Ovarian Metastasis Originating from Bronchioloalveolar Carcinoma: a Rare Presentation of Lung Cancer

Kun-Yun Yeh¹, John W.-C. Chang¹, Swei Hsueh², Ting-Chang Chang³ and Meng-Chih Lin⁴,⁵

¹Division of Hemato-oncology, Department of Medicine, ²Department of Pathology, ³Department of Gynecology & Obstetrics, and ⁴Division of Pulmonary & Critical Care Medicine, Department of Medicine, Chang Gung Memorial Hospital and ⁵Department of Respiratory Care, Chang Gung University, Taipei, Taiwan

Received April 7, 2003; accepted July 28, 2003

Ovarian metastasis originating from bronchioloalveolar carcinoma (BAC) has not been reported previously. We report a 63-year-old Chinese woman who was diagnosed as BAC with pleural metastasis in 1997. Four years later, she complained of vaginal bleeding, and a pelvic mass was discovered by an abdominal computerized tomography scan. Tumor debulking and total hysterectomy with bilateral salpingo-oopherectomy were performed. Pathology disclosed well-differentiated adenocarcinoma, with abundant clear cytoplasm, in the ovaries. Furthermore, immunohistochemical staining revealed that the tumor cells from the ovary and pleura were reactive to thyroid transcription factor 1 (TTF-1) and cytokeratin-7 (CK-7) but were negative for cytokeratin-20 (CK-20). The results of immunohistochemical staining, clinical course, and pathological features were compatible with the diagnosis of BAC with ovarian metastasis. In conclusion, to investigate the primary site of a metastatic ovarian cancer, clinicians should not forget the lungs since the incidence of lung cancer in females is increasing. Moreover, a monoclonal antibody panel for TTF-1, CK-7, and CK-20 may facilitate discrimination between primary and metastasized ovarian adenocarcinomas and/or identifying tumors of pulmonary origin.

Key words: bronchioloalveolar carcinoma – ovarian metastasis – thyroid transcription factor 1

INTRODUCTION

Ovarian adenocarcinoma can be a primary ovarian neoplasm, or metastasis from other sites such as the stomach, breast, pancreas, kidney, or colon. Differentiating between primary ovarian and metastatic adenocarcinoma is crucial since the treatment and prognosis for these cancers are markedly different. Although the clinical course of the tumor, its close resemblance to a number of recognized categories of primary malignancy, and the rarity of ovarian cancers of similar histological type may prove helpful in conclusively establishing diagnosis, clinicians may still occasionally encounter difficulties. Advanced techniques, such as specific immunohistochemical staining, may provide additional evidence to differentiate primary from metastatic ovarian neoplasm.

Recently, sensitivity and specificity for lung adenocarcinoma of 76% and 100%, respectively, have been demonstrated for a monoclonal antibody to thyroid transcription factor 1 (TTF-1), a protein mediating thyroid-specific transcription of thyroglobulin, expressed in the thyroid, diencephalon, and bronchioloalveolar epithelia (1). Chhieng et al. (2) described that an adenocarcinoma is likely to be a primary lung tumor when it is of the cytokeratin-7 (CK-7) positive/ cytokeratin-20 (CK-20) negative phenotype and demonstrates either TTF-1 or PE-10 positive staining. Herein, we report a case in which immunohistochemical staining with TTF-1, CK-7, and CK-20 has been utilized to confirm ovarian metastasis originating from a bronchioloalveolar carcinoma (BAC).

CASE REPORT

A 63-year-old Chinese woman was admitted to our institution in October 1997. She complained of cough with occasional blood-tinged phlegm. The patient did not have a history of smoking, exposure to asbestos, or radiation. No evidence of lymphadenopathy or breast nodules was noted on physical examination. A chest X-ray revealed right-upper-lobe collapse with pleural effusion. Computerized tomography (CT) of the chest and upper abdomen revealed an 8 cm mass in the right-upper lobe, without liver, subcranial, or mediastinal lymph-node involvement (Fig. 1a). Pleural biopsy revealed a well-differentiated adenocarcinoma with abundant clear cytoplasm (Fig. 2a). The clinical picture and evidence from a microscopic
examination of the tumor cells were consistent with the diagnosis of BAC with pleural metastasis (Stage IIIIB). Despite the potentially fatal implications of such a decision, the patient refused to undergo chemotherapy or radiotherapy. Regular follow-up of the patient was conducted at the clinic after pleurodesis.

In May 2001, the patient was hospitalized with a three-month history of progressive vaginal bleeding and lower-abdominal discomfort with urinary incontinence. An abdominal CT scan revealed a multilobulated ovarian tumor (10 × 6 cm) with ascites in the pelvic cavity (Fig. 1b). The CEA (52.7 μg/l; normal range <5) and CA-125 (337 U/ml; normal range <20) were elevated. No significant progression of the co-existing bronchioloalveolar carcinoma was noted in the follow-up chest X-rays. The patient underwent abdominal hysterectomy, followed by maximal tumor debulking and bilateral salpingo-oophorectomy. Microscopic examination of the ovaries revealed that the tumor was a uniform, well-differentiated adenocarcinoma, with cells characterized by abundant clear cytoplasm (Fig. 2b and inset). The goblet-cell pattern typically seen in primary ovarian neoplasm was not observed in this patient. The clinical course and pathological features supported the diagnosis of BAC with ovarian metastasis. To confirm the same result, immunohistochemical staining with monoclonal antibodies against TTF-1 (TTF-1 DAKO), CK-7 (CK-7 DAKO) and CK-20 (CK-20 DAKO) was performed. Both lung and ovarian-tumor cells showed marked nuclear TTF-1 (Fig. 2c and d) and CK-7 staining but negative CK-20 staining. Thus, this immunohistochemical staining profile for the present case confirmed the diagnosis of BAC with ovarian metastasis. Although the patient refused postoperative chemotherapy and

Figure 2. Pleural biopsy (A: hematoxylin & eosin staining, 400×) and ovary specimen obtained from tumor debulking and bilateral salpingo-oophorectomy (B and inset: hematoxylin & eosin staining, 400×). The positive nuclear staining for TTF-1 in pleural (C: 400×) and ovary specimens (D: 400×).

Figure 1. Computerized tomography scans of (a) bronchioloalveolar carcinoma and (b) ovarian metastasis.
was discharged, her condition was stable during the 12-month regular follow-up at our clinic.

**DISCUSSION**

In this report, we described a patient who presented BAC with pleural metastasis. A similar tumor involving the ovaries was discovered during the subsequent clinical course. It is uncommon for lung carcinoma to spread to the ovaries. Fujiwara et al. analyzed 313 patients with ovarian metastases. Among these patients, lung cancer was determined as the primary site only in one patient (3). In a review of the literature of the past two decades (Table 1), only nine cases have been documented where lung cancer has spread to the ovaries (4–6). The ages of the women in these reports ranged from 26 to 66 years. On microscopic examination, four of these cancers were identified as small-cell carcinomas, two as large-cell carcinomas, two as poorly differentiated adenocarcinomas, and one as an atypical carcinoid. Of these nine cases, ovarian metastasis was detected prior to \( n = 3 \), at the same time as \( n = 4 \), or after \( n = 2 \) the discovery of pulmonary neoplasms. Ours is the only case of BAC with ovarian metastasis. Furthermore, the interval for the development of ovarian metastasis after BAC was extended to 4 years for comparison with two other reported cases diagnosed after 11 and 14 months, respectively.

In the present case, main evidence for the pulmonary origin of malignancy was derived from the identification of microscopic features that demonstrated a strong similarity to a familiar group of lung cancers, but was an uncommon histological type for ovarian cancer (7). Young and Scully also pointed out that the combination of characteristic clinical course and distinctive pathological features may prove useful for delineating lung cancer from ovarian metastasis (4). Based upon microscopic evidence and the time sequence of tumor development for our patient, and the relative probability of the other entities considered for differential diagnosis, a diagnosis of BAC with ovarian metastasis was made. Although almost any type of tumor may occasionally originate in the ovary, and the occurrence of primary alveolar cell carcinoma is extremely rare, positive immunohistochemical staining for TTF-1 and CK-7 and negative staining for CK-20 delivers the requisite diagnostic assurance and, in the present case, excluded the possibility of two independent cancers.

Furthermore, BAC is characterized by the lack of invasive growth (8). Volpino et al., analyzed the clinical course for 34 BAC patients, demonstrating a longer mean survival time (>60 months) for stage I patients, or with radiographic presentation of a solitary pulmonary nodule or mass, independent of nodal involvement (9). For stage II–IV patients >60 years, the presence of multiple tumors, alveolar spread, tumor size >3 cm, pleural invasion, and lymph-node metastasis were associated with poor prognosis (mean survival time ~18 months) (9).

Our patient was 63 years old, and as her tumor was 3 cm in diameter and characterized by pleural involvement, which suggested relatively poor survival prospects. Although progression of the primary site of lung cancer was not proven when the ovarian metastasis was detected, it is yet not clearly understood as to why the patient survived for 4 years without receiving chemotherapy or radiotherapy for the lung cancer.

In conclusion, clinicians must keep in mind the possibility of metastasis if an ovarian tumor is atypical in clinical course, or, if the pathological features do not support ovarian origin. Additionally, given the increasing incidence of lung cancer in females, lungs should not be excluded from the list of potential primary tumor sites. When attempting to differentiate between primary and metastasized ovarian adenocarcinomas and/or identifying tumors of pulmonary origin, it should be noted that a monoclonal antibody panel for TTF-1, CK-7, and CK-20 may facilitate this discrimination.

**References**


