

[CASE REPORT]

Miliary Lung Metastases from Genital Large Cell Neuroendocrine Carcinomas

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Abstract:

We herein report two cases of miliary lung metastases from genital carcinoma in uterine cervix and endometrium. Notably, these patients were unable to receive any anti-tumor chemotherapy due to rapid progression causing respiratory failure, and they ultimately died of disease progression within only a month after the first visit to our hospitals. A postmortem examination confirmed the diagnosis of genital large-cell neuroendocrine carcinoma (LCNEC). Chest physicians should be aware of genital LCNEC with a dismal prognostic entity as an important differential diagnosis of miliary lung metastases.

Key words: large-cell neuroendocrine carcinoma, miliary lung metastases, uterus, cervix, corpus

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Introduction

Miliary lung metastases are most frequently seen in lung cancer (1, 2), although previous studies report that they can rarely occur from malignancies of other organs, such as thyroid (3-6) and stomach (7). However, there are no current reports of miliary lung metastases from genital carcinomas. We herein report two cases of miliary lung metastases from genital large-cell neuroendocrine carcinomas (LCNEC).

Case Reports

Case 1

A 32-year-old never-smoking woman visited the previous hospital due to persistent cough occurring for a month. Chest radiography revealed multiple pulmonary nodules, raising the suspicion of miliary tuberculosis (Fig. 1A). The patient was referred to our hospital on the same day already presenting with respiratory failure with a partial pressure of

arterial oxygen (PaO₂) of 46.8 Torr on room air. Chest computed tomography (CT) showed tiny, miliary nodules throughout the bilateral lungs (Fig. 1B). The patient also had metastases to the liver, right kidney, adrenal glands, and bones. The tumor markers were elevated with carcinoembryonic antigen (CEA) of 10.3 ng/mL, cytokeratin 19 fragment (CYFRA) of 264.0 ng/mL, and CA125 of 75 U/mL. Since her detailed medical history included a one-month history of metrorrhagia, pelvic magnetic resonance imaging (MRI) was performed. MRI revealed a swollen cervix of the uterus with an obscure boundary between the normal myometrium and the tumor, which had invaded the corpus uteri (Fig. 1C). The patient was then diagnosed with Stage 4 uterine cervical cancer.

Since the performance status was already 4 and the patient was suffering from severe dyspnea, it was not possible to perform an invasive pathological evaluation or to administer any anti-tumor agents. The patient ultimately died of disease progression 13 days after admission to our hospital.

A necropsy of the lungs and uterus was performed; both specimens presented microscopic uniform, round-shaped

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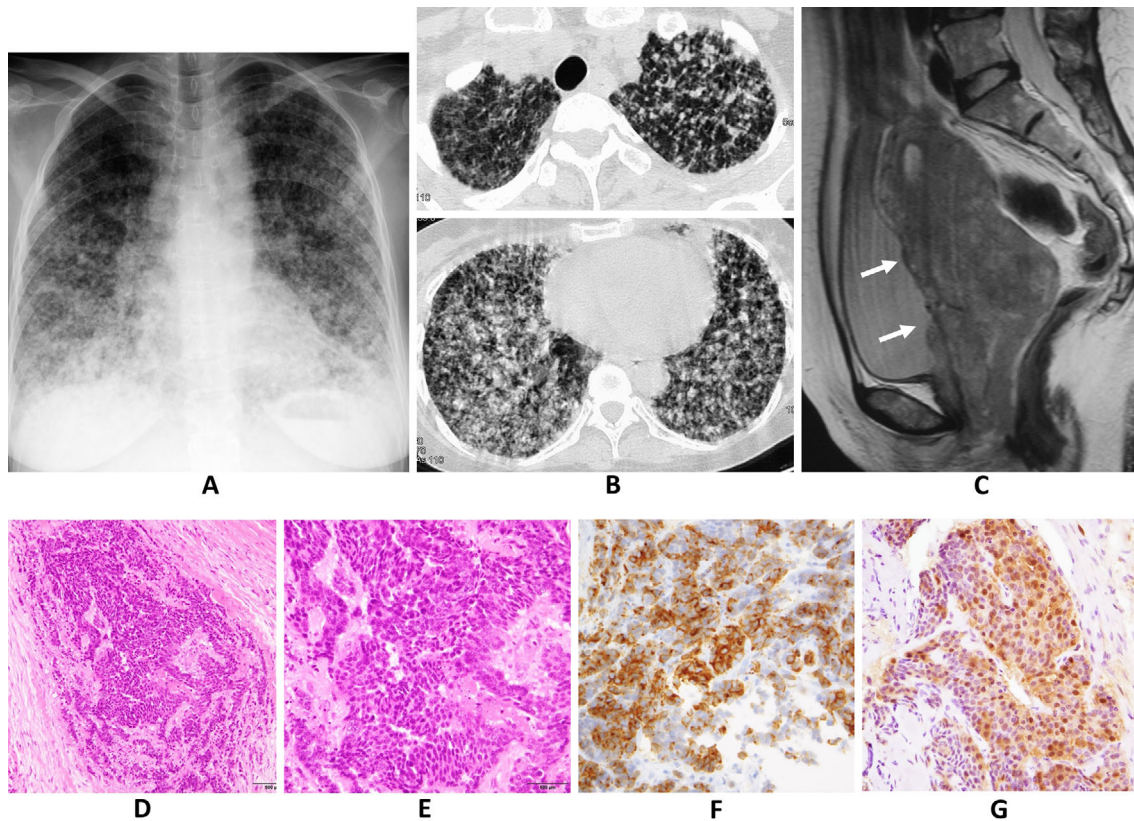


Figure 1. Chest radiography showed multiple small nodules in the bilateral lungs (A). Chest CT revealed miliary nodules present bilaterally throughout the lungs (B). Pelvic MRI revealed a diffusely swollen mass throughout the uterine cervix and corpus with hyperintensity on T2-weighted images (arrow) (C). At a lower magnification [Hematoxylin and Eosin (H&E) staining, $\times 40$], the tumor in the uterus consisted of solid nests and cords (D). At a higher magnification (H&E staining, $\times 200$), the tumor cells showed uniformly large, round shapes (E). The tumor cells were immunohistochemically positive for synaptophysin (F, $\times 400$) and p16 (G, $\times 400$).

large tumor cells with moderate cytoplasm and nuclei of granular chromatin pattern forming solid nests and cords (Fig. 1D, E). Necrosis was prominent along with lymphangitis. The mitotic counts in the solid nests were up to 20 mitoses per 2 mm^2 , and small nucleoli were occasionally observed. Immunohistochemistry showed that the tumor cells were positive for synaptophysin and p16 (Fig. 1F, G) but negative for neural cell adhesion molecule (NCAM) and chromogranin A, thus confirming the diagnosis of genital LCNEC. No components other than LCNEC were observed in any evaluated specimens.

Case 2

A 56-year-old, never-smoking woman with a history of adenomyosis visited the previous hospital due to metrorrhagia. The radiological evaluation revealed an enlarged uterus and multiple lung nodules. Twenty-seven days later, the patient was referred to our hospital already presenting with respiratory failure. Chest radiography revealed multiple small nodules in the bilateral lungs (Fig. 2A); chest CT revealed tiny, miliary nodules throughout the bilateral lungs (Fig. 2B). Pelvic MRI revealed a diffusely swollen endometrial mass with hypointensity on T1-weighted images

and hyperintensity on T2-weighted images (Fig. 2C). The tumor markers were elevated with CA125 of 439 U/mL, CA 19-9 of 1,296 U/mL, and CEA of 32.1 ng/mL. The patient was clinically diagnosed with Stage 4 endometrial carcinoma.

However, her respiratory condition rapidly deteriorated, requiring sedation, and she was unable to receive any anti-tumor agents. The patient ultimately died of disease progression six days after admission. The autopsy showed multiple organ metastases, including the lungs, liver, bilateral adrenal glands, and left kidney, in addition to carcinomatous lymphangitis in the lungs. Diffuse alveolar damage was present in the right upper and middle lobes. A pathological evaluation of the uterine corpus showed uniform, round-shaped large tumor cells with moderate-to-abundant cytoplasm and granular nuclear chromatin forming solid nests with a minor component of glandular structures. The mitotic counts in the solid nests were up to 40 mitoses per 2 mm^2 . Necrosis was prominent (Fig. 2D, E). Immunohistochemistry showed that the tumor cells in the solid nests were positive for synaptophysin (Fig. 2F) and focally positive for NCAM and chromogranin A, thus confirming the diagnosis of genital LCNEC combined with endometrioid adenocarcinoma. Of

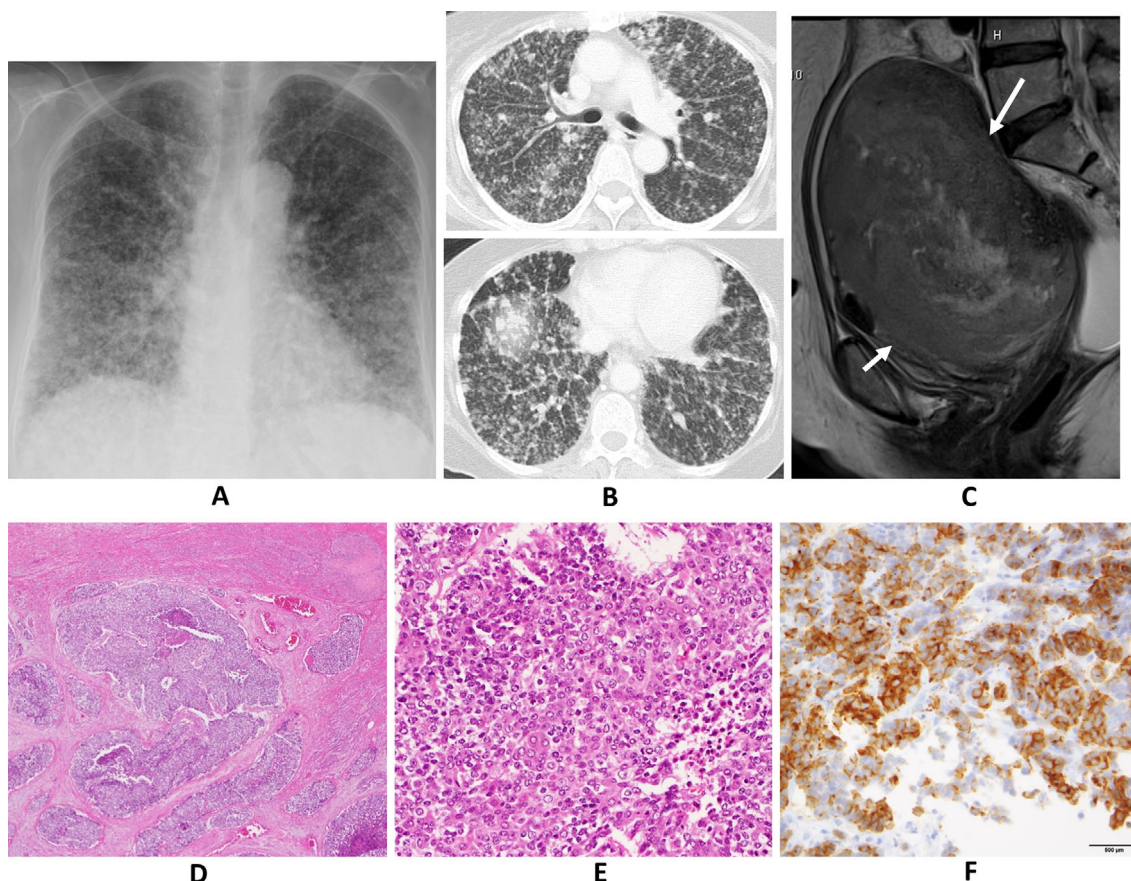


Figure 2. Miliary nodules were present bilaterally throughout the lungs (A, B). Pelvic MRI revealed a diffusely swollen endometrial mass with hypointensity on T2-weighted images (arrow) (C). At a lower magnification [Hematoxylin and Eosin (H&E) staining, $\times 40$], the tumor in the uterus consisted of solid nests, and necrosis was remarkable (D). At a higher magnification (H&E staining, $\times 200$), the tumor cells showed uniformly round shapes (E). The tumor cells were immunohistochemically positive for synaptophysin (F, $\times 400$).

note, the lung metastases pathologically consisted only of the LCNEC component.

Discussion

The clinical course of our two cases provides the following two clinical implications:

First, miliary lung metastases can develop in patients with genital LCNEC. Generally, miliary lung metastases are common in primary lung cancer, particularly non-small cell lung cancer (NSCLC) with an epidermal growth factor receptor (EGFR) mutation (1, 2). Of note, EGFR signaling and ligands has been reported to play an important role in cancer progression in terms of the secretion and synthesis of various angiogenic growth factors in tumor cells, resulting in hematogenous metastases (1, 8). With regard to non-NSCLC, thyroid and gastric carcinomas rarely present with lung metastases of the miliary type (3-7). Genital carcinomas predominantly spread by direct local extension and lymphatic metastases, and there have been no previous reports of miliary lung metastases from genital tumors. At present, neuroendocrine carcinomas (NECs) of the uterine cer-

vix and endometrium, account for only 5% and <1% of all uterine cervix and endometrium carcinomas, respectively, with most being small-cell carcinomas (9, 10). Although genital LCNEC is extremely rare, chest physicians should recognize that genital LCNEC may be an origin of miliary lung metastases.

Second, LCNEC with miliary lung metastases can present with rapid progression, requiring a prompt diagnosis and treatment. In fact, our two patients were unable to receive any anti-tumor agents and ultimately died due to disease progression within a month. In addition, the pathological findings indicated that the rapidly progressive respiratory failure was caused by lymphangitis and focal acute respiratory distress syndrome (ARDS), as shown in Case 2. Genital LCNEC reportedly displays an aggressive biological behavior with a high tendency for distant metastases and disease recurrence, and most patients die within two to three years of their diagnosis (9, 10). At present, there are no treatment guidelines based on prospective, well-designed clinical trials due to the rarity of these tumors (9, 10). Therefore, the current therapeutic approach is mainly extrapolated from data published on lung NECs (10). However, in a study evaluat-

ing 62 patients with LCNEC of the uterine cervix, the use of platinum with or without etoposide was associated with a statistically significant improvement in the overall survival compared with other regimens (11). When interpreting our two cases in light of those reports, we propose that although the prognosis for patients with miliary lung metastases from genital LCNEC is poor, it can potentially be improved through treatment with platinum agents. Therefore, taking a detailed medical history emphasizing symptoms such as metrorrhagia is crucial for achieving a prompt diagnosis and treatment, particularly in women with miliary lung metastases. In addition, a tumor biopsy of the uterus or lung should be immediately performed, as the disease progresses very rapidly once respiratory failure develops.

In conclusion, we encountered two cases of miliary lung metastases from genital LCNEC. Although rare, since this condition can progress rapidly, chest physicians should be aware of genital LCNEC as a potential origin of miliary lung metastases in order to initiate aggressive treatment promptly.

The authors state that they have no Conflict of Interest (COI).

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