

BRONCHIAL ADENOMA

A Clinicopathologic Study of 21 Cases

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BRONCHIAL adenoma diagnosed clinically and bronchoscopically was reported by Kramer¹ in 1930; two years later Wessler and Rabin² designated bronchial adenoma as a definite clinicopathologic entity. The same type of tumor had been described by Ephraim³ in 1911 as "sarcoma of alveolar pattern," by Kreglinger⁴ in 1913 as "cylindrical cell sarcoma," and by Geipel⁵ in 1931 as "benign basal cell cancer."

In 1937 Hamperl⁶ published a meticulous histologic study of the disorder and suggested that the adenoma was derived from mucous glands of the bronchi. He described nine cases; in two the histologic pattern was similar to the cylindromatous pattern of certain salivary gland tumors so he referred to the neoplasms as "cylindromas." Five of the remaining seven cases Hamperl called "carcinoid variant" on the basis of the resemblance of the histologic pattern to that of carcinoid tumors of the appendix reported previously. In the remaining two neoplasms, he found a special type of epithelial cell that he called an "oncocyte," a cell that he believed was present in other parts of the body besides the salivary glands, such as thyroid, parathyroid, pancreas, liver, and pituitary gland; he was unable to determine whether oncocytes have a function.

Concerning the possible etiology of bronchial adenoma, Stout⁷ in 1943 reported finding all of the features of the oncocytes previously described by Hamperl.⁶ Stout stressed the great difference between the oncocytes and other cells in the bronchial mucous membrane, and concluded that the oncocyte warrants serious consideration as the probable cell of origin, for no other cell, either in the bronchus or in the surrounding lung, offers itself as a possible origin of the bronchial neoplasms. To him, the presence of oncocytes in the bronchial glands and their ducts, and the absence of oncocytes from the ciliated lining cells of the mucosa offered further support to this concept.

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This etiologic concept has not satisfied all observers. Womack and Graham^{8,9} found bone and cartilage in the tumors and expressed the belief that bronchial adenomas originate from arrested bronchial buds rather than from the mucous glands of the bronchi and their ducts. They noted that sometimes associated with these "mixed tumors," as they preferred to call them, were various congenital anomalies. The most frequent associated congenital anomaly was abnormal lobulation of the affected lung, and the next most frequent was the abnormal course of accessory bronchi direct from the trachea to the affected lung. These observations supported their belief that bronchial adenomas originate from anlagen that have failed to develop normally.

The theory of Womack and Graham was criticized first by Mallory¹⁰ on the basis that bone may form in any pulmonary tumor as a result of stromal metaplasia, and that the fragments of cartilage found in some bronchial adenomas may be regarded as remnants of bronchial cartilage surrounded by infiltrating tumor strands. Furthermore, in none of the 20 specimens of bronchial adenomas studied by Stout⁷ was bone or cartilage an integral part of the tumor; for this reason he agreed with Mallory¹⁰ that the hypothesis of Womack and Graham^{8,9} concerning the etiology of these tumors has insufficient foundation. Most recent observers adhere to this criticism of Womack and Graham's theory and accept the viewpoint of Hamperl and Stout that bronchial adenomas originate from the bronchial glands and their ducts.

Bronchial adenomas have been the source of considerable controversy as to the degree of their aggressive potentialities. The first published case of metastasis from the lesion was that of Zamora and Schuster¹¹ in 1937. In 1941, Goldman and Stephens¹² reported 18 cases of bronchial adenoma without a single case of vascular invasion or distant metastasis. They classified these neoplasms as epithelial in origin with growth potentialities midway between distantly metastasizing carcinomatous lesions and entirely local polypoid bronchial tumors. In 1942, Adams, Steiner, and Block¹³ reported five cases, three of which metastasized respectively to lumbar vertebrae, to liver, and to a tracheal bronchial lymph node. In 1943, Anderson¹⁴ reported a case that he labeled "malignant adenoma" because of hepatic metastasis. Stout⁷ called these neoplasms "adenomatous," but objected to the descriptive term "benign" because of the aggressive infiltrative growth displayed by many of them and the occasional occurrence of metastasis.

Moersch and McDonald¹⁵ expressed the belief that a bronchial adenoma should be considered as a carcinoma of low-grade malignancy, which possesses the ability to metastasize, and that when metastasis occurs to the liver, the patient's condition rapidly deteriorates as a result of hepatic insufficiency.

More recently Liebow¹⁶ stated that bronchial adenomas could be easily differentiated from bronchogenic carcinoma because of the following characteristics of the adenomas: slow rate of growth and late recurrence, only slight tendency to destroy despite some tendency to invade adjacent tissue, and rare, sluggish, and usually inconsequential metastatic lesions.

It is our purpose to present the findings in 21 patients in whom bronchial adenoma was diagnosed at the Cleveland Clinic during a period of more than

nine years. Emphasis is placed on the benign course of the disease in these patients so far. The so-called "peripheral" and "multiple" bronchial adenomas reported by Felton, Liebow, and Lindskog,¹⁷ which are thought to originate from the lining epithelium of the bronchioles, are not included in this study.

Material and Methods

The clinical records and pathologic findings in 21* cases of bronchial adenoma were reviewed. All cases were diagnosed at the Cleveland Clinic between January 1948 and May 1957.

Most of the surgical specimens had been removed by either lobectomy or pneumonectomy; consequently the entire neoplasm and any extension was available for study. Multiple blocks, including both endobronchial and extra-bronchial portions of the neoplasm were prepared with special consideration given to the margin of the tumor bordering adjacent lung. Special attention was given to all regional lymph nodes that were removed at operation. Histologic specimens were stained routinely by a hematoxylin-eosin—methylene blue stain. Certain sections were stained for the presence of argentaffin granules without success.

Sex and Age

In our series the tumor occurred in 14 women and in 7 men. The ages of the patients ranged from 18 to 73 years, with a mean age of 49 years for the entire group. Six patients were less than 40 years of age.

Symptomatology

The duration of symptoms in 20 patients before the diagnosis was established ranged from 2 months to 20 years, or an average of 5 years. One patient was asymptomatic. The symptoms varied according to the size of the tumor, its location, and the degree of bronchial obstruction that it produced. The three most common symptoms were cough, hemoptysis, and pulmonary suppuration.

A cough was the presenting complaint in 15 of the patients. The cough was slight at onset, but apparently with the growth of the tumor the bronchial irritation increased and the cough became more distressing. Sometimes it was most troublesome at night, or when the patient assumed a particular position (postural cough). In the early stages of the disease, the cough usually was non-productive. Sputum was present in variable amounts in 11 patients; initially it was mucoid, then, as the growing neoplasm brought about bronchial obstruction and its sequel, pulmonary infection, the sputum became purulent.

*One case was previously reported by one of us (D.B.E.).¹⁸

Hemoptysis was one of the common symptoms of bronchial adenoma. It occurred in 11 of the patients and in 2 was the presenting complaint. The hemoptysis was sudden both in onset and in termination; it was not profuse. Usually it was spontaneous in character and independent of any preceding paroxysms or physical effort, and in some of the women it was especially severe during the menstrual period.

Pulmonary suppuration ranging from obstructive pneumonitis through bronchiectasis to frank pulmonary abscess is commonly associated with bronchial adenoma. Bronchiectasis or obstructive pneumonitis or both conditions were present in 15 of the 21 patients.

None of the patients had clubbing of the fingers.

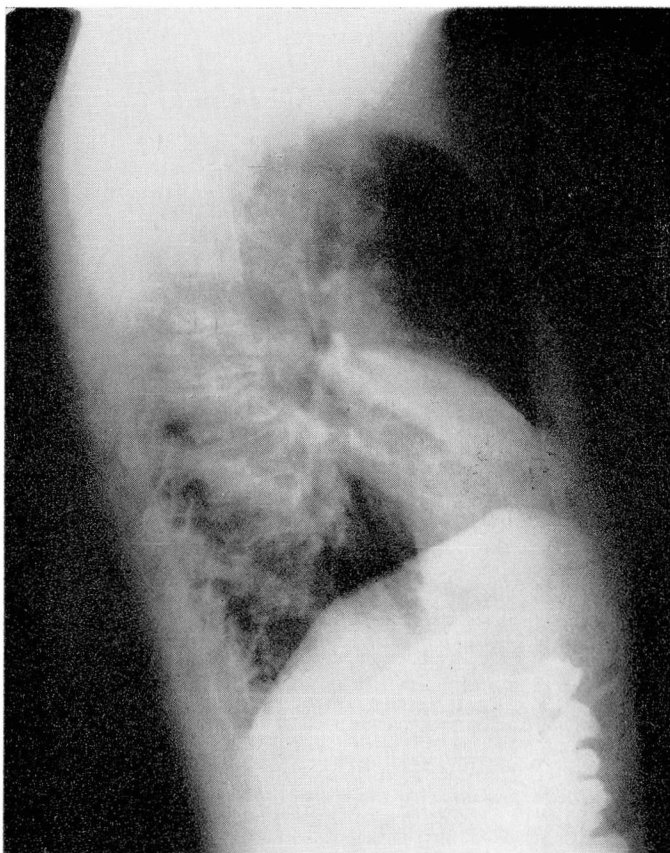


Fig. 1. Total collapse of right middle lobe caused by occlusion of the middle lobe bronchus by bronchial adenoma. The patient was cured by middle lobectomy.

Roentgen Findings

A rather wide range of roentgen findings was visualized. In 10 of the 21 cases the tumor was masked by concomitant inflammatory changes such as distal pneumonitis or thickening of the pleura producing radiopacity of a pulmonary segment or of an entire lobe (Fig. 1). In seven cases the tumor was outlined as a round or an oval opacity without evidence of bronchial obstruction (Fig. 2). In one case roentgenograms showed only a hilar mass. In three cases the roentgen findings of the chest were normal. Bronchiectasis and shifting of the mediastinum were evident in some patients. It must be emphasized that none of these findings were pathognomonic of bronchial adenoma. Whether present singly or in combination, they indicate only a mechanical interference with the normal bronchial drainage. We were unable by roentgen study alone to differentiate an adenoma from other types of bronchial tumors.

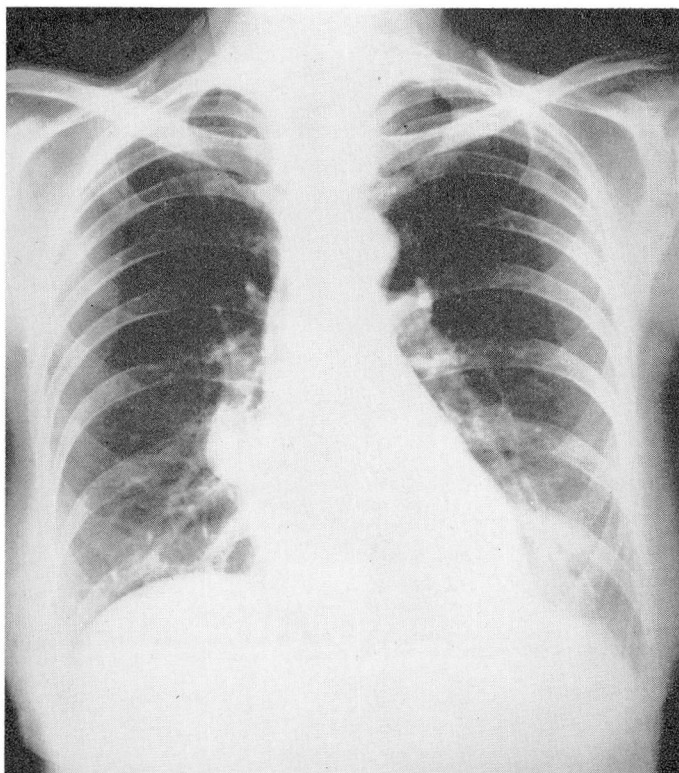


Fig. 2. The circumscribed shadow proved at operation to be caused by bronchial adenoma. It was possible to resect the tumor with its bronchial origin without sacrificing any pulmonary tissue.

Bronchoscopic Findings

Nineteen of the 21 patients underwent bronchoscopic examination. The findings were positive in 15 of the 19 patients, an incidence that is in sharp contrast to that in carcinoma of the lung. In 12 of the 19, the bronchoscopic biopsies were positive for bronchial adenoma. In one, a mass was seen, but a biopsy provided only granulation tissue. The biopsy was not repeated because of severe bleeding at the time of the original examination. In two other instances, tumor was seen, but biopsy was not performed—in one because of the cherry-red, vascular appearance of the external surface, and in the other because the biopsy forceps could not be engaged. Bronchoscopic findings were without significance in four patients.

In two patients, bronchoscopic smears for cytologic study were positive for neoplastic cells (Fig. 3). The bacteriologic findings were without significance. None of the patients had an associated active tuberculous infection.

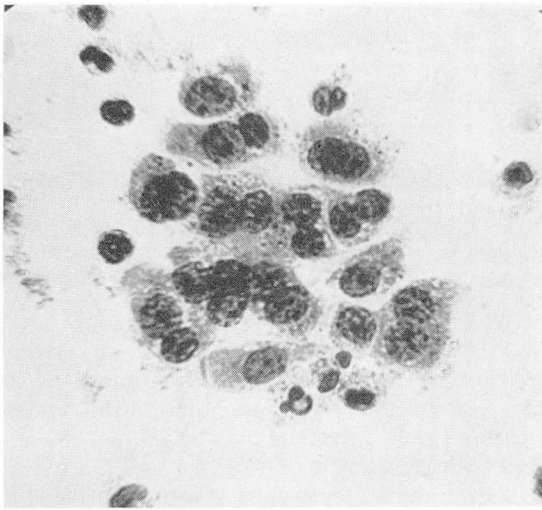


Fig. 3. Neoplastic cells found in bronchoscopic swabbing. Note nuclear stippling. Wet-film preparation stained with toluidine blue; X670.

Pathologic Findings

In our series the tumor occurred with approximately equal frequency in the right and in the left lung. Of those adenomas in the right lung, two involved the right main bronchus, four involved the right upper lobe, two involved the

right middle lobe, and two involved the right lower lobe. Of those adenomas in the left lung, two involved the main bronchus, four involved the upper lobe bronchus, and five originated in the lower lobe bronchus.

In most instances the neoplasm was composed of an endobronchial portion that ranged from 0.5 to 4.0 cm. in diameter, and a much larger extrabronchial portion as great as 7 cm. in diameter (Fig. 4). None of the tumors was entirely

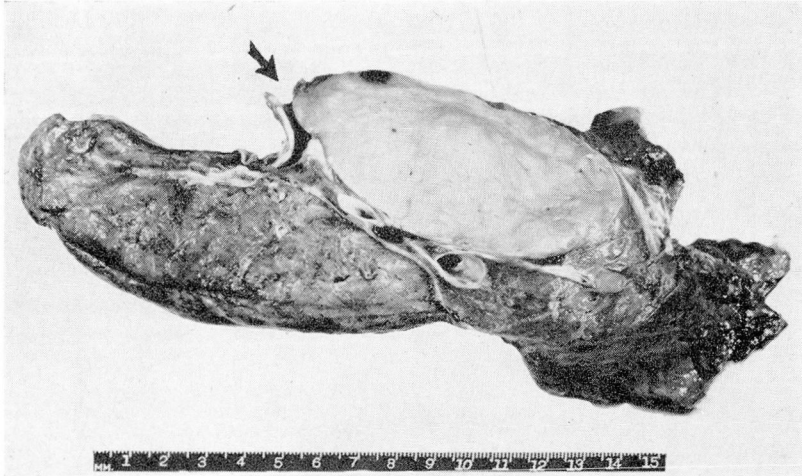


Fig. 4. Large bronchial adenoma; this is a total left pneumonectomy. Note lack of necrosis within the tumor. The arrow indicates the left main bronchus.

endobronchial or intramural. The shape and amount of the endobronchial portion of the neoplasm were no indication of the amount of extrabronchial extension that had occurred. The endobronchial portion corresponded grossly to the bronchoscopist's general description: a polypoid mass, pink to purple, soft to firm, and usually bosselated. The extrabronchial portion usually was sharply demarcated from the adjacent lung. The color ranged from tan to pink to pale gray. Gross necrosis was not noted. In one patient two separate tumors were present involving main bronchi to both upper and lower lobes.

Microscopic sections of the polypoid portion of the adenoma showed an epithelial covering that usually had undergone squamous metaplasia. Areas of ulceration with attached blood clot were occasionally demonstrated. Generally there was a band of fibrous tissue of variable thickness beneath the epithelial layer. The histologic features of the various neoplasms were remarkably constant. The individual cell was of moderate size, with a uniform, round nucleus that commonly showed conspicuous chromatin stippling. The nuclear membrane was distinct. The cellular borders often were indistinct and appeared to

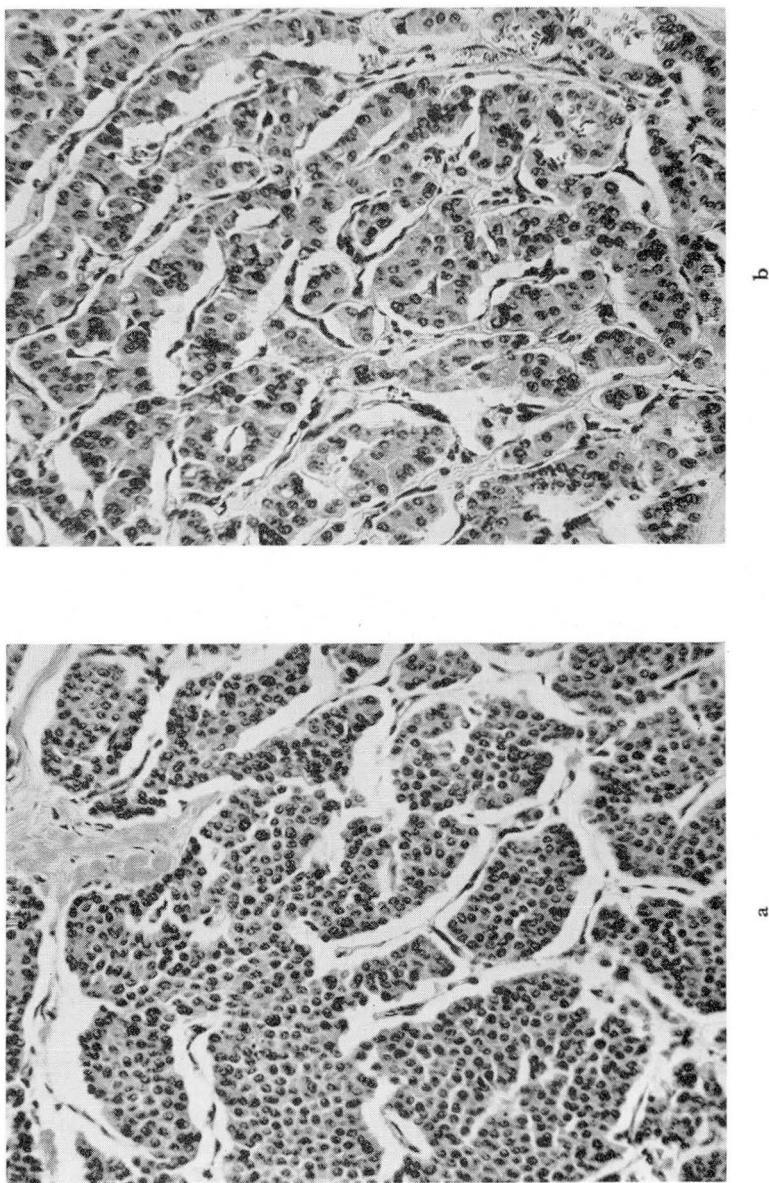


Fig. 5. The major variations in the histologic features of an adenoma. (a) Typical carcinoid appearance. Hematoxylin-cosin — methylene blue stain; X220. (b) Trabecular arrangement of somewhat larger cells. Hematoxylin-cosin — methylene blue stain; X220.

blend with one another. In the present material, cytoplasmic coloration ranged from pink to gray. Mitosis was uncommon. The cells were arranged into two general patterns within the neoplasm (Fig. 5). Nests and small sheets of these cells closely packed and separated by fine collagenous bands were a prominent feature, with a clustering that most resembled the intestinal carcinoid (Fig 5a). Lumens occasionally were present in the otherwise solid masses. In other regions of the neoplasm, anastomosing cords separated by blood vessels and fibrous strands were prominent (Fig. 5b). Deeply the neoplasm had an abrupt gross junction with surrounding pulmonary tissue. Microscopically, there usually was some evidence of invasion of the lung by small islands of tumor. The blood vessels were profuse among the cords and islands of neoplasm. Although blood vessels occasionally were compressed, there was no evidence of intravascular extension in any of the specimens. In many patients the bronchial cartilages were retained within the tumor (Fig. 6). Only two of the neoplasms showed evidence of osseous metaplasia. In only one tumor was extension to a lymph node demonstrated; the extension was by direct invasion.



Fig. 6. Total mount of a small adenoma. Note the retention of bronchial cartilages within the tumor. Hematoxylin-eosin—methylene blue stain; X5.

Tumor size precluded any attempts to demonstrate origin from mucous glands, although neoplastic islands could be seen intermingled with mucous glands along the bronchial margins of the tumor.

Results of Treatment

In this group all tumors were operable and all 21 patients have remained well. Eleven of the patients were treated by lobectomy and eight by pneumonectomy, one by local resection of the neoplasm through the bronchoscope, and one by removal of the tumor by means of a bronchotomy. The neoplasm removed through the bronchoscope was in the immediate vicinity of the carina. The tumor removed by bronchotomy arose from the left upper lobe bronchus and at the time of operation there was no evidence of extrabronchial growth. The bronchotomy was performed because there was no roentgen evidence of atelectasis. Eighteen months postoperatively the patient was readmitted because of recurrent hemoptysis. A small pea-sized mass was found at the site of the previous operation and a biopsy specimen proved it to be a recurrence of the neoplasm. The roentgen findings, at that time, again did not disclose any evidence of pulmonary change. The patient, who was pregnant, underwent a second bronchotomy for removal of the tumor, and the base of the tumor was cauterized. The patient is being examined at six-month intervals, and there has been no recurrence of the tumor to this date.

Discussion

On the basis of microscopic findings, several classifications and many names have been proposed for bronchial adenomas. The confusion has been such that Liebow¹⁶ was able to collect 27 terms that referred to bronchial adenomas. However, there appears to be increasing agreement that only two major histologic patterns exist, namely, the *cylindromatous* and the *carcinoid*. At the present time many writers recognize the "carcinoid" adenoma and the "cylindroma" as separate entities on the basis of cellular pattern as well as of clinical behavior. The carcinoid adenoma is the commonest of these two types; all 21 of our cases and approximately 90 per cent of all bronchial adenomas reported are of the carcinoid type. We have not seen any examples of the cylindromatous neoplasm in more than 500 primary pulmonary neoplasms diagnosed at the Cleveland Clinic. From the published descriptions of cylindromas they seem to be more invasive than carcinoid adenomas and they often are inoperable. Even when cylindromatous adenocarcinomas of the trachea and bronchi have been treated surgically, they may recur locally and eventually metastasize distantly. According to Clark, Clagett, and McDonald,¹⁹ of all malignant tumors of the trachea, cylindromas are most amenable to treatment because of their slow growth. Although they grow at a slower rate and metastasize less

frequently than bronchogenic carcinomas, in a high percentage of cases they eventually are fatal.

Cylindromas occur most commonly in the trachea but they also occur in the major bronchi. Grossly they are similar to carcinoid adenomas and may grow in the same manner. According to Tinney, Moersch, and McDonald,²⁰ cylindromas are the second most common malignant tumors of the trachea. In the 15 cases reported by Clark, Clagett, and McDonald,¹⁹ the most frequent symptom was dyspnea caused by a valvular type of obstruction. However, cough, wheezing, hemoptysis, and hoarseness were common symptoms. In six of their patients the tumor was located in the upper third of the trachea; in another six in the lower third; and in the remaining three it was in the middle third of the trachea. The duration of symptoms ranged from four weeks to eight years. The final diagnosis was based upon biopsy findings.

It appears that a difficult situation exists so far as nomenclature of these neoplasms is concerned. The problem of the term "cylindroma" always has been a knotty one. The reason for the diversity of opinion seems, in part, to be a lack of knowledge of the biologic behavior of this neoplasm. Although it appears to metastasize slowly, in most locations in the body, when followed adequately it has been shown to be a relentlessly progressive neoplasm. Undoubtedly, 10 years should be the minimum follow-up interval for this particular group of neoplasms.²¹ In salivary gland and nasopharyngeal cylindromatous adenocarcinomas, metastasis may occur long after the patient has been discharged as cured. One such of our tumors of the submaxillary gland did not metastasize until 11 years after the initial surgical operation. The patient still is living several years after the demonstration of pulmonary metastasis. We prefer the term "cylindromatous adenocarcinoma" for such lesions, to the more benign-sounding term "cylindroma."

None of the adenomas in our 21 patients metastasized distantly, but one tumor invaded a regional lymph node. Of the metastasizing "adenomas" reported by others, approximately 55 per cent had metastasized to the regional lymph nodes alone and in the remaining 45 per cent metastasis was present in the following organs in decreasing order of frequency: liver, opposite lung, same lung, pleura, esophagus, bone, brain, kidney, adrenals.

According to published reports, bronchial "adenomas" with distant metastasis were atypical and showed nuclear irregularity, significant pleomorphism, and mitotic figures. All of these changes could be interpreted as indications of a definite increase in malignancy of the tumor. On the other hand, the vast majority of the tumors, like those in our series, which had an orderly carcinoid pattern did not metastasize distantly.

As mentioned previously, a most striking finding in bronchial adenomas is their location either in a primary bronchus or close enough to one so that they are easily accessible to the bronchoscopist. However, words of caution should be interjected at this point. The biopsy of these lesions can be a dangerous procedure. Because of the extreme vascularity of the lesions many bronchoscopists merely like to look at them and note their location without performing

a biopsy. Also, biopsy specimens may show sufficient crushing and distortion of the neoplastic cells to result in an erroneous diagnosis of small-cell carcinoma of the bronchus. The cells, when partially crushed, become dense and spindly. Experience with this distortion, together with a lack of evidence of mitosis, is required to prevent the pathologist from making this diagnostic error.

Although we do not adhere to the concept of an "adenoma syndrome," because of a lack of pathognomonic symptoms of bronchial adenoma, we do believe that the diagnosis of bronchial adenoma should be considered as a possibility in every young adult patient who presents a history of chronic cough with hemoptysis and repeated bouts of pulmonary infections. This is particularly true in female patients, who are statistically less likely to have bronchogenic carcinoma. The prime requisite to the diagnosis of bronchial adenoma is awareness that the lesion may exist and that bronchoscopic studies usually will confirm or refute a suspected diagnosis.

Normal findings on roentgen study of the chest do not exclude the possibility of the existence of an adenoma. Indeed a small-sized neoplasm in a large bronchus, which does not cast a distinct shadow or cause interference with bronchial drainage, may escape detection. In 7 of our 21 cases the tumor was visualized as a circumscribed, solitary nodule on the roentgenogram, as in some of the 23 cases presented by Good and Harrington.²² Although none of their cases had roentgen evidence of calcification, such calcification was found grossly in one. According to Good, Hood, and McDonald,²³ bronchial adenomas comprise about 8 per cent of the solitary mass lesions of the lung.

Although there is almost unanimous agreement concerning the nature and biologic characteristics of bronchial adenomas, until recently there has not been agreement concerning the most satisfactory method of treating the lesions. About 10 years ago, when the hazards of thoracic surgery still were great, surgeons were reluctant to undertake pulmonary resections except for emergency treatment or for proved malignant lesions. The treatment of choice then was endoscopic removal. Although the recognition of these tumors is possible by bronchoscopy, this examination gives but little specific information as to the degree of extrabronchial extension. Inasmuch as the wholly endobronchial polypoid type of adenoma is unusual, the endoscopist seldom offers the patient a definitive cure.

Cognizance of the anatomic extent and biologic course of these tumors has resulted in abandonment of their bronchoscopic extirpation except as a palliative procedure in the elderly or poor-surgical-risk patient, or in the rare patient in whom the location of the adenoma in the bronchus precludes the successful accomplishment of any other procedure. For example, local removal may be the only feasible treatment of adenomas in the vicinity of the carina. A pedunculated tumor that has a narrow attachment to one of the main bronchi might by choice be treated initially bronchoscopically. However, surgical removal of such a tumor, including its base, with plastic reconstruction of the bronchus would minimize risk of recurrence and at the same time avoid major pulmonary resection.

Almost all patients with bronchial adenomas are good surgical risks, and surgical resection is the treatment of choice. With the present-day development of thoracic surgery, virtually no mortality and but little morbidity need be anticipated regardless of the extent of the resection. Adequate surgical treatment entails complete resection of the tumor and, of the irreversibly damaged pulmonary tissue, at the same time preserving as much of the normal pulmonary tissue as possible.

Summary

1. The clinical and pathologic findings in 21 cases of bronchial adenoma are presented. The lesion was twice as frequent in women as in men, and in our series the age groups represented are older than those usually reported.

2. The outstanding clinical symptoms included: cough, hemoptysis, and prolonged suppuration.

3. Bronchoscopic examination of patients having unexplained pulmonary suppuration should lead to earlier diagnosis of bronchial adenoma and consequent lessening of the frequency of chronic pulmonary disability.

4. The histologic pattern in all of the cases was that of the carcinoid variant. None of the neoplasms in this series metastasized.

5. The majority of the patients were treated either by lobectomy or by pneumonectomy and all are now well.

6. Cylindromatous carcinomas of the trachea and bronchi should not be classified as bronchial adenomas.

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