**Case report**

**CASE REPORT OF A PATIENT PRESENTING WITH PYREXIA OF UNKNOWN ORIGIN (PUO): ENTERIC FEVER WITH LUNG ADENOCARCINOMA**

**Abstract**

Adenocarcinoma is the most common type of lung cancer, accounting for approximately one-half of lung cancer cases. Patient can present with symptoms such as cough, fever, dyspnea, chest pain, night sweats, anorexia, weight loss and weakness. Enteric fever is a systemic disease which is characterized by fever and abdominal pain and caused by Salmonella typhi or Salmonella paratyphi, usually seen in areas of poor sanitation and hygiene. Fever is documented at presentation in majority of cases of salmonella infection. The co-existing of Salmonella typhi bacteraemia and adenocarcinoma lung is uncommon in clinical practice. We report a case of an individual who presented with fever of unknown origin and later diagnosed with Adenocarcinoma lung, and during the evaluation of fever was incidentally found to have Salmonella typhi infection. This rare clinical association presenting only with fever as symptom is a diagnostic challenge for the clinicians and we would like to highlight the importance of extensive workup, early diagnosis and initiation of appropriate treatment for such rare clinical scenarios.

**Introduction**

In Enteric fever, fever is the major symptom documented at the time of presentation in >75% of cases (2). So, a high index of suspicion for this disease is necessary when a person presents with fever with a history of recent travel to an endemic area and also history of food intake from suspected non-hygienic areas (1). The average incubation period for Salmonella typhi is 10–14 days, but it can range from 5 to 21 days (2). The infectivity depends on the inoculum size and the host’s immunity status (8). Salmonella typhi and Salmonella paratyphi infections are often indistinguishable. The common medical presentation often includes headache (80%), chills (35–45%), cough (30%), sweating (20–25%), myalgias (20%), malaise and arthralgia (2). Gastrointestinal presentations include anorexia (55%), abdominal pain (30–40%), nausea (18–24%), vomiting (18%), diarrhoea (22–28%) and constipation (13–16%) (2). Physical findings include coated tongue, splenomegaly and abdominal tenderness. Fever, if untreated, can continue for up to 4 weeks. Clinically, non-typhoidal salmonella is found to cause complications like gastroenteritis, sepsis, focal infections such as septic arthritis, osteomyelitis, cholecystitis, endocarditis, meningitis and also carrier state (3 - 5). Extra-intestinal manifestation of infection with Salmonella occurs less frequently and are mostly seen in immunocompromised individuals (9).

The World Health Organisation classifies epithelial lung cancers into 2 major types namely small-cell lung cancer (SCLC) and non-small-cell carcinomas (NSCLCs) (2, 4 - 5). The latter includes - Adenocarcinoma, Squamous cell carcinoma and Large-cell carcinoma. Adenocarcinoma of carcinoma has high prevalence among the smokers and accounts for about 50% of lung cancers (10).

**Case** **Presentation**

We report a case of 51-year-old female, with no known comorbidities, who was admitted with complaints of fever for 3 weeks. Fever was intermittent, low grade and occasionally associated with chills. She had evening rise of temperature. There was no history of cough, breathlessness, abdominal discomfort, weight loss. Her bowel and bladder habits were normal. She was admitted in a local hospital and received multiple antibiotics. She came to our hospital for further evaluation and management.

At the time of admission, she was febrile (temperature of 100.8-degree Fahrenheit), had pulse rate of 84 beats per minute, blood pressure of 110/70 mmHg and respiratory rate of 20 breaths per minute with oxygen saturation of 97% on room air. Systemic examination did not reveal any obvious abnormality. Considering her symptoms with no obvious clinical finding to suggest a diagnosis, we went ahead with further Investigations.

The initial laboratory investigations revealed: White Blood Cell count of 4750/µL, with Neutrophils of 59.5% and Lymphocytes of 32.9%; elevated inflammatory markers: C-Reactive Protein (CRP) of 116 mg/dL and Erythrocyte Sedimentation Rate (ESR) of 64 mm/hour. Haemoglobin of 11.8 g/dL, Haematocrit of 35.1%, Mean corpuscular volume (MCV) of 86.8 fL, Platelet count of 1,55,000/µL. Serum electrolytes revealed, Serum sodium of 135.9 mmol/L, Serum potassium of 3.7 mmol/L. Her serum creatinine was 0.72 mg/dL. Random blood sugar was 130 mg/dL, HbA1C of 5.6% and coagulation studies were within normal limits. Total bilirubin was 0.25 mg/dL and Direct bilirubin 0.11 mg/dL, AST (SGOT) 75.6 IU/L, ALT (SGPT) 47.8 IU/L and ALP 133 IU/L, total serum protein 7.6 g/dL, serum albumin 3.9 g/dL and serum globulin 3.74 g/dL. Her serum iron levels were 21.9 µg/dL, serum ferritin of 410.8 ng/mL, TIBC of 226.1 µg/dL and TSAT of 9.6 %. Urine routine examination revealed 4-6 pus cells / high power field and 5-8 RBCs / high power field. (Table 1 depicts the relevant lab parameters and observed values for easy reference)

**Table 1:** Relevant Lab parameters and Observed values

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| **LAB PARAMETER** | **OBSERVED VALUES** |
| Total White Blood Cell Count | 4750 /µL |
| Neutrophil count | 59.5% |
| Lymphocyte count | 32.9% |
| C – Reactive Protein (CRP) | 116 mg/dL |
| Erythrocyte Sedimentation Rate (ESR) | 64 mm/hour |
| Haemoglobin | 11.8 g/dL |
| Haematocrit | 35.1% |
| Mean Corpuscular Volume (MCV) | 86.8 fL |
| Platelet Count | 1,55,000 /µL |
| Serum Creatinine | 0.72 mg/dL |
| Serum Sodium | 135.9 mmol/L |
| Serum Potassium | 3.7 mmol/L |
| Random Blood Sugar | 130 mg/dL |
| HbA1C | 5.6% |
| Total Bilirubin | 0.25 mg/dL |
| Direct Bilirubin | 0.11 mg/dL |
| AST (SGOT) | 75.6 IU/L |
| ALT (SGPT) | 47.8 IU/L |
| Alkaline Phosphatase (ALP) | 133 IU/L |
| Total serum protein | 7.6 g/dL |
| Serum Albumin | 3.9 g/dL |
| Serum Globulin | 3.74 g/dL |

Blood cultures were sent and she was empirically started on iv antibiotics (Ceftriaxone) and other supportive measures. Her routine Chest X-ray revealed a homogenous opacity involving the right mid and lower zones suggestive of a mass (Figure 1). We went ahead with a Contrast Enhanced Computerised Tomography (CECT) of Chest and Abdomen which revealed large hypodense lesion involving the anterior and lateral segments of right lobe away from the mediastinum (Figure 2). The lesion was found to have areas of calcification within. Post contrast images showed heterogenous enhancement. CECT findings were suspicious of malignant etiology.

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| **Figure 1:** Depicts Chest X - ray showing homogenous opacity involving the right mid and lower zones suggestive of a mass lesion. |
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| **Figure 2:** Depicts Contrast Enhanced Computerised Tomography (CECT) of Chest and Abdomen which revealed large hypodense lesion involving the anterior and lateral segments of right lobe away from the mediastinum. | |

Pulmonology consult was taken and Radial Endobronchial Ultrasound (Radial EBUS) guided cryo-biopsy was done and samples were sent for Histopathological examination. She was having fever spikes during the course of hospital stay. Meanwhile, her blood cultures were reported to have growth of Salmonella typhi sensitive to Ceftazidime, Trimethoprim-Sulfamethoxazole, Ampicillin, Amoxicillin, Chloramphenicol and Azithromycin. She was started on culture sensitive antibiotic (Trimethoprim-Sulfamethoxazole), antipyretics and other supportive measures. She became afebrile after starting antibiotics. Patient improved symptomatically during the hospital stay. After 6 days of hospital stay and antibiotic treatment, she was discharged in a hemodynamically stable state with Oral Cotrimoxazole (Trimethoprim-Sulfamethoxazole).

The patient was followed up in OPD after 1 week. She improved clinically and her inflammatory markers were down-trending, C-Reactive Protein (CRP) of 5.26 mg/dL. Her Right lower lobe lung mass - Histopathological examination of cryo-biopsy was reported as Adenocarcinoma, lepidic pattern with mucinous areas. She was referred to Department of Pulmonology and Department of Medical Oncology for further management.

**Discussion**

Salmonellae are gram-negative, non-spore-forming, facultatively anaerobic bacilli (2, 4). Bacteremia caused by Salmonella usually characterized by the presence of a high-grade fever which lasts for days to weeks (6). Salmonella infection in an immunocompromised individual is very important as it can present with atypical symptoms and clinical presentations. Diagnosis in this setting is also challenging and can mislead the clinician. Therefore, a higher level of suspicion is needed and is crucial for diagnosing the disease early and initiating appropriate treatment (8). The definitive diagnosis of salmonella typhi infection is isolation of the organism from blood, bone marrow and other sterile sites. Administering of proper antibiotics can prevent the severe complications associated with Salmonella infection and further reduces the mortality. Empirical anti-microbial of choice are Ceftriaxone and Azithromycin. Both these antibiotics are extensively used in both complicated as well as uncomplicated salmonella infections (14). If there is a concern of Ceftriaxone resistance, empirical Carbapenems are used (2, 13). Always anti-microbial therapy should be titrated based on culture and sensitivity reports. In our patient the strain of Salmonella was sensitive to Trimethoprim-Sulfamethoxazole and the same was initiated.

Optimal management of malignancies like lung cancer requires prompt tissue diagnosis (11). Most of the lung cancers tend to present in an advanced stage and are often diagnosed based on biopsies or cytological assessment (2). Most common presentation of lung cancer is chronic cough (8–75%) and fever constitutes 20% (2). Adenocarcinomas may be seen on imaging as bilateral nodular, interstitial or ground glass opacities or less commonly it can be seen as unilateral solid or ground glass nodules or masses (7). Moreover, lung cancers have high metastatic potential and commonly spreads to brain, liver, adrenal gland and bone (12).

In our case we encountered a homogenous opacity involving the right mid and lower zones, more in favour of a mass lesion. Tissue sampling is mandatory to confirm the diagnosis in patients with high suspicion of lung cancer. Transbronchial biopsy using fibreoptic bronchoscopy, Fine-needle Aspiration (FNA) or percutaneous biopsy using image guidance or Endobronchial ultrasound (EBUS)-guided biopsy are the minimally invasive preferred modalities for obtaining a tissue diagnosis in case of lung cancer. In our case, Radial Endobronchial Ultrasound (Radial EBUS) guided cryo-biopsy was done and the histopathological examination of specimen revealed Adenocarcinoma, lepidic pattern with mucinous areas.

**Conclusion**

Coexisting salmonella typhi infection and adenocarcinoma is not very common and almost always incidental as in this case. In this case the patient presented with fever for 3 weeks and there was no history supporting the possibility of adenocarcinoma lung. Extensive workup of the patient with pyrexia of unknown origin including imaging and further proceeding with tissue diagnosis led us to the diagnosis of adenocarcinoma lung. Here, we want to highlight that the presentation in this patient was only fever and the possibilities turned out to be either an infection or malignancy. So, the fever can be due to Salmonella infection or due to underlying lung adenocarcinoma. As a take home message, we want to highlight that in a patient with malignancy, fever can be due to malignancy per se, immunocompromised state predisposing to infections or co-existing infection.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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