# Clinical Characteristics and Treatment Responses of Tuberculosis Complicating Lung Cancer: A Systematic Review

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*Abstract-* Coexistent lung cancer (LC) and pulmonary tuberculosis (TB) were sources of clinical and pathological interest and speculation for many years. Nowadays, there is compelling evidence that TB increases the risk for LC. Furthermore, active TB has been reported to complicate LC. It is well documented that lung inflammation and fibrosis could induce genetic damage, increasing the risk for LC.

The patients usually have already suffered from TB when cancer was diagnosed. In such a case, the disease was confined to the upper lobes, with or without cavities, or was spread to the lymph nodes. Whereas, when TB appeared later in the course of the cancer, after anticancer chemotherapy, TB was extended and disseminated.

Clinical/radiological characteristics of TB and LC resembled each other. It is extremely difficult to verify the diagnosis of active TB from clinical and/or and radiological features in LC patients. Definite diagnosis requires pathological confirmation from biopsies and microbiologic studies.

TB treatment in an immune compromised host requires individualized therapeutic decisions. There are no significant differences in TB treatment responses and/or toxicity of the anti-tuberculosis medication when combined with anticancer therapy. As poor survival and high mortality rates have been reported, interactions between anti-tuberculosis and anticancer medication, affecting the efficacy of the latter, deserve further studying.

Keywords- Tuberculosis; Lung Cancer; Chemotherapy; Treatment

## I. INTRODUCTION

The relationship between tuberculosis (TB) and lung cancer has been discussed for many years, in the following ways: First, TB increases the risk for lung cancer. Second, lung cancer may be complicated by active TB and, third, any eventual relationship is purely coincidental. Nowadays, there is compelling evidence that TB increases the risk for development of lung cancer [1]. Furthermore, active TB has been often reported to complicate lung cancer [2-15].

Since the activity of TB depends in a great measure on the immunologic competence of the host, the disease should behave differently in the immunologically compromised cancer patients. However, the clinical characteristics of active TB complicating lung cancer have been discussed only rarely. Furthermore, the clinical response of TB to anti-tuberculosis treatment in patients receiving anticancer chemotherapy, has been not known well.

Thus, a systematic review was performed to investigate, whether there is good quality evidence to elucidate the clinical characteristics and treatment responses of TB in lung cancer patients.

## II. MATERIAL AND METHODS

# A. Eligibility Critera

To select and retain a large group of homogenous studies, from different regions of the world, we did not exclude any study on the basis of language and used wide criteria:

1. The studies should contain data, concerning demographic characteristics of the patients, timing of diagnosis, clinical presentation, clinical course and response to anti-tuberculosis treatment and mortality from TB.

2. As in clinical series misclassification of TB could not be excluded, we included only studies with histological and bacteriological proofs for lung cancer and TB respectively.

3. All studies included in the review, should be unique contributors, to avoid giving double weight to repeated data.

4. In case of studies referring data from the same populations, during the same period of time, was included only the earlier publication. Exception was made when presented conflicting data.

## B. Study Selection and Data Extraction

MEDLINE, PubMed, EMBASE and Medscape databases were searched for studies in which quantitative data on the relation of TB to lung cancer were reported. As the introduction of anti-tuberculosis chemotherapy changed the overall prognosis of TB we searched for reports since 1952 (last research September 2013). Studies were identified using the following Medical Subject Headings term "tuberculosis" and the text-word terms "TB" and "Mycobacterium infection" and the Medical Subject Headings term "neoplasm" and "lung neoplasm" or the text-word term "lung cancer". The reference list of the obtained articles, were screened to identify other eligible references which were then retrieved.

The following information was extracted and coded by using standard form: year of publication, age, race, male:female ratio, quantitative data on the relation of TB to lung cancer, clinical and radiological features, clinical course and response to treatment, mortality and survival rates. All data were abstracted independently by one reviewer and checked by another.

## C. Data Analysis

If TB was clinically active when the diagnosis of lung cancer was first made, then it was considered to be present "concurrently" with lung cancer. Whereas, if TB appeared within 18 months following the diagnosis and or/treatment of the neoplasm, then it was termed "sequential" to lung cancer.

Mortality was ascribed to TB when caused respiratory failure, or in the case that TB was extended and involved multiple organs, while the neoplastic disease was not extended and there was no other obvious cause of death.

Five terms were used to describe the presentation of TB:

1. Pulmonary TB. When the infection was confined to the upper lobes of the lungs with or without cavitations.

2. Pneumonic TB. A form of infection in which multiple lobes of the lung were involved with diffuse infiltration predominating over caseation necrosis.

- 3. Disseminated TB. Infection involving the lungs and multiple organ systems.
- 4. TB adenitis. The infection was confined to lymph nodes in the neck, axilla or mediastinum.
- 5. Focal TB indicates infection limited to a single organ system other than the lungs or lymph nodes.

The reference list of the obtained articles, were screened to identify other eligible references which were then retrieved.

## III. RESULTS

A total of 78 articles were retrieved to determine eligibility for the current review. In forty-eight of them sufficient information to determine mortality from TB was not provided. In sixty-four of thestudies there was no adequate information concerning the clinical/radiological presentation of TB. In only five of the studies the response to anti-tuberculosis treatment was discussed. Ten retrospective case/control studies and four case series were finally included. (Table 1)

Year	Author	TB cases	Age	Male: female	Caucasians/Asians /Black	TB Mortality%
1952	Goldberg	5	44	5:0	5/0/0	25
1953	Nuessle	4	54	4:0	4/0/0	50
1965	Holden	15	65	13:2	15/0/0	-
1971	Kaplan	44	60	39:5	42/1/1	7.0
1975	Solomon	6	57	5:1	0/0/6	-
1984	Lioyd	5	57	5:0	4/0/1	25.0
1991	Aoki	6	66	5:1	0/6/0	33.3
1994	Yuh-Min	31	68	-	0/31/0	35.4
1998	Tamura	25	70	23:2	0/25/0	12.0
1999	Watanabe	16	65	15:1	0/16/0	18.7
2001	Kim Y	51	64	48:3	0/51/0	-
2005	Kim D	44	56	3:1	0/44/0	0.0
2007	Tamura	56	69	6:1	0/56/0	12.5
2007	Cicenas	46	54	4:1	46/0/0	30.4

TABLE 1 AGE SEX RACE AND MORTALITY RATE

All reported histological and bacteriological proved cases of active pulmonary TB complicating lung cancer. They were unique contributors as to the reported region and time period. Table 1 details the year reported, the averaged age, basic demographic characteristics of the patients and reported mortality from TB. Sample sizes ranged from 4 to 56, with a total of 354 TB cases complicating lung cancer studied.

The types of control subjects used as well as the population at risk varied between studies and included randomly selected community controls, general hospital and/or even sanatorium patients.

There was a male predominance reported in all the contributing studies (mean averaged 13:1). The mean  $\pm$  SD ages of the reported TB cases, were 60  $\pm$  14.1 years, range 44-70). Black race patients were reported in only 3 studies. A history of heavy smoking was reported in the majority of both TB and lung cancer patients in seven studies.

X-rays findings suggestive of old healed TB were defined in 44% of the cases, while history of pre-existing TB was reported in 12% of the patients. A high percent of preexisting diabetes mellitus was reported in one study (37.5%) [9]. There was not any trend noticed, as to the relationship of the location of lung carcinoma and TB lesions.

Table 2 summarizes the timing of the appearance of TB. TB was more often present when lung cancer first appeared (concurrently group 66.3% of cases). The type of TB that appeared seemed to depend on whether TB appeared concurrently or sequentially to lung cancer. As shown in Table 2, generally patients with TB present at the time that lung cancer was diagnosed had pulmonary TB, whereas those who developed the infection sequentially, after treatment of lung cancer, had severe disseminated or pneumonic TB in almost one third of cases.

X	TB cases	TB concurrent				TB sequential			
Year Author		Р	F/A	Pn	D	Р	F/A	Pn	D
1952 Goldberg	5	1	0	1	3	0	0	0	0
1953 Nuessle	4	2	0	1	1	0	0	0	0
1971 Kaplan	44	24	6	0	1	9	0	3	2
1975 Solomon	6	5	0	0	1	0	0	0	0
1984 Lioyd	5	5	0	0	0	0	0	0	0
1991 Aoki	6	1	0	0	0	3	0	1	1
1994 Yuh-Min	31	11	0	3	2	9	0	0	6
1998 Tamura	25	12	1	1	0	5	1	3	2
1999 Watanabe	16	9	1	0	1	3	0	2	0
2005 Kim D	42	10	4	0	0	26	0	1	1
2007 Tamura	56	39	1	2	1	7	0	2	4
2007 Cicenas	46	12	3	1	2	18	1	4	5

TABLE 2 TYPE OF TUBERCULOSIS AND TIME OF APPEARANCE

Note: P for pulmonary, F/A for focal/adenitis, Pn for pneumonic and D for disseminated

The efficacy of anti-tuberculosis treatment was almost comparable to that in patients without lung cancer. After antituberculosis treatment the mean  $\pm$  SD of the negative conversion rate of sputum cultures, in both the concurrently and sequentially detected groups were reported 56  $\pm$  5% within one month and 94  $\pm$  2% within two months.

Survival was poor in lung cancer patients with active TB (median 4 months) as compared with those without TB (median 8 months). A high mean  $\pm$  SD of the mortality rate from TB was estimated 22.6  $\pm$  14.4% (Table 3).

¥7 A4h	Rate of culture Conv	rention	Mean Overall Surveillance (months)		
Year Author	2st month	3nd month	TB pts	non TB pts	
1971 Berroya RB	-	-	3	-	
1996 Chen YM	-	-	4	8	
1999 Tamura A	35%	60%	3		
1999 Watanabe A	-	95%	5		
2005 Kim DK	-	100%	-		
2007 Tamura A	56%	94%	5	-	

TABLE 3 RESPONSE TO THERAPY AND OVERALL SURVEILLANCE

# IV. DISCUSSION

# A. Time of Onset and TB Type

The time of onset of TB during the evolution of lung cancer may differ. In the majority of cases, a history of smoking, alcohol abusing, diabetes mellitus, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and/or TB, preexisted the development of cancer [16, 17]. Findings also verified in the current study. Some patients develop TB early in the course of the neoplastic disease. Others develop TB after the neoplasm has advanced and required intensive antineoplastic therapy. In the series reviewed, TB was more often present when lung cancer first appeared. In such a case, lung cancer patients usually presented a limited pulmonary TB confined to the upper lobes of the lungs with or without cavitation. Whereas,

those who developed TB after anti-cancer treatment have severe, extended or disseminated disease in almost one-third of cases.

The type of TB seems to depend on whether or not a patient had received therapy for the lung cancer. Some patients receive radiation therapy, others anticancer chemotherapy and/or surgery, adrenocortisteroids, or combinations of these forms of treatment. It was observed that as more modalities of treatment were utilized, the severity and mortality of TB increased. Tuberculous pneumonia and disseminated TB in particular, when developed following the therapy for the primary lung neoplasm were almost 100% fatal.

## B. The Location of the Lesions

TB and lung cancer can be located in general proximity of each other, in the same lung (the same lobe or even the same cavity included) or at widely divergent sites in the same lung or in either lung [3, 5, 7, 18, 19]. Carcinomas arising in pulmonary scars are usually adenocarcinomas, originating in the peripheral portions of the lungs [5, 20].

Eventually both diseases may arise in different areas of the respiratory tract, although they were found at autopsy to exist adjacently within single, specific pulmonary lesions [3, 20, 21].

The manner of radiographic presentation of this carcinoma-TB combination is indeed varied and may take the form of either of the two diseases. They might possibly present singly, or as a blending, along the full range of composite morphology [3, 7, 21]. One of the most difficult challenges presented to a clinician, is trying to determine the pathological nature of a pulmonary lesion in the presence of lung cancer or TB, or both, from x-ray alone.

#### C. Diagnostic Dilemmas

Pulmonary TB and lung cancer may closely resemble each other [18]. It is possible for the tuberculous process to dominate the clinical picture for a number of years. As physicians tend to consider only one disease process at a time, it is easy to overlook the slow progress of malignant disease in a patient who has residual fibronodular TB. In this case the cancer growth can be easily overlooked and the diagnosis delayed.

On the other hand, TB can produce masses and nodes which can imitate or complicate staging of the cancer. It is a common belief that nodal TB makes evaluation of the neoplastic disease inaccurate [5, 15]. Occasionally, more radical surgery than necessary may be done for the presence of nodes which are actually tuberculous rather than neoplastic. It is especially important to examine carefully, by gross inspection and frozen section, neck and axillary nodes and to culture all that are suggestive of granulomatous disease. A radical neck dissection is unnecessary for the treatment of scrofula.

Nowadays outstanding progress in imaging techniques has led to increasing accuracy in the diagnosis of lung cancer. High Resolution CT (HRCT) features of pulmonary nodules and masses such as speculated margin, distortion of adjacent vessels, mixed ground glass and solid density, pseudocavity, air-bronchogram sign, diffuse and amorphous calcification and enhancement more than 20 HU were reported to be found in malignant more than benign lesions [18]. However, these features have been commonly described in TB lesions too [22]. A finding also verified by the current review.

Furthermore, Kim Y and coworkers studying CT findings in whom pulmonary TB and bronchogenic carcinoma coexisted in the same lobe, found that most cancers concurrent with TB were large, lobulated masses with mediastinal lymphadenopathy similar to those of lung cancer without TB [12]. Obviously, HRCT does not distinguish pulmonary TB from lung cancer clearly.

As to the positron emission tomography with CT (PET-CT), false positive scans are known to occur in benign pulmonary lesions with high metabolic rates, infectious granulomatous lesions arising from TB included. That is why physicians need to be aware of the above limitation of this imaging modality, when TB is an issue [23]. However, Hara and coworkers found that using C-choline as an additional tracer to 18-fluorodeoxyglucose (FDG), could help to distinguish lung cancer and pulmonary TB [24]. Although these results are promising, they certainly warrant further investigation, particularly evaluating patients with combined disease.

## D. Treatment Responses

Clinical response of TB in anti-tuberculosis treatment in patients receiving anticancer chemotherapy has not been known well, except for a few case series [10, 11, 13, 14, 25, 26]. It was observed that when TB was concurrently detected with lung cancer, the treatment was successful and coexisting TB seemed not to affect the course of the malignancy. Whereas, when TB was sequential to lung cancer, it was more extensive and severe. In this case an increased overall mortality rate was recorded.

Kim DK and coworkers also studied the clinical course and response to antituberculosis treatment during anticancer chemotherapy [13]. All patients were treated with a rifampicin-based, daily, self-administrated regimen.

Time to bacteriologic conversion and radiographic responses to anti-tuberculosis treatment, as well as frequency of severe side effects from anti-TB drugs, were not different from those reported in a group of TB patients without malignancy. Despite earlier reports, all deaths in that group of patients, receiving anticancer chemotherapy, resulted from progression of the underlying malignancy, not from the aggravation of TB.

These differences in clinical responses could be explained in several ways. First, patients enrolled in the latter study, were receiving cyclic anticancer chemotherapy. The immune suppression caused in such a case, might not be as severe as the suppression induced by long-term continuous use of anticancer agents or long-term steroid treatment. Second, the severity and duration of neutropenia in these patients were rather mild as compared to the earlier reports. Third, because malnutrition and weight-loss play a crucial role in TB development, their absence, judged by the levels of cholesterol, proteins and body mass index in TB patients of this study, could explain the differences in clinical responses previously reported. Eliminating the above factors, anticancer chemotherapy was not an obstacle to treating TB.

For the treatment of TB in an immune-compromised host, individualized therapeutic decisions are recommended [27]. With regard to radiological and clinical response to treatment, TB developing during anticancer chemotherapy is not different from TB developing under ordinary situations. However, the presence of active pulmonary TB in a patient with lung cancer cannot be expected to favorablely affect the generally grim prospect of this highly lethal neoplasm. Furthermore, survival analysis has shown that patients with coexistent active TB and lung cancer survive for a shorter period than those without TB [9]. As successful bacteriologic cure of TB was usually reported in this group of patients, there is no dubbed as to the efficacy of anti-tuberculosis treatment. However, how could we explain the poorer surveillance of lung cancer patients with active TB, under anticancer chemotherapy? Whether that was the result of an advanced cancer stage due to delay in diagnosis and/or the result of not appropriate treatment selection because of inaccurate staging or even the result of excessive immune-suppression, we could not know. In addition, we found no data in the literature concerning the efficacy of anticancer chemotherapy when combined to anti-tuberculosis treatment.

## E. Drugs Interactions

The drugs used to treat TB affect the metabolism of many other drugs and can result in a lack of efficacy (interactions with rifamycins) or toxicity (interactions with isoniazid and fluoroquinolones). All of the rifamycins are inducers of a variety of metabolic pathways, particularly those involving the various isozymes of the cytochrome P450 system. By inducing the activity of metabolic enzymes, rifamycin therapy results in a decrease in the serum concentrations of many drugs, sometimes to levels that are subtherapeutic [27].

It is important to note that many possible interactions between anticancer chemotherapeutic agents and rifamycins have not been investigated fully, thus, additional clinically relevant interactions might be described.

## V. CONCLUSIONS

Along the lines of this comprehensive review, we attempted to describe important clinical characteristics of the coexistent active TB and lung cancer. It was reported an overlap in the clinical/radiologic characteristics of both diseases. Even today, it is extremely difficult to verify the diagnosis of active TB from clinical and radiological features when the latter complicates lung cancer. The diagnosis of TB in this group of patients requires pathological confirmation based on the findings of biopsy and microbiologic studies.

Preexisting TB increases the risk for lung cancer, which results in a considerable number of lung cancer patients with Latent Tuberculosis Infection (LTBI). Malignant disease and anticancer chemotherapy and/or radiotherapy are risk factors for reactivation of TB or new exogenous infections. Debility, neutropenia and malnutrition are additional factors contributing to further impairment of the host defense mechanisms and poor survival.

Although anticancer chemotherapy is not an obstacle and anti-tuberculosis treatment remains effective, high mortality and decreased survival rates are usually reported. Misleading or delayed diagnosis and inaccurate staging are certainly involved. Further investigation will identify any eventual drug/drug interactions, decreasing the efficacy of anticancer chemotherapy.

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