

ORIGINAL ARTICLE

Pulmonary tuberculosis as a confounder for bronchogenic carcinoma due to delayed and misdiagnosis

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Article Cycle

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Abstract

Background: There are many similarities between lung cancer and tuberculosis as both are common and present with almost similar symptoms and radiological findings, a large number of lung cancer patients treated for tuberculosis initially and that leads delay in diagnosis and progression of disease. **Aim:** In this present study we intend to find out the impact of past and present tuberculosis on the diagnosis and treatment of lung cancer. **Results:** Out of 195 diagnosed cases of bronchogenic carcinoma, 79 (40%) were taking anti-tubercular therapy for at least 1 month duration (range 1 month- 12 months). Fifty one (26%) patients had received ATT in past. Twenty six patients (12.5%) were found to have co-existent tuberculosis and lung cancer, only 18 patients were newly diagnosed and the remaining were relapse cases. Mean delay for diagnosis of lung cancer in patients who were taking ATT inadvertently, owing to wrong diagnosis, was 3.2 months (range 1 month to 12 months). **Conclusion:** We found that large numbers of the bronchogenic carcinoma patients were misdiagnosed as a case of tuberculosis, this leads to significant delay in diagnosis and progression of cancer and results in poor outcome and lower survival. We recommend an early search for malignancy in suspected tubercular patients having risk factors for bronchogenic carcinoma. Moreover sputum negativity for AFB and poor response to empirical anti-tubercular therapy in these setting should arouse suspicion for malignancy.

Key Words

Lung Cancer; Tuberculosis; Misdiagnosis

Introduction

Tuberculosis is a widely prevalent and deadly disease. India shares an estimated one quarter of global burden. Many respiratory diseases may mimic tuberculosis; bacterial pneumonias, fungal infections, Allergic Broncho-Pulmonary Aspergillosis (ABPA) and bronchogenic carcinoma are such common

diseases among others which can be mistaken as tuberculosis because of non-specific symptoms and similar radiological findings. Over-reliance on Chest X-Ray for diagnosis is big reason for misdiagnosis.

Due to high TB prevalence and radiological similarities, a large number of lung cancer patients initially get wrongly treated for TB,

this leads to significant delay in diagnosis and progression of disease. In a few patients, tuberculosis and lung cancer may exist together and that poses another diagnostic dilemma.

Relationship between tuberculosis and lung cancer has remained controversial.(1) Some scientists have shown that tuberculosis promotes development of lung cancer while others contradicted this relation.(2-6) Some research implicated that post-tubercular scars could develop lung cancer ("scar cancer").(7) Tuberculosis has been supposed to increase a person's risk of lung cancer because of pulmonary inflammation and fibrosis, which can induce genetic damage.(8-9) Tuberculosis also increases the lung cancer deaths in elderly patients¹⁰. On the other hand presence of lung cancer can lead to reactivation of latent tuberculosis because of malnutrition, chemotherapy and immune-modulatory therapy.

Aims & Objectives

In this present study we intended to find out impact of past and present tuberculosis on the diagnosis and treatment of lung cancer.

Methods

In our study we analysed retrospective data of patients, presented to our OPD and diagnosed as bronchogenic carcinoma, during a period of 2 years (1st Jan 2011 to 31st Dec 2012). A total of 195 cases were diagnosed of bronchogenic carcinoma, using various diagnostic modalities like sputum cytology, fiberoptic bronchoscopy, lavage and biopsy and CT guided percutaneous needle aspiration cytology or biopsy, pleural fluid examinations, pleural biopsy, lymph node FNA/Biopsy, liver FNA/ biopsy. A detailed history was taken in each case about the previous history of tuberculosis or its treatment and all the available records of the

patients were studied. Apart from other routine investigations like complete hemogram, renal and liver function tests were performed, where indicated. Chest radiograph P-A view, lateral view/ special view (if needed), USG abdomen, Contrast Enhanced CT thorax were main imaging investigations. Finally all the collected was analysed, using STAT DIRECT Ltd version 10-70-2000. P values were obtained by using chi square test.

Result

Lung malignancy was confirmed in 195 patients, majority were males (M:F= 6:1) and smokers (n=135, 69%). Squamous cell carcinoma was the main diagnosis (n=49, 25%), followed by Adenocarcinoma (n=43, 22%), small cell carcinoma (n= 34, 17%) and poorly differentiated carcinoma (n=14, 7%). Fifty five (28%) patients were diagnosed with malignancy but histological typing could not be confirmed. During the same period 1065 sputum positive cases of TB were diagnosed.

Of 195 confirmed cancer patients, 51(26%) patients had past history of anti-tubercular treatment, with duration ranging from 4 months to 2 years. A total of 79 (40%) patients were receiving ATT at the time of presentation. Of these 12 were sputum positive for AFB (4 new, 8 relapse) and 12 of them were adequately treated cases of tuberculosis. Rest 55 patients with findings suggestive of lung carcinoma were also receiving ATT. Of remaining 116 patients who were not receiving ATT, 14 patients were found to be sputum or Bronchial wash positive for AFB at our hospital. Thus a total of 26 (12.5%) patients were found to be suffering from concomitant lung cancer and tuberculosis ([Table 1](#)).

Younger age <50 years, female sex, non-smokers, upper zone involvement, bilateral lesions, multi-zone lesions and pleural effusion were more common than older age >50 years,

male sex, smokers, complete lung collapse, hilar mass and lower zone mass lesion in the patients who were taking Anti-Tubercular Treatment ([Table 2](#)).

Comparison of older chest radiographs with newer one, in the cancer patients on ATT, revealed that many of them progressed to higher stages (increase in size of the mass, complete collapse, development of pleural effusion, presence of superior vena cava syndrome, bony involvement). Mean duration of symptoms in patients who were taking ATT was significantly high (6.4 months vs 3.2 months). Thus the mean delay for diagnosis was 3.2 months (range 2 month - 10 months). ([Table 3](#))

Discussion

Lung Cancer is among the commonest cancers in men and it is the biggest cause of cancer related mortality among both sexes around the world. There are many similarities between Lung cancer and Tuberculosis as they are both common and characterized by almost similar symptoms such as feverishness, cough, expectoration, haemoptysis, weight loss and anorexia. However, age of the patient, history of smoking, and symptoms such as hoarseness of voice, Superior Vena Cava (SVC) obstruction, and dysphagia favour the diagnosis of lung cancer. On examination, there may be signs of collapse or mass, clubbing and signs of complications of lung cancer. In our study of 195 confirmed cases of carcinoma lung, majority were males (n=167; M:F= 6:1) and smokers (N=139, 69%), 105 (75%) of them were heavy smokers (More than 20 pack years). Majority of the patients had symptoms of cough / expectoration, breathlessness, chest pain, haemoptysis, weight loss, appetite loss and hoarseness of voice for a mean duration of 4.5 months. Squamous cell carcinoma was the main diagnosis (n=49, 25%), followed by Adenocarcinoma (n=43, 22%) and

small cell carcinoma (n= 34, 17%). Fourteen (7%) patients had poorly differentiated carcinoma ([Table 1](#)). Fifty five (28%) patients were diagnosed to have malignancy but histological typing could not be confirmed for various reasons including poor health, poor finances and presence of distant metastasis.

In our country, where tuberculosis is very prevalent, it is quite common to find a lung cancer patient being treated for tuberculosis initially, leading to delay in the correct diagnosis, progression of disease as well as exposure to inappropriate medication. In our study, of 195 confirmed cancer patients, a total of 79 patients were receiving ATT at the time of presentation. Of these only 12 were sputum positive for AFB (4 new, 8 relapse), while 12 of the adequately treated cases of tuberculosis were also receiving ATT. Rest 55 patients with the findings suggestive of lung carcinoma were also receiving ATT. [Table 2](#) shows that age <50 years (76%), female sex (54%), non-smokers (52%), upper zone involvement (54%), bilateral lesions (63%) multizone lesions (58%) and pleural effusion (57%) were more common than older age >50 years (13%), male sex (38%), smokers (36%), lower zone mass (19%), complete lung collapse (29%) and hilar mass (14%) lesions in the patients who were receiving ATT. A total of 51 patients had received anti-tubercular treatment in past. Duration of ATT is ranging from 4 months to 2 years while time gap ranged from 3 years to 40 years. Of these patients, 20 patients were taking ATT again, though only 8 patients shown features consistent with relapse of tuberculosis (sputum/ bronchial wash positive for AFB). Additional 14 patients were also found to be sputum or BAL positive for AFB at our hospital. Thus a total of 26 patients were suffering from concomitant lung cancer and tuberculosis.

In our study, mean duration of the symptoms was 4.5 months (range, 1- 14 months). Mean

duration in patients who were taking ATT was higher at 6.4 months in comparison to those who were not taking ATT in which it was 3.2 months. Mean delay for diagnosis of lung cancer in patients, who were taking ATT inadvertently owing to wrong diagnosis, was 3.2 months (range, 2 month to 10 months). According to some studies, delay in diagnosis of lung cancer was significantly high in patients who had received anti-tubercular treatment for current symptoms compared with those who did not receive anti-tubercular treatment.(11) An additional disturbing fact was that majority of these patients had no conclusive microbiological evidence of tuberculosis. The majority of lung cancers (> 80%) are diagnosed at an advanced stage, when they are beyond the scope of curative resection.(12) Comparison of older chest X-rays with newer one in the cancer patients on ATT, revealed that most of them progressed to much higher stage during the period of first consultation at periphery to the consultation with us (increase in size of the mass, complete collapse, development of pleural effusion, presence of superior vena cava syndrome, bony involvement, etc). Delay in the diagnosis and treatment of lung cancer results in poorer outcome and lower survival.

Patients with coexistence of lung cancer and tuberculosis could be divided into various groups 3. 1) Tuberculosis and lung cancer are unrelated. 2) There is relation between both processes as post tuberculosis changes, deformation of bronchi and alveoli, epithelial dysplasia are risk factors for lung cancer. 3) As lung cancer progresses, old foci of tuberculosis reactivates. 4) Metastatic carcinoma developing in an old TB lesion. 5) Secondary infection of cancer with TB. Coexistence of tuberculosis and lung cancer has remained controversial since the middle of 19th century. Some scientists stated that tuberculosis promotes development of cancer; others

assert that tuberculosis and cancer are antagonists. Rokitsky (2) (1854) found that cancer was more common in non-tubercular patients and concluded that tuberculosis and cancer were antagonistic. Lubarsch (3) (1888) and Pearl (4) (1929) also favoured antagonism theory, Carlson and Bell (5) disapproved it, while Carry and Greer (6) felt that there was no relation. Raeburn and Spencer (7) found that post tubercular scars could cause development of lung cancer ("scar cancer"). Carrol (13) in his study examined more than 100 cases of lung cancer and concluded that 67% of Adenocarcinoma and only 3.5% Squamous cell carcinoma were associated with scars, and that changes depend on the degree of damage. In our study a total of 51 patients had received anti-tubercular treatment in past. Of these 51 patients with a past history of ATT intake, 13 patients were suffering from Adenocarcinoma and 9 patients from Squamous cell carcinoma. According to Tamura (1999) (14) and Watanabe (1999) (15) post tuberculosis scars deform blood and lymphatic vessels. Lymphostasis, conditions for deposit of carcinogens and development of malignant process occur.

In our study, a total of 26 patients were suffering from concomitant lung cancer and tuberculosis. Pathologists N. A. Dacosta and G. G. Kinare (1991) (16) reported that combination of lung cancer and tuberculosis of lung was found in 13.1% of all autopsies. Watanabe et al.(15), published analysis of 758 of lung cancer, and coexistence of cancer and tuberculosis was found in 2.1% of cases. At present it's clear that tuberculosis and other chronic lung diseases increase the risk of lung cancer. (17) Yu YH, et al (18) found in a cohort of 716,872 insured subjects that the incidence of lung cancers was approximately 11-fold higher in the cohort of patients with tuberculosis than non-tuberculosis subjects (26.3 versus 2.41 per 10,000 person-years).

Tuberculosis has been supposed to increase a person's risk of lung cancer because of pulmonary inflammation and fibrosis, which can induce genetic damage. (8-9) This incidence of gene mutation is found to be higher in East Asian countries where prevalence of TB is high.(19) There were various studies on association of tuberculosis with other malignancies including leukemias also, but none were confirmatory. Various hypotheses were made to explain the positive relationship including tumour neovascularisation, altered pH, and altered immune response. Stover and Kaner (20) observed that in most of the cancer patients, tuberculosis results from reactivation of a latent disease.

In our study carcinoma lung seem to mimic pulmonary tuberculosis, as a vast number of these patients (79 of 195, 40%) were taking Anti-tubercular treatment without any confirmation. This tells about the lack of knowledge of recent guidelines to treat tuberculosis or awareness of carcinoma lung, among general practitioners. There is very high reliance on Chest X-Ray for the diagnosis of tuberculosis despite clear guidelines on sputum smear examination for AFB. A large numbers of patients (51 of 195, 26%) have received Anti-tubercular treatment in distant past too. Only a few patients (12) have relapse of tuberculosis (sputum positive for AFB) along with carcinoma lung. Thus even sputum positivity cannot rule out the possibility of carcinoma. If clinically evident, search for carcinoma yielded good results. Atypical course of TB, presence of pain, radiological evidence of rib erosion and ipsilateral hilar lymphadenopathy should raise the alarm of coexistent malignancy. In our study, 1065 cases were diagnosed with sputum positive pulmonary tuberculosis and 26 of them were harbouring lung cancer too. Thus presence of sputum positive pulmonary tuberculosis or

history of previous tuberculosis emerges as a major co-morbid condition or perhaps important risk factor for the development of carcinoma lung. Wrong or incomplete diagnosis in cases of lung cancer causes a delay in diagnosis too. Wofford et al (21) reported 34 cases of coexisting carcinoma lung and pulmonary TB and reported the average delay in making the diagnosis when TB and cancer co-exist to be 13 months. Some authors (22) recommend that increasing incidence of lung diseases is associated with increased incidence of lung cancer and therefore one should be watchful about early detection of carcinoma in these patients.

Conclusion

Due to high TB prevalence and radiological similarities, a large number of lung cancer patients were initially got wrongly treated for TB, that caused delay in diagnosis and progression of disease. From our study we recommend an early search for malignancy in suspected tubercular patients having risk factors for bronchogenic carcinoma like old age, history of smoking and atypical symptoms like presence of thoracic pain, hoarseness of voice and dysphagia, moreover sputum negativity for AFB and poor response to empirical anti-tubercular therapy in these setting should arouse suspicion for malignancy. Any patient with suspected malignancy on chest X-ray should be worked up for early and confirm diagnosis by every possible means including inexpensive sputum cytology for malignant cells to invasive fiberoptic bronchoscopy, from lymph node FNA to CT Guided biopsy of lung lesion. Bhatt, et al (23) concluded that attempts are needed to minimize delay by maintaining a high index of suspicion, low threshold for referral for appropriate investigative work up and treatment as this can increase the chance of

tumour respectability and may provide better quality of life.

References

- Pandey M. Tuberculosis and cancer. In: Sharma SK, Mohan A, editors. Tuberculosis. New Delhi: Jaypee Brothers Medical Publishers; 2001; p. 396-403.
- Rokitansky C. Manual Pathol Anat vol.1. Blanchard and Lea; Philadelphia: 1954.
- Lubarsch O. Ueber den primären Krebs des ileum, nebst bemerkungen über das gleichzeitige vorkommen von krebs und tuberculose. Virchows Arch 1888; 111: 280-317.
- Pearl R. Cancer and tuberculosis. Am J Hyg 1929; 9: 97-159.
- Carlson A, Bell ET. J Cancer Res Comm Univ Sydney 1929;13:126.
- Carry JM, Greer AE. Bronchogenic carcinoma complicating pulmonary tuberculosis: a report of eight cases and a review of 140 cases since 1932. Ann Intern Med 1958; 49: 161-80.
- Raeburn C, Spencer H. Lung Scar Cancer. Br J Tuberc 1957; 51:237-45.
- Saunders BM, Britton WJ. Life and death in the granuloma: immunopathology of tuberculosis. Immunol Cell Biol 2007; 85:103-11.
- Nalbandian A, Yan BS, Pichugin A. Lung carcinogenesis induced by chronic tuberculosis infection: the experimental model and genetic control. Oncogene 2009; 28:1928-38.
- Shieh SH, Probst JC, Sung FC, Tsai WC, Li YS, Chen CY. Decreased survival among lung cancer patients with co-morbid tuberculosis and diabetes. BMC Cancer 2012;12:174. Cited in PubMed PMID:22578056 Available from www.ncbi.nlm.nih.gov/pubmed/22578056
- Singh VK, Chandra S, Kumar S, Pangtey G, Mohan A, Guleria R. A common medical error: Lung cancer misdiagnosed as sputum negative tuberculosis. Asian Pacific J Cancer Prev 2009;10:335-8.
- Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710-7.
- Carroll R. The influence of lung scars on primary lung cancer. J Path Bact 1962; 83:293-7.
- Tamura A, Hebisawa A, Hayashi K, Sagara Y, Kawabe Y, Nagayama M, et al. Lung cancer in patients who had received thorocoplasty for pulmonary. Kekkaku 1999; 74:797-802.
- Watanabe A, Tokue Y, Takashi H, Sato K, Nukiwa T, Honda Y, et al. Management of mycobacteriosis in general hospital without isolation ward for tuberculosis patients. Clinical study on pulmonary tuberculosis associated with lung cancer patients. Kekkaku 1999; 74:157-162.
- Dacosta NA, Kinare SG. Association of lung carcinoma and tuberculosis. J Postgrad Med 1991; 37:185-189.
- Wu CY, Hu HY, Pu CY. Pulmonary tuberculosis increases the risk of lung cancer: a population-based cohort study. Cancer 2011;117: 618-24. Cited in PubMed PMID:20886634. Available from www.ncbi.nlm.nih.gov/pubmed/20886634
- Yu YH, Liao CC, Hsu WH. Increased lung cancer risk among patients with pulmonary tuberculosis: a population cohort study. J Thorac Oncol 2011;6: 32-7. Cited in PubMed PMID: 21150470. Available from www.ncbi.nlm.nih.gov/pubmed/21150470
- Chen YM, Perng RP, Lee YC. The link between TB and a gene mutation that causes lung cancer. J Thorac Oncol 2012 Feb;?
- Stover DE, Kaner RJ. Pulmonary complication in cancer patients. Cancer J Clin 1996;46:303-20
- Wofford JL, Webb WR, Stauss HK. Tuberculous scarring and primary lung cancer. Clinical and aetiologic considerations. Arch Surg 1962; 85:928-35.
- Kodolova IM, Kogan EA. Morphogenetic relationships between tuberculosis and peripheral lung carcinoma. Arkh Patol 1996;3:52-60.
- Bhatt M, Kant S, Bhaskar R. Pulmonary tuberculosis as differential diagnosis of lung cancer. South Asian J Cancer 2012; 1:36-42.

Tables

TABLE 1: DIAGNOSIS OF LUNG CARCINOMA IN RELATION TO PAST HISTORY OF ATT INTAKE

SN	Diagnosis	Total No.	Receiving ATT at presentation	Old Treated	AFB+ Cases (n=26)	
					Relapse	New
1	Squamous Cell Carcinoma	49	12	9	1	6

2	Small Cell Carcinoma	34	12	6	NIL	2
3	Adenocarcinoma	43	9	13	3	NIL
4	Poorly Differentiated	14	8	4	1	2
5	Unconfirmed Malignancy	55	38	19	3	8
	TOTAL	195	79	51	8	18

TABLE 2: CLINICAL VARIABLES VIS A VIS HISTORY OF ATT INTAKE

SN	CLINICAL VARIABLE	TOTAL	No. of the patients on ATT	No. of the patients not taking ATT	Significance P value
1	Age= / < 50 years	85	65 (76%)	20 (24%)	X ² =80.8 p= 0.000
2	Age > 50 years	110	14 (13%)	96 (87%)	
3	Male	167	64 (38%)	103 (62%)	X ² =2.31 p= 0.128
4	Female	28	15 (54%)	13 (46%)	
5	Smokers	135	48 (36%)	87 (64%)	X ² =8.91 p= 0.003
6	Non-smokers	60	31 (52%)	21 (48%)	
7	Upper zone lesions	74	40 (54%)	34 (46%)	X ² =28.7 p= 0.000
8	Lower zones lesion	27	5 (19%)	22 (81%)	
9	Hilar mass	37	5 (14%)	32 (86%)	
10	Bilateral lesions	8	5 (63%)	3 (37%)	
11	Multizone lesions	12	7 (58%)	5 (42%)	
12	Collapse	14	4 (29%)	10 (71%)	
13	Pleural effusion	23	13 (57%)	10 (43%)	

TABLE 3: DURATION OF SYMPTOMS VS HISTORY OF ATT INTAKE AND DELAY IN DIAGNOSIS

S. N.	Patients Characteristics	No. of patients	Duration of symptoms in months		
			Mean	Median	Range
1	All patients	195	4.5	4.6	1- 14
2	Patient on ATT	79	6.4	6.0	2-14
3	Patients not on ATT	116	3.2	3.0	1-10
	DIAGNOSTIC DELAY	-	3.2	-	2-14