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Case report

Metastatic large cell neuroendocrine carcinoma of the lung arising from the uterus: A pitfall in lung cancer diagnosis

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ABSTRACT

A 41-year-old female smoker presented with a vaginal mass. Gynecological examination showed a mass filling the uterine corpus, cervix, and vagina. A total abdominal hysterectomy was performed. Macroscopic findings included a large fragile mass involving the uterine cavity, cervix, and vagina. Histology revealed atypical ducts admixed with solid components consisting of large atypical cells. The initial pathological diagnosis was grade 3 endometrioid adenocarcinoma. The patient was designated as stage II according to the 2008 International Federation of Gynecology and Obstetrics (FIGO) staging. Two years later, two nodules were found in the upper lobe of the left lung, and the patient underwent an upper lobectomy. The masses, which exhibited solid and organoid growth patterns of large atypical cells, had histological characteristics of large cell neuroendocrine carcinoma (LCNEC) of the lung. However, the tumor was immunohistochemically positive for neuroendocrine markers, such as synaptophysin in addition to estrogen receptor and progesterone receptor, and the tumor was negative for thyroid transcription factor-1. These immunohistochemical results were almost identical to those of the solid portions of the uterine carcinoma. The final diagnosis was LCNEC combined with endometrioid adenocarcinoma of the uterine corpus and lung metastasis of the LCNEC component of the endometrial carcinoma. LCNEC often arises in the lung, but it rarely arises in other organs. Some patients with metastatic components exhibited only a LCNEC pattern although the primary tumor was a mixed carcinoma consisting of LCNEC and other histology, like the present case. LCNEC is often poorly differentiated, especially in extrapulmonary primary organ LCNEC. Therefore, pathologists should consider metastatic carcinoma when they encounter lung LCNEC in a patient with a preceding extrapulmonary carcinoma composed of a poorly differentiated component or LCNEC component, and they should clarify tumor immunohistochemical characteristics to confirm the diagnosis.

1. Introduction

Large cell neuroendocrine carcinoma (LCNEC) has characteristic neuroendocrine morphology and neuroendocrine marker expression on immunohistochemistry, and LCNEC stains positively with antibodies for CD56, synaptophysin, and/or chromogranin A. LCNEC primarily occurs in the lung and is generally known to have high neuroendocrine immunoreactivity, at 80–90% for CD56, 50–60% for synaptophysin, and 80–85% for chromogranin A. On the other hand, LCNEC occasionally arises in extrapulmonary organs, such as the head and neck, pancreas, gallbladder, colon, and uterine cervix or corpus [1]. Therefore, if LCNEC arises in the lung after a history of poorly differentiated carcinoma in another organ, the differential diagnosis between a primary lung LCNEC and metastatic extrapulmonary LCNEC is a critical issue in practice.

This paper describes a case of metastatic lung LCNEC from a uterine endometrial LCNEC. We would like to emphasize that the previous extrapulmonary malignancy should be examined

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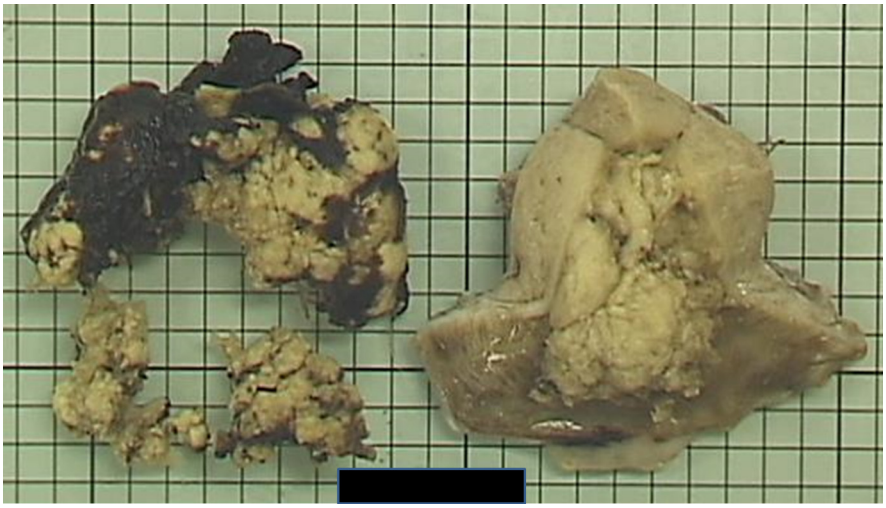

Fig. 1. Gross features of the uterus. The tumor, which filled the uterine corpus, cervix, and vagina, was fragmented during the operation. The base of the tumor was located in the uterine corpus. The tumor was grayish white, and the surface was covered with a blood clot.

again carefully when lung LCNEC is diagnosed and the previous tumor contained poorly differentiated carcinoma components within which neuroendocrine morphology and phenotype were not previously examined.

2. Materials and method

Histological specimens were obtained via a total abdominal hysterectomy and a left upper lobectomy of the lung. The uterus and left upper lobe of the lung were fixed with 10% buffered formalin and embedded in paraffin. They were stained with hematoxylin and eosin (HE).

Immunohistochemistry was performed on the formalin-fixed, paraffin-embedded tissues. Tissues were incubated with antibodies that recognize synaptophysin, chromogranin A, CD56, estrogen receptor (ER), progesterone receptor (PgR), thyroid transcription factor-1 (TTF-1), p53, cytokeratin 7 (CK7), and cytokeratin 20 (CK20). The HISTOSTAINER 48A (Nichirei, Tokyo, Japan) was used for CK7 and CK20 staining, and the BenchMark ULTRA (Ventana Medical Systems, Tucson, USA) was used for p53, TTF-1, synaptophysin A, chromogranin, CD56, ER, and PgR staining.

3. Clinical and pathological summary

A 41-year-old woman (gravida 0, para 0) presented with a vaginal mass. On gynecological examination, a tumor filling the uterine body and continuously filling the uterine cervix and vagina were observed. The tumor was suspected to be uterine endometrial carcinoma. The carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), CA125, and SCC serum tumor marker levels were within the normal range, and neuroendocrine markers were not examined. The patient underwent an emergency total abdominal hysterectomy on the day of her first visit due to massive bleeding from the tumor.

Macroscopically, there was a huge fragile mass involving the uterine cavity, cervix, and vagina (Fig. 1). The mass was fragmented, but measured approximately 10 cm in diameter. The pathological diagnosis at that time was grade 3 endometrioid adenocarcinoma. She was designated stage II according to the 2008 International Federation of Gynecology and Obstetrics (FIGO) staging and pT2, cN0, and cM0, according to the TNM staging.

Based on these findings, the patient received 6 cycles of adjuvant chemotherapy with paclitaxel and carboplatin (TC therapy) and underwent follow-up examination. Two years after the operation, computed tomography (CT) revealed two nodules in the upper lobe of the left lung, and the patient underwent a left upper lobectomy.

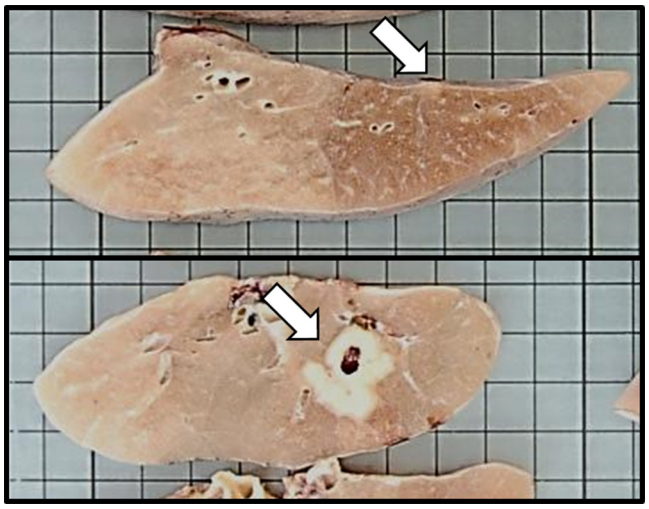

Fig. 2. Gross features of the lung tumors. Two tumors are seen (arrows).

Macroscopically, there were two well-defined white masses with maximum diameters of 22 mm and 6 mm in the lung (Fig. 2). Histologically, the masses exhibited expansive growth with geographic necrosis and a palisading pattern. The tumor cells were large and slightly spindle- or pleomorphic-shaped with moderate cytoplasm. The nucleoli were prominent. Mitotic figures, including heterotopic division, were frequently observed. Mitotic counts were over 30 per 10 high-power fields. Rosette formations were observed (Fig. 3). Both lung tumors had similar histological findings. Immunohistochemically, the tumor was positive for synaptophysin (Fig. 4). The lung tumor histological findings were compatible with LCNEC and lacked adenocarcinoma components.

However, the patient's clinical characteristics did not match the clinical features of LCNEC. She was young and not a heavy smoker (Brinkman index, 110), there were multiple masses, and she had an antecedent endometrial carcinoma. We had to discriminate between primary lung masses and metastatic tumors. Therefore, immunohistochemistry was performed, and there was similar reactivity for both the endometrial and lung tumors. Both tumors were positive for synaptophysin, ER, PgR, p53, and CK7 and negative for CK20 and TTF-1. Only the solid portion of the endome-