The Spectrum of Pulmonary Mucinous Cystic Neoplasia
A Clinicopathologic and Immunohistochemical Study of Ten Cases and Review of the Literature

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Key Words: Mucinous cystic tumor; Cystadenoma; Cystadenocarcinoma; Lung

Abstract

We describe 10 new cases and review 66 previously reported cases of primary pulmonary mucinous cystic neoplasia (PMCN). The 3 men and 7 women were 44 to 73 years old (mean, 60.0 years) at diagnosis. Lesions were found by chest radiograph (featuring a solitary, lobulated nodule with soft tissue density that enlarged slowly), or patients had major bronchial occlusion by mucus or hemoptysis. Tumors were well-circumscribed, lobulated soft masses with a central cavity filled with gray to greenish translucent mucus and were 1.5 to 5.5 cm in greatest dimension (mean, 3.3 cm). Microscopically, confluent lakes of mucin characterized all cases. Tumor epithelium ranged from bland to focal cytologic atypia to frankly malignant. The adjacent lung parenchyma was stretched, compressed, or showed an inflammatory reaction to dissected mucus. After 1- to 10-year follow-up (mean, 3.7 years), 3 patients died of metastasis and 1 of amitriptyline toxic effects; 6 were alive without tumor. Combined analysis of our cases and previously reported cases suggests a histologic spectrum from benign cystadenoma to mucinous cystic tumor with atypia to well-differentiated mucinous cystadenocarcinoma. The histomorphologic criteria derived from this analysis can help distinguish PMCN from other types of primary or metastatic mucinous tumors and predict outcome.

Since the original report by Eck et al in 1969 in Germany and a subsequent description by Sambrook-Gowar in 1978 in England, primary mucinous cystic neoplasia (PMCN) of the lung has become a recognized entity. As of April 2004, about 66 cases had been reported in the English literature. PMCN has been referred to by various names, including mucinous cyst, mucinous carcinoma, mucinous cystadenoma (MCA), mucinous multilocular cyst carcinoma, mucinous cystadenocarcinoma (MCAC), pseudomyxomatous pulmonary adenocarcinoma, mucinous cystic tumor (MCT) of low malignant potential, and MCT of borderline malignancy. Recurrences or metastases have been described in cases designated as borderline malignancy, whereas cases with microscopic foci of “carcinoma” were reported to have no evidence of recurrence or metastases. Further adding to the confusion, different types of histologic features have been given the same diagnostic designation by different authors. In addition to the necessity for classifying PMCN according to sensible prognostic groups, well-defined diagnostic criteria are required for differentiating it from a variety of pulmonary neoplasms, including bronchioalveolar carcinoma, bronchial mucous gland adenoma, mucoepidermoid carcinoma, and metastatic mucinous adenocarcinoma.

We describe the clinicopathologic and immunohistochemical features of 10 new cases of PMCN obtained from the Tom Baker Cancer Center Registry (Calgary, Canada) using clearly defined morphologic criteria for PMCN. We also reviewed the clinical manifestations, demographics, gross and microscopic morphologic features, and immunohistochemical findings for tumors from 66 cases reported in the English literature. The analysis of our series combined with the previously reported cases strongly suggests a spectrum of entities from benign MCA to MCT with atypia (MCT-A) to well-differentiated...
MCAC. The fact that MCAC, although it can be fatal, usually is less aggressive than other types of pulmonary mucinous carcinoma warrants its designation as a distinct tumor type. Based on the analysis of the 76 cases, we propose comprehensive histomorphologic criteria for distinguishing PMCN from other types of mucinous tumor, primary or metastatic, and determining the position of an individual tumor in the spectrum of PMCN to predict clinical outcome.

Materials and Methods

Diagnostic Criteria

The following histologic criteria were used to define PMCN: (1) cystic gross appearance with or without a fibrous wall; (2) solitary, well-circumscribed lesion in the lung parenchyma with no evidence of carcinoma in situ in the bronchial mucosa to suggest endobronchial origin of the tumor; (3) greater than 90% of the tumor bulk consisting of mucin; (4) neoplastic epithelial cells are mucin-producing cells that can be floating in the mucin or lining the fibrous wall; and (5) no other primary mucinous malignant neoplasm after extensive clinical workup.

Case Selection

Among the 264 cases of pulmonary mucinous adenocarcinoma in the Tom Baker Cancer Center Registry (January 1970 to November 2003), 13 cases met the histologic criteria for PMCN. We excluded 3 cases, 2 because they proved to be metastatic colorectal adenocarcinoma and 1 because the patient was lost to follow-up. We reevaluated a minimum of 2 H&E-stained slides from each case. Clinical, radiologic, and therapeutic data were analyzed. Follow-up data were obtained by reviewing the patients' medical charts and communication with attending physicians.

Immunohistochemical Staining

Immunohistochemical staining was performed on 4-µm-thick, formalin-fixed, paraffin-embedded tumor tissue sections from the 10 selected cases using a panel of commercially available antibodies. The color was developed by using the streptavidin-biotin-peroxidase technique using 3,3′-diaminobenzidine as the chromogen, and appropriate positive and negative control samples were used. The sources and dilutions of the antibodies are listed in Table II.

Literature Review

A total of 66 reported cases of PMCN were found in the English literature. Because the diagnostic criteria and terminology used by different authors vary, we analyzed the detailed gross and microscopic description, including images and immunohistochemical staining data for each reported case in association with corresponding clinical outcome information.

Results

Clinical Features

A summary of the clinical features in our series is given in Table II. Patients’ ages ranged from 44 to 73 years (mean, 60.0 years) at diagnosis; there were 3 men and 7 women. In 7 of 10 patients, the lesions were found incidentally on chest radiograph. Characteristic radiographic features of a solitary, lobulated, nodular mass lesion that enlarged slowly over time are shown in Image 1. Computed tomography showed soft tissue density without evidence of calcification. In case 1, initial evaluation by computed tomography revealed mediastinal lymphadenopathy. Case 3 showed mucus in right middle lobe with central bronchial obstruction found on bronchoscopic examination. In 8 of 10 patients, the tumor was located in the right lung, 5 of them in the right upper lobe. Lobectomy was the common treatment choice in our series. One patient (case 3) underwent resection of a segment of main stem bronchus and the right middle lobe owing to the perihilar location of the tumor. After follow-up for 1 to 10 years (mean, 3.7 years), 3 patients died of metastasis and...
A summary of the clinical features of the 66 previously reported cases is given in Table 3. Demographic data were available for 64 cases. Patients were between 32 and 81 years old (mean, 60 years) at diagnosis; there were 36 men and 28 women. Clinical manifestations were well documented in 59 cases: 68% (40/59) of patients were asymptomatic with the lesions found incidentally by chest radiograph. The most common initial symptoms were cough (14% [8/59]), chest pain (5% [3/59]), and hemoptysis (5% [3/59]). Other symptoms included recurrent bronchitis, pneumonia, weight loss, dyspnea, exacerbation of chronic obstructive pulmonary disease, and pneumothorax. In 3 patients, mucous occlusion of the bronchial lumen was found by bronchoscopy.4,10,15 A history of smoking was explored in 32 cases in 9 previous reports.5,7-12,14,17 The overall rate of smoking was 75% (24/32). Tumor locations, types of surgery, and survival data were documented in 61 cases. Of the tumors, 69% (42/61) were located in the right lung, and 28% (17/61) were in the right upper lobe. The most common treatment choice was lobectomy in 61% (37/61) of cases, followed by wedge resection in 28% (17/61), segmental resection in 5% (3/61), and pneumonectomy in 5% (3/61). The overall tumor-related mortality rate was 18% (11/61).

In 5 previously reported cases, progressive tumor enlargement was well documented radiologically.4,8,10,13 Davison et al9 described “adenocarcinoma arising in a mucinous cystadenoma” owing to the presence of a small invasive focus (0.2 x 0.3 cm) in an otherwise benign MCA. In 1 previously reported case of MCA, the patient declined any surgical procedure and was followed up with chest radiographs and pathologic examination of aspirated endobronchial mucous plugs for 8.5 years.4 During this period, the tumor grew from 2.5 to 15 cm in maximum dimension. Cytologic atypia became more and more apparent in subsequent mucus examination, and evidence of tumor metastasis was seen in the autopsy specimen.4 These cases prompted our speculation that a process of slow progression from a benign to malignant phenotype might exist in some cases. However, there is no molecular evidence to support such a concept.

Pathologic Features

Gross Morphologic Features

In our series, all 10 tumors were well-circumscribed, lobulated, soft masses with a central cavity filled with gray to greenish translucent mucus. Image II. Pulmonary mucinous cystic neoplasia. Chest radiograph revealed a lobulated, solitary mass lesion in the right lower lobe of the lung.
size ranged from 1.5 to 5.5 cm in greatest dimension (mean, 3.3 cm). A well-defined cyst wall less than 1 mm thick was seen in 2 cases (2 and 6). In 9 cases, the tumors were located at the subpleural area with no connection to the large airway. Case 3 showed a gelatinous, mucoid, circumscribed neoplasm filling the lumen of the bronchus but no evidence of carcinoma in situ in the adjacent bronchial mucosa. A solid area of the tumor can be seen grossly in 2 cases (1 and 5). Case 1 also showed pleural adhesion and an enlarged lymph node.

Individual tumor size information was available for 42 previously reported cases.2,4,5,7-16 Tumors ranged from 0.5 to 15 cm (mean, 4.5 cm). The tumor size from the 13 cases reported by Rossi et al17 was 1.5 to 5.5 cm (mean, 2.8 cm). Gross morphologic features were well documented in 59 previously reported cases.2,5,7-10,12,13,16,17 The tumor was unilocular or multilocular with locules separated by fibrous septa or stretched alveolar walls. In 3 reports that described the cyst wall, 2 cyst walls were 0.1 cm thick and 1 was up to 5 cm thick.2,5,15 A well-defined cyst wall was absent in other reported cases. Most tumors were located subpleurally with no connection to the large airway. In 1 reported case, the tumor was located at the right hilum, but comments on its association with a major bronchus were not made.7 In the 3 reported cases with bronchial mucous occlusion, there was evidence of mucus dissection through the bronchial wall. Neoplastic cells were present in the mucus in 2 cases, but there was no histologic evidence of carcinoma in situ in the bronchial mucosa.4,15

Moran et al16 described 24 cases of “poorly circumscribed, soft, tan to grey mucoid lesions without grossly visible cystic structures”: 8 patients died of the tumor. Davison et al9 described a case of adenocarcinoma arising from cystadenoma featuring a cystic lesion in the lateral segment of the right middle lobe adherent to the anterior segment of the right upper lobe with a firm, pale area (0.3 × 0.2 cm) at one edge of the cyst, which corresponded to microscopic tumor invasion. Gross features such as an ill-defined border, firm areas, and interlobar or pleural adhesion, especially when accompanied by pleural effusion, seemed to be signs of malignancy.

### Histomorphologic Features

Microscopically, lakes of mucin characterized all of our 10 cases (Image 3). There were detached clumps or strands of mucinous epithelium within the lakes of mucin. In 3 cases, the adjacent lung parenchyma showed a foreign body–type inflammatory reaction to the dissected mucin. The adjacent lung parenchyma of the remaining 7 cases showed variable degrees of stretching or compression by the tumor.

### Table 3

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Cases</th>
<th>Age/Sex</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Designation</th>
<th>Therapy</th>
<th>Follow-up/Outcome</th>
</tr>
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<tbody>
<tr>
<td>Sambrook-Gowar2</td>
<td>1</td>
<td>68/F</td>
<td>RLL</td>
<td>15</td>
<td>MC</td>
<td>LBT</td>
<td>5 y/well</td>
</tr>
<tr>
<td>Davaney et al3</td>
<td>2</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>MCT-LMP</td>
<td>WR</td>
<td>NC</td>
</tr>
<tr>
<td>Urbanski et al5</td>
<td>2</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>MCT-LMP</td>
<td>PNT</td>
<td>NC</td>
</tr>
<tr>
<td>Kragel et al5</td>
<td>2</td>
<td>67/M</td>
<td>RML</td>
<td>2.5</td>
<td>PPA</td>
<td>LBT</td>
<td>NC</td>
</tr>
<tr>
<td>Graeme-Cook and Mark7</td>
<td>11 (M, 4; F, 7)</td>
<td>41-71 (mean, 57)</td>
<td>RUL 2, R hilum 1, LLL 2, LUL 1 (mean, 5.1)</td>
<td>1-15</td>
<td>MCT-BM</td>
<td>WR, 1; Seg, 1; LBT, 9</td>
<td>1-9.5 y (mean, 4.7)/well</td>
</tr>
<tr>
<td>Higashiyama et al8</td>
<td>2</td>
<td>75/M</td>
<td>RUL</td>
<td>2.8</td>
<td>MCAC</td>
<td>Seg</td>
<td>10 mo/died of MI</td>
</tr>
<tr>
<td>Davison et al9</td>
<td>1</td>
<td>69/F</td>
<td>RML</td>
<td>4.5</td>
<td>MCAC</td>
<td>LBT</td>
<td>4 mo/well</td>
</tr>
<tr>
<td>Dixon et al9</td>
<td>1</td>
<td>59/M</td>
<td>LUL</td>
<td>2</td>
<td>MCA</td>
<td>WR</td>
<td>6 mo/well</td>
</tr>
<tr>
<td>Divisi and Crisci11</td>
<td>1</td>
<td>56/M</td>
<td>RML</td>
<td>4.5</td>
<td>MCT-BM</td>
<td>LBT</td>
<td>NC</td>
</tr>
<tr>
<td>Roux et al12</td>
<td>2</td>
<td>53/M</td>
<td>RUL</td>
<td>5</td>
<td>MCA</td>
<td>LBT</td>
<td>2 y/died of stroke</td>
</tr>
<tr>
<td>Palpa et al13</td>
<td>2</td>
<td>40/F</td>
<td>RUL</td>
<td>3</td>
<td>MCT-BM</td>
<td>LBT</td>
<td>7/y/well</td>
</tr>
<tr>
<td>Mann et al14</td>
<td>1</td>
<td>66/F</td>
<td>LLL</td>
<td>3</td>
<td>MCT-BM</td>
<td>WR</td>
<td>4/y/recurrence</td>
</tr>
<tr>
<td>Mongahan et al15</td>
<td>1</td>
<td>48/M</td>
<td>RLL</td>
<td>15</td>
<td>MCA</td>
<td>LBT</td>
<td>NC</td>
</tr>
<tr>
<td>Morice et al16</td>
<td>24 (M, 15; F, 9)</td>
<td>33-81 (mean, 57)</td>
<td>RUL 6, RML 4, RLL 4, LUL 2, LLL 5, NC 3</td>
<td>0.5-10</td>
<td>MCA</td>
<td>LBT, 11; WR, 8; PNT, 2; Seg, 1; NC, 5</td>
<td>97 mo/died, 8; recurrence, 1; metastasis, 1; NC, 5; alive with no tumor, 9</td>
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<tr>
<td>Rossi et al17</td>
<td>13 (M, 7; F, 6)</td>
<td>40-59 (mean, 64.5)</td>
<td>RUL 6, RML 1, RLL 2, LUL 2</td>
<td>1-5.5</td>
<td>MCA</td>
<td>WR, 7; LBT, 6</td>
<td>26 mo/died, 2; alive with no tumor, 11</td>
</tr>
</tbody>
</table>

BM, borderline malignancy; LBT, lobectomy; LLL, left lower lobe; LMP, low malignant potential; LUL, left upper lobe; MC, mucinous cyst; MCa, mucinous carcinoma; MCA, mucinous cystadenocarcinoma; MCT, mucinous cystic tumor; MCT-A, MCT with atypia; MI, myocardial infarction; MMCA, mucinous multilocular cyst carcinoma; NC, not clear; NT, not treated; PNT, pneumonectomy; PPA, pseudomyxomatous pulmonary adenocarcinoma; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; Seg, segmental resection; WR, wedge resection.
The neoplastic mucinous epithelium in cases 2 and 4 demonstrated basally located small nuclei, inconspicuous nucleoli, lack of mitosis, and apically situated mucin. In case 9, mucin was largely located extracellularly, which made it difficult to find the neoplastic epithelium. After follow-up for 10, 6, and 1 year, respectively, cases 2, 4, and 9 had no evidence of tumor recurrence, metastasis, or tumor-related death. These 3 cases were designated benign MCA.

The neoplastic epithelium in cases 3 and 8 demonstrated nuclear stratification with papillary epithelial projections, tufting, mild to moderate nuclear atypia, and occasional mitoses. The tumor in case 6 extended to but did not invade the visceral pleura. After follow-up of 6 and 5 years, respectively, patients in cases 3 and 6 were alive with no tumor. The patient in case 8 died of an unrelated cause (toxic effects of amitriptyline) without evidence of tumor metastasis or recurrence. We designated these 3 cases MCT-A to alert the treating physician to the possibility of malignant transformation and the necessity for close follow-up.

Solid invasive tumors were found at the periphery of the cystic lesion in cases 1, 5, 7, and 10. Lymphovascular space invasion and lymph node metastasis were seen only in case 1. Case 5 showed signet-ring cell morphologic features. The patients in cases 1, 5, and 7 died of tumor during the follow-up period. There was no evidence of metastasis or recurrence in the 1-year follow-up in case 10; however, the patient is under close clinical observation. Tumors with histologic malignant features were designated MCAC.

All tumor cells contained acidic and neutral epithelial mucin as highlighted by positive alcian blue, periodic acid–Schiff, and mucicarmine staining. In comparison with the grayish translucent mucin produced by bland tumor epithelium, the mucin produced by atypical tumor epithelium sometimes appeared more concentrated and eosinophilic and contained cell debris and inflammatory cells. Whether this represents unique mucin components or is merely a phenomenon of overproduction of mucin with inflammatory reaction requires further study.
The microscopic description and selected images of the previously reported 66 cases were reviewed in conjunction with the clinical outcome. In cases with a grossly well-formed fibrous wall, there always was focal disruption of the cyst wall visible microscopically with mucin dissection into the adjacent parenchyma. This was not related to a compromised clinical outcome. There was no difference in clinical outcome between unilocular and multilocular tumors. The tumor cell types included tall columnar cells, low cuboidal cells, pseudostratified cells with cilia and goblet cells resembling bronchial epithelial cells, and signet-ring–type cells. Single cells or clusters of tumor epithelial cells or cellular debris and inflammatory cells were described within the pools of mucin. Some tumors were extremely paucicellular, with only rare mucin-producing epithelial cells floating in the mucin. There is no documented association between cellularity and clinical outcome. The adjacent lung tissue was described as...
stretched, compressed to atelectatic, or showing a foreign body–type inflammatory reaction to the dissected mucin.

As shown in Table 3, 7 of 66 reported cases were in the MCA category under the names mucinous cyst for 1 case,2 MCT for 1 case,10 and MCA for 5 cases.5,9,12 Histologically, these cases were extremely paucicellular or lacked cytologic atypia.

Fourteen previously reported cases with well-documented clinical features fell into the MCT-A category.7,13,14 The single largest series, 11 cases, was reported by Graeme-Cook and Mark7 in 1991. In that series, columnar mucus-producing cells lined the cysts in all cases, with cytologic and architectural atypia varying from minimal to microscopic foci of carcinoma. Patients were followed up for an average of 4.7 years, and no recurrence or metastasis was found.

Of the previously reported cases, 41 were designated malignant mucinous tumor under the names mucinous carcinoma (37 cases), mucinous cystic carcinoma (2 cases), and pseudomyxomatous pulmonary adenocarcinoma (2 cases).4,8,16,17 Among the 41 patients, 11 patients died of the tumor; 2 were alive with tumor, including 1 who had intrapulmonary tumor recurrence and 1 who had metastasis to the bone. The remaining patients were alive and well without tumor at the end of the follow-up period. The mortality rate in the malignant group was 27% (11/41). The presence of solid invasive areas and marked architectural or cytologic atypia, including prominent nuclear stratification, nuclear enlargement or high nuclear/cytoplasmic ratio, prominent nucleoli, and frequent mitoses, indicated malignancy.9,10,16,17 Signet-ring cell morphologic features were described in 3 reports13,16,17; however, association of these features with a worse clinical outcome was documented in only 1 report.17 Some authors consider that the tumor should be called mucinous adenocarcinoma only when unequivocal foci of invasive carcinoma are present.5,6

Immunohistochemical Analysis

As shown in Table 4, tumor cells of the 10 present cases showed strong positivity for high-molecular-weight keratins (AE1/AE3), low-molecular-weight cytokeratin, and cytokeratin 7, but they were negative for cytokeratin 20. Staining for thyroid transcription factor-1 (TTF-1) was variable. Tumor cells from 3 of 4 patients who eventually died of tumor metastasis stained positively for p53 in association with significantly high Ki-67 proliferation indices.

Various immunohistochemical stains were performed in 6 previous studies of 34 cases.7,5,7,10,12,14,17 The tumor cells stained positively for polyclonal (AE1/AE3) and monoclonal cytokeratin (CAM5.2) and negative for S-100, chromogranin, and bombesin. Staining results for epithelial membrane antigen and carcinoembryonic antigen were variable. In 10 of 13 cases, 12 of 14 cases, and 7 of 14 cases, the tumor cells stained positively for TTF-1, cytokeratin 7, and cytokeratin 20, respectively. In 1 report of 2 cases with benign clinical behavior, lower expression of proliferative cell nuclear antigen and Ki-67 was documented.12 Rossi et al17 demonstrated positive staining of CDX2 and MUC2 in 2 cases in association with poor outcome.

Electron Microscopy

Electron microscopic studies were performed in 3 reported cases.5,10 These highlighted the presence of intracytoplasmic mucin, convoluted oval nuclei, prominent nucleoli, and homogeneous euchromatin with peripheral chromatin condensation. Microvilli, junctional complexes, and primitive lumen formation also were seen. The lack of lamellar bodies and large dense granules essentially excluded the tumor cell origin of either type II pneumocytes or Clara cells.

Discussion

PMCN deserves to be a separate entity not only because of its unique morphologic features but also because it has clinical behavior different from other primary lung neoplasms. It usually is asymptomatic and manifests as an incidental finding on chest radiographs. It progresses slowly by enlargement of the tumor without compromising respiratory function. The
malignant variant has a relatively low mortality rate (27%) and usually can be cured by complete resection. Pathologists need to recognize this distinct entity and distinguish it from other primary mucinous lesions of the lung and metastatic mucinous tumors from other sites. The second goal is to attempt to make prognostic predictions based on analysis of the gross and microscopic morphologic features, immunohistochemical findings, and, in rare cases, electron microscopic studies.

**Diagnosis of PMCN**

To qualify for the diagnosis of primary MCT, we suggest that the tumor possess all or most of the histologic features described in the preceding text. The positive immunohistochemical staining for TTF-1 and cytokeratin 7 and negative staining for cytokeratin 20 help narrow the differential diagnosis and support the pulmonary origin of these tumors. In a small biopsy or fine-needle aspiration specimen, neoplastic epithelial cells might be overshadowed by copious mucin and/or granulomatous inflammation. It also is conceivable that differentiation from the more common mucinous bronchioalveolar carcinoma might not be possible, and evidence of invasion cannot be assessed confidently. We prefer using the term mucinous neoplasm when evaluating a small biopsy or fine-needle aspiration specimen and diagnosing MCT only on a resection specimen.

**Differential Diagnosis**

Nonneoplastic lesions that enter the differential diagnosis include developmental bronchogenic cysts and congenital adenomatoid malformations. Both can have foci of mucinous epithelium but more commonly are lined by ciliated columnar epithelium, in contrast with the purely mucinous epithelium of MCT. Developmental bronchogenic cysts are extrapulmonary, located in the midline, and have a fibromuscular wall containing cartilage and seromucinous glands. MCTs are intrapulmonary, located peripherally, and have a fibrous wall that does not contain muscle, cartilage, or seromucinous glands. Congenital adenomatoid malformations occur most often during the first 2 years of life and do not have a fibrous, inflamed cyst wall.

Neoplasms considered in the differential diagnosis are mucous gland adenoma, mucoepidermoid carcinoma, mucinous bronchioalveolar carcinoma, and metastatic carcinoma. Mucous gland adenoma and mucoepidermoid carcinoma share an endobronchial location and microcystic appearance, in contrast with the peripheral location and macrocystic morphologic features of pulmonary MCT. Squamous and intermediate cells that are typical for mucoepidermoid carcinoma cannot be seen in pulmonary MCT. Well-differentiated mucin-producing bronchioalveolar carcinoma might be most difficult to distinguish from pulmonary MCTs, especially when secondary cavitations or cysts develop through necrosis. However, the nonnecrotic area of bronchioalveolar carcinoma usually shows characteristically homogeneous cellularity with a lepidic growth pattern along preexisting alveolar walls. Necrosis is not a feature of pulmonary MCT by definition. A thorough clinical workup and immunohistochemical analysis help to exclude the possibility of a metastatic neoplasm, particularly from the ovary, breast, pancreas, and gastrointestinal tract.

**Classification**

The recent World Health Organization classification recognizes mucinous cystadenoma as “a localized cystic mass filled with mucin and surrounded by a fibrous wall lined by well differentiated columnar mucinous epithelium.” Mucinous carcinoma is defined by “invasive growth into the surrounding tissue, significant atypia and prominent pseudostratification.” MCAC is “a cystic adenocarcinoma with copious mucin production resembling tumors of the same name in the ovary, breast and pancreas.” Strict adherence to this classification system will exclude all previously reported mucinous cystadenomas because careful microscopic examination revealed that none of the cases cited had an intact fibrous wall. The World Health Organization classification system also did not recognize the entity of “borderline MCT” described by Graeme-Cook and Mark and other authors. Based on the review of previously reported cases and our series, we classify PMCN into 3 categories.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Proposed Classification of Pulmonary Mucinous Cystic Neoplasia</th>
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<tbody>
<tr>
<td></td>
<td>Mucinous Cystadenoma</td>
</tr>
<tr>
<td>Solid area at periphery</td>
<td>–</td>
</tr>
<tr>
<td>Adhesion to adjacent lobe or pleura</td>
<td>–</td>
</tr>
<tr>
<td>Nuclear stratification or tufting</td>
<td>–</td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td>–</td>
</tr>
<tr>
<td>Pleura extension/penetrationa</td>
<td>–/-</td>
</tr>
<tr>
<td>Microscopic focus of invasion</td>
<td>–</td>
</tr>
<tr>
<td>p53</td>
<td>–</td>
</tr>
<tr>
<td>Ki-67 (%)</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

*+, present; −, absent.
*a Pleural extension indicates the tumor is in contact with but does not breach the elastic layer of visceral pleura; pleural penetration indicates breach of the elastic layer by the tumor.
The category of MCT-A dealt with several fundamental issues that justify its existence. First, all cases behaved in a benign manner during the follow-up period, despite the presence of cytologic atypia. Second, the presence of atypical or malignant foci suggests that the tumor might become malignant if left untreated. Third, the presence of these histomorphologic features requires the pathologist to sample the tumor more extensively to search for malignant tumor cells or an invasive focus, especially at the periphery of the tumor. Last, this diagnostic term will alert the clinician to follow up the patient more closely after surgery to detect early recurrence or metastasis.

This review of the clinicopathologic features of 76 cases, including 10 new cases from our institution, suggests a spectrum of entities from benign MCA (n = 18), through MCT-A (n = 18), to well-differentiated MCAC (n = 43). Due to the lack of sufficient clinical information, 5 previously reported cases remain unclassified. Of the tumors, 67% belong to the malignant spectrum, and a mortality rate of 27% indicates a progression of PMCN. The diagnosis of PMCN can be suggested in biopsy or cytologic preparations, but can be established only in resection specimens after excluding other types of primary and secondary mucinous tumors. Extensive sampling to search for evidence of invasion is essential for the diagnosis of pulmonary mucinous cystadenocarcinoma, especially when atypia is present. We hope that the information in this comprehensive review will provide better understanding of the spectrum of pulmonary mucinous cystic neoplasia and will allow separation of pulmonary mucinous cystic lesions in future classifications of lung tumors.

References