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(CASE REPORT)

Pleural empyema due to *Salmonella enterica* in a patient affected by lung adenocarcinoma: A clinical case report

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Abstract

During last years, lung cancer treatment has rapidly changed thanks to novel drugs, such as immunotherapy and target therapy. Hence, an improvement of life expectancy, notwithstanding with a higher infectious risk. This is probably due to many factors, such as longer survival and immunosuppression; furthermore, novel drugs could increase infectious risk with different biologic mechanisms. However, correlation between infections and immunotherapy has not been completely clear, although lately has increasingly been described.

Salmonella enterica spp is an intracellular facultative anaerobe gram-negative bacillus that can spread to different sites, such as lung and pleura; nevertheless, an association between lung cancer and pleural empyema due to salmonella infection is rarely highlighted in literature and its management is challenging.

Hereby we outline the case of a 62-year-old woman affected by extended lung adenocarcinoma who developed salmonella-related pleural empyema during its active oncological treatment with chemo-immunotherapy by describing our multidisciplinary management model.

Keywords: NSCLC; Lung adenocarcinoma; Immunotherapy; Pleural empyema; Salmonella enterica; Antibiotics

1. Introduction

Salmonella was first described by Salmon and Smith in 1884, named after Daniel E. Salmon who isolated *Salmonella cholerasuis* from porcine intestine, one of its main reservoirs [1]. *Salmonella spp*. is an intracellular facultative anaerobe Gram-negative bacillus of the family of Enterobacteriaceae; this genus was last updated in the White-Kauffman-Le Minor scheme and embodies a wide range of serotypes [2].

European Union reports accounted a 17,9% of foodborne infections to *Salmonella spp.* for 2019, making it one of the most spread gut infections [3]. Salmonellosis can debut in two clinical outcomes: a minor salmonellosis, which is usually a self-limited enterocolitis, and a major salmonellosis characterized by typhoid fever [1], with more aggressive outcomes. Most infections are sustained by *S. enterica* subspecies *enterica*, as *S. typhimurium* and *S. enteritidis* [2], which mostly cause enterocolitis.

Extraintestinal focal infections (EFIs) are responsible for a 7-12% of all infections and can affect different sites, such as cardiovascular (endocarditis, aortitis, pericarditis), abdominal (cholecystitis), neurological (meningitis), genital and

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urinary tract, osteoarticular (osteomyelitis and arthritis) and pleuro-pulmonary [4]. Predisposing factors to develop such EFIs are increasing age, diabetes mellitus, hypertension, and chronic lung disease [5].

Pleural empyema is a manifestation of bacteremia from *S. enteritidis*, known for high blood invasiveness capacity [4]. Nevertheless, pulmonary lung infections in patients with lung cancer are rarely described in literature [6,7,8,9].

Here we outline the case of a 62-year-old woman affected by lung adenocarcinoma who developed salmonella-related pleural empyema during her active oncological treatment at San Luigi Gonzaga University Hospital, Orbassano (Turin), Italy.

2. Case presentation

A 62-year-old woman, administrative employee, ex-light smoker, was diagnosed with stage IV non-small cell lung cancer (adenocarcinoma, NSCLC) in 2016. Comorbidities were hypertension, hypertensive cardiopathy, cholecystectomy, Graves-Basedow disease (treated with tapazole), and osteopenia. Her medical history included previous deep venous thrombosis and pulmonary embolism. Atenolol 100 mcg/die was her only drug intake at the time of cancer diagnosis. Her familiar anamnesis did not report any oncologic disease.

From February to April 2016 the patient underwent through a left power port-a-cath first-line treatment with cisplatin 75 mg/mq -pemetrexed 500 mg/mq every three weeks for 4 cycles, followed by 20 cycles of pemetrexed maintenance with stable disease as best response.

During the treatment she developed three oligo-progressions, controlled by loco-regional therapy alone. Specifically, a first brain front-temporal metastasis treated with radiosurgery (18 Gy in one fraction); a further one on a relapse of left bronchogenic lesion, on which cytoreductive radiotherapy was practiced (54 Gy in 27 fractions across two months); eventually, a further brain left temporal metastasis, treated with radiosurgery six months later (18 Gy in one fraction).

Five years following the diagnosis, a lung re-biopsy was performed because of adrenal and left lung progression disease. Histological finding was K-RAS G12C mutant lung adenocarcinoma with PD-L1 tumor proportion score (TPS): 20%. EGFR, ROS-1, ALK, RET, BRAF and ERBB2 were wild type.

The patient received rechallenge of carboplatin, pemetrexed and pembrolizumab 200 mg flat dose every 21 days for 4 cycles for three months, followed by pemetrexed plus pembrolizumab maintenance for five months more for an overall 8 cycles, of which last of pembrolizumab alone, due to pemetrexed-related toxicity. She obtained partial response as best response and disease was then monitored every 3-4 months with total body CT scans.

A CT scan performed in June 2022 described a pleural chamber in the posterior costophrenic sinus, associated with homolateral diaphragm elevation and huge hemithorax retraction *[see fig.1]*.

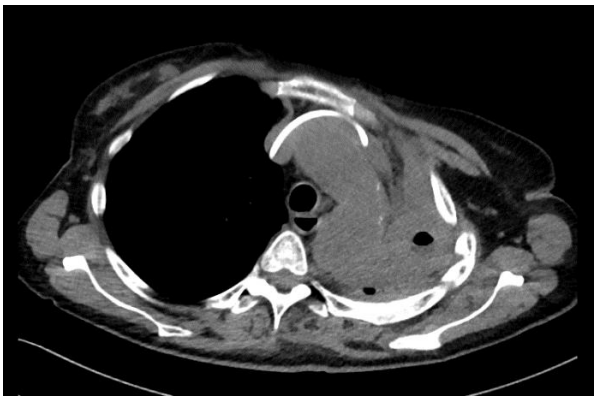
Three months later she began to develop fever (37.8 °C), inappetence, weight loss, diarrhea, fatigue and cough with foul-smelling sputum. Blood exams revealed increased C-Reactive Protein (CRP) to 9,84 mg/dl with negative peripheral and central venous blood hemoculture. She was treated with levofloxacin 500 mg once per day until seven days and she was tested negative for Sars-Cov-2.

A further later CT scan highlighted an increase of the known posterior-basal pleural chamber with atelectasis of adjacent parenchyma and amputation of the upper lobar bronchus *[see fig.2]*. The radiologic conclusion was pleural empyema/lung abscess. A chest tube drainage (CTD) was placed and subsequently the patient was hospitalized to the oncological department. Analysis on pleural fluid and bacterial culture grew *Salmonella enterica*. The specimen was judged inadequate for chemical examination.

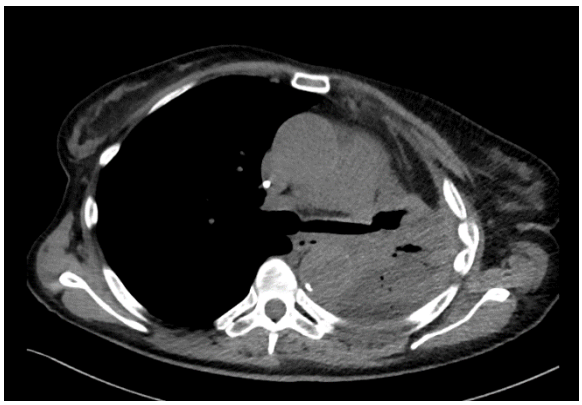
Urine culture and six sets of blood cultures were obtained for the onset of hyperthermia (38.8 °C) with negative results. She was treated with intravenous Piperacillin/Tazobactam 4.5g three times daily for two weeks. No antifungal therapy was practiced.

Subsequently, a CT scan detected a slight reduction in the pleural collection, communicating with a pulmonary abscess, with a significant hydro aerial level *[see fig. 3]*.

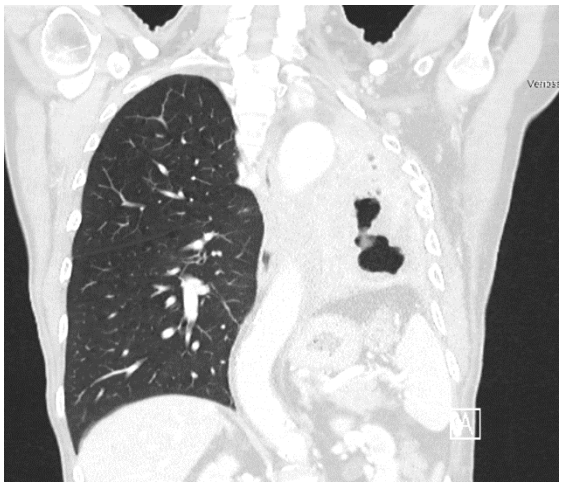
Figure 1 Coronal cut, CT scan (1st of June 2022)



A

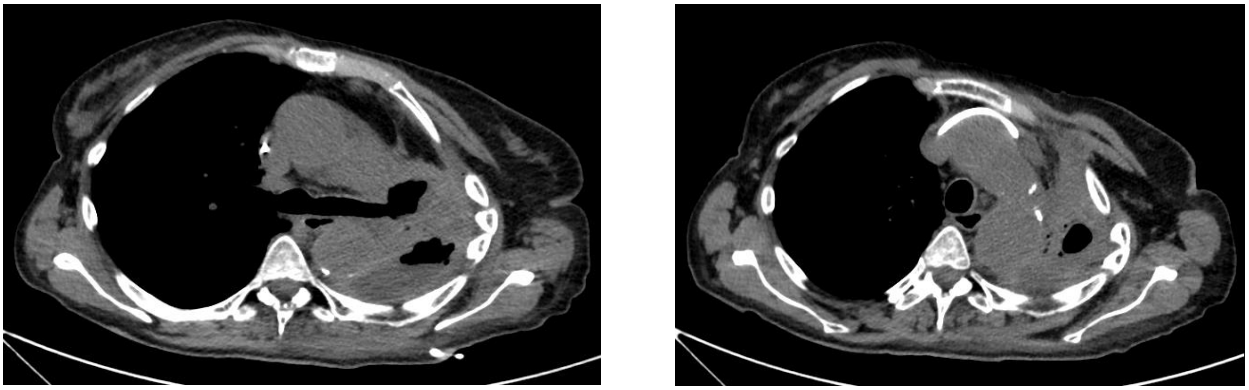


B



C

Figure 2 Axial cuts (A = upper, B = lower) and coronal cut, CT scan (14th of September 2022)



A **B**

Figure 3 Axial cuts (A=upper, B=lower), CT scan (27th of September 2022)

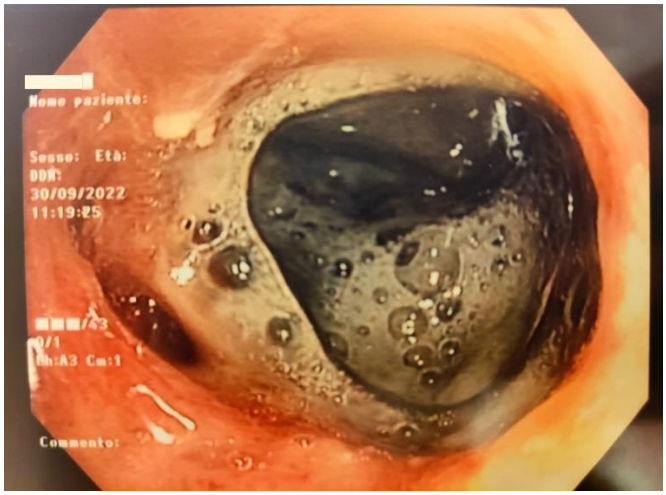


Figure 4 Fibrobronchoscopy (30th of September 2022)

Figure 5 Underwater sealed drainage (UWSD) system

Table 1 Overview of patient's oncological treatments

Treatment	Time frame	Cycles/dose
Cisplatin and pemetrexed	3 months	4
Pemetrexed maintenance	17 months	20
Radiosurgery on brain front-temporal lesion	-	18 Gy/one fraction
Cytoreductive radiotherapy on left bronchogenic lesion	2 months	54 Gy/27 fractions
Radiosurgery on brain left temporal metastasis	-	18 Gy/one fraction
Carboplatin, pemetrexed and pembrolizumab	3 months	4
Pemetrexed and pembrolizumab maintenance	6 months	8[a]
[a]*Pembrolizumab was infused alone in the 8th cycle due to leukocytosis and elevated liver enzymes.*		

Table 2 Timeline of patient's medical treatments

Treatment/procedure	Dose	Time frame
Levofloxacine	500 mg daily	8 days
Chest drainage tube (CDT) placement	-	5 weeks
Piperacillin/tazobactam	4,5 g three times daily	2 weeks
Underwater sealed drainage system (UWSD) placement	-	2 weeks
Alteplase irrigation through the CDT	4 mg daily	single infusion
Meropenem/ceftarolin/amikacin	1 g/600 mg/0,5 g daily	2 weeks
Ceftriaxone	2 g daily	4 weeks
Remdesivir	100 mg daily	4 days

One week later, a further respiratory specimen was obtained through a bronchoscopy, performed to explore bronchial architecture and exclude any potential visible pulmonary fistula. Nevertheless, terminal bronchus in left hemi system was described as ending in a hollowed formation, with no recognizable structure of the bronchial tree *[see fig. 4]*.

Cultures on bronchial washing turned negative, while cytological analysis revealed inflammatory granulocytes. In agreement with thoracic surgeon, an underwater sealed drainage (UWSD) system was placed to accelerate discharge of empyema, collecting a total of 660 ml of purulent exudate with a pace of 100 ml/die *[see fig. 5]*. Afterwards, her case was discussed collegially with thoracic surgeons; the patient was offered the option of fibrinolytic therapy, indicated to ease fluid evacuation as an effective alternative to video-assisted thoracoscopy (VATS) in the treatment of pleural empyema [10]. She accepted to receive intrapleural alteplase irrigation applied through the chest tube, and post-procedural outcome was monitored through a digital thoracic drainage system (DTDS).

Afterwards, due to several episodes of fever, increasing inflammatory indexes (procalcitonin: 20 ng/dL), pancytopenia (platelets: 122.000/μL and grade 4 neutropenia with 360 neutrophils/mm^3), we performed a CT scan detecting pneumonitis and requiring enhancement in antibiotic therapy with meropenem 1g, amikacin 0.5g and ceftaroline 600 mg for two weeks. Echocardiography showed no suspected vegetations and excluded endocarditis suspicion.

Subsequently, fever decreased and procalcitonin normalized. After consultation with an infectious disease specialist, switch to ceftriaxone alone 2 g/day was prescribed for a total of 12 weeks. Furthermore, she received remdesivir 100 mg for four days for positivity to Sars Cov-2 testing.

Patient's vital signs kept in range of normality during the whole hospitalization and she never suffered from dyspnea, neither needed oxygen therapy support. She was discharged apyretic, without dyspnea nor cardiovascular symptoms and in-situ tube drainage, although it was accidentally removed later. A CT scan was performed one month later with stable disease as best response; afterwards, she started an oncological "watchful wait" strategy with regular follow-ups. All antibiotics treatments were stopped. A timeline of patient's medical treatments is available below *[table 2].*

She underwent regular CT scans every three months which shown stable disease maintenance; she did not develop fever and/or infectious symptoms and kept conducing active life.

3. Discussion

Salmonella enterica can burst through EFIs, such as pleural empyema, especially in immunocompromised patients affected by malignancy. Our case report highlights the possible association between salmonellosis and lung adenocarcinoma. New drugs recently developed, as immunotherapy and targeted therapy [11], guaranteed patients longer life expectancy and higher life quality, although few consequences deserve consideration. Firstly, novel oncological treatments have several toxicities and correlations with rare infections yet to be investigated. Secondly, oncological population is more prone to suffer from diseases intrinsic to their condition, such as second malignancies, cardiovascular diseases and infections. Additionally, these patients mainly consist of elderlies with a rich past medical history, including risk factors for pneumonia.

Specifically, the patient in our case report had a long and various history of oncological treatments *[see Table 1]*, since 2016, receiving immunotherapy, chemotherapy and radiotherapy, the two latter well-known for being immunocompromising: impaired cell-mediated immunity is directly related to higher risk of EFIs [8]. Regarding immunotherapy, only few studies describe its link with lung infections [12,13].

Interestingly, our patient was asymptomatic for respiratory and gastrointestinal symptoms, and we found signs of salmonellosis mainly through imaging (and generic inflammatory signs), making the diagnosis more challenging; the different treatments (lung irradiation, prolonged chemotherapy, previous steroid intake), may justify the local and systemic anergy, letting Salmonella seed in the lung. Indeed, consistent previous immunosuppression is described as a promoter of primary bacteremia without organ involvement [4,14,15].

3.1. Patient's perspective

The patient was discharged in good clinical conditions, apyretic and without dyspnea or infective symptoms. She resumed her job as an administrative employee. Two weeks later, we had a phone-based assessment of her clinical conditions, reporting active life without significant clinical impairments with a satisfying life quality. She showed good tolerance of antibiotic drugs and she completely recovered since treatment stop. Lastly, she was seen as outpatient in March 2023, pursuing a "watchful wait" monitoring strategy; all she complaint was asthenia, most likely due to her oncological history; no other symptom was referred.

4. Conclusion

Pleuropulmonary infections sustained by non-typhoidal Salmonella showed high mortality especially in patients with lung cancer; nevertheless, in our case the patient is still alive and in good clinical conditions.

From all the evidence above, we conclude that in patients treated with several lines and techniques rare lung infections should be ruled out, particularly if patients are long-treated, with significative comorbidities and without specific respiratory or gastrointestinal symptoms. This rare lung infections should be managed in a multidisciplinary setting, with the support of oncologist, pneumology, thoracic surgeon and infectious disease physician.

Compliance with ethical standards

Disclosure of conflict of interest

The authors F. Passiglia and S. Novello declare the following financial interests/personal relationships which may be considered as potential competing interests:

- F. Passiglia: advisory/Consultant fee: Astrazeneca, Janssen, Amgen, Sanofi, MSD, BMS, Beigene, Thermofisher Scientific
- S. Novello: speaker bureau/advisor's fee from Eli Lilly, MSD, Roche, Bristol Myer Squibb, Amgen, Takeda, Pfizer, Thermo Fisher Scientific, Astra Zeneca and Boehringer Ingelheim

The authors O. Cantale, A. Mogavero, S. Carnio, L. Consito, C. Mecca declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Statement of informed consent

Consent to publication was obtained from the person whose anonymized individual data are contained in this work. A copy can be provided at any stage if requested.

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