Primary Pulmonary Mucinous (Colloid) Adenocarcinoma with Postoperative Bone Metastasis

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We describe rare primary pulmonary mucinous (colloid) adenocarcinoma in an 80-year-old man. Chest computed tomography revealed a lobulated, well-defined nodule with a diameter of 3.2 cm in the right middle lobe. Transbronchial biopsy via endobronchial ultrasound with a guide sheath did not uncover malignancy. Right middle lobectomy proceeded because the tumor was located close to the pulmonary hilum. Macroscopically, the cut surface of the nodule comprised a well-demarcated area of somewhat transparent granular aggregates and a yellow-white gelatinous substance. Computed tomography findings of a solitary metastatic lesion in the left fifth costal head 28 months thereafter were consistent with those of a mucin-rich tumor, which was effectively treated by radiotherapy.

Keywords: bronchogenic carcinoma, carcinoembryonic antigen, lung

Introduction

Mucinous (colloid) adenocarcinoma (MCA) of the lung is a rare, but distinctive variant of primary pulmonary adenocarcinoma, which usually has a well-differentiated pathology and a favorable prognosis. Here, we describe a patient with a well-demarcated nodule in the right middle lobe that could not be definitively diagnosed by transbronchial biopsy before curative surgery. Twenty-eight months after the primary lesion was surgically removed and the lymph nodes were dissected, a solitary bone metastasis was identified.

Case Report

A chest X-ray of an asymptomatic 80-year-old man to define the spread of a known renal tumor indicated a shadow in the right middle lung field in September 2009. Chest computed tomography (CT) revealed a lobulated, well-defined homogenous nodule measuring 3.2 × 2.8 cm (Fig. 1A). The nodule was assessed by fiberoptic bronchoscopy on November 4. Five samples obtained via endobronchial ultrasound with a guide sheath (EBUS-GS) included mucous ingredients and peripheral lung tissues, but whether the tumor was MCA could not be concluded. Right nephrectomy on November 18 confirmed that the renal tumor was clear-cell carcinoma (G1, INFa, v(-), pT1aN0M0, pStage I). Preoperative findings of serum tumor markers including carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC) and neuron specific enolase (NSE) were normal. A right middle lobectomy performed to obtain a definitive diagnosis

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on December 9, 2009 was well-tolerated and the postoperative course was uneventful.

The cut surface of the nodule consisted of well demarcated semi-transparent aggregates containing a yellow-white gelatinous substance (Fig. 1B). Microscopically, the tumor contained abundant mucin, which appeared to distend and destroy alveolar spaces in the marginal area and divide the lung parenchyma into lobules by thin irregular fibrous bands (Fig. 1C). Columnar, mucin-producing epithelial cells with hyperchromatic nuclei focally lined the alveoli (Fig. 1D) and single or clustered cancerous cells floated in mucin pools (Fig. 1E). The columnar mucinous epithelium lining the alveolar wall and the floating tumor cells were immunohistochemically positive for CK7, CK20, CDX-2, and MUC2, partly positive for Napsin A, and negative for TTF-1 and SP-A. Postoperative histopathological findings agreed with diagnosis of primary pulmonary MCA (goblet cell-type one without any vascular invasion and with enough surgical margin). Additional immunohistochemical staining was found to be positive for CEA; distant metastasis and elevated serum CEA levels were also subsequently found (Fig. 1F).

The patient agreed to undergo adjuvant chemotherapy with oral tegafur-uracil (UFT). Ten months later, CEA levels increased to 14.6 ng/mL from the perioperative (normal) range of 0–5.0 ng/mL (Fig. 2). Systemic investigation using upper gastrointestinal endoscopy, colonoscopy, abdominal ultrasonography (US), CT and 18-fluorodeoxyglucose positron emission tomography (FDG-PET) did not identify malignant recurrence. A retrospective comparison with preoperative CT findings indicated a slight change in the left fifth costal head (Fig. 3A and 3B). The patient agreed to switch from UFT to tegafur, gimeracil, and oteracil (TS-1) because CEA levels continued to increase, reaching 39.9 ng/mL at 12.5 months after surgery. However, the patient developed a severe gastrointestinal disturbance that prevented the oral administration of TS-1 for 2 months. The CEA level temporarily decreased to 28.1 ng/mL, but then increased to 47.6 ng/mL on December 2011, four months after starting TS-1. Findings of CT indicated that the bone lesion had become enlarged during the same period, although we did not recognize this at the time (Fig. 3C). The CEA level peaked, and then gradually decreased to 8.6 ng/mL in the absence
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Fig. 2 Clinical course and serum CEA level. Preoperative CEA was within normal limits but became elevated after right middle lobectomy. Primary or secondary lesions were undetectable by several modalities and oral anticancer agents could not control CEA levels. Oral intake was terminated due to severe gastrointestinal disturbances and then CEA levels rapidly declined. Sixth postoperative CT uncovered cystic bone metastasis in left fifth costal head as CEA rapidly elevated. Solitary left fifth costal head metastasis shriveled after 50 Gy of irradiation. CEA: carcinoembryonic antigen; CT: computed tomography; Op: operation; RT: radiation therapy; TS-1: oral tegafur, gimeracil, and oteracil; UFT: oral tegafur-uracil.

Fig. 3 Changes in computed tomography findings of left fifth costal head. (A) Normal preoperative carcinoembryonic antigen (CEA) level is 4.4 ng/mL. (B) Appearance of posterior head of rib slightly changed compared with both right and preoperative left sides when CEA was 10.7 ng/mL. (C) Osteolytic change apparent when CEA value was 8.6 ng/mL. (D, E) Cystic lesion with heterogeneous internal density has obviously eroded rib when CEA was 34.2 ng/mL. (F) Metastatic bone lesion shriveled after irradiation when CEA was 7.7 ng/mL. Arrow: metastatic lesion.
of anticancer medication. When the CEA level rapidly increased again to 34.2 ng/mL, postoperative chest CT on April 2012 confirmed a solitary cystic lesion with a diameter of 3 cm and features consistent with those of MCA on the left fifth costal head (Fig. 3D and 3E). Magnetic resonance imaging (MRI) showed a lesion with low-to-intermediate signal intensity on T1-weighted images and heterogeneous as well as obviously high and low signal intensity on contrast-enhanced T2-weighted spin-echo images. The MRI findings suggested MCA metastasis. No other potentially malignant lesion was detected on upper or lower GI tract endoscopy, brain MRI, or FDG-PET. Linear accelerator radiotherapy given in doses of 50 Gy was very effective for the solitary metastasis and the CEA value consequently decreased to 7.7 ng/mL (Fig. 3F).

Discussion

MCA is a rare, but distinctive variant of pulmonary adenocarcinoma. In one of the largest series described by Rossi, et al.,\(^1\) MCA accounted for 0.24% of all lung cancers and the prognosis was often favorable. However, some recent reports have described a rare and aggressive clinical feature.\(^2,3\) According to the latest WHO classification of lung and pleural tumors, a diagnosis of MCA should be limited to findings of neoplastic cells floating in large pools of mucus and focally lining the alveolar spaces, similar to tumors arising from the gastrointestinal tract, ovary, pancreas and breast.\(^4\)

The fluctuating serum CEA levels in our patient could not be rationalized in the context of the apparent absence of an original malignant lesion determined by several modalities. However, CT revealed a single abnormal lesion with mucinous features in the left fifth costal head 28 months after the initial right middle lobectomy. We did not recognize the likelihood that the pulmonary MCA could produce CEA because pre-operative serum CEA values were within normal limits for this type of tumor. After the discovery of the distant metastasis and elevated serum CEA levels, the tumor was immunohistochemically stained for CEA. If the likelihood of CEA production from the pulmonary tumor had been clarified early by immunohistochemical staining, the metastasis might have been detected earlier, because we would have searched for low-density areas on CT images as indicating recurrent MCA. The fluctuations in CEA were nonetheless inexplicable. The serum CEA level tended to increase during the oral administration of anticancer drugs and decrease when these drugs were stopped. The tumor contained a large volume of mucin where immunohistochemical staining revealed CEA accumulation. A high volume of pooled CEA released rapidly into the blood could explain the fluctuating serum CEA levels, independent of tumor size. High levels of tumor CEA expression might be an adverse prognostic factor for stage IB NSCLC.\(^5\)

Even if preoperative serum CEA levels remain within normal limits, high postoperative CEA expression confirmed by immunohistochemical staining might be taken as an indicator of potential early metastasis and recurrence when a high level of serum CEA is observed postoperatively.

The most important issue for surgical pathologists is to distinguish whether the tumor is a primary mucin-rich pulmonary neoplasm or a metastasis, particularly at sites where similar tumors are more likely to arise, such as the gastrointestinal tract, ovary, pancreas and breast. The clinical grounds and radiological findings remain essential in making this distinction.\(^1,6\) Clinical examination such as endoscopy for upper and lower GI tract, abdominal US, FDG-PET, brain CT and CT from the chest to the pelvis, could not detect primary lesions other than renal clear-cell carcinoma, so we considered that this tumor might have been derived from pulmonary parenchyma. Furthermore, mucinous lesions other than the pulmonary MCA and its solitary fifth costal head metastasis have yet to be detected, which supports the diagnosis of primary MCA of the lung.

Invasive preoperative diagnostic procedures, including transbronchial biopsy and transthoracic needle biopsy, or even intraoperative diagnosis from frozen sections of a resected tumor, are generally insufficient for a histological diagnosis\(^7,8\) because floating mucin-secreting tumor cells might comprise only a small ratio of the total tumor.\(^9,10\) Tumor cells could comprise goblet cells or other types of mucin-secreting cells. Cytological atypia of the neoplastic epithelium is usually minimal and thus a cytological diagnosis might be more challenging.\(^10\) Although samples can be collected from peripheral pulmonary lesions using EBUS-GS,\(^11\) this method did not result in a definitive diagnosis for our patient. A first biopsy tissue sample revealed clustered mucinous cells in the cytoplasm that were similar to cells floating in mucous pools in the resected tumor. Malignancy was difficult to confirm because only a few malignant cells were evident, and the grade of cellular atypism was low, even in the retrospective biopsy samples. Considering that if an appropriate biopsy does not lead to a diagnosis and if repeated clinical CT and MRI imaging indicates MCA, the possibility of a better prognosis would be improved by anatomical lobectomy.
Conclusions

Primary pulmonary MCA is regarded as a rare variant lung cancer, with low-grade malignancy. However, distant metastasis occurred in the left fifth costal head in our patient. Early tumor recurrence with mucinous radiological characteristics should be considered during postoperative assessments of primary pulmonary MCA that might produce CEA.

Disclosure Statement

All authors have no financial conflicts of interests to disclose concerning the manuscript.

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