Immunohistochemical Confirmation of Pulmonary Papillary Adenocarcinoma Metastatic to Ovaries

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Metastatic papillary adenocarcinomas of the ovary are rare compared to primary ovarian papillary serous carcinomas. We report a case of pulmonary papillary adenocarcinoma metastatic to the ovary and show how this tumor can be differentiated immunohistochemically from an ovarian primary. Paraffin blocks of the ovarian tumor were analyzed for carcinoembryonic antigen, CA 125, surfactant, E-cadherin, N-cadherin, and vimentin. These markers are useful in differentiating epithelial tumors of lung versus ovarian origin. The papillary tumor showed expression of carcinoembryonic antigen, surfactant, and E-cadherin, but was negative for CA 125, N-cadherin, and vimentin. These findings support a lung carcinoma metastatic to the ovary.

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Metastasis of primary lung cancer to the ovary is fairly uncommon.1,2 When it does occur, it can often be in the absence of clinical symptoms. Ovarian neoplasms presenting in the setting of a previously diagnosed pulmonary malignancy can pose a diagnostic dilemma, and differentiating primary ovarian cancer versus metastasis from a known lung primary can be difficult clinically. We report the case of a young woman with a 5-year history of progressive papillary adenocarcinoma of the lung who presented with bilateral ovarian tumors.

REPORT OF A CASE

The 42-year-old patient with a 12-pack-year history of smoking first presented to her internist with symptoms of bronchitis and pleuritic chest pain. A chest radiograph revealed a 5-cm mass in the right lower lobe of the lung, with a second 1-cm nodule observed in the right upper lobe of the lung. Bronchoscopic washings and biopsies were positive for papillary adenocarcinoma, with evidence of pleural involvement. A thyroid primary was excluded clinically, histologically (lack of cytologic features of papillary thyroid cancer), and immunohistochemically (thyroglobulin negative). A metastatic workup at the time was negative for other lesions. A second opinion at the University of Pennsylvania Medical Center concurred with the diagnosis of a lung primary. At this time, the patient’s gynecologic examination (Papanicolaou test, pelvic examination, pelvic ultrasound and computed tomography, and endometrial biopsy) revealed no abnormalities. The patient was treated with multiple chemotherapeutic agents, including etoposide, cisplatin, paclitaxel, gemcitabine, vinorelbine, and docetaxel. She was monitored with annual computed tomographic scans. Her disease has progressed, but she has been relatively asymptomatic with a good quality of life.

Five years following her initial diagnosis, a computed tomographic scan of the pelvis revealed a small to moderate amount of free fluid. Ultrasound showed a normal uterus but enlarged ovaries (3.1 and 5.8 cm). Both ovaries were interpreted to have simple cysts without evidence of free fluid. A 3-month follow-up ultrasound showed enlargement of the right ovary with multiple bilateral cysts with a few septations. Clinical examination showed palpable enlargement of the ovaries.

At laparoscopy, multinodular tumor implants on the surfaces of the ovaries were observed (Figure 1, A), and a biopsy was performed. The uterus and fallopian tubes appeared normal at this time. Tumor nodules studding the hemidiaphragm (Figure 1, B) and a small amount of bloody pelvic ascites were present. The remainder of the abdomen appeared grossly free of tumor. On microscopic examination, the biopsy specimen showed a papillary adenocarcinoma that was morphologically similar to the lung primary with relatively broad fibrovascular stalks in the papillae of the tumor (Figure 2, A). Immunohistochemistry confirmed the tumor to be consistent with a lung primary, positive for carcinoembryonic antigen (monoclonal, Zymed, South San Francisco, Calif) (Figure 2, B) and E-cadherin (clone 36, Transduction Lab, Lexington, Ky), but negative for CA 125 (clone OV 185, Ventana, Tucson, Ariz), vimentin (clone VIM 384, Ventana), and N-cadherin (Zymed) (Table).

A repeat computed tomographic scan of the pelvis 2 months later showed bilateral cystic ovarian masses that had enlarged to 11 cm in aggregate diameter. The patient was symptomatic with pelvic pressure. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed due to the enlarging masses with involvement of the uterus. At pathologic examination, sectioning of the ovaries showed a focally cystic tumor. Additional pathologic studies showed the tumor had moderate mucin production and expressed surfactant (clone SPB01, NeoMarker, Fremont, Calif) and cytokeratin 7 (clone K72, Cell Marque, Austin, Tex), but did not express cytokeratin 20 (clone Ks20.8, Cell Marque), consistent with a lung primary.4

COMMENT

The ovary is the predominant female genital organ for development of secondary malignancies,2 and metastatic tumors comprise a significant proportion of ovarian neoplasms.1 Extragenital metastatic tumors to the ovaries more frequently are from breast or gastrointestinal tract...
Figure 1. At the time of laparoscopy, multiple tumor nodules were present on the surfaces of the ovaries (A) and on the diaphragmatic surfaces (B).

Figure 2. Pathology of papillary adenocarcinoma metastatic to ovary. A, The tumor showed broad fibrovascular cores with epithelial cells with moderate cytopathic atypia (hematoxylin-eosin, original magnification X40). B, Tumor cells showed positive staining for monoclonal carcinoembryonic antigen (immunohistochemistry, original magnification X40).

Staining Pattern of Pulmonary Papillary Adenocarcinoma in Ovary

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Staining Pattern</th>
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<tbody>
<tr>
<td>Carcinoembryonic</td>
<td>Positive</td>
</tr>
<tr>
<td>CA 125</td>
<td>Negative</td>
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<tr>
<td>E-cadherin</td>
<td>Positive</td>
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<tr>
<td>N-cadherin</td>
<td>Negative</td>
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<tr>
<td>Surfactant</td>
<td>Positive</td>
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<tr>
<td>Vimentin</td>
<td>Negative</td>
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* Staining was performed on a Ventana Nexxus automated stainer (Ventana Medical Systems Inc, Tucson, Ariz) using monoclonal antibodies with standard antigen-retrieval protocols. Staining was considered positive when there was moderate to strong staining in more than 25% of the cells. Negative cases showed no staining or only weak staining in less than 10% of the cells. Staining was observed in the cell–cell membrane region for cadherins and in the cytoplasm for the other antibodies.

Pulmonary metastases to ovaries are much less frequent and account for 2% to 5% of cases in large autopsy series. The interval from detection of the primary tumor to ovarian metastasis has been reported to be up to 2 years in some series. Occasionally, the metastatic ovarian tumor preceded the diagnosis of the extraovarian primary tumor. In our case, the interval between the primary lung tumor diagnosis and subsequent ovarian tumors was 5 years. This interval may reflect the more indolent behavior of a well-differentiated papillary adenocarcinoma and/or initial response to chemotherapy.

The patient's history of smoking and the initial presentation of malignancy in the lung are compatible with a lung primary. Additionally, the tumor was initially confined to lung and pleura with normal ovaries on clinical and radiologic examination. If the initial lung tumor had been metastatic ovarian carcinoma, it would have represented stage IV disease at presentation. We believe the survival data favor a lung primary, as the 5-year survival data for papillary adenocarcinoma of the lung is about 24%, compared to about 10% 5-year survival for stage IV ovarian epithelial cancer.

In addition to the sequence of tumor development in the lung followed by ovaries, the presence of bilateral ovarian surface involvement by multiple bosselated nodules and the immunohistochemical profile of the tumor are consistent with a pulmonary primary. Positivity for carcinoembryonic antigen and negativity for CA 125 are more likely to be seen in tumors of lung origin and are rarely seen in ovarian primaries. Furthermore, in this setting a lack of immunoreactivity to N-cadherin also argues for a lung rather than an ovarian origin.

N-cadherin is present in more than 95% of ovarian serous carcinomas and is not found in more than 95% of pulmonary adenocarcinomas. The papillary adenocarcinoma is mucin producing and has an immunohistochemical profile that is typical of lung primaries, but not of ovarian serous origin.

Although there are reports of other types of lung tumors to the ovaries, we are not aware of any other reported cases of a papillary adenocarcinoma of the lung metastatic to the ovaries. Morphologic similarity between the tumors is important, and when the histology is more consistent with one site over the other, the identification of the primary site is more readily discernible on morphologic grounds. However, as shown in this case, immunohistochemical markers can be useful in this and other specific settings to help elucidate the site of origin of
tumors in which the morphologic features could be compatible with a primary from either site.

References