 kb molecular ladder; 1 – first strain; 2 - second strain

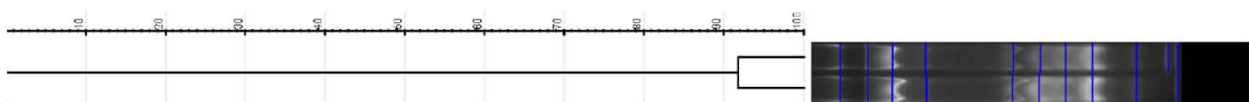


Fig. 11. Dendrogram comparing the two strains of *Salmonella* spp. A similarity of approximately 92% was found between the strains, proving the fact that the strains were almost identical, the second strain acquiring a gene which conferred it a higher degree of resistance to certain antibiotics

ver or enterocolitis. *Salmonella* bacteriemia can be caused by any serotype [3]. There are only several cases of pleuropulmonary salmonellosis described in literature [1–4].

In the present case, there are several possible explanations for the pleural empyema with *Salmonella* spp. and the way it caused the pleural empyema. Both start from the hypothesis that the patient was, at some point in their life, an intestinal carrier of *Salmonella* spp.

Firstly, as the patient already had several risk factors, during an episode of fever and transient bacteriemia a few weeks prior to the presence of the symptoms, *Salmonella* spp. could have disseminated from the gut to the lungs (causing the pleural empyema), and likely, to the spleen (producing the splenic abscess). In the case of the splenic abscess, due to the enlarged spleen caused by his leukemia, exploratory puncture and drainage of fluid from the abscess for bacteriological examinations was not possible, as it could easily lead to complications, therefore the exact etiology of the abscess is still unknown. Even though it was specifically looked for, the potential carriage in the intestine could have gone undetected, as the patient was already undergoing antibiotic treatment at the time when the stool sample was taken.

Secondly, similarly to the first hypothesis, the patient could have undergone an episode of transient bacteriemia, but *Salmonella* spp. could have only disseminated to the spleen, firstly causing only the splenic abscess. As time passed, the bacteria could have passed through the diaphragm, causing an irritation of the area, and superinfecting the pleural fluid, finally leading to the clinical manifestations of the patient.

Another important factor that should be considered is that the patient had multiple comorbidities, including myelofibrosis, for which he was receiving treatment with Ruxolitinib. A systematic review from 2017 published by Lussana et al [7] evaluated approximately 400 studies published between 2005 and 2017 related to the effect of Ruxolitinib on the chances of acquiring different types of infections. The reviewers concluded that infections can be considered a side effect of this treatment, most worthy to be mentioned out of the associated infections being herpes zoster infection, bronchitis, urinary tract infections, sepsis, tuberculosis, *Pneumocystis jirovecii* infections and hepatitis B reactivation. There are no studies directly connecting the Ruxolitinib treatment to *Salmonella* spp. infections, but chances are that this could play an important role in the patient's susceptibility to acquiring the bacteria.

There are several pathophysiological mechanisms taken into consideration regarding Ruxolitinib and its association with opportunistic infections. More and more studies suggest that Ruxolitinib has immunosuppressive effects through several mechanisms [8]: it interferes with several cytokines and growth factors and their signaling pathways and it lowers pro-inflammatory cytokines in patients with myelofibrosis [9]; it impairs natural killer (NK) cell func-

tion [10]; it has been associated with impairment of dendritic cell function [11].

Salmonella spp. serogroups can be assessed through agglutination tests with polyvalent sera for somatic O antigens, followed by slide agglutination with monovalent antisera for specific O antigens. However, a limitation of this procedure is that *Salmonella* serotypes can have different antigenicity. This can appear due to a modification or loss of surface antigens of the bacterial cell, which consequently lowers the sensitivity of the test [12].

Regarding the alterations in the pattern of the susceptibility and resistance to antibiotics, studies show that different strains of *Salmonella* have several ways by which they can acquire resistance to different classes of antibiotics [13]: the acquisition of plasmids (e.g., mph(A) gene on plasmid pU302L for resistance to macrolides); alteration of genes that confer resistance (e.g., a mutation of the gyrA gene could play a role in the resistance to fluoroquinolones); and different enzymes such as beta-lactamases which can inactivate aminopenicillins and cephalosporins. The occurrence of an extra amplicon band in ERIC-PCR suggests an important change in the bacterial genetic material, potentially related to acquisition of antibiotic resistance factors.

According to WHO Bacterial Priority Pathogen List (2024) [14], fluoroquinolone-resistant strains of *Salmonella* spp. are one of high priority groups of bacterial pathogens, their importance increasing steadily every year since 2017.

Conclusion

Pleural empyema with *Salmonella* spp. is an extremely rare secondary dissemination, but it should be taken into consideration, especially when a patient has risk factors for developing opportunistic infections or if they are known asymptomatic intestinal carriers of *Salmonella* spp.

In the present case, an interesting phenomenon appeared while the patient was undergoing antibiotic treatment, the strain acquiring resistance to the antibiotics that were used for treatment, underlying the importance of routine follow-up after antibiotic treatment administration as well as performing antibiotic susceptibility testing if the same bacteria is isolated, even if the etiology might initially seem the same.

Authors' contribution

AC (Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft)

CEB (Conceptualization; Writing – review & editing)

TC (Conceptualization; Formal analysis; Methodology; Supervision; Writing – review & editing)

ADM (Conceptualization; Formal analysis; Methodology; Supervision; Writing – review & editing)

AM (Conceptualization; Methodology; Supervision; Writing – review & editing)

Conflict of interest

None to declare.

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