Pulmonary Adenocarcinoma

The Expanding Spectrum of Histologic Variants

Cesar A. Moran, MD

Pulmonary adenocarcinoma is one of the most common types of lung cancer. Traditionally, adenocarcinomas have been divided based on their degree of resemblance to their parent tissues into 3 histopathologic types: well, moderately, and poorly differentiated. In the majority of cases, this schema is sufficient to categorize these lung tumors. However, there is a considerable group of tumors in which the histology is not that of the classic gland-forming neoplasm. Thus, although the terminology of adenocarcinoma is applied in such cases, the histopathologic features are different from those of the more conventional variants. The current review addresses these unusual variants and the importance of recognizing and properly categorizing them to avoid unnecessary additional workup or possible misdiagnosis.

(Arch Pathol Lab Med. 2006;130:958–962)

Epithelial tumors are by far the most common type of primary malignancies in the lung and constitute the leading cause of cancer morbidity and mortality worldwide. Environmental hazards, including tobacco use, have been linked to the development of pulmonary carcinoma. In recent years, several important trends have been observed in lung cancer, for instance an increased frequency of squamous cell carcinoma among African American men in contrast with white men and an increased frequency of squamous cell carcinoma among white women. Histologically, adenocarcinomas appear to be the most common histologic type of lung cancer diagnosed, while squamous cell carcinoma appears to be more commonly associated with tobacco use.1,2 Regardless of the histologic type and ethnic group affected, the survival rate for lung cancer after 5 years is still poor. It is possible that in the future we may be able to see some improvement in prognosis as techniques for early detection become more effective.

CLINICAL ASPECTS

Non–small cell carcinomas of the lung are by far the most common malignancies of this organ. They usually occur in the sixth to seventh decades of life. The clinical symptoms depend largely on the anatomic location of the tumor and its size. Tumors with a central location are more likely to produce early symptoms such as cough, dyspnea, wheezing, hemoptysis, and pneumonia. Tumors that are located in the periphery of the lung need to attain a relatively large size before they become symptomatic. Some types of symptoms may be correlated with certain types of malignancy. For instance, bronchorrhea (expectoration of large amounts of mucus) is more commonly seen in bronchioloalveolar carcinoma (BAC) of the mucinous type.3 In other instances, symptoms such as pleuritic pain, Pancoast syndrome, or superior vena cava syndrome develop when there is extensive tumor burden within the thorax.4,5 Paraneoplastic syndromes such as inappropriate secretion of antidiuretic hormone, Cushing syndrome, or acromegaly may also be present.6–11 In addition, non–small cell carcinomas may also be associated with other conditions such as bronchiectasis, pulmonary fibrosis, tuberculosis and other infectious processes.12–14 Radiologically, adenocarcinomas may present as solitary tumors, which can be ill or well defined within the lung parenchyma.15 Pleural seeding of adenocarcinoma in a manner similar to that seen in mesothelioma can also be observed. The use of more advanced radiological techniques such as magnetic resonance imaging and computerized tomography has greatly improved the detection of lung cancer.16,17

GROSS FEATURES

Grossly, the 2 most common non–small cell carcinomas of the lung, adenocarcinoma and squamous cell carcinoma, tend to have different anatomic distributions. Adenocarcinomas tend to be peripheral tumors, which may be accompanied by pleural retraction and scarring. In years past, the scarring process was believed to be the inciting stimulus for the development of carcinoma (‘‘scar’’ cancer). However, more recently it has been shown that the scarring may only represent a desmoplastic reaction to the tumor. Squamous cell carcinomas are more likely to be central tumors, frequently leading to bronchial obstruction. Nevertheless, both adenocarcinomas and squamous cell carcinomas can present either as peripheral or central lesions. Both tumors are treated surgically if technically resectable, and adjuvant radiation or chemotherapy may be added. Clinical staging represents the most clinically important parameter for the prognosis of lung cancer.

HISTOLOGY OF LUNG ADENOCARCINOMA

Adenocarcinoma is defined as a malignant epithelial neoplasm characterized by gland formation. Depending
on the degree to which the glandular elements in these tumors resemble their normal counterparts, they can be divided into well, moderately, and poorly differentiated tumors. In well and moderately differentiated tumors, the glandular structures are easily demonstrated on routine microscopy. The malignant glands are composed of tall columnar or mucinous epithelium, with large, round nuclei and prominent nucleoli. Mitotic figures are commonly present. In moderately differentiated tumors, the glands are not as well developed as in well-differentiated neoplasms. Poorly differentiated adenocarcinomas are composed of a neoplastic cell population showing very poor glandular development, with small abortive or distorted glands scattered among sheets or solid islands of poorly differentiated epithelial cells. In such cases, histochemical stains for intracellular mucin (periodic acid–Schiff, mucicarmine, etc) have been utilized as an aid for diagnosis.

In addition to these conventional types of adenocarcinoma, other unusual variants of primary lung adenocarcinomas have been described that may pose a more significant challenge for histopathologic diagnosis, as follows:

**Bronchioloalveolar Carcinoma**

This tumor is characterized by a distinctive growth pattern, the so-called lepidic pattern, in which the tumor cells line the alveolar walls and appear to gradually replace the normal lining epithelium of the airspaces while preserving its basic architecture (Figure 1). Unfortunately, this growth pattern is shared by a variety of unrelated neoplasms in the lung; in particular, metastatic carcinomas to the lung can often adopt an identical morphologic growth pattern, and well-differentiated lung adenocarcinoma can also be characterized by BAC-like features. Because true examples of BAC have been associated with a significantly better behavior than that of conventional well-differentiated adenocarcinomas of the lung, the current World Health Organization classification of lung tumors incorporates much more stringent criteria for this diagnosis. Essentially, to qualify as a BAC, the tumor must not show any evidence of infiltration of the stroma or adjacent lung parenchyma or the pleura, or lymphatic spread to lymph nodes. Tumors showing the characteristic lepidic growth pattern of BAC but that also show, even if focally, infiltration of either the lung parenchyma or the pleura are currently categorized as well differentiated adenocarcinomas with a “bronchioloalveolar growth pattern.” A BAC may present as a solitary pulmonary nodule or as a diffuse process involving the lung simulating a pneumonic process. In cases in which the tumor presents as a solitary nodule, the size of the lesion is of importance. Tumors measuring less than 0.5 cm in greatest dimension are best categorized as examples of atypical adenomatous hyperplasia, a benign lesion that is believed to be a possible precursor to BAC.

Given the need to examine the entire lesion for assessment of invasion, it is no longer possible to make a diagnosis of BAC on cytological specimens or on small endoscopic or percutaneous needle biopsy specimens. Cytologically, BAC may be composed of 2 different cell types, one characterized by mucinous epithelium and the other by nonmucinous epithelium composed of small cuboidal cells with scant cytoplasm and hyperchromatic nuclei, the “hobnail” pattern. The mucinous type must be differentiated from metastases from mucin-secreting adenocarcinomas of enteric, pancreatic, or biliary origin. The nonmucinous type can often show a florid papillary architecture, requiring distinction from metastases of papillary carcinomas of internal organs. Strong positivity for thyroid transcription factor-1 (TTF-1) in the latter is a particularly useful feature that can help establish the primary lung origin of the lesion.

In today’s practice the diagnosis of BAC is essentially reserved for cases in which there is a complete surgical resection of the neoplasm with lymph node sampling and with the proper evaluation of representative histological sections.

**Mucinous (“Colloid”) Carcinoma**

This tumor has been reported under several designations and has been interpreted as a benign to borderline to outright malignant neoplasm. Terms that have been used to designate this tumor include mucinous cystadenoma, mucinous cystic tumor, and mucinous cystic tumor of borderline malignancy. Mucinous (colloid) carcinoma is the latest term coined for this lesion. In a study of 24 patients, the tumors showed features similar to those described for cases previously published under the designations of cystadenomas or borderline cystic tumors. However, in contrast with previous reports, the follow-up for these patients (from 2 to 192 months) showed that some developed metastases to bone and/or brain. Clearly, the presence of distant metastases attests to the tumor’s malignant potential. Radiologically, the tumor may present as a solitary subpleural tumor or as a more diffuse process. Histologically, these tumors are characterized by extensive areas showing pooling of mucinous material with destruction of the underlying lung architecture (Figure 2). Small clusters of epithelial cells or single cells floating in the mucin are characteristically present. Mucinous epithelium with minimal atypia can usually be identified focally lining the walls of the alveoli. It is important to note that in the last edition of the World Health Organization classification of lung neoplasms, these tumors are distinguished from benign cystadenomas of the lung. However, the distinction between the two entities may be quite difficult since there appears to be significant overlap in morphologic features between these two conditions, and cases of mucinous cystic neoplasms with very low-grade and innocent morphology have metastasized distally. The generic designation of “mucin-rich tumors of the lung” may thus be preferable for these lesions.

Because tumors with identical morphology are more commonly observed in other organs, such as breast, ovary, and gastrointestinal tract, a detailed clinical history and other studies are needed to rule out the possibility of a metastasis from an occult primary. The use of immunohistochemical stains, namely a panel with cytokeratin (CK) 7, CK20, TTF-1, and CDX2, may also be of aid to distinguish between a metastasis and a primary lung mucinous carcinoma.

**Papillary Carcinoma**

Papillary carcinoma represents an unusual histopathological growth pattern characterized by complex papillary infoldings. In most cases, conventional areas of adenocarcinoma or bronchioloalveolar carcinoma can be identified in these tumors, but in pure form they need to be distinguished from other types of tumors. Papillary lung carcinoma can show histopathologic features similar to...
Figure 1. Bronchioloalveolar carcinoma showing the characteristic lepidic growth pattern of neoplastic cells lining the alveolar walls (hematoxylin-eosin, original magnification ×40).

Figure 2. Mucinous carcinoma showing pools of mucin, partially destroying normal lung architecture. Note the presence of mucinous epithelium lining the alveolar wall (hematoxylin-eosin, original magnification ×100).

Figure 3. Papillary carcinoma showing the typical growth pattern. Note the presence of psammoma body (hematoxylin-eosin, original magnification ×200).

Figure 4. Morular papillary carcinoma. Note the presence of the morular component in the alveolar spaces (hematoxylin-eosin, original magnification ×200).

Figure 5. Signet-ring cell carcinoma showing acinar pattern and composed almost exclusively of signet-ring cells (hematoxylin-eosin, original magnification ×400).

Figure 6. Adenocarcinoma with prominent secretory endometrioid-like features (hematoxylin-eosin, original magnification ×40).
those seen in the ovary or thyroid gland. Thus, a detailed clinical history is of importance. In the study by Silver and Askin,26 27 patients presented with solitary lesions while 4 had multifocal lesions. In 45% of patients, mediastinal lymph nodes were involved with metastases, while 10% showed extensive lymphatic permeation. Papillary carcinoma of the lung is composed of papillary tufts containing fibrovascular cores (Figure 3). Psammoma bodies can also be seen. The papillae are lined by large, atypical cells with enlarged, hyperchromatic nuclei, prominent nucleoli, and frequent mitotic figures. Necrosis is often observed in the lumens of the alveoli. More recently, a variant of this tumor closely resembling similar tumors in the urinary bladder has been described as micropapillary carcinoma.29 Some of the pure papillary carcinomas of the lung can easily mimic a papillary thyroid carcinoma. In this setting, the use of a thyroglobulin stain should help in the differential diagnosis. Separation from metastatic papillary carcinoma of ovarian origin can prove difficult in some cases. A good clinical history, pelvic examination, and radiologic studies usually should permit adequate identification of the latter. Distinction from BAC with a papillary growth pattern can also be difficult, particularly on small biopsy material. True papillary carcinoma, however, is characterized by marked cytologic atypia, with high mitotic rate and tumor necrosis, unlike BAC, which is characterized by very low-grade, well differentiated cystic features.

Papillary Carcinoma With Prominent “Morular” Component

This is a recently described tumor that essentially represents a morphologic variant of “true” papillary carcinoma of the lung.30 This unusual variant is distinguished by the presence of cell aggregates that form squamoid “morules,” similar to those observed in pulmonary blastomas (Figure 4). In papillary carcinoma, the morules are distributed randomly within the alveolar spaces and interstitium, while in cases of pulmonary blastoma, these structures are more inconspicuous and commonly located at the bases of glandular structures rather than within alveolar spaces. However, in small biopsy specimens in which the morular component is present, the distinction from pulmonary blastoma may be difficult to make. Needless to say, the prognosis for these two entities is quite different, with monophasic pulmonary blastoma demonstrating a much better prognosis than that of papillary adenocarcinoma. Accurate distinction between these two conditions is therefore of clinical importance. The use of immunohistochemistry may be of limited value in this setting since both tumors can show reactivity for the same antibodies, such as keratin, TTF-1, and carcinoembryonic antigen. Identification of papillary structures with high nuclear grade will favor a diagnosis of morular papillary carcinoma, whereas identification of cribriform glandular structures lined by clear cells will favor a diagnosis of pulmonary blastoma.

Signet-Ring Cell Carcinoma

Signet-ring cell carcinoma is another unusual variant of lung adenocarcinoma. This tumor essentially represents a poorly differentiated adenocarcinoma in which there is a prominent signet-ring cell component. This tumor is very aggressive, and the survival rate at 5 years is quite poor. In a study of 15 patients,31 my colleagues and I were able to document 2 distinct histopathological patterns: acinar (Figure 5) and diffuse. The tumor cells were characterized by large mucin vacuoles within the cytoplasm that displaced the nuclei towards the periphery. Cytoplasmic mucin is easily demonstrated in these tumors with histochemical stains, including periodic acid–Schiff and mucicarmine. The tumors were composed of at least 75% signet-ring cells. In 11 patients for whom follow-up was available, 6 died within 12 months, and 5 were alive during a period of 3 to 36 months.

Because of the shared histology with similar gastrointestinal tumors, it is essential to obtain a detailed clinical history before rendering a diagnosis of primary signet-ring cell carcinoma of the lung.31,32 Immunohistochemical studies for CK7, CK20, CDX2, and TTF-1 can be of aid in separating the two; the lung primary tumors will react strongly only with CK7 and TTF-1, whereas the gastrointestinal lesions will only show positivity for CK20 and CDX2.

Secretory Endometrioid-like Adenocarcinoma of the Lung

This represents the latest histopathological growth pattern described in primary pulmonary adenocarcinomas.33 The tumor is characterized by a glandular proliferation that closely resembles normal secretory endometrium (Figure 6). The glands are distributed back to back and show clearing of the cytoplasm and alignment of the nuclei toward the base of the glands. In some areas the glandular proliferation can elicit a mild desmoplastic reaction similar to the stromal component seen in secretory endometrium. Mitotic figures and marked pleomorphism are not features of these tumors. The morphology of these tumors can sometimes closely resemble that of a monophasic pulmonary blastoma (fetal-type adenocarcinoma). Useful distinguishing features are the presence of the characteristic morules adjacent to the base of the glands in pulmonary blastoma. The use of immunohistochemical markers may not be helpful in this setting since both tumors can share a similar immunophenotype. Immunohistochemical stains, however, may be of help in distinguishing this tumor from a metastasis from a well differentiated endometrioid adenocarcinoma of the female genital tract; the lung primaries are usually strongly positive for CK7 and TTF-1.

SUMMARY

Primary pulmonary adenocarcinomas may display a wide variety of histopathologic growth patterns, which in small biopsy specimens may prove difficult to recognize as primary lung neoplasms. Because of the unusual histologic features seen in some of these tumors and the lack of awareness of such unusual patterns, one may mistakenly arrive at an incorrect diagnosis. In certain circumstances, some of these lesions may even be interpreted as benign because of their unusual growth patterns. Familiarity with these various unusual growth patterns, coupled with the use of immunohistochemical stains and careful clinical history, can help to provide a correct interpretation of these lesions.

References