

## Endobronchial Metastasis of Uterine Cervix Cancer: A Two Case Reports and a Review of the Literature

Yong Soo Kim<sup>1</sup>, Joon Chang<sup>1,3</sup>, Young Sam Kim<sup>1,3</sup>, Dong Hwan Shin<sup>2,3</sup>, Hy Sook Kim<sup>6</sup>, Sung Kyu Kim<sup>1,3</sup>, and Se Kyu Kim<sup>1,3,4,5</sup>

Departments of <sup>1</sup>Internal Medicine, <sup>2</sup>Pathology, <sup>3</sup>The Institute of Chest Diseases, <sup>4</sup>Brain Korea 21 Project for Medical Sciences, and <sup>5</sup>Cancer Metastasis Research Center, Yonsei University College of Medicine, Seoul, Korea;

<sup>6</sup>Department of Pathology, Sungkyunkwan University College of Medicine, Seoul, Korea.

Endobronchial metastasis from uterine cervix cancer defines a bronchoscopically visible nonpulmonary neoplasm metastatic to the bronchus and histologically identical to cervix cancer. Endobronchial metastasis of uterine cervix cancer is rare, therefore, it is difficult to diagnose without pulmonary symptoms or abnormal radiological findings. Moreover, endobronchial metastasis of a nonpulmonary neoplasm is difficult to differentiate from a primary pulmonary neoplasm. The incidence of endobronchial metastasis is increasing because of the regular use of fiberoptic bronchoscopy and the longer survival of cancer patients.

This study describes our experience of two patients with pulmonary symptoms and abnormal radiologic findings during the follow up of uterine cervix cancer, who were diagnosed as having endobronchial metastasis from uterine cervix cancer, and includes a brief review of related articles.

**Key Words:** Endobronchial metastasis, uterine cervix cancer

### INTRODUCTION

Endobronchial metastasis is by definition bronchoscopically visible nonpulmonary tumors metastatic to the subsegmental or more proximal central bronchus, with lesions histologically identical to previously demonstrated primary tumors.<sup>1</sup>

The endobronchial metastasis of a nonpulmonary neoplasm is important when making a

differential diagnosis from primary bronchogenic cancer, and for primary tumor treatment with regard to histological subtype.<sup>2,3</sup> If the histological differentiation of endobronchial tissue from the tumor is unclear, the demonstration of carcinoma in situ in the adjacent bronchial epithelium strongly suggests a diagnosis of a primary bronchogenic tumor.<sup>4</sup>

A variety of tumors are associated with endobronchial metastasis, which the major contributors include breast, colorectal and renal cell carcinomas, and the minor ovarian, thyroid, uterine, testicular, nasopharynx, prostate, stomach, and adrenal gland cancers, sarcoma, melanomas, and plasmacytoma.<sup>5,6</sup>

We report upon two rare cases of endobronchial metastasis from uterine cervix cancer, which were pathologically confirmed by fiberoptic bronchoscopic biopsy, and presented with pulmonary symptoms and abnormal radiological findings, and include a brief review of the literature.

### CASE REPORT

#### Case 1

The 62 year old woman was referred to the pulmonology department with 2 months history of progressive dyspnea and cough. She had no history of pulmonary tuberculosis or bronchial asthma. She was diagnosed as having uterine cervix cancer of stage IIIA three years previously as a result of abnormal vaginal bleeding. The

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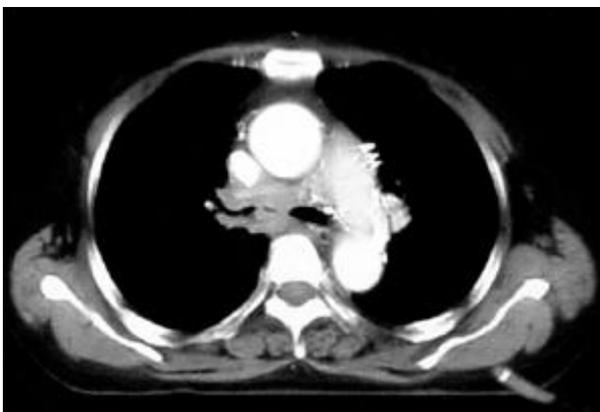
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Reprint address: requests to Dr. Se Kyu Kim, Department of Internal Medicine, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea. Tel: 82-2-361-5429, Fax: 82-2-393-6884, E-mail: sekyukim@yuonc.yonsei.ac.kr

histological type of cancer was infiltrative squamous cell carcinoma. She received six cycles of systemic anti-cancer chemotherapy, which consisted of 5-fluorouracil and neoplatin, and this was followed by radiation therapy to both the inguinal area and the whole pelvis at a dose of 5040cGy. Subsequently, she received a 1800cGy-dose of ICR. She had been in a status of complete remission and had been regularly followed up.

On physical examination, the patient had a chronically ill-looking appearance and pale conjunctiva. She had a temperature of 37°C, a respiratory rate of 22/min, a blood pressure of 150/100 mmHg, and a pulse rate of 120/min. Chest auscultation revealed localized inspiratory rhonchi on right upper and middle lung fields, the remainder of the physical examination was unremarkable. The white blood cell count was 3,790 cells/mm<sup>3</sup>, with 72.5% neutrophils, 12.1% lymphocytes, 7.3% monocytes, and 4.2% eosinophils. Her hemoglobin was 9.9 g/dL, hematocrit 31.4% and platelet count 284,000 cells/mm<sup>3</sup>, and serum chemistry was normal. A sputum smear for acid-fast bacilli and sputum cytology for malignancy were both negative. Chest radiography showed a right hilar lymphadenopathy and an irregular narrowing of the right main bronchus (Fig. 1).

Fiberoptic bronchoscopy revealed concentric near total obstruction of right main bronchus by an infiltrative round mass located on the first carina, which had nodular, erythematous and friable mucosa. Pathologically, invasive squamous cell carcinoma was found identical to the previously diagnosed uterine cervix cancer (Fig. 2).



**Fig. 1.** Chest CT. Right hilar lymphadenopathy and irregular narrowing of right main bronchus.

Gynecological evaluation and pelvis magnetic resonance imaging did not find any evidence of cancer recurrence. She received radiation therapy for the endobronchial tumor with dose of 4500 cGy. One month later, left iliac bone metastasis was found and treated by palliative radiation therapy at 3000 cGy. Six months later, superior vena cava syndrome and a large amount of right pleural effusion developed. The patient was treated with closed thoracostomy with pleurodesis and palliative aimed radiation therapy. However, she died of respiratory failure 10 months after the first diagnosis of endobronchial metastasis.

## Case 2

The 44 year old woman was admitted to the hospital with a 1 month history of a cough. She denied a history of pulmonary tuberculosis. Three years previously, she had been admitted with a vaginal spot originating from an invasive uterine cervix cancer of stage IIIB. She subsequently underwent surgical intervention followed by adjuvant radiation therapy, which consisted of whole pelvis irradiation, parametrial boost and ICR at doses of 4500, 900, and 2400 cGy, respectively.

On physical examination, the patient was particularly ill-looking. She had a temperature of 36.4°C, a respiratory rate of 16/min, blood pressure of 120/80 mmHg, and a pulse of 78/min. Chest auscultation revealed localized inspiratory rhonchi on right upper lung field, the remainder of the physical examination was unremarkable. Her white blood cell count was 4,200 cells/mm<sup>3</sup>, with 56.5% neutrophils, 34.1% lymphocytes, 7.7% monocytes, and 1.4% eosinophils. Hemoglobin was 12.9 g/dL, hematocrit 38.4% and platelet count 223,000 cells/mm<sup>3</sup>. Her serum chemistry was normal. Sputum smear for acid-fast bacilli and sputum cytology for malignancy were both negative. Chest radiography revealed right upper lobe atelectasis (Fig. 3), and bronchoscopy revealed a concentric total obstruction of right upper lobar bronchus with hyperemic and edematous mucosa. The bronchoscopic biopsy showed nonkeratinizing carcinoma exactly same as the previously diagnosed cervix cancer (Fig. 4). An abdomen-pelvis computed tomographic scan was

performed, and revealed that no evidence of local recurrence of the uterine cervix cancer, such as a mass lesion or an enlarged lymph node. She received radiation therapy for endobronchial metastasis at a dose of 3000 cGy and was free from pulmonary symptoms and 10 months after diagnosis of endobronchial metastasis.

## DISCUSSION

Although the incidence of pulmonary metastasis of non-pulmonary primary tumor is high, approximately 20-50%, that of endobronchial metastasis is very low, and at most 5%.<sup>5,7,8</sup> About 15.3% of all patients with uterine cervical cancer experience distant metastasis.<sup>9</sup> The proportion of distant metastasis increases with the stage of the

treated tumor, and it can occur at any time before or after treatment is instituted.<sup>10</sup> Distant metastasis



Fig. 3. Chest CT. Right upper lobe atelectasis.

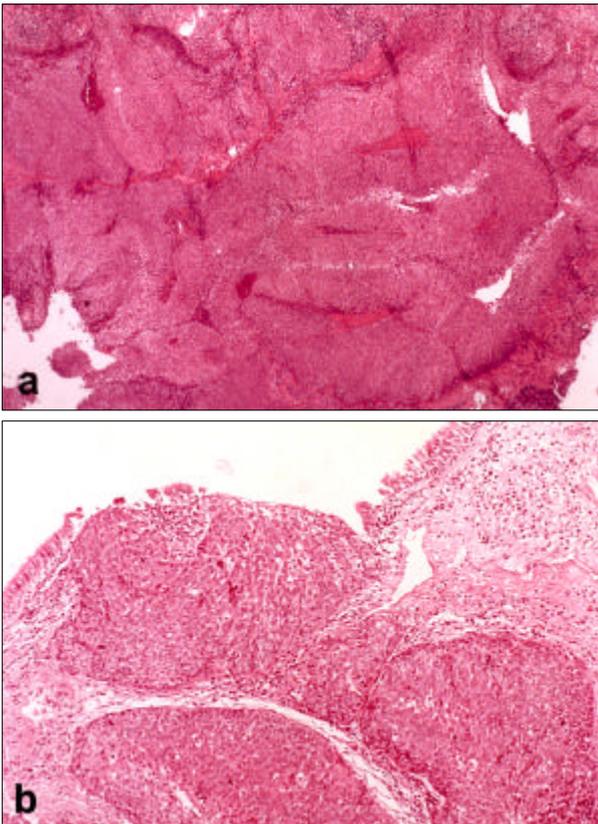


Fig. 2. Biopsy. (A) Cervix; invasive nonkeratinizing squamous cell carcinoma involving the cervical transformation zone (hematoxylin-eosin,  $\times 100$ ). (B) Bronchus; extensive infiltration of poorly differentiated carcinoma without pre-cancerous epithelial alteration such as dysplasia, squamous metaplasia in the adjacent bronchial epithelium (hematoxylin-eosin,  $\times 100$ ).

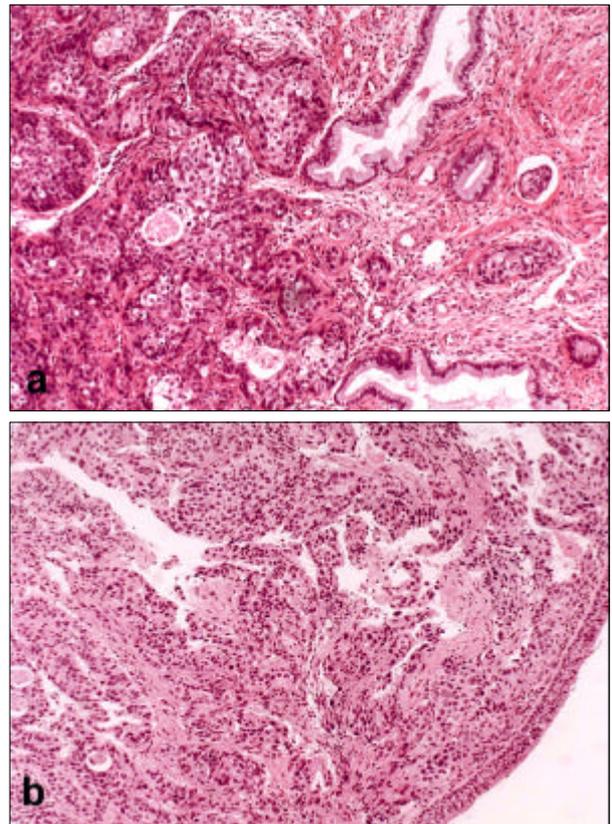


Fig. 4. Biopsy. (A) Cervix; nonkeratinizing squamous cell carcinoma (hematoxylin-eosin,  $\times 40$ ). (B) Bronchus; subepithelial infiltration of poorly differentiated carcinoma with focal surface disruption (hematoxylin-eosin,  $\times 100$ ).

of uterine cervical cancer has become more common in recent years because of longer patient survival. Although there were many reports about endobronchial metastasis after Zenker's first report of sarcoma, its reported incidence varies.<sup>6,11,12</sup> This variation in incidence depends on not only the different definitions of endobronchial metastasis, but also upon the routine use of bronchoscopy. However, the endobronchial metastasis of nonpulmonary neoplasms and primary bronchogenic cancers are difficult to differentiate, and biochemical and molecular marker followed by serial histologic comparison is probably the best way to obtain an exact diagnosis. One case report of adenoid cystic carcinoma of the cervix presenting as a primary bronchial neoplasm was easily confirmed by typical histopathologic findings, which differed from those of primary bronchogenic carcinoma.<sup>13</sup> There is an increasing need for a more precise and generalized definition of endobronchial metastasis.<sup>1</sup>

The route of metastasis uterine cervix cancer is presumed to be via the blood stream to the caval venous system via veins and lymphatics, to invade the lung parenchyma, and then the systemic circulation (bronchial arteries), and eventually to emerge as endobronchial metastasis.<sup>8</sup>

The major symptoms of endobronchial metastasis are a cough, hemoptysis, and dyspnea, but asymptomatic patients account for 50-60%.<sup>1,14</sup> Early effective treatment of asymptomatic patients is often delayed, which impairs the prognosis, because clinically a diagnosis is unlikely unless symptoms and signs are present. Survival is dependent to a great extent on the biological behavior of the primary tumor and its responsiveness to treatment. Mean survival times vary from 12 to 18 months.<sup>1,3,15</sup> However, some authors have insisted that aggressive treatment should be considered for long-term survival.<sup>16,17</sup>

The radiologic manifestations of endobronchial metastasis are quite diverse. Patients commonly present with evidence of hilar or mediastinal lymphadenopathy, atelectasis, or normal chest radiographic findings,<sup>7,16,18,19</sup> though infrequently they present with nonspecific pulmonary infiltration and multiple pulmonary nodules.

Because chest computed tomographic scans have a high sensitivity for detecting and localizing

endobronchial lesions, it should be taken when the bronchoscopy cannot be performed and when to detect multiple pulmonary metastasis or hilar, mediastinal lymphadenopathy.<sup>20</sup> When chest computed tomographic scans is used in combination with cytologic examination of the sputum and bronchial washes, precise and accurate diagnosis can be made.

Fiberoptic bronchoscopy is the most important and the simplest diagnostic tool, and is essential in the diagnosis of endoluminal lesions. In particular, its diagnostic accuracy is very high for a centrally located lesion.<sup>7,18,19</sup> In addition, when a patient with a prior history of a non-pulmonary neoplasm has persistent pulmonary symptoms but normal chest radiographic findings, bronchoscopy should be considered to evaluate the possibility of endobronchial metastasis.<sup>3</sup>

In both of our two cases, bronchoscopic biopsy served to confirm the diagnosis, and revealed the same histological findings as obtained for the previously demonstrated uterine cervix cancer. However, no absolute histopathologic criteria exist that differentiate primary and secondary tumors in such cases, and the most useful indicators are the cell type characteristics and a comparison of both biopsy specimen. Baumgartner et al. emphasized that the demonstration of carcinoma in situ in the adjacent bronchial epithelium excluded the diagnosis of endobronchial metastasis.<sup>4</sup>

It is well known that there is no predilection for the airway location of endobronchial metastasis. Although Heitmiller et al. reported that 20 of 25 lesions were localized to the right side, the cause of this predilection remains uncertain.<sup>14</sup> In our two cases, the endobronchial metastasis were located in the right bronchus.

Endobronchial metastasis tends to occur at a significant interval, an of average 5.4 years, from the diagnosis of the primary tumor because of its slow progression. In our cases, the intervals were 3 years and 2.2 years, respectively.<sup>14,16,19</sup> In some reports, metastasis has been diagnosed before the primary tumor, whereas endobronchial metastasis is more usually a late manifestation of non-pulmonary neoplasm.<sup>3,21</sup> The therapeutic approach to endobronchial metastasis is controversial, but in most cases this depends on the histology of the

primary cancer, its location, the evidence from other metastatic sites, and the patient's performance status.<sup>11,16</sup> The majority of patients with endobronchial metastasis usually have other metastatic involvements. Therefore, the therapeutic strategy usually has palliative intent, as a result, the standard treatment of endobronchial metastasis is chemotherapy and local radiation therapy. However, chemotherapy does not seem to prolong the patient's survival, and therefore, is reserved for multiple metastatic disease. When an endobronchial metastasis represents at a single metastatic site, surgical resection is the most effective preferable treatment modality and the prognosis of such patients is favorable.

Radiation therapy improves the symptoms of airway obstruction and hemoptysis. Baumgartner et al. reported that in the case of localized obstructive lesions with predominantly respiratory symptoms, external radiation therapy is the treatment of choice with good response and acceptable survival.<sup>16,19</sup> Generally, endobronchial metastasis is a slowly progressive disease, so clinicians have to consider before deciding upon aggressive treatment. Laser treatment has been recently used in combination with intraluminal brachytherapy, and achieved considerable success in terms of symptom relief.<sup>16,19,22,23</sup>

Palliative radiation therapy was performed in our two cases, although appropriate radiation therapy was introduced, our first case developed progressive superior vena cava syndrome, on the other hand the second case, became symptom free after external radiation therapy.

Other palliative treatments include phototherapy, electrocoagulation, cryotherapy,<sup>24</sup> forcep removal, intratumoral ethanol injection, and simple stent placement.<sup>22,25</sup> However, it is difficult to predict patients' survival according to the treatment modality, and generalized treatment guidelines are needed.

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