"Occult" Carcinoma of the Bronchus: A Study of 15 Cases of In Situ or Early Invasive Bronchogenic Carcinoma*

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The importance of duration of an in situ stage in the evolution of bronchogenic carcinoma has yet to be determined. Black and Ackerman and Carlisle and associates have reported that carcinoma in situ frequently surrounds an invasive bronchogenic carcinoma. In a study of necropsy specimens Ryan and co-workers found carcinoma in situ in the opposite lung in 12 per cent of the cases in which resection had been performed for bronchogenic carcinoma. Auerbach and co-workers used serial block section and found carcinoma in situ (or atypical metaplasia) in the bronchi of 75 per cent of heavy smokers and an equally high incidence in patients known to have bronchogenic carcinoma.

Pulmonary resection for carcinoma in situ of the bronchus has seldom been reported. Theoretically such early lesions should not show evidence of abnormality on thoracic roentgenograms unless some degree of associated obstructive pneumonitis is present and, in the absence of a tumor, they should not be detected readily on bronchoscopic examination. Although exfoliative cytology has proved to be valuable in the diagnosis of bronchogenic carcinoma in cases with suspicious symptoms or roentgenologic findings, its usefulness as a screening device in roentgenologically asymptomatic patients has not yet been determined. It has been postulated that such screening, perhaps with the aid of aerosol technics, might result in the detection of bronchogenic carcinoma at an earlier stage or even in the in situ or intramucosal phase of its development.

A review of apparently early cases of resected bronchogenic carcinomas was undertaken to determine the incidence of positive cytologic findings and the means by which the diagnosis was established. Follow-up data were obtained to determine the prognosis after resection of these early lesions.

Materials and Methods

A survey of pathologic reports on resected bronchogenic carcinomas over a 13-year period, 1946 to 1958 inclusive, at the Mayo Clinic revealed a number of cases in which the lesion was occult in that no tumor was visible on gross examination of the specimen. In many of these cases the carcinoma proved to be predominantly or entirely in situ. Many sections were obtained from all such lesions by means of the serial block technic to determine the extent of the in situ change and the depth of associated infiltration if such was present.

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The study included five cases in which lesions had been reported previously as predominantly in situ carcinomas. These were re-examined by serial block technic to determine whether areas of infiltration could be found on more complete sampling. An absolute or exact line between in situ and infiltrative carcinoma of the bronchus proved somewhat difficult to establish in that involvement of ducts of mucosal glands cut tangentially may at times be difficult to distinguish from early superficial infiltration.

After excluding all cases with infiltration beyond the bronchial wall, a total of 15 bronchogenic carcinomas in the early stages of development were selected for study. These were divided into three groups as
### TABLE 1 — IN SITU BRONCHOGENIC CARCINOMA WITH NO OR EQUIVOCAL EVIDENCE OF INFILTRATION

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex, age yr</th>
<th>Symptoms</th>
<th>Duration</th>
<th>X-ray of thorax</th>
<th>Result of bronchoscopic examination</th>
<th>Result of cytologic examination</th>
<th>Operation</th>
<th>Pathologic findings</th>
<th>Last report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M 55</td>
<td>Dry cough</td>
<td>2 mo.</td>
<td>Emphysema; apical segment, left upper lobe lung</td>
<td>Negative</td>
<td>Sputum: positive (squamous cell cancer); bronchial secretions, left upper lobe: positive</td>
<td>Lobectomy, left upper lobe (no tumor palpable)</td>
<td>Squamous cell carcinoma in situ, grade 3, with equivocal superficial infiltration involving 1.2 cm. of the apical segment of left upper lobe branch</td>
<td>No report, recent case</td>
</tr>
<tr>
<td>2</td>
<td>M 63</td>
<td>Severe cold with fever 7 mo. prior to admission; one episode hemoptysis; cough</td>
<td>3 wk.</td>
<td>Poorly defined infiltration in left upper lobe</td>
<td>Negative</td>
<td>Sputum and bronchial secretions from left upper lobe: positive</td>
<td>Pneumonecctomy, left lung</td>
<td>Moderate obliterative pneumonitis; cancer in situ of left upper lobe bronchus at its division into apical posterior and anterior divisions</td>
<td>Died 3 1/2 yr.*</td>
</tr>
<tr>
<td>3</td>
<td>M 62</td>
<td>&quot;Virus pneumonia&quot; followed by cough and intermittent hemoptysis</td>
<td>1 yr.</td>
<td>Negative</td>
<td>Roughened mucosa right upper lobe bronchus; biopsy positive</td>
<td>Sputum positive for cancer cells; bronchial secretions: positive</td>
<td>Pneumonecctomy, right lung (tumor normal to palpation)</td>
<td>Extensive squamous cell carcinoma in situ over 3 cm. of right main and upper lobe bronchus</td>
<td>Died 1 mo. after operation</td>
</tr>
<tr>
<td>4</td>
<td>M 67</td>
<td>No pulmonary symptoms: in situ S.C.E. of vocal cord treated 8 1/2 yr. earlier; no residual</td>
<td>——</td>
<td>Pneumonitis, right upper lobe</td>
<td>Nodular mucosa right upper lobe bronchus; biopsy positive</td>
<td>Bronchial secretions: negative</td>
<td>Pneumonecctomy, right lung</td>
<td>Carcinoma in situ, extensive involvement of right upper lobe bronchus and orifices of its 3 main subdivisions</td>
<td>Died 3 1/2 yr. after operation; cause of death unknown</td>
</tr>
<tr>
<td>5</td>
<td>M 58</td>
<td>None referable to chest</td>
<td>——</td>
<td>Widening of mediastinum; possible pleural thickening on right</td>
<td>Blood noted coming from right upper lobe bronchus; no tumor seen; biopsy negative</td>
<td>Bronchial secretion from right upper lobe: positive for cancer cells</td>
<td>Pneumonecctomy, right lung</td>
<td>Carcinoma in situ, with questionable infiltration of mucosa surrounding orifice of apical division right upper lobe bronchus</td>
<td>Alive and well 4 yr. after operation</td>
</tr>
<tr>
<td>6</td>
<td>M 52</td>
<td>Cold; chills followed by cough with some yellowish sputum</td>
<td>4 wk.</td>
<td>Exaggerated right hilar shadow with infiltration of adjacent right upper lobe</td>
<td>Mucosal abnormality: posterior lateral wall, right main bronchus; biopsy negative</td>
<td>Bronchial secretions: positive</td>
<td>Pneumonecctomy, right lung</td>
<td>Carcinoma in situ, right main bronchus</td>
<td>Alive and well 8 yr. after operation</td>
</tr>
</tbody>
</table>

* Necropsy findings: subdiaphragmatic abscess; no evidence of carcinoma.

†Pulmonary embolism with infarction.

‡Carcinoma in situ of right bronchial stump developed 3 years after operation; x-ray treatment.
follows: group 1 — carcinoma in situ with no demonstrable infiltration or with minimal or equivocal evidence of infiltration (six cases), group 2 — carcinoma in situ with associated superficial infiltration extending maximally down to bronchial cartilages (five cases), and group 3 — carcinoma in situ with associated infiltration but not beyond the bronchial wall (four cases).

FIGURE 2 (case 1). a. Carcinoma cells (squamous type) in sputum (hematoxylin and eosin; x600). b. In situ squamous cell carcinoma of apical branch of left upper lobe bronchus. Ducts of mucous glands were involved but infiltration was equivocal (hematoxylin and eosin; x80). c. Higher magnification showing transition between normal and in situ carcinomatous surface epithelium (hematoxylin and eosin; x25).
Carcinoma In Situ, Group 1 (Six Cases)

In the six cases the resected carcinomas were considered to be entirely in situ or at most showing minimal or equivocal invasion (fig. 1a and b). A description of a typical case follows and the salient findings in all six cases are shown in table 1. In group 1 a diagnosis of bronchogenic cancer was based on finding carcinoma cells in the sputum followed by the demonstration of positive bronchial secretions from the affected lobe in two cases and on positive bronchial secretion alone in one case. In three other cases specimens obtained for biopsy from an area of abnormal mucosa seen on bronchoscopic examination showed positive findings. In these three cases, obstructive pneumonitis was found in the affected lobe in one case only. Of the three cases in which resection was carried out on the basis of positive cytologic findings with negative bronchoscopic examination, obstructive pneumonitis was present in only one case. In the other two cases the resected lobe was normal to palpation at the time of operation.

Case 1: A dry cough had developed in a 55-year-old white man 2 months prior to his arrival at the Mayo Clinic. A roentgenogram of the thorax had been interpreted as normal, but a specimen of sputum had been reported positive for carcinoma cells. Three bronchoscopic examinations had disclosed a source of these abnormal cells. Bronchograms had been normal except for the lack of opaque medium in the bronchi of the left upper lobe. The thoracic roentgenogram made after the patient's arrival at the clinic revealed some evidence of emphysema of the apical segment of the left upper lobe but no mass could be detected in the left upper lobe. Otolaryngologic and bronchoscopic examinations gave normal results. The left upper lobe bronchus was carefully examined with the right-angled telescope at the time of bronchoscopy but no evidence of a lesion could be seen. The left upper lobe bronchus was irrigated with 10 cc. of normal saline solution and secretions were aspirated for cytologic study. The right side was also apparently normal to inspection and smears and secretions were removed for cytologic study. Results of cytologic examination for carcinoma cells included positive sputum (fig. 2a), positive washings from the left upper lobe and negative secretions from the right side.

Since cytologic and bronchographic evidence pointed to a carcinoma of the left upper lobe, surgical exploration was carried out. No tumor could be felt in the left upper lobe, but lobectomy was performed on the left upper lobe on the basis of the positive cytologic findings. Pathologic examination revealed a squamous carcinoma, grade 3 and 1.2 cm. in length, which surrounded the apical segment of the left upper lobe bronchus. The carcinoma was almost entirely in situ with involvement of ducts of mucous glands (fig. 2b and c). Serial block sectioning showed small areas of equivocal superficial infiltration. The hilar lymph nodes were not involved by tumor.

Bronchogenic Carcinoma In Situ With Superficial Infiltration, Group 2 (Five Cases)

In five cases the lesion, while largely in situ, was associated with definite mucosal infiltration which extended at most to the inner aspect of the bronchial cartilages. Clinical and pathologic data on these cases are shown in table 2 and one case (case 7) with evidence of an unusually prolonged in situ stage is reported briefly. A diagnosis of bronchogenic cancer was based on positive bronchoscopic specimens in two cases. In two cases the results of both cytologic and bronchoscopic examinations were negative and lobectomy was carried out for unexplained obstructive pneumonitis in a portion of the parenchyma of the involved lung. In one case positive sputum and bronchial secretions were obtained although the results of bronchoscopic examination were otherwise negative. In this case obstructive pneumonitis was present in the affected lobe. Pathologic examination revealed obstructive pneumonitis distal to the carcinoma in four cases while in the fifth case (case 7) no obstructive element was present.
Case 7: A 61-year-old man had had chronic asthmatic bronchitis of long duration associated with a small amount of mucoid sputum for many years. There had been no recent change in symptoms. A thoracic roentgenogram did not show evidence of any abnormality but cytologic examination of the sputum revealed carcinoma cells of squamous type (fig. 3a). The results of bronchoscopic examination and cytologic examination of bronchial secretions removed from each side of the bronchial tree were negative. A total of 13 specimens of sputum were examined during the ensuing 7 months and five gave positive results for carcinoma cells. Two additional bronchoscopic examinations as well as bilateral bronchograms failed to reveal any abnormality in the bronchial tree. Careful examination of the nasal passages including the nasopharynx, pharynx and larynx gave negative results and smears from these locations were normal cytologically.

By this time the patient began to doubt the validity of our studies, and he failed to return until 2 years and 9 months after the initial discovery of malignant cells in his sputum. In the interim mild asthmatic bronchitis continued unchanged. Roentgenograms of the thorax still did not show any abnormality (fig. 3b) but three specimens of sputum were positive for carcinoma cells. Bronchoscopic examination was advised but the patient deferred for 5 months. A mass was then seen in the left upper lobe bronchus and biopsy revealed a squamous cell carcinoma of grade 3.

FIGURE 3 (case 7). a. Carcinoma cells (squamous type) in sputum (hematoxylin and eosin; reduced from x800). b. Roentgenogram of thorax considered negative 3 years after first positive sputum. c. Gross appearances of in situ and superficially infiltrative squamous carcinoma of right upper lobe bronchus. d. Histologic section through edge of lesion (hematoxylin and eosin; reduced from x120).
Bronchial secretions were positive for carcinoma cells. Thus, over a period of 3 years and 2 months, 20 sputum examinations were carried out, 10 of which gave positive results.

At the time of thoracotomy the surgeon was able to feel only a slight thickening in the region of the upper lobe bronchus. Left pneumonectomy was performed. Pathologic examination revealed a small squamous cell carcinoma of the left upper lobe bronchus which was in situ and infiltrative, extending to but not beyond the mucosal aspect of the bronchial cartilages (fig. 3c and d). No lymph nodes were involved and obstructive pneumonitis was not present. The patient has remained well up to the time of this report which is 2 years after pneumonectomy and 5 years after the initial positive findings in the sputum.

Carcinoma In Situ With Infiltration Limited to the Bronchial Wall, Group 3 (Four Cases)

Deeper infiltration of the lesion was found in this group but it did not extend into the surrounding pulmonary parenchyma. In most cases the infiltration was detected only on serial block sections, the bulk of the lesion being in situ or superficial (fig. 4a and b). Clinical and pathologic features are outlined in table 3.

Resection was based on positive results of biopsy in two cases, and in two cases positive secretions and associated obstructive pneumonitis were the significant preoperative findings. Pathologic examination revealed obstructive pneumonitis in all four cases. In case 12 the in situ change was extensive, involving the greater portion of the bronchial mucosa, while in case 11 the carcinoma was limited to a segment of the lingular division of the left upper lobe bronchus, 2 cm. in length.

FIGURE 4. a. (case 13). Histologic section through lower lobe bronchus showing in situ carcinoma, also area of infiltration. The in situ change involved almost the entire bronchial tree with infiltration limited to the lower lobe bronchus (hematoxylin and eosin; x50). b. (case 15). In situ carcinoma involving surface epithelium and ducts of mucous glands. An area of infiltration extending almost through the bronchial wall was found on serial block section (hematoxylin and eosin; x60).
| Case No. | Symptoms | Duration | Operation | Result of Operation | Embolization | X-ray of Chest | Necropsy | Pathologic Findings | Operative Notes | Preoperative Notes
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>49</td>
<td>No Symptoms</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>48</td>
<td>Productive cough</td>
<td>1 mo.</td>
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<tr>
<td>47</td>
<td>Cough with expectoration</td>
<td>2 mo.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>46</td>
<td>Excruciating pain in chest</td>
<td>3 mo.</td>
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<tr>
<td>45</td>
<td>Chest pain</td>
<td>6 mo.</td>
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<tr>
<td>44</td>
<td>Chest pain</td>
<td>9 mo.</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>43</td>
<td>Chest pain</td>
<td>1 yr.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>42</td>
<td>Chest pain</td>
<td>2 yr.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>41</td>
<td>Chest pain</td>
<td>3 yr.</td>
<td></td>
<td></td>
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</tbody>
</table>

**Table 2** — IN SITU AND SUPERFICIALLY INVLVATE BRONCHOCARCINOMA
### TABLE 3 — IN SITU AND INVASIVE BRONCHOGENIC CARCINOMA CONFINED TO BRONCHIAL WALL

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (yr.)</th>
<th>Symptoms</th>
<th>Duration</th>
<th>X-ray of thorax</th>
<th>Result of bronchoscopic examination</th>
<th>Result of cytologic examination</th>
<th>Operation</th>
<th>Pathologic findings</th>
<th>Last report</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>M</td>
<td>54</td>
<td>Episode of cold with pleuritic pain; before examination; productive cough</td>
<td>6 wk.</td>
<td>Pneumonitis, lingular portion of left upper lobe</td>
<td>Negative</td>
<td>Sputum and bronchial secretions in left upper lobe bronchus, positive</td>
<td>Pneumonectomy, left lung</td>
<td>Squamous carcinoma involving proximal 1.2 cm. of lingular division, left upper lobe</td>
<td>Died 3 yr.*</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>50</td>
<td>Symptoms of pneumonitis, fever, productive cough</td>
<td>3 wk.</td>
<td>Diffuse infiltration with linear fibrosis, base of right lung</td>
<td>Roughened mucosa, right bronchus intermedius, biopsy positive</td>
<td>Sputum and bronchial secretions, positive</td>
<td>Pneumonectomy, right lung</td>
<td>Extensive carcinoma in situ, right bronchial tree; infiltration in right lower lobe only</td>
<td>Alive and well 8 yr.</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>63</td>
<td>Episode chest cold, fever, slight pleurisy</td>
<td>3 mo.</td>
<td>Segmental pneumonitis, posterior division, right upper lobe</td>
<td>Negative, slight deformity, right upper lobe bronchus</td>
<td>Sputum and bronchial washings, negative</td>
<td>Lobectomy, right upper lobe</td>
<td>Squamous cell carcinoma partially in situ, partially invasive in right upper lobe bronchus</td>
<td>Alive 5 yr.</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>64</td>
<td>Nonproductive cough; one episode of hemoptysis</td>
<td>6 mo.</td>
<td>Pathologic process left lung extending out from hilus</td>
<td>Lesion with purulent secretion left upper lobe bronchus, biopsy positive</td>
<td>Bronchial secretions, positive</td>
<td>Pneumonectomy, left lung</td>
<td>Bronchial carcinoma in situ and infiltrative in left main bronchus</td>
<td>Alive 4½ yr.</td>
</tr>
</tbody>
</table>

*Coronary artery disease: no evidence of carcinoma.
Comment

Although few in number, these 15 cases represent the discovery and definitive treatment of bronchogenic carcinoma at an early and presumably curable stage of the disease. Symptoms relating to the thorax were entirely or virtually absent in four cases, while in the remainder cough, slight hemoptysis or more frequently an episode of pneumonitis was responsible for further investigation of the bronchial tree. The duration of symptoms, when present, ranged from 3 weeks to 7 months but in one case a pneumonic episode had occurred 1 year prior to the patient's admission to the clinic and in a second case the patient had noted hemoptysis 2 years prior to coming to the clinic.

Roentgenologe examination of the thorax gave normal results in two cases and in a third a widening of the mediastinum proved to be due to a tortuous aorta. In a fourth case, localized emphysema was the only abnormality noted. In the remaining 11 cases evidence of pneumonitis was substantiated by pathologic examination of the resected specimen. In all cases the shadow observed on the roentgenogram was apparently the result of varying degrees of associated peripheral pneumonitis rather than a tumor in the lung.

Cytologic examination of either sputum or bronchial secretions gave positive results in 11 of 15 cases (73 per cent). In case 7 positive cytologic findings had been noted for more than 3 years in spite of negative findings on repeated x-ray and bronchoscopic examinations. In two of four cases in which results of cytologic examination were negative, the results of bronchoscopic biopsy were positive; the results of bronchoscopic biopsy remained indetermined preoperatively in the other two cases and lobectomy was carried out because of unexplained obstructive pneumonitis.

Bronchoscopic examination gave a surprising number of positive results in spite of the absence of a visible tumor in the bronchial tree. Results of biopsy were positive in seven of 15 cases (47 per cent). In some cases no abnormality was seen but a random biopsy taken by the bronchoscopist proved to be positive while in others some roughening of mucosa or tendency toward excessive bleeding directed the bronchoscopist to the area of involvement.

Follow-up data would indicate that the lesion is curable at this stage of evolution, but the dangers of recurrence of carcinoma in situ in the stump are emphasized in case 5; in this case a superficial lesion or carcinoma in situ recurred in the stump 3 years after the patient's operation. Roentgen therapy was used and the patient had no evidence of residual tumor in the stump 1 year later. Two patients died in the immediate postoperative period. One patient died 3½ years after operation and necropsy showed the presence of subdiaphragmatic abscesses. One patient died of coronary artery disease 3 years subsequent to operation and another patient died 3½ years after operation at the age of 72 years. In the latter case the cause of death was unknown but there was no known evidence of recurrence. The remaining nine patients are alive at the time of this writing from 4 to 8 years after operation without any known evidence of carcinoma.

SUMMARY

A small group of cases of bronchogenic carcinoma in situ or with associated early invasion have been reviewed. The results of cytologic examination were positive in approximately 73 per cent of cases and bronchoscopic biopsy was positive in 46 per cent. Although the condition of the patients has not been followed sufficiently long for thorough evaluation, highly favorable results of treatment in these early lesions are indicated.

RESUMEN

Un grupo pequeño de carcinoma broncopénico in situ o asociados a invasión temprana han sido objeto de revisión. Los resultados del examen citológico fueron positivos en 73 por ciento aproximadamente de los casos y la biopsia a través del broncoscopio fue positiva en 46 por ciento.

Aunque la condición del enfermo no fue observada por tiempo suficientemente largo para una valoración completa indica que el tratamiento temprano de estas lesiones es altamente favorable.

RESUMÉ

Les auteurs ont étudié un petit groupe de cas de cancer bronchique in situ dont l'extension était très récente. Les résultats de l'examen cytologique furent positifs dans environ 73% des cas, et la biopsie par bronchoscopie dans 46%.

Bien que les maladies n'aient pas été suivis pendant un temps suffisamment long pour une estimation complète, les auteurs ont état des résultats extrêmement favorables du traitement dans ces lésions précoces.

ZUSAMMENFASSUNG

Mitteilung einer kleinen Zahl von Fällen mit Bronchokarzinom in situ oder mit von ihnen ausgehender frühzeitiger Metastasierung. Die Resultate der cytotologischen
Untersuchung waren positiv in etwa 73% der Fälle und die bronchoskopische Biopsie war positiv in 46%.
Obgleich der Zustand der Patienten für eine gründliche Auswertung nicht genügend lange beobachtet werden konnte, werden besonders günstige Behandlungsergebnisse bei diesen Frühformen angegeben.

REFERENCES