Review Article

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TANAFFOS

A Comprehensive Study on the Correlation of Treatment, Diagnosis and Epidemiology of Tuberculosis and Lung Cancer

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The correlation between tuberculosis (TB) and lung cancer (LC) in diagnosis, epidemiology, and treatment is still unclear. Based on different cohort and retrospective studies, this correlation could be justified by immune weakness because of exposure to TB which may increase the risk of LC. In this study, we tried to exhibit a prominent connection between TB and LC. The diagnosis and treatment of patients with concomitant TB and LC differ from patients with only one of the diseases. In this review, it was well clarified that the most practical diagnostic method for LC is chest tomography, biopsy, and histopathology, and for pulmonary TB sputum microscopic examination, Autofluorescence bronchoscopy (AFB), culture, and PCR. Also, immunological methods can be a good alternative for differential diagnosis. Most epidemiological studies were about concomitant TB and LC in TB-endemic areas, especially in the Middle East. The most suggested methods for definite treatment of LC are chemotherapy, radiotherapy, and surgery while for TB, a long course of anti-TB therapy can be used. Moreover, immunotherapy is considered a good treatment for lung cancer if the interferon-gamma release assay (IGRA) is negative.

Keywords: Tuberculosis; Lung cancer; Differential diagnosis; Treatment; Epidemiology

INTRODUCTION

Mycobacterium tuberculosis (MTB) causes tuberculosis (TB), which is now one of the world's most common and deadliest infectious diseases. In 2019, there were 10 million new cases of multi-drug resistant TB, almost one-third of the population, affected worldwide according to the World Health Organization (WHO) (1). Lung cancer (LC) is one of the main causes of cancer-related deaths worldwide, and 80% of the cases are non-small cell lung cancer (NSCLC) (2). LC also has had an increasing rate due to various reasons such as unhealthy lifestyle, air pollution, and population aging (3). In 2019, it was reported that LC was the cancer with the highest mortality rate (18.4%). It is predicted that the number of lung cancer-affected people will significantly increase in 2040 (4). Several studies report that there is a positive relationship between TB and LC (5-7). The reason for this relation can be a tumor-supporting microenvironment made by TB that can induce innate immunity and cytokines, which can cause tumor growth (8). Because of the TB and LC similarities, it is difficult to distinguish these two deadly conditions which makes the diagnosis and treatment even harder. Epidemiologic studies have indicated an increasing rate of LC in TB-endemic areas.

In this review, we selected the articles with TB and LC in the title in Scopus and PubMed databases since 2000. Case reports, comments, conference papers, editorials, non-English, and review articles were excluded. The others were categorized into three main groups diagnosis, treatment, and epidemiology. Articles in each group were assorted into subgroups with more details. Since the majority of studies proved the correlation of MTB with LC (9), TB patients with a high risk of LC like people older than 55 years old or a history of smoking more than 30 packs of cigarettes per year should be assessed with chest CT. Also, they should be evaluated for the tumor markers like miR128, miR210, and mir1266 to get sure if they have LC or not, before starting the TB treatment (10, 11). Lots of studies compared TB and LC in different approaches but in this article, we tried to gather all these data and categories in diagnosis, epidemiological, and treatment methods to present the best way in each one. This review will examine the previous LC and TB-based studies written in the English language since 2000. We used PubMed and Scopus databases to identify these studies using the keywords, ("TB" OR "tuberculosis") AND ("LC" OR "lung cancer" OR "lung carcinoma" OR "Pulmonary Carcinoma"). The search yielded 105 potential studies.

Figure 1 is a simple representation of the areas involved in exposure, diagnosis, and treatment related to TB, LC, and their comorbidity that is discussed in this review.

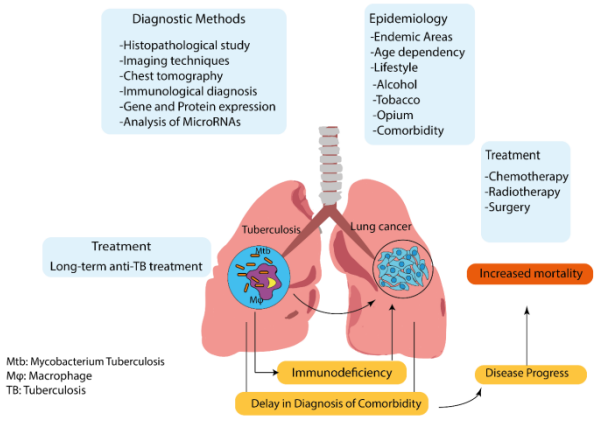

Figure 1. A brief illustration of the connection between LC and TB in terms of epidemiology, diagnosis, and treatment; misdiagnosis or delay in diagnosis of the diseases due to the similarities may lead to the progress of the disease and affect the mortality rate

DIFFERENTIAL DIAGNOSIS

The coexistence of LC and TB is often misdiagnosed as a single disease. Even when the right diagnosis is made, the treatment methods are controversial. The hardest aspect of this diagnosis is how to differentiate TB and LC.

Imaging Techniques and Tomography

Radiological images that prove smear-negative or positive TB in patients can lead to neglecting the diagnosis of coexistent LC at the right time and thus patients will only undergo anti-TB treatments (12). Qi et al. (13) revealed differences in imaging features between TB and LC through conventional MRI. Although it is demonstrated that there is a clear difference between the image of TB and LC patients' lungs (14), radiological similarities in many cases cause misdiagnosis (15).

Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) image is also a method to diagnose TB that mimics LC. But, it should be carried out with accuracy, especially in TB-endemic areas, because it may lead to misdiagnosis (16). CT screening and ^{18}F-FDG PET / CT have shown low specificity and a high number of false positives in discerning LC in TB-endemic areas (17, 18).

Although maximum standardized uptake value (SUV max) and nodule size are not considered good parameters for differential diagnosis, higher SUV max and larger short-axis of the solitary pulmonary nodule (SPN) may reflect malignant tumors (17). WHO suggested that a threshold for nodule size should be used as a criterion to reduce the false-positive rate in lung cancer diagnosis. Other criteria, such as considering the endemicity of the habitat, can play an important role in reducing false positives (19). If the size of the solid pulmonary nodule is so small that no definitive differential diagnosis can be made with bacteriology or pathology, whether it is TB or LC, PET scans can do this diagnosis to some extent in the early stages. In lung cancer patients, the SUVs of both FDG and ^{11}C-choline were high. In tuberculosis patients, the SUV of FDG was high, but the SUV of ^{11}C-choline was low.

In atypical mycobacterial infection patients, the SUVs of both FDG and ^{11}C-choline were low (20).

Several studies emphasize tomography outcomes as well as comparison of uptake rates of 18 F- FDG and 11 C-choline (20). PET/CT was studied in different endemic areas to examine its efficiency (21-30). Perhaps the accuracy of nodal staging using CT or FDG-PET/CT is low in LC patients with parenchymal TB (31, 32). FDG PET/CT and 68 Ga-Alfatide II with 18 F-FDG can be a way of differential diagnosis, but findings should be interpreted with caution in TB-endemic regions (16, 33).

When the diagnosis is difficult, computed tomographic (CT) findings on a hybrid PET/CT are an important way to distinguish TB from LC (34-36). Radiomic features from CT Radiomics have been recently proposed as a potent tool for differentiating TB and LC (37). In addition, a combination of radiomics and semantic selected features derived from PET/CT images in a radiomics nomogram has shown considerable diagnostic improvement in differentiating pulmonary TB and LC (38). A study in 2021 on two separate groups of patients with either mass-like TB or LC has shown that there are significant differences in morphological and texture features and also radiomic models between these groups (39).

Clinical Symptoms

Clinical symptoms have a crucial role in the differential diagnosis. For example, cough, expectoration, fever, hemoptysis, weight loss, and breathlessness are common symptoms of both diseases; whereas, sudden weight loss, change in chronic cough, hemoptysis, and history of tobacco consumption are more common in LC. Although fever is common between both diseases, it is nonspecific in LC (40, 41). Zheng et al. (42) reported irritant cough, expectoration, hemoptysis, fever, and CT features of irregular mass and pleural thickening as indicators of concomitant TB and LC with particular emphasis on fibrous calcification as an LC predictor in TB patients. Some differential clinical symptoms are presented in Table 1.

Table1. Differential diagnosis with clinical symptoms (40)

Symptoms and indications	LC	Pulmonary TB
Fever	Non-specific	Low-grade fever with rising in the evening
Weight loss	Sudden	Gradual
Dyspnea	Present	Absent or present
Clubbing nails	Present	Not often
Response to anti-tubercular drugs	No	Yes and immediate
Specific diagnostic technique	Biopsy	CT Thorax, culture
Hemoptysis	Yes, more common	Yes
History of smoking	Yes, more usual	Not often

Expressional Diagnosis

An increasing number of publications focus on the genetic differential diagnosis of TB and LC. Loss of heterozygosity and increased protein expression of *FHIT* is more prominent in LC patients infected with TB than in uninfected patients (43). In addition, *SPIUNC1* expression increases in LC much more than TB (44). Cellular abnormalities and the extent of DNA damage varies in different lung diseases. Among TB, LC, and COPD patients, TB is associated with higher odds of DNA damage alongside higher levels of apoptosis, necrosis, and impaired cytokinesis, while LC patients had the least chromosomal aberration (45). Higher levels of cell-free DNA and its integrity in NSCLC a distinguishing marker between LC and TB (46). In LC patients, sensitivity to EGFR mutation and, subsequently, response to EGFR-tyrosine kinase inhibitors as well as TB-induced inflammation and carcinogenesis depends on the gender type and TB history (47). Matrix metalloproteinase MMP-9 is increased in TB compared to LC (48). TB patients have shown higher sputum adenosine deaminase activity (ADA) than patients with LC (49). Interestingly, in a recent cohort study using end-point and *in-situ* PCR methods, it has been shown that Mtb IS6110 transposon was integrated with tumor tissue genome in NSCLC patients (50). This finding can pave the way for identifying the presence of TB infection in LC patients and also explaining the effects that MTB has on lung tumor status.

Immunological Diagnosis

Mycobacterium tuberculosis antigen promotes LC metastasis through the immunological way as well as the PD-1/PDl-1 signaling pathway (51). The immunological approach mostly is used to determine the severity of TB and LC disease. For example, patients with higher levels of BAL fluid neopterin were in the advanced condition of TB. Likewise, an increased level of BAL fluid neopterin was observed in patients with adenocarcinoma and SCLC (52). Moreover, higher levels of serum human epididymis protein 4 (HE4) in LC may also be counted as a specific differential marker (53). The rate of T-SPOT was much more prominent in TB rather than LC (3). Macrophages also may have a key role in the propagation of TB into LC cells (44). Although IL-18 is not specific to TB, it can be useful for the diagnosis of this disease (54). Moreover, Kuo et al. (55) showed that the concomitance of active TB and LC exhibits a higher immune response.

MicroRNA-Based Diagnosis

The expression level of miRNAs varies among prevalent lung diseases and some intergenic miRNAs were identified with potential functions in cell cycle arrest, thereby making them valuable non-invasive diagnostic biomarkers (56). Compared to controls, serum levels of miR-182 and miR-155 were substantially higher only in LC patients, whilst greater levels of miR-197 were only observed in patients with TB (57). In addition, miR-378i expression was only increased in TB, while miR-200b expression was increased in LC (58). The expression pattern of miR-155, miR-125b, and miR-146a in the patients' blood showed different expression profiles in both TB and NSCLC in comparison to healthy controls (59, 60). Also, in a bioinformatics study, Barh et al. (61) proposed 45 common miRNAs that deregulate in both TB and LC.

EPIDEMIOLOGY

Association of TB and LC in the Endemic Areas

There are several studies in which TB and LC comorbidity has been evaluated in a particular time and place. Rybacka-Chabros et al. (62) inferred that the immunodeficiency caused by chronic TB infection is the main reason for the correlation between both diseases. There was a high frequency and an upward trend in the presence of TB in the years 1976, 1987, and 1999 not only in LC patients but also in patients with leukemia and lymphoma (63). A study in Belgium revealed that 5.1% of LC patients had tuberculous lymphadenitis simultaneously (64). PET/CT was used to detect NSCLC in populations with a high prevalence of TB (21, 23). The coexistence of TB and LC had been studied and proved in Lithuania, China, Serbia, Taiwan, Iran, Japan, and a group of Caucasian patients in the Netherlands (8, 65-74). It has also been reported that a history of tuberculosis can increase the risk of lung cancer (75). Positive interferon-gamma release assay (IGRA) test ratio in people with LC in consecutive decades in Japan revealed that LC and TB comorbidity is declining in the Japanese population. This decrease is due to the prognostic methods of TB in people with cancer, early detection of cancer, and cancer medication (76). In a recent nationwide, population-based cohort study in Taiwan on patients with primary cancer, having TB has increased the risk of developing secondary LC about 1.67 times compared to the condition where TB is absent, and the presence of other comorbidities as well plays a contributing role (77).

Role of lifestyle and behavior in TB and LC

A variety of studies proved that the risk of TB and LC would increase in the case of tobacco smoking (71, 78-83). There is also a positive correlation between alcohol consumption and LC (78). There may be a correlation between opium smoking and developing LC, but it demands more investigation (84). Sikjær et al. (85) suggested that there may exist an association between psychiatric disorders and respiratory diseases; therefore, the treatment of these patients should be followed up. In contrast, in a cohort study, Silva et al. (86) suggested that alcohol consumption and TB may not be associated with the risk of LC, despite confirming cigarette smoking as a risk factor for LC. Both LC and pulmonary TB exhibit age-

dependent characteristics and risk factors. In a cohort study, it was shown that the risk of LC was higher in TB patients at younger ages rather than older ages (87). This may be due to more dangerous and impulsive behavior in younger people.

Epidemiology of diagnosis

Since TB and LC mimic each other, differential diagnosis is really important in these cases, especially in endemic areas. Adenosine deaminase can be a useful marker for differentiating TB from LC or mesothelioma (88). The association between TB and LC can be detected by microbiological approaches, such as performing acid-fast bacilli smear and mycobacterial culture of bronchial aspirates in all patients with suspected LC, especially in high TB prevalence areas (89). Shu et al. (90) revealed that radiological findings of the military pattern and positive culture for non-tuberculous mycobacteria (NTM) could be a good marker to distinguish TB from LC. In terms of microbial epidemiology, in the Netherlands, all TB cases were rooted in fungal infection, Pneumocystis carinii pneumonia (PCP), and TB (91). Compared to other types of cancer, the L form of Mtb (MTB-L) had the highest frequency in LC samples (92).

Mortality in Different Population Groups

Mortality seemed to be increased due to LC among whetstone cutters, but it needs more investigation (93). Diabetes and TB comorbidity also elevated the mortality rate (94). Among workers with a history of pulmonary tuberculosis (PTB), an excess risk of LC mortality was observed, whereas the risk was lower than that seen among workers without a history of PTB (95). In 2013, a population study on LC victims had shown that TB could increase LC mortality (96). Post-inhaled corticosteroid pulmonary TB increased LC risk in patients with asthma. Because of the high mortality associated with LC, screening tests are recommended for patients with post-inhaled corticosteroid pulmonary tuberculosis (post-ICS TB) (97).

DILEMMA IN TREATMENT

In patients with LC, the best treatments seem to be cytotoxic chemotherapy, targeted therapy, and emergent immune therapy after surgery. But among these treatments, targeted therapy is not associated with TB patients, so it is not useful enough for patients who have both diseases together (98). A study in Turkey attempted to evaluate the complication of concomitant TB and LC treatment. Though postoperative adjuvant chemotherapy has no extra effect on patients, the detection of the best treatment for these patients is a big challenge in developing countries where TB is endemic (99).

It is about a decade since immune checkpoint inhibitors (ICIs) are used as an immunotherapy treatment for malignancies as well as lung cancer. It should be noted that there have been reports worldwide that this method leads to tuberculosis in high-risk patients. As a result, the great challenge in NSCLC treatment is to prevent it from leading to other diseases such as TB due to a compromised immune system (100). It can be good to take an IGRA test and hepatitis B serology before initiating ICI therapy, as ICI therapy can lead to the reactivation of hepatitis and TB (101-103). However, according to the results of Kim et al. (104), in NSCLC patients, treatment with ICI after chemotherapy did not increase the incidence of TB, although prolonged use of steroids was considered a TB risk factor. Overall, studies underline the importance of assessing the ICI treatment crosstalk with TB development and the necessity of interrogating the presence of MTB infection in LC patients who undergo this treatment.

Currently, the procedure used to treat LC is such that in its early stages, the diagnostic test for TB is first performed utilizing PCR and the result will be confirmed by CT scan. Anti-TB treatments are started and surgery is performed if they do not improve the clinical condition. If TB is not confirmed, surgery will be performed first, and then anti-TB treatment will be prescribed. In patients with LC metastasis, treatment methods such as immunotherapy and chemotherapy are prescribed depending on the patient's condition. If tuberculosis is confirmed, immunotherapy will not be performed due to the possible

reactivation of TB. In other treatments, anti-cancer treatment is given to the patient at the same time or before initiating cancer treatment (98). Moreover, immunotherapy in LC patients using PD-1/PD-L1 blockade has shown safety and efficiency in LC patients with latent TB, although this treatment has been associated with TB reactivation and TB-related mortality (105). Besides, pneumonectomy, lobectomy, and segmentectomy are some surgical approaches to cure pulmonary TB and LC coexistent. Using FDG PET/CT before lobectomy surgery can provide valuable information (34). Figure 2 shows the algorithm for the treatment of co-existent TB and LC (98).

CONCLUSION

Several different diagnosis methods for simultaneous TB and LC have been used in different countries but the most relevant clinical approach to the diagnosis of concomitant TB and LC is radiological evidence together with a compatible clinical picture. The most suggested diagnostic method for concomitant pulmonary TB and LC is chest tomography, although the immunological approach can be a good alternative. It is important to diagnose TB before starting the treatment because several studies have clarified that there is an undeniable relationship between TB and LC, especially in TB-endemic area. The most TB endemic areas are India, Indonesia, China, the Philippines, Iran, Turkey, and Pakistan, and also in less well-developed countries.

In recent years, the scientists' approaches ran into easier and also less expensive methods. Since time plays an important role in diagnosis, the shorter the diagnosis time is, the better treatment can occur. Thus, immunological approaches seem to be the most interesting issue for a scientist. After determining the appropriate diagnosis, it is important to choose the best treatment that can decrease the symptoms of both TB and LC. Cytotoxic chemotherapy and emergent immune therapy seem to have the best answer in clinical studies. However, the existence of TB and HBV should be examined before initiating the immunotherapy. The limitation of our study is that there are still a few articles on the side effects of immunotherapy or other new treatments for co-existent TB and LC. So, we suggest that the side effects of simultaneous treatment of tuberculosis and lung cancer should be examined in patients.

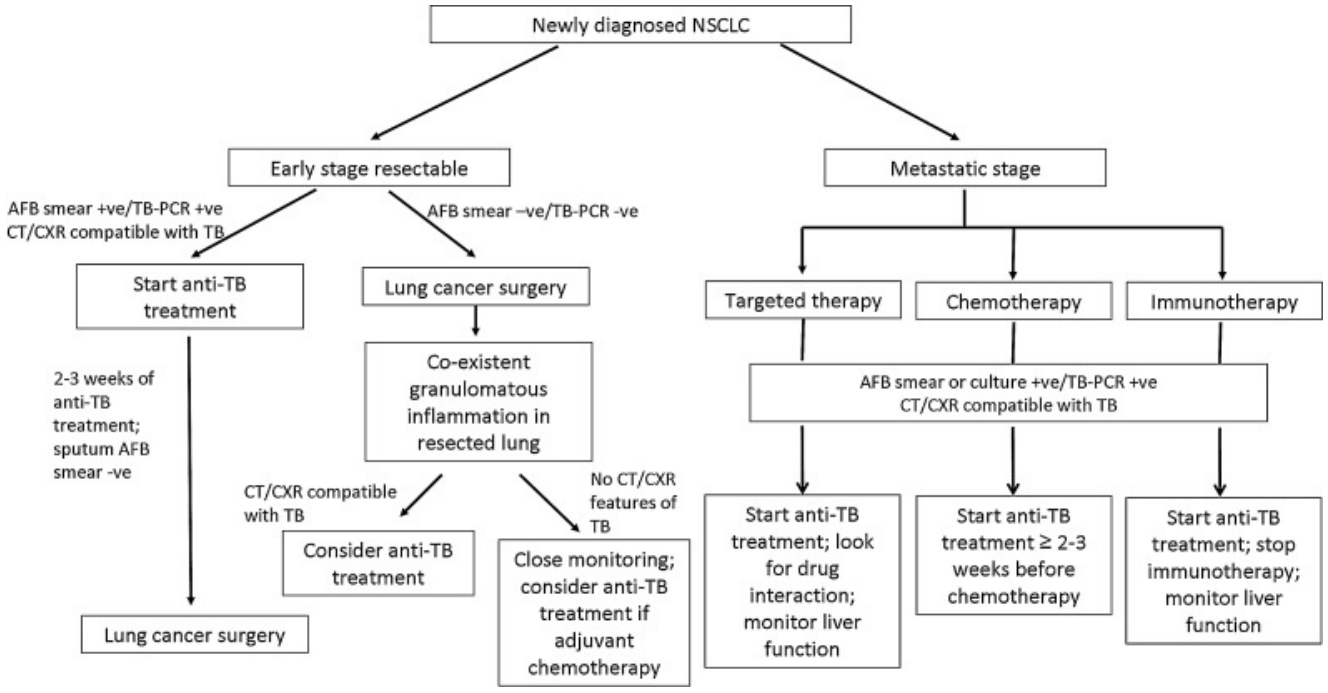

Figure 2. Algorithm for treatment of co-existent TB and lung cancer in early-stage and metastatic cases [Reprinted with permission from Elsevier] (98)

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Competing interests

The authors declare that they have no competing interests.

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