Primary Pulmonary Adenocarcinoma With Intestinal Differentiation Mimicking Metastatic Colorectal Carcinoma

Case Report and Review of Literature

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Key Words: Primary pulmonary adenocarcinoma; Metastatic colorectal carcinoma; Cytokeratin 7; Cytokeratin 20; Thyroid transcription factor-1; TTF-1; CDX-2; Immunohistochemistry

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Abstract

Pulmonary adenocarcinoma with intestinal differentiation is rare and typically expresses proteins common to lung primaries. We report a case in a 51-year-old woman with a solitary 3.3-cm mass in the left lower lobe. Additional clinical investigation, including positron emission tomography scan with fluorine 18–labeled fluorodeoxyglucose, colonoscopy, and capsule endoscopy of her small bowel, revealed no evidence of tumor elsewhere. She underwent left lower lobectomy with mediastinal lymphadenectomy. Histologic examination revealed tall columnar cells without goblet cell differentiation arranged in a cribriform and acinar pattern with extensive central necrosis. Metastatic carcinoma was present in multiple hilar lymph nodes. Mediastinal lymph nodes were negative. Immunohistochemical stains demonstrated diffuse positivity for cytokeratin (CK) 20 and CDX-2 in neoplastic cells with negative staining for CK7 and thyroid transcription factor-1. CK7 expression has been documented in all 14 cases previously reported. This is the first description of pulmonary adenocarcinoma with intestinal differentiation with histopathologic and immunophenotypic findings indistinguishable from metastatic colorectal adenocarcinoma.

The histologic heterogeneity of primary pulmonary carcinoma, particularly adenocarcinoma, is well recognized.1 Several uncommon adenocarcinoma variants have histologic and immunohistochemical characteristics that overlap with counterparts in the gastrointestinal tract.1–3 In 1991, Tsao and Fraser4 described pulmonary adenocarcinoma with intestinal differentiation, an uncommon subset of primary pulmonary adenocarcinomas characterized by a predominant component (>50%) of neoplastic tall columnar cells, goblet cells, and Paneth cells with occasional neuroendocrine differentiation. A subsequent report documented ultrastructural findings previously considered specific for metastatic colorectal carcinoma in a single case of pulmonary adenocarcinoma with intestinal differentiation.5

The distinction of pulmonary adenocarcinoma with intestinal differentiation from metastatic colorectal carcinoma is important because of obvious differences in therapeutic strategies and prognosis. Clinical history, disease distribution, and routine histologic examination can resolve the differential diagnosis in most cases. Immunohistochemical studies using a small panel of antibodies have emerged as a powerful tool in more difficult cases. Cytokeratin (CK) 20 is positive in almost all colorectal carcinomas (especially cases with microsatellite stable morphologic features) but is detectable in fewer than 10% of primary lung adenocarcinomas, typically showing only focal weak immunoreactivity.6 CDX-2 is a homeobox gene related to the Drosophila caudal gene that encodes a nuclear transcription factor. CDX-2 is a sensitive and specific marker for primary and metastatic colorectal adenocarcinomas,7,8 although it has been reported in 13% of lung adenocarcinomas and occasionally in other nongastrointestinal adenocarcinomas.8,9 Thyroid transcription...
factor (TTF)-1 is expressed in the majority of lung adenocarcinomas and nearly all thyroid carcinomas but has only rarely been reported in adenocarcinomas originating at other sites. Yousem demonstrated strong diffuse immunoreactivity for CK7 and at least focal staining for TTF-1 in 6 cases of pulmonary adenocarcinoma with intestinal differentiation, with variable expression of other immunohistochemical markers. It is important to note that none showed staining for CK20 or CDX-2 in the absence of immunoreactivity for CK7 and TTF-1, a profile most likely to be confused with metastatic colorectal carcinoma.

To alert pathologists to this potential diagnostic pitfall, we describe our experience with 1 case of pulmonary adenocarcinoma with intestinal differentiation in which histologic and immunohistochemical findings were indistinguishable from colorectal adenocarcinoma.

Case Report

A 51-year-old woman with a 35- to 40-pack-year smoking history underwent evaluation elsewhere for nonproductive cough. She had no history of malignancy, and no gastrointestinal complaints were given during the review of systems. A computed tomographic (CT) scan of her chest displayed a spiculated mass in the left lower lobe. Fiberoptic bronchoscopy with transbronchial biopsy failed to yield a diagnosis, and she underwent percutaneous core needle biopsy under radiologic guidance. The needle biopsy showed an adenocarcinoma with an acinar growth pattern and extensive “dirty necrosis” that strongly suggested metastatic colorectal carcinoma. Fluorine 18–labeled fluorodeoxyglucose (FDG)–positron emission tomography (PET) scan revealed high FDG avidity in the left lower lobe lesion without abnormal uptake elsewhere. Abdominal CT scan, colonoscopy, and capsule video endoscopy failed to demonstrate a gastrointestinal primary tumor. She underwent left lower lobectomy and mediastinoscopy for a presumptive diagnosis of lung carcinoma.

Materials and Methods

The tissue sample for light microscopy was fixed in 10% neutral buffered formalin and processed for routine histologic examination. Immunohistochemical analysis was performed with the labeled streptavidin-biotin system by means of an automated immunostainer (Ventana NexES, Ventana Medical Systems, Tucson, AZ). The following monoclonal antibodies were applied: TTF-1 (dilution 1:400; DAKO, Carpinteria, CA), CDX-2 (dilution 1:100; BioGenex, San Ramon, CA), and CK7 and CK20 (dilution for both, 1:50; DAKO). Negative control samples consisted of antibody diluent (catalog No. 251-018, Ventana). Positive control samples reacted accordingly.

Results

Gross and Microscopic Pathologic Findings

An extensively necrotic 3.3 × 2.0 × 1.3-cm ill-defined gray-tan mass closely abutted overlying puckered visceral pleura in the resected left lower lobe. Microscopically, the tumor was composed of medium to large complex glands with infolding and bridging of the epithelium in a desmoplastic stroma. In some areas, the tumor had a cribriform and solid growth pattern with minimal lumen formation. Neoplastic cells were cuboidal to columnar with stratified ovoid nuclei.
and eosinophilic cytoplasm. Neoplastic glandular spaces were filled with nuclear and cellular debris resulting in a characteristic pattern of “dirty necrosis” Image 1B. Of 16 hilar (N1) lymph nodes, 11 were positive for metastatic adenocarcinoma. Mediastinal (N2) lymph nodes were negative.

**Immunohistochemical Analysis**

Immunostains performed on paraffin sections were diffusely and strongly positive for CK20 Image 2A and CDX-2 Image 2B in neoplastic cells. Negative staining for CK7 Image 2C and TTF-1 Image 2D was demonstrated. Control samples stained appropriately.

**Follow-up**

After surgery, the patient completed 4 cycles of adjuvant chemotherapy. CT and PET scans performed at the last follow-up visit 10 months after surgery showed a new FDG-avid soft tissue mass at the surgical resection site. Multiple FDG-avid left hilar, supraclavicular, paratracheal, subcarinal, pericardial, and internal mammary lymph nodes were seen, compatible with recurrent metastatic disease. There was a focus of FDG uptake in the right posterior ninth rib suggestive of osseous metastasis. There was no lesion or FDG avidity below the diaphragm.

**Literature Review**

Clinicopathologic and immunohistochemical features of pulmonary adenocarcinoma with intestinal differentiation have been previously reported in the English literature for 15 patients, including the subject of our report Image 2. Pulmonary adenocarcinoma with intestinal differentiation in which the immunostaining profile closely mimicked colorectal carcinoma. Neoplastic cells contrasted with nonneoplastic respiratory epithelium in being diffusely and strongly immunoreactive for cytokeratin (CK) 20 (A, ×100) and CDX-2 (B, ×100) and negative for CK7 (C, ×100) and thyroid transcription factor-1 (D, ×100).
Patients include 7 women and 8 men with a median age of 67 years (range, 51-82 years). The tumors ranged from 1.5 to 7.0 cm (median, 3.4 cm) in greatest dimension. Of 15 patients, 10 (67%) initially had T2 (9 patients) or T3 (1 patient) disease; 6 of the 10 patients had nodal metastases. Of 14 patients for whom follow-up information was provided, 5 had died, 1 without evidence of disease. Of the 15 tumors, 14 (93%) were CK7+, 3 (20%) coexpressed CK20, and 6 (40%) were CDX-2+ with patchy immunoreactivity in 3. Ten (67%) cases were positive for TTF-1. Ours is the only case demonstrating absence of staining for CK7 and TTF-1 in the face of strong diffuse staining for CK20 and CDX-2.

**Discussion**

Separating pulmonary adenocarcinoma with intestinal differentiation from metastatic colorectal carcinoma can be difficult on the basis of histopathologic findings alone. Adenocarcinomas with intestinal differentiation have been described in a wide variety of anatomic sites, including paranasal sinuses,\(^\text{13,14}\) extrahepatic biliary tree,\(^\text{15}\) uterine cervix,\(^\text{16}\) ovary,\(^\text{17}\) and lung.\(^\text{4,6,11,12}\) The morphologic spectrum and immunohistochemical profiles of these adenocarcinomas overlap with those of colonic adenocarcinomas. Most primary pulmonary adenocarcinomas are characterized by heterogeneous morphologic features, whereas metastatic adenocarcinomas are more likely to show uniform histologic features resembling those typical of the primary site. The tumor in our case was challenging because it was composed entirely of malignant cells forming glands with associated dirty necrosis, closely resembling metastatic colorectal carcinoma.

Our patient’s tumor illustrates that pulmonary adenocarcinoma with intestinal differentiation can have an immunostaining profile indistinguishable from that of metastatic colorectal carcinoma. Immunohistochemical analysis is often helpful in separating primary lung adenocarcinomas, including those with associated intestinal differentiation, from metastases. Nearly all pulmonary adenocarcinomas with intestinal differentiation reported to date expressed CK7, and a majority were positive for TTF-1. CDX-2 is a relatively sensitive and specific marker for enteric differentiation and is diffusely expressed in most colorectal carcinomas. CDX-2 is occasionally present in primary pulmonary carcinomas, however, including about 40% of pulmonary adenocarcinomas with intestinal differentiation. Of the 5 previously reported cases of pulmonary adenocarcinoma with intestinal differentiation that were positive for CDX-2, 3 showed concomitant staining for CK20, but all were also immunoreactive for CK7 and 1 showed focal staining for TTF-1. Ours is the only case of pulmonary adenocarcinoma with intestinal differentiation reported to date in which the immunophenotype perfectly mimicked that of metastatic colorectal carcinoma.

The preoperative evaluation and natural history of disease in our patient strongly support our conclusion that this was a primary lung carcinoma. At initial examination, she had a solitary lung mass and no other known primary tumors. FDG-PET and fiberoptic colonoscopy have very high sensi-

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**Table 1**

**Reported Cases of Primary Pulmonary Adenocarcinoma With Intestinal Differentiation**

<table>
<thead>
<tr>
<th>Reference/Sex/Age (y)</th>
<th>Size (cm)/Site</th>
<th>CC-like Component (%)</th>
<th>CK7</th>
<th>CK20</th>
<th>TTF-1</th>
<th>CDX-2</th>
<th>Stage</th>
<th>Clinical Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inamura et al(^\text{11})</td>
<td>M 5.0/RUL 50</td>
<td>+ – + –</td>
<td>T3N1M0</td>
<td>D (60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M 4.0/LUL 60</td>
<td>+ – + +</td>
<td>T2N2M0</td>
<td>D (47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F 2.6/LLL 70</td>
<td>+ P+ – P+</td>
<td>T1N0M0</td>
<td>A (43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M 3.4/RLL 50</td>
<td>+ P+ – P+</td>
<td>T2N0M0</td>
<td>A (43)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>M 2.3/RLL 80</td>
<td>+ – + +</td>
<td>T1N0M0</td>
<td>A (30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M 1.7/RLL 80</td>
<td>+ – P+ P+</td>
<td>T1N0M0</td>
<td>A (16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M 3.9/LUL 80</td>
<td>+ – – –</td>
<td>T2N1M0</td>
<td>A (12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yousem(^\text{10})</td>
<td>F/74 3.6/RUL NA</td>
<td>+ – + –</td>
<td>T2N1M0</td>
<td>DOD (26)</td>
<td></td>
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<tr>
<td>F/70 1.7/RUL NA</td>
<td>+ – + –</td>
<td>T2N1M0</td>
<td>DOD (18)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>M/82 6.5/RUL NA</td>
<td>+ – P+ –</td>
<td>T2N0M0</td>
<td>DNED (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>F/63 1.5/RUL NA</td>
<td>+ – +</td>
<td>T1N0M0</td>
<td>ANED (7)</td>
<td></td>
<td></td>
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<tr>
<td>F/73 7.0/LLL NA</td>
<td>+ – +</td>
<td>T2N0M0</td>
<td>ANED (3)</td>
<td></td>
<td></td>
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<tr>
<td>F/57 2.0/RUL NA</td>
<td>+ – +</td>
<td>T2N0M0</td>
<td>ANED (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Maeda et al(^\text{12})</td>
<td>M/69 2.5/RLL Predominant</td>
<td>+ – + NA</td>
<td>T1N0M0</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Present case</td>
<td>F/51 3.3/LLL 100</td>
<td>– + – +</td>
<td>T2N1M0</td>
<td>ALR (10)</td>
<td></td>
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</tbody>
</table>

A, alive; ALR, alive, local recurrence; ANED, alive, no evidence of disease; CC, colorectal carcinoma; CK, cytokeratin; D, died; DNED, died, no evidence of disease; DOD, died of disease; LLL, left lower lobe; LUL, left upper lobe; NA, not available; P, patchy; RLL, right lower lobe; RUL, right upper lobe; TTF, thyroid transcription factor; +, positive; –, negative.

* When reported.

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tivity and specificity for the detection of primary colorectal carcinomas and were both negative in our case, as was the capsule video endoscopy of the upper and lower gastrointestinal tract. Furthermore, neither a primary gastrointestinal lesion nor evidence of metastatic liver disease was identified 10 months after resection of the lung tumor.

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References


