Cytologic Diagnosis of Bronchogenic Carcinoma*

LEWIS B. WOOLNER, M.D.† and JOHN R. MCDONALD, M.D.†
Rochester, Minnesota

With the development of thoracic surgery, accurate preoperative diagnosis of bronchogenic carcinoma has become increasingly important. It has been found that cytologic examination of sputum and bronchial secretions provides a useful adjunct to already established methods of diagnosis.1-4 Cytologic examination of sputum and bronchial secretions has been carried out in our laboratory for the past three years. During this time specimens from approximately 6,000 patients have been examined and a cytologic diagnosis of carcinoma has been made in more than 400 cases. Cytologic examination of sputum was the basis for the diagnosis in approximately four fifths of the total number; in the remaining cases the diagnosis was based on the examination of bronchial secretions, washings or smears made by direct swabbing of the bronchial wall.

Technic

In the collection of sputum for examination, patients are instructed to collect material actually coughed up and to avoid dilution with pharyngeal and nasal secretions. The sputum is collected in a few cubic centimeters of 95 per cent alcohol. Fresh sputum is somewhat easier to handle technically and is used for hospital patients when the time factor between collection of sputum and smearing of slides is not important. Five slides are made from each specimen and an attempt is made to examine three specimens from each patient. Bronchial secretions are brought to the laboratory and smeared directly. We have utilized the alcohol-ether fixation as described by Papanicolaou,5 with hematoxylin-

*Presented at the 15th Annual Meeting, American College of Chest Physicians, Atlantic City, New Jersey, June 2 to 5, 1949.
†Division of Surgical Pathology, Mayo Clinic, Rochester, Minnesota.
eosin stain. The slides are carefully scanned under low magnification, high dry magnification being used for cellular detail. In practice it has been found satisfactory to have the scanning procedure carried out by properly trained technicians, who mark suspicious cells or clumps for further study. Actual diagnosis is, however, always made by the pathologist. The time required for examination of slides varies. In a positive case in which many carcinoma cells are present, the examination may be completed in a few minutes. In a negative case in which all slides need to be carefully scanned, it may require 25 to 30 minutes, depending on the experience of the examiner. Smears are examined as complete unknowns and the results are reported positive or negative or, if an insufficient number of atypical cells is found to make a definite diagnosis, another specimen is called for.

We have found sputum and bronchial secretions to be of approximately equal value in the detection of carcinoma cells. Both have certain advantages and disadvantages. Bronchial secretions provide better localization and require somewhat less time for examination. Sputum examination, by virtue of the dilution factor, is more time consuming, but this is offset somewhat by the ease of obtaining additional specimens, a very important consideration when few cells are present in a given case and more evidence is required to make a definite positive diagnosis. We have found that an appreciable number of additional positive diagnoses of carcinoma may be made by the routine use of both sputum and secretions whenever possible.

The characteristics of exfoliated carcinoma cells as seen in various secretions have been adequately described.6,7 In general, carcinoma cells are distinguished by their large cells, variation in size and shape of the cells, hyperchromatism of the nucleus and the presence of prominent nucleoli. Diagnosis is most readily made on the basis of clumps of exfoliated cells but equally accurate results can be obtained by finding a sufficient number of isolated single cells. Small-cell or "oat-cell" carcinomas are the most difficult to diagnose by the smear technic because of the small size of the cancer cells.

Care must be taken to distinguish immature phagocytes without pigment and clumps of squamatized bronchial epithelium from cancer cells.

Accuracy of Diagnosis

*False Positive Diagnoses:* It has been found that false positive diagnoses cannot be completely avoided in routine cytologic work. In our experience the false positive error has been approximately 2 per cent. In 400 cases in which a positive diagnosis of carcinoma
was made from smears of sputum or bronchial secretions there have been seven proved false positive reports. In an additional three cases, the clinical impression was not carcinoma but no follow-up on these patients has been obtained. In approximately 30 per cent of these 400 cases, tissue proof of the presence of carcinoma was not obtained. In the majority of these cases, however, the clinical and roentgenologic evidence of carcinoma was supported by such secondary evidence as metastasis to bone or enlarged lymph nodes, fixed vocal cord, pleural effusion, Horner's syndrome, superior vena caval obstruction or gross findings at bronchoscopic examination. In a few cases, the origin of the carcinoma cells was from the esophagus via a tracheo-esophageal fistula or from the upper part of the respiratory tract. In a small number, the lesion in the lung was assumed to be metastatic from a primary carcinoma elsewhere in the body. It has been our experience, however, that metastatic carcinoma does not regularly exfoliate cancer cells because of the somewhat infrequent bronchial involvement and because the mucosa tends to remain intact over the tumor.

False Negative Results: The presence or absence of cancer cells in a given case of bronchogenic carcinoma varies somewhat with the type and situation of the lesion. In general, tumors at the hilus or those involving large or medium-sized bronchi give a uniformly positive result. However, of tumors situated in the periphery, those for which no gross communication between the tumor and the bronchial tree can be traced will obviously give negative results. In a series of 588 patients with miscellaneous diseases of the thorax previously reported on by us, a routine cytologic examination of sputum or bronchial secretions was carried out. Of this number, 147 patients were proved to have or were suspected of having bronchogenic carcinoma. In 100 of these, or 68 per cent of the total, a positive diagnosis of carcinoma was given by cytologic studies. This figure is probably lower than the true incidence since some of the false negative reports were based on an inadequate number of sputum examinations.

Value of Method as an Adjunct to Established Methods of Diagnosis: In our experience cytologic examination of sputum or bronchial secretions frequently gives positive results when the findings at bronchoscopic examination are negative or equivocal. In the series of 400 patients previously referred to, 144 underwent surgical exploration. Of this total, 79 (54.9 per cent) had a preoperative microscopic diagnosis of carcinoma on the basis of positive results obtained on bronchoscopic biopsy. In the remainder, positive smears provided the only preoperative microscopic evidence of malignancy. In 77 of these cases, pneumonectomy or
FIGURE 1: Bronchogenic carcinoma of the lingular division of the upper lobe bronchus. (a) Roentgenographic appearance. (b) Carcinoma cells found in sputum. (c) Gross lesion. The segment of bronchus involved measured 1.2 cm. in length. There was infiltration of the carcinoma through the entire thickness of the bronchial wall but not into the surrounding lung.
lobectomy was carried out, 45 of the operations being on the basis of positive results on biopsy and 32 on the basis of positive results obtained when smears were examined. To illustrate the type of case in which the results of sputum examination are positive and the results of bronchoscopic examination completely negative, the following case is cited.

A 64-year-old male came to the clinic for an examination. Four months before admission, he had had pain in the left side of the thorax. The pain extended down the arms and was thought to be on a cardiac basis. One month before admission, he had had a slight thoracic pain and an attack of influenza. He had had a slight cough with mucoid sputum but no hemoptysis. On admission, roentgenograms of the thorax revealed chronic pneumonitis with some reduction in volume of the lingular portion of the left upper lobe; no definite tumor was identified but the possibility of bronchogenic carcinoma or bronchlectasis was suggested (Fig. 1a). Bronchoscopic examination gave completely negative results. Secretions were removed for cytologic study but an insufficient number of atypical cells were found on which to base a diagnosis. The sputum, however, was positive for carcinoma cells (Fig. 1b). A diagnosis of bronchogenic carcinoma was thus made and a left pneumonectomy was carried out. A very small bronchogenic carcinoma, squamous type, was found surrounding the orifice of the lingular division of the left upper lobe bronchus (Fig. 1c). The lingular portion of the upper lobe distal to the carcinoma showed chronic pneumonitis. No lymph nodes were involved.

Value in the Diagnosis of Surgically Resected Bronchogenic Carcinomas

In an attempt to correlate the incidence of positive cytologic findings with the type and location of bronchogenic carcinoma, a group of 80 consecutive surgically removed bronchogenic carcinomas over a two-year period was studied. In this group, 40 were squamous-cell carcinomas, 20 were carcinomas of the large-cell type, 15 were adenocarcinomas and five were carcinomas of the small-cell or "oat-cell" type. In the 80 cases bronchoscopic biopsy gave positive results in 38 or 47.5 per cent. Sputum or bronchial secretions were examined in 73 of these cases and positive results were reported in 51, or 70 per cent. By combining the two methods, a positive preoperative microscopic diagnosis of carcinoma was made in 59 out of 80 cases, or 73.8 per cent.

Squamous-cell Carcinoma: Squamous-cell carcinoma is the most frequent histologic type of bronchogenic carcinoma. There is a marked tendency for it to involve the larger bronchi; hence the cytologic findings are usually positive. Of the 40 patients with squamous-cell carcinomas in this group, 35 had cytologic examinations, in 28 (80 per cent) of whom positive results were reported. Of the seven cases in which cytologic examination gave negative results, the biopsy gave positive results in two. In all cases there
was at least some degree of gross bronchial involvement by the tumor.

**Large-cell Type:** Of the 20 patients with large-cell carcinomas, 19 were examined cytologically, in 12 (63.2 per cent) of whom positive results were reported. Of the seven cases in which cytologic examination gave negative results, the lesion in one was peripheral, in two it involved a very small bronchus, in one it was cavernous or cystic and was situated in the upper lobe and in three it involved fairly large bronchi.

**Adenocarcinoma:** Adenocarcinoma is probably the least frequent histologic type of bronchogenic carcinoma. It tends to be more peripheral in situation frequently forming a subpleural nodule to which no direct bronchial communication can be traced. Histologically it may be impossible to differentiate such tumors from metastatic adenocarcinoma. In this series all 15 of the patients with adenocarcinoma were examined cytologically. In only eight of the 15 were there positive findings (53.3 per cent). Of the seven cases in which cytologic studies gave negative results, the lesion in four was subpleural with no demonstrable bronchial involvement, in two it was peripheral with minimal ulceration of a bronchus and in one it was a peripheral nodule which was possibly metastatic from an ovarian carcinoma removed four years previously. Of the eight cases of adenocarcinoma in which cytologic

![FIGURE 2: Peripherally placed bronchogenic carcinoma. The sputum examination gave negative results in this case.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=data/journals/chest/21187/ on 06/21/2017)
studies gave positive results, in only one was the lesion peripherally situated, the lesion in the remainder involving the major bronchi or one of the moderate-sized subdivisions. It is apparent that there is a group of cases of peripherally situated carcinomas frequently of the adenocarcinoma type in which no, or very minimal, communication with the bronchial tree can be traced and in which the cytologic findings will be fairly consistently negative. Of the lesions in the 80 cases of bronchogenic carcinoma in this series, eight or 10 per cent, were peripheral and no communication could be traced between the tumor and the bronchial tree. In a recent case, such a carcinoma was found at operation in spite of the fact that 15 consecutive sputum examinations had been carried out with negative results (Fig. 2). In some peripheral bronchogenic carcinomas, however, the tumor communicates with a moderate sized bronchus and carcinoma cells may be found in the sputum. One such tumor is shown in Figure 3.

Small-cell Group: Small-cell bronchogenic carcinomas are the least frequent in a surgical series because of their rapid growth and widespread early metastasis. In this series only five were of the small-cell type, and three of these out of four cases examined were associated with sputum or bronchial secretions that were positive for carcinoma cells (75 per cent). In our experience patients with these tumors show consistently positive cytologic findings in keeping with the tendency of such tumors to involve the larger bronchi.

FIGURE 3: Peripherally placed bronchogenic carcinoma. There was gross bronchial involvement by the tumor in this case and sputum examination gave positive results.
Alveolar-cell Tumor: Our experience with alveolar-cell tumors has been based on seven surgically removed specimens. It is difficult to establish a preoperative diagnosis of tumors of this type. The symptoms are nonspecific although voluminous mucoid or watery sputum may be noted. The bronchosopic examination gives consistently negative results and the roentgenogram of the thorax may simulate sarcoidosis or other inflammatory conditions. On five of the patients with this type of tumor, cytologic examination was carried out preoperatively. The sputum was positive for carcinoma cells in three, equivocal in one and negative in one. It would appear that the findings of atypical cells in the sputum may aid considerably in the preoperative diagnosis of alveolar-cell tumor.

Adenoma and Cylindroma: Adenoma and cylindroma constitute possibly 5 per cent of primary pulmonary neoplasms but a somewhat larger portion of surgically removed pulmonary tumors. Because of the intact mucosa over the surface of the tumor, the cytologic findings in this group have been consistently negative. The findings of carcinoma cells in the sputum may aid considerably in the differential diagnosis between adenoma and "oat-cell" carcinoma.

SUMMARY

Our experience with cytologic diagnosis of bronchogenic carcinoma has been summarized. To date in more than 400 cases of bronchogenic carcinoma the diagnosis has been made cytologically with a false positive error of approximately 2 per cent. In our experience the false negative error has been approximately 30 per cent. Of 80 consecutive surgically removed bronchogenic carcinomas, 10 per cent were peripherally placed showing slight or no gross communication with the bronchial tree. Cytologic examination in the case of these peripherally located tumors gave negative results. Cytologic studies are of value in the diagnosis of alveolar-cell tumor but of no value in bronchial adenoma or cylindroma.

RESUMEN

Se ha resumido nuestra experiencia en el diagnóstico citológico del carcinoma broncogénico. Hasta ahora en más de 400 casos de carcinoma broncogénico, se ha hecho el diagnóstico citológico con error de falsos positivos aproximadamente de 2 por ciento. En nuestra experiencia el error por falsos negativos ha sido de 30 por ciento. De 80 carcinomas broncogéncicos quirúrgicamente extirpados, 10 por ciento estaban ubicados periféricamente mostrando muy pequeña o ninguna comunicación con el árbol bronquial. El examen citológico de estos tumores periféricos dio resultados nega-
tivos. Los estudios citológicos son de valor en el diagnóstico en el tumor de células alveolares, pero no tienen valor en el diagnóstico del adenoma bronquial o en el del cilindroma.

REFERENCES


Discussion

PETER A. HERBUT, M.D.
Philadelphia, Pennsylvania

It is the opinion of Dr. Clerf and myself that cytological examination of bronchoscopically removed secretions is scientifically more accurate and clinically more rewarding than examination of sputa. We have no doubt that a diagnosis of bronchial carcinoma can be made by examining the sputum, but the purpose of this whole procedure is to arrive at an "early" diagnosis of cancer and everybody knows that early in the course of the disease there is no sputum available. In fact our best results are in those cases in whom the bronchial segment is gingerly washed with saline—a step that is necessary when there are no secretions available even at the time of bronchoscopic examination. If neoplastic cells are found in sputum a bronchoscopic examination must be performed to determine the location of the tumor and the operability. If, on the other hand, neoplastic cells are not found in the sputum and the patient is suspected of having cancer a bronchoscopic examination must also be performed. Therefore, why not do it in the first place?

Our results as of May 26, 1949, are as follows: In a total of 307 cases of cancer of the lung neoplastic cells were found in bronchoscopically removed secretions in 272 or 88.6 per cent. A bron-
choscopic biopsy was possible in 104 of the cases or 33.8 per cent. Indirect evidence of tumor in the form of stenosis, fixation, etc., was present in 87 cases. Neoplastic cells were present in secretions and bronchoscopic examination was entirely negative in 94 cases or 30.6 per cent. It might be of interest also to correlate the bronchoscopic findings with the stage of the disease. In a consecutive series of 69 total pneumonectomies performed by Dr. Gibbon bronchoscopic examination was completely negative in 25, and in 18 of these neoplastic cells were present in the secretions. In only two of these 25 cases were there metastases to the peripheral and mediastinal lymph nodes. In 44 cases in which there was bronchoscopic evidence of tumor (positive biopsy in 21 and deformity, etc., in 23) neoplastic cells were present in secretions in 39 cases. In 23 of these 44 cases the tumor had already spread to the draining lymph nodes.

In conclusion, I heartily concur with Dr. McDonald that cytologic diagnosis of cancer of the lung is an extremely valuable adjunct in the fight against this disease. I am sure the procedure is here to stay.

SEYMOUR M. FARBER, M.D., F.C.C.P.
San Francisco, California

This has been a most interesting and important report in the cytologic field. Unfortunately there are very few groups where careful statistics have been kept of the attempts to find malignant cells in the sputum and bronchial secretions of patients. Doctor McDonald's analysis of his experience in a diagnostic center reveals the importance of these studies.

We have been accepting specimens at the University of California from various medical schools, teaching and private hospitals, veterans administration hospitals, tuberculosis sanatoria and from private physicians. Specimens from 1243 patients were submitted and in this group there were 319 patients who had malignant pulmonary disease. When five or more sputum specimens were submitted, 88 per cent of the proved cases of bronchogenic carcinoma were diagnosed by cytologic methods. When only one specimen was submitted or when incomplete sputum studies were offered for examination, we were able to diagnose 61 per cent of the proved cases.

There is very little that one can add to the excellent presentation of Doctor McDonald except to indicate again a warning. The reliability and the sensitivity of the cytologic technique can be readily obtained by competent cytologists, but it must be remembered that the reliability in particular requires experience.