Cancer and tuberculosis

J Harikrishna*, V Sukaveni**, D Prabath Kumar***, Alladi Mohan****

Abstract

Lung cancer and pulmonary tuberculosis (TB) are two major public health problems. The association of cancer and TB is intriguing and diverse. Clinicians often encounter patients with co-existent lung cancer and pulmonary TB. These patients may be lung cancer developing active pulmonary TB; or occurrence of cancer in patients treated for pulmonary TB. Chronic inflammation due to TB is thought to be responsible for the genesis of cancer. Co-existence of cancer and TB often causes a delay in the diagnosis. Patients with cancer are vulnerable to develop active TB because of immunosuppression due to malnutrition, or due to the use of intensive treatment modalities, such as aggressive chemotherapy. A high index of clinical suspicion and a focused diagnostic approach is essential to establish the diagnosis early.

Key words: Tuberculosis, cancer.

Introduction

Lung cancer and pulmonary tuberculosis (TB) are two major public health problems associated with significant morbidity and mortality. Cancer is a global health problem causing more than 7 million deaths accounting to nearly 13% of all deaths worldwide. The burden of cancer is increasing globally, with an expected 20 million new cases per year in 2020, half of which will be in the low-and middle-income countries1. TB is one of the major causes of death amongst infectious diseases and it is estimated that one-third of the human population is infected with Mycobacterium tuberculosis. In 2010, there were an estimated 8.8 million incident cases of TB (range 8.5 - 9.2 millions) and 1.1 million deaths (range 0.9 - 1.2 millions) among human immunodeficiency virus (HIV)-negative cases of TB and an additional 0.35 million deaths (range, 0.32 - 0.39 million) among people who were HIV-positive (20/100,000 population). India alone accounted for an estimated one-quarter (26%) of all TB cases worldwide2.

The co-existence of TB and cancer has attracted attention for several years and has remained controversial3. The association of TB and cancer is intriguing and diverse. Simultaneous occurrence of both TB and cancer in the same organ causes a diagnostic dilemma. Inflammation and scarring due to chronic TB results in metaplasia, dysplasia, and cancer. On the other hand reactivation of latent TB in patients with cancer can occur because of immunosuppression due to malnutrition, aggressive chemotherapy, and immunomodulatory therapy.

Historical account

Co-existence of carcinoma and TB was described by many pathologists. Berroya4 cites an early description of ‘cancerous ptthesis’ by Bayle (1815). Meyer4 quoted Penard documenting co-existence of bronchogenic carcinoma and pulmonary TB with definitive histological evidence. Pearl6 based on autopsy findings at Johns Hopkins Hospital, USA, suggested that carcinoma lung was less common in patients who died of pulmonary TB than in those who died of other causes, and went on to even suggest that “this formed sufficient evidence to support the treatment of cancer patients with tuberculin”.

Berroya4 stated that Rokitansky (1854) considered pulmonary TB and carcinoma of lung were thought to be mutually antagonistic. Lubarsch (1888)7 cited by Berroya4 also endorsed Pearl’s view6.

Randall and Spalding8 state that Carlson and Bell (1929) opposed Pearl’s conclusions8 and opined that the less frequent occurrence of lung cancer in patients with pulmonary TB could be because of the fact that TB killed the patients before lung cancer could develop in them. Carry and Greer9 studied 140 cases of bronchogenic carcinoma complicated by pulmonary TB and felt that there was no relationship between TB and bronchogenic carcinoma. As per Miller10, Pilliet and Piattot were the first to describe the coexistence of TB and cancer. Since then many reports have been published in the literature refuting and supporting the causal relationship between TB and cancer.
Pathogenesis
The association between TB and cancer can occur in several ways (Table I). Even though the relationship between chronic inflammation and cancer is well established, causal relationship between TB and cancer is not well understood. Pulmonary TB in immunocompetent individuals is a chronic infectious process characterised by the formation of “granuloma”. In the natural course of evolution of the granuloma, imbalance between tissue damaging agents that can result in deoxyribonucleic acid (DNA) damage and tissue repair mechanisms is thought to generate a microenvironment that predisposes to malignant transformation. Experimental work in mice intended to prove the causal relationship between TB and cancer has shown that chronic TB infection can result in a multistep transformation of cells resulting in dysplasia and malignant squamous cell carcinoma by accumulation of genome alterations and effect of growth factors. Mycobacterium tuberculosis infected macrophages express high levels of inducible nitric oxide synthase, resulting in the production of reactive nitrogen and oxygen species (ROS) leading to DNA damage. Activation of transcription factor, nuclear factor E2 related factor by oxidative stress, directly induced squamous cell metaplasia. Proliferation of cells with damaged DNA would normally be blocked through G2/M check point or these cells would be eliminated through p53 mediated pro-apoptotic pathway. This is antagonised by activation of nuclear factor-KappaB mediated pro-inflammatory pathway leading to pro-liferation of cells with damaged DNA. Thus, factors that are essential for protective immunity also participate in initiation and promotion of lung tumourigenesis. Mycobacterium tuberculosis infected macrophages produce a potent epithelial growth factor epiregulin, which acts as a potent growth factor for premalignant epithelial cells.

Table I: Possible associations between cancer and TB.

- A chance coincidence without any apparent relation
- Metastatic carcinoma developing in an old TB lesion
- Secondary infection of cancer with TB
- Chronic progressive tubercle in which a carcinoma develops
- Simultaneous development of both TB and cancer

TB = tuberculosis; Source: reference 7.

A hypothetical pathway has been postulated based on in vitro and in vivo experiments to explain inflammation as a cause of scar-cancer of lung. Production of ROS, prostaglandins, leukotrienes (LT), cytokines due to cell mediated response by macrophages infected with Mycobacterium tuberculosis leads to damage to DNA, enhanced rate of cell division by inhibiting synthesis of p21, inhibition of apoptosis of cells with damaged DNA by enhancing synthesis of B-cell lymphoma 2 family of apoptosis regulator proteins. These result in mutagenesis of progeny cells, enhanced angiogenesis stimulated by cyclooxygenase-2 products and extensive fibrosis associated with recurrent infection eventually causing tumourigenesis.

Tuberculosis as a cause of lung cancer
The causal relationship between TB and carcinoma was studied by case reports, case-control studies, and cohort studies. In a population-based cohort study in 5,657 TB patients and 23,485 age- and gender-matched controls that were followed-up for 12 years it was observed that the incidence of lung cancer was significantly higher in patients with pulmonary TB compared with controls with incident risk ratio (IRR) of 1.76. Cox proportional hazards model revealed pulmonary TB infection (hazard ratio [HR], 1.64; 95% confidence intervals [CI], 1.24 - 2.15; p < 0.001) and chronic obstructive pulmonary disease (COPD) (HR, 1.09; 95% CI, 1.03 - 1.14; p = 0.002) to be independent risk factors for lung cancer and concluded that pulmonary TB was associated with an increased risk of lung cancer.

In a cohort analysis of data from prostate, lung, colorectal, and ovarian cancer screening trials, 66,863 cancer-free trial participants aged 55 to 74 years who had undergone a baseline chest radiographic examination and were followed-up subsequently for up to 12 years were studied. Scarring was evident on the baseline chest radiograph in 5,041 (7.5%) subjects. Scarring was associated with elevated lung cancer risk (809 lung cancer cases; HR, 1.5; 95% CI, 1.2 - 1.8); specifically for occurrence of cancer in the lung ipsilateral to the scar (HR, 1.8; 95% CI, 1.4 - 2.4). Ipsilateral lung cancer risk remained elevated throughout the follow-up duration. The authors hypothesised that localised inflammatory processes associated with scarring promote the subsequent development of lung cancer.

In another cohort study conducted in 716,812 subjects
including 4,480 patients with newly diagnosed TB who were followed-up for 7 years, the incidence of lung cancer was found to be 11-fold higher in patients with TB with a HR of 4.37 for TB cohort. After further adjustment for COPD, the HR increased to 6.22 with the combined effect of TB with COPD. The authors concluded that the there was an increased risk of lung carcinoma in patients with pulmonary TB. In a meta-analysis of 37 case-control and 4 cohort studies published during the period from 1966-2009, a statistically significant 1.8-fold increased risk of lung cancer was found among pulmonary TB patients.

Co-existent pulmonary tuberculosis and lung cancer

Clinical diagnosis of co-existing TB and cancer is often challenging. This often causes a delay in diagnosis and institution of appropriate treatment and is associated with poor prognosis. Wofford et al. reported 34 cases of co-existing carcinoma lung and pulmonary TB and reported the average delay in making the diagnosis when TB and cancer co-exist to be 13 months. Atypical course of TB, presence of pain, radiological evidence of rib erosion and ipsilateral hilar lymphadenopathy casts doubt on the possibility of coexistence of a malignancy.

Tuberculosis complicating cancer

TB has been known to complicate the course of cancer. Kaplan studied 201 patients with cancer who developed TB during the period 1945-1971. High TB prevalence was seen in patients with Hodgkin’s disease and lung cancer compared to carcinoma bladder, carcinoma colon. The TB rate for patients with lung cancer varied widely (52 - 320 cases per 100,000 persons). Wu and colleagues in Taiwan studied 16,487 patients with cancer and 65,948 controls. In conclusion, chronic inflammation and scarring due to TB can lead to the development of cancer. Co-existence of TB and cancer causes diagnostic dilemma due to similarities in presentation leading to delay in the diagnosis and institution of appropriate therapy. Patients with lung cancer are also vulnerable to develop active pulmonary TB due to immunosuppression and malnutrition resulting from the use of intensive treatment modalities such as aggressive chemotherapy. A high index of clinical suspicion and a focussed diagnostic approach is essential to establish the diagnosis early.

References