CO-EXISTENT EPIDERMAL GROWTH FACTOR RECEPTOR POSITIVE METASTATIC LUNG ADENOCARCINOMA WITH PULMONARY TUBERCULOSIS

Muhammad Ramzan*, Talha Mahmud*

ABSTRACT

57-year-old male resident of Gilgit and worker at a medical dispensary was diagnosed to have pulmonary tuberculosis (PTB) and was on anti-tuberculous treatment (ATT) for 3 weeks. He had a 20 pack-years cigarette smoking history, without any medical co-morbid conditions. He came to emergency department with worsening of dyspnea, cough, sputum & weight loss and required oxygen inhalation to maintain saturation. His chest radiology revealed bilateral diffuse pulmonary nodules; current 3 sputa smears were negative for acid fast bacilli (AFB) and spirometry had restrictive pattern. Histopathology of transbronchial biopsies (under fluoroscopy) was consistent with metastatic lung adenocarcinoma and bronchial washings (negative for AFB staining) were positive for mycobacterium tuberculosis complex without resistance to rifampicin (GeneXpert MTB/Rif assay). Molecular analysis of biopsy tissue was positive for epidermal growth factor receptor (EGFR) mutation showing exon-19 deletion. Besides continuing oxygen and ATT, tyrosine kinase inhibitor (TKI) drug erlotinib was started. He showed remarkable improvement in dyspnea, gained weight and was off oxygen for 12 months along with considerable radiological clearing of lesions. After one year, he was hospitalized again due to intractable dyspnea, respiratory failure and worsening in radiological shadows and passed away.

Key Words: Adenocarcinoma; EGFR; Epidermal Growth Factor Receptor; Pulmonary Tuberculosis; Transbronchial Lung Biopsy

INTRODUCTION

Disseminated bronchogenic carcinoma can mimic or be masked by PTB and is suspected when a predominant or growing nodule or patch is present and show little or no improvement despite ATT. Co-existent tuberculous and metastatic lung cancer lesions in the same patient can cause diffuse shadowing on chest radiograph/CT scan and may impose diagnostic confusion. Molecular analysis of cancer tissue (EGFR and anaplastic lymphoma kinase/ALK mutations) in patients with non small cell lung cancer (NSCLC) has become the standard recommendation of international guidelines. In patients with who have positive EGFR or ALK mutation, treatment with a TKI has become the first line management and only non responders are offered anti cancer chemotherapy.

CASE REPORT

57-year-old male resident of Sikardu (Gilgit) presented in emergency room with worsening of dyspnea (mMRC grade 4), cough with mild sputum & weight loss. One month ago, he was diagnosed to have PTB due to 2 months history of cough with sputum and widespread shadowing on his chest radiograph and was on empirical ATT started by his physician. He was an ex-cigarette smoker (20 pack-years), used wood/coal stove during winters, was a worker at a medical dispensary and had no domestic exposure to pet animal or birds. He had no medical co-morbidities and also had a negative surgical history. He was married, his wife was in good health and he had 4 healthy children. His younger sister suffered from pulmonary tuberculosis a few years ago and completed ATT.

Upon examination, he was cyanosed and anxious with a pulse of 110/m, BP 100/70 mmHg, temperature 98.6 F and regular respirations of 28/m. His SpO2 was 78% on room air and 92% on nasal O2 inhalation at 5 L/m. Chest examination revealed reduced chest movements in lower parts, increased vocal resonance right middle part and bilateral coarse inspiratory crackles in middle and lower parts. Chest radiograph (figure 1a) showed preserved lung volumes, bilateral nodular...
opacities with patchy confluent shadows bilaterally in lower zones and shaggy heart borders. Based on these findings, he was hospitalized in suspicion of diffuse lung disease (TB versus interstitial lung disease versus disseminated malignancy); ATT (EHRZ) was continued and he was given oxygen, pyridoxine 25 mg, prednisolone 30 mg daily, and further work up was planned.

After 2 weeks of supportive treatment, he could maintain oxygen saturation while breathing oxygen at 3 L/m. Arterial blood gas analysis showed PH 7.32, PO\textsubscript{2} 67 mmHg, PCO\textsubscript{2} 48 mmHg and HCO\textsubscript{3} 24.3. He could walk 240 meters (with 2 L/m oxygen inhalation) during 6 minute walk test (6MWT) and desaturated to 82% at the end of exercise. His 3 sputa smears were negative for AFB and spirometry showed restrictive pattern with FVC 1.20 L (36% predicted), FEV\textsubscript{1} 0.93 L (34% predicted) & FEV\textsubscript{1}/FVC 77.5% (figure 1b). Laboratory tests included HB 17.2 gm/dl, WBC 11.01/cmm, platelets 123000/cmm, HCT 52.84%, MCV 72, MCHC 32.5, BUN 28 mg/dL, creatinine 0.9 mg/dL, AST 63 IU, ALT 47 IU, ALP 252 IU, bilirubin 0.8 mg/dl, Na 139 mmol, K 4.1 mmol, albumin 3.5 gm/dL and viral serology was negative for hepatitis B and C. Ultrasound examination of abdomen and pelvis was normal. HRCT chest had extensive randomly distributed nodules with few areas of conglomerate shadows (figure 2).

Bronchoscopy was done using flouroscope guidance (without sedation) and bronchoalveolar lavage (BAL) was taken from right middle lobe (80% lymphocytes, 20% neutrophils, positive for malignant cells, AFB smear negative and MTB DNA detected but rifampicin resistance not detected on Gene-Xpert-MTB/RIF
Transbronchial lung biopsies (TBLB) from right lower lobe segments were consistent with moderately differentiated lung adenocarcinoma whose molecular analysis was positive for EGFR mutation (exon-19 deletion).

Besides continuing oxygen and ATT, TKI erlotinib (tarceva®) 150 mg once daily was started. Regular follow up visits were conducted initially every 2 weeks for 1 month and then every 3 months. Follow up after 6 months showed remarkable improvement in his general health (dyspnea mMRC 2, 240 meters distance covered during 6MWT without oxygen), gained 6 kg weight and was off oxygen (SpO₂ 88-90% on air) along with much radiological clearing both on chest radiograph and CT (figure 3a, b, c, d). There was also improvement in spirometric measurements including FVC 2.40 L (72% predicted), FEV₁ 1.85 L (66% predicted) & FEV₁/FVC 77%. He remained in good health for 12 months and stayed at his home in Sakardu with the family. After one year, he was hospitalized again due to intractable dyspnea, respiratory failure and worsening in radiological shadows. He was given antibiotics, steroids, oxygen, bronchodilators and non invasive positive pressure ventilation (NIPPV) to whom he partially responded. He underwent bronchoscopy again and had BAL and TBLB in suspicion of pulmonary infection versus change in histology of lung cancer or development of resistance to EGFR TKI, which many patients tend to develop over time and can have worsening of radiological shadowing. To our surprise, he still had EGFR positive adenocarcinoma lung with the same exon 19 deletion and BAL was also negative for any infectious etiology. His erlotinib was continued along with other supportive treatment for 2 weeks but unfortunately he could not make it and passed away.

**DISCUSSION**

Miliary PTB is a rare cause of acute respiratory failure and ARDS with a potential of delayed diagnosis as opposed to more typical symptoms of pulmonary or pleural TB. Besides AFB staining and culture for diagnosis of TB, the recently adopted GeneXpert MTB/RIF assay is an automated nucleic acid amplification test (useful in both pulmonary and extrapulmonary forms of TB) that can simultaneously detect Mycobacterium tuberculosis DNA and rifampicin resistance; having the sensitivity and

![Figure 3a](image1.png) ![Figure 3b](image2.png)
specificity of 81 and 99 percent, respectively. Both PTB and disseminated lung cancer can also present with diffuse radiological shadowing and therefore impose diagnostic confusion. Procedures performed through flexible fiberoptic bronchoscopy (FOB) can provide greater diagnostic utility in patients with PTB and lung cancer. BAL is a minimally invasive procedure performed during FOB to obtain a sample of alveolar cells and can be diagnostic in a variety of conditions including PTB and malignant infiltrate. TBLB is the most helpful investigation in the evaluation of diffuse parenchymal lung disease and can be diagnostic in disseminated lung cancer including lymphangitis carcinomatosis, sarcoidosis, hypersensitivity pneumonitis, transplant rejection, and mycobacterial and invasive fungal infections.

Lung cancer is generally classified as either small cell (20%) or non-small lung cancer (NSCLC) in 80% including adenocarcinoma (30-35%), squamous cell carcinoma (20-25%) and large cell carcinoma (10-15%). Treatment of small cell lung cancer is related to the stage at diagnosis, with 70% of patients having extensive disease at presentation being eligible for chemotherapy alone. Treatment of NSCLC differs significantly by stage. Stage IA, IB, IIA, and IIB cancers are all candidates for surgery. Advanced stages are dealt with chemo-radio therapy (stage III) and chemotherapy alone (stage IV). Molecular selection of patients improves therapy outcomes for patients with advanced NSCLC. Somatic genomic alterations known as driver mutations occur in cancer cells that encode for proteins critical to cell growth and survival and targeted therapy involves agents that target these specific molecular pathways including EGFR (most common in non smoker female patients of East Asian decent with adenocarcinoma) and ALK. EGFR exists as a monomer on the normal human cells surface; it must dimerize to activate the enzyme tyrosine kinase (TK) whose activity is tightly controlled in normal cells & the mutant TK receptor is responsible for uncontrolled tumor growth in NSCLC. Successful therapeutic targeting of oncogenically activated EGFR TK (erlotinib, gefitinib, afatinib) is first line treatment of patients with advanced NSCLC exhibiting EGFR mutations, commonest being exon 19 deletion or the exon 21 L858R mutation. These targeted agents improve progression-free survival compared with traditional chemotherapy. Non responders & patients with disease progression should be given cancer chemotherapy (second line). A secondary mutation during course of treatment in EGFR has been associ-
ated with acquired resistance to EGFR TKIs. 7

Our patient presented with respiratory failure in the presence of diffuse lung disease and was managed initially with ATT & prednisolone in the suspicion for disseminated pulmonary tuberculosis. After 2 weeks of management when he did not show expected improvement, bronchoscopy (BAL, TBLB) was carried out and transbronchial biopsies were diagnostic of disseminated lung adenocarcinoma. According to international recommendations, we proceeded with molecular testing and found the tumor to be EGFR positive (exon 19 deletion). His prognosis was dismal at the time of presentation but treatment with erlotinib showed remarkable clinical and radiological improvement and restored his life quality and probably span for at least a year.

REFERENCES


5. Stephanie YC. Common Respiratory Symptoms, Pulmonary Imaging, and Procedures. ATS review for the pulmonary boards 2015.


7. Sujith VC, Kheir F. Lung Neoplasms. ATS review for the pulmonary boards 2015.