Aspiration Cytomorphology of Fetal Adenocarcinoma of the Lung

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Abstract

Fetal adenocarcinoma (FA) of the lung is an exceedingly rare malignancy. Many patients with the well-differentiated form are relatively young and with the high-grade variant are older. We describe the cases of 4 women with FA examined by fine-needle aspiration biopsy. Aspirates were moderately cellular with malignant, mostly aggregated cells. Glands and acini were present. The columnar neoplastic epithelial cells had homogeneous round nuclei with fine chromatin, smooth membranes, and indistinct nucleoli. With the rapid Romanowsky stain, subnuclear vacuoles were evident in some tumor cells; at times, this was associated with a focal extracellular tigroid pattern. Morule formation was present in the 3 specimens. Immunochemically, all tumors manifested epithelial and neuroendocrine differentiation. Cytomorphologic attributes included the following: (1) distinct subnuclear vacuoles, sometimes with an associated tigroid picture; (2) small, uniform, round nuclei; (3) morules; and (4) neuroendocrine differentiation in glandular epithelial cells.

Until recently, fetal adenocarcinoma (FA) of the lung was considered a variant of pulmonary blastoma.1,2 Today, we recognize it as a very uncommon form of lung adenocarcinoma with pathogenesis, clinical manifestations and course, and microscopic morphologic features quite distinct from pulmonary blastoma.1-5 It is now known that FA occurs in low-grade (well-differentiated [WD]) and high-grade (HG) forms.3,4 FA typically occurs in young patients, many of whom are asymptomatic and have the pulmonary mass found during routine radiologic examinations. The mean and median ages at diagnosis hover between 30 and 40 years, and there may be a slight female predilection for the development of this tumor. The HG variant typically occurs several decades later in life and histologically resembles the well-differentiated variant but is associated with more complex and disorganized glands, necrosis, and larger nuclei with more prominent nucleoli and/or may be combined with other more common forms of lung adenocarcinoma.

Although many patients with WDFA are tobacco smokers, up to 24% of patients may be nonsmokers.3 In contrast with most conventional lung adenocarcinomas, perturbation in β-catenin maintenance is thought to be a crucial step in its evolution; this may be related to mutations in the gene encoding for this protein, which results in altered accumulation and nuclear distribution of β-catenin.6-8 Owing to the very improved prognosis, it is important to distinguish FA from the more common forms of primary lung adenocarcinoma, pulmonary blastoma, and metastatic adenocarcinoma. The major purpose of this writing is to provide cytomorphicologic clues to the specific diagnosis of this rare and relatively indolent cancer.
Case Reports

Case 1 involved a 17-year-old woman with a medical history of asthmatic spasms, chronic bronchitis, and reduced hearing bilaterally. She had a 1-year history of smoking one-half pack of cigarettes per day. At initial examination, she had an incidentally identified perihilar mass found on a chest radiograph during workup for lower respiratory symptoms. A subsequent chest computed tomography (CT) scan showed a 20 × 14-mm homogeneous, smoothly marginated perihilar mass that abutted the fissure in the left upper lobe. A CT-guided fine-needle aspiration biopsy (FNAB) was performed and revealed cellular smears consistent with a glandular neoplasm with neuroendocrine differentiation. Subsequently, the patient was taken to the operating room for a wedge resection with frozen section. The specimen revealed a 3.0 × 2.0 × 1.5-cm tan-white mass that was diagnosed as a “glandular neoplasm, rule out pulmonary blastoma” on intraoperative consultation. It was therefore decided that a completion lobectomy with unilateral lymph node sampling be performed. Postoperatively, the patient did well with no major complications. She reported rib pain around the operative site and dyspnea with exertion. Pulmonary function tests and chest radiographs were normal and negative for tumor. She did not receive any adjuvant therapy. During her regular follow-up examinations for 2 years, there has been no evidence of recurrent or metastatic carcinoma. She continues to smoke at the same level.

Case 2 involved a 32-year-old woman with an incidentally found large mass in the periphery of the upper lobe of the left lung. FNAB was followed by a lobectomy and lymph node dissection. The tumor was staged as a T2 N0 neoplasm. She did not receive postoperative radiation or chemotherapy. Subsequently, thymic hyperplasia developed, which was treated by thymectomy. Nine years after her pulmonary resection, she did not receive any adjuvant therapy. During her regular follow-up examinations for 2 years, there has been no evidence of recurrent or metastatic carcinoma. She continues to smoke at the same level.

Case 3 involved a 38-year-old woman with diplopia and decreased deep tendon reflexes in three extremities. CT scanning and magnetic resonance imaging of the central nervous system were negative, and several cerebrospinal fluid samples were normal. However, a CT examination of the chest done 5 weeks after initial examination revealed a 3.6-cm, irregular, lobulated mass in the lower lobe of the right lung. The mass manifested increased uptake with a positron emission tomography examination. A CT-directed FNAB was performed; this led to a surgical resection of the right lower and middle lobes. Although her diplopia persisted postoperatively, she has had no evidence of cancer for 32 months.

Case 4 involved a 38-year-old woman with a 1-month history of cough and left-sided chest pain. Her history was significant for pleurodesis on the right side for spontaneous pneumothorax 7 years earlier and a cigarette smoking history of more than 1 pack per day for 23 years. A chest radiograph and CT scan revealed a 7-cm mass in the upper lobe of the left lung with probable pleural involvement. A positron emission tomography scan showed hypermetabolic activity in the mass and in probable left hilar lymph nodes. One month after her initial evaluation, she underwent a left upper lobectomy with resection of part of the left chest wall, including parts of ribs 2 and 3. This was followed by thoracic radiotherapy and chemotherapy with cisplatin and vinorelbine. Six months postoperatively, she complained of headaches and was found to have 2 separate cerebral metastases, 1 each involving the right parietal and the left frontal lobes. The former was surgically resected, followed 3 weeks later by gamma-knife radiosurgery on the second. Whole brain radiation was given over 3 months. No evidence of cancer has been found for 34 months since the second craniotomy.

Results

Aspiration Cytomorphology

The specimen types included different forms of preparations among the cases. Cases 1 and 4 were direct smears, half of which were air dried and stained with rapid Romanowsky and half that were fixed in 95% ethanol and Papanicolaou stained. These cases also had Papanicolaou-stained cytocentrifuged preparations and a cell block. The specimens for case 2 included ThinPrep samples with the Papanicolaou stain and a cell block. The specimens for case 2 included ThinPrep samples with the Papanicolaou stain and a cell block. Only a cell block was prepared of the aspirated material in case 3. However, all specimens were moderately cellular and composed largely of cohesive aggregates of malignant cells.

Table I

Clinicopathologic Aspects in Cases of Fetal Adenocarcinoma of the Lung

<table>
<thead>
<tr>
<th>Case No./Sex/Age (y)</th>
<th>Tumor Location</th>
<th>Tumor Size (cm)</th>
<th>Grade</th>
<th>Positive Immunochemical Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/17</td>
<td>LUL</td>
<td>3</td>
<td>Low</td>
<td>CK, TTF-1, CRG, SYN</td>
</tr>
<tr>
<td>2/F/32</td>
<td>LUL</td>
<td>11</td>
<td>Low</td>
<td>CK, TTF-1, CRG, PE10</td>
</tr>
<tr>
<td>3/F/38</td>
<td>RLL</td>
<td>3.6</td>
<td>Low</td>
<td>CK, TTF-1, CRG, PE10</td>
</tr>
<tr>
<td>4/F/38</td>
<td>LUL</td>
<td>9.5</td>
<td>High</td>
<td>CK, CK7, CRG, TTF-1</td>
</tr>
</tbody>
</table>

CK, cytokeratin; CRG, chromogranin; LUL, left upper lobe; PE10, surfactant antigen; RLL, right lower lobe; SYN, synaptophysin; TTF-1, thyroid transcription factor-1.
Although a small proportion of intact, individually dispersed cells was also present, the vast majority of isolated cellular elements consisted of nuclei devoid of visible cytoplasm.

In all cases, the cohesive tumor cell aggregates dominated the specimens and ranged from flat sheets to 3-dimensional masses, both spheres and irregular aggregates Image 1 and Image 2. Within the cohesive groups, distinct acinar formation was evident, as were rarer lumen-containing true glands and obvious palisading at the periphery of clusters (Image 2) Image 3.

It is important to note that in the rapid Romanowsky-stained smears, distinct subnuclear vacuoles were well visualized and preserved (Image 2 and Image 3) Image 4, whereas such structures were not readily apparent with the alcohol-fixed, Papanicolaou-stained preparations Image 5. Furthermore, at times, a well-developed tigroid material was selectively located at the base of glands in the immediately adjacent extracellular zone (Image 2) Image 6 and Image 7. Although the volume of this material in any one area was small, it resembled that present in the smear backgrounds of aspiration biopsy specimens of seminomas and rarely in other glycogen-rich tumors.10-12 Thus, it consisted of acellular zones composed of gray fragments, sometimes with a linear contour, alternating with empty background spaces. Presumably, this pattern was derived from the cytoplasmic glycogen vacuoles. Otherwise, the cytoplasm was rather homogeneous, delicate, and faintly basophilic.

The nuclei were quite uniform in appearance and characterized by relatively small size, smooth round to slightly ovoid contours, variable staining intensity of finely granular chromatin, and inconspicuous nucleoli (Images 3-7) Image 8. The cytoplasm varied in volume from scant to moderate, resulting in relatively high nuclear/cytoplasmic (N/C)
With the rapid Romanowsky–stained preparations, rare cytoplasmic blue body–like structures were apparent (Image 8). In the Papanicolaou-stained preparations, especially the ThinPrep samples, a feathering effect was apparent focally in that neoplastic cells with a more columnar appearance projected from the otherwise smooth edges of the aggregates (Image 5). In the ThinPrep samples, a second cellular population was present characterized by somewhat larger cells with bigger nuclei with more prominent nucleoli (Image 9). In case 4, the neoplastic nuclei were minimally to moderately larger and at times housed more prominent nucleoli. The cytoplasmic qualities and architectural arrangements, however, resembled those of the tumor cells from the WDFAs.

Subnuclear vacuoles and homogeneous neoplastic nuclei are evident. In several foci, immediately adjacent to the edge of the aggregates, a focal tigroid appearance is present, represented by reticulated cytoplasm and glycogen (rapid Romanowsky, ×100).

Image 6

With a Papanicolaou stain, the finely granular and uniformly dispersed nature of the chromatin is readily appreciated, as are the delicate nuclear membranes. Many of the cells possess minute nucleoli. Scant cytoplasm results in high nuclear/cytoplasmic ratios. Focally, a feathering effect is evident, as a few of the peripherally oriented neoplastic glandular cells project from the edges of the aggregates (×100).

Image 5

In case 4, the neoplastic nuclei were minimally to moderately larger and at times housed more prominent nucleoli. The cytoplasmic qualities and architectural arrangements, however, resembled those of the tumor cells from the WDFAs.

Image 7

The focal tigroid pattern is well represented in this image, which also demonstrates acinar formation and homogeneous malignant nuclei (rapid Romanowsky, ×200).
Perhaps a slightly greater proportion of the malignant cells were individually distributed in the smears. There was no recognizable evidence of the other adenocarcinomatous components Table 2.

The cell blocks from all cases demonstrated complex tubules composed of homogeneous and rather bland columnar tumor cells Image 11. Only a minority of the neoplastic cells in the cell blocks from all cases demonstrated subnuclear vacuoles. Still, there was a suggestion of endometrial-like differentiation among the tumor cells. The cell blocks demonstrated, to varying degrees, the presence of morules, especially in case 2. These consisted of small intraluminal sheets of larger cells with more perfectly rounded and centrally situated nuclei and inconspicuous to distinct solitary nucleoli. These probably correspond to the larger cells in the ThinPrep samples. Focally in case 1, some of the nuclei in the morular structures were optically clear.

Immunocytochemical studies were done on the cell blocks from cases 1, 3, and 4. The glandular cells were intensely and diffusely positive for pancytokeratin and/or cytokeratin 7 and thyroid transcription factor-1 (TTF-1). A proportion of the tumor cells within the glandular units were positive for synaptophysin and/or chromogranin, with the former decorating a larger fraction of the cells. In case 3, the tumor cells were positive for PE10 (surfactant antigen). The cells were nonreactive for α-fetoprotein in case 1, cytokeratin 20 and thyroglobulin in case 3, and CD56 and synaptophysin in case 4.
Surgical Pathology

Grossly, the tumors were rather well circumscribed but unencapsulated, with solid and lobulated white surfaces. The histologic features of the resected neoplasms were quite similar in cases 1 through 3. On a background of loose but cellular fibroblastic stroma, interlacing and fused glands and tubules with variably contoured lumens formed the bulk of the tumor. The glands were lined by 1 or more layers of epithelial cells that varied from low to tall columnar in shape. Each cell had a solitary nucleus; as a group, the nuclei were small, round, uniform, and somewhat hyperchromatic. Nucleoli were also single and ranged from inconspicuous to small. Well-formed vacuoles were present in the cytoplasm of a minority of the tumor cells. Although some were clearly supranuclear, most were subnuclear. Otherwise, the cytoplasm was homogeneous and basophilic; often, a distinct accentuation of the cytoplasmic density was apparent at the luminal surface. A minority of the lumens were occupied by morules of larger polygonal cells with central round nuclei that frequently appeared optically clear.

In case 4 with HGFA, the nuclei of the glandular cells were larger and clearly more pleomorphic than in the other tumors; nucleoli were also larger and more prominent within relatively vesicular chromatin. The cytoplasm was optically clear in many of the malignant cells and included frequent, well-developed subnuclear vacuoles. Compared with the first 3 patients’ neoplasms, papillary structures projecting into glandular lumens and complexity of glandular contours were obvious. Squamoid morules were not identified. This histologic picture of HGFA occupied at least 90% of the tumor. The remainder consisted of conventional adenocarcinomas with both acinar and solid components.

In case 1, the tumor lacked visceral pleural invasion but approached within 1 mm of the pleura, whereas in case 2, the visceral pleura was invaded. The pleura was free of tumor in case 3. In case 4, the tumor invaded directly into the soft tissue of the chest wall, surrounding but not invading the bone of the ribs. All final margins were uninvolved by the malignancy. In the 3 cases of WDFA, all lymph nodes were benign. Of 10 examined lymph nodes in case 4, 4 contained metastatic adenocarcinoma that resembled HGFA. In this case, the histologic findings for both craniotomy specimens were also HGFA without other components present; in both metastases, multifocal tumor necrosis was evident.

In case 1, the synaptophysin immunostain was repeated on the resected tumor and manifested a pattern and distribution similar to those of the cell block (Table 1). In the resected tumor of case 2, chromogranin and neuron-specific enolase were positive in a proportion of the malignant cells, whereas cytokeratin 7 was diffusely positive. Surprisingly, the tumor cells were negative for synaptophysin and for cytokeratin 20, TTF-1, and calretinin. In case 3, TTF-1, cytokeratin 7, and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cytomorphologic Features of Well-Differentiated Fetal Adenocarcinoma</th>
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<tbody>
<tr>
<td>Distinct subnuclear vacuoles</td>
<td>Focal basal tigroid pattern</td>
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<tr>
<td>Small homogeneous round nuclei</td>
<td>Inconspicuous nucleoli</td>
</tr>
<tr>
<td>Acinar and lumen formation</td>
<td>Morules</td>
</tr>
<tr>
<td>Neuroendocrine differentiation</td>
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Image 11 (Case 3) The cell block includes rather bland-appearing neoplastic glands with small basally oriented nuclei and rather low nuclear/cytoplasmic ratios. In this particular field, subnuclear vacuoles are not well developed. Plasma cells are present in the adjacent stroma (H&E, ×400).

Image 12 (Case 3) The grossly resected tumor bulges above the cut surface of the lung. It manifests a well-circumscribed and highly lobulated contour. There is no evidence of hemorrhage or necrosis.
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Vacuoles. Thus, there is a morphologic resemblance to early secretory endometrium and normal early fetal lung. In addition, many cases include neoplastic squamoid morules in the lumens of some of the glands. The malignant glands tend to be rather densely packed and situated within loose to moderately cellular fibroblastic stroma; the latter is composed of clearly benign mesenchymal elements. Compared with conventional lung adenocarcinoma, the neoplastic nuclei are smaller and

Discussion

Previously considered a form of pulmonary blastoma, FA is now thought to be a most infrequent form of primary adenocarcinoma. Its recognition is important for individual patients in that it conveys a prominently better prognosis than conventional lung adenocarcinoma, at least in part owing to the very high proportion detected as stage I disease. This is especially true in the well-differentiated form. Demographically, WDFA is also different in that there is a rather young age at the time of diagnosis, including pediatric patients, it generally affects both sexes equally, and it is not as strongly associated with cigarette smoking.

Histologically, WDFA is composed of complex tubular glands, at times with papillae, composed of columnar tumor cells with bland nuclei, low N/C ratios, and distinct subnuclear vacuoles. Thus, there is a morphologic resemblance to early secretory endometrium and normal early fetal lung. In addition, many cases include neoplastic squamoid morules in the lumens of some of the glands. The malignant glands tend to be rather densely packed and situated within loose to moderately cellular fibroblastic stroma; the latter is composed of clearly benign mesenchymal elements. Compared with conventional lung adenocarcinoma, the neoplastic nuclei are smaller and

Image 13 (Case 1) The histologic features of the resected tumor demonstrate the classic microscopic appearance of well-differentiated fetal adenocarcinoma. The malignant cells form lumen-containing glands; have uniform, small, hyperchromatic nuclei that are basally oriented; and optically clear to faintly eosinophilic cytoplasm. Subnuclear vacuoles are well developed in a minority of the neoplastic cells. Centrally, a morule is composed of large squamoid cells with distinctly denser, eosinophilic cytoplasm and larger round nuclei with pale chromatin and small but distinct nucleoli. The scant stroma is composed of bland spindle shaped fibroblasts (H&E, ×100).

Image 14 Subnuclear vacuoles are well maintained in the histology of this high-grade fetal adenocarcinoma. The malignant nuclei are larger and more pleomorphic and irregular and have more prominent nucleoli than in the well-differentiated variant. Morules are not evident (H&E, ×400).

Image 15 (Case 4) A small proportion of the carcinoma was composed of lung adenocarcinoma of the solid subtype. An abrupt transition between the fetal adenocarcinoma and the solid adenocarcinoma is apparent (H&E, ×40).
more uniform, nuclear membranes are smoother, nucleoli are smaller and less prominent, and neuroendocrine differentiation (as detected by immunohistochemical analysis) is usual and often prominent. A major differentiating attribute of HGFA is the presence of nuclei that are larger and more pleomorphic with more obvious nucleoli than in the low-grade variant. Greater complexity of the architecture is also evident, as may be an admixture of other forms of conventional adenocarcinoma of lung, as in case 4 in this series.

The pathogenesis of FA is also likely quite different from that of conventional adenocarcinomas. Abnormalities in β-catenin, often related to mutations in its gene and, thus, aberrations in the WNT signaling pathway, are crucial to its development.6-8,13 By immunohistochemical analysis, distinct nuclear and cytoplasmic staining for β-catenin in the tumor cells is noted in FA. This finding is similar to the expression pattern for this protein in embryonic pulmonary tissues. In distinction, conventional adenocarcinomas typically manifest an obvious cell membranous pattern for β-catenin and do not contain mutations in the β-catenin (or related) genes. Furthermore, we are aware of only 2 cases of W DFA associated histologically with a lepidic (bronchioalveolar) growth pattern of in situ carcinoma, and in those reports, the appearance of the malignant cells growing along the intact alveoli was not well detailed.3,14

In FNAB of conventional adenocarcinomas, smears are usually highly cellular, and, often, 3-dimensional structures including spheres, papillary-like structures, and other masses are abundant.15 Often, nuclear palisading is evident, at least focally, at their edges. Within the aggregates, acinar formation or true lumens may be recognized. In higher grade neoplasms, syncytial arrays, that is, clusters with inapparent intercellular borders and overlapping nuclei, are expected, as is an increase in the proportion of individually scattered malignant cells. Most adenocarcinoma cells have solitary, enlarged nuclei that are relatively round or ovoid, but with small irregularities of their membranes, which may also be variably thickened. Hyperchromasia is the rule but may not always be present. Nucleoli are usually prominent based on their sizes, shapes, and numbers. Cytoplasm is typically basophilic, delicate, and variably vacuolated or foamy. If distinct vacuoles are evident, they are almost always supranuclear. The volume of cytoplasm varies, but compared with normal respiratory epithelial cells, the N/C ratios are somewhat to greatly elevated. Necrotic debris may be noted in the smear background.

In our experience with WDFAs, smear cellularity and the proportion of intact individual tumor cells are lower than in conventional adenocarcinomas. Homogeneity of the nuclear sizes and appearances was more prominent than expected in usual glandular cancers; they were smaller and smoother. Nucleoli were much less well developed than in conventional tumors. Cytoplasmic vacuoles, as witnessed in air-dried preparations, are at times distinctly subnuclear, as opposed to the more typical apical cytoplasmic positions. In addition, the supranuclear vacuoles tend to be smaller and less distinct. Despite these attributes, aspiration samples of WDFAs are not difficult to discern as neoplastic and malignant.

The cytomorphic features of WDFAs have been previously published in 6 single case reports; 1 of the WDFAs had initially been diagnosed as a pulmonary adenocarcinoid tumor.8,9,16-20 This includes a combination of 5 FNABs, 3 bronchial washings, and 2 brushings. Overall, the previously described features of W DFA mirror the attributes described herein. Common cytoarchitectural features include rather well-preserved intercellular cohesion with variably sized and shaped aggregates with sharply defined borders, acinar formation, gland lumens, and columnar tumor cells with small basally oriented, smooth round (to ovoid) nuclei with relatively bland chromatin, and inconspicuous nucleoli. Individual cell attributes include morules composed of larger cells with more abundant cytoplasm and prominent nucleoli (although Aleong et al20 stated the syncytial masses were composed of the smaller tumor cells) and an absence of nuclear molding. It is important to note that none of the prior reports described well-formed cytoplasmic vacuoles. This is likely related to the lack of air-dried, Romanowsky-stained smears (in contrast with the alcohol-fixed, Papanicolaou-stained specimens). In the rapid Romanowsky–stained slides in cases 1 and 4, well-defined cytoplasmic vacuoles were obvious in some of the tumor cells, including those with a clear-cut subnuclear position. The same is true for the focal tigroid pattern occasionally present just extrinsic to the base of the glands. In our single case of HGFA, although the nuclei were more clearly malignant than in W DFA, the cytoplasmic and architectural attributes were quite similar; this includes subnuclear vacuoles and a focal tigroid picture.

In addition to conventional lung adenocarcinoma, the differential diagnosis also includes carcinoid tumors, more primitive embryonal malignancies and endometrioma, and metastatic endometrial adenocarcinoma. Carcinoids are usually composed of homogeneous tumor cells as well, but they have round to ovoid, not columnar, contours.15 The small round nuclei have more distinctly and coarsely granular (“salt and pepper”) chromatin. Tumor cell cytoplasm is not vacuolated, but rather may be granular; this is especially well seen in Romanowsky-stained preparations in which they may appear as fine red minute granules on a basophilic background. Plasmacytoid forms are characteristic, as are capillary vessels dissecting into tumor cell aggregates. Immunocytochemical studies may not be helpful. Both are expected to express neuroendocrine markers of differentiation, and both may express TTF-1. Primitive neuroectodermal neoplasms are rare as primary pulmonary neoplasms. However, the relatively high N/C ratios, the lack of well-developed nucleoli, and young...
patient age may suggest such. Teratomas would also apply here, especially if more than 1 cell type appears, including columnar, small neuroendocrine, and squamoid forms. The one immunoreaction that may truly be useful in these settings is β-catenin with its abnormal nuclear expression in WDFA. Although infrequent in the lung, lesions composed of rather well-differentiated endometrial elements must be considered because FA share morphologic attributes with secretory endometrium. This is especially true in premenopausal women and in patients receiving a progestational agent therapeutically. The recognition of endometrial stromal cells with the glands will help in the interpretation of pulmonary endometriosis. In addition, in endometriosis, the benign glandular cells have lower N/C ratios. The nuclei in metastatic endometrial carcinomas will be more obviously malignant than in WDFA. This distinction, however, may be complicated by the fact that a minority of endometrial adenocarcinomas are positive for TTF-1.21

The specific cytologic diagnosis of FA may be challenging. The young age of patients may be helpful in considering this neoplasm. Recognition of 2 distinctly different-appearing neoplastic epithelial tumor cell populations, some with columnar shapes and others forming squamoid morules including optically clear nuclei, indistinct nucleoli, and subnuclear vacuoles (in air-dried samples and cell blocks), should lead to a correct diagnosis or at least the suspicion of such. Immunohistochemical studies with markers of epithelial and neuroendocrine differentiation and with β-catenin certainly will support WDFA preoperatively. Distinction of WDFA from conventional lung adenocarcinoma is important owing to the better prognosis.

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