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Case Report

Omental metastatic adenocarcinoma from lung cancer with EGFR mutations: a case report

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Abstract: Lung cancer with a mutation in the epithelial growth factor receptor (EGFR) and metastasis to the greater omentum is very rare. Here we report a case of a 52-year-old woman with lung adenocarcinoma that metastasized to the greater omentum. Case presentation: The patient was hospitalized for abdominal pain following exploratory surgery and chemotherapy. Following exploratory surgery, a mass on the right ovary and multiple granular nodules on the greater omentum were found. Preliminary pathological results revealed a benign mucinous cystadenoma on the ovary and adenocarcinoma of Mullerian origin on the greater omentum in her city's health service. In our hospital, pulmonary computed tomography (CT) revealed a nodule-like high-density shadow on the superior lobe of right lung. Similar morphology was observed between the greater omentum nodules and lung biopsy; round or columnar shaped cells arranged in a cord-like or adenoid structure. Immunohistochemistry results showed both samples had the same thyroid transcription factor-1 (TTF-1) +, cytokeratin7 (CK7) + immunophenotype. Cobas real-time quantitative fluorescent polymerase chain reaction detection of lung and greater omentum nodules biopsy samples showed a deletion mutation in exon 19 of the EGFR gene. Conclusions: The greater omentum lesion was diagnosed as an EGFR-mutated lung adenocarcinoma metastasis. When identifying nodules on the omentum, consideration should be given to primary tumors including mesothelioma and tumors of the second Mullerian system origin. Metastatic tumors from other organs such as the female genital tract and gastrointestinal tract should be considered as well.

Keywords: Lung adenocarcinoma, EGFR, greater omentum metastasis, TTF1, CK7

Introduction

Lung cancer is the most common cancer in adults worldwide and the leading cause of cancer-related deaths [1]. It accounts for 25% of all cancer deaths and has a 5-year survival rate of 10-20% [2]. Lung adenocarcinoma accounts for 50% of all lung cancers [3]. Approximately 40-50% of lung cancer patients present with metastases at the time of diagnosis [4]. The most common regions of metastases are the liver, adrenal glands, brain and bone [5]. Metastasis to the greater omentum is a rare event and there have been few studies to date [6-8]. In this case study, we report a case of lung adenocarcinoma with an EGFR mutation that metastasized to the greater omentum.

Case presentation

A 52-year-old woman presented to her city's health service in February 2015 complaining of abdominal pain that had occurred for 5 months. The patient had no nausea or vomiting, no acid reflux or hematemesis, no cough or sputum, no vaginal bleeding or abnormal drainage. Physical examination showed a swollen abdomen with distending pain and rebound tenderness, but no fever. Ultrasound results showed fluid on the pelvis, suggesting pelvic inflammation. Laboratory examinations revealed negative results for tumor markers including alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), and CA199 but positive results for CA125 125.4 (0.0-35.0 U/ml). However, there was no improvement after 6 weeks of anti-inflammatory therapy. In August 2015, exploratory laparotomy under general anesthesia was performed and found the left ovary was normal, but identified a mass on the right ovary with a diameter of 1 cm as well as multiple millet granular nodules of greater omentum. Bilateral ovary and omentum nodule biopsies were conducted. Imm-

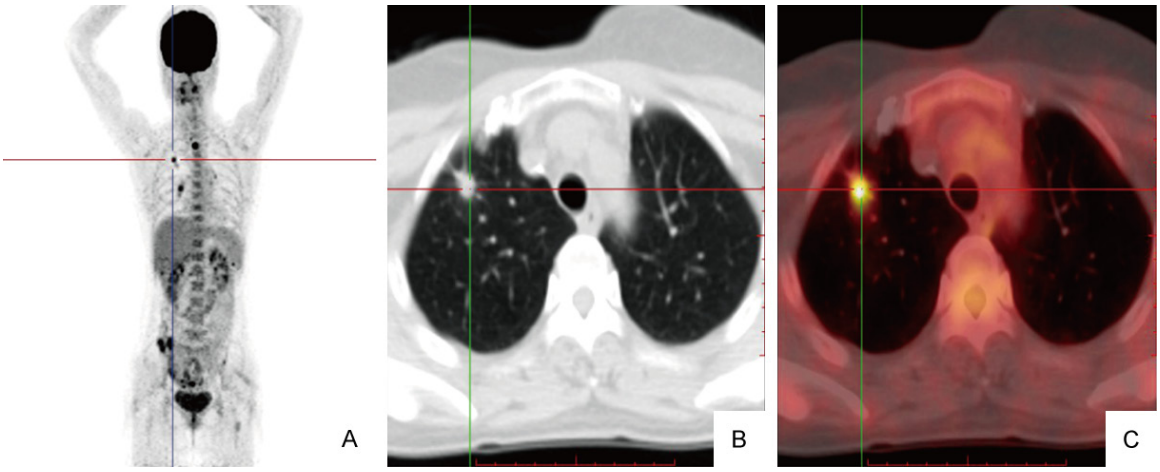

Figure 1. The imaging manifestation of the lung lesion. A nodule with increased fluorodeoxyglucose (FDG) uptake was demonstrated in the right lung on PET imaging (A), the average standard uptake value (SUV) was 6.7. Axial slice of CT (B) showed that the nodule characteristic of multiple spiculations was located in the subpleural area of the apical segment of the upper lobe, approximately 15 mm × 10 mm in size. Fused PET-CT (C) displayed CT and PET features of nodule simultaneously.

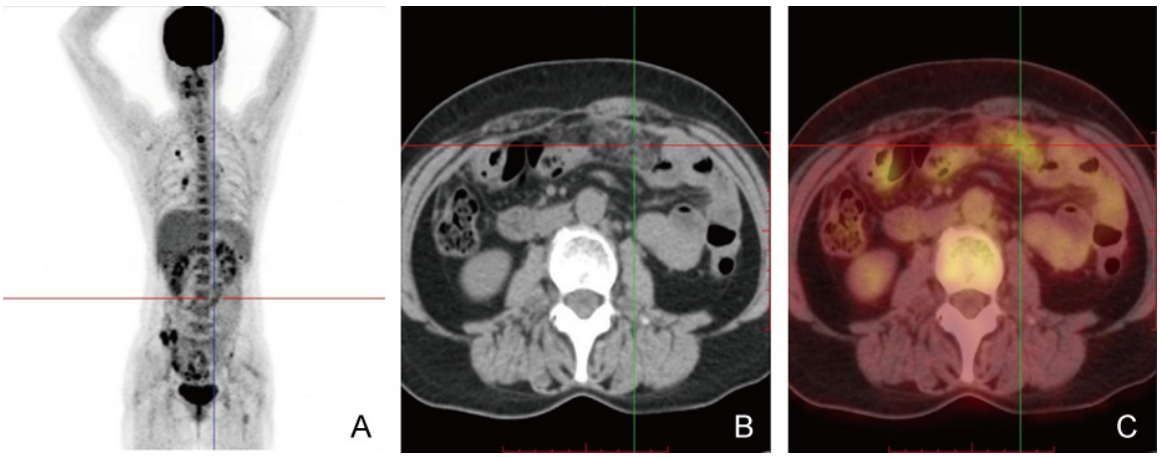

Figure 2. The imaging manifestation of the greater omentum lesion. Elevated FDG uptake with an average SUV of 3.0 was found in left abdomen on PET imaging (A). Axial CT image (B) showed a patchy clouding opacity in the greater omentum. The location of the lesion and characteristics of FDG uptake were visible at the same time on fused PET-CT (C).

unohistochemically, the cells of the greater omentum were CK7+, cytokeratin 20 (CK20)-, CEA+, caudal type homeobox transcription factor (CDX2)-, Wilms' tumor 1 (WT1)-, and calretinin-. The right ovary was CK7+, CK20-, and CDX2-. The preliminary pathological results showed adenocarcinoma of Mullerian origin on the greater omentum, mucinous cystadenoma on the right ovary, and inclusion cysts on the left ovary.

After surgery, the patient was given three courses of intravenous chemotherapy with paclitaxel and carboplatin, and admitted to our hospital for further treatment in March 2016. A physical exam was performed with the following results: body temperature, 36.5°C; heart rate, 72 beats/min; blood pressure, 121/78 mmHg. No heart or lung abnormalities were detected; however, the abdomen was soft with rebound tenderness. Results from a gynecological exam showed normal vulva, vaginal patency, a normal cervix with smooth surface, absent uterus, thick pelvic tissue, and no palpable mass. The patient had supracervical hysterectomy 12 years prior because of uterine

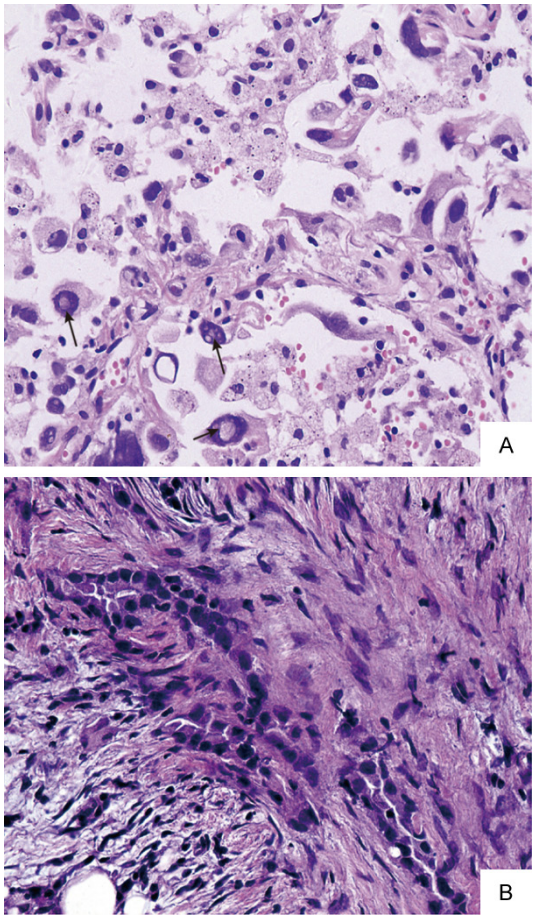

Figure 3. Morphological change of the tumors (HEx400). A. Microscopic features of the lung lesion. Cancer cells were arranged in lepidic pattern or adenoid structure with obvious atypia. Some cells had vacuoles (as indicated by the arrows) in the nucleus and cytoplasm that were caused by chemotherapy (HEx400). B. Microscopic features of the omentum nodules. Cancer cells were arranged in adenoid or cord-like structure. Cells were cube in shape with coarse granular chromatin and grew invasively with fibrous tissue hyperplasia (HEx400).

leiomyoma. Laboratory test results showed: CEA 10.12 (0.0-15.0 ng/ml), CA125 14.59 (0.0–35.0 U/ml), CA199 8.36 (0.0-37.0 U/ml), CA153 5.30 (0–31.3 U/ml), and cytokeratin-19-fragment (CYFRA) 1.51 (0.0-3.3 ng/ml). Pulmonary CT revealed a nodule-like high-density shadow on the superior lobe of right lung, approximately 15 mm × 10 mm in size. The lung showed rough edges of lesions, with elongated burrs. Magnetic resonance imaging (MRI) showed an abnormal signal on bilateral adnexa, abnormal signals on left hip and right lower abdominal incision, multiple enlarged celiac lymph nodes, and multiple abnormal enhancements on the spine. The positron emission tomography-computed tomography (PET-CT) results showed lesions on the superior lobe of right lung. The level of glucose metabolism was increased in the lung, suggesting it is the location of the primary tumor (**Figure 1**). Additionally, increased glucose metabolism was observed in the greater omentum (**Figure 2**), right hilar lymph node, with metabolic lesions seen in the thoracic spine and ribs, suggesting the cancer metastasized to these areas.

Biopsy samples were taken from the lung and compared with the omentum nodules. Microscopically, the biopsy sample of lung showed cancer cells arranged in lepidic pattern or adenoid structure. Cells were morphologically atypical, having a cuboidal shape, enlarged nuclear, and coarse granular chromatin. Some cells had vacuoles in the nucleus and cytoplasm which were the reactive change after chemotherapy (**Figure 3A**). The biopsy sample from the omentum nodules showed cancer cells arranged in an adenoid or cord-like structure. Cells were also cuboidal in shape with coarse granular chromatin. The cells grew invasively with fibrous tissue hyperplasia (**Figure 3B**).

Immunohistochemistry results of omentum tissue showed the following immunophenotype: TTF-1+ (**Figure 4A**), CK7+ (**Figure 4B**), and CA-125, PAX8, estrogen receptor (ER) - (not shown). The same staining results were observed in the biopsy sample of lung. Based on these results, we diagnosed the omental nodules as lung adenocarcinoma metastasis.

Cobas real-time quantitative fluorescent PCR detection of the lung and omentum nodules biopsy sample revealed a deletion mutation in exon 19 of the EGFR gene. Based on these results, we diagnosed the patient with adenocarcinoma of the right upper lobe, greater omentum metastasis, bone metastasis, T1N-1M1, phase IV.

Discussion

Pulmonary adenocarcinoma arises from type II alveolar epithelial cells of the lungs. It is the most common type of non-small cell lung cancer (NSCLC) and usually originates in peripheral lung tissue. Because lung parenchyma lacks nerve cells, the primary lung adenocarcinoma is often not identified until it is at an advanced

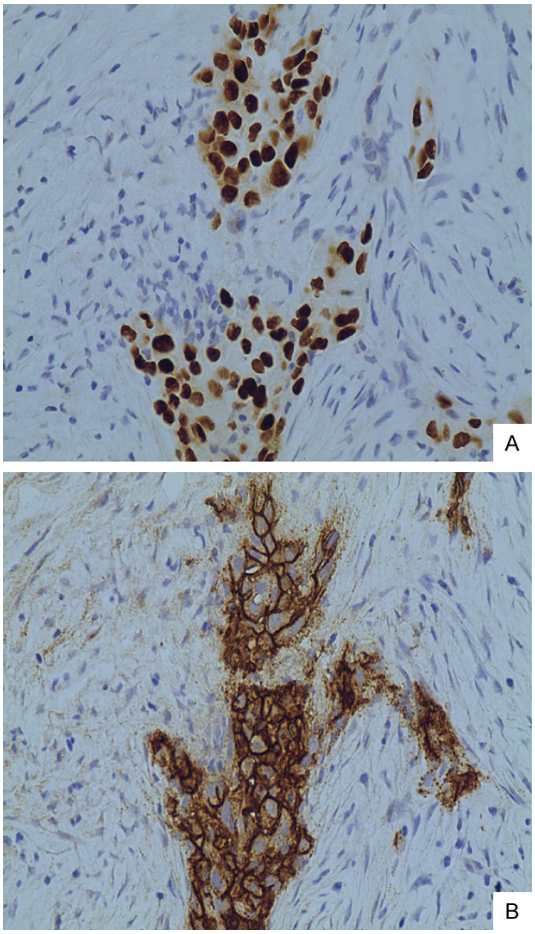

Figure 4. Immunohistochemical staining of the omentum nodules. A. Cancer cells showed nuclear staining for TTF-1 (Envision x400). B. Cancer cells showed cytomembrane staining for CK7 (Envision x400).

stage after metastatic lesions appear elsewhere in the body [3]. In early stages of the disease, imaging may show atypical results but are often misdiagnosed as inflammation or old lesions. In this study, our patient was first admitted because of abdominal distension, but had no cough, chest tightness, shortness of breath or other respiratory symptoms. As there was only evidence of a mass on her right ovary, it was easy to misdiagnose her with ovarian cancer with an omentum metastasis.

The immunohistochemical results of the omental nodules and the lung biopsy tissue samples were both positive for TTF-1 and CK7. TTF-1 is a 38-kd homeodomain-containing protein mainly expressed in thyroid follicular cells, parathyroid chief cells, and type II alveolar epithelial cells. It is highly specific to tumors of lung epithelial cell origin and it is not expressed in the epithelial cells of the ovary, gastrointestinal tract, or breast. TTF-1 expression is often used in the diagnosis of lung adenocarcinoma [9]. CK7 is a 54-kd cytokeratin found in the glandular epithelium and transitional epithelial cells of most normal tissues. It is expressed in adenocarcinomas originating from lung, breast, and ovarian tissue, and is often used for the differential diagnosis of metastatic tumors [10]. Therefore, our immunohistochemistry results strongly support the source of the omentum tumor in our patient as lung adenocarcinoma metastasis.

Lung cancer metastasis usually occurs via lymphatic metastasis, and less commonly by hematogenous metastasis. Lung cancer can metastasize to distant organs including the liver, bone, and brain, and less commonly the kidney, adrenal gland, stomach, intestine, skeletal muscle, and mammary gland [11]. In rare cases, lung cancer can metastasize to sites such as skin [12], skull [13], orbital [14], phalanx, subungual areas, salivary gland, gums [15], and choroid [16]. This patient's first symptom was omentum metastasis, which is rare.

Because of the omentum's unique anatomical structure, cancer cells easily infiltrate it. Milky spots are the primary immune tissue of omentum, and are the first sites of infiltration. Immune cells make up of most of omentum including T lymphocytes (46.1%), B lymphocytes (28.4%), macrophages (12.4%), and other immune cells (13.1%) [17]. Milky spots contain rich blood vessels, which may enable survival of cancer cells. The surrounding mesothelium cells produce growth factors, including VEGF, which promote the angiogenesis necessary for tumor growth. Mesenchymal stem cells are recruited to the tumor cells and secrete VEGF, thus also playing an important role in the omentum tumor metastasis. In addition, fat cells can be an energy reserve for the growth of metastatic carcinoma [18].

We also identified a deletion mutation in exon 19 of EGFR in the lung adenocarcinoma of our patient. EGFR is a receptor tyrosine kinase. The EGFR signaling pathway plays a critical role in regulating cell proliferation, differentiation, and apoptosis in normal cells. EGFR mutations and amplification represent the gene's main deregulation mechanisms in cancers of different histogenetic origin. EGFR is over-expressed and/or

mutated in many tumors. Disruption of the signal transduction affects angiogenesis, tumor invasion and metastasis [19, 20]. In our case, the deletion mutation in exon 19 of EGFR may be the cause of that although the lung primary tumor was small in size, both omentum metastasis and bone metastasis had occurred in this case.

The differential diagnosis of the omental lesion in our case included two types of tumors: metastatic tumors from other organs and a primary tumor of the omentum. While many metastatic tumors can involve the greater omentum, they are most commonly seen with primary tumors of the ovary, uterus, gastrointestinal tract, and pancreas [21, 22]. Ovarian and uterine tumors involving the greater omentum are often serous tumors. Although our patient had a mass in her right ovary, the postoperative pathological diagnosis clearly showed it was a mucinous cystadenoma. The presence of cuboidal epithelial cells and mucus in the cytoplasm, as well as different morphology to the greater omentum lesions and its benign nature, led us to exclude the primary tumor as ovarian. In addition, immumohistochemical staining of omentum lesion showed that CA125, PAX8, Estrogen receptor (ER) is negative, which also suggests that the tumor did not originate in the ovary. There was no clear mass observed in the patient's gastrointestinal tract, pancreas, liver or other digestive organs, so we further excluded the possibility of gastrointestinal cancer metastasis.

The second type of tumor that we considered for our differential diagnosis is a primary tumor of the omentum. For this diagnosis we first considered the mesothelioma. Pleural mesothelioma accounts for 90-95% of mesothelioma cases and develops in the lining of the lungs. In contrast, peritoneal mesothelioma develops in the abdomen and accounts for only 5-10% of cases [23]. Peritoneal benign mesothelioma is mainly isolated while malignant mesothelioma is mostly multiple scattered plaques or nodules. About half of mesothelioma patients have a history of exposure to asbestos. The usual clinical manifestations are recurrent ascites, which may be accompanied by abdominal cramping and distension [24]. The cellular morphology is extremely diverse; the most common is papillary or tubular structures covered with atypical mesothelial cells with polygonal morphology and eosinophilic cytoplasm. The papillary structures have fibrovascular axis, which may contain psammoma bodies. Microscopically, epithelioid mesothelioma has a very similar morphology to metastatic adenocarcinoma; therefore, immunohistochemistry is important for differentiating the two. In epithelioid mesothelioma, keratin marker CK5/6, EMA, calretinin, WT1, HBME-1, D2-40, and Vimentin are all positive [25]. The patient in our case had no known history of asbestos exposure. Moreover, immunohistochemically, the omentum lesions were CK7 positive and TTF-1, Napsin A positive, but negative for mesothelial markers. We therefore excluded epithelioid mesothelioma.

For the differential diagnosis of an omentum primary tumor, tumors originating in the second Mullerian system should also be considered. The second Mullerian system is the mesenchymal tissue from the female pelvic and lower abdominal mesothelium, which has a close embryological relationship with the Mullerian ducts. Accordingly, the neoplastic lesions from the second Mullerian system are similar to lesions in the ovaries, uterus, and other female reproductive organs. According to the microscopic morphology of omentum lesion in this case, it is important to identify whether the serous carcinoma and borderline serous tumor originated from the second Mullerian duct of the omentum. The latter two are morphologically arranged in adenoid or branched papillary structures, and cells are cubic or columnar. In immunohistochemical analysis, markers for CK7, PAX8, WT1, and CA125 were positive, but Vim, CK20, and TTF-1 were negative. Combined with the immunohistochemistry of this case, primary omental second Mullerian tumor can be excluded. In addition, CA125 is an important tumor marker of the Mullerian system tumors. In the first visit, this patient's CA125 was 125.4 U/ml, which dropped to 14.59 U/ml after the surgery. Further analysis showed the elevated CA125 level was due to mucinous cystadenoma of the right ovarian. Additionally, the greater omentum had multi-nodular lesions, one of which was surgically resected for pathological diagnosis. Residual lesions remained in the greater omentum. Therefore, if the adenocarcinoma were of Mullerian origin (either primary or metastatic), the initial level of CA125 would not be reduced after surgery. This finding suggests other possibilities should be considered for the origin of omental nodules.

Conclusion

In summary, EGFR-mutated lung adenocarcinoma with greater omentum metastasis is very rare. The possibility of lung adenocarcinoma metastasis needs to be considered when there are multiple nodules on the greater omentum. A pathological examination must be conducted to ensure a correct diagnosis.

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Disclosure of conflict of interest

None.

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