CALIFORNIA TUMOR TISSUE REGISTRY
96TH SEMI-ANNUAL CANCER SEMINAR
ON
PLEURO-PULMONARY NEOPLASMS

CASE HISTORIES

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June 5, 1994
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CLINICAL ABSTRACT:

A 72-year-old, asymptomatic, hypertensive, retired, non-smoking salesperson, 21 years status-post multiple blunt trauma to the right chest, and two years status-postoperative left modified radical mastectomy for extensive intraductal carcinoma without evidence of lymphatic metastases, was identified on a routine chest radiograph to have a 3.5 x 3.5 x 5.0 cm well-demarcated right middle lobe solitary pulmonary nodule. Bronchial washings and bronchial brushings were negative for malignancy, as were a transbronchial biopsy and fine needle aspiration biopsy. A right middle lobectomy was performed. Your section is from a 3.5 cm well-demarcated grayish-white mass in the right middle lobe.

RADIOGRAPHS:

PA (A) and lateral (B) radiographs show a lobulated, homogeneous, non-calcified right middle lobe mass (arrows), 4 x 6 cm. Principal diagnostic considerations besides primary lung tumor (hamartoma, carcinoid, adenocarcinoma) are metastasis and arteriovenous malformation. Incidental findings are healed right rib fractures. (Apparent pleural thickening on the left side is actually overlap of the arm.)
CLINICAL ABSTRACT:

A 58-year-old man with an 84 pack-year history of cigarette smoking, a history of chronic obstructive pulmonary disease, large granular cell lymphocytic leukemia, chronic neutropenia and rheumatoid arthritis, was found on a routine chest radiograph to have an enlarging 1.5 cm mass in the right upper lobe. Bronchoscopic examination, bronchial biopsies, bronchial washings, and bronchial brushings were negative for malignancy. A right upper lobectomy was performed. Your section is from a well-circumscribed 1.5 cm mass in the right upper lobe.

RADIOPHGRABS:

Lateral radiograph (A) and CT-scan (B) show a 5 x 3 cm irregular, spiculated mass (arrows) in the anterior segment of the right upper lobe. It abuts the chest wall and mediastinum, but there is not clear evidence of invasion. The mass is inhomogeneous on CT. There is no hilar or mediastinal lymph node enlargement. Principal diagnostic consideration besides primary lung tumor is granulomatous infection. Mediastinal tumor might be considered, but the borders of the mass are ill-defined, which argues that the lesion is pulmonary rather than mediastinal. Other findings are large lung volumes and bullae, indicating COPD.
CLINICAL ABSTRACT:

A 72-year-old woman with a 50 pack-year history of cigarette smoking, having quit smoking five years previously, underwent a wedge resection of a mass present in the left upper lobe in 1991. She received no post-operative chemotherapy or irradiation, and was well until approximately July of 1993 (22 months after the wedge resection) when she presented with a 35-lb weight loss, and was found to have a massive left pleural effusion and hepatic metastasis. She is currently receiving chemotherapy. Your section is from the 2.5 cm mass in the wedge resection from the left upper lobe.

RADIOGRAPHS:

No films available.
CLINICAL ABSTRACT:

A 75-year-old man with a 75 pack-year history of cigarette smoking and a history of exposure to asbestos presented with fever and intermittent left-sided pleuritic chest pain. A chest radiograph showed a heterogeneous left upper lobe infiltrate. The patient had a slight degree of blood-tinged sputum but no frank hemoptysis. His past medical history was significant for an abdominal aortic aneurysm and chronic but stable angina pectoris. Besides the left upper lobe infiltrate, a CT-scan showed a right upper lobe infiltrate and marked mediastinal adenopathy. Mediastinoscopy and biopsy were performed and a diagnosis made. The patient was treated with four cycles of chemotherapy but showed no regression of his tumor. He died approximately 4 months after diagnosis. Post-mortem examination showed the right lung to weigh 1250 grams and to contain a large grayish-white tumor involving the right upper lobe with infiltration into the bronchial wall, and massive infiltration into the right bronchopulmonary, right hilar and mediastinal lymph nodes. The autopsy showed metastatic tumor in the brain, bones, adrenal gland and liver. Your section is from the right upper lobe mass.

RADIOGRAPHS:

PA radiograph (A) and CT-scan (B) show an ill-defined, inhomogeneous right upper lobe mass (arrows) abutting the pleura. There is not clear evidence of invasion of the chest wall. There is hilar and mediastinal lymph node enlargement (arrowheads). Other findings are emphysema, some coarse scarring in the right mid lung, and cardiac and aortic enlargement. A radionuclide bone scan showed several lesions consistent with metastases to the ribs, spine, and calvarium. Besides primary lung tumor, the only diagnostic consideration is fungal infection or actinomyces infection. Metastatic tumor would usually not have such ill-defined borders.
CLINICAL ABSTRACT:

A 62-year-old man had been in excellent health until March 1993, when he developed a right lower lobe pneumonia that was treated with antibiotics, with resolution of his cough, fever and sputum production. A follow-up chest radiograph showed resolution of the right lower lobe pneumonia, although it was noted that there was a persistence of a right lower lobe density in the posterior portion of the lobe. This abnormality persisted, and was described as an oval area of homogeneous density abutting the posterior pleura at the right lung base, slightly above the costophrenic angle. It was associated with a small pleural effusion. A CT-scan obtained on July 23, 1993, showed a number of small nodular densities in the mediastinum, suggesting lymphadenopathy. Bronchoscopy was performed and biopsies were taken, which were diagnosed as showing abnormalities suggestive of a lung cancer. His abnormality persisted, and he was referred to a surgeon who, on August 3, 1993, performed a right posterolateral thoracotomy and right lower lobectomy. At surgery, 300 cc of serosanguineous pleural fluid were identified, as well as several inflammatory pleural adhesions, and a mass in the posterior basal segment of the right lower lobe. The lobe measured 10.5 x 9.5 x 5.0 cm, and contained a poorly circumscribed area of consolidation measuring 3.5 cm. Your section is from the area of consolidation in the right lower lobe.

RADIOGRAPHS:

Lateral radiograph (A) and CT-scan (B) show an ill-defined, inhomogeneous mass (arrows) in the right lower lobe. There is also some posterior and lateral pleural thickening. There is no lymphadenopathy. Besides primary lung tumor, diagnostic considerations include fungal infection, scar from remote infection or infarction, round atelectasis, and sequestration.
CLINICAL ABSTRACT:

A 66-year-old, cigarette-smoking man was found to have a mass in the left lower lobe. A left lower lobectomy was performed that contained a 3.0 x 2.5 x 2.5 cm gray-white nodule with no apparent communication to the closest bronchus. The remainder of the lobe showed no other tumors, and no other significant changes. Your section is from the left lower lobe nodule.

RADIOGRAPHS:

CT-scan shows a lobulated, sharply marginated 3 x 3 cm mass (arrow) in the left lower lobe. There is no hilar or mediastinal lymph node enlargement. Other findings include large lung volumes, suggesting COPD, and enlargement of the central pulmonary arteries, suggesting pulmonary arterial hypertension. The sharp definition suggests carcinoid, adenocarcinoma, hamartoma, or metastasis. The central location favors carcinoid.
CLINICAL ABSTRACT:
A 79-year-old man was in his usual state of health when he presented for a routine physical examination in 1990. As part of that evaluation, a chest radiograph was taken that showed a left lower lobe solitary pulmonary nodule. The patient gave no history of excessive coughing, shortness of breath, chest pain, or hemoptysis, and denied anorexia or weight loss. He had no known history of tuberculosis and had a negative PPD. He had an approximate 100 pack-year history of cigarette smoking, and had worked at Puget Sound Naval Shipyards as a shipfitter for many years, during which time he was exposed to asbestos. He was evaluated by a pulmonologist, and a flexible fiberoptic bronchoscopy was positive for a non-small cell carcinoma. The patient underwent a left lower lobectomy. Your section is from a 4.5 cm spiculated mass in the left lower lobe.

RADIOGRAPHS:
PA radiograph shows an ill-defined, spiculated 5 x 3 cm mass (arrow) in the left midlung. There is questionable left hilar enlargement, which, if real, would indicate lymphadenopathy. Other findings are large lung volume, indicating COPD, and apical scarring (left greater than right), probably from remote infection, such as tuberculosis.
CLINICAL ABSTRACT:
The patient is a 73-year-old retired gold miner, fish processor and paper mill truck driver, with a 30 pack-year history of cigarette smoking who quit smoking in 1958. The patient had a possible history of exposure to asbestos, and presented with a 4.0 x 3.0 cm "infiltrate-like mass" in the left upper lobe. Review of previous chest radiographs showed the mass to have been present since November, 1989. On April 26, 1990, fiberoptic bronchoscopy was performed, which was followed by cervical mediastinal exploration with multiple lymph node biopsies and a left upper lobectomy. Your section is from the left upper lobe mass.

RADIOGRAPHS:
PA radiograph shows an ill-defined lesion (arrow) above the left hilum. There is no hilar enlargement to suggest lymphadenopathy. Since it has no sharp margins, the lesion resembles pneumonia more than tumor. However, some tumor types (bronchioloalveolar cell carcinoma) spread like pneumonia, from alveolus to alveolus, and thus have radiographic characteristics resembling pneumonia.
CLINICAL ABSTRACT:

A 62-year-old attorney had worked at the Puget Sound Naval Shipyard, beginning at age 15 (May, 1943) until September of 1946, from January, 1948, to September, 1950, and again during the summer months in the years 1951-1954. He worked primarily as an electrician and was exposed to asbestos insulation. He had a 38-52 pack-year history of cigarette smoking, but had quit smoking in 1970. In 1971, he was diagnosed as having an adenocarcinoma of the left upper lobe, which was successfully treated with left upper lobectomy on May 18, 1971. At the time of surgery, hyaline pleural plaques were identified involving the left parietal pleura. He was well until 1985, when he was diagnosed as having a metastatic adenocarcinoma in his brain which was resected and irradiated. In 1986 and 1987, he was diagnosed as having a right lateral lung density that was described as being vague. He was also diagnosed as having left pleural thickening that was thought to be due to the previous surgery. The left pleural thickening increased, and a mass developed in the left lower lung zone. The mass was biopsied, and post-operatively the patient had a steadily downhill course and died on September 24, 1990. Post-mortem examination showed a 12.0 x 7.0 x 5.0 cm cystic mucinous mass in the left lower lobe; your section is from this mass.

RADIOGRAPHS:

PA radiograph shows an ill-defined 3 x 4 cm left apical lung mass (arrow) projected behind the clavicle. There is no hilar lymph node enlargement. The right costophrenic angles is blunted, probably from solid pleural thickening from remote inflammation, but possibly from a pleural effusion. Besides primary lung tumor, the only differential consideration is tuberculous or fungal infection. Of tumors, adenocarcinoma is suggested by the peripheral location and the small size.
CLINICAL ABSTRACT:

A 29-year-old, non-smoking woman developed vague right-sided chest pain four years earlier. Chest radiograph at that time showed a well-demarcated mass in the right lower lobe. The patient refused surgery, and was followed clinically. A chest radiograph taken at age 29, four years after the lung mass was identified radiographically, showed enlargement of the mass with evidence of hilar and mediastinal adenopathy suggestive of metastatic tumor. A right thoracotomy and wedge resection of the mass were performed. Macroscopically, the tumor was grayish-tan, well-demarcated, and about 4.0 cm in maximum dimension. Hilar and mediastinal lymph nodes were involved by tumor. Your section is from the well-demarcated mass.

RADIOGRAPHS:

PA (A) and lateral (B) radiographs show a well-defined, homogeneous 5 x 6 cm right lower lobe mass (arrows), partly hidden by the heart on the PA view. There is no lymphadenopathy. Besides tumor (hamartoma, carcinoid, adenocarcinoma), diagnostic considerations include solitary metastasis, lung cyst, and sequestration. The suggestion of a medial border separating the mass from the mediastinum argues that the lesion arises in the lung rather than the mediastinum.
CLINICAL ABSTRACT:
A 44-year-old woman had a history of rheumatoid arthritis and progressive anemia, thought to be due to iron deficiency. She had a 60+ pack-year history of cigarette smoking, and presented with severe productive cough. She had severe exertional dyspnea and night sweats but had no documented fever. P/A and lateral chest radiograph showed a huge mass in the right upper lobe, with an air-fluid level. A chest CT-scan showed a 12-15 cm mass that was diagnosed radiographically as an abscess. A metastatic evaluation showed no evidence of metastatic tumor, and a right pneumonectomy was performed. The right upper lobe was nearly completely replaced by an abscess, with firm grayish-white tissue present toward the hilar region of the lobe; the entire mass measured about 10.0 cm in greatest dimension. The bronchopulmonary, hilar and mediastinal lymph nodes that were taken at the time of surgery showed no evidence of metastatic tumor. Your section is from the right upper lobe mass.

RADIOGRAPHS:
PA radiograph shows a large right upper lobe cavity with fluid level (arrowheads) replacing most of the lobe. The wall of the cavity is thick and lobulated, suggesting tumor. Centrally, along the mediastinum, there is a lobulated mass. This mass could be part of the wall of the cavity, or it could represent, at least in part, mediastinal lymph node enlargement. The findings are consistent with a cavitated, possibly infected, lung tumor, which, in view of its large size, would likely be a large cell carcinoma. The findings could also be explained as a lung abscess, which might have been caused by a smaller, central (squamous) tumor that had obstructed the right upper lobe bronchus.
CLINICAL ABSTRACT:

An 85-year-old retired marine machinist at Puget Sound Naval Shipyard, with a 60+ pack-year history of cigarette smoking and a history of chronic obstructive pulmonary disease and asbestos exposure, over the last several months was noted to have a left retrocardiac lung mass. This had been slowly increasing in size, and a CT-scan confirmed the presence of a 2-3 cm mass in the medial basilar segment of the left lower lobe of the lung. There was no evidence of mediastinal adenopathy, and bronchoscopy was performed that did not show any endobronchial masses. The patient had a family history of cancer. He had had a previous transurethral resection of the prostate, and had a resection of a bladder carcinoma. Wedge resection of the left lower lobe mass was performed, and a frozen section of the tumor was thought to possibly represent squamous cell carcinoma. A completion left lower lobectomy was performed. Further medical history indicated the patient had a lentigo maligna removed from his right cheek two years ago, and also had several pigmented skin lesions that were thought to represent seborrheic keratoses. Your section is from a 3.0 cm left lower lobe mass.

RADIOGRAPHS:

CT-scan shows a solitary, well-defined, homogeneous, 3 cm mass (arrow) medially in the left lower lobe. The lesion could represent a primary lung tumor, such as carcinoid, hamartoma, or adenocarcinoma. It could be a solitary metastasis. Besides tumor, other, less likely, diagnostic considerations include granuloma and cyst. Incidental findings include large lung volume, suggesting COPD.
CLINICAL ABSTRACT:

A 71-year-old retired steamfitter with a history of asbestos exposure and a 55 pack-year history of cigarette smoking, who quit smoking in January of 1993, was diagnosed clinically as having mild chronic obstructive pulmonary disease, benign prostatic hypertrophy, and chronic leukocytosis of uncertain etiology. A routine chest radiograph showed a 2.0 cm diameter mass in the posterior segment of the right upper lobe abutting the pleura. No other masses were identified, and there was no evidence of mediastinal adenopathy. A wedge resection was done that showed a 2.0 cm diameter subpleural mass that extended through the thickened visceral pleura. The bronchial margin of resection was free of tumor, and the bronchopulmonary and hilar lymph nodes showed no evidence of metastatic tumor. The pulmonary parenchyma showed mild interstitial fibrosis with asbestos digestion analysis showing 640 asbestos bodies per gram of wet lung tissue; your section is from the right upper lobe mass.

RADIOGRAPHS:

PA radiograph shows a well-defined, 2.5 cm mass (arrow) in the right upper lobe. There is no hilar or mediastinal lymphadenopathy. The peripheral location and the small size suggest adenocarcinoma as the most likely tumor type. Other diagnostic considerations include granuloma.
CLINICAL ABSTRACT:

A 59-year-old woman with a history of rheumatic heart disease and congestive heart failure, and who had a 34 pack-year history of cigarette smoking, having quit smoking five years ago, presented with clinical evidence of chronic obstructive pulmonary disease, a recurrent supraventricular tachycardia, systemic lupus erythematosus, steroid-induced diabetes mellitus, and a history of right breast cancer in 1969, status post-operative modified radical mastectomy. In April, 1989, she presented with chest discomfort, facial rash, hair loss and arthralgias, and a single episode of hemoptysis. A chest radiograph showed a 6.0 x 4.5 x 4.0 cm homogeneous lobulated mass in the superior segment of the left upper lobe. A left lower lobectomy was performed that contained a 6.5 x 6.0 x 4.5 cm mass in the mid-lateral portion of the left lower lobe, with focal extension of the tumor through the visceral pleura. Your section is from the left lower lobe mass.

RADIOGRAPHAS:

PA radiograph (A) and CT-scan (B) show a 5 x 6 cm, ill-defined left lower lobe mass (arrows). The mass is inhomogeneous on CT, and contains air bronchograms. It abuts the pleura, which is thickened, but there is no clear invasion of the chest wall. There is no enlargement of hilar or mediastinal lymph nodes. Of primary lung tumors, adenocarcinoma or large cell carcinoma would be most likely, given the peripheral location. Besides tumor, the principal diagnostic consideration is fungal infection. Incidental findings include cardiac enlargement, prosthetic aortic and mitral valves, and minimal scarring in the right lung base.
CLINICAL ABSTRACT:

A 62-year-old, non-smoking woman presented with back pain. A chest radiograph showed a left lung mass, and a CT-scan showed a 3.0 cm pleural-based mass in the left lower lobe. The patient had no symptoms of shortness of breath, dyspnea on exertion, hemoptysis, anorexia or weight loss. Physical examination was normal. Bronchoscopy was done, followed by left video-assisted thoracoscopic and wedge resection of the left lower lobe mass. Your section is from the 3.0 cm pleural-based mass.

RADIOGRAPHS:

CT-scan shows a sharply marginated, peripheral, 3 cm mass abutting the posterior left pleura. Its margin has enhanced with the injection of contrast agent. There is no hilar or mediastinal lymphadenopathy. It is not clear whether the mass arises in the lung or in the pleura. Favoring lung origin is the lack of displacement of adjacent lung vessels and the acute angles at the pleural margins. Favoring pleural origin are the sharp definition of the edges and the broad base against the pleura. The differential diagnosis for a lung lesion includes primary tumor (especially adenocarcinoma, given the peripheral location), solitary metastasis, granuloma, indolent infection (such as cryptococcosis), and organized infarct or infection. The differential diagnosis for a pleural lesion includes primary fibrous tumor, metastasis, and, less likely, residuum from remote infection or hematoma.
CLINICAL ABSTRACT:
In July, 1992, a 60-year-old man developed right-sided chest pain while doing yard work and was thought to have "pulled" a muscle. He complained of a non-productive cough over the next several weeks that resulted in shortness of breath. A chest radiograph and CT-scan showed an extensive right pleural process with diffuse right pleural thickening and calcifications. A right thoracotomy, right pleural biopsy, and partial right pleurectomy were performed. The patient continued to have pleural pain, and survived approximately 9 months, expiring in April, 1993. Post-mortem examination showed nearly complete encasement of the right lung by a neoplasm that invaded into the mediastinum and involved bronchopulmonary, hilar and mediastinal lymph nodes. Your section is from the tumor that encased the lung, obtained at autopsy.

RADIOGRAPHS:
PA radiograph (A) and CT-scans (B,C) show extensive right pleural disease, composed of fluid and lobulated soft tissue elements. The soft tissue lobulation (arrows) is strongly suggestive of tumor, either metastatic or primary (mesothelioma). There are a few pleural calcifications on the initial CT-scan (B), but they become much more marked on the second CT-scan (C), performed four months later. Such calcifications could be dystrophic or metastatic, or they could result from formation of cartilage or bone. Other findings include enlargement of mediastinal lymph nodes, suggesting tumor metastasis, and questionable contiguous spread of pleural tumor into mediastinal fat. An incidental finding is left mediastinal lymph node calcification, likely from a remote granulomatous infection.
CLINICAL ABSTRACT:

A 72-year-old, non-smoking man noted the gradual onset of left subcostal pain over a two-month period. Chest radiograph and CT-scan of the chest showed a 10.0 cm well-demarcated mass in the left lower lobe that was stated to be pleural based, without evidence of hilar or mediastinal lymph node involvement. The patient had a history of asbestos exposure for 2-3 years in the 1950's and had a history of stage I-A prostatic adenocarcinoma. He had experienced a left pleural effusion about five years previously that spontaneously regressed. A left thoracotomy showed extensive left pleural adhesions and hyaline pleural plaques involving the diaphragmatic surface. A large tumor was found in the left lateral posterior portion of the thoracic cavity, and a left lower lobectomy and resection of the tumor were performed. The tumor measured 10.0 cm in maximum dimension and weighed 320 grams, being grayish-white and firm. Approximately 8 months later, the patient developed left-sided chest pain, and chest radiograph showed massive recurrence of the tumor, with infiltration into the chest wall and lung. The patient was treated with combination chemotherapy, and expired in about 3 months. The tumor metastasized to mediastinal, cervical and retroperitoneal lymph nodes, adrenal glands, pericardium, myocardium, brain and kidneys. Your sections are from the initial surgical resection specimen and from the autopsy specimen.

RADIOGRAPHS:

PA radiograph (A) and CT-scan (B) show a 5 x 10 cm lobulated mass (arrows) in the left lower lobe. The mass is inhomogeneous, and its rim is enhanced with contrast. It abuts the pleura, and there is adjacent pleural thickening; there is possible chest wall invasion. There is no hilar or mediastinal lymph node enlargement. Liver and adrenal glands are normal. A radionuclide bone scan showed rib lesions consistent with metastasis. The large size of the mass and the peripheral location suggest large cell carcinoma as the most likely primary tumor type. Metastasis is unlikely to be so large. Besides tumor, the only other diagnostic consideration is infection with fungus or an actinomycete.
CLINICAL ABSTRACT:

A 96-year-old man presented with a right pleural effusion and shortness of breath. Thoracentesis was performed, and pleural fluid was negative for malignant cells. A thoracoscopic pleural biopsy was done, and a biopsy was taken. The patient was treated conservatively and died two months after the initial pleural biopsy. At autopsy, there was partial encasement of the right lower lobe by a ring of grayish-tan tumor. There was evidence of metastatic tumor in the right hilar lymph nodes. Your section is from the tumor encasing the lung, identified at autopsy.

RADIOGRAPHS:

PA radiograph shows a moderate right pleural effusion. There is extensive bilateral calcified pleural plaque, indicating asbestos exposure. There is no visible nodular component to the pleural disease in the right hemithorax to suggest that the effusion is malignant, but tumor - either metastatic or primary (mesothelioma) - remains the first consideration. Other explanations for the pleural effusion include benign asbestos pleurisy, infection, and infarction. Incidental findings are cardiomegaly, and enlargement and calcification of the aorta.
CLINICAL ABSTRACT:
A 39-year-old man was in good health until November, 1992, when he presented with right shoulder pain. A chest radiograph showed a right perihilar mass. Flexible fiberoptic bronchoscopic examination was performed, and no endobronchial tumor was identified. Cytologic preparations made from a percutaneous needle biopsy under CT-guidance revealed abnormal cells. A CT-scan of the chest was stated to show a pleural mass measuring approximately 11.0 x 14.0 x 12.0 cm, extending to the hilar structures and to the diaphragm, but without any evidence of invasion of these structures. The patient had a 15 pack-year history of cigarette smoking, and was an unemployed aircraft mechanic. His pulmonary function tests were within normal limits. He was diagnosed clinically as having a right pulmonary mass. A thoracotomy was performed, and the mass was predominantly mediastinal in distribution; your section is from tissue taken at thoracotomy.

RADIOGRAPHS:
PA (A) and lateral (B) radiographs and CT-scan (C) show a huge mass (arrows) in the base of the right hemithorax. It is not clear whether the mass arises from the lung, the mediastinum, or even the basal pleura. The fact that the mediastinum is not displaced away from the mass and that the right side of the heart is compressed by the mass implies that the mass arises from the mediastinum. The mass compresses the right lung as well. There is mediastinal lymph node enlargement. On CT-scan, the mass is inhomogeneous. If the lesion arises in the mediastinum, the large size favors germ cell tumor. If it arises in the lung, the large size favors large cell carcinoma. Other considerations include lung sarcoma and fibrous tumor of the pleura.
CLINICAL ABSTRACT:

A 47-year-old man presented with fever of undetermined origin (highest temperature 103° Fahrenheit). He had a 10 lb. weight loss, and a chest radiograph showed multiple nodular infiltrates. A fine needle aspiration biopsy was done of one of the nodules, but the material was non-diagnostic, and an open lung biopsy was subsequently performed. A diagnosis was made from the open lung biopsy specimen, and the patient was treated with chemotherapeutic agents but had a rapidly downhill course, dying about 7 months later. The autopsy lungs were heavy, and contained multiple grayish-white, focally necrotic nodules ranging from 1.5 to 5.0 cm in diameter. They were present most notably in the lower lobes in a subpleural location. Similar nodules were also identified in the kidneys. Several nodules were radiographically identified in the brain. Your section is from one of the nodules in the autopsy lung specimen.

RADIOGRAPHS:

PA radiograph (A) and CT-scan (B) show multiple, ill-defined lung nodules and patchy consolidation, concentrated at the bases. A CT-scan through the kidneys showed bilateral renal masses. The "air-space" characteristic of the lung nodules suggests infection (septic emboli or fungus) or certain tumors, such as bronchioloalveolar cell carcinoma or lymphoma. Lymphoma-like conditions such as pseudolymphoma or lymphomatoid granulomatosis are other possibilities. Some other causes of large, indistinct lung nodules include sarcoidosis, histiocytesis X and BOOP.
CLINICAL ABSTRACT:

A 44-year-old woman was initially identified as having what was thought to represent an anterior mediastinal mass. A fine needle aspiration biopsy of the mass was done, and a diagnosis of a large cell malignant neoplasm was made, with the differential diagnosis including germ cell neoplasm and thymoma. The attending surgeon proceeded with a resection of what was thought to be a probable thymoma, and after performing a median sternotomy, visualized the tumor and noted that it was far less in the anterior mediastinum and much more in the right hilar area, and in fact, most of the mass involved the pulmonary parenchyma. In the resected right upper lobe was a 6.8 x 5.5 x 4.5 cm grayish-tan, relatively well-demarcated, somewhat irregularly-shaped mass. The mediastinal soft tissue and thymic tissue were dissected, and consisted of fibroadipose tissue containing a few lymph nodes, and tissue consistent with thymus. Your section is from the right upper lobe mass.

RADIOGRAPHS:

CT-scan shows an inhomogeneous mass (arrow) anteriorly in the right hemithorax. It is more likely a lung lesion than a mediastinal mass, in view of its somewhat irregular margin and the location of its center. It has an ill-defined margin against the mediastinum, which suggests invasion of the mediastinum. It does not appear to invade the anterior chest wall. The most likely diagnostic consideration is a primary lung cancer, and I would favor adenocarcinoma or large cell carcinoma.
CLINICAL ABSTRACT:
A 64-year-old with a 50+ pack-year history of cigarette smoking had a routine chest radiograph that showed a nodule in the left upper lobe. This nodule measured about 1.5 cm in diameter, and there was no evidence of other abnormalities in the lungs, and no evidence of hilar or mediastinal abnormality. A wedge resection of the nodule present in the left upper lobe was performed. Your section is from this nodule.

RADIOGRAPHS:
PA radiograph shows a solitary, small (about 1.5 cm), non-calcified nodule in the left lung apex. Differential diagnosis is lung cancer or granuloma.
CLINICAL ABSTRACT:

A 35-year-old gay, HIV-negative man had no risk factors for the development of AIDS for the last 8 years. He developed fever, night sweats and weight loss, and radiographically was found to have a right upper lobe lung mass that was relatively well-demarcated. The right upper lobe measured 20.0 x 11.0 x 7.0 cm, and weighed 454 grams, with the lower half of the lobe being almost completely consolidated, and the pleural surface covered by shaggy fibrovascular adhesions. On sectioning, the lower lobe was composed of rock-hard, yellow-brown to grayish tissue, with areas of necrosis and possible golden-tan post-obstructive pneumonia. Your section is from an area of consolidation in the lower portion of the right upper lobe.

RADIOGRAPHS:

CT-scan shows a large, inhomogeneous mass (arrow) in the medial right lung. The mass clearly involves the lung, since the right upper bronchus extends into it. It likely has arisen in the lung, but it may have arisen in the right side of the mediastinum and then grown out into the lung. There is lymph node enlargement in the right hilum and in the middle mediastinum. There is also mediastinal invasion by the tumor, as indicated by the effacement of the mediastinal pleura and the linear radiation of the tumor through the mediastinal fat. Right pleural effusion is present. The findings suggest a non-obstructing lung tumor with secondary involvement of the mediastinum. Small cell carcinoma is a strong possibility, given the bulkiness of the tumor and the central location. Lymphoma is also a consideration for a lesion that extends into both lung and mediastinum.
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ADDENDA

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June 5, 1994
The Westin South Coast Plaza
Costa Mesa, CA
Introduction

Lung cancer is the most frequently diagnosed malignant neoplasm throughout the world, and currently is the number one cause of cancer death in the United States. Not only is it the number one cause of death in males, in most states it is the number one cause of death in females, having surpassed breast cancer. Lung cancer is stated to cause about 25% of all cancer deaths, and 6% of all deaths in the United States. In 1991, an estimated 161,000 people were diagnosed as having lung cancer in the United States. The vast majority (90-95%) of lung neoplasms are of the four major types or variations thereof; namely, adenocarcinoma, squamous cell carcinoma; large cell undifferentiated carcinoma and small cell undifferentiated carcinoma. The vast majority of lung cancers in the United States (approximately 85%) are thought to be caused by the carcinogens present in cigarette smoke. As all pathologists know, it is impossible to determine the cause of a lung cancer from its histologic appearance.

Staging of Lung Cancer

There have been many studies evaluating the prognosis of lung cancers. The single most important factor in determining prognosis is the anatomic stage of the neoplasm. There are numerous publications concerning the staging of lung cancer.¹ As one might expect, there are differences between the pathologic staging of lung cancer and the clinical staging of lung cancer, with the clinical staging being less accurate. In my practice as a pathologist, I try to state in the comment to my report the anatomic stage of a primary lung neoplasm based on the pathologic findings. This staging is based on the assumption that there is no evidence of metastatic disease outside of the chest, and the "M" designation is always "0". A fairly useable graphic illustration of the currently-accepted stages of lung cancer is shown in Fig. 1. If the pathologists do not want to indicate the anatomic stage of a tumor in their report, they should try to provide the necessary information in the pathology report, specifically in the diagnosis, that allows for the anatomic stage to be determined. In our hospital, we require that a staging form be filled out on all patients with lung cancer, as well as other types of neoplasms.
The Histologic Classification of Lung Cancer

The second edition of the World Health Organization, Histologic Typing of Lung Tumors was published in 1982.\(^2\) Their classification for malignant lung neoplasms is shown in Fig. 2.

The histologic criteria that we use for diagnosing common malignant lung neoplasms is shown in Fig. 3. If these histologic criteria are accurately employed, there should be a fairly good inter-observer correlation between pathologists evaluating the same slides. There have been several studies evaluating the inter-observer variation in the diagnosis of common lung neoplasms. The attendees of this conference are referred to the articles by Feinstein, et al.,\(^3\) Vincent, et al.,\(^4\) Larsson, et al.,\(^5\) Watkin, et al.\(^6\) that discuss this issue. In my experience, the greatest inter-observer variability occurs in the classification of certain neuroendocrine neoplasms of the lung, specifically atypical carcinoid and large cell neuroendocrine carcinoma.

Keene, et al.\(^7\) recently studied the reproducibility of major diagnoses in a bi-national study of lung cancer in uranium miners and atomic bomb survivors; these authors studied 208 neoplasms and an average of 3 sections examined per case, with each neoplasm being classified using the revised World Health Organization scheme for the classification of lung cancers (Fig. 2). 58% of their case material was from autopsies, 20% from surgical resections, and 22% from biopsy specimens. Agreement by 6 of 8 observers was required for a consensus. A consensus diagnosis with respect to the major diagnosis was obtained in 78% of all cases. Agreement was best for small cell carcinoma (72% agreement), intermediate for adenocarcinomas (56% agreement) and squamous carcinomas (48% agreement). Inter-observer agreement was extremely poor for large cell undifferentiated carcinoma, in which there was only 4.8% of inter-observer agreement. A consensus was also infrequently obtained for tumor subtyping, such as that observed in adenocarcinoma. Roggli, et al.\(^8\) had performed a somewhat similar study in 1985, in which five pathologists examined sections from 100 consecutive cases of lung cancer; 65% of their cases were from autopsies and 35% from surgically resected specimens. An average of ten sections of each tumor or all of the tumor was evaluated by five pathologists, and agreement by three of five pathologists was required for a consensus diagnosis. Consensus diagnosis of 94% was reached in the cases of non-small cell carcinoma, and 93% of small cell carcinoma. The most inter-observer variability in diagnosis was for the group of bronchioloalveolar cell carcinoma. Roggli, et al.\(^8\) also found a significant degree of lung cancer heterogeneity, in that 45% of the 100 consecutive cases showed major heterogeneity as defined by one slide showing a major histologic type different than that seen in one other slide. Adelstein, et al.\(^9\) reported that 10% of 176 small cell carcinomas showed a non-small cell component.
Pleural Neoplasms

Compared to primary pulmonary neoplasms, primary pleural neoplasms are relatively uncommon. The most frequently-observed primary pleural neoplasms is a mesothelioma. Currently, about 1500-2000 new cases of mesothelioma are diagnosed each year in the United States. In my experience, which may be somewhat biased because of my location in a shipyard community, there appears to be an increased incidence of mesothelioma. This may represent an increased awareness of this type of neoplasm, and an increased ability to diagnose mesothelioma based on immunohistochemical and ultrastructural analysis of the neoplasm.

Other primary pleural neoplasms include localized fibrous tumors of the pleura, primary pleural sarcoma and lymphoma.

Neuroendocrine Neoplasms of the Lung

The first four cases presented in this conference comprise neuroendocrine neoplasms of the lung, and a brief introduction to these neoplasms is appropriate. The basic concept is that neuroendocrine neoplasms of the lung are derived from normal neuroendocrine cells that occur within the lung. The concept of neuroendocrine cells can be traced to the late 1930s, when Feyrter referred to epithelial clear cells as part of a diffuse epithelial endocrine system that had similar morphologic and biochemical features. These cells were subsequently referred to as APUD cells, based on their ability to take up and decarboxylate amine precursors, such as 3,4-dihydroxyphenylalanine and 5-hydroxytryptophan. Pearse initially conceptualized that all neuroendocrine cells were of neural crest origin, and as many pathologists remember, the term neurocristopathy was introduced as an encompassing term of abnormalities (primarily neoplasms) of these cells. Over the years, a great deal of information accumulated, indicating that not all neuroendocrine cells were of neural crest origin. Pearse and Takor later suggested that neuroendocrine cells had three derivations: (1) derivatives of neural crest, which included the adrenal medulla, all paraganglion cells, parafollicular C-cells of the thyroid, melanocytes and possibly Merkel cells of the skin; (2) derivatives of neural tube and ridge-derived cells, which included the neuroendocrine cells in the epiphysis, hypophysis and hypothalamus; and (3) derivatives of neuroendocrine-programmed ectoblast, which included the neuroendocrine cells of the gastroenteropancreatic system, the bronchopulmonary tree, the parathyroid chief cells, placental endocrine cells, and various other related cells. Pearse introduced the term "diffuse neuroendocrine system" to refer to these cells, and later Gould, et al. suggested the term "dispersed neuroendocrine system" to refer to these cells (Fig. 4).
Neuroendocrine cells and the cells forming neuroendocrine neoplasms can be potentially identified by several different methods:

1. Histochemical identification: argyrophilic stains [Grimelius or Sevier-Munger silver nitrate stain];
2. Immunohistochemical-biochemical identification: neuron-specific enolase, chromogranin, neurofilament, synaptophysin;
3. Ultrastructural cytochemistry: uranaffin reaction;
4. Transmission electron microscopy: neuroendocrine granules;
5. Biochemical techniques: identification of various amines, polypeptides or other neuroendocrine substances;

The nomenclature of neuroendocrine neoplasms of the lung is shown in Figure 5. As one can see, there are several synonyms for tumors that are referred to as atypical carcinoid, large cell neuroendocrine carcinoma, and small cell neuroendocrine carcinoma. The one type of neuroendocrine neoplasm that often creates the most controversy or the most misunderstanding is the atypical carcinoid. Clinicians who are not aware of the biologic behavior of this neoplasm often think the term "carcinoid" implies that this is a benign neoplasm, whereas we know this tumor can be aggressive and metastasize.

In 1882, Mueller described a bronchial carcinoid at post-mortem examination, and in 1980, Kramer described a bronchial carcinoid under the designation "adenoma of the bronchus". In 1937, Hamperl recognized the similarities between bronchial carcinoids and gastrointestinal carcinoids that had been described by Oberndorfer in 1907, who was credited for the term "carcinoid", which was a description for a carcinoma-like neoplasm.¹²

Most mature pulmonary carcinoids occur in large bronchi and are surfaced by bronchial mucosal epithelium. Bronchial carcinoid tumors are relatively uncommon, accounting for about 5% of all primary lung cancers. Approximately 10% of carcinoids arise in the mainstem bronchi, 75% in the lobar bronchi, and approximately 15% in the periphery of the lung, usually at a segmental bronchial level or beyond. As shown in Case 1, most carcinoid tumors are well circumscribed, and if more centrally located, can cause bronchial obstruction. Most carcinoids macroscopically are yellow-tan and well demarcated, and when they are within the larger bronchi, they often invade or extend into the adjacent parenchyma. They may show a wide range of histologic growth patterns, including a trabecular, insular, papillary, interstitial, solid, oncocytic, spindle or melanocytic growth pattern.
Case 1 Diagnosis: Spindle Cell Carcinoid

(Accession 27432)

Ranchod and Levine\textsuperscript{13} reported a clinicopathologic study of 35 spindle cell carcinoid lung neoplasms. Fifteen occurred in men, and twenty occurred in women, with an age range of 33-78 years (mean 57.6 years). Six of the neoplasms occurred in the right upper lobe, three in the right lower lobe, six in the left upper lobe, six in the left lower lobe, and the majority (ten) in the right middle lobe. The reason for this increased frequency of spindle cell bronchial carcinoids in the right middle lobe is unknown. In their series, the neoplasms ranged between 7 mm to 4 cm in greatest dimension, and 83\% were less than 2 cm in maximum dimension. The majority were located peripherally in the lung, being subpleural, and were composed almost entirely of spindle cells, frequently arranged in an organoid pattern. Twelve of their cases were evaluated by electron microscopy and found to contain dense core neuroendocrine type granules. In their series, 12 of the neoplasms were resected by wedge or segmental resection, and in 18 cases the tumor was removed via lobectomy. In two of seven cases in which lymph nodes were removed with the specimen, there was microscopic evidence of metastases. One patient also had a single focus of metastasis to bone. Twenty-two of the thirty-five patients were followed between one and thirteen years, and no other sites of metastasis were identified. None of the twenty-two patients followed died from their tumor.

Twenty of the thirty-five neuroendocrine neoplasms described by Travis, et al.\textsuperscript{14} were typical mature carcinoid tumors. The patients were stated to have a mean age of 46.4 years, and median age of 45 years. In their series, a large number (thirteen) of the carcinoid tumors were associated with Cushing syndrome, and hilar lymph node metastases were noted in four cases. Of the twenty patients with carcinoids, the only death that occurred was in a patient with ectopic ACTH syndrome, and that death was thought to be due to cardiac arrhythmia in the immediate postoperative period. The remaining nineteen patients were alive, with mean follow-up of 2.16 years. In the study from the Mayo Clinic, 90\% of patients with mature carcinoids were alive and well five years after pulmonary resection.\textsuperscript{15} There is some debate as to whether the presence of lymph node metastases is a bad prognostic finding; in some studies it seems to decrease the expected survival rate, while in other studies it has no correlation with survival rate.

The primary differential diagnosis in Case 1 is between a spindle cell carcinoma of the lung, most likely squamous cell carcinoma, a metastatic spindle cell melanoma, and a primary low-grade spindle cell sarcoma. Of these, spindle cell melanoma may closely resemble a spindle cell carcinoid.
Case 2: Diagnosis - Oncocytic Carcinoid

This case shows a histologic variant of mature carcinoid that can cause diagnostic confusion, unless one is aware of this neoplasm. An oncocytic variety of carcinoid was reported by Sklar, et al. in 1978, and since then, several reports of oncocytic bronchial carcinoids have appeared in the literature.

The primary differential diagnosis in such a neoplasm includes an adenocarcinoma, a primary oncocytoma of the lung, a metastatic tumor with oncocytic features such as metastatic renal cell or Hurthle cell carcinoma from the thyroid, and a primary carcinoma of the lung that has oncocytic features, which can occasionally be seen in all non-small cell type carcinomas.

The case reported by Santos-Briz, et al. discusses a rare type of neoplasm referred to as an oncocytoma. An oncocytoma of the lung is generally considered to be a benign lung neoplasm made up of oncocytes. Oncocytes can form the entire tumor, or can be a large component of the tumor. Oncocytes are thought to be derived from normal cells that undergo metaplasia, with an increased number of cytoplasmic mitochondria, with loss of other organelles from the cytoplasm. The exact cause of the increased number of mitochondria is uncertain. In this case the presence of neuroendocrine granules, and the positive staining for chromogranin and synaptophysin, proves that this tumor is an oncocytic carcinoid and not an oncocytoma.

Case 3: Diagnosis - Atypical Carcinoid (Malignant Carcinoid)

In 1972, Arrigoni, et al. reviewed their files of lesions that had been categorized as bronchial carcinoid, and described twenty-three neoplasms that they referred to as atypical carcinoid. Since then, a variety of reports have appeared in the literature concerning this type of neoplasm, and they have been variably referred to as malignant carcinoid, well-differentiated neuroendocrine carcinoma, peripheral small cell carcinoma of the lung resembling carcinoid tumor, and Kulchitsky cell carcinoma-II.

The description of atypical (malignant) carcinoids has been similar in all reports. More than 60% of these neoplasms occur in the periphery of the lung, and like mature carcinoids, they are usually yellow-tan and well demarcated. Histologically they often exhibit an organoid pattern, especially at their periphery. The nests of tumor cells are separated by fibrovascular septa, and there may be some palisading of the peripheral cell layer of these organoid nests. The neoplastic cells may occasionally show glandular formation, and in some instances, the neoplasms are mucicarmine positive.
Immunohistochemical studies show the neoplastic cells to immunostain for keratin, occasionally for vimentin, and routinely for neuron-specific enolase and synaptophysin. In about half of the cases, the neoplastic cells are positive for chromogranin and carcinoembryonic antigen.

Ultrastructurally, malignant carcinoids display great variability in size and may have hyperconvoluted nucleus and prominent nucleolus.

Several studies have discussed the differences between typical and atypical carcinoids. Yousem and Taylor studied twelve mature pulmonary carcinoids and eight atypical pulmonary carcinoids for DNA content by image analysis, and found that most mature carcinoids were diploid, whereas about half of the atypical carcinoids were aneuploid. However, they found no correlation between prognosis and DNA content in these neoplasms. In their study, all twelve patients with typical carcinoid were free of disease at follow-up, while five of the eight atypical carcinoids recurred, and three patients died of metastatic disease.

The primary differential diagnosis in these cases includes primarily mature carcinoid and small cell undifferentiated carcinoma of the lung. The distinction between mature carcinoid and atypical carcinoid is the presence of necrosis, greater cellular pleomorphism, greater mitotic activity, and areas of necrosis in the atypical carcinoid versus the mature carcinoid. There have been studies suggesting that atypical carcinoids behave in a much less aggressive manner than small cell undifferentiated carcinoma of the lung, although in my experience, many cases of atypical carcinoid that I have diagnosed have acted in an aggressive manner, usually causing death due to metastatic tumor.

**Case 4: Small Cell Neuroendocrine Carcinoma**

(Small Cell Carcinoma; Oat Cell Carcinoma)

(Accession 27468)

Small cell undifferentiated carcinoma constitutes about 20-25% of all lung neoplasms, and is often referred to as oat cell carcinoma or small cell neuroendocrine carcinoma. Historically, this neoplasm was initially thought to represent a sarcoma or a lymphoma, and it was not until 1926 that it was recognized as an epithelial neoplasm. It was initially classified with the large cell carcinomas of the lung as "anaplastic carcinoma." In 1982, World Health Organization classification of lung cancer divided small cell undifferentiated carcinoma into three categories: (1) oat cell carcinoma, which was referred to as "lymphocyte-like type of small cell carcinoma" in the
1967 classification W.H.O. classification of lung tumors, and was characterized by a tumor composed of small round uniform cells, 1 1/2 to 3 times larger than a lymphocyte; (2) small cell carcinoma intermediate cell type, characterized as being composed of polygonal or fusiform cells, less regular in appearance than oat cell carcinoma, having more cytoplasm than oat cell carcinomas; and (3) a combined oat cell carcinoma characterized by a combination of oat cell carcinoma and squamous cell carcinoma or adenocarcinoma.

Azzopardi's 1959 light microscopic description of oat cell carcinoma remains excellent, and this tumor was reviewed in detail by Yesner 32 and by Carter 33 in 1983. In 1985, Yesner and other members of the Pathology Committee for the International Association for the Study of Lung Cancer thought there was no significant biologic difference between the oat cell subtype and the intermediate subtype of small cell undifferentiated carcinoma. They suggested that the terms "oat cell", "lymphocyte-like" and "intermediate" be discarded, and be replaced with the term "small cell carcinoma" to refer to such undifferentiated tumors. 34 They further suggested that two variants of small cell carcinoma could be recognized: (1) mixed small cell - large cell carcinoma, a neoplasm composed of small cells with a significant proportion of large cells arranged in nests or diffusely present throughout the tumor; and (2) combined small cell, composed of a combination of small cell carcinoma and neoplastic squamous or adenocarcinoma.

Macroscopically, the vast majority of small cell undifferentiated carcinomas are centrally located in the lung, and in only about 10% of the cases are these neoplasms peripheral. These tumors have a tendency to invade and to metastasize early, most frequently to the bronchial lymph nodes, but also to the brain, bone and liver. As stated, they are composed of cells that histologically usually have a slightly spindle-shaped appearance, which when cut in cross section, appear round. As shown in this case, the neoplastic cells show a high mitotic rate and extensive areas of necrosis with lymphatic and vascular invasion.

**Case 5: Diagnosis - Adenocarcinoma Possibly Arising in Sequestered Lobe**  
*(Accession 27372)*

This case consisted of a region of lung tissue that showed extensive scarring and distortion of the architecture, with focal ossification. In the region of scarring, a moderately- to poorly-differentiated acinar adenocarcinoma was present. In one area of the section there appeared to be a region of in situ carcinoma in a relatively large bronchus. There was also a region of spindle cell proliferation, interpreted to probably be reactive and not part of the tumor. The person who submitted this case felt that the tumor was arising in a sequestered lobe.
Bronchopulmonary sequestration refers to a mass of pulmonary parenchyma that is anatomically separate from the normal lung, and has no connection with the bronchial tree. The intralobular type shares a common pleura with the normal lung. In this case, it was difficult to prove or disprove that the sequestration was present. Dr. Godwin commented that one can occasionally radiographically identify a vessel arising from the aorta that is the vascular supply to the sequestered lobe, although that could not be identified in this case. Savic, et al. reviewed 540 published cases of lung sequestration, and added seven cases of their own. In the 540 cases, one neoplasm was identified, and that was a squamous cell carcinoma.

Although the radiographic changes in this case suggested that the area of consolidation was confined to the right lower lobe, one must remember that there is an increased incidence of lung cancer, characteristically adenocarcinoma (bronchioloalveolar cell carcinoma most frequently) in cases of pulmonary fibrosis.

**Case 6: Diagnosis - Small Cell Adenocarcinoma**

*(Accession 27434)*

This case concerned a 66-year-old cigarette-smoking man, who was identified by chest radiograph to have a 3 x 2.5 x 2.5 cm mass in the left lower lobe. A left lower lobectomy was performed and showed a relatively well-demarcated mass that at low power microscopic evaluation was composed of small to medium-sized cells that exhibited an organoid pattern with a moderate number of areas of necrosis in the center of the nests of tumor cells. At higher powers of magnification, these tumor cells were polygonal and somewhat spindle shaped, and showed areas of nuclear molding and a moderately high mitotic rate, with up to 3-4 mitoses/hpf. The tumor cells had a high nuclear:cytoplasmic ratio, and the nuclei generally lacked nucleoli and had a somewhat salt-and-pepper type chromatin pattern.

By light microscopy this neoplasm was thought to most likely represent a neuroendocrine carcinoma, with the differential diagnosis being between an intermediate form of small cell carcinoma and an atypical (malignant) carcinoid. This neoplasm was studied by immunohistochemistry and electron microscopy. By immunohistochemistry the neoplastic cells expressed keratin, but showed no immunostaining for neuron-specific enolase, synaptophysin, or chromogranin-A. Ultrastructurally, the neoplastic cells appeared primitive with relatively few cytoplasmic organelles. In many areas these cells were forming small acini, with the cells being connected to each other by junctional complexes, and showing microvilli projecting into these acini. By electron microscopy this tumor was classified as a small cell adenocarcinoma rather than a neuroendocrine carcinoma, based on the glandular formation, the lack of neuroendocrine granules, and the absence of neuroendocrine cell immunohistochemical markers.
This type of neoplasm is uncommon. It may be analogous to neoplasms that Brambilla, et al. reported. These authors reported 38 examples of the neoplasm they referred to as basaloid carcinoma in a total of 671 resected lung tumors. They indicated that this type of tumor somewhat resembled a basal cell carcinoma of skin and exhibited a lobular growth pattern, composed predominantly of small cells with hyperchromatic nuclei. In 19 of the cases, the tumor had a pure basaloid morphology, whereas in the other 19 cases there was a mixed pattern with squamous cell carcinoma, adenocarcinoma and large cell undifferentiated carcinoma admixed with the basaloid component. Immunohistochemically the neoplastic cells usually did not show immunostaining for the typical neuroendocrine markers, and when they did, there were only a few cells that were staining. By electron microscopy the neoplastic cells showed no neuroendocrine granules but showed evidence of glandular and squamous differentiation. These authors raised the possibility that this tumor was derived from pleuripotential reserved cells or the basal bronchial epithelial stem cell. They indicated that in their series, the prognosis was poor, with median survival of 22 months for stage I and stage II disease.

In this case, the main difficulty is distinguishing this tumor from a neuroendocrine carcinoma, specifically an atypical (malignant) carcinoid. Immunohistochemistry and electron microscopy should be able to accomplish the differentiation of these two type of neoplasms, although it is not clear whether the so-called "basaloid" tumor described by Brambilla, et al. or the tumor that this author refers to as a small cell adenocarcinoma, respond to the therapy that is typically used in treating oat cell carcinoma. It is also uncertain whether this neoplasm should be treated with adjuvant chemotherapy/radiation therapy once it has been resected.

**Case 7: Diagnosis - Adenocarcinoma showing Variable Differentiation**

*Accession 27435*

This case concerns a 70-year-old man with a 100 pack-year history of cigarette smoking, and a history of exposure to asbestos, who was identified to have a 4.5-cm in diameter epiculated mass in the left lower lobe. A transbronchial biopsy was performed that identified a non-small cell carcinoma, and the biopsy was followed by a left lower lobectomy.

This tumor was not a problem from a diagnostic viewpoint, and was used to illustrate the significant histologic heterogeneity in pulmonary adenocarcinomas. In areas, this tumor was composed of cells that were forming distinct glandular structures, while in other areas the tumor had a bronchioloalveolar cell pattern, and in yet other areas exhibited a solid pattern. The clinician in this case was concerned that this neoplasm represented a large cell neuroendocrine carcinoma. This case was studied by electron microscopy and immunohistochemistry, and showed no features of neuroendocrine differentiation.
A relatively recently published study was performed by Sorensen, et al.\textsuperscript{45} concerning inter-observer variability in histopathologic subtyping and grading of pulmonary adenocarcinoma. This study evaluated 189 tumors that were stage III-A or stage IV; these were subtyped and graded by three panelists in a blind manner. The overall agreement for the panelists concerning the subtype and grade was only 41%. These authors concluded that the degree of agreement in subtyping and grading of adenocarcinoma of stage III-stage IV lung adenocarcinoma was low, and suggested that more objective criteria were needed before a prognostic impact of such variables could be assessed. They further indicated that the quality and quantity of the material available for subtyping obviously influenced the results, which was reflected in a better agreement when the histologic material was obtained by thoracotomy.

This inter-observer variability in subtyping and grading adenocarcinoma has also been observed by this author in the context of the Lung Cancer Study Group. However, when all members of the group abided by exactly the same criteria for subtyping and grading adenocarcinomas, there was a high degree of inter-observer agreement (>80%).

\textbf{Case 8: Diagnosis - Bronchioloalveolar Cell Carcinoma with Surfactant Production (Accession 27436)}

This case concerned a 72-year-old cigarette-smoking man with a rather complex occupational history, including a history of exposure to asbestos, who was found on routine chest radiograph to have a mass in the superior anterior bronchopulmonary segment of the right upper lobe. This mass was wedged out and a completion lobectomy performed. This tumor was composed of cuboidal to columnar epithelial cells that frequently showed cytoplasmic vacuolation, and overall were rather bland. Mitoses were virtually nonexistent. Not infrequently, there were large masses of eosinophilic material present within the spaces surrounded by these cells; the neoplastic cells in areas were in direct continuity with normal-appearing alveolar lining cells and were growing in a bronchioloalveolar pattern. This tumor was studied by electron microscopy and showed evidence of type II pneumocyte differentiation. Many of the nuclei contained intranuclear 45-nanometer in diameter tubules that were in contact with the inner nuclear membrane. These tubules have been identified by immunohistochemistry to stain with the antibodies against the apoprotein portion of surfactant. These nuclear inclusions are thought to be specific for a cell producing surfactant, and are seen in reactive type II pneumocytes as well as neoplastic type II pneumocytes. The dense extracellular eosinophilic material was composed of lamellar bodies and tubular myelin, thus representing surfactant. The vacuoles in the cells consisted of large aggregates of glycogen, and in many tumor cells one could see various stages of development of lamellar bodies. Based on the histologic and ultrastructural morphology of the tumor, it was thought to be best classified as a surfactant-producing bronchioloalveolar cell carcinoma of type II pneumocyte derivation.
Bronchioloalveolar cell carcinomas are a subtype of pulmonary adenocarcinoma that frequently have been shown by various techniques to be derived from Clara cells and type II pneumocytes. In 1960, Averill Liebow reviewed bronchioloalveolar cell carcinomas and offered the following definition of this neoplasm: "a well-differentiated adenocarcinoma primary in the periphery of the lung beyond a grossly-recognizable bronchus, with a tendency to spread chiefly within the confines of lung, by aerogenous and lymphatic route, the walls of the distal air spaces often acting as supporting stroma for the neoplastic cells". Dr. Liebow felt that an absolute distinction between a bronchioloalveolar cell carcinoma and a "ordinary" pulmonary adenocarcinoma could not be made, although emphasized the peripheral origin of the bronchioloalveolar cell carcinoma, the good cytologic differentiation, and the tendency to spread within the lungs. He also felt that to insist that the bronchioloalveolar cell carcinomas grow on the unaltered walls of alveoli without destruction or distortion of the pulmonary architecture caused confusion, since in some cases, one could see these changes to varying degrees.

The exact incidence of bronchioloalveolar cell carcinoma is unknown, although in this author’s experience, these neoplasms account for a significant number of peripheral pulmonary adenocarcinomas. Macroscopically they may occur as an isolated nodule, as multiple nodules, or as a diffuse pneumonic form. They have been reported to arise in the background of pulmonary fibrosis, such as that associated with idiopathic pulmonary fibrosis or collagen vascular-disease associated pulmonary fibrosis. Histologically they can be divided primarily into two forms, a mucinous and a non-mucinous form. In the mucinous form, the nuclei are usually at the base of the cells, with much of the cell being composed of membrane-bound mucus granules. In the non-mucinous form, no mucus granules are seen, and these cells often will show ultrastructural features of either Clara cells or type II pneumocytes.

One must always be aware of the possibility that a tumor in the lung that has a bronchioloalveolar cell pattern could represent a metastasis. One should also be aware of lesions referred to as either bronchioloalveolar cell adenoma or as alveolar adenoma, which occasionally can be confused with bronchioloalveolar cell carcinoma, or which can often coexist with bronchioloalveolar carcinoma.
Case 9: Diagnosis - Cystic Mucinous Adenocarcinoma

[Accession 27437]

This case concerns a 62-year-old man with a 38-52 pack-year history of cigarette smoking and a history of exposure to asbestos. In 1971, he was identified to have a left upper lobe mass that was diagnosed as a malignant neoplasm, and underwent a left upper lobectomy. In 1985, he was diagnosed as having a metastatic adenocarcinoma in the brain that had a similar appearance to the tumor that was resected in 1971 from the lung. In 1988 he developed right and left pleural thickening, and subsequently developed a 12 x 7 x 5 cm mass in the left lower lobe.

This neoplasm represents a relatively infrequent type of adenocarcinoma of the lung that has been referred to as a cystic mucinous tumor of the lung, a mucinous carcinoma of the lung, or a colloid carcinoma of the lung. This type of neoplasm usually presents as a solitary nodule, and macroscopically is often cystic, with large masses of mucinous material present within the cyst lumen. It can also have a somewhat gelatinous mucinous appearance, and look nearly identical to a colloid carcinoma of the breast.

Graeme-Cook and Mark reported on eleven patients with solitary pulmonary nodules in which mucus was the major histologic component of these nodules. They described cystic spaces that were lined by columnar mucus-producing cells with cytologic and architectural atypia varying from minimal to foci of microscopic carcinoma. They emphasized the relatively benign nature of these neoplasms. In their series there was no evidence of local recurrence or metastatic dissemination in 1 - 9.5 years followup (mean 4.7 years).

Moran, et al. described 24 cases of lung neoplasms they referred to as mucinous (colloid) carcinomas of the lung. In their series the tumors were circumscribed, soft, grey-tan mucoid masses measuring between 5 mm - 10.9 cm. In their series of cases they did not observe distinct cystic spaces. Histologically they described small clusters of atypical cells within intraalveolar pools of mucin, and foci of neoplastic columnar epithelial cells that lined some alveoli. In seven of their cases they found solid foci of welldifferentiated glands adjacent to the pools of mucin. In their follow-up of 19 patients between six days to sixteen years, two had died post-operatively and 11 of 17 were alive between 2-192 months (median 97 months).

In this author's opinion, cystic mucinous adenocarcinoma can be confused with metastatic colonic adenocarcinomas, and that diagnosis always has to be considered. When this author identifies such a tumor on transbronchial biopsy he will ask the clinician to determine if there is any evidence of a primary colon adenocarcinoma before a pulmonary resection is performed.
This case concerns a 29-year-old non-smoking woman who, in 1984, was identified to have a mass in her right lower lobe. She refused therapy and was lost to follow-up until 1988, when she presented with chest pain and a chest radiograph showed an increased size of the right lower lobe mass. A wedge resection of the right lower lobe mass was performed and biopsies of mediastinal lymph nodes were taken.

The mass was well demarcated, and composed of glandular structures made up of a pseudostratified layer of columnar epithelial cells, with clear cytoplasm and basally-located nuclei. Histologically the glandular structures resembled endometrial glands. In some areas there was a moderately-cellular spindle-cell stroma between the glandular structures, although this was infrequent. In other areas there was an undifferentiated neoplasm composed predominantly of small cells that had high nuclear:cytoplasmic ratios and resembled neuroendocrine cells. This neoplasm was studied by immunohistochemistry, and the undifferentiated cells showed immunostaining for neuron-specific enolase and synaptophysin. Ultrastructurally, these undifferentiated cells contained dense core neuroendocrine type granules, and the neuroendocrine nature of these granules was confirmed by the uranaffin stain.

This neoplasm represents an example of a pulmonary blastoma that is showing neuroendocrine differentiation. The term "pulmonary blastoma" was coined by Spencer in his 1961 publication of three cases. Dr. Spencer felt the neoplasm was analogous to a nephroblastoma. Barnett and Barnard had described a case of pulmonary blastoma in a 1945 publication of unusual neoplasms, and in 1952 Barnard described a case in which he named the tumor "embryoma of lung".

Pulmonary blastoma is a neoplasm composed of malignant epithelial tissue and mesenchyme that resemble the embryonal lung between 10-16 weeks gestation. These neoplasms are stated to recapitulate the pseudoglandular stage of pulmonary development. Kradin, et al and Kodama, et al described a predominantly epithelial variant of pulmonary blastomas which had been referred to by Naatori, et al as a pulmonary endodermal tumor resembling fetal lung. More recently, Yousem, et al reported on nine cases of pulmonary blastomas and compared the appearance of their cases to ten fetal lungs in the pseudoglandular stage of development. They subclassified pulmonary blastomas into epithelial, mixed, or primary mesenchymal types, and showed by immunohistochemistry that the neoplasm and embryonal lung displayed similar immunohistochemical features. In both instances they were able to identify scattered chromogranin-positive neuroendocrine cells. In addition, they identified rare cells that showed immunostaining characteristics for surfactant and Clara cell antigen.
In 1991, Koss, et al. compiled 52 cases of pulmonary blastoma that had been evaluated at the Armed Forces Institute of Pathology. In their study, they defined pulmonary blastoma as neoplasms composed of malignant mesenchyme or epithelium in which either one or both components resembled embryonal lung at 10-16 weeks gestation. They found that the tumor composed predominantly of epithelial elements and resembling fetal lung had a significantly better prognosis than those that had a biphasic appearance, or those that were composed predominantly of mesenchymal elements.

This case is somewhat unique in that there was a well-defined neuroendocrine neoplasm associated with the epithelial type of pulmonary blastoma. It is not surprising that this type of differentiation could occur, since neuroendocrine cells are first identified at approximately eight weeks in the fetal lung, and are easily seen between 10-16 weeks of gestation.

**Case 11: Diagnosis - Giant Cell Carcinoma**

*(Accession 27439)*

This case concerns a 44-year-old woman with a 60+ pack-year history of cigarette smoking, who presented with severe productive cough, exertional dyspnea, night sweats, and fever. She had a history of rheumatoid arthritis and severe anemia that was thought to be due to iron deficiency. A P/A and lateral chest radiograph showed a large mass in the right upper lobe, and by CT scan this mass measured between 12-15 cm in greatest dimension, and was thought radiographically to represent abscess formation. A metastatic evaluation was performed and the patient had no evidence of metastatic disease. A right pneumonectomy was performed.

Macroscopically, the right upper lobe was nearly completely replaced by a large cavitary mass consistent with an abscess, composed of yellow-tan necrotic and purulent material. At the hilar region of this necrotic abscess-like mass was firm greyish-white tumor which histologically represented a malignant neoplasm that showed the features of a giant cell carcinoma. Over 40% of the cells were composed of large pleomorphic cells measuring >40 \( \mu m \) in diameter, with most of these cells have large multilobed nuclei or multiple nuclei. There was an acute and chronic inflammatory cell infiltrate associated with these cells. Immunohistochemically, some neoplastic cells expressed keratin and vimentin. Ultrastructurally the cells were rather poorly differentiated, although occasional intercellular junctions and cytoplasmic tonofilaments were observed.
Giant cell carcinoma is classified as a subtype of large cell undifferentiated carcinoma by the World Health Organization. It is a tumor composed of highly pleomorphic and frequently multinucleate tumor giant cells, that not infrequently contain neutrophils in their cytoplasm. Giant cell carcinoma does not include lung neoplasms that show areas of squamous and glandular differentiation. To be considered a primary giant cell carcinoma of the lung, the tumor must be composed of at least 40% giant cells that are greater than 40 μm in diameter.

In 1958, Nash and Stout\(^6\) reported an autopsy series of five cases of giant cell carcinoma of lung. These patients were found to have survival times between five days and seven months, and showed extensive metastases. Other reports have substantiated the poor prognosis of this tumor.\(^6^-^8\) In 1961, Ozello and Stout\(^6\) showed by tissue cultured the epithelial nature of the giant cell carcinoma. In this case the epithelial nature of the tumor was identified by immunohistochemistry (expression of keratin) and by electron microscopy (intercellular junctions and tonofilaments). The presence of neutrophils within the cytoplasm of tumor giant cells was studied by Wang, et al.\(^6\) The neutrophils entered the tumor giant cells by emperipoiesis.

In 1992, Ginsberg, et al.\(^6\) retrospectively evaluated 16 cases of giant cell carcinoma, of which nine were anatomic stage I or stage II neoplasms. In contrast to previous studies, their evaluation suggested that these neoplasms behave like other non-small cell carcinomas of the lung. Like other series, they found an increased frequency of metastases to the gastrointestinal tract by giant cell carcinoma.

**Case 12: Diagnosis - Metastatic Melanoma**
*(Accession 27440)*

This case concerned an 85-year-old returned Puget Sound Naval Shipyard marine machinist, with a 60+ pack-year history of cigarette smoking and a history of chronic obstructive pulmonary disease and asbestos exposure. Over the past several months he was noted to have a left retrocardiac lung mass that had been slowly increasing in size, and which was found by CT scan to be present in the medial basilar segment of the left lower lobe. On CT scan the tumor measured approximately 2-3 cm in diameter. The patient had a family history of lung cancer and had had a previous transurethral resection of a bladder tumor that was a grade III/III transitional cell carcinoma with invasion into the stroma.
The tumor consisted of a well-demarcated subpleural nodular mass measuring 2 cm in diameter. In areas, the tumor was composed of nests of large, round, polygonal and irregularly-shaped epithelial-appearing cells, and in areas, many of the tumor cells contained brownish-black granular pigment in their cytoplasm that had the appearance of melanin.

The tumor was studied by immunohistochemistry and electron microscopy. By immunohistochemistry the neoplastic cells expressed S100 protein and human melanoma black-45 antigen, and did not express keratin. Ultrastructurally, the tumor cells contained stage I-IV melanosomes in their cytoplasm. Based on the histologic, immunohistochemical and ultrastructural features, the tumor was diagnosed as a metastatic melanoma.

Metastatic melanomas are frequently metastatic to the lung. In one series of 652 cases, 70% of the melanomas metastasized to the lungs, and in 7% of the cases, the lungs were the only site of metastases.

Between 1970 and 1991, 7564 patients with melanoma had been seen at Duke University Medical Center. These authors found the probability of metastases at 5, 10 and 20 years after the initial diagnosis of melanoma was 0.18, 0.19 and 0.30 respectively. Pulmonary metastases were diagnosed in 945 patients (12% of cases). The patients with pulmonary metastases had a one, three, and five-year survival rate of 30%, 9% and 4%, respectively. The authors found advanced pulmonic spread, including bilateral disease, in 543 patients, and more than two nodules in 595 patients. Multivariate analysis showed there was improved survival when there was complete resection of metastases in the lungs. Survival in patients with one nodule that was resected was significantly better than in those who had similar disease and no resection. Univariate predictors for early formation of pulmonary metastases included male sex, black race, increased thickness of the primary tumor (higher Clark level), nodular or acro lentiginous histology, location on trunk, head or neck, and regional lymph node metastases.

This author has seen several cases of metastatic melanoma in the lung in which a primary tumor could not be identified. One must always be aware that some metastatic melanomas can have a spindle-cell configuration and can resemble spindle cell neuroendocrine lung neoplasms.
Case 13: Diagnosis - Giant Cell Neoplasm of Lung  
(Accession 27467)

This case concerned a 71-year-old retired steamfitter with a 55 pack-year history of cigarette smoking, a history of occupational exposure to asbestos, and a history of chronic obstructive pulmonary disease. A routine chest radiograph showed a 1-cm in diameter mass in the posterior segment of the right upper lobe. A wedge resection of this mass was performed followed by a completion lobectomy.

This tumor was composed of large, neoplastic cells with over 40% of them being >40 μm in diameter, thus fulfilling the histologic criteria for a giant cell carcinoma. Trapped within the tumor cells were residual small bronchi and bronchioles that could be identified histologically, as well as by immunohistochemistry and electron microscopy.

By immunohistochemistry the neoplastic cells showed no immunostaining for low or high molecular weight keratin, although did show immunostaining for KP1 (CD68 - macrophage marker) and to a lesser extent, S100 protein. Ultrastructurally these cells were undifferentiated and did not show any epithelial features of differentiation. The possibility of this tumor representing a metastasis was evaluated, although clinically and by CT scan of chest and abdomen, there was no evidence of a primary neoplasm elsewhere.

The exact nature of this giant cell neoplasm remains uncertain. Based on the immunohistochemical and ultrastructural findings it does not appear to be a carcinoma, although such neoplasms raise the possibility that some primary carcinomas undergo differentiation in which they can no longer be recognized as carcinomas.

Case 14: Diagnosis - Squamous Cell Carcinoma of Lung  
Showing Variable Differentiation  
(Accession 27471)

This case concerned a 59-year-old woman with a history of rheumatic heart disease, congestive heart failure, a 34 pack-year history of cigarette smoking, a history of chronic obstructive pulmonary disease, a history of systemic lupus erythematosus, steroid-induced diabetes mellitus, a history of right breast cancer status post-operative modified radical mastectomy, and a history of an aortic and mitral valve replacement. In April 1989, she presented with chest discomfort, face rash, hair loss, arthralgias and a single episode of hemoptysis. A chest radiograph showed a 6 x 4.5 x 4 cm lobulated mass in the superior segment of the left lower lobe. A left lower lobectomy was performed that contained this large mass, that focally extended through the visceral pleura.
Histologically, this tumor showed squamous differentiation in the form of distinct keratinizing squamous epithelial cells with keratin pearls and other areas of fairly large aggregates of keratin. This case was used to illustrate the heterogeneity that squamous cell carcinomas (and other lung cancers) can show. In many areas, this tumor had a spindle-cell appearance, which is a known form of squamous cell carcinoma, and in other areas was composed of large tumor giant cells associated with neutrophils. In yet other areas the tumor was composed of cells that frequently had clear cytoplasm, and did not show obvious keratinization.

Pathologists should be aware of lung tumor heterogeneity. This author uses the rule of taking one section per cm size of tumor, unless there are strategic areas that need to be examined, such as certain margins. When tumors abut against the pleural surface, this author sections the entire pleural surface that the tumor is potentially invading.

Case 15: Diagnosis - Localized Fibrous Tumor of the Pleura

(Accession 27465)

This case concerned a 62-year-old non-smoking woman who presented with back pain. The chest radiograph showed a left lung mass, and CT scan of the chest showed a 3-cm pleural-based mass in the left lower lobe. The patient had no symptoms of shortness of breath, dyspnea on exertion, hemoptysis, anorexia or weight loss. Physical examination was normal, as was fiberoptic bronchoscopy. Video-assisted thoracoscopy was performed and the left lower lobe nodule was wedged out.

This 3-cm in greatest dimension tumor was in a distinct subpleural location, and was well demarcated from the surrounding lung tissue. This neoplasm was composed of rather bland spindle-shaped cells that in some areas formed small nodular regions that resembled those present in meningioma. In other areas the tumor cells were more haphazardly dispersed, and in some areas the cells were arranged in a hemangiopericytoma-like pattern. Immunohistochemical analysis of the neoplasm showed the neoplastic cells to express vimentin and to be negative for keratin, epithelial membrane antigen, muscle-specific actin (HHF-35) and desmin. The tumor was studied by electron microscopy, and was composed of fibroblastic-appearing cells that had a moderate number of micropinocytotic vesicles at the cell membrane. The cells had processes and occasionally were connected to each other by poorly-formed intercellular junctions. In the nodules of cells, there was a centrally-located vessel. These cells did not show the intercellular junctions that one sees in cases of meningioma. The lack of staining for epithelial membrane antigen would also rule against the diagnosis of meningioma.
This tumor was diagnosed as a localized fibrous tumor of the pleura, with the only other serious diagnostic consideration being hemangiopericytoma.

Localized fibrous tumors of the pleura have been referred to in the past as localized fibrous mesotheliomas, although there is no evidence that these cells are derived from the cells forming the pleura. Briselli, et al.\textsuperscript{70} reported eight new cases of localized fibrous tumor of the pleura and reviewed 380 previously-reported cases in the literature. In 1986, Doucet, et al.\textsuperscript{71} reported ten examples of localized fibrous tumors of serosal surfaces that were studied by immunohistochemistry and electron microscopy. Carter and Otis\textsuperscript{72} reported 17 examples of spindle cell tumors of the pleura, of which 8 were localized fibrous tumors. The largest and most complete study to date concerning localized fibrous tumors of the pleura was by England, et al.\textsuperscript{73}

The article by England, et al.\textsuperscript{73} includes a thorough description of the macroscopic, microscopic, immunohistochemical and ultrastructural features of these neoplasms. As shown by England, et al.,\textsuperscript{73} these neoplasms occur in the subpleural zone of the lung, within the pleural cavity attached to the visceral pleura by a pedicle, and within the parietal pleura bulging into the chest cavity. Histologically, the majority of the benign form of this neoplasm shows a nondeacript pattern referred to a "patternless pattern". About 25\% of the cases show a hemangiopericytoma pattern. Multinucleate histiocytic giant cells were noted in 15\% of the benign tumors, but in only three malignant tumors reported by England, et al.\textsuperscript{73} The criteria used by England, et al.\textsuperscript{73} for malignancy included a high cellularity, mitotic rate of >4 mitoses/10 hpf, cellular pleomorphism, hemorrhage, necrosis, and invasion.

In this case there was no evidence of necrosis, hemorrhage or mitotic activity, and the tumor is considered benign.

**Case 16: Diagnosis - Sarcomatoid Mesothelioma with Osteocartilaginous Differentiation**

*(Accession 27441)*

A 62-year-old man with a history of occupational exposure to asbestos developed right-sided chest pain in July, 1992, while doing yard work. He was thought to have pulled a muscle, although over the next several weeks, developed a nonproductive cough and shortness of breath. A chest radiograph and CT scan of the chest showed an extensive right pleural process, with diffuse right
pleural thickening and calcifications. A right thoracotomy, right pleural biopsy, and partial right pleurectomy were performed. The patient continued to have pleural pain and expired in April, 1993, approximately nine months after pleurectomy. Post-mortem examination showed near-complete encasement of the right lung by a neoplasm that invaded into the bronchopulmonary, hilar and mediastinal lymph nodes, and into the soft tissue of the mediastinum.

Histologically this tumor had the appearance of osteosarcoma, being composed of spindle-shaped cells and somewhat irregular and occasionally somewhat polygonal-shaped cells in association with extensive areas of ossification, and focal cartilaginous areas. In most sections there were extensive multinucleate histiocytic giant cells scattered throughout the tumor. Tumor extended into the lung parenchyma, and directly invaded into the chest wall. The pleurectomy tumor specimen and the autopsy tumor specimen were studied by immunohistochemistry; the neoplastic spindle-shaped cells showed immunostaining for vimentin, and showed no immunostaining for keratin, muscle-specific actin, S100 protein or desmin. The lung tissue obtained at autopsy was analyzed by digestion, and showed up to 300 asbestos bodies per gram of wet lung tissue, which in this author's laboratory, is approximately 15 times the upper limits seen in persons who are not occupationally exposed to asbestos. Given the macroscopic description of this tumor and the history of asbestos exposure, this tumor was diagnosed as a sarcomatoid mesothelioma showing osteocartilaginous differentiation.

Spindle cell neoplasms of the pleura include sarcomatoid mesotheliomas, desmoplastic mesotheliomas, biphasic mesotheliomas, localized fibrous tumors of the pleura, spindle cell sarcomas, metastatic or invasive spindle cell carcinomas such as metastatic spindle cell renal carcinomas, metastatic spindle cell carcinomas of lung, metastatic spindle cell pancreatic carcinomas, and metastatic or invasive carcinoma. Yousem and Hochholzer presented ten diffuse pleural tumors felt to represent primary malignant mesotheliomas that showed osseous and cartilaginous differentiation. Seven of these cases were fibrosarcomatous in nature and three showed biphasic differentiation, with all showing evidence of osseous and/or cartilaginous differentiation. Immunohistochemical studies were performed on six cases of the fibrous mesothelial type proliferations, and in only three cases was there keratin decoration of cells, and this keratin decoration was only focal.

Krisha and Haquani presented a case of liposarcomatous differentiation in diffuse pleural mesothelioma. The patient was a 77-year-old woman who presented with shortness of breath and pleural effusions, and was found to have a malignant mesothelioma with areas of epithelial differentiation and areas of liposarcomatous differentiation. This patient had evidence of asbestosis,
and a significantly elevated asbestos pulmonary fiber concentration. Donna and Betta\textsuperscript{76} proposed a new approach to the classification of tumors of coelomic surfaces (mesotheliomas). They indicated that the mesothelium lining the serous cavities is of mesodermal derivation, with an epithelial-like arrangement of the superficial layer. They suggested that the term "mesodermoma" was justified to define neoplasms arising from undifferentiated and multipotential mesoderm. The mesoderm exhibits a wide range of differential activity and gives rise to neoplasms showing myoblastic, angioblastic, lymphoblastic, chondroblastic, osteoblastic, fibroblastic or epithelial-like features.\textsuperscript{76} Along somewhat similar lines, Henderson, et al.\textsuperscript{77} classified sarcomatoid mesotheliomas as follows: homologous type (fibrosarcomatous, malignant fibrous histiocytoma-like; leiomyosarcomatous); heterologous type (chondrosarcoma; osteosarcoma; rhabdomyosarcoma; neurogenic sarcoma-like); lymphohistiocytoid mesothelioma; and desmoplastic mesothelioma. Thus, sarcomatoid mesotheliomas exhibit a rather wide range of differentiation.

In this case the primary differential diagnosis was an osteosarcoma. Given the macroscopic distribution of the tumor and the occupational history of exposure to asbestos, it seems likely that this neoplasm represents a primary sarcomatoid mesothelioma showing osteocartilaginous differentiation, and not an osteosarcoma of the pleura encasing the lung.

**Case 17: Diagnosis - Malignant Spindle Cell Neoplasm; Differential Diagnosis between Malignant Localized Fibrous Tumor of the Pleura and Primary Spindle Cell Carcinoma of Lung**

**(Accessions 27473 & 27464)**

This case concerned a 72-year-old non-smoking man who developed the gradual onset of left subcostal pain over two months. A chest radiograph and CT scan of the chest showed a 10-cm well-demarcated mass in the left lower lobe stated to be pleural based, without evidence of hilar or mediastinal adenopathy. The patient had a history of asbestos exposure for 2-3 years in the 1950s, and a history of stage I-A prostatic adenocarcinoma. He had experienced a left pleural effusion five years previously that spontaneously regressed. A left thoracotomy was performed, at which time hyaline pleural plaques were identified. A large tumor was found in the left lateral posterior portion of the thoracic cavity, that involved the left lower lobe. The tumor and left lower lobe were resected.

The initial neoplasm was composed of rather bland spindle-shaped cells. The tumor was initially diagnosed as a benign spindle-cell neoplasm consistent with a localized fibrous mesothelioma.
The tumor recurred eight months later, and infiltrated into the left upper lobe and extensively into the chest wall. Despite treatment with chemotherapy, the patient expired three months later. At necropsy, metastatic tumor was identified in mediastinal, cervical and retroperitoneal lymph nodes, adrenal glands, pericardium, myocardium, brain and kidneys. The autopsy tumor appeared significantly more pleomorphic than the initially-resected tumor. This neoplasm was evaluated using six different keratin antibodies, including antibodies on methacarn-fixed tissue. The neoplastic cells showed no keratin staining, although there were nests of neoplastic epithelial-like cells present in lymphatic channels. Based on the metastatic pattern of spread and the areas of epithelial differentiation of the tumor, we diagnosed this tumor as most likely representing a spindle cell carcinoma that was expressing only vimentin. The possibility exists, however, that this tumor represents a malignant localized fibrous tumor of the pleura.

The lung tissue showed evidence of grade 1 asbestosis, and digestion analysis showed up to 9000 asbestos bodies per gram of wet lung tissue. If this tumor represented a primary spindle cell carcinoma of the lung, it would be considered to be causally related to asbestos, based on the concentration of asbestos in the lung tissue and the presence of asbestosis.

**Case 18: Diagnosis - Pseudomesotheliomatous Carcinoma versus Epithelial Mesothelioma**
*(Accession 27442)*

This case concerned a 96-year-old man who presented with a right pleural effusion and shortness of breath. Thoracentesis was performed, and no neoplastic cells were identified in the pleural fluid. The patient was treated conservatively and died two months after the initial pleural biopsy. Post-mortem examination showed partial encasement of the right lung by a rind of greyish-white tumor. There was evidence of metastatic tumor in the right hilar lymph nodes. The chest cavity also showed extensive hyaline pleural plaques involving the left parietal pleura.

The initial pleural biopsy and the autopsy tumor showed a biphasic neoplasm with a surface of cuboidal to columnar epithelial cells with an underlying malignant spindle cell proliferation associated with these epithelial cells. The neoplasm was initially diagnosed as a biphasic mesothelioma. This neoplasm was evaluated in our laboratory by immunohistochemistry and electron microscopy. The neoplastic epithelial and spindle-shaped cells showed immunostaining for keratin, and the spindle cells expressed keratin and vimentin. The epithelial cells showed no immunostaining for CEA, LeuM1 or BerEP4, although approximately 50% of the neoplastic
epithelial cells showed cell membrane staining for B72.3. By electron microscopy, the neoplastic cells were remarkable for relatively short and straight microvilli that arose from the cell surface and which were covered by a fuzzy glycoalyx, and did not have the extensive bushy sinuous appearance of the microvilli of a moderately- to well-differentiated epithelial mesotheliomas. Based on the immunohistochemical staining for B72.3 and the ultrastructural appearance of the microvilli, this author strongly felt this neoplasm represented a biphasic pseudomesotheliomatous carcinoma of the lung. The sections of lung parenchyma showed focal areas of glandular tumor in a subpleural location, but it was not clear whether this was tumor invading from the pleura, or invading into the pleura. This tumor macroscopically fulfilled the criteria of a neoplasm referred to as a pseudomesotheliomatous carcinoma. This type of tumor was probably first described in 1956 by Babolini and Blasi79. Babolini and Blasi cited reports of similar tumors that had observed in Italy in earlier years. The best known report concerning pseudomesotheliomatous carcinoma was by Harwood, et al.80 who in 1976 described six cases of adenocarcinoma that they referred to as pseudomesotheliomatous carcinomas. Their concept was that these peripheral lung neoplasms invaded into the pleura and grew like a mesothelioma. More recently, Kees81 published a series of pseudomesotheliomatous adenocarcinoma, of which 15 were from their files at the Armed Forces Institute of Pathology, and 15 were cases they had collected from the literature. Their paper indicates that these neoplasms have the macroscopic appearance of a mesothelioma, and a histologic appearance similar to a mesothelioma, including a biphasic mesothelioma. In Kees' series,81 17% of the cases had a possible or definite association with asbestos. We82 recently reported a series of 27 cases of pseudomesotheliomatous carcinoma, and found a history of occupational exposure to asbestos in 16 of 17 cases, with 8 of 11 cases showing increased concentrations of asbestos bodies in the lung tissue. In this author's experience, the tumor described in this patient represents a pseudomesotheliomatous biphasic carcinoma and not a biphasic mesothelioma.

Case 19: Diagnosis - Thymoma
(Accession 27469)

This case concerned a 39-year-old man who was in good health until November, 1992 when he presented with right shoulder pain. A chest radiograph showed a right perihilar mass. Bronchoscopic examination was performed, and no endobronchial tumor was identified. A fine needle aspiration biopsy was performed under CT guidance, and showed abnormal cells. A CT scan of the chest was stated to show a pleural mass that extended from the diaphragm to the hilar area, but without definite invasion. The chest radiographs and CT scans were reevaluated and the mass was thought to be arising in the mediastinum, growing in a way to produce an image that suggested a pleural mass.
Histologically this tumor had the appearance of a mature thymoma composed of spindle-shaped cells admixed with varying numbers of lymphocytes. The spindle-shaped cells expressed low and high molecular weight keratins, and the majority of the lymphocytes showed immunostaining for T cell antigen. By electron microscopy, the spindle-shaped cells showed epithelial differentiation in the form of well-formed desmosomes connecting the cells to one another, and cytoplasmic tonofilaments.

Thymomas are neoplasms derived from thymic epithelial cells, and in the thoracic cavity are usually seen in the anterior/superior mediastinum. Several reports have detailed the clinical and pathologic features of thymomas. Thymomas are relatively frequently associated with various clinical disorders including neuromuscular syndrome, such as myasthenia gravis, hematologic conditions such as red cell hyperplasia, collagen vascular diseases such as systemic lupus erythematosus, endocrine disorders, including hyperparathyroidism and Hashimoto thyroiditis, and bone disorders such as hypertrophic osteoarthropathy. Rarely, thymomas have been identified in the posterior and middle portion of the mediastinum, and rarely an intrapulmonary and pleural location has been observed.

Kung, et al., described two cases of intrapulmonary thymomas and reviewed nine other cases that had been previously reported in the literature. They noted that Kalish had categorized intrapulmonary thymomas into a perihilar and hilar category, depending on proximity to the hilar region. The report by Moran, et al. is of interest in that these thymomas simulated a mesothelioma in macroscopic appearance. There is one type of mesothelioma that could be potentially confused with a thymoma, specifically, a lymphohistiocytoid mesothelioma. This type of mesothelioma is composed of plump spindle-shaped cells that could be misinterpreted as histiocytes, which are admixed with numerous inflammatory cells, most of which are lymphocytes, and plasma cells. One might wonder if any of the cases reported by Moran, et al. were examples of lymphohistiocytoid mesotheliomas and not thymomas.

A great deal of work has been performed concerning the immunohistochemical features of thymomas. For diagnostic purposes these are relatively straightforward. The spindle-shaped cells present in the proliferation have epithelial features as determined by keratin staining or by electron microscopy. Most of the lymphocytes are various types of T lymphocytes.
Case 20: Diagnosis - Lymphomatoid Granulomatosis  
(Accession 27443)

This case concerned a 47-year-old man who presented with fever of unknown origin, a 10-lb weight loss, who was found on chest radiograph to have multiple peripheral nodular infiltrates. A fine needle aspiration biopsy was done on one of these nodules but the material was considered to be nondiagnostic, which resulted in the patient having an open lung biopsy. A diagnosis was made from the open lung biopsy specimen and the patient was treated with chemotherapeutic agents, but had a rapidly downhill course, dying about 7 months after the initial biopsy. The autopsy lungs were heavy and contained multiple greyish-white, focally necrotic peripheral nodules ranging from 1.5 to 5.0 cm in diameter. They were most dominant in the lower lobes in a subpleural location. Similar nodules were also identified in the kidneys, and radiographically there were nodules present in the brain.

The pathologic changes noted in the autopsy lung tissue were similar to those noted in the initial biopsy. The initial biopsy showed a variegated "lymphoreticular" infiltrate with an angiocentric distribution of the lymphoid cells and angioinvasion. The infiltrate consisted of lymphocytes, plasma cells, transformed lymphocytes, and large atypical cells, some of which represented macrophages. In the autopsy tissue there were areas in which the infiltrate was more monomorphous, composed of medium-sized lymphoid cells that showed evidence of mitotic activity. There were large areas of necrosis in the initial biopsy and in the autopsy tissue. The nodules present in the kidneys showed a histologic appearance similar to the nodules in the lung.

This variegated lymphoid infiltrate is characteristic of lymphomatoid granulomatosis. Lymphomatoid granulomatosis was first reported by Liebow, et al.99 in 1972, and their publication remains the best pathologic description of lymphomatoid granulomatosis. Forty patients were included in their study, and over half presented with symptoms similar to those seen in this patient. Over half of the patients were dead within one year. In 1979, Katzenstein, et al.100 reported a clinicopathologic study of 152 cases of lymphomatoid granulomatosis. This publication reviewed some information concerning the clinicopathologic features of lymphomatoid granulomatosis. Katzenstein, et al.100 found that adverse factors in the outcome of lymphomatoid granulomatosis included an age of less than 25 years, an increased white blood cell count, neurologic manifestations, hepatosplenomegaly, and an increased number of atypical lymphoid cells in the infiltrate.
Over the years, lymphomatoid granulomatosis evolved into a condition that was thought to represent an angiocentric lymphoma, specifically, an angiocentric T-cell lymphoma, based on immunohistochemical studies. More recently, Guinee, et al.\textsuperscript{101} analyzed five cases of lymphomatoid granulomatosis/angiocentric immunoproliferative lesion involving the lung by immunohistochemistry and in situ hybridization for CD20 (L26), and for Epstein-Barr virus, and by polymerase chain reaction for IgG heavy chain gene rearrangement. These authors found that in all cases, the majority of the small and medium-sized lymphocytes were CD45-RO positive (T lymphocytes). A much smaller population of large atypical cells were CD20 positive B cells. In each case, combined immunohistochemistry and in situ hybridization confirmed the presence of Epstein-Barr virus in CD20-positive B cells. These authors concluded that the proliferating cell in a subset of lymphomatoid granulomatosis angiocentric immunoproliferative lesion involving the lung was a B lymphocyte. They also concluded that some cases of lymphomatoid granulomatosis may be the pulmonary manifestation of Epstein-Barr virus-associated lymphoproliferative disease.

Lymphomatoid granulomatosis continues to be somewhat of an enigma to both clinicians and pathologists, with respect to its exact nature and clinical course. As previously stated, most patients who develop this condition have a relatively rapidly downhill course, and die. Some success has been found by treating these patients with Cytoxan, as reported by Fauci in the 1980s.\textsuperscript{102}

**Case 21: Diagnosis - Primary Large Cell Lymphocytic Lymphoma of Lung**

\textit{(Accession 27470)}

This case concerned a 44-year-old woman who was initially identified as having what was interpreted to be an anterior mediastinal mass. A fine needle aspiration biopsy of the mass was performed, and a diagnosis of large cell malignant neoplasm was made with the differential diagnosis including germ cell neoplasm and thymoma. The attending surgeon proceeded with a resection of what was thought to be a probable thymoma, but after entering the chest via a median sternotomy, visualized the tumor and noted that it was far less in the anterior mediastinum and much more in the right hilar area, specifically, in the lung. Most of the mass was found to be in the pulmonary parenchyma. The resected right upper lobe contained a 6.8 x 5.5 x 4.5 cm greyish-tan, relatively well-demarcated mass. A portion of mediastinal soft tissue was removed and contained benign lymph nodes and thymus.
Histologically, this neoplasm was relatively well demarcated and was composed of somewhat nodular masses of large, round and polygonal cells with large round nuclei and one or more prominent nucleoli. These cells were closely associated with one another but did not show obvious intercellular junctions, and did not show glandular differentiation. Immunohistochemical analysis showed the cells to exhibit focal immunostaining for vimentin and no immunostaining for low or high molecular weight keratin. The cells showed moderately intense cell membrane immunostaining for L26 (B lymphocyte antigen). The section stained for placental alkaline phosphatase appeared to be focally positive in a cell membrane distribution. The neoplasm was studied by electron microscopy, and was composed of large, rather primitive cells that had large, blunt cellular processes. The cells showed no intercellular junctions and had the ultrastructural appearance of neoplastic lymphocytes.

This tumor was diagnosed as a primary non-Hodgkin's large cell lymphocytic lymphoma of lung. The criteria for diagnosing primary non-Hodgkin's lymphoma of lung are: (1) involvement of the lung or involvement of a lobar or mainstem bronchus, either unilaterally or bilaterally, with or without mediastinal lymph node involvement; (2) no evidence of extrathoracic lymphoma at the time of diagnosis or for three months thereafter. Most patients with primary non-Hodgkin's lymphoma of the lung are greater than 60 years old, and 50% of them are asymptomatic at the time of having been found to have an abnormal chest radiograph. The symptomatic patients usually have symptoms, consisting of fever, night sweats and weight loss, and may have dyspnea on exertion, cough, and chest pain. A significant number of non-Hodgkin's lymphomas of the lung are associated with von Willebrand syndrome, erythema nodosum, or Sjogren syndrome. The chest radiograph usually shows a single or multiple well-defined nodules, and sometimes multiple infiltrates with pleural effusions and regional adenopathy.

Colby and Yousem classified primary non-Hodgkin's lymphomas in the lung as follows: (1) lymphomas composed predominantly of small lymphocytes with minimal cytologic atypia and those with plasmacytoid features; (2) lymphomas composed predominantly of large lymphoid cells; (3) lymphomas composed of a mixed population of lymphoid cells. In this case, the tumor would fit into the second category; namely, lymphoma composed predominantly of large lymphoid cells.
Case 22: Diagnosis - Localized Pulmonary Histiocytosis X
(Accession 27480)

This case concerned a 64-year-old man with a 50 pack-year history of cigarette smoking, who was identified on a routine chest radiograph to have a nodule in the left upper lobe measuring approximately 1.5 cm in diameter. There was no evidence of other abnormalities on the chest radiograph, and no evidence of hilar or mediastinal lymphadenopathy. The nodule was removed via wedge resection.

Histologically, the nodule was composed of aggregates of mostly round cells with hyperconvoluted nuclei and somewhat foamy cytoplasm. These cells were admixed with varying numbers of inflammatory cells, including lymphocytes, plasma cells, eosinophils and neutrophils. The surrounding lung tissue was abnormal and showed varying degrees of fibrosis and focal accumulation of macrophages in distorted alveolar spaces. At greater magnification, the round and polygonal cells that seemed to form the majority of the nodules had hyperconvoluted nuclei. By immunohistochemistry, these cells expressed vimentin and S100 protein and were negative for keratin. By electron microscopy, these cells showed Langerhans cell granules in their cytoplasm which were sometimes in the region of the Golgi apparatus, and sometimes close to the cell surface, and occasionally attached to the cell membrane. The histologic, immunohistochemical and ultrastructural features of these cells were characteristic of Langerhans cells. The nodular aggregates of these cells indicate that this is an example of pulmonary histiocytosis X (pulmonary eosinophilic granuloma - pulmonary Langerhans cell granulomatosis) that in this case is present in a localized form rather than being in the more usual diffuse form.

Langerhans cells are normally found in several different tissues, including the epidermis, esophagus, anus-rectum, cervix, thymus, lymph nodes, and rarely in the normal lung. They were identified in 1869 by Paul Langerhans and make up about 3-8% of the cells of the epidermis. They were shown by Michael Birbeck, in 1961 to have unusual cytoplasmic inclusions which are sometimes referred to as Birbeck granules, which represent the Langerhans cell granules. Langerhans cells can be identified histochemically or immunohistochemically by an ATPase reaction, and by S100 protein. Langerhans cells have C3 and OKT-6 receptors (CD1 receptors), plus receptors for IA antigen on the cell surface. They are of bone marrow origin, and are involved in the uptake and processing of antigen and the presentation of antigen to T lymphocytes. Langerhans cells are known to migrate freely between the skin and regional lymph nodes via dermal lymphatics.
Pulmonary histiocytosis X occurs almost exclusively in cigarette smokers. It is a disease that frequently is misdiagnosed clinically, and is often not included in the differential diagnosis pathologically. The tissue adjacent to the nodules of histiocytosis-X cells frequently show changes of respiratory bronchiolitis and/or desquamative interstitial pneumonitis. Besides this case, there has been one other case of localized eosinophilic granuloma of the lung reported. An increased incidence of lung cancer in persons with pulmonary histiocytosis X has been suggested, as has an increased incidence of other types of neoplasms. Lombard, et al. described four patients who developed pulmonary histiocytosis X and carcinoma of the lung. These authors concluded that the association between lung cancer and pulmonary histiocytosis X was rare, and may be coincidental, since cigarette smoke was the cause of both conditions. Sadown, et al. reported five cases of lung cancer observed in 93 patients with pulmonary histiocytosis X. They found that the mean age of diagnosis of pulmonary histiocytosis X was 42 years, whereas the average age of those with PHX and lung cancer occurred 10.5 years later. Among four patients who had pulmonary histiocytosis X and lung cancer who were greater than 45 years old, cigarette consumption was significantly greater than in those 15 patients who had pulmonary histiocytosis X only. These authors concluded that cigarette smoking played the predominant role in the pathogenesis of lung cancer in patients with pulmonary histiocytosis X.

Tomashefski, et al. reported finding ten neoplasms in 21 patients with pulmonary histiocytosis X. One patient had a benign neoplasm whereas nine patients had malignant neoplasms. Patients who had neoplasms were older at the time of diagnosis than those patients with pulmonary histiocytosis X who did not have tumors (48.9 years versus 34.5 years). The neoplasms observed by the authors included three lung carcinomas, one pulmonary carcinoid tumor, two lymphomas, five extrapulmonary carcinomas, and one mediastinal ganglioneuroma. These authors concluded that their studies suggested there may be more than a random association between pulmonary histiocytosis X and neoplasms.

With respect to the diagnosis of pulmonary histiocytosis X by transbronchial biopsy, Housini, et al. evaluated the findings on transbronchial biopsy specimens in reference to open lung biopsy specimens in 12 patients diagnosed by open biopsy to have pulmonary eosinophilic granuloma. These authors concluded that there was a low diagnostic yield of pulmonary histiocytosis X via transbronchial biopsy, which was due to either an inadequate sampling and/or the nonspecific appearance of discrete lesions in small tissue samples.
This case concerned a 35-year-old gay HIV-negative man with no risk factors for the development of AIDS for the past 8 years who presented with fever, night sweats and weight loss. Radiographically he was found to have a right upper lobe lung mass that was relatively well demarcted. The right upper lobe was resected and the visceral pleural surface was covered by shaggy fibrovascular adhesions. On sectioning, the lower portion of the lobe was composed of rock-hard, yellow-brown to greyish tissue with areas of necrosis and golden-tan post-obstructive pneumonia.

Histologically, the lung tissue showed marked inflammation and necrosis. The primary change was one of rather vague aggreages of highly atypical, round to irregularly-shaped cells which were associated with a moderate number of small mature lymphocytes and other inflammatory cells, such as histiocytes and occasionally eosinophils and neutrophils. These larger cells had histologic/cytologic features of Reed-Sternberg cells. Immunohistochemical studies were performed with Leu1 (CD15) and Ki1 (CD30), and these atypical cells showed moderately-intense cytoplasmic immunostaining for these antigens. The tissue was also evaluated by electron microscopy and the large neoplastic cells had ultrastructural features consistent with Reed-Sternberg cells. A diagnosis of Hodgkin's disease, primary in the lung, was made.

In 1990, Radin reported on 61 cases of primary pulmonary Hodgkin's disease. In their series, there were 36 females and 25 males, with the average age of the entire group being 42.5 years, with the range being between 12 and 82 years. The most common histologic type of Hodgkin's disease identified was nodular sclerosing, with the second most frequent being mixed cellularity. The criterion used for diagnosing primary pulmonary Hodgkin's disease was documentation of pulmonary parenchymal involvement that primarily affected the lung, with only minimal enlargement of hilar and mediastinal lymph nodes. The most frequent symptoms before diagnosis included cough, weight loss, chest pain, dyspnea, hemoptysis, fatigue, rash, sweats, and wheezing. Physical examination was often normal, although many of the patients had auscultation evidence of consolidation of lung tissue. Bronchoscopic examination was performed in 35 of the 61 patients, and was normal in 18, and abnormal in 16. Radiologic abnormalities were dominated by nodular mass-like lesions in 45 of 61 patients, and pneumonic infiltrates in 13 of 61 patients. In this case, the diagnosis was based on the appearance of the atypical cells and the demonstration that these cells expressed antigens known to be present in Reed-Sternberg cells; namely LeuM1 (CD15) and Ki1 (CD30).
REFERENCES


Figure 1

Lung Cancer Staging

Graphic illustration of currently accepted stages of lung cancer. (Reprinted with permission from Chest 1991; 99:1258-1260.)

(Reprinted with permission from Chest 1991; 99: 1258-1260. for use in the addenda for the 96th Semi-Annual Conference - "Pleuro-Pulmonary Neoplasms"; California Tumor Tissue Registry 1994.)
Figure 2

Histologic Classification of Malignant Lung Tumors

1. Squamous cell carcinoma (epidermoid carcinoma) variant
   a. spindle cell carcinoma
2. Small cell carcinoma
   a. oat cell carcinoma
   b. intermediate cell type
   c. combined oat cell carcinoma
3. Adenocarcinoma
   a. acinar adenocarcinoma
   b. papillary adenocarcinoma
   c. bronchioloalveolar cell carcinoma
   d. solid carcinoma with mucus production
4. Large cell carcinoma variants
   a. giant cell carcinoma
   b. clear cell carcinoma
5. Adenosquamous carcinoma
6. Carcinoid tumor
7. Bronchial gland carcinomas
   a. adenoid cystic carcinoma
   b. mucoepidermoid carcinoma
Figure 3

Histologic Criteria for Diagnosing
Common Lung Neoplasms

1. Squamous cell carcinoma: keratin production by tumor cells; keratin pearls; intercellular junctions (bridges) between adjacent neoplastic cells.

2. Adenocarcinoma: Definite gland formation; mucus production in solid tumor, as demonstrated by mucin stain such as PAS-D or mucicarmine.

3. Large cell undifferentiated carcinoma: Large cells that often have vesicular nuclei and large nucleoli; no evidence of squamous or glandular differentiation; negative mucin stain

4. Multicomponent Carcinoma: Neoplasms composed of more than one histologic type, according to the criteria for squamous carcinoma, adenocarcinoma, large cell undifferentiated carcinoma, and small cell undifferentiated carcinoma.
Figure 4

Dispersed Neuroendocrine System

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**Figure 5**

**Nomenclature of Neuroendocrine Lung Neoplasms**

1. Tumorlet
2. Mature carcinoid
3. Atypical carcinoid
   a. Malignant carcinoid
   b. Well-differentiated neuroendocrine carcinoma
   c. Kulchitsky cell carcinoma-II
   d. Peripheral small cell carcinoma of the lung resembling carcinoid tumor
4. Large cell neuroendocrine carcinoma
   a. Atypical endocrine tumor of lung
   b. Neuroendocrine carcinoma of intermediate cell type
5. Small cell undifferentiated carcinoma
   a. small cell neuroendocrine carcinoma
   b. neuroendocrine carcinoma of small cell type
   c. oat cell carcinoma