BRONCHIOGENIC CARCINOMA IN ASSOCIATION WITH PULMONARY ASBESTOSIS *

Report of Two Cases

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Following the report of a case of carcinoma of the lung in the presence of pulmonary asbestosis by Lynch and Smith [2] in 1935, several similar papers appeared in rapid succession. In the same year, Gloyne [3] presented two cases of squamous-celled carcinoma of the lung occurring in asbestosis, and in the following year,[3] a case of oat-celled carcinoma. Egbert and Geiger [4] reported one case in 1936. Two years later, Nordmann [5] analyzed the recorded cases after adding two of his own to the literature. His views on the relationship between the two diseases were revealed by the title of his paper, "Der Berufkrebs der Asbestarbeiter" [Occupational Cancer of the Asbestos Worker]. The eighth case was reported by Lynch and Smith [6] together with an additional case of squamous metaplasia of the bronchial epithelium in an asbestotic lung. The two cases here reported bring the total number recorded in the literature to ten.

Reports of Cases

Case 1

W. M., a white male, 52 years old, was admitted to Queens General Hospital complaining of a chronic morning cough which for many years had been productive of small amounts of tenacious sputum. During the 4 weeks prior to admission, the cough became progressively more severe and he was compelled to stop work. The sputum now amounted to approximately ½ oz. (120 cc.) each day and was occasionally blood-streaked. This was accompanied by right chest pain, marked anorexia and a weight loss of about 15 lbs. (6.5 Kg.).

There was no history of past medical, surgical or venereal disease except for a nasal operation at the age of 25.

For the past 25 years the patient had been employed almost continuously by various manufacturers of asbestos products. His duties always entailed the covering of steam and water pipes with asbestos fabric. He stated that many of his co-workers had died of "silicosis."

Physical examination revealed a weakened, emaciated, white male breathing noisily and with difficulty, and coughing frequently. The neck veins were distended. There were signs of consolidation over the upper right portion of the chest anteriorly. The breath sounds were distant over the lower posterior areas on both sides of the chest. The cardiac apex and the trachea appeared shifted to the right. There were no other unusual findings in the heart, abdomen, extremities or nervous system.

Laboratory Data. Temperature, 99.8° F. Pulse, 124 per min. Respirations, 22 per min. Blood pressure, 110/80. Urine, negative except for occasional red

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and white blood cells. Blood count, 4,600,000 red cells per cmm. and 11,000 cells per cmm., of which 72 per cent were polymorphonuclear cells. Hemog 12.5 gm. per 100 cc. Venous pressure, 140 mm. of blood. Ether circulation 15 sec. Saccharin circulation time, 3 min. (probably unreliable). The sputum negative for acid-fast bacilli. A Kline test of the blood was negative.

Roentgenograms of the chest taken shortly after admission showed a large of diminished illumination involving the entire right upper lobe with "patch filtration of the lower lobe." The lower cardiac shadow was deviated to the r The left lung field presented prominent pulmonary markings which, however, c not be regarded as definitely pathological. On the fifth hospital day bronchos revealed a sessile mass protruding from the posterior wall of the trachea abou cm. above the carina, leaving a narrow crescentic lumen about 2 mm. in w Biopsy from this region showed bronchial tissue with only an inflammatory r tion. During the next 12 days the patient received small daily doses of l voltage roentgen-ray therapy to the anterior aspect of the chest, totaling 2,6 This was accompanied by a marked improvement in respiration. The intratrac mass had now been reduced in size sufficiently to allow passage of the bron scope into the right main bronchus, where ulceration and constriction were no Biopsy from this region showed definite carcinoma.

During the first 4 weeks in the hospital he had a low-grade fever which gra ally declined. On the 30th hospital day, his temperature rose to 105.2° F. and complained of a sore throat. Blood cultures taken at this time and repeate days later showed the presence of hemolytic streptococci. In spite of sulfapyrid and, later, sulfathiamide therapy, his temperature remained elevated (101° 102° F.). He grew rapidly weaker and expired on the 36th hospital day.

The final clinical diagnoses were bronchiogenic carcinoma in the region of carina, *Streptococcus hemolyticus* septicemia and terminal pulmonary edema.

Postmortem Findings. The pertinent descriptive data are limit essentially to the thorax.

The right pleural cavity was completely obliterated by dense fibro adhesions. The left pleural cavity contained approximately 200 cc. watery yellow fluid with numerous flakes of fibrin. A shaggy yell coating covered the posterior parietal pleura. Section of the right lu (Fig. 1) revealed an irregular, globular, hard, grayish white mass cm. in diameter. The mass had completely eroded and encircled t right main bronchus. Some portions of the mass were softened and h been partially excavated. Grayish white neoplastic tissue was seen i filtrating beneath intact bronchial epithelium upward to a point 2.5 c above the carina, and downward along the right main bronchus for distance of 5 cm. beyond the lower margin of ulceration. The r mainder of the right upper lobe presented several prominent, irregula grayish white septa extending out to the pleura which measured 3 mm in thickness in this region, and was composed of firm, opaque, whit tissue. The parenchyma of the right upper and middle lobes presente numerous pneumonitic areas. The cut surfaces of the right lower lob and the entire left lung were grayish red and crepitant.

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trachea, there was an irregular, nodular mass of necrotic neoplastic tissue 5 cm. in diameter which was adherent to and compressed both trachea and esophagus. (This probably corresponded to the mass visualized bronchoscopically.) The pulmonary vessels were intact except for the main branch to the right upper lobe which was so compressed by the intrapulmonary tumor mass that a probe was passed only with difficulty.

Within the pericardial sac there was approximately 300 cc. of fluid similar to that found in the left pleural cavity. A thick, shaggy, yellowish gray coating covered both visceral and parietal pericardium. The myocardium of the right ventricle was 6 mm. thick.

The only extrathoracic metastasis seen grossly was a mass measuring 4 by 2 cm. at the lower pole of the right kidney. Multiple sections of the brain revealed no metastasis. The right adrenal gland showed a cortical adenoma measuring 3 cm. in diameter.

Microscopical study showed that the neoplastic tissue in the lung was composed chiefly of fairly large polyhedral cells with moderately small, round hyperchromatic nuclei. There was no evidence of either intercellular bridges or of "pearl" formation. Many areas showed considerable variation in the size and shape of these cells and in some, large multinucleated cells were present. In a few regions these cells were spindle-shaped and were arranged in cordlike bundles. There was a definite tendency to invade along the alveolar walls, which occasionally gave a superficial resemblance to large glands. Lymphatic permeation was prominent throughout all involved areas. Small islands of neoplastic tissue were present beneath intact bronchial epithelium, corresponding to the picture seen grossly. Many of these islands were in the lumina of distended lymphatics of the lamina propria (Fig. 2).

Small and large masses of the neoplasm, many of which were necrotic, were found within the wall of the bronchus to the right upper lobe, the adjacent lung tissue, the mediastinal lymph nodes and the right kidney. A routine section revealed a minute metastasis lying in the substance of the adrenal cortical adenoma.

Of interest was the presence of squamous metaplasia of the epithelium of the right main bronchus and of several of the bronchial mucous-gland ducts in this region. Distinct intercellular bridges were seen. Structure was slightly atypical, but there was no definite malignant change in the metaplastic epithelium.

Many sections of both lungs showed considerable diffuse interstitial fibrosis, numerous foamy mononuclear cells within the alveolar spaces and a moderate number of golden yellow asbestosis bodies (Fig. 3). These varied from rod-shaped "early" forms to beaded "weathered"

forms. Many were partially or completely engulfed by mononuclear and multinuclear macrophages. Sections treated with potassium ferrocyanide gave positive results for iron. In several regions the alveoli were filled with polymorphonuclear cells and fibrin. In areas of fibrosis a marked obliterative endarteritis was present.

Chemical examination yielded 240 mg. of silicon dioxide per 100 gm. of dried lung.

The final diagnoses were: Bronchiogenic, non-keratinizing, squamous-celled carcinoma of right upper lobe; metastases to mediastinal lymph nodes, to right kidney and to a cortical adenoma of right adrenal gland; pulmonary asbestosis; right ventricular hypertrophy; squamous metaplasia of bronchus; bronchopneumonia of right upper and middle lobes; left pleural effusion; fibrinous pericarditis (*Streptococcus hemolyticus*) with effusion.

Case 2

The history was obtained from the patient's son after the autopsy was completed. His knowledge of some details was admittedly inaccurate.

E. R., a white male, 58 years old, began to experience dyspnea on exertion approximately 15 years before his death. This progressed slowly but steadily so that during his last few years of life he was almost completely exhausted after climbing only one flight of stairs. He had frequent bouts of coughing which were especially severe in the morning but occurred throughout the day and night. This was productive of moderately large amounts of sticky brown sputum which was never blood-streaked. During the spells of coughing, "wheezing" noises in his chest could be heard many feet away. After several years, he was examined by a physician who made a roentgenogram of his chest and told him he had "asbestosis of the lungs." There was no history of cyanosis, orthopnea, paroxysmal dyspnea, angina pectoris or ankle edema.

Several months before his death the patient began to lose weight rapidly. He complained of continual fatigue and his cough became more frequent and more severe. There was no change in the character of his sputum. A physician told the family that the patient had developed "complications following asbestosis." He sank slowly, became comatose and finally expired.

The patient had been employed by a manufacturer of asbestos products since the age of 23 years until a few months before his death. During the first 25 years of this period he was employed as a pipe-coverer, the same occupation as in case 1. Although there was no known association between the two men, the conditions under which they worked were essentially the same. The patient's work called for covering steam and water pipes with asbestos. He was seldom in the same place for more than a few days or weeks, but the work usually was done in unventilated cellars. Large amounts of powdered asbestos cement were used in addition to the asbestos fabric. The patient's son worked with his father for a year but quit because the air was "too dusty" and because several of the employees were "getting sick." During the 10 years before his death, the patient was employed as a salesman and was not exposed to asbestos dust.

Postmortem Findings. Both pleural cavities were almost completely obliterated by fibrous adhesions between the pleural surfaces. The cut surface of the right lung presented a diffuse infiltration of firm white neoplastic tissue replacing most of the lower lobe. There was prominent encirclement of the bronchi and invasion of the septa by the new growth (Fig. 4). Posteriorly, the adjacent tissue of the right upper lobe showed similar parenchymal, peribronchial and septal infiltration by neoplasm. At the apex of the right upper lobe there was an area of fibrous induration and distortion. No actual specific primary bronchial site could be established, but the major location of the tumor-tissue suggested origin in the right lower lobe.

The remaining lobes of both lungs presented numerous, small, firm, irregular greenish black nodules.

Numerous metastatic foci were present beneath the pleura of the right lung, in the mediastinal and peripancreatic lymph nodes, cerebral cortex, liver, kidneys, thoracolumbar vertebrae and several ribs.

No other noteworthy lesions were present in the remaining viscera.

Microscopical Study. The neoplasm was composed of moderately large, round to oval cells with round, dense, hyperchromatic nuclei. There was considerable variation in the size and shape of the cells with varying amounts of cytoplasm. Many cells contained several nuclei. There was a compact grouping of the neoplastic cells between fine fibrous trabeculae producing a somewhat alveolar arrangement. No true glandular or squamous features were noted.

In the sections of bronchi studied, no ulceration of the mucosa was present. In many regions, however, there was infiltration of tumor-tissue into the lamina propria with invasion and destruction of the remainder of the bronchial wall (Fig. 5). Many of the large neoplastic masses were necrotic. Lymphatic permeation was prominent in all sections. The metastases presented similar histological and cytological characteristics throughout, but the multinuclear tendency was more marked in the liver. The carcinoma cells in the cerebral cortex were less compactly arranged and showed extensive necrosis and hemorrhage.

Sections of lung showed a widespread interstitial fibrosis somewhat unevenly distributed. Only occasional asbestosis bodies were found (Fig. 6). They were smaller but similar to those seen in case 1. Only a few were seen within large macrophages. Sections treated with potassium ferrocyanide were positive for iron.

Additional findings in the lungs included marked hypertrophy of the muscular coat of the small and large bronchi, obliterative pulmonary endarteritis with recanalization, pulmonary edema and organizing fibrinous exudate on the pleural surfaces.

TABLE I

Summary of Reported Cases of Pulmonary Asbestosis and Carcinoma

Authors	Year	Sex and age	Occupation	Duration of exposure	Freedom from exposure before death	Nature of tumor	Primary site	Metastases
*1. Lynch and Smith	1935	M 57	Weaver	21 yrs.	8 mos.	Squamous-celled	Right lower lobe	Many nodules in right lower lobe
*2. Gloyne	1935	F 35	Spinner	8 yrs.	9 yrs.	Squamous-celled	Right upper lobe	Pleura
*3. Gloyne	1935	F 71	Mattress and opening depts.	19 mos.	25 yrs.	Squamous-celled	Right lower lobe	None
4. Egbert and Geiger	1936	M 41	Weaver	17 yrs.	2 yrs.	Glandular	Left lower lobe	Widespread
*5. Gloyne	1936	M 59	Packer, stores department	10½ yrs.	7 mos.	Oat-celled	Left lower lobe	Left upper lobe and pleura
*6. Nordmann	1938	F 35	Carder, spinner, weaver	7 yrs.	9 yrs.	Squamous-celled	Left lower lobe	Liver, kidneys
*7. Nordmann	1938	M 55	Pre-spinning assembly room	7 yrs.	12 yrs.	Squamous-celled	Left lower lobe	Widespread
8. Lynch and Smith	1939	M 50	Weaver	13 yrs.	3 yrs.	Squamous-celled with glandular features	Right lower lobe	Pleura, mediastinal nodes
9. Holleb and Angrist	1941	M 52	Pipe Insulator	25 yrs.	9 wks.	Non-keratinizing squamous-celled	Right upper lobe	Mediastinal nodes, kidney, adrenal
10. Holleb and Angrist	1941	M 58	Pipe Insulator	25 yrs.	10 yrs.	Oat-celled.	Right lower lobe	Widespread, including brain

*Included in previous tabulation by Nordmann.

7. Nordmann	1938	M 55	Pre-spinning assembly room	7 yrs.	12 yrs.	Squamous-celled	Left lower lobe	Widespread
8. Lynch and Smith	1939	M 5[illegible]	Weaver	13 yrs.	3 yrs.	Squamous-celled with glandular features	Right lower lobe	Pleura, mediastinal nodes
9. Halleb and Angrist	1941	M 52	Pipe insulator	25 yrs.	9 wks.	Non-keratinizing squamous-celled	Right upper lobe	Mediastinal nodes, kidneys, adrenal
10. Halleb and Angrist	1941	M 58	Pipe insulator	25 yrs.	10 yrs.	Out-celled	Right lower lobe	Widespread, including brain

*Included in previous tabulation by Nordmann.

Chemical examination yielded 4.5 mg. of silicon dioxide per 100 gm. of dried lung.

The final diagnoses were: Bronchiogenic, large out-celled carcinoma of the right lower lobe with extension to right upper lobe and metastases to mediastinal and peripancreatic lymph nodes, liver, kidneys, cerebral cortex, ribs and thoracolumbar vertebrae; pulmonary asbestosis; chronic bronchitis; tuberculous apical scar of right upper lobe.

Comment

No reference could be found in the literature providing strict criteria for the diagnosis of pulmonary asbestosis. Silica has been shown [7] to constitute a significant, though somewhat variable, portion of the asbestos fiber (39 to 51.5 per cent). Determinations of silica were therefore carried out with the idea that the demonstration of definitely increased values would furnish final confirmation of the diagnosis of asbestosis. This was considered justified since there was no reason, on the basis of clinical record or autopsy findings, to suspect appreciable exposure to any of the silicates other than asbestos.

The dried lungs of case 1 were found to contain 240 mg. per cent of silica, while those of case 2 yielded only 4.5 mg. per cent. McNally [8] and Kettle and Archer [9] stated that lungs may contain as much as 200 mg. per cent without showing histological evidence of silicosis. If this value were used as a standard, the silica content in case 1 would be only slightly elevated while case 2 definitely would fall within known non-pathological limits. The diagnosis of pulmonary asbestosis in both cases must, therefore, rest on the usual criteria: (1) A history of prolonged exposure to the dust—25 years in both cases; (2) the presence of chronic respiratory symptoms, productive cough in one and cough and severe exertional dyspnea in the other without cardiac disease; (3) histological findings of asbestosis; namely, diffuse, interstitial, pulmonary fibrosis, asbestosis bodies, macrophages and giant cells.

The apparent discrepancy between the presence of pulmonary asbestosis and the absence of elevated silica values can be resolved. First, it is known that inhaled asbestos fibers undergo dissolution and phagocytosis, and may eventually disappear entirely, leaving behind irreparable damage.[10] An additional, though probably minor factor, is the elimination of asbestos by expectoration. This occurs not only as fibers but in the form of asbestosis bodies, showing that a tissue reaction has already occurred in the lung.[11] Second, both of these individuals were employed for unusually long periods in occupations in which the exposure to asbestos dust was relatively low. It is therefore conceivable that extensive damage could result as a summation effect,

without appreciable accumulation of asbestos in the lung at any one time. The combination of both factors may account for the particularly low silica content in case 2 in which there was, in addition, freedom from exposure for 10 years before death.

Nordmann [5] presented in tabular form the relevant data on his own two cases of pulmonary asbestosis and carcinoma, and of the four cases previously recorded. After analyzing the results, he came to the conclusion that pulmonary cancer is an occupational disease among asbestos workers. Gloyne,[12] in a recent text, stated that no definite conclusions can be drawn on the relation between these two diseases until more material is available. Table I presents a tabulation similar to Nordmann's, but brought up to date by the addition of four cases, including the two here reported. It should be made clear that the data are presented merely as a summary and not necessarily as supportive evidence for Nordmann's conclusions.

It may be of interest to review briefly, for comparison, the incidence of carcinoma in the material examined in this department. The figures are derived from the autopsy material of a general city hospital for acute illnesses, with 696 beds of which 498 are devoted to adults. In a total of 2,451 routine autopsies performed in a 5-year period, there were 401 instances of carcinoma of all types. This is an incidence of 16.36 per cent. Of these, 59 were bronchiogenic, comprising 14.71 per cent of all carcinomas and 2.41 per cent of the routine autopsies. It was striking, although naturally of no statistical significance, to find bronchiogenic carcinoma in the only two cases of pulmonary asbestosis seen here.

Conclusions

1. Two cases of bronchiogenic carcinoma in association with pulmonary asbestosis are presented.

2. An attempt to demonstrate unusual amounts of silica in the lungs of both cases was unsuccessful.

3. An explanation for the absence of elevated silica values in the presence of asbestosis is offered.

4. The relevant data of all reported cases of pulmonary asbestosis and carcinoma are presented in tabular form.

Note: The authors wish to express their grateful appreciation to Goodwin A. Dibler for the clinical data and to Richard Grimes and Howard W. Neal, of the Office of the Chief Medical Examiner, for the opportunity to study the autopsy material.

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