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Is Tuberculosis a Challenge in the Management of Lung Cancer?

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Abstract

Objective: The coincidence of tuberculosis (TB) and lung cancer (LC) at the initial diagnosis or the development of TB during the course of LC is a challenge in the management of both diseases. Herein we reviewed 10 LC patients who coincidentally had TB and evaluated the challenges in the management of both diseases.

Methods: The files of patients were retrieved from an archive, and available study forms were completed.

Results: The study included 10 LC and TB patients during a 4 year-period. The sites of TB were the lung (seven patients), mediastinal lymph nodes (LN) (one patient), cervical LN (one patient), and subcutaneous nodules (one patient). LC and TB were simultaneously diagnosed in four patients. The diagnosis of pulmonary TB was confirmed by sputum culture two months after LC diagnosis in four patients. TB was diagnosed later in the follow-up period in two patients. Only one patient with early-stage LC who had undergone surgical resection tolerated anti-TB therapy well. In one patient, TB caused the over-staging of LC. In one patient, LC had progressed during the course of anti-TB therapy. Hepatotoxicity was the leading adverse reaction due to anti-TB therapy.

Conclusion: These patients highlighted the importance of considering TB in the course of LC, especially in countries with a high TB prevalence. TB may cause the advanced staging of LC at the initial diagnosis; chemotherapy may worsen the TB course or cause reactivation TB. Reactivation TB may be considered as the progression of LC without tissue diagnosis or sputum analysis. The tolerability of anti-TB therapy is poor in these patients.

Keywords: Lung cancer, positron emission tomography, tuberculosis

INTRODUCTION

Lung cancer (LC) is the leading cause of cancer and cancer-related death worldwide (1). Tuberculosis (TB) is a major cause of morbidity and mortality, especially in countries with a high incidence. It is well known that old pulmonary TB lesions are associated with an increased risk of LC (2), and a history of pulmonary TB is reported as an independent poor prognostic factor for LC survival (3, 4). While the exact mechanism of this association has not been delineated, the presence of chronic inflammation could be a reasonable link (5). Recently, in an experimental study, it has been shown that macrophages might play a key role in the progression of TB to LC (6). It has also been reported that the scarring of lung after TB predisposes patients to the development of LC, especially adenocarcinomas (7, 8). Malignancy per se and cytotoxic chemotherapy for its treatment are both recognized risk factors for the development of active TB in LC patients. The deterioration of immunity due to local or systemic effects of the tumor itself, insufficient nutrition, and/or administered chemotherapeutics or radiotherapy may play roles in the reactivation of TB. The presence of active TB has also been reported to increase the risk of LC mortality (9).

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The coincidence of TB and LC at the initial diagnosis or the development of TB during the course of LC is a challenge in the management of both diseases. In the literature, there are case reports and series indicating the challenge of treating patients who concurrently have TB and LC (10-13). Herein we report a case series and aim to investigate the challenges in evaluating and treating patients who concurrently have LC and active TB, referring to new imaging methods for diagnosis and staging.

METHODS

The study included 10 male LC patients who were coincidentally diagnosed with TB between August 2009 and August 2013 in Atatürk Chest Diseases and Chest Surgery Training and Research Hospital, which is a referral center for chest diseases. LC and TB constitute a significant portion of our patient population.

All patients were followed up by the authors. Informed consent forms could not be obtained from the patients as this was a retrospective study using existing hospital records, documents, and data that belonged to patients diagnosed with both LC and TB. The study was conducted in accordance with the Declaration of Helsinki. The files of patients were retrieved from the archive, and available study forms were duly completed. Demographic, clinical, and radiological characteristics; basal laboratory parameters; microscopy results and cultures for TB; diagnostic methods; pathological findings; applied treatment modalities; drug toxicities; and follow-up data were recorded on these forms. The staging of patients was clinically or pathologically done according to the 7th TNM staging system as proposed by the International Association for the Study of Lung Cancer (14).

The diagnosis of active TB was proved by the isolation of *Mycobacterium tuberculosis* or in the absence of bacteriologic confirmation by histological grounds revealing granulomatous inflammation with caseous necrosis. The diagnosis of LC was proved by radiological and histopathological findings. The chemotherapy regimen was cisplatin-based doublet chemotherapy in patients who received chemotherapy. Anti-TB therapy included four standard drugs: isoniazid (5 mg/kg, max: 300 mg/day), rifampicin (10 mg/kg, max: 600 mg/day), pyrazinamide (25 mg/kg, max: 2000 mg/day), and ethambutol (20 mg/kg, max: 1500 mg/day).

Hepatotoxicity was defined as an increase in the transaminase levels (AST, ALT) by more than three times of the upper limits of normal values while eliminating other causes of liver injury (15).

Statistical Analysis

The descriptive statistics of the patients, which were expressed in terms of frequency, mean, and standard deviation, were performed by IBM Statistical Package for the Social Sciences Statistics for Windows, Version 19.0 (IBM Corp, Armonk, NY).

RESULTS

Clinical characteristics of patients diagnosed with both LC and TB are summarized in Table 1. The study included ten male patients with a mean age of 57.4±9.4 (range: 43–71) years. All patients were smokers with a mean smoking history of 48.8±1.7 (range: 30–80) pack years. While nine patients had non-small cell LC (NSCLC), one patient had small cell LC (SCLC). The subtype was squamous cell carcinoma in six patients. The stages of LC were early stage in two (IB and IIA), locally advanced stage in three (one patient IIIA, two patients IIIB), and advanced stage in four patients. There was one patient who was initially staged as cT3N2M0 (clinical stage including 18-F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) evaluation), but after two cycles of chemotherapy and six months of anti-TB therapy, the restaging was compatible with yT2aN0MO. Treatment for LC was surgery in one, sequential chemoradiotherapy in one, chemotherapy in five, and best supportive care in two patients. One patient refused any therapy for LC. Chronic obstructive pulmonary disease (n=3) and coronary artery disease (n=3) were the most common comorbidities.

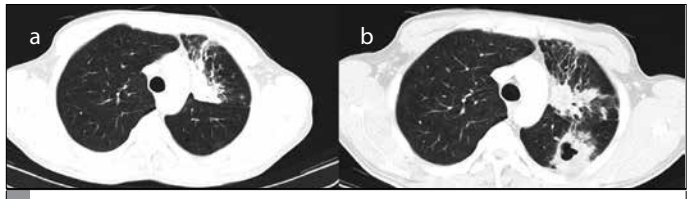

Figure 1. a, b. CT scan sections of patient number 8 at the initial diagnosis (a) and after 2 months. A new cavitary lesion is seen on the superior segment of the left lower lobe (b). CT: computed tomography

There was only one patient with a history of pulmonary TB 20 years ago. All other patients were new TB cases. The sites of TB were lung in seven patients, mediastinal lymph nodes (LN), cervical LN, and subcutaneous nodules on calf in one patient each. While four patients were diagnosed simultaneously with LC and TB, six patients were diagnosed with TB after the diagnosis of LC (median: 2.5, range: 2–14 months). The diagnosis of TB was confirmed by mediastinoscopic lymph node biopsy in one, transthoracic lung biopsy in one, and sputum smear and culture positivity in two patients. In four patients, the diagnosis of pulmonary TB was confirmed by sputum culture two months after the diagnosis of LC. All four patients were suspicious for pulmonary TB at the time of LC diagnosis, but sputum smears were negative for acid-fast bacilli (AFB). In figure 1, computed tomography (CT) of thorax images of patient number 8 are seen. A new cavitary lesion on the superior segment of left lower lobe was seen two months after the diagnosis of LC.

In two patients TB was diagnosed 11 and 14 months later in the follow-up period of the patient. One was diagnosed as TB lymphadenitis by cervical lymph node biopsy; the other by biopsy of subcutaneous nodules on the right calf. The histopathological examination revealed necrotizing granulomatous inflammation. Ehrlich-Ziehl-Nielsen stain was negative for AFB. AFB culture or DNA tests were not performed.

There was only one patient who tolerated anti-TB therapy well. This patient was an early-stage LC patient who had merely undergone surgery. Two patients tolerated anti-TB therapy fairly well. But one of these patients could not receive chemotherapy and the tumor progressed during anti-TB therapy. The adherence of seven patients to anti-TB therapy was poor. They could not take the medications due to gastrointestinal intolerance. Median anti-TB therapy time was 3.5 (range: 0.5–6) months. Hepatotoxicity was the leading adverse reaction (in 3 patients, 30%) due to anti-TB therapy and one of these patients died, probably because of hepatotoxicity.

Only one patient was alive by August 2015. One patient died due to venous thromboembolism. Mean and median survival time was 11.3±1.2 (range: 0.5–40) and 8.25 months, respectively.

Table 1. Clinical characteristics of patients diagnosed with both lung cancer and tuberculosis

Patient No	Date of diagnosis	Age	Tumor histology	Stage	CA therapy	Comorbidity	Ancient TB history	Time of TB diagnosis	Method of TB diagnosis	Site of TB	TB therapy compliance	Overall survival
1	Aug 2009	43	NSCLC (Adenoca)	IIIA	CT (4 cycles)	COPD	-	Simultaneously with CA	Mediastinoscopy	Mediastinal LAP	Poor, treated for 2 months	10 months
2	Oct 2011	54	NSCLC (Adenoca)	IV	CT (4 cycles)	-	-	11 months after CA	Tissue biopsy	Subcutaneous nodules on right calf	Poor, treated for 1 month	12 months
3	Dec 2011	62	NSCLC (Squamous)	IIIB	CT (4 cycles)	-	-	14 months after CA	Lymph node biopsy	Cervical LAP	Poor, treated for 4 months	18 months
4	Feb 2012	66	NSCLC (Squamous)	*	2 cycles CT followed by RT	COPD	-	2 months after CA	Sputum culture	Lung	Fairly well, 6 months	14 months Died due to VTE
5	Feb 2012	55	NSCLC (Squamous)	IIA	Refused therapy	-	-	Simultaneously with CA	Sputum smear and culture	Lung	Poor, treated 2 weeks hepatotoxicity	1 month
6	Apr 2012	59	NSCLC (Squamous)	IB	Surgery	CAD	20 years ago pulmonary TB	2 months after CA	Sputum culture	Lung	Well, 6 months	Alive (August 2015) 40 months
7	May 2012	71	SCLC	IV	CT (3 cycles)	CAD, HT	-	3 months after CA	Sputum smear and culture	Lung	Poor, treated for 3 months	6 months
8	Oct 2012	46	NSCLC (Squamous)	IV	CT (2 cycles)	-	-	2 months after CA	Sputum culture	Lung	Poor, treated for 4 months hepatotoxicity	6,5 months
9	Feb 2013	68	NSCLC (NOS)	IIIB	-	CAD	-	Simultaneously with CA	Sputum smear and culture	Lung	Fairly well, 5 months mass progresses during anti-TB therapy	5 months
10	Mar 2013	50	NSCLC (Squamous)	IV	-	COPD	-	Simultaneously with CA	Transthoracic lung biopsy	Lung	Poor, 2 weeks hepatotoxicity	2 weeks

CA: Carcinoma; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CT: chemotherapy; HT: hypertension; NOS: not otherwise specified; NSCLC: non-small cell lung carcinoma; RT: radiotherapy; SCLC: small cell carcinoma, TB: tuberculosis, VTE: venous thromboembolism; *This patient's initial stage was T3N2MO, but after two cycles of chemotherapy and 6 months of anti-TB therapy, restaging was compatible with T2aN0MO

DISCUSSION

It is well known that there is a significant relationship between the history of pulmonary TB and the risk of LC (5, 16). It has also been reported that there is a synergistic interaction with the daily amount and duration of smoking and the history of pulmonary TB. Based on this synergistic interaction, a heavy smoker with a history of pulmonary TB is expected to have a higher risk for LC (17). The increased risk of LC in men with TB has also been shown in an alpha-tocopherol, beta-carotene cancer prevention study (8). In that study, TB was associated with an increased LC risk, mainly squamous cell carcinoma, in male smokers. In another study investigating the effect of active TB on the survival of NSCLC patients, active TB was more frequently seen alongside squamous cell carcinoma (18). This situation is supported by the experimental study demonstrating that a chronic TB infection can trigger a series of events leading to the extensive remodeling of lung tissue or activation of a pathway resulting in a malignant transformation such as squamous cell metaplasia (19). On the contrary, in a meta-analysis of 37 case control and four cohort studies, the association was significant for adenocarcinoma (20). In our case series, all patients were smokers. Squamous cell carcinoma (six patients) was the most prevalent diagnosis. There was only one patient with a history of pulmonary TB that occurred 20 years ago.

Tuberculosis and LC both have a large public health impact, especially in high-incidence countries. Turkey is a high-incidence country for both TB and LC. The incidences of TB and LC are 24/100,000 and 81.6/100,000, respectively (21, 22). In a previous prospective study from Turkey, including 73 patients (66 LC, seven other malignancies) who had undergone fiberoptic bronchoscopy, the incidence of active TB was found to be 8% (n=6), which was diagnosed via routine bronchial washing and/or post-bronchoscopic sputum cultures (23). In a study including 1111 LC patients in a medical center in Taiwan, TB was the third most common comorbidity with a ratio of 9.7% following hypertension and diabetes mellitus (24). In a recent published series from Spain, the incidence of LC was 4.7% in 319 TB patients during a seven-year period. For this reason, the Spanish study advised performing AFB smears and bronchial aspirate cultures in all patients with presumed LC, particularly in areas with high TB prevalence (25). In our series, we had six patients with concomitant TB at the initial diagnosis of LC. Three of them were diagnosed by an AFB smear and three by an AFB culture.

Lung cancer and TB share certain risk factors such as smoking, alcoholism, and chronic obstructive pulmonary disease. Both diseases have overlapping symptoms and radiological similarities. If there is a clinical bias for TB, especially in high-incidence countries, this may result in clinical errors and delay the diagnosis of LC. Therefore, every TB patient, particularly ones with a poor response to anti-TB therapy, should be considered for the diagnosis of LC. A new lesion atypical for the course of LC, new-onset pleural effusions, or new pulmonary infiltrations, especially in tree-in-bud appearances, should be confirmed by microbiological and histopathological investigations (26). Otherwise, approaching to these lesions as disease progression may result in disastrous consequences. In our series, we had two patients (patient numbers 2 and 3) diagnosed with TB after 11 and 14 months of LC diagnosis. Patient number 2 was diagnosed by biopsy of subcutaneous nodules on the calf and patient number 3 by cervical lymph node biopsy. Unfortunately, none of the patients had microbiological confirmation as the materials were not microbiologically evaluated. However, histopathological analysis revealed granulomatous inflammation with caseous necrosis.

Positron emission tomography/computed tomography (PET/CT) is a metabolic non-invasive imaging technique that has been used for diagnosing and staging LC. The basic principle of PET/CT is based on the accumulation of FDG in areas of increased glucose metabolism. It has the ability to accumulate not only in malignant tissues but also in inflammatory cells such as neutrophils, activated macrophages, and lymphocytes at the site of inflammation or infections such as TB (27). Maximum standardized uptake values are not useful for differentiating LC from TB. Therefore, the coincident presence TB is an important diagnostic dilemma when interpreting PET/CT results with regard to staging and management. It is important to be aware of the interpretation issues of PET/CT, particularly in high-TB burden countries. In our series, one patient was initially staged as cT3N2M0 clinically and radiologically by PET/CT, but after two cycles of chemotherapy and six months of anti-TB therapy, restaging with repeated PET/CT was compatible with yT2aN0MO. At that point, we cannot be certain about the initial stage, but it is highly probable that we initially overstaged that patient.

It is well known that comorbid conditions can affect LC patient survival in many ways (28). Patients with comorbidities are more likely to experience treatment related toxicities, and treatments may exacerbate underlying comorbidities (29). Comorbidities decrease the likelihood of completing treatments for LC. In a large trial, patients with advanced NSCLC who had a Charlson comorbidity index higher than 2 were more likely to discontinue chemotherapy (30). There is a controversy on the effect of TB on LC patient survival. In a prospective population-based cohort study, a history of pulmonary TB was reported to be a poor prognostic factor for LC patient survival in Caucasian patients. The survival of LC patients was significantly shorter in patients with a history of pulmonary TB than in those without a history of TB, with a mean difference of 311 days (3). After that study, active TB was reported as an independent predictor of LC death with a hazard ratio of 2.01 (95% CI: 1.4–2.9) (7). Kuo et al. (18) suggested that concomitant active TB prolongs survival in patients with NSCLC (median). They explain this phenomenon by probable effective T-cell immunity at nearby tumor sites. It is certain that our case series offers insufficient data to reach a conclusion. However, we believe that coincident TB shortens survival by decreasing performance status, preventing therapies for cancer, and causing higher toxicity due to the administration of anti-TB drugs. Apart from one patient who had an early-stage LC, all our patients had difficulties in tolerating anti-TB therapy. Three patients had hepatotoxicity, and one died, probably because of hepatotoxicity.

CONCLUSION

These patients highlighted the importance of considering TB in the course of LC, especially in countries with a high TB prevalence. TB may cause the advanced staging of LC at the initial diagnosis based on PET/CT results; chemotherapy may worsen the TB course or cause reactivation TB. Reactivation TB may be considered as the progression of LC without a tissue diagnosis. The tolerability to anti-TB therapy is poor in these patients. Guidelines should refer to how to manage these patients, especially in certain areas with a high TB prevalence.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

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