Synchronous Triple Lung Cancers after Treatment for Non-Hodgkin’s Lymphoma: Metachronous Quadruple Cancers

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Abstract

After chemotherapy and radiotherapy for non-Hodgkin’s lymphoma during a one-year period, a 66-year-old man developed synchronous triple lung cancers in both lungs. Of the three resected tumors, one was advanced large cell carcinoma with neuroendocrine morphology, and the other two were early squamous cell carcinoma without lymph node metastasis. Although he received repeated chemotherapy for lung cancer, the patient died of hepatic failure due to multiple liver metastases. Autopsy revealed disseminated metastasis of the large cell carcinoma with neuroendocrine morphology throughout the entire body, but no recurrence of malignant lymphoma or squamous cell carcinoma was found. To our knowledge, this is the first report of triple lung cancers occurring after treatment for malignant lymphoma.

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Key words: lung cancer, malignant lymphoma, secondary cancer, chemotherapy, multiple cancer

Introduction

As a result of successful treatment of lymphomas with chemotherapy, radiation therapy, or both, patients with lymphoma are living longer. However, this improved survival has increased the risk of treatment-related complications, including second malignancies.

Here, we report a rare case in which synchronous triple lung cancers developed in one patient after treatment for non-Hodgkin’s lymphoma (NHL).
TOKUCHI et al

Figure 1. Chest computed tomography findings in February 2000 (A, B) and in July 1999 (C, D). A) A 15 mm round nodule is observed in right S6. B) A 6 mm faint round nodule is observed in left S1+2.

antigen (SCC), pro-gastrin-releasing peptide (ProGRP) and soluble IL-2 receptor (sIL-2R) were in the normal ranges, but the serum level of CYFRA was high at 2.8 ng/ml (normal <2.0).

On March 16, 2000, video-assisted thoracic surgery (VATS) was carried out on right upper lobectomy, with mediastinal lymph node dissection and partial resection of right S6, for the purpose of treatment and definitive diagnosis. Histologically, the nodule of right S6 was a large cell carcinoma with neuroendocrine morphology and metastasis of mediastinal lymph node (Fig. 3A); there was also a microscopic metastasis under the pleura pulmonalis of the right upper lobe. TNM staging of right S6 tumor showed pT1N2M1 stage IV, while histology of the tumor in the right upper lobe bronchus showed a moderately differentiated squamous cell carcinoma without lymph nodes metastasis, and TNM staging showed pT1N0M0 stage IA (Fig. 3B). Our diagnosis was synchronous double lung cancers, and we speculated that the nodule of left S1+2 was metastasis from the right S6 tumor. The patient was treated with one course of chemotherapy, cisplatin and irinotecan, from August 11, 2000, but the left S1+2 tumor was not reduced.

We followed up this patient in the out-patient department, and on June 27, 2001, the left S1+2 tumor was found to be enlarged to 10 mm in diameter on his chest CT. However, no other tumors were detected in abdominal CT, brain MRI or bone scintigraphy. The patient chose to receive surgical treatment for the tumor, and VATS partial lung resection of left S1+2 was performed on August 30, 2001. Pathological findings showed that the left S1+2 tumor was a poorly differentiated squamous cell carcinoma, but, since the former squamous cell carcinoma of the right upper lobe was in the early stage, it should not have metastasized (Fig. 3C). In addition, the differentiations of the two tumors were at variance. Therefore, the tumor of the left lung was the primary lung cancer. Retrospectively, there were three tumors in both lungs, in February 2000: one tumor a large cell carcinoma with neuroendocrine morphology, the others, early squamous
Triple Lung Cancers after Lymphoma

intensive chemotherapy and radiotherapy have transformed the prognosis of patients with malignant lymphoma, and it has thus become increasingly important to evaluate the occurrence of second cancers. Both radiotherapy and chemotherapy are known to sometimes induce mutagens and animal carcinogenesis, and alkylating agents in particular have been responsible for the pathogenesis of second cancers (2).

Furthermore, it is well known that the incidence of acute non-lymphocytic leukemia and bladder cancer increases after treatment for Hodgkin’s disease (2), and that patients with Hodgkin’s lymphoma develop lung cancer at a rate of two to eight times that of the general population (3).

Although the increased risk of occurrence of solid tumors after treatment for NHL has been a matter of controversy, several studies indicating an association have been reported. Travis et al reported that 1,231 of 29,153 NHL patients (4.2%) developed second cancers, and the increased risk was significant (4). The largest number of second tumors, 274 of the 1,231 patients (22.3%), occurred in the lung at a median 40 months after diagnosis of NHL (4). Travis et al recently also reported that a significant risk of lung cancer after Hodgkin’s disease was apparent within 1–4 years after treatment with alkylating agents, whereas excess risk after radiotherapy became a factor 5 years after treatment and persisted for more than 20 years (5). The triple lung cancers in the present patient developed over the course of a year, during treatment for malignant lymphoma after initial diagnosis. The period of one year was quite short, but it was compatible with the second report, above (5). To the best of our knowledge, however, double second lung cancers after malignant lymphoma had not been reported before, nor have synchronous triple lung cancers. We do not really understand how these three lung cancers developed in such a short term, but we have made a speculation. Recent understanding of molecular carcinogenesis has provided a concept of multistage carcinogenesis that is separated into initiation, promotion, conversion, and progression. Combined chemotherapy for malignant lymphoma might accelerate these steps, possibly resulting in the three lung cancers that appeared synchronously.

There have been reports of a positive correlation between a history of smoking and the development of lung cancer after malignant lymphoma (6, 7), and, since our patient was a heavy smoker, his habit probably played a role in the development of the lung cancers. Although he had been treated with radiation, his lung cancers were outside the radiation area, so there was little likelihood of a causal relationship between radiation and the lung cancers.

In this case, we diagnosed triple primary lung cancers and proceeded to operate for a tumor. Had we not done so, we would have diagnosed recurrence of the former malignant neoplasm. Thus, obtaining tumor tissue from patients with a history of treatment for malignant neoplasm can lead clinicians to more definitive diagnoses. According to the Annual of the Pathological Autopsy Cases in 1999 in Japan, the frequency of triple lung cancers was 6 cases of 26,619 autopsy cases (0.02%), and the occurrence of quadruple cancers was 30 cases (0.1%) (8). Both were very rare incidents.

In conclusion, the present case suggests that the current treatment of lymphomas has improved survival but that it can also lead to an increased risk of second malignancies. We report this case to remind physicians to take this risk into consideration.
Figure 3. Microscopic appearances of three lung tumors. A) The right S6 tumor cells have a fine cytoplasm and a moderately large nucleus with a nucleolus. This tumor does not show any squamous cell or glandular differentiation, but it shows palisading and trabecular arrangement. Morphologically, this is regarded as a type of neuroendocrine tumor. However, immunohistochemical staining with a neuroendocrine marker, such as chromogranin A, NSE, Leu-7 or Synaptophysin, were all negative (data not shown), thus this tumor is compatible with large cell carcinoma with neuroendocrine morphology, by WHO classification. B) Endobronchial growth by moderately differentiated squamous cell carcinoma is seen in right upper lobe bronchus tumor; normal mucosa is also observed. C) The left S1+2 tumor proliferate with a nesting pattern sometimes showing central necrosis. The cell membranes are conspicuous, and the eosinophilic cytoplasm appears to have a pale perinuclear halo. The tumor was diagnosed as poorly differentiated squamous cell carcinoma.

References