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Uterine metastasis of lung adenocarcinoma revealed by the same epidermal growth factor receptor mutation in both lung and endometrial biopsies

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ABSTRACT

We experienced a rare case of uterine metastasis of non-small cell lung cancer in an 82-year-old Japanese woman revealed by detecting the same epidermal growth factor receptor (EGFR) gene mutation in both lung and endometrial biopsy specimens. The patient noticed abnormal genital bleeding at the first presentation. Further examination revealed huge masses in both lung and uterus. Biopsies from the lung and endometrium were performed. Although the pathological findings of both specimens showed similar adenocarcinomatous features including intracytoplasmic luminas, immunohistochemical analyses could not clarify whether these two tumors are lung metastasis of endometrial adenocarcinoma, uterine metastasis of lung adenocarcinoma or double primary adenocarcinomas of the lung and endometrium. Mutational analyses of EGFR gene using genomic DNA revealed that both lung and endometrial tumors had the same substitution mutation (L858R) at exon 21 which is often observed in lung adenocarcinomas. Since EGFR mutations are rarely detected in primary endometrial cancers and especially L858R mutation has not been reported in them, detection of the same L858R EGFR gene mutation in both lung and endometrial tumors strongly suggested that uterine tumor is the metastasis of lung adenocarcinoma. Mutational analyses might be useful to determine whether the tumor is primary or metastatic when the particular mutational types are observed in particular tumor types and/or particular organs.

1. Introduction

Primary lung cancers often metastasize to various organs even at the time of the first presentation. When the tumors are observed in both lung and other organs, discrimination is needed for the decision of treatment strategy whether the tumors are primary lung cancer with metastasis to other organs, primary cancer of other organs with lung metastasis, or multiple primary cancers originating in the lung and other organs. Quite different histology in the multiple tumors suggests multiple primary cancers developing in the lung and other organs. However, when histology in the lung and other organs is similar, the differential diagnosis on the above-mentioned three situations is difficult only by histology. Although immunohistochemistry (IHC) might be useful for the differential diagnosis, similar results obtained do not necessarily mean that the tumors have the same origin.

It is well-known that specific mutations are observed in particular tumor types and/or in particular organs. For example, c-*kit* gene mutations are basically detected only in gastrointestinal stromal tumors, melanomas, seminomas, leukemias and mastocytomas [1]. Similarly, epidermal growth factor receptor (EGFR) gene mutations at intracytoplasmic region are frequently observed in lung adenocarcinomas but rarely in cancers of other organs [2]. Therefore, the mutational analyses in such specific situations might be useful for determination of tumor origin.

Here, we present a rare case of uterine metastasis of lung adenocarcinoma revealed by detecting the same EGFR gene mutation in both lung and endometrial biopsy specimens. Substitution mutation of EGFR gene at codon 858 (L858R) which is quite common in lung adenocarcinoma [3–5] has not been reported in endometrial adenocarcinomas, suggesting that uterine tumor is the metastasis of lung adenocarcinoma.

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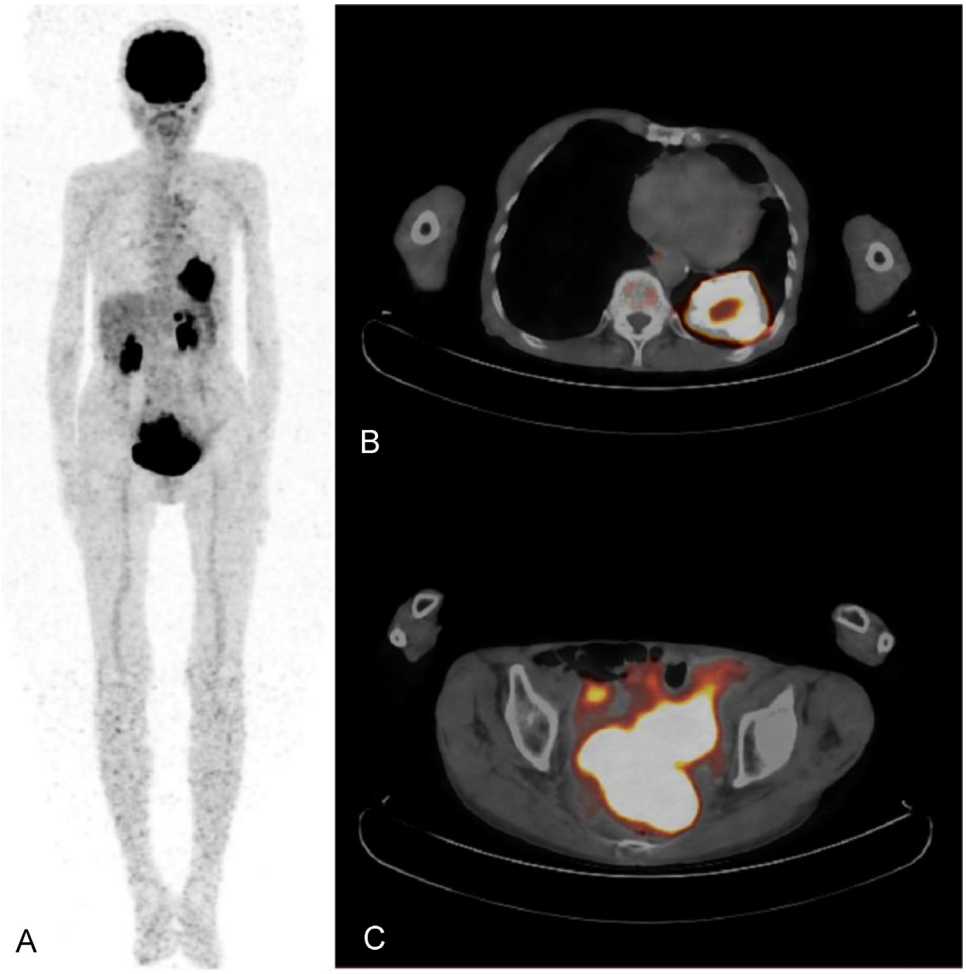

Fig. 1. PET–CT findings. Panel A shows maximum intensity projection (MIP) of PET of the whole body. The MIP shows high uptake of 18-FDG in the lung, uterus, and left adrenal gland. Panels B and C show PET–CT of the lung and uterus, respectively. In the lung and uterus, marked uptake of 18-FDG is observed as shown in MIP.

2. Presentation of case

An 82-year-old woman with no significant past history and no smoking history noticed abnormal genital bleeding 2 months before visiting a regional hospital. By radiological examination using computed tomography (CT), huge masses were identified in both left lung and uterus (data not shown). A mass lesion was also detected in left adrenal gland. Under the clinical diagnosis of lung cancer with uterine and adrenal metastases, the patient was referred to Hyogo College of Medicine for further evaluation and treatment. Whole body 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) was done. As shown in Fig. 1, large nodules with marked uptake of 18-FDG were seen in both left lower lung and uterus. Bronchoalveolar lavage fluid (BALF) for cytology was collected, and biopsies from the lung and endometrium were performed. As shown in Fig. 2, histopathological findings of lung biopsy were quite similar to those of endometrial biopsy. Tubular formation of the tumor cells was not apparent but intracytoplasmic luminas (ICLs) were observed in both biopsy samples, suggesting adenocarcinomatous features. Moreover, ICLs were more prominent in cytological samples of both BALF and endometrial brushing. Immunohistochemical analyses on both lung and endometrial tissues were done [6]. In both samples, cancer cells were positive for pankeratin and CK7, and negative for CK20, TTF-1, Napsin A, estrogen receptor (ER), progesterone receptor (PgR) and anaplastic lymphoma kinase (data not shown). Polymerase Chain Reaction (PCR) primers were designed according to the previous reports [3] for amplification of genomic DNA fragments including EGFR exon 18–21. As the result of sequencing of the amplified DNA fragments as shown in Fig. 3, paraffin embedded materials of the lung and endometrium revealed the same mutation (L858R) of EGFR gene at exon 21. Tumor markers of CEA, SCC and proGRP were within normal range, but SLX (95 u/ml; normal range, 0–38.0), CYFRA (10 ng/ml; 0–3.5), KL-6 (608 u/ml; 0–499) and CA125 (298 u/ml; 0–35) were elevated. Unfortunately, the patient quickly deteriorated and died of disease progression without further treatment. An autopsy was not done because of the disagreement of the bereaved.

3. Discussion

In the present report, we showed a rare case of uterine metastasis of lung adenocarcinoma revealed by detecting the same EGFR gene mutation in both lung and endometrial biopsy specimens. Substitution mutation of EGFR gene at codon 858 (L858R) which is quite common in lung adenocarcinoma [3–5] has not been reported in endometrial adenocarcinomas, suggesting that uterine tumor is the metastasis of lung adenocarcinoma.

In the present case, multiple lesions including a lung mass and a uterine mass were radiologically detected. Although the patient was clinically diagnosed as lung cancer with uterine metastasis, common primary sites of the metastatic carcinomas to the uterus are the breast, colorectum and stomach [7]. Lung cancers with metastasis to the ovary have been reported in several cases [8–11], while those to the uterus have been rarely reported [12–16]. Therefore, the clinical situation of the present case did not strongly suggest primary lung cancer with uterine metastasis, but we could neither verify nor deny