Respiratory Medicine Case Reports 32 (2021) 101368

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

A case of bilateral invasive mucinous adenocarcinoma of the lung with severe productive cough and dyspnea successfully treated with palliative lung lobectomy

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ARTICLE INFO

Keywords:
Invasive mucinous adenocarcinoma
Palliative lung lobectomy
Bilateral intrapulmonary dissemination
Performance status
Pneumonic type

ABSTRACT

Invasive mucinous adenocarcinoma (IMA) of the lung is a chemo-refractory type of lung cancer with frequent intrapulmonary dissemination. Patients with IMA of the lung often suffer from a productive cough and rapid deterioration of performance status (PS). There is currently no standard therapeutic strategy against this unrelenting condition. Here we report a patient with bilateral IMA of the lung with severe productive cough and dyspnea successfully controlled by palliative lung lobectomy. A 67-year-old Japanese man presented with a 3-month history of productive cough. Chest computed tomography (CT) revealed a mass lesion in the left lower lobe and a small nodule and multiple thin-walled cystic lesions in the right lung. He was diagnosed with stage IIB IMA of the lung. Over the next two weeks, his productive cough and dyspnea drastically worsened and his PS declined from 0 to 4. Chest CT showed increases in size of both the nodule and cystic lesions in the right lung and the mass lesion in the left lower lobe. He was re-diagnosed as stage IVA. Given the extreme heterogeneity of the tumor distribution, we decided to perform palliative resection of the left lower lobe. After the surgery, he experienced complete relief of respiratory symptoms, and his PS improved dramatically, enabling chemotherapy. Thirty-one months after surgery, he maintains good PS. In conclusion, our report suggests that aggressive introduction of palliative lung lobectomy played a substantial role for in the excellent outcome of our patient with relatively well confined, advanced-stage IMA.

1. Introduction

Invasive mucinous adenocarcinoma (IMA) of the lung is a relatively rare type of lung adenocarcinoma [1–3]. IMA of the lung frequently entails bilateral intrapulmonary dissemination, which results in a significant reduction in quality of life (QOL) due to the production of large amounts of mucus and respiratory failure [4,5]. In addition, this intrapulmonary dissemination of IMA drastically limits opportunities for surgical tumor resection. Moreover, no effective therapeutic agent against this disorder currently exists. Here we describe a patient with bilateral IMA of the lung complicated with severe productive cough and dyspnea that was successfully controlled with palliative lung lobectomy, which led to significant improvement of the patient's QOL and prolongation of the patient's survival.

2. Case report

A previously healthy 67-year-old Japanese man with a 3-month history of productive cough visited a primary care physician. He was a former smoker (48 pack-years) and a social drinker. He did not take any medications or dietary supplements routinely. Chest computed tomography (CT) at presentation showed a 66-mm mass lesion in the left lower lobe surrounded by a ground-glass opacity (GGO), a 6-mm GGO nodule in the posterior (S2) right upper lobe, and multiple thin-walled cystic lesions in the right lung (Fig. 1, A–C). He underwent transbronchial biopsy for the mass lesion in the left lower lobe. Histologically, the biopsy specimen was composed of alveoli lined by mucin-containing columnar cells. The tumor cells exhibited immunopositivity for cytokeratin 7 (CK7) and hepatocyte nuclear factor 4 alpha (HNF4α). He was

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https://doi.org/10.1016/j.rmcr.2021.101368
Received 25 January 2021; Received in revised form 3 February 2021; Accepted 13 February 2021
Available online 18 February 2021

diagnosed as having invasive mucinous adenocarcinoma (IMA) of the lung. No metastatic lesions were observed on brain magnetic resonance imaging or positron emission tomography/CT. We initially diagnosed the clinical stage of IMA as T3N0M0, stage IIB, and scheduled radical lobectomy of the left lower lobe of the lung.

Three weeks after diagnosis, however, his productive cough and dyspnea had drastically worsened making it impossible for him to sleep. Due to these symptoms, his Eastern Cooperative Oncology Group performance status (PS) declined from 0 to 4 in this period, and his arterial oxygen saturation on ambient air decreased to 93%. Chest CT the day before surgery demonstrated increases in size of the GGO nodule in the right S2 segment (from 6 mm to 12 mm), the multiple thin-walled cystic lesions in the right lung, and the mass lesion in the left lower lobe (from 66 mm to 97 mm, Fig. 1, D–F). We thus definitively judged the shadows in the right lung as contralateral pulmonary metastasis of IMA, and re-determined the clinical stage of IMA as T4N0M1a, stage IVA. We considered starting chemotherapy, but could not justify it due to his severe respiratory symptoms and poor PS, and were faced with a tough decision about the viability of any curative therapy. In consideration of the extreme heterogeneity of the tumor lesion and his good PS score until recently, we decided to perform palliative resection of left lower lobe, where the main lesion responsible for mucin production was situated. After obtaining the patient's informed consent, the palliative pulmonary lobectomy was successfully completed. Pathological assessment of the surgical specimen revealed an IMA mass lesion characterized by columnar cells with eccentric nuclei and cytoplasmic mucin accumulation (Fig. 2). Small satellite lesions were observed throughout the lobe. The tumor cells were negative for *EGFR* mutations and *ALK* and *ROS1* gene rearrangements. Immunohistochemistry results showed that the programmed cell death ligand-1 tumor proportion score of the tissue sample was 0%.

After the operation, the patient enjoyed complete relief from productive cough and dyspnea, and his PS score improved from 4 to 0. We then started intravenous pemetrexed 500 mg/m^2 combined with carboplatin at area under the curve 6 and bevacizumab 15 mg/kg every 3 weeks for four cycles. Nine months after surgery, the regimen was

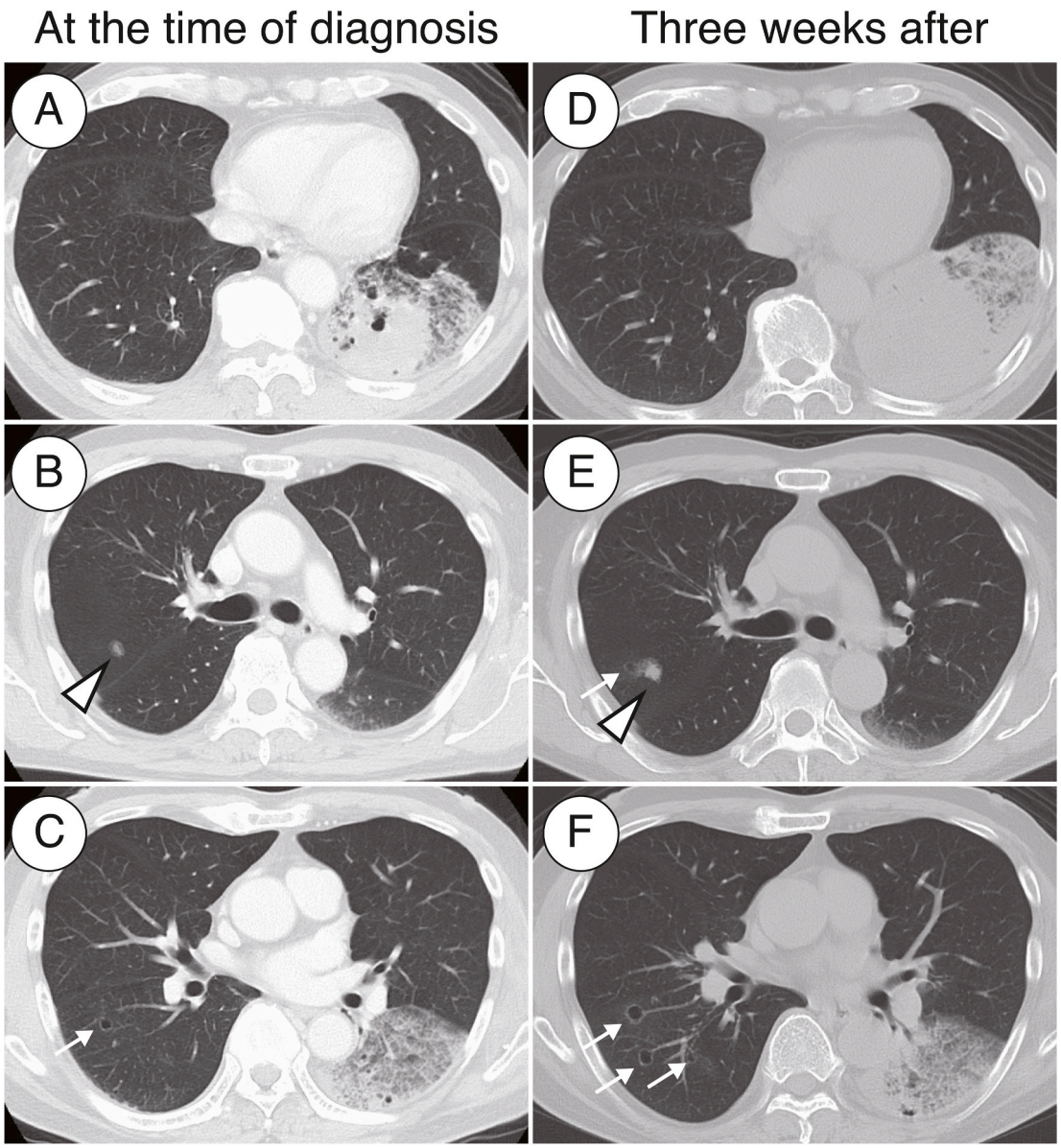

Fig. 1. Computed tomography (CT) at the time of diagnosis (A–C) and three weeks after diagnosis (D–F). Chest CT three weeks after diagnosis showed increases in size of the ground-glass opacity nodule (arrowhead) in the right S2 segment, multiple thin-walled cystic lesions (arrows) in the right lung, and the mass lesion in the left lower lobe.

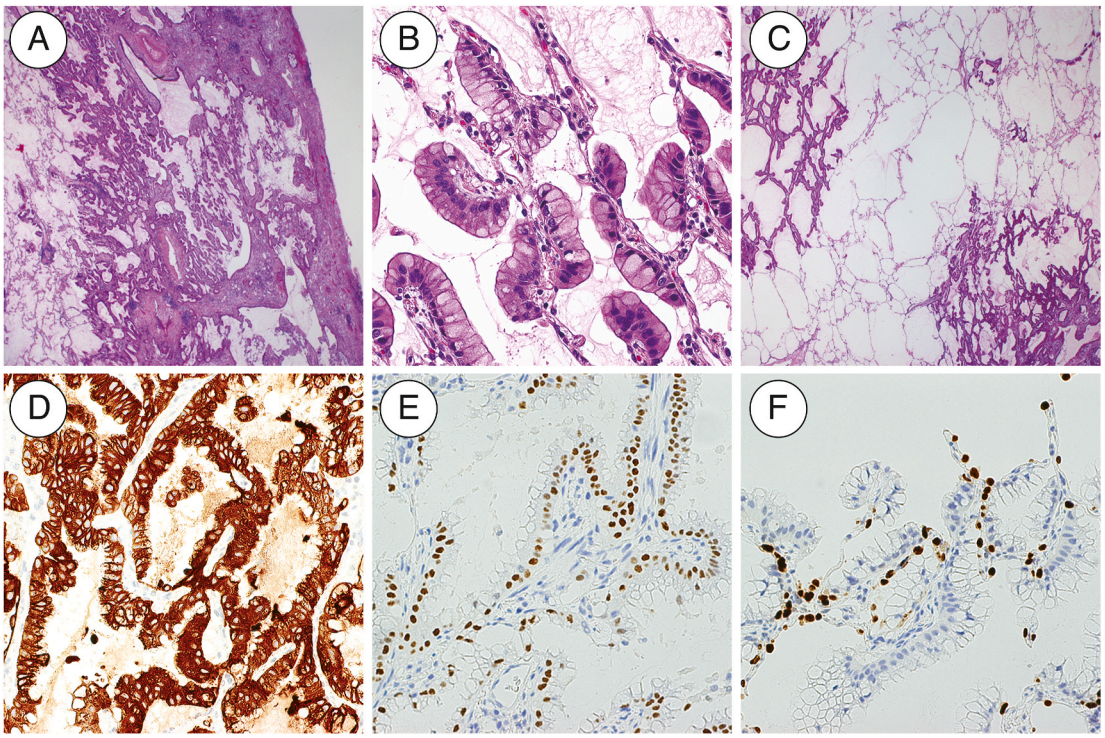

Fig. 2. Histological and immunohistochemical findings of the surgical specimen of the lung. The mass lesion was an invasive mucinous adenocarcinoma, characterized by columnar cells with eccentric nuclei and cytoplasmic mucin accumulation (A, B). Small satellite lesions can be observed within the lung parenchyma (C). Immunohistochemically, the tumor cells were positive for cytokeratin 7 (D) and hepatocyte nuclear factor 4 alpha (E) but negative for thyroid transcription factor-1 (F).

changed due to increases in the sizes of the tumor lesions in the right lung and the appearance of left adrenal metastases. The tumor lesions in the right lung and the left adrenal gland repeatedly deteriorated, and the anticancer therapeutic regimen was changed each time they worsened. At present, 31 months after surgery, the patient is continuing anticancer treatment and maintaining a good PS (information about the anticancer therapeutic regimens; carboplatin plus pemetrexed plus bevacizumab for four cycles as the first-line treatment, pemetrexed for three cycles as the maintenance treatment, atezolizumab for two cycles as the second-line treatment, docetaxel plus ramucirumab for four cycles as the third-line treatment, nab-paclitaxel and bevacizumab for six cycles as the fourth-line treatment, nivolumab for four cycles as the fifth-line treatment, nab-paclitaxel and bevacizumab for six cycles as the sixth-line treatment, and gemcitabine plus bevacizumab for two cycles as the seventh-line treatment).

3. Discussion

We here report a case of patient with advanced stage of IMA of the lung who was successfully controlled with palliative lobectomy. With consideration of several factors such as distribution of tumor lesions and recent patient history, palliative lobectomy can be a valuable therapeutic strategy for controlling cases of bilateral IMA of the lung for which chemotherapy has failed or is not an option.

IMA of the lung is a relatively rare type of lung cancer comprising only 2–10% of lung adenocarcinoma [1–3]. The tumor cells of IMA have a goblet cell morphology, with abundant intracytoplasmic mucin [6]. Immunohistochemically, IMA cells are typically positive for CK7, CK20, HNF4α, and Mucin 5AC but negative for thyroid transcription factor-1 and Napsin A [7,8]. With regard to the molecular characteristics of IMA, *K-RAS* mutations are the most frequent oncogenic driver mutations in IMA [9]. The incidence of *KRAS* mutations is higher in IMA than in non-IMA lung adenocarcinoma [1,9]. On the other hand, targetable mutations such as *EGFR* mutations, *ALK* gene rearrangements, and *BRAF* V600E mutation are rare in IMA patients [1,10–12]. Furthermore, the expression of PD-L1 in ≥1% of cells is found in only 6.1% of IMAs, but 59.7% of conventional lung adenocarcinomas [13]. IMA patients treated with conventional chemotherapy show no improvement in overall survival compared to untreated IMA patients [11]. Currently, no available effective drugs against advanced-stage lung IMA are known to exist.

IMA frequently causes bilateral intrapulmonary dissemination through the bronchi or lymph vessels [4]. Based on high-resolution CT findings, IMA are classified as solitary-type and pneumonic-type; the latter show alveolar consolidation, as seen in our case [5]. Patients with pneumonic-type IMA are more frequently associated with respiratory symptoms such as cough and sputum expectoration than patients with solitary-type IMA [5]. The survival rates are significantly worse for pneumonic-type IMA: in one study, the 5-year overall rates in patients with solitary-type and pneumonic-type IMA were 83.3% and 20%, respectively [5]. Lung transplantation has been attempted for patients with advanced-stage IMA, but recurrence of the original tumor within the donor lungs after transplantation is common [14,15].

In patients with pneumonic-type IMA, the QOL is markedly compromised due to the large amount of sputum. Our patient suffered from a severe productive cough and dyspnea, which markedly impaired his systemic condition. Oral administration of erythromycin or inhalation of indomethacin has been tried to ameliorate refractory bronchorrhea in patient with IMA, but their clinical effects have proven limited [16,17].

The efficacy of palliative surgery for improvement of symptoms have been demonstrated in patients with various organs of advanced mucinous carcinoma, such as mucinous ovarian cancer and mucinous carcinoma of the breast [18,19]. However, since the lung is a vital organ and has a low regenerative capacity, the determination of surgical indication in patients with bilateral pneumonic-type IMA must be rigorous. Barlesi and colleague reported four cases of bilateral IMA who underwent palliative pneumonectomy [20]. Three of these experienced an uneventful immediate post-operative course, and were able to

undergo conventional chemotherapy. The survival of these patients was 3, 12, and 18 months; the authors mentioned that these outcomes should be considered as an appreciable results [20]. Since the report from Barlesi 20 years ago, no case of IMA of the lung undergoing palliative surgery has been reported. In our case, we decided to conduct palliative lung lobectomy based on the following criteria: 1) absence of past medical history, 2) relatively young age, 3) short duration of disease progression, 4) patient's recent good PS, and 5) extremely uneven distribution of IMA of the lung. After the surgery, our patient experienced complete relief of respiratory symptoms and dramatically improved systemic condition, and could receive continuous anticancer treatment for a long period. Recent studies have developed a pharmacologic inhibitor of $KRAS^{G12C}$, one of the most common activating mutations in IMA, and have demonstrated its clinical efficacy in patients with lung adenocarcinoma [21,22]. These hopeful studies suggest an effective therapeutic strategy against chemo-refractory IMA of the lung. Taken together, we propose that palliative lung lobectomy should be discussed as a management option of bilateral IMA in a careful multidisciplinary approach to preserve the opportunity for amelioration of respiratory symptoms, enable the use of anticancer drugs, and prolong patient survival.

In summary, we have described a case of IMA of the lung associated with severe productive cough and deteriorated PS that was successfully controlled with palliative pulmonary resection. With consideration of several criteria including tumor distribution and patient's recent PS, aggressive lung lobectomy for relatively well confined IMA may bring about an excellent outcome even in patients with advanced-stage IMA.

Declaration of competing interest

The authors declare that there were no conflicts of interest.

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