Metastatik Akciğer Adenokarsinom Tanılı Hastada Afatinib Tedavisi Altında Gelişen Tüberküloz Enfeksiyonu

Tuberculosis Infection Under Afatinib Therapy in a Patient with Metastatic Lung Adenocarcinoma

Özet:

Akciğer kanseri ile akciğer tüberkülozunun (TB) aynı anda teşhis edilmesi nadir bir durum olmakla beraber, akciğer kanseri tanılı hastalar süreçleri boyunca immünsüpresif durumları (hastalığın seyri ve tedavi süreçlerine bağlı) ve ortak risk faktörlerinden dolayı tüberküloz açısından risk altındadırlar. Akciğer kanseri ile akciğer tüberkülozu arasında klinik ve radyolojik özelliklerin neredeyse her zaman benzer olması ise tanıyı geciktirebilmektedir. Bu nedenle akciğer kanserli olgularda TB' dan şüphelenilen her durumda mikrobiyolojik testler cömertlikle kullanılmalıdır. *Mycobacterium tuberculosis* çevresindeki değişikliklerin algılaması ve bunlara yanıt vermesini sağlayan önemli bir düzenleyici olan tersinir protein fosforilasyonu, konakçıda hayatta kalması için gerekli dinamik adaptif yanıtların altında yatan ana sinyal mekanizmasıdır. Bu fosforilasyon serin/tirozin kinaz inhibitörleri ile sağlanmaktadır. Bu makale akciğer kanserinde kullanım yaygınlığı gittikçe artan tirozin kinaz inhibitörlerini kullanan olgularda tüberküloz tanı ve tedavisinin yönetimine dikkat çekmek amacı ile yazılmıştır. Burada tirozin kinaz inhibitörü (afatinib) tedavisi sırasında geniş spektrumlu antibiyotik tedavisine rağmen devam eden ateş ve öksürüğü sonrasında akciğer TB tanısı alan akciğer adenokarsinomlu olgu sunulmuştur.

Anahtar Kelimeler: Akciğer kanseri, tüberküloz, tirozin kinaz inhibitörleri

Abstract

Although it is rare for lung cancer and pulmonary tuberculosis (TB) to be diagnosed at the same time, patients diagnosed with lung cancer are at risk for TB due to their immunosuppressive status (related to the course of the disease and treatment) and common risk factors. The fact that clinical and radiological features are almost always similar between lung cancer and pulmonary TB may delay the diagnosis. Therefore, microbiological tests should be used generously whenever TB is suspected in patients with lung cancer. Reversible protein phosphorylation, an important regulator that enables *Mycobacterium tuberculosis* to sense and respond to changes in its environment, is the main signalling mechanism underlying

the dynamic adaptive responses required for host survival. This phosphorylation is provided by serine/tyrosine kinase inhibitors. In this article, we report a case with lung adenocarcinoma diagnosed as pulmonary TB after persistent fever and cough despite broad-spectrum antibiotic treatment during afatinib treatment, a tyrosine kinase inhibitor.

Key Words: Lung cancer, tuberculosis, tyrosine kinase inhibitors

Introduction:

While lung cancer is the leading cause of cancer-related deaths in the world, tuberculosis (TB) is the leading cause of infection-related deaths. It has been reported that TB may increase the risk of lung cancer and affect the prognosis of lung cancer (1). The coexistence of pulmonary TB and lung cancer is rare and the estimated incidence rate is around 2% (2). Varol et al. (3) retrospectively evaluated 3350 active TB patients, 1.1% of whom had lung cancer. Squamous cell lung cancer was the predominant histology. Since the clinical and radiological features of pulmonary TB are similar to lung cancer, it may lead to misdiagnosis or delayed diagnosis.

Previous literature has reported that lung cancer and TB occur simultaneously (4,5). Lung cancer is reported to be advanced in the development of TB (6,7). The risk factor of solid organ malignancies for TB should be taken into consideration, and there should be protective strategies for cancer patients, especially during the treatment period. Although parenteral system therapy is considered one of the immunosuppressive therapy agents, a small number of cases have been reported indicating the risk of pulmonary TB infection during oral TKI therapy.

This article was written to draw attention to the management of tuberculosis diagnosis and treatment in patients using tyrosine kinase inhibitors, which are increasingly used in lung cancer. Here, we report a case with lung adenocarcinoma who was diagnosed with pulmonary TB after persistent fever and cough despite broad-spectrum antibiotic treatment during tyrosine kinase inhibitor (afatinib) therapy.

Case:

A 55-year-old male patient had nasal discharge and associated cough for more than 10 years. Thoracic computed tomography (CT) of the thorax, which was performed at an external center due to increased cough and hemoptysis for the last 6 months, showed a mass atelectasis complex with a maximum axial dimension of 6x4 cm in the left lung at the suprahilar level

obliterating the bronchial branch leading to the upper lobe, invading the left main pulmonary artery and extending towards the mediastinum, accompanied by parenchymal consolidation laterally in the apical upper lobe (Figure 1). Magnetic resonance imaging (MRI) of the liver with contrast showed a 5.5x6.7 mm nodular lesion with a similar contrast pattern and similar appearance at the junction of liver segments 4A-8 in addition to the lesion defined in liver segment 5 and was accepted as metastasis. No metastasis was detected on brain MR imaging. Positron Emission Tomography (PET CT) showed hypermetabolic lymph nodes located in the center of the upper lobe of the left lung, invading the left pulmonary artery, probably in the left hilar area (Figure 2a, 2b). But interestingly, there was not enough pathological uptake in the liver on PETCT.

Bronchoscopy was performed with a diagnosis of lung carcinoma and endobronchial lesion was observed in the upper lobe of the left lung and the pathology result was adenocarcinoma. Exon 21 mutation was positive as a result of mutation analysis in the patient with stage 4 lung adenocarcinoma. The patient was started afatinib 40 mg treatment. Radiofrequency ablation treatment was performed for the metastatic lesion in the liver. In the 2nd month of afatinib treatment, the patient developed fever and increasing cough. The patient also used 2nd generation cephalosporin for about 2 weeks and moxifloxacin for 1 week with the diagnosis of pneumonia due to the newly emerging consolidation on the PA chest radiograph. The patient was hospitalized in the ward due to persistence of high fever despite these antibiotics.

The patient was given broad-spectrum antibiotic treatment and thorax CT was performed. ARB could not be analysed because the first sputum culture requested was contaminated. On thorax CT, there is a mass atelectasis complex in the left lung at the suprahilar level obstructing the bronchial branch to the upper lobe, invading the left main pulmonary artery and extending towards the mediastinum, with the largest axial dimension measured 6x4 cm. There is parenchymal consolidation laterally in the upper lobe apical region (post obstructive pneumonic consolidation?) Nonspecific pulmonary nodules measuring 3 mm in the lateral basal region of the right lung, 3 mm in the lower lobe superior segment, and several nonspecific pulmonary nodules measuring 2-3 mm in the lower lobe superior segment of the left lung were observed. (Figure 3) Bronchoalveolar lavage (BAL) was obtained for opportunistic infections. In addition, a biopsy was taken from the endobronchial lesion located in the upper lobe of the left lung for repeat mutation analysis. BAL and sputum cultures showed no growth. Sputum ARB was sent for 3 days from the patient whose sputum ARB PCR was found to be highly positive. ARB was found to be positive in BAL and sputum

direct examination results obtained on three consecutive days after BAL. The patient was consulted with oncology regarding the continuation of afatinib treatment while under TB treatment and considering the interaction of afatinib with rifampicin, afatinib treatment was planned to be started 1 month later since the patient also had stage 4 lung adenocarcinoma. Isoniazid (5 mg/kg), rifampicin (10 mg/kg), pyrazinamide (25 mg/kg) and ethambutol (15 mg/kg) were started as antituberculosis treatment. In the 1st week of antituberculosis treatment, the patient's fever decreased and cough symptom decreased. Meanwhile, EGFR and ALK mutations were negative in tissue mutation analysis. T790M mutation was also negative. The patient's lung adenocarcinoma treatment was planned to continue with standard chemotherapy. The timing was considered to be the end of the initial phase of antituberculosis treatment and the negative sputum ARB test at the end of the 2nd month. When the sputum ARB result was negative at the end of the 2nd month, antituberculosis treatment was continued with INH and RIF and cisplatin +premetrexed treatment was planned.

Discussion

In this article, we present a case of pulmonary TB developing during oral TKI treatment in a patient diagnosed with lung adenocarcinoma. TKIs are the standard treatment strategy for metastatic NSCLC with detected EGFR mutation. We know that more than 50 percent of patients receiving TKIs develop opportunistic infections, with *Aspergillus fumigatus* and *Pneumocystis jirovecii* being the most dramatic pulmonary infections. It has also been advocated to administer vaccines against influenza and pneumococci before starting TKI therapy and to add a recombinant, adjuvant vaccine against varicella-zoster virüs (8).

In the 2nd month of TKI treatment, fever and cough complaints resolved with antibiotic treatment and two weeks later the patient presented with cough again in our case. Sputum ARB and culture were sent from the patient with a preliminary diagnosis of opportunistic infection. ARB and nonspecific culture were obtained from BAL smear taken by bronchoscopy. Microbiologic examination of BAL was positive for ARB and *mycobacterium tuberculosis* PCR. In immunosuppressed patients with persistent fever and cough, underlying opportunistic infections should be considered both radiologically and clinically. In addition, TB may become active if the patient without a history of anti-TB treatment is receiving immunosuppressive treatment. Screening and treatment strategies for latent tuberculosis

infection (LTE) in patients with solid organ malignancies should be re-evaluated with more case reports and researches.

The risk of pulmonary TB has been reported in solid organ tumors. Kim et al. found that the risk of developing TB was increased in solid organ malignancies, including lung cancer, compared to the control group [incidence rate (IRR): 4.69, 95% CI:1.52-14.46] (7). In addition, the presence of sequela TB lesions on chest X-ray (IRR:45.05, 95% CI:5.74 353.88) and cancer chemotherapy were found to be predictive of TB development (IRR:4.32, 95% CI:1.10-16.89) (7). A meta-analysis showed that among 593 TB cases in 324,041 cancer patients, lung cancer had the third highest risk of active TB (83/100,000 population; IRR:9) compared with non-cancer patients. (9). Our patient had no old TB scar on chest X-ray. The complaints of fever and persistent cough that started on the 2nd month of afatinib treatment continued, opportunistic infections were suspected and the diagnosis of TB was reached with bronchoscopic materials.

Other meta-analyses found that active TB may occur simultaneously with or shortly after cancer diagnosis in more than half of lung cancer patients (10). TB was discovered simultaneously with malignancy in 30% of patients and 18 months after cancer diagnosis in 21% (11). These results support the importance of screening for active TB and LTBI, as well as using targeted LTBI therapy in the initial diagnosis and follow-up of cancer.

Hwang et al. examined 477 pulmonary adenocarcinoma patients with EGFR mutation status between patients with previous TB lesions and patients without TB lesions (12). The frequency of EGFR mutation was significantly higher in the TB group than in the non-TB group (56% vs. 34%, $p = 0.038$). In addition, both progression-free survival (PFS; 9.1 vs. 11.6 months, $p = 0.02$) and overall survival (19.4 vs. 24.5 months, $p = 0.014$) were significantly shorter in the TB group. However, it is difficult to be assertive about the coexistence of active TB with EGFR-mutant lung cancer because of the limited number of case reports (13,14). The impact of active TB on the prognosis of concomitant lung cancer is unclear based on available data. In our case, no progression was observed at the 2nd month of first-line treatment with afatinib, but the EGFR mutation in the tissue obtained from the second bronchoscopy was negative and the patient was tested for the T790M mutation. During this time, the patient was under antituberculosis treatment. The treatment of the patient with negative T790M mutation was planned to continue with chemotherapy. At the end of the 2nd month of antituberculosis treatment, sputum ARB was negative and 3 courses of pemetrexed and cisplatin were administered. At the end of the 3rd course, no local recurrence was detected on PET CT, but

bone metastases were present in the sternum. In addition, as the cytology of the newly developed pleural effusion was malignant, progression was accepted and immunotherapy was planned to be started. Co-administration of rifampicin has been reported to decrease the plasma concentrations and efficacy of TKIs. In our case also received anti-TB treatment including rifampicin for 2 months, which may have affected the efficacy of this treatment. The fact that the mutation was negative is an indication of resistance in a short time.

To summarize, there is an increased risk of infections such as tuberculosis, hepatitis B and varicella zoster in patients taking TKIs. They exert this effect by altering the T-cell-mediated immune response (15). Kim et al. presented a patient with CML who developed TB after nilotinib (TKI) and although he was found to be susceptible to TB drugs, his symptoms did not regress, which they thought was due to drug-drug interactions between antituberculosis drugs and TKIs (16). Some antituberculosis drugs impair the bioavailability of other drugs metabolized in the liver via the hepatic cytochrome P450 enzyme system. This also happens in patients with TB infection who are taking TKIs. In one review, co-administration of first-line antituberculosis drugs (mainly rifampicin) with the standard TKIs Imatinib and Dasatinib led to sub-therapeutic levels of these drugs due to induction of the CYP4503A enzyme. It has been reported that changing the tuberculosis treatment regimen with a fluoroquinolone combination with a non-rifampicin-based treatment or increasing the dose or switching to a different TKI class may result in clinical improvement (17).

The possibility that TB and lung cancer may be associated should not be ruled out. To confirm the diagnosis of TB and lung cancer, it is very important to combine clinical and radiological features with pathological and microbiological tests. Although anti-TB drugs, especially rifampicin, interact with TKIs, simultaneous treatment of EGFR mutant lung cancer patients with active TB with anti-TB drugs and TKIs is a safe and selectable treatment regimen (15). However, it should be kept in mind that EGFR mutation may be negative in patients who do not respond radiologically, and if there is a T790M mutation, targeted therapy should be given, and if there is no mutation, it would be appropriate to continue treatment with systemic chemotherapy.

References

1. Brenner AV, Wang Z, Kleinerman RA, Wang L, Zhang S, Metayer C, et al. Previous pulmonary diseases and risk of lung cancer in Gansu Province, China. Int J Epidemiol. 2001;30(1):118–24)

2. Byun HG, Yoo JY, Kim SJ, Lee OJ, Yoo MY. Coexistence of lung adenocarcinoma and pulmonary tuberculosis within a single lesion: a rare case report. Medicine. 2019;98(39):e17378.

3. Varol Y, Varol U, Unlu M, Kayaalp I, Ayranci A, Dereli MS, et al. Primary lung cancer coexisting with active pulmonary tuberculosis. Int J Tuberc Lung Dis. 2014;18(9):1121–5.

4.Evman S, Baysungur V, Alpay L, Uskul B, Misirlioglu AK, Kanbur S et al. Management and Surgical Outcomes of Concurrent Tuberculosis and Lung Cancer. Thorac Cardiovasc Surg 2016. [Epub ahead of print].

5. Kim Y I, Goo J M, Kim H Y, Song J W, Im J G. Coexisting bronchogenic carcinoma and pulmonary tuberculosis in the same lobe: radiologic findings and clinical significance. Korean J Radiol 2001;2:138-44.

6. Karnak D, Kayacan O, Beder S. Reactivation of pulmonary tuberculosis in malignancy. Tumori 2002;88:251-4.

7. Kim HR, Hwang SS, Ro YK, Jeon CH, Ha DY, Park SJ et al. Solid-organ malignancy as a risk factor for tuberculosis. Respirology 2008;13:413-9.

8. Shyam Sunder, S., Sharma, U.C. & Pokharel, S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. *Sig Transduct Target Ther* **8**, 262 (2023).

9. Auerbach O, Garfinkel L, Parks VR. Scar cancer of the lung: increase over a 21 year period. Cancer 1979;43:636-42.

10. Chen YM, Chao JY, Tsai CM, Lee PY, Perng RP. Shortened survival of lung cancer patients initially presenting with pulmonary tuberculosis. Jpn J Clin Oncol 1996;26:322-7.

11. Libshitz HI, Pannu HK, Elting LS, Cooksley CD. Tuberculosis in cancer patients: an update. J Thorac Imaging 1997;12:41-6.

12. Hwang IK, Paik SS, Lee SH. Impact of pulmonary tuberculosis on the EGFR mutational status and clinical outcome in patients with lung adenocarcinoma. Cancer Res Treat. 2019;51(1):158–68

13. Lee HY, Kim JW, Yeo CD. A case of tuberculosis reactivation suspected of cancer progression during oral tyrosine kinase inhibitor treatment in a patient diagnosed as non-small cell lung cancer. J Thorac Dis. 2017; 9(8):E709–13.

14. Gothi D, Spalgais S. Tuberculosis in epidermal growth factor receptor mutation in lung adenocarcinoma on treatment with gefitinib/erlotinib. Indian J Cancer. 2017 Jan-Mar;54(1):1.

15. Reinwald M, Boch T, Hofmann WK, Buchheidt D. Risk of infectious complications in hemato-oncological patients treated with kinase inhibitors. Biomark Insights 2016;10(Suppl 3):55-68.

16. Kim DJ , Jeong S , Kong SG , Lee HS. First case report of latent tuberculosis reactivation complicating treatment with nilotinib in chronic myeloid leukemia. Blood Res 2019;54:149-156.

17. Iqbal P, Soliman A, De Sanctis V, Yassin MA. Association of tuberculosis in patients with chronic myeloid leukemia: a treatment proposal based on literature review. Expert Rev Hematol. 2021 Feb;14(2):211-217.

18. Jin C, Yang B. A Case of Delayed Diagnostic Pulmonary Tuberculosis during Targeted Therapy in an EGFR Mutant Non-Small Cell Lung Cancer Patient. Case Rep Oncol. 2021 Apr 6;14(1):659-663.

LEGENDS

Figure 1. Thorax CT is showed a mass atelectasis complex with a maximum axial dimension of 6x4 cm in the left lung at the suprahilar level obliterating the bronchial branch leading to the upper lobe, invading the left main pulmonary artery and extending towards the mediastinum, accompanied by parenchymal consolidation laterally in the apical upper lobe

Figure 2a, 2b: Positron Emission Tomography (PET CT) showed hypermetabolic lymph nodes located in the center of the upper lobe of the left lung, invading the left pulmonary artery, probably in the left hilar area

Figure 3 : Parenchymal consolidation laterally in the upper lobe apical region (post obstructive pneumonic consolidation?) Nonspecific pulmonary nodules measuring 3 mm in the lateral basal region of the right lung, 3 mm in the lower lobe superior segment, and several

nonspecific pulmonary nodules measuring 2-3 mm in the lower lobe superior segment of the left lung were observed on Thorax CT.