Alveolar Cell Carcinoma of the Lung: A Case Presentation at the Weekly Thoracic Conference at the Mayo Clinic*


Dr. Olsen: This patient was a healthy-appearing man, 52 years of age, who was a machinist by trade. He registered here on July 25, 1968. He came to us because his doctor at home had made an x-ray of the chest and found a lesion in the left lung. He had had some shortness of breath for six or eight months and a cough productive of white mucoid sputum for three or four months. He had smoked a package of cigarettes a day from the time he was a teen-ager up until six years before his visit here. He also described a wheezing sensation in the left chest. Our examination disclosed that he had an enlarged nodular thyroid, especially on the right side. There was a pleural rub on the left, and rather distant tubular breathing was present. [The PA roentgenogram of his chest was placed on the viewing box (Fig 1A).]

Dr. Kolker, would you describe what you see on the x-ray of the chest on the patient's admission?

Dr. Paul Kolker (Resident in Thoracic Surgery): The x-ray film of July, 1968, shows a density in the left lower lung field. The bony structures are normal and the cardiac contour is within normal limits. The mediastinum and the trachea seem to be shifted toward the patient's left.

Dr. Olsen: What additional view would you like to see?

Dr. Kolker: A left lateral view, please.

Dr. Howard A. Andersen: Dr. Kolker, before examining the lateral view, would you be able to tell us where the lesion is on the PA film alone?

Dr. Kolker: Yes. This lesion should be in the posterior thorax.

Dr. Andersen: Why?

Dr. Kolker: There is a distinct cardiac contour with no confluence of the shadow of the pulmonary lesion with the heart border.

Dr. Olsen: Dr. Miller, would you comment on that?

Dr. Miller: I agree with Dr. Kolker and with the point Dr. Andersen is making; the density must lie posteriorly because its margins are distinct. If it were anterior and adjacent to the heart, its margins would merge with the heart shadow and not be so clearly defined. The appearance of possible loss of volume in the left lower lobe and shift of the mediastinal structures may actually be simulated by thoracic scoliosis.

Dr. Olsen: Here is the lateral view. [A left lateral view is placed on the viewing box.]

Dr. Kolker: The lateral view (Fig 1B) does show that this area of radiodensity is posterior to the heart silhouette. It involves most of the left lower lobe.

Dr. Olsen: On the basis of what you know so far do you have an opinion as to what the diagnosis might be?

Dr. Kolker: A differential diagnosis would include an obstructive pneumonitis, perhaps secondary to neoplasm or possibly an inflammatory process. Did this patient have any exposure to asbestos?

Dr. Olsen: Not that we know of. What further diagnostic procedures are indicated?

Dr. Kolker: Sputum specimens should be obtained for culture and for cytologic study. Then...
bronchoscopy is indicated.

Dr. Olsen: Bronchoscopic examination was performed before the results of sputum studies were available. I had expected to see a mass in the left lower lobe bronchus and was rather surprised to find an unobstructed lumen. However, on inspection of the superior division of the lower lobe bronchus with a right-angle telescope, I saw a small polypoid lesion. It was possible to get a biopsy from this, and quick-frozen examination showed evidence of malignancy. The sputum specimen was also positive for malignant cells. The pathologist classified the lesion as a terminal bronchiolar carcinoma. Dr. Clagett saw the patient and did a thoracotomy. Dr. Clagett, would you tell us about the surgical findings?

Dr. Clagett: On opening the chest, I found some bloody pleural fluid in the pleural space, not a large quantity but some. The lower lobe was almost entirely consolidated but the hilus was free. There were no adhesions. A lower lobectomy was performed. The upper lobe was entirely normal to palpation and inspection. The regional nodes around the hilus were free of metastatic disease at the time of operation and a lobectomy seemed to be an adequate procedure for this lesion.

Roentgenograms made after operation showed satisfactory expansion of the remaining left upper lobe. The postoperative course was uneventful and the patient did indeed get along very well.

Dr. Woolner, will you tell us about the gross and the microscopic findings at that time?

Dr. Woolner: The specimen consisted of the left lower lobe of the lung. The gross pathologic findings are shown in this slide (Fig 2A). You will note that much of the resected lobe is replaced by tumor and that a lobar configuration is maintained. At first glance, the process might be mistaken for pneumonic consolidation of the lobe. Historically, these are the classic gross findings of what has been called alveolar cell or terminal bronchiolar carcinoma of the lung. On histologic examination, the tumor is composed of tall columnar cells with some papillary infoldings; in much of the lobe the tumor uses the preexisting framework of lung parenchyma as supportive stroma (Fig 2B). This is again the classic microscopic definition of alveolar cell carcinoma. Turning back to the gross specimen, however, one finds that the cut surface of the tumor is not altogether uniform. What I have shown up to this point is representative of the peripheral portion of the lobe. Further cuts through the substance of the consolidated tumor mass demonstrate an area of puckering and scarring of the pleura at one point, and a zone of infiltrative carcinoma up to 2.5 cm in diameter is seen in this area (Fig 2C). Histologically, the tumor in this area does not maintain the alveolar pattern just described but is infiltrative and produces fibrosis, scar formation, peribronchial lymphatic permeation.
and extension of tumor into small bronchioles (Fig 2D). I have no objection to a diagnosis of alveolar cell carcinoma for this tumor provided that one recognizes that the histologic picture is not uniform throughout the lobe. As an alternative descriptive diagnosis, one might say that a grade 2 papillary adenocarcinoma involves approximately 90 percent of the lower lobe of the lung. The tumor is infiltrative in one area but spreads throughout much of the remainder of the lobe in an “alveolar” fashion.

**Dr. Olsen:** At this point I would like to bring you up to date on what happened to this patient. He got along quite well and he came back to see us in February of this year, at our request. He had virtually no complaints so I was rather startled when I saw his chest x-ray film (Fig 3). The appearance strongly suggested a metastatic process involving both lungs, plus a pleural effusion on the left. The patient was not coughing but a specimen of sputum was obtained after he had inhaled a heated mist of hypertonic saline. This induced sputum was positive for adenocarcinoma cells. The situation was reviewed in the oncology department by Dr. David Carr, who felt that there was no reason for considering any type of roentgen therapy. Dr. Carr wrote to the home physician and suggested the possibility that this patient might be treated...

**Figure 2.** Alveolar cell carcinoma. A, cut surface of resected lobe. Note extension of tumor to pleura to provide a lobar configuration. B, histologic section representative of much of the periphery. Tall columnar cells with papillary infoldings line the alveoli in an orderly fashion (reduced from × 50). C, zone of pleural puckering and scarring seen on further sectioning of gross specimen. D, infiltrative carcinoma involving an area 2.5 cm in diameter in vicinity of scar (reduced from × 75).

**Figure 3.** PA view seven months after left lower lobectomy showing diffuse nodular lesions in both lungs.
ALVEOLAR CELL CARCINOMA OF THE LUNG

FIGURE 4. Roentgenographic features of alveolar cell carcinoma. A, nodule in the left midlung field at the level of the third interspace anteriorly. B, tomogram of this nodule showing irregular radiolucent spaces within the lesion. C, pneumonitic-like lesion RLL. D, diffuse bilateral form with disseminated nodules and areas of coalescence.

with either Cytoxan or 5-FU. At this point I would like to ask Dr. Miller if he would discuss the radiologic aspects of this problem.

Dr. Miller: I would like to review the work of Belgrad, Good, and Woolner in which the roentgenographic features of 32 cases of alveolar cell carcinoma from this institution were described. The roentgenographic features of alveolar cell carcinomas reflect either localized or diffuse pulmonary involvement by tumor. When localized, the tumor will present as an indeterminate nodule (Fig 4A). As Kittredge and Sherman have pointed out, some nodules have poorly-defined, radiolucent spaces within them, possibly representing alveolar spaces not involved by tumor. We have observed this feature and suggested the diagnosis of alveolar cell carcinoma on at least two occasions. This feature, best seen on tomograms (Fig 4B), possibly may be specific for the roentgenographic diagnosis of alveolar cell carcinoma. Another common form of localized disease is pneumonitis-like alveolar involvement (Fig 4C) or consolidation of an entire lobe by tumor, as seen in the case presented today (Fig 1A and B). An “air bronchogram” may be visible, indicating that the disease is located in the alveolar spaces and surrounding the bronchial tree.

Unfortunately, many patients have the diffuse form of alveolar cell carcinoma when first seen. Roentgenographically, diffuse multialveolar disease is present throughout the lungs, frequently with some areas of coalescence (Fig 4D). These disseminated nodules have ill-defined fluffy margins, which indicate alveolar involvement. Roentgenographically, other diseases enter into the differential diagnosis when a disseminated alveolar pattern is present. These include pulmonary edema, pneumonia of unusual etiology, pulmonary hemorrhage, sarcoidosis, lymphoma, and alveolar proteinosis. Metastatic neoplasm would not usually enter into
the differential diagnosis because such nodules have sharp, discrete margins, whereas the alveolar pattern consists of ill-defined fluffy nodules which are the tip-off to the fact that diffuse alveolar involvement is present. In a sense you may consider diffuse alveolar carcinoma to be metastatic, but at least the location of the nodules of alveolar carcinoma is within alveolar spaces.

Dr. Olsen: Dr. Woolner, would you tell us more about the pathologic aspects of this disease?

Dr. Woolner: There has been some confusion about the definition of alveolar cell tumor, so much so that in a recent review of lung tumors the question is raised as to whether there is such a pathologic entity. The term "alveolar cell carcinoma" has been used in connection with three pathologic situations: (1) a small localized tumor in the lung parenchyma, often rather soft in consistency as compared with "ordinary" adenocarcinoma; (2) a lobar or pulmonary consolidation by tumor, more or less as we saw in today's case; and (3) a diffuse x-ray picture involving both lungs, such as described by Dr. Miller. It would appear that the term "alveolar cell carcinoma" should imply a method of spread of glandular cancer within the lung rather than a precise pathologic entity. I think that I can explain this point of view and the reason for the confusion in definition by showing the varied histologic structure seen in a group of small peripheral glandular cancers of the lung.

We have recently completed a study involving prognosis on peripheral bronchogenic carcinomas up to 4 cm in diameter. In addition a detailed
pathologic study has been conducted on all small peripheral carcinomas of the lung treated over a 15-year period (1950-1965). These tumors were all surgically resected and were all 2 cm or less in diameter. Of the 76 carcinomas in the series, 50 are of the glandular type. Detailed histologic study of these 50 adenocarcinomas reveals a remarkable spectrum of morphology, both as to histologic grading of tumor and extent of alveolar spread within the neoplasm.

Briefly stated, the amount of "alveolar" architecture—that is, tumor cells lining preexisting alveolar walls and alveolar ducts—varied from zero in many high-grade adenocarcinomas to virtually 100 percent in a few well-differentiated papillary adenocarcinomas. All variations within these two extremes are found. Two of these cases may be used to illustrate the problem of definition of alveolar cell carcinoma.

**Case 1**

A woman, 59 years old, on surgical exploration had a 2-cm mass situated subpleurally. Histologic sections through the entire tumor (Fig 5A) show a papillary glandular carcinoma, all of which appears to use preexisting alveolar walls as supportive stroma. The tumor spreads peripherally along alveolar walls as shown in Figure 5B.

**Case 2**

A man, 65 years old, was found to have an indeterminate nodule in the left upper lobe. The resected tumor measured 2 × 1.9 × 1.5 cm. Histologic section reveals a grade 2 adenocarcinoma consisting of a central infiltrative zone of carcinoma making up approximately 50 percent of the total area (Fig 5C). Surrounding this infiltrative cancer is a zone of peripheral spread using alveolar walls as framework (Fig 5D).

In the entire series of 50 cases of localized glandular carcinoma involving the periphery of the lung, one case appears to be entirely "alveolar" in architecture and in six cases the bulk of the tumor (50 percent to 90 percent) is of similar structure. In 19 additional cases the tumor has a large central infiltrative component but up to 50 percent of the tumor shows peripheral "alveolar" type spread. The remaining 24 glandular tumors show only infiltrative cancer with no alveolar extension. Obviously, the number of cases within this series which might be termed "alveolar cell or terminal bronchiolar" carcinoma will vary according to the definition used.

It would appear that the same general statement might be made regarding larger glandular tumors involving much or all of a lobe. In the past we have placed in the category of alveolar cell carcinoma only those in which the bulk (90 percent to 95 percent) of the tumor lines alveoli. Those with lesser degrees of this type of spread have been excluded.

For cases having a diffuse bilateral infiltrate on the chest x-ray, cases often diagnosed as "alveolar cell carcinoma," we frequently have poor pathologic documentation unless autopsy is performed. In many such cases, spread within the lung in a multicentric "alveolar" fashion is probably present. Diffuse lymphatic permeation by carcinoma from either a pulmonary or extrapulmonary source can produce a comparable diffuse shadow by x-ray. Perhaps Dr. Olsen will include in his discussion some data on prognosis of the various types of tumor just outlined.

Dr. Olsen: The first description of alveolar cell carcinoma as an entity is credited to Malassez in 1876. His description of the histologic nature of the lesion correlates well with present-day descriptions. In 1903 Musser reported a diffuse form of cancer of the lung. He pointed out that this type of tumor may involve a single lobe or an entire lung and that it may simulate lobar pneumonia in the stage of gray hepatization. He also commented that satellite nodules were present in the opposite lung. He made particular reference to the fact that no tumor was demonstrated in the major bronchi. Our case today is an example not only of the pneumonic form (Fig 1A and B) but also of the diffuse, nodular variety (Fig 3) seen in the late stages of the disease. Numerous contributions have appeared which describe the morphologic, roentgenologic, clinical, and surgical aspects of alveolar cell carcinoma. Of particular interest is the recent contribution of Watson and Farpour, which reports the experience of the Memorial Hospital of New York with 265 patients with this entity, and I shall take the liberty of quoting them quite liberally.

The Mayo Clinic report by Belgrad, Good, and Woolner in 1962 was limited to the surgically resected cases and included 28 patients. It is a much smaller group than the 265 patients from Memorial Hospital, 119 of whom came to surgery.

Alveolar cell carcinoma is a relatively rare form of bronchogenic carcinoma. Le Roux from Edinburgh reports that out of 4,000 cases of bronchogenic carcinoma in the Edinburgh area only 17 or 0.4 percent were of the alveolar type. Galofré and associates, when reporting on a series of 1,090 surgically-resected cases of bronchogenic carcinoma, found that 19 were classified as alveolar cell carcinomas, an incidence of 1.6 percent. On the other hand, Watson and Farpour reported 265 patients out of a total of 4,068 patients with...
bronchogenic carcinoma. This represents an incidence of 6.5 percent of the cases of bronchogenic carcinoma seen at their hospital between the years 1926 and 1960 and includes both surgical and nonsurgical cases.

All authors are agreed that the incidence of alveolar carcinoma is much higher in women than one would ordinarily expect for bronchogenic carcinoma. Thirty-two percent of Watson and Farpour's group were women. In a Mayo Clinic series in which both the localized and the diffuse forms of alveolar cell carcinoma were considered, 20 of 28 patients were women. This should be contrasted with the later report of Jackman and associates which was concerned with peripheral bronchogenic carcinomas less than 4 cm in diameter. In Jackman's group, 19 (or 9.8 percent) were of the alveolar type and 11 of these 19 were in women.

The high incidence of alveolar cell carcinoma in women is of particular interest. According to Watson and Farpour, only 11 percent of all bronchogenic carcinomas occur in women. If one considers only carcinomas of the glandular or adeno type, 20 percent of the carcinomas occur in women. Hence, it is apparent that alveolar cell carcinoma has a greater predilection for women than is observed in any other type of bronchogenic carcinoma. Likewise, there is less correlation with smoking in alveolar cell carcinoma. Watson and Farpour state that 98.5 percent of all males who develop bronchogenic carcinoma are smokers, and therefore only 1.5 percent are nonsmokers. In contrast, they found that 9 percent of men who developed alveolar cell carcinoma are nonsmokers and 35 percent of women who developed alveolar cell carcinoma are nonsmokers.

In the 28 cases reported by Belgrad, Good, and Woolner there were 11 localized tumors which measured 4 cm or less and 17 diffuse carcinomas of which nine represented a pneumatic form involving a single lobe; the remainder were even more extensive. As one might expect, the symptoms were much more obvious in the diffuse than in the localized form. For example, eight of the 11 localized tumors had no symptoms whatsoever, while 16 of the patients with the diffuse form had some type of respiratory symptoms. The most common symptom was a cough. Only three patients of the entire series produced the frothy, white, profuse sputum supposedly characteristic of alveolar cell carcinoma.

From the standpoint of symptoms, Watson and Farpour's group was equally interesting. Forty-six (17 percent) of their 265 cases had a history of pneumonia or pleurisy, 88 complained of cough, 57 described pleurisy as their initial symptom, and 20 had hemoptysis. Most had symptoms that were less than six weeks in duration and only 40 had symptoms for as long as 18 months. In this group of 265 patients, 76 (29 percent) were found to have a pleural effusion at the time of admission. Thoracentesis was performed in 46 of these 76 patients and carcinoma cells were demonstrated in 33. Eighty-eight of the 265 patients were found to have palpable cervical nodes, and biopsies were performed. Positive biopsies were obtained in 62 percent of the 88.

Watson and Farpour found that 162 cases involved the right lung and 91 involved the left lung. Only one patient had a tracheal lesion. Both lungs were involved in only 11 patients. Also of interest was the fact that the upper lobes were involved about twice as often as the lower lobes. Approximately two thirds of the entire group of 265 cases were of the solitary peripheral type, with the lesion being approximately 2 to 4 cm in diameter. The lesions resembled other peripheral lung cancers. As Dr. Miller pointed out, the margins were often irregular, less sharply circumscribed, and less dense than one would expect with metastatic nodules. In the remaining one third of Watson and Farpour's cases the x-ray pictures showed diffuse involvement, either pneumonic in nature or with multiple nodules.

A definite diagnosis was made by cytologic techniques in 83 of the 265 patients. There were 45 with positive sputum, 23 with positive bronchial washings, and 15 with pleural fluid that was positive. In an additional 82 patients the correct diagnosis was made by exploratory thoracotomy. However in 60 cases the diagnosis was established by biopsy of a metastatic lesion, usually a scalene lymph node but sometimes a liver biopsy. In 12 instances the diagnosis was made by transbronchial needle lung biopsy. In 41 cases the diagnosis was made at postmortem examination.

Bronchoscopy was done in 144 of the 265 cases; in only seven cases was the diagnosis made by endobronchial biopsy. In other words, bronchial involvement is indeed rare. As previously indicated, the incidence of metastatic involvement to the cervical lymph nodes and liver was fairly high. There were 88 patients in whom scalene nodes demonstrated the lesion, and in 43 patients liver metastases were demonstrated.

Of Watson and Farpour's 265 cases, 119 had surgery. There were 43 pneumonectomies, 30 lobectomies, and nine wedge resections. Of the
119 cases, 37 proved to be inoperable and all of these died within three years' time (20 died within one year). Treatment had relatively little effect on this group, although 24 of the 37 inoperable cases received roentgen therapy; four were treated by chemotherapy (nitrogen mustard) and three had a combination of both. Of the 119 cases who had surgery, 82 resections were done with a mortality of 5.8 percent. Sixteen of the 82 who had successful resections lived for five years or more, and an additional five were living at the end of four years.

Of all of the patients who were deemed inoperable and were not subjected to surgery, 32 were given roentgen therapy only and 30 of the 32 were dead in less than two years. An additional 15 patients were given both roentgen therapy and chemotherapy, and all of these died within a two-year period. An additional 17 patients were given chemotherapy alone, and all of these died within a one-year period.

The overall prognosis of alveolar cell carcinoma, therefore, is indeed poor. On the other hand, there is a striking difference between the prognosis in patients with the diffuse disease as compared with the localized form in which the lesion is 4 cm or less in size. Although the prognosis is extremely dismal in patients with diffuse disease, the prognosis is favorable in those patients who have the localized lesions.

Dr. Clagett, would you please comment on the Mayo Clinic experience with alveolar cell carcinoma and on the surgical aspects of the problem?

Dr. Clagett: From a surgical standpoint there are indeed two types of lesions; the localized group has a relatively good prognosis; 80 percent of the patients with small, localized tumors in our series were alive and well five years after resection. Patients with diffuse lesions have a practically hopeless prognosis. They present in these two ways grossly at the time of operation: one is as a diffuse pneumonic consolidated lesion; the other is a localized circumscribed lesion. The prognosis for each seems to depend upon its gross and not its microscopic characteristics. The pneumonic variety is almost hopeless. You can, however, accomplish some palliation by relieving their cough temporarily in some cases. Some of these people do have a profuse, productive, wet, frothy sputum and you can occasionally get some relief of cough by resection. However, curing this diffuse pneumonic variety surgically just does not seem to be in the cards. I remember a patient some years ago who had a small pneumonic process in the left lower lobe.

I resected the left lower lobe. Just out of interest, we got some sputum specimens while she was still in the hospital. Her sputum was positive. Six months later her left upper lobe showed involvement on roentgenograms. It had been entirely normal to palpation at the time of operation. The right lung still looked all right so we went back in and took out the left upper lobe. While she was still in the hospital her sputum was still positive and in a few months she had diffuse disease in her other lung. So I think we would have to admit that from a surgical standpoint the pneumonic variety is hopeless except perhaps for providing a little palliation. The localized variety, on the other hand, does offer a significantly worthwhile salvage and we need to go after them. We cannot tell from the x-ray picture, except perhaps with the information Dr. Miller has given us today about the vacuolation of the lesions, what these circumscribed lesions are without surgical exploration. I cannot tell the difference between localized adenocarcinoma or large-cell carcinoma or an alveolar cell carcinoma by palpation of the lesion alone.

Dr. Olsen: To summarize: alveolar cell or terminal bronchiolar carcinoma may present roentgenographically (and anatomically) as a solitary nodule, in pneumonic form, or as a diffuse nodular process. It occurs much more frequently in women than do most bronchogenic carcinomas. The clinical symptoms do not differ materially from other lung cancers although at times patients with this disease will produce large quantities of a frothy, liquid sputum.

From the pathologic standpoint the lesions, whether unicentric or multicentric, resemble other glandular carcinomas of the lung, and the histologic appearance of the lesion varies considerably even in different portions of the same tumor. They do differ from the usual adenocarcinomas of the lung because of the infrequent involvement of the bronchi and the method of spread throughout the glandular structures of the lung and the alveoli.

The prognosis of the disease is good if the disease is discovered in the solitary nodular stage and surgical resection is promptly carried out. However, if the tumor is multicentric in origin or has metastasized to neighboring lung tissue, the outlook is almost always bad. Alveolar cell carcinoma does not respond to radiation or to chemotherapy.

A case of alveolar cell carcinoma of the pneumonic type is reported which is of particular interest because of the unusual involvement of a bronchus, enabling us to make a histologic diagnosis from a bronchoscopic biopsy. The patient's sputum and
bronchial washings contained malignant cells characteristic of alveolar cell carcinoma. At surgery the disease seemed to be localized to the left lower lobe and a lobectomy was performed. However, seven months later the patient returned with diffuse bilateral nodular disease.

REFERENCES

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DIGNITY THROUGH BENEVOLENCE AND HUMILITY

The hidden forces of goodness are embodied in those persons who carry on as a secondary pursuit the immediate personal service which they cannot make their life work. The lot of many is to have as a profession, for the earning of their living and the satisfaction of society's claim on them, a more or less soulless labor in which they can give out little or nothing of their human qualities. Yet no one finds himself in a position of having no possible opportunity of giving himself to others as a human being. Anyone can rescue his human life, in spite of his professional life, who seizes every opportunity of being a man of personal action, however unpretending, for the good of fellow men who need the help of a fellow man. Such a man enlists in the service of spiritual and good. No fate can prevent man from giving to others this direct human service side by side with his life work. If so much of such service remains unrealized, it is because the opportunities are missed.