CASE REPORT

Multiple primary malignancies of laryngeal cancer, small cell lung cancer and squamous cell lung cancer in a patient: how to approach MPMs

Eun Kyoung Kim,¹ Joo-Yeon Kim,² Bo Mi Kim,² Sung-Nam Lim³

¹H Plus Yangji Hospital, Seoul, Republic of Korea

²Department of Pathology, Inje University Haeundae Paik Hospital, Busan, Republic of Korea

³Department of Internal Medicine, Inje University Haeundae Paik Hospital, Busan, Republic of Korea

Correspondence to
Professor Sung-Nam Lim,
sungnaml@gmail.com

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SUMMARY

Lung malignancies presenting in association with head and neck cancers are well documented, while laryngeal cancers presenting with simultaneous small cell lung cancer and squamous cell lung cancer have been rarely reported. We report a case of a man aged 65 years with a triple primary malignancy of the lung and larynx. Without a meticulous approach, the patients may not receive curative aim treatment due to incomplete staging. The patient underwent concurrent chemoradiotherapy for locally advanced laryngeal cancer, small cell lung cancer and squamous cell lung cancer followed by combination chemotherapy with etoposide and cisplatin for synchronous double primary lung cancer. Following this therapy, he achieved a complete response of larynx cancer, but a partial response of small cell lung cancer and a stable disease of squamous cell lung cancer. A meticulous diagnostic approach should be encouraged to pursue the possibility of curative treatment and achieve better outcomes for such patients.

BACKGROUND

The incidence of multiple primary malignancies (MPMs) including synchronous or metachronous cancers is increasing in parallel with the prolonged life expectancy.^{1–2} Several studies have presented MPM including lung cancer, as either synchronous or metachronous cancer.^{3–7} Synchronous multiple primary lung cancer is rare and is not easily distinguished from metastases of other primary cancers.⁸ When multiple lung masses are found, it is important to distinguish between metastatic tumours and independent tumours to determine an appropriate treatment approach. In this report, we present a rare case of triple synchronous primary cancers with a laryngeal cancer and two distinct primary lung cancers in a patient who was initially planned to receive palliative therapy for advanced laryngeal cancer with multiple lung metastases.

CASE PRESENTATION

A man aged 65 years with foreign body sensation for 5 months was referred to our hospital. His main symptom was voice change, which occurred 4 weeks ago. He had a 45 pack-year history of smoking and he had stopped smoking 5 years ago. On physical examination, there was no lymph node enlargement in the neck, axillary or inguinal area. The throat examination by laryngoscope showed a

protruding irregular-shaped mass on the laryngeal surface of the epiglottis.

INVESTIGATIONS

Routine complete blood count and chemical laboratory data were all within the normal range. Neck CT and neck MRI revealed a supraglottic mass about 2.0 cm in size and a lung mass in the left upper lobe about 6.3 cm in size, directly invading the left pericardium and pulmonary artery and vein (figure 1A). The pathological specimen from the laryngoscopic biopsy performed under general anaesthesia revealed squamous cell carcinoma (figure 2). There were several enlarged cervical lymph nodes with T2 high signal intensity in the left neck level IV and V on the neck MRI. However, they had lower standardised uptake value (SUV) than the average SUV of the liver on the F-18 fluorodeoxyglucose (FDG)-avid positron emission tomography (PET)-CT (not shown). The chest CT showed another pulmonary mass invading the chest wall in the right lower lobe about 5.6 cm in size (figure 1B). It was suspected as another primary lung cancer rather than pulmonary metastasis of laryngeal cancer, considering the discrepancy in the cervical lymph node findings between the neck MRI and PET-CT. The patient underwent a bronchoscopic biopsy for the lung mass in the left upper lobe and a CT-guided biopsy for another mass in the right lower lobe. Pathology reports revealed two different cell types including small cell carcinoma and squamous cell carcinoma (figure 3A, D). Subsequent immunohistochemical (IHC) staining was positive for thyroid transcription factor-1 (TTF-1) and CD56 (figure 3B) and negative for p63 (figure 3C) in the small cell lung cancer in the left upper lobe and negative for CD56 (figure 3E) and positive for p63 (figure 3F) in the squamous cell lung cancer in the right lower lobe. Mutation in the epidermal growth factor receptor and anaplastic lymphoma kinase rearrangement was not observed in the squamous cell lung cancer in the right lower lobe (not shown). Finally, based on these pathological findings, he was diagnosed with synchronous triple primary cancers, including clinical stage T4N0 supraglottic laryngeal cancer, T4N2 small cell lung cancer and T3N0 squamous cell lung cancer.

TREATMENT

Owing to his locally advanced small cell lung cancer and poor pulmonary function, the predicted

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Figure 1 CT scan result identifying two masses, including 6.3 cm mass in the left upper lobe, which invaded the left pericardium, left pulmonary artery and left pulmonary vein (A), and another 5.6 cm mass, which invaded the chest wall without bony destruction (B).

Figure 2 Laryngeal tumour is moderately differentiated squamous cell carcinoma. Carcinoma in situ showing dysplastic change throughout full thickness of squamous epithelium is identified at the right side, and tumour cells invade the left side.

forced expiratory volume in 1 s value was <2 L, and he received concurrent chemoradiation therapy (CCRT) with weekly cisplatin 40 mg/m² for synchronous triple primary cancers. The radiation dose had been 4000 cGy in the supraglottic laryngeal cancer by intensity-modulated radiation therapy (IMRT) followed by 2400 cGy in both neck lymph nodes and 4000 cGy in each double primary lung cancer in the left upper lobe and right lower lobe.

OUTCOME AND FOLLOW-UP

On completion of CCRT, the supraglottic laryngeal cancer was markedly decreased without newly developed cervical lymph

node metastasis. A laryngoscopic examination and biopsy for remnant tissue revealed no evidence of disease. A follow-up chest CT showed a partial response for the small cell lung cancer in the left upper lobe; however, the squamous cell lung cancer in the right lower lobe remained stable. Thereafter, additional chemotherapy with etoposide and cisplatin for the small cell lung cancer and squamous cell lung cancer was performed.

DISCUSSION

Head and neck cancer with synchronous or metachronous lung cancers during follow-up is not rare; however, our case with simultaneous triple primary cancers is uncommon.

In this report, we presented a patient showing head and neck cancer with two distinct lung masses who almost would inadvertently have received palliative therapy only.

Head and neck cancer is the sixth most common cancer in the world and ~500 000 new cases are projected annually.⁹ Approximately 60% of these patients present with locally advanced disease (stage III/IV). Supraglottic laryngeal cancer is usually diagnosed in the advanced stages with cervical lymph node metastasis because of its non-specific presenting symptoms and its anatomical characteristics with its very rich lymphatic network.^{6 10} This was why we presumed this patient might have advanced supraglottic laryngeal cancer with two metastatic lung foci at his initial presentation. However, because the laryngeal mass considered the index primary tumour site seemed to be a small protruding mass without regional cervical lymph node involvement, as shown by neck MRI and PET-CT; with high suspicion of MPMs, we performed a bronchoscopic biopsy of the lung mass in the left upper lobe. Surprisingly, the pathological result showed small cell lung cancer. Therefore, we also decided to try to confirm the pathology of the lung mass in the right lower lobe by CT-guided biopsy. The pathological result showed squamous cell carcinoma such as that of supraglottic laryngeal cancer. We concluded that it was not a metastatic laryngeal cancer with two lung metastases but MPMs with a larynx and two lung lobes.

According to Warren and Gates,¹¹ MPMs are defined by two or more malignant tumours occurring at different locations with distinct histology such that one tumour is not a metastasis of the other. MPMs are classified into two groups according to the time of their occurrence: the synchronous (including simultaneous) group is defined as MPMs diagnosed within 6 months of the initial primary cancer diagnosis, while the metachronous group consists of MPMs diagnosed more than 6 months after the initial primary cancer diagnosis. The incidence of MPMs is ~9% according to the data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER).¹² Head and neck cancer with synchronous or metachronous primary lung cancers was reported in previous case series,^{6 7} and the incidence ranged from 4.5% to 14%.^{13 14} The most common secondary primary cancer following a first primary head and neck cancer is lung cancer.¹⁵ Our case had two simultaneous secondary primary lung cancers with laryngeal cancer at first presentation, which is not common and, among synchronous primary lung cancer cases, the coexistence of small cell lung cancer and squamous cell lung cancer has rarely been reported. Therefore, if there were no high suspicion or effort to confirm the two distinct lung masses by invasive diagnostic procedures, a patient with MPM would have received only palliative therapy instead of curative aim treatment.

Eventually, the patient in our case was diagnosed with simultaneous triple primary cancers, including laryngeal supraglottic cancer (cT4N0), small cell lung cancer (cT4N2, limited stage)

Figure 3 In the bronchial biopsy, tumour cells have scant cytoplasm and ill-defined cell borders, and the chromatin tends to be finely granular with inconspicuous nucleoli (A). The diagnosis is small cell carcinoma with positive staining for CD56 (B) and negative staining for p63 (C). The lung parenchymal lesion is atypical cellular proliferation showing keratinisation (D). On the contrary, in the bronchial lesion, the results of immunohistochemical staining are negative for CD56 (E) and positive for p63 (F). The lung mass is consistent with squamous cell carcinoma.

and squamous cell lung cancer (cT3N0). Initially, he received CCRT for the laryngeal supraglottic cancer and two synchronous lung cancers. According to the follow-up CT and biopsy after CCRT, the supraglottic laryngeal cancer showed a complete response, the small cell lung cancer showed a partial response and the squamous cell lung cancer remained stable. Consequently, he was scheduled to receive platinum-based chemotherapy for the small cell lung cancer and squamous cell lung cancer.

Unfortunately, we did not evaluate the clinical N2 lymph nodes which were the left lower paratracheal lymph node (SUV9.1) and the subcarinal lymph node (SUV5.3) of PET-CT. If a mediastinoscopy had been performed for the N2 lymph node pathological evaluation, we could have confirmed whether it had metastasised from small cell lung cancer or laryngeal cancer. However, radiation therapy was already planned for this patient for the small cell lung cancer in the left upper lobe, and because the N2 lymph nodes were included in the radiation treatment field of small cell lung cancer, we decided not to hesitate to execute curative aim treatment unimpeded by an invasive procedure simply for diagnosis.

Two squamous cell carcinomas in the larynx and lung were presented simultaneously in this case; however, primary squamous cell carcinoma of the lung is difficult to distinguish from metastatic squamous cell carcinoma of the head and neck. Although a few studies have proposed various methods, they remain questionable. There is no IHC marker that helps in that differential, but we tried to differentiate and examine available markers. At first, additional HPV p-16 IHC staining and EBV in situ hybridisation were examined for laryngeal cancer. We expected to identify concordance between laryngeal squamous cell cancer and lung squamous cancer, but HPV IHC staining and EBV in situ hybridisation were negative in the larynx, so we did not conduct a pathological examination for squamous cell

lung cancer in the right lower lobe. As a few previous studies have noted,^{16 17} a comparison of the clonality between the two lesions could be applied and yield helpful information. However, such genetic approaches are not yet generally feasible, and they require confirmation.

As previous studies have shown promising outcomes with curative aim approaches in such patients,^{5 18–20} we also approached this patient initially suspected of having laryngeal cancer with two metastatic lung cancers with curative aim treatment, and he survived without recurrence.

MPMs continue to pose difficult challenges to oncologist. While putting as much effort into identifying the pathology of each malignancy as possible, more meticulous approaches with curative aim treatment have to be considered for patients with MPMs.

Learning points

- ▶ Multiple cancerous lesions are not always advanced stage metastatic cancer.
- ▶ Meticulous diagnostic approach is required for patients with suspected multiple primary malignancies.
- ▶ Effort to establish the pathological diagnosis for each separate lesion is important.

Contributors EKK planned and wrote the manuscript. BMK and J-YK reviewed and described the pathological results of this manuscript. SNL approved and supervised final manuscript.

Competing interests None declared.

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