Coexistent Pulmonary Tuberculosis and Malignancy

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Historical Review

It was probably Bayle,1 who first, in 1810, reported coexistent pulmonary tuberculosis and malignancy under the description of caseous phthisis; it is doubtful, however, whether this can be considered an authentic case. The first authenticated case of both conditions existing in the same patient at the same time was reported by Penard2 in 1846. Cooper,3 in 1952, collected 40 cases of coexistent pulmonary tuberculosis and carcinoma which had been reported between 1853 and 1930. At least several hundred cases have been reported subsequently.

Etiology

As far as the etiology of tuberculosis and bronchogenic carcinoma is concerned, there are several opinions. Rokitansky,4 in 1852, stated that both diseases are definitely antagonistic and that, therefore, it is rare for these diseases to occur together in the same patient. Graham5 felt that in his experience the association of pulmonary tuberculosis and cancer has been rare; that their coexistence is purely coincidental.

It is quite easy to understand that such a serious, productive and debilitating disease as cancer can easily activate a smoldering tuberculous infection and it is well known that such foci in the lungs are frequent. Nuessle6 stated that centrally located bronchogenic carcinoma could readily cause a pre-existing pulmonary tuberculosis to become active because of altered circulation and bronchial stenosis, produced by the malignancy.

On the other hand, Nuessle does not think that pulmonary tuberculosis might be a factor in causing cancer of the lung. He stated: "the pulmonary tuberculosis is usually a central one; if pulmonary tuberculosis were a factor in producing carcinoma of the lung, more peripheral malignancies would be expected."

Ewing,6 in 1928, stated that tuberculosis is the chief etiological factor in bronchogenic carcinoma, but retracted that statement later.

A relationship between bronchogenic carcinoma and calcified foci of the lungs and tracheobronchial lymph nodes has been noted by Woodruff and co-workers.7 They found that many old tuberculous foci showed spaces filled with cholesterol crystals, a substance which has been shown to have carcinogenic properties. Bronchiectasis is a frequent finding in pulmonary tuberculosis and especially the saccular bronchiectasis seems

From the Medical, Pathology and Tuberculosis Services of the Veterans Administration Center.
Coexistence of Pulmonary Tuberculosis and Hodgkin's Disease: It is now agreed that Hodgkin's disease is not a variant of tuberculosis. Woodruff thought, therefore, that whereas tobacco tar in a normal bronchus will not cause cancer, its accumulation in saccular bronchiectasis might be a factor in causation of bronchogenic carcinoma and that tuberculosis leading to calcification and bronchiectasis may cause carcinoma in smokers.

As far as the statistical incidence of pulmonary tuberculosis and bronchogenic carcinoma is concerned, figures vary with the authors and the era. That, of course, is not surprising, because not only do statistics vary depending on the number of cases studied, but also because there has been a change in the picture of both pulmonary tuberculosis and of bronchogenic carcinoma. Even before the introduction of chemotherapy, the incidence of tuberculosis decreased and the incidence of bronchogenic carcinoma had increased, at least in this country.

Two situations have to be considered: Statistics for bronchogenic carcinoma developing secondarily in a patient who has had pulmonary tuberculosis were found to be .75 per cent by Drymalski and Sweany,9 based on 2,000 cases of pulmonary tuberculosis and 1.5 per cent by Robbins and Silverman,10 based on 400 cases. Figures for pulmonary tuberculosis developing secondarily in a patient with bronchogenic carcinoma vary from 3.8 per cent by Farber11 to 8.6 per cent by Carlson and Bell.12

Coexistence of Pulmonary Tuberculosis and Hodgkin's Disease: It is now agreed that Hodgkin's disease is not a variant of tuberculosis. Hodg-
kin's disease was found in only .3 per cent of patients who had tuberculosis. The figure is not significantly higher than the general incidence of Hodgkin's granuloma.

As for tuberculosis developing in a pre-existing Hodgkin's disease the incidence is high. Ewing stated that "In New York tuberculosis follows Hodgkin's disease like a shadow." It is 20 per cent according to Parker and Jackson. The explanation would be similar to tuberculosis developing in pre-existing pulmonary carcinoma. The incidence of tuberculosis following Hodgkin's disease is higher because patients with Hodgkin's disease, on the whole, live longer and have more time to develop tuberculosis. Schier and co-workers and others showed that in Hodgkin's disease there is a defective immune mechanism in production and transport of cellular antibodies.

That the diminished resistance of the patient is a plausible explanation for tuberculosis developing in a pre-existing Hodgkin's disease is supported by recent reports of patients with Hodgkin's disease treated with ACTH and cortisone. For instance, in 1954, there was a report in the French Literature by Marchal, about four cases of Hodgkin's disease which were treated with ACTH and cortisone, who died within a short time from widespread tuberculosis, due to the administration of ACTH or cortisone. The author warns not to treat patients with Hodgkin's disease with ACTH or cortisone without protecting them with INH.

Why patients with tuberculosis should develop Hodgkin's disease is unknown, since the etiology of Hodgkin's disease is unknown. It is now generally accepted that Hodgkin's disease is a tumor arising from the reticulo-endothelial system. Without having proof to offer, it could be that the

FIGURE 2A (Case 2): X-ray of September 18, 1946, showing a cavity in the left middle lung field.—FIGURE 2B (Case 2): November 21, 1955, showing linear fibrotic shadows extending from the left hilum to the apex.
pre-existing tuberculosis, by altering immunological reactions, irritates or primes or blocks in some unknown way the reticulo-endothelial system, favoring thereby the subsequent development of Hodgkin's disease.

**Diagnosis of Coexisting Pulmonary Tuberculosis and Malignancy**: The diagnosis of these coexisting conditions is difficult. Many symptoms and signs (cough, expectoration, bloody sputum, pain, loss of weight, low grade temperature, x-ray findings, secondary anemia, and cachexia) are common in both diseases.

However, if one is aware of the possibility of coexistence of these two diseases, certain symptoms and signs should arouse attention. Bloody sputum, rather than copious hemoptysis, and severe persistent dull boring pain, often after cough are more suggestive of bronchogenic carcinoma. Likewise, paroxysm of extreme dyspnea out of proportion to the existing x-ray findings, change in character of sputum, or if a previously positive sputum becomes negative in spite of progression of x-ray findings, are more indicative of pulmonary malignancy. Also, a dense prominent opacity near the hilum, especially if unilateral, or a cavity which is thick-walled and has a ragged lining, is more in favor of a bronchogenic carcinoma. Paralysis of hemidiaphragm, retraction of ribs on the affected side and hypertrophic pulmonary osteoarthropathy are also more suggestive of pulmonary malignancy. Awareness of these signs will arouse the examiner's suspicion and instigate further diagnostic procedures such as cytological study, biopsy and bronchoscopy.

While the recognition of pulmonary tuberculosis plus a coexistent malignancy was of purely academic interest in the past, it is now of practical importance because we have a better chance to cure pulmonary tubercu-

**FIGURE 2C (Case 2)**: Photomicrograph of lungs showing a healed tubercle, completely surrounded by masses of undifferentiated carcinoma cells which invade a vein.
lossis and in some cases also to treat, at least, the malignancy. It is, therefore, important to make an exact diagnosis or diagnoses.

Two cases of bronchogenic carcinoma coexisting with pulmonary tuberculosis and two cases of Hodgkin’s disease coexisting with pulmonary tuberculosis are reported. In each case the first disease was tuberculosis and subsequently the patient developed malignancy.

**Case 1:** B. J. W. (R-108603). This 78 year old white man was admitted to the hospital in April 1953, because of pain in the right lower chest of two months’ duration, aggravated by coughing, and weight loss for the past 12 months.

On physical examination there was absence of breath sounds in the lower axillary region on the right and a lag in the respiratory excursions in that area.

Sputum and cultures were positive for acid fast bacilli. After June 1953, cultures became negative. An x-ray film taken on April 10, 1953 (Figure 1A), showed an area of increased density in the left second anterior interspace which compared to the old films appeared to be slightly increased in size. There was also an opaque density in the right base and evidence of pleural thickening of both apices. An x-ray film of the thoracic spine was taken and showed what was probably tuberculous spondylitis with collapse and destruction of the fourth thoracic vertebra. He expired in October 1953.

At postmortem the lungs showed extensive fibrosis and scattered, small nodular densities, some of which were hard and shotty. Other nodules contained caseous material. The liver, fourth thoracic vertebra, and left adrenal gland contained metastases.

Microscopically the lungs showed healing tuberculosis and primary adenocarcinoma (Figure 1B).

**Summary:** This 78 year white man had pulmonary tuberculosis with positive cultures until June 1953, after which date they became negative. He was treated for tuberculosis which improved bacteriologically without a clinical response and postmortem examination showed healing tuberculous foci in the lungs and extensive primary pulmonary adenocarcinoma with metastases to the liver, adrenals, and bone.

**Case 2:** S. R. R. (R-119462). This 59 year old white man was admitted to the hospital on November 30, 1955 because of shortness of breath. He was semicomatose, dyspneic and expired the next day.

Pulmonary tuberculosis was first diagnosed in September 1946, when he had a cavity in the left middle lung field and was treated with pneumoperitoneum (Figure 2A).

In December 1954, he entered the hospital because of pain, malaise, headaches, fever, chilly sensation and night sweats which he developed four days prior to admission. On December 17, 1954, *M. tuberculosis* was obtained from the sputum and three cultures were positive for tuberculosis. On November 21, 1955, an x-ray film showed linear shadows extending from the left hilum to the apex with evidence of contraction (Figure 2B).

On postmortem the lungs showed, bilaterally, increased fibrosis and several nodular lesions, the cut surface of which was caseous and grayish. Microscopically the lungs showed a small focus of healed tubercles, completely surrounded by masses of undifferentiated carcinoma cells. In several fields there appeared to be actual invasion into the most peripheral portion of the tubercles, and invasion of a venous channel by the tumor (Figure 2C). Other portions of the lung, however, showed active tuberculosis involvement. The tubercles were poorly delineated and centrally showed neutrophiles and nuclear fragments along with caseation. Fite’s stain demonstrated acid fast bacilli. Metastatic tumor was also demonstrated in the vertebral marrow, liver, and mediastinal lymph nodes.

**Summary:** This man had a positive sputum and cavitation in 1946; later his disease became completely inactive. In 1954, he again had positive sputum culture for acid fast bacillus. Dyspnea was the most prominent symptom. An x-ray film taken 10 days before death was interpreted as showing pulmonary tuberculosis with further contraction and hardening.

Autopsy revealed both active and old pulmonary tuberculosis, and microscopic examination showed an undifferentiated carcinoma of the lung, (so-called oat cell) which had metastasized to the liver, bone, and mediastinal lymph nodes.
Figure 3A (Case 3): X-ray of October 19, 1950, showing an infiltrative process involving the right supraclavicular region.

Figure 3B (Case 3): G.I. series of May 13, 1955, showing an outpouching of the lesser curvature at the approximate junction, consistent with a gastric ulcer, however, malignancy could not be ruled out on basis of this x-ray examination.

Figure 3C (Case 3): Photomicrograph of the stomach showing the histological picture of Hodgkin's disease with multinucleated Reed-Sternberg cells.
Case 3: R. F. J. (R-117162), a 41 year old white man. Pulmonary tuberculosis was first diagnosed in 1950, on the basis of x-ray films (Figure 3A), positive tuberculin test, and clinical history of cough, expectoration, weakness and slight weight loss. Acid fast bacilli were not found in the sputum. He was followed on an out-patient basis and entered the hospital in November 1954, because of tubercle bacilli in the sputum culture. Following chemotherapy the sputum became negative and he left the hospital against medical advice in March 1955. Epigastric pain appeared in April 1955, and after hematemesis and melena occurred, he came to the hospital in May 1955. A gastric lesion was demonstrated by x-ray study (Figure 3B) and at surgery an in-operable tumor of the stomach was found, grossly interpreted as carcinoma. He expired in July 1955.

On postmortem the stomach was surrounded and imbedded by masses of firm tissue, particularly along the lesser curvature. The lungs were not remarkable. Both the spleen and the liver contained small, firm, yellowish-gray cellular appearing foci. Similar tissue replaced the vertebral marrow.

Microscopically sections from the lungs showed a single small zone of peribronchial infiltration by the neoplasm. Sections through the stomach revealed the histological picture of Hodgkin's disease (Figure 3C). The presence of Hodgkin's infiltration was also found in the abdominal lymph nodes, liver, spleen, bone marrow, and thyroid gland.

Summary: This patient had tuberculosis of the lungs with positive sputum and later developed Hodgkin's disease.

Case 4: B. J. F. (R-113009), a white man of 43 years, had rheumatic heart disease at the age of 10 and an old diagnosis of rheumatic valvular heart disease with mitral stenosis and insufficiency and aortic stenosis and insufficiency. He was hospitalized from February 18, 1952 to May 14, 1952, because of shortness of breath on slight exertion. An x-ray film of the chest on February 25, 1952, showed an infiltrative density in the right apex and right infraclavicular are (Figure 4). He was rehospitalized in 1954, because of weakness, pain around the heart. Sputum for Mycobacterium tuberculosis was positive in May of 1954. The last positive sputum was obtained on July 28, 1954, after which all specimens were negative. An x-ray film of May 1954, showed a thin-walled cavity in the right infraclavicular area and density involving the lower lung fields, probably the mid lung.

**FIGURE 4** (Case 4): X-ray of February 25, 1952, showing an infiltrative density in the right apex.
He was disproportionately sick. In August 1954, lymph nodes were noted and a biopsy established the diagnosis of Hodgkin’s disease. He expired on December 6, 1954.

At postmortem the heart showed mitral stenosis and pale gray vegetations on the aortic and mitral valves. Grossly, there was Hodgkin’s involvement of the mediastinal, abdominal, para-aortic and para-iliac nodes, of the spleen, and of the bone marrow.

Microscopically sections through the lungs showed small tubercles with caseation necrosis and epithelioid cells. With Fite’s stain, acid fast rods were demonstrated. In addition to the lymph nodes, Hodgkin’s infiltration was also present in the spleen and bone marrow.

Summary: This man had pulmonary tuberculosis and later became disproportionately sick when Hodgkin’s disease was found. He also had rheumatic valvular heart disease and subacute bacterial endocarditis.

SUMMARY

Four cases of coexistent pulmonary tuberculosis and malignancy have been presented; differential diagnostic features which would arouse suspicion that one is dealing with two lesions instead of one, have been discussed. The coexistence of malignancy and pulmonary tuberculosis is probably on the increase and, therefore, the recognition is of importance.

RESUMEN

Se relatan cuatro casos de tuberculosis pulmonar coexistente con neoplasia maligna. Se hace una discusión de las características diagnósticas que harían sospechar que uno se encuentra ante dos padecimientos en lugar de uno solo. Probablemente coexistencia de malignidad y tuberculosis está en aumento ahora y por tanto, su reconocimiento es de importancia.

RESUME

Les auteurs rapportent quatre observations de tuberculose pulmonaire coexistant avec une néoplasie; ils exposent les éléments qui permettent de ne laisser aucun doute sur le fait qu’il s’agit de deux affections et non d’une seule. La coexistence de cancer et de tuberculose pulmonaire est probablement maintenant de plus en plus fréquente, et c’est pourquoi il est important de savoir reconnaître cette association.

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REFERENCES