The Enigma of Bronchiolar Carcinoma*, **
Histopathologic Clues in Fifty-three Cases

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INTRODUCTION

A clinically useful understanding of bronchiolo-alveolar carcinoma hinges on the solution to a fundamental problem: what are valid criteria for the pathologic diagnosis? At present, a sharp separation of these tumors from "ordinary" adenocarcinomas has not been made. Indeed, there are extreme views that most, if not all, of the tumors of this type are metastatic. Until the problem of identification is solved, little can be said about amenability to resection and prognosis; the conflicting reports in the literature about them should not be surprising. However, certain tumors in this broad group do have unique features and this study has attempted to amplify them. In addition, certain pathologic aspects which have received little attention have been emphasized, e.g., change in tumor architecture or pattern (including dedifferentiation) and "host-resistance" factors. An elastic tissue study has been expanded to include vascular invasion, parenchymal destruction (as opposed to superficial spreading), scar tissue evaluation, and a peculiar elastic-type proliferation in association with tumor. The histologic details will be reported separately, but their bearing on the clinical course is discussed.

MATERIAL AND METHODS

In 53 patients undergoing thoracotomy between 1957 and 1961 at several hospitals in the Boston area, a histologic diagnosis of "bronchiolar" or "alveolar" carcinoma was recorded. There were 33 men and 20 women. Ages ranged from 36 to 76 years, with a heavy concentration in the sixth and seventh decades. In eight patients, only biopsy was possible; a definitive resection was accomplished in the remainder, namely, 14 pneumonectomies, 28 lobectomies, two segmentectomies, and one wedge resection. The postoperative course in all patients was evaluated with particular reference to survival and recurrence. Follow-up, from one to 18 years, was complete in 48 patients as of April, 1962; one patient was lost to follow-up after five years, and four patients after less than one year. Of the 31 individuals known to have died, postmortem examinations were performed in ten.

All surgical and necropsy material was reviewed histopathologically, with emphasis on growth pattern, architecture, and cytology of the tumors. Routine histologic techniques were supplemented by Verhoeff's elastic tissue stain in 49 of the 53 cases. The clinical and pathologic data were assessed independently. The tumor from each case was categorized according to certain major patterns that were recognized as the study evolved.

RESULTS

Necropsy Cases

Nine cases were acceptable as primary lung tumors on the basis of complete necropsy studies. In five of the nine patients, tumor involvement was restricted entirely to the thoracic contents. One patient had intrathoracic metastases with a single, small, adrenal gland tumor nodule. Two patients had para-aortic, lymph node metastases (thoracic and abdominal), and involvement of bowel serosa (one of the two

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also had a few small liver nodules). One patient had widespread metastases, including spread to the remaining lung tissue. The primary tumor site in a tenth necropsy case was questionable, but probably was lung. The patient developed a solitary metastasis to the submucosa of the duodenum one year after lobectomy. The duodenal mass was resected and was similar histologically to the poorly differentiated portion of the lung tumor. The well-differentiated portion of tumor in the lung was consistent with bronchiolar carcinoma; the cancers were not separable. The patient died shortly after operation; a necropsy revealed several poorly differentiated tumor nodules in the liver, but none elsewhere. (Tumor was not found in the pancreas, either at operation or at necropsy.) The longest survival of the ten necropsy cases was in a patient who died 48 months post-lobectomy with local spread of disease; he had been clinically free of disease for three years. The second longest survival was 25 months, with tumor also restricted to the lung. Eight remaining patients died four to 21 months after operation.

Histologically, the tumors in eight of the ten necropsied patients were consistent with bronchiolo-alveolar origin; six of the tumors were partly "fibroelastic" in type (Fig. 1), including the questionable case mentioned, and two were of the "epiphytic" type (Fig. 2). One tumor was a papillary adenocarcinoma and the other an undifferentiated carcinoma. Except for one "epiphytic" tumor, all of these cancers had destructive and infiltrating areas of adenocarcinoma.

Eight patients had tumors that were considered to be primary because of long survival without clinical evidence of recurrent disease (28 to 72 months in four instances, 20 months each in three instances, and one instance of 60 months without subsequent follow-up). The tumors in three of the eight patients, the 20-month survivors, had a predominantly fibroelastic pattern. Two others of the "fibroelastic" type were associated with large scar areas. A third "scar cancer" in this group of eight showed an "adenomatosis" pattern (mucinar and,
in part, “epiphytic”). Although “adenomatosis” is usually considered unfavorable, the patient has been well and clinically free of disease for 65 months. He is the only one of the eight patients who had pneumonectomy. A seventh tumor was a papillary adenocarcinoma and the eighth a nonspecific adenocarcinoma with associated elastica proliferation, or condensation.

**Recurrent Tumors**

Three patients died of recurrent tumor at 88, 48, and 36 months, postoperatively. All three had tumors of the fibroelastic type but, in addition, showed areas of poorly-differentiated or “ordinary” type adenocarcinoma. One, a 53-year-old man, was clinically free of disease for six years and then succumbed at 88 months post-lobectomy to either a recurrent or a second carcinoma of the lung on the same side. The tumor of the resected lung showed an associated “giant-cell” carcinoma (Fig. 3). A patient succumbing at 48 months had tumor restricted to the lung, as shown by necropsy (cf. necropsy cases). The third patient died 36 months postoperatively, also with presumable localized tumor.

Of two patients with recurrent disease who are still living, one, a 72-year-old man, has had an incomplete wedge resection for diagnosis only, and yet is asymptomatic 48 months later. Recent x-ray films show enlarging lung masses; an associated tuberculosis cannot be excluded. The biopsy sections reveal well-differentiated adenocarcinoma, but evaluation is difficult due to the small size of the specimen and the marked tumor necrosis. The second patient, a 68-year-old man, has possible hilar recurrence 45 months postoperatively, as judged by x-ray examination and the presence of hemoptysis. A “fibroelastic” pattern was noted in this tumor.

**“Scar” Cancers**

Fifteen cancers were associated with significant “scarring” mainly of the infarct type, i.e., parenchymal collapse rather than destruction and fibrosis. Occasionally, true scar was present, usually with intermixed anthracotic pigment; birefringent bodies were not found. One of the “scar cancer” patients died 18 months after a lobectomy. At necropsy, the tumor was restricted to the chest despite blood vessel invasion. There have been four other deaths in the “scar cancer” group, due to tumor spread (details unknown), at three, six, 13, and 18 months postoperatively. Ten patients are living, seven of them without recurrent disease. A 62-year-old woman has been free of disease for 66 months following a right pneumonectomy, despite hilar node metastases. A 74-year-old man has been free of disease 45 months following right upper lobectomy. Three have had short follow-up: 28, 17, and six months. Two have been lost to follow-up at ten and 12 months postoperatively; both were free of disease at the time.
Blood vessel invasion was not found in the lesions of patients who were still alive and free of disease 20 months or more. Six of the ten necropsied patients had blood vessel invasion as did five of the 15 living patients with recurrent and metastatic disease.

Lymph node metastases were found in two of the long-term survivors. In both patients, the metastases were composed of less differentiated carcinoma than the primary tumor and did not show bronchiolar type proliferation. Of ten patients who died because of tumor, but who did not have lymph node involvement, five had tumor restricted to the lung (includes three necropsy cases), and five had poorly differentiated carcinomas, at least two of which were very likely metastatic lung cancers.

**Discussion**

Bronchiologenic carcinoma, like bronchogenic carcinoma, is a heterogeneous group of tumors (Table 1). This is due, in part, to the multicellular composition of the bronchiolar mucosa, particularly of mucous and ciliated cells. Little is known about the potential of the basal cells, but they very likely give rise to special cells such as those of the carcinoid type. Tumorlets and atypical hyperplasias of bronchi and bronchioles appear to be composed of basal cells. Squamous metaplasia of neoplastic bronchiolar epithelium very likely accounts for peripheral epidermoid tumors. In addition to cell variation in the respiratory tract mucosa, there are structural differences, notably the pseudopapillary infolding of the terminal bronchiole. The infolding found in some primary lung carcinomas has served to support the concept of terminal bronchiolar origin.\(^2\)

"Bronchiolo-alveolar" carcinoma has been singled out of the bronchiologenic carcinoma group because it has the strongest identity. Liebow\(^1\) has defined the tumor through the use of mixed criteria, i.e., well-differentiated adenocarcinoma, peripheral location (unrelated grossly to a bronchus), often supported by the distal air spaces, and likely to spread by aerogenous and lymphatic routes. Liebow's associates\(^8\) have recently emphasized the tendency to "papillary" formation (infolding of tumor). These criteria are of great help in excluding tumors from the bronchiolo-alveolar group, but do not establish primary origin in the lung. Hutchinson\(^9\) has demonstrated contiguity of these tumors with bronchiolar epithelium and states that this indicates primary origin. However, acceptable proof would be in situ carcinoma in continuity with invasive tumor and this was not shown.

With the preceding problems in mind, the present group of tumors was studied to determine which were primary in the lung and what characteristics supported origin from bronchiolar epithelium. **The Fibroelastic Pattern**

The most characteristic type of growth in the group of bronchiolo-alveolar carcinomas is one that imitates the terminal (dis-
tal) bronchiole. In addition to a low columnar or sometimes cuboidal epithelium with infolding, there is a thin to thick supporting stroma. The surprising finding is the presence of increased elastica-like material in the stroma in many of the tumors. In the "sclerotic form," especially, (Fig. 1) it is difficult to account for the abundant elastica except as an associated proliferation; condensation elastosis, as in infarct-type scars, may be involved as a background factor. Twenty tumors of this type were in the series, including six in the ten necropsy cases and three in patients who appear to be free of disease 20 months after lobectomy. Two patients are living with disease 45 and 48 months following lobectomy and wedge resection (biopsy only), respectively. Three of the deaths in this group were at 88, 48, and 36 months postoperatively.

Narbenkrebs (Scar Cancers)

The tumors in 15 patients of the series were associated with a central and significantly large scar area. Five of the patients had tumors of the fibroelastic type. Five of the 15 died in 18 months or less postoperatively. Ten are living, three with disease and seven without clinical evidence of recurrence (see Results). These findings support the earlier suggestion by Hukill and Stern\(^{10}\) that these tumors have a more favorable course. Although cancers may metastasize to scar areas in the lung,\(^1\) the typical scar cancer is unlikely to be imitated and therefore serves as a strong indicator of primary origin.

Epiphytic Carcinoma

An intact lung parenchyma, supporting a tumor tissue lining, demonstrates superficial spread of cancer. Since the method of growth plays an important role in the natural history of cancers (e.g., endophytic\(^1\) and exophytic\(^1\) carcinomas) it seemed worthwhile to coin a term for the phenomenon of superficial spreading. "Epiphytic" was chosen inasmuch as it implies "growth upon." It is well known that tumors metastatic to the lungs, especially those from the pancreas, can proliferate in this fashion. On the other hand, primary lung cancers, particularly the fibroelastic bronchiolocentric type, grow in part in this fashion. However, predominant growth of the "epiphytic" type, without significant alteration of the alveolar wall, was uncommon in our series. Two tumors of this nature were verified at necropsy: one patient died of widespread involvement of both lungs (Fig. 2); the other died with extensive lung involvement and visceral metastases (the metastatic tumor was similar to isolated areas of infiltrating adenocarcinoma in the resected tumor specimen). Statistical significance relative to prognosis cannot be attached to the findings in our study of the epiphytic pattern; however, destruction of lung parenchyma (as shown by the absence of an elastica pattern) is probably an unfavorable sign. A second apparently ominous sign is the presence of tumor cell clusters within the lumen formed by the tumor layer; unfortunately this could not be correlated with Papanicolaou smears (Fig. 4). Of course, the presence of multiple foci is an ominous finding.

Hyperplasia

Several of the tumors of the fibroelastic and scar types showed associated bronchiolar hyperplasia which was difficult to differentiate from the neoplasia. In one particular case, that of a 49-year-old Caucasian woman, an extraordinary and variegated proliferation of bronchioles was found.

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=data/journals/chest/21386/ on 03/30/2017)
ENIGMA OF BRONCHIOLAR CARCINOMA

There was an associated lipoid type of pneumonitis (patient had been using an oily type of nose-drop solution). Most of the lesion was not frank adenocarcinoma and, indeed, a lung biopsy one year prior to resection was interpreted as reactive hyperplasia of bronchioles. We reviewed the biopsy sections and found orderly but extensive bronchiolar hyperplasia. The widespread, heavy involvement of the resected specimen (pneumonectomy) indicates that the proliferation is the equivalent of low grade cancer (Fig. 5). The resected specimen also showed areas of epiphytic, mucinous-type bronchiolar carcinoma and a few scattered foci of infiltrating adenocarcinoma. A clinical search for extrapulmonary cancer was negative. The patient developed extensive tumor involvement of her opposite lung and, subsequently, rib metastases. She expired several months after resection, presumably of thoracic disease only; necropsy was not obtained. Of unusual interest is the patient’s background: her sister died of lung cancer a few years earlier; she had spent a long vacation at her sister’s sheep ranch in Australia and she went directly to a chest surgeon, requesting exploration in view of symptoms similar to those of her sister.

Mixed Types of Tumor

Infiltrating, often poorly differentiated, adenocarcinoma was frequently associated with bronchiolo-alveolar carcinomas. Other types of cancer were also found to accompany these tumors. One is a true papillary carcinoma, as shown by the presence of a true stromal stalk. Of the three papillary carcinomas acceptable as primary in the lung, two resulted in widespread metastases (including one verified by necropsy), and one was successfully resected; the patient is living and well, apparently free of disease 60 months post-pneumonectomy; he has not been seen since that time. Two additional patients with papillary carcinomas died shortly after operation. These two and the necropsied patient just mentioned had tumors with prominent psammoma bodies.

“Giant-cell carcinoma” was associated with the fibroelastic type of bronchiologenic cancer in four cases; all four patients died with recurrent cancer. The giant cell component in one case was not apparently the aggressive component and may in fact be regressive, in view of the heavy neutrophil infiltrate about each cell (the patient died of presumable local recurrence 88 months postlobectomy, as described previously).

Contiguity

Contiguity was often found between bronchiolo-alveolar type cancers and the bronchiolar epithelium. In situ carcinoma was not evident, at least not conclusively so. Where contiguity was present, the tumor was acceptable as having a primary origin in the lung. However, in a few instances, contiguity also involved very small bronchi and it was not possible to exclude tumor origin from the distal bronchial mucosa; the cells were tall, columnar, and definitely not those of the distal (terminal) bronchiole, but they could have arisen in a “proximal bronchiole.”

Tumor Necrosis and Leukocytic Response

Necrosis of tumor was present to a noticeable degree in the scar cancers, but any evaluation is complicated by the limited area of the sections available, as well as by the prominent pneumonitis that accompanied the scar cancers. In one of these cases there was extensive necrosis of
the advancing margin of the tumor, so much so that tumor cell clusters were often hardly visible; it is perhaps significant that the patient is still living and well 45 months postlobectomy. A second patient with extensive necrosis and "scar" in association with an adenomatosis type cancer is also living and well 65 months postpneumonectomy. The tumor may very well have originated from the bronchiolar mucosa, but does not have a characteristic growth pattern. The scar tissue consists of a large amount of elastica-type material. The presence of heavy elastica deposits within cancer tissue may have a favorable import since a heavy deposition also occurred within a nonspecific adenocarcinoma of the series and the patient, a 44-year-old woman, is living and well 72 months post-lobectomy (Fig. 6).

**Identification**

Bronchogenic and bronchiologenic adenocarcinomas have in common their origin from the respiratory tract mucosa. Adenocarcinomas arising from the glands and ducts emptying into bronchi should be considered separately, although there is no question that they cannot always be distinguished from those of the mucosa. Mucosal adenocarcinomas of both bronchi and bronchioles can be expected to produce nonsecretory, mucous, or combined types of tumors. There is little knowledge about

**Table 2—Factors of Prognostic Import**

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<th>I. Properties of the Tumor</th>
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<td>A. Growth Rate (Mitoses; Size Change on X-ray film)</td>
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<td>B. Cohesiveness (Differentiation—Anaplasia)</td>
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<td>C. Metabolism (Necrosis)</td>
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<td>D. Growth Direction (Exophytic, Endophytic, Implantation, Infiltrative, In Situ, Superficial Spreading)</td>
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<th>II. Properties of the Tumor Site</th>
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<td>A. Location</td>
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<td>B. Vascularity</td>
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<td>C. Special Conduits or Cavities (Alveoli, Ducts, Glands, Compartments)</td>
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<tr>
<td>D. Susceptibility to Tumor (Multicentric Cancer)</td>
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<td>E. Associated or Complicating Diseases</td>
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<th>III. Host Factors</th>
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<td>A. ?Humoral Inhibition Factors</td>
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<td>B. ?Tissue Resistance</td>
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<th>IV. Clinical Factors</th>
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the origin of special cell types (e.g., the cell of the carcinoid type). It is also very likely that functional differences among cells of the respiratory tract mucosa are greater than the histologic changes imply. The mucosa of the terminal bronchiole is noticeably different from proximal segments. Hence recognition of a terminal bronchiolar carcinoma is reasonable, especially when the histology is supported by bronchiolar-like infolding and elastica proliferation. Although the vigorous skeptic will not accept similarity of architecture as proof of origin, we believe the diagnosis of "fibroelastic mucosal adenocarcinoma" can be a reliable one for the clinician. Of course, a search for an extrapulmonary tumor site is clearly expected when dealing with any suspected lung neoplasm. We believe that a typical scar cancer, where the scar is central and the tumor oriented to the scar tissue, is also strong reassurance to the clinician that he is dealing with a primary tumor, most likely of bronchiologic origin. Purely epiphytic adenocarcinomas are particularly suspect as metastases, especially the mucinous variety, but it is significant that tumors of this type can be
primary in the lung. The participation of bronchioles in the neoplastic process by hyperplasia and contiguity phenomena is a suggestive indicator of primary origin.

**Prognosis**

Prognosis is, of course, determined by many clinical and pathologic factors (Table 2). Each carcinoma then must be considered an individual disease. The death of the patient with cancer is not tantamount to death because of cancer; a more precise recording of the cause of death will be of great aid in the evaluation of tumor aggressiveness and in the exclusion of multiple neoplasms. It is anticipated that tumors of the fibroelastic type and the scar cancers will prove to have a more favorable clinical course.

**SUMMARY**

Fifty-three lung cancers with a pathologic diagnosis of bronchiolo-alveolar carcinoma were reviewed, particular attention being paid to the validity of the diagnosis and prognosis. Twenty-one cases were acceptable as primary lung tumors on the basis of complete necropsy study (nine cases), long-term survival following operation without recurrence (eight cases), and recurrent disease with unusually long survival times (four cases). Origin of these tumors from bronchiolar mucosa could not be proved. Contrariwise it is likely that an occasional tumor with characteristics of the terminal bronchiolar type may arise from the mucosa of small bronchi. The most consistent pattern believed to represent a bronchiologic proliferation is the "fibroelastic" form; an associated elastica proliferation or condensation was found. Scar cancers of the classical type, i.e., central scar and peripherally oriented carcinoma, offer reassurance that the tumors are primary in the lung; their peripheral location implies that the mucosal type proliferation arises in a bronchiole. (A fibroelastic pattern was seen in some of the scar cancers in this series.) Contiguity of tumor and bronchiolar mucosa favors a primary origin for the tumor, but is not a conclusive finding at this time. A spectrum of bronchiologic proliferation was noted, ranging from benign hyperplasia to infiltrating and destructive adenocarcinoma. Tumor growth along alveolar walls is interpreted as a superficial spreading phenomenon ("epiphytic" growth). Invasion, as opposed to superficial spread, is not always obvious with ordinary stains, but can be identified readily by elastic stains. Predominantly mucinous "epiphytic" adenocarcinomas are the ones most likely to be mimicked by metastatic cancer. Unfavorable histologic features are the presence of destructive-type invasion, intra-alveolar tumor cell clusters, multifocal tumor, blood vessel invasion, and lymph node metastases. There is a strong suggestion that scar cancers and tumors of the fibroelastic type are more amenable to resection as a group. The routine use of elastic stains will probably identify scar cancers of the condensation type that otherwise might be missed.

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**Resumen**

Se estudiaron 53 cánceres con el diagnóstico de carcinoma bronquiolo-alveolar poniendo particular atención sobre la exactitud del diagnóstico y del pronóstico. Veintiún casos fueron aceptables como tumores primitivos del pulmón, basándose en necropsias completas (nueve casos), sobrevivida a largo plazo después de operación sin recurrencia (ocho casos) y enfermedad recurrente después de términos inesperadamente largos (cuatro casos). No se pudo probar el origen de estos tumores en la mucosa bronquiolar. Por el contrario, es posible que un tumor ocasional con las características del tipo término-bronquiolar pueda nacer en los pequeños bronquios. El aspecto más sólidamente creído como representante de la proliferación bronquiologénica es la forma "fibroelástica"; se encontró una proliferación elástica asociada o condensación. Los tumores originados en cicatrices del tipo clásico, por ejemplo cicatriz central y carcinoma orientado hacia la periferia, proporcionan la seguridad de que los tumores son primarios en el pulmón; la ubicación periférica implica que la proliferación de forma mucosa nace en un bronquiolo. (Un aspecto fibroelástico se ha
visto en algunos de los cánceres en cicatrices, en esta serie.) La contigüidad del tumor con la mucosa bronquial favorece el pensar en un primario, pero por ahora esto no es concluyente. Se ha notado una gama de proliferación broncziológenica que va desde la hiperplasia benigna hasta el adenocarcinoma infiltrante destructor. El crecimiento del tumor a lo largo de as paredes alveolares se interpreta como un fenómeno de disminución superficial (crecimiento "epífico"). La invasión, opuesta a la diseminación superficial, no es siempre evidente con ciertos colorantes, pero puede identificarse con facilidad por los colorantes elásticos. Los adenomas predominantemente mucinosos "epíficos" son los que más se parecen al cáncer metastásico. Son características histológicas desfavorables la presencia de invasión destructiva, conglomerados de celdillas tumorales intra-alveolares, tumores multifocales, invasión de vasos sanguíneos y metástasis de los ganglios linfáticos. Hay la sugestión acentuada de que los cánceres nacidos en cicatrices y los tumores del tipo fibroelástico son más susceptibles de resección en conjunto. El uso rutinario de los colorantes elásticos probablemente indentificará cánceres de cicatrices del tipo de condensación que de otra manera serían pasados por alto.

ZUSAMMENFASSUNG


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