Lung Cancer Detected 5 Years after Resection of Cancer of Unknown Primary in a Mediastinal Lymph Node: A Case Report and Review of Relevant Cases from the Literature

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We report the rare and interesting case of a primary lung cancer detected 5 years after cancer of unknown primary (CUP) of a mediastinal lymph node (LN) was resected. A 40-year-old male was diagnosed with adenocarcinoma of unknown primary in a mediastinal lymph node after resection of the mediastinal tumor. Five years after resection of the CUP in mediastinal LN, a small, abnormal nodular shadow in left upper lobe was detected by chest CT. This pulmonary tumor was diagnosed as a lung adenocarcinoma. The pathological and immunohistological findings of the resected pulmonary tumor resembled those of the LN resected 5 years before. We speculated that the pulmonary lesion represented primary lung cancer that enlarged later than the metastatic mediastinal LN. This case illustrates the importance of careful observation and long-term follow-up in patients treated for CUP of a thoracic LN.

Keywords: cancer of unknown primary site, lung cancer

Introduction

Cancer of unknown primary (CUP) site is not an unusual phenomenon. It has been reported that patients with CUP make up 3%–5% of all cancer patients.1–3) However, CUP of the thoracic lymph nodes (LNs) is comparatively rare, representing 1%–1.5% of all CUP cases.1,4,5) It is typically difficult to detect the primary lesion even when a systemic, detailed evaluation is performed, and the primary site rarely becomes manifest during the long-term clinical course. Here, we report a rare and interesting case in which primary lung cancer was detected 5 years after resection of CUP of a mediastinal LN.

Case Report

A 40-year-old male was referred to our hospital for evaluation of an abnormal shadow in the left pulmonary hilum on a chest X-ray taken in November 2004. The patient’s past and family histories were unremarkable. He had smoked 20 cigarettes per day since the age of 15 years. Physical examination revealed no abnormalities and no lymphadenopathy. Routine laboratory tests were within the normal range except for a slight elevation of carcinoembryonic antigen (CEA) to 5.9 ng/ml. Chest X-ray showed a slightly high-intensity shadow in the left pulmonary hilum. Chest CT revealed a well-circumscribed tumor,
Lung Cancer Detected 5 Years after Resection of Cancer of Unknown Primary

2.7 cm in diameter, located on the left side of the aortic arch. The tumor was well defined and homogenous, and it was enhanced on contrast CT (Fig. 1A). These features were suggestive of an anterior mediastinal solid tumor such as a thymoma. There were no abnormal findings in the lung fields or other organs, and there was no lymphadenopathy in other regions.

In January 2005, thoracoscopic resection of the mediastinal tumor with the thymus was performed. The resected specimen weighed 81 g. The dimensions of the resected specimen were as follows: thymic right lobe, 9 × 4 cm; left lobe, 11 × 7 cm. A tumor located on the left side of the upper thymic pole measured 2.7 × 2.5 × 2.0 cm in size. The cut surface of the tumor revealed a well-encapsulated, homogenous solid tumor with a dark reddish color. Pathology revealed large cells with nuclear atypia growing in a glandular structure within the lymphatic structure (Fig. 1B). Immunohistochemical studies showed the tumor to be positive for TTF-1 (Fig. 1C) and CAM5.2 (Fig. 1D) but negative for cytokeratin 5/6 and CD56. These findings suggested the presence of metastatic adenocarcinoma of the lymph node originating from another organ such as the lung. At this time, we performed systemic evaluation, including gastrointestinal endoscopy, in an effort to detect the primary lesion. However, we were unable to detect a primary lesion, so the patient was diagnosed with CUP of the mediastinal LN. Postoperative chemotherapy was recommended but declined by the patient.

The patient was followed at an outpatient clinic at 3- to 6-month intervals. Starting in 2006, his serum CEA gradually rose again. We added annual 18F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) for systemic evaluation from 2007 onward, but there was no abnormal FDG accumulation. In May 2010, a small, abnormal nodular shadow in the left upper lung lobe was detected by chest CT. The nodular shadow measured 1.2 cm in diameter and had an irregular shape and spicula; it was suggestive of lung cancer (Fig. 2A). FDG-PET/CT showed abnormal accumulation in the
Kawasaki H, et al.

A nodular shadow within the left upper lobe (SUV\(_{\text{max}}\) = 8.3) and in the left pulmonary hilar LN (SUV\(_{\text{max}}\) = 6.1). In August 2010, we performed wedge resection of the left upper lobe; adenocarcinoma was diagnosed by rapid frozen section pathological examination, so we proceeded to perform an upper lobectomy of the left lung and lymph node dissection.

Pathological examination of the tumor showed lepidic growth of the alveolar epithelial wall; some areas showed a solid glandular structure, and both structures exhibited a shift to continuity (Fig. 2B). Immunohistochemical studies of the left lung showed to be positive for TTF-1 (C) and CAM5.2 (D).

![Fig. 2](image)

**Fig. 2** Chest CT revealed a small, nodular shadow 1.2 cm in diameter with an irregular shape and spicula in the left upper lobe (A). Pathological examination of the pulmonary tumor resected in 2010 revealed lepidic growth on the alveolar epithelial wall; some areas exhibited a solid glandular structure, and both structures showed a shift to continuity (B). Immunohistochemical studies of the left lung showed to be positive for TTF-1 (C) and CAM5.2 (D).

The patient’s postoperative course was uneventful. His serum CEA level decreased to 3.7 ng/ml in 2 months after the operation, and he received postoperative chemotherapy. However, 1 year after the left upper lobectomy, in April 2011, the patient’s serum CEA level elevated again. The tumor had recurred at the right paratracheal and subcarinal LNs, so he had received chemoradiotherapy. We evaluated mutation of EGFR gene and EML4-ALK fusion gene in a pulmonary tumor resected in 2010, but neither study was positive. As of July 2015, the patient was alive with relapsed disease and was undergoing continuous chemotherapy.

**Discussion**

There are several possible explanations for the development of CUP in the LNs. First, the primary lesion may not
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<th>Surgical treatment of CUP</th>
<th>Adjuvant treatment of CUP</th>
<th>Time from treatment of CUP to detection of PL (mo)</th>
<th>Location of PL</th>
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CUP: cancer of unknown primary; LN: lymph node; TM: tumor marker; PL: pulmonary lesion; AD: adenocarcinoma; SQ: squamous cell carcinoma; LCNEC: large cell neuroendocrine carcinoma; LA: large cell carcinoma; ND: no data; SCC: squamous cell carcinoma antigen; SLX: Sialyl Lewis X antigen; CEA: carcinoembryonic antigen; Cyfra: Cytokeratin subunit 19 fragment; Med: mediastinum; Hil: hilum; LB: lobectomy; LND: lymph node dissection; EX: extirpation; BX: biopsy; CT: chemotherapy; RT: radiation therapy; Rt. UL: right upper lobe; Rt. LL: right lower lobe; Lt. UL: left upper lobe; PN: pneumonectomy; PR: partial resection
be detectable because of insufficient size or because it grew too slowly to be detected on clinical, radiologic, or pathologic examinations; the primary lesion may also be hidden by an enlarged metastatic LN.4,5 The second possibility is that the host defense mechanism has destroyed the primary tumors, termed spontaneous regression. However, spontaneous regression of primary lesions other than metastatic LNs is rare, especially in lung cancer.6 Another possible theory is that the cancer may arise from epithelial inclusions in the LN. Benign epithelial inclusions have occasionally been reported to exist in the LNs7,8 and rarely in the pulmonary LNs.5 We speculate that, in our case, the primary lesion in the left upper lobe was too small to detect when CUP of the mediastinal LN was detected and that it progressed so slowly that it took 5 years to become detectable. This fits into the first theory described above. We hypothesize that the lung cancer in the left upper lobe was the primary lesion because of the following reasons: (1) no primary lesions developed in organs other than the lung over a period of more than 10 years, (2) the CUP of the LN was located in the lymphatic pathway of the left upper lobe, and (3) pathological and immunohistochemical examination showed similar findings in the lung and mediastinal LN tumors (i.e., both specimens were positive for TTF-1 and CAM5.2 but negative for cytokeratin 5/6 and CD56).

Various imaging procedures have been developed to detect the primary site in cases of CUP. The development of FDG-PET/CT has contributed to human cancer detection and staging, and its usefulness has been well established. The use of FDG-PET/CT has improved the diagnosis of CUP.2,3,9 In our case, based on the pathological and immunohistological findings of the LN CUP, we estimated that there was a high possibility of lymph node metastasis from lung cancer. One year after resection of the CUP, serum CEA was again elevated. Accordingly, we proceeded to conduct an extensive work-up that included PET, but it took 4 years to detect the pulmonary lesion. This indicates the limitations of PET/CT with regard to detecting extremely small foci.

In our review of the Japanese literature, there were only ten case reports that described the detection of lung cancer after resection of CUP of the intrathoracic LNs.10–18 The patient characteristics of all eleven cases (including our case) is shown in Table 1. All of these patients were men; their average age was 62.4 years (range, 41–76 years). Five patients had adenocarcinomas, four had squamous cell carcinomas, one had a large cell neuroendocrine carcinoma, and one had a large cell carcinoma. In eight patients, certain tumor markers exceeded the normal range. The CUPs were located in the LNs of the mediastinum in eight cases, the pulmonary hilum in two cases, and both sites in one case. Adjuvant treatment after CUP resection consisted of chemotherapy in four cases, radiation therapy in one case, chemoradiation therapy in one case, and no additional treatment in four cases. The period between diagnosis of CUP in the LN and detection of the pulmonary lesion averaged 48.3 months (range, 2–112 months). The pulmonary lesion was treated with surgery in nine cases and chemotherapy in two cases. The outcomes after pulmonary lesion treatment were as follows: five patients were alive without recurrence at an average of 16.8 months (range, 6–30 months), two patients were alive with recurrence at an average of 44 months (29 and 59 months), two patients had died of their disease after an average of 17 months (6 and 28 months), and two patients had died of other diseases after an average of 27 months (18 and 36 months). In general, when all CUPs are considered, the prognosis has been reported to be poor, with a 5-year survival of 2%–6% and a median survival time of 2–7 months.1–3 However, patients with CUP in the mediastinal LNs have been reported to have a relatively good prognosis when compared with patients diagnosed with primary lung cancer and mediastinal lymph node involvement.4,5,19,20 The median survival time of the former has been reported as 28 months19 and 30.7 months,20 representing a relatively good outcome.

Conclusion

We have presented a rare case in which lung carcinoma was detected 5 years after the resection of CUP in the mediastinal LN. This case illustrates the importance of careful observation and long-term follow-up in patients treated for CUP in the intrathoracic LNs even when initial PET/CT results are negative.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Disclosure Statement

The authors declare that they have no competing interests.
Lung Cancer Detected 5 Years after Resection of Cancer of Unknown Primary

References