Case Report

Metastatic Thoracic Lymph Node Carcinoma of Unknown Origin on Which We Performed Two Kinds of Immunohistochemical Examinations

Naoyuki Yoshino, MD,[1] Shigeo Yamauchi, MD,[1] Mitsunori Hino, MD,[2]
Yoshiharu Ohaki, MD,[3] Kiyoshi Koizumi, MD,[4] and Kazuo Shimizu, MD, FACS[4]

Metastatic cancers of the thoracic lymph nodes without primary sites are rare. Such cancers are difficult for clinicians to manage as identifying the primary sites is difficult in using routine histologic examinations alone. We searched for the site of the primary lesion using immunohistochemical exploration of cytokeratin (CK) and thyroid transcription factors 1 (TTF-1), and 2-[18F] and fluorodeoxyglucose positron emission tomography (FDG PET) in a patient with cancer of the hilar lymph node without any known primary site. To our knowledge, there are no previous similar reports. A 45-year-old man presenting with a tumor in the right hilar region, underwent surgical resection of the tumor, resulting in a diagnosis of metastatic cancer of the bronchopulmonary lymph nodes. An immunohistochemical examination revealed the neoplastic lesion to be positive for CK7, negative for CK20, and negative for TTF-1. Repeated searches to identify the site of the primary lesion by FDG PET over the 35 months since operation have failed to locate a primary site. (Ann Thorac Cardiovasc Surg 2006; 12: 283–6)

Key words: thoracic lymph node carcinoma, immunohistochemistry, cytokeratin, thyroid transcription factor 1, 2-[18F] fluorodeoxyglucose positron emission tomography

Introduction

Metastatic cancers of the thoracic lymph nodes without primary sites are rare. There have recently been several attempts to discover the primary sites of cancers through immunohistochemistry investigation of cytokeratin (CK) and thyroid transcription factor 1 (TTF-1).[1–4] Moreover, there are also some reports that 2-[18F] fluorodeoxyglucose positron emission tomography (FDG PET) is useful in patients with unknown primary tumor.[5–7]

From Departments of [1]Thoracic Surgery, [2]Internal Medicine, and [3]Pathology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, and [4]Department of Surgery II, Nippon Medical School, Tokyo, Japan

Received November 9, 2005; accepted for publication January 1, 2006.
Address reprint requests to Naoyuki Yoshino, MD: Department of Thoracic Surgery, Nippon Medical School Chiba Hokusoh Hospital, 1715 Kamagari, Inba, Chiba 270–1694, Japan.

Case Report

A 45-year-old man underwent a medical examination in September 2002, at which time a tumor in the right hilum was detected. He was admitted for thorough examination and treatment. The hematological data were all within the normal range. Tumor markers indicated normal levels. Radiography of the thorax revealed a 4.5×3.0 cm well-defined mass in the right hilum. A computed tomography (CT) scan of the thorax showed a 2.5 cm clearly-demarcated mass at the bifurcation of the right upper lobe branch and the truncus intermedius (Fig. 1). Gallium scintigraphy revealed a mass with a "hot uptake" area. He underwent a surgical resection in December of the same year. A tumor was located below a white covering at the bifurcation of the upper, middle, and lower lobes. After a complete removal of the covering, the tumor was resected. The tumor was opalescent and rigid. An intraoperative rapid histological examination resulted in a diagnosis of metastatic carcinoma.

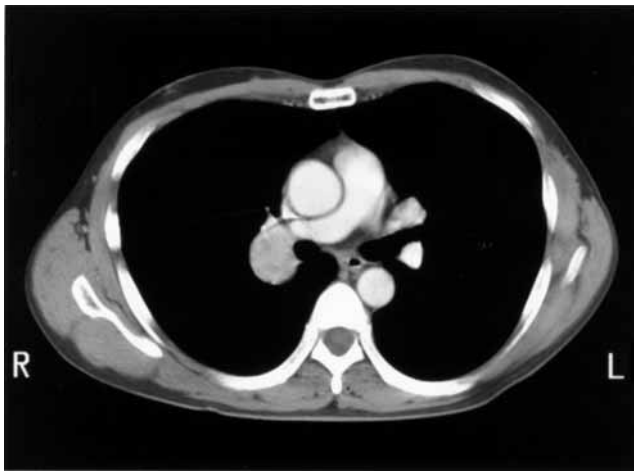

Fig. 1. CT scan of the thorax showed a 2.5 cm clearly-demarcated mass at the bifurcation of the right upper lobe branch and the truncus intermedius.

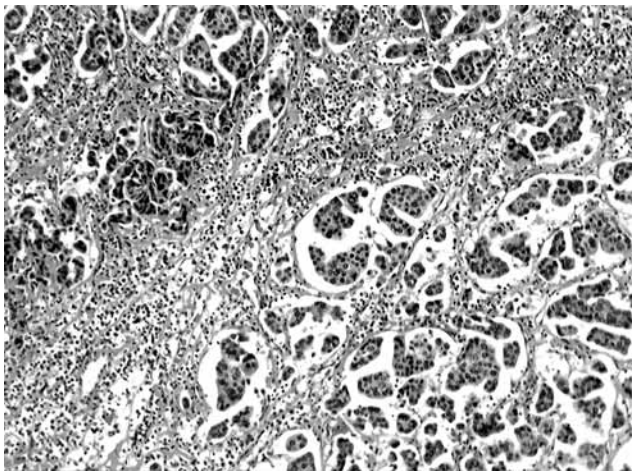

Fig. 2. Histological findings of the resected mass resulted in a diagnosis of poorly differentiated adenocarcinoma. (HE stain: ×20)

Palpation of the right lung failed to detect any other tumors. Pathological examination demonstrated cuboidal to polygonal cells forming a small papillotrabecular structure. A marked sheet-like arrangement of cells in the periphery of the tissue was also observed. The tumor basically consisted of adenocarcinoma. The tumor had a small amount of glycogen, but mucin was not observed. Based on the aforementioned findings, a diagnosis of poorly differentiated adenocarcinoma was made. (Fig. 2). After surgical treatment, radiographic irradiation of 50 Gy was administered to the resection site. Thereafter otorhinolaryngology, urology, and gastrointestinal tract examinations were performed to search for the primary lesion, however, no primary site could be identified. In the present case, immunohistochemical staining for CK7, CK20, TTF-1, human chorionic gonadotropin (hCG) and chromogranin was performed to search for the primary lesion. Consequently, tumor cells were negative for TTF-1 (Fig. 3A), positive for CK7 (Fig. 3B), and negative for CK20 (Fig. 3C), hCG and chromogranin. According to these immunohistochemical findings, it is unlikely that the tumor had originated in the gastrointestinal tract, the lung the germ cell tumor and the neuroendocrine tumor. We used FDG PET for follow-up monitoring to detect either recurrent or primary lesions. The patient has had no recurrence in the 35 months since surgery.

Discussion

Metastatic cancer from an undetermined primary site is known to occur in the lymph nodes and it remains one of the most frustrating clinical problems for oncologists. Approximately 3% of all cancers present with a metastatic lesion from an occult primary tumor. Overall, the lymph nodes are the most common metastatic site.[8] However, metastatic cancer in the thoracic lymph nodes (peribronchial, hilar, or mediastinal; N1 or N2) without a primary site is rare and has so far been seldom reported.[8] Regarding mediastinal, hilar, or peribronchial lymph node metastases, histologic and immunohistochemical studies may help determine the nature of the primary tumor (lung, other organs, or endogenous lymph node cells).[8] In the present case, we further searched for a primary site using immunohistochemical analysis.

CK intermediate filaments are known to have 20 subtypes. These subtypes have different molecular weights and show different expressions in various cell types and tumors. Monoclonal antibodies to specific CK subtypes have been used in an attempt to classify tumors according to the site of origin. CK immunohistochemistry has important applications for surgical pathology.[9] CK7, a 54-kd basic protein, is expressed in a wide variety of epithelia, including the lung, breast, endometrium, urothelium, stomach, pancreatobiliary tract, and skin adnexal glands.[3] CK20 is a 46-kd acidic CK protein which is distributed predominantly in carcinomas of the gastrointestinal and pancreatobiliary tracts, the urothelium, and mucinous ovarian tumors.[3] The combination of CK7 and CK20 immunoprofiling has been helpful in identifying the primary site of origin of lung tumors.[3] For

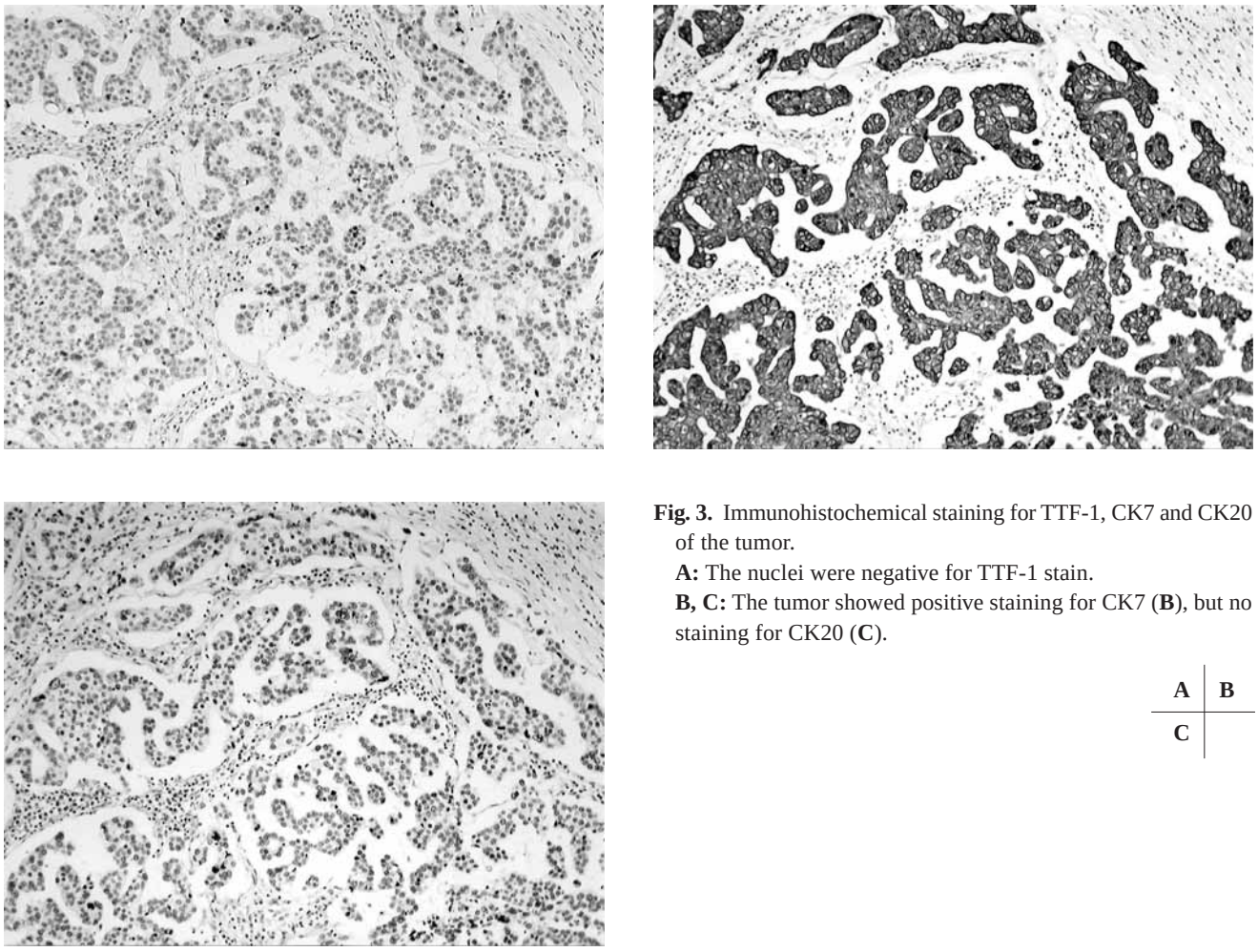

Fig. 3. Immunohistochemical staining for TTF-1, CK7 and CK20 of the tumor.
A: The nuclei were negative for TTF-1 stain.
B, C: The tumor showed positive staining for CK7 (**B**), but no staining for CK20 (**C**).

A	B
C	

example, a CK7 negative/CK20 positive phenotype is often associated with carcinomas of colorectal origin, whereas a CK7 positive/CK20 negative phenotype is seen in a wide variety of carcinomas, including those of the lung, breast, and female genital tract.[3] TTF-1 is a nuclear transcription protein that was first identified in 1989, and it is a 38-kDa homeodomain-containing nuclear protein that is a member of the *Nkx2* gene family, and plays a role in transcriptional activation during embryogenesis in the thyroid, diencephalons, and respiratory epithelium.[4] TTF-1 is a very sensitive and specific marker to confirm the pulmonary origin of a tubular or papillary adenocarcinoma when a thyroid origin can be ruled out.[1] The immunohistochemical expression of CKs and TTF-1 may be correlated with the histological type of primary lung epithelial tumors, thus allowing them to be distinguished from non-pulmonary carcinomas. In this case, immunohistochemical staining was positive for CK7, negative for CK20, and negative for TTF-1. The results ruled out any possible metastasis from adenocarcinoma of the gastrointestinal tract and from transitional cell carcinoma of the urinary tract, and a primary lesion was also thought to be unlikely in the lungs. Most metastatic cancers of the mediastinal lymph nodes are frequently caused by lung cancer.[8] In the present case, however, it is highly unlikely that the metastatic carcinoma primarily occurred in the lung. We therefore need to continue to search for the primary site of this disease.

The advantage of using FDG PET is that this technique allows us to visualize metabolically active but small superficial or possibly submucosal lesions, which are invisible on both clinical examinations and conventional imaging. The usefulness of PET in searching for primary lesions of metastatic carcinomas has occasionally been reported.[5–7] However, there is no report of using both immunohistochemistry and FDG PET to establish the origin of metastatic thoracic lymph node carcinoma.

No conclusion has been reached regarding the extent of resection of a metastatic thoracic lymph node carcinoma with unknown origin. It is difficult to determine whether to undertake lung resection where preoperative diagnostic imaging showed no tumor mass, suggesting a primary lesion in the lung and in whom no overt mass could be detected on palpation at operation. Kaneko et al. have described that even in cases where the lung has been resected, no primary lesion may be detected in the resected lung, and that such patients had no differences in prognosis from those who had not been treated with lung resection.[10] However, one report has shown that a pulmonary tumor, which was considered a primary lesion, was resected after surgical removal of a metastatic thoracic lymph node carcinoma with unknown origin.[11] These findings suggest that a lung resection should not necessarily be performed insofar as removal of lymph nodes at the lesion and ample regional lymphadenectomy are appropriately carried out. However, in such a case the patient should be carefully followed over a long period, and if a primary lesion is found, it should be resected. Our patient has been receiving radiation over the area of lymph node resection following the operation, but from now on, in lungs, a primary lesion may be discovered and it will be raised as a point examining itself.

We searched for the primary lesion with immunohistochemical staining of CK, TTF-1, and FDG PET, but could not identify it. We could not prove the usefulness of immunohistochemistry and FDG PET. However, since the identification of the primary lesion is closely related to the subsequent treatment and the patient's outcome, we will continue to use FDG PET at regular intervals in the follow-up of this patient.

References

1. Jerome Marson V, Mazieres J, Groussard O, et al. Expression of TTF-1 and cytokeratins in primary and secondary epithelial lung tumours: correlation with histological type and grade. *Histopathology* 2004; **45**: 125–34.
2. Cai YC, Banner B, Glickman J, Odze RD. Cytokeratin 7 and 20 and thyroid transcription factor 1 can help distinguish pulmonary from gastrointestinal carcinoid and pancreatic endocrine tumors. *Hum Pathol* 2001; **32**: 1087–93.
3. Chhieng DC, Cangiarella JF, Zakowski MF, Goswami S, Cohen JM, Yee HT. Use of thyroid transcription factor 1, PE-10, and cytokeratins 7 and 20 in discriminating between primary lung carcinomas and metastatic lesions in fine-needle aspiration biopsy specimens. *Cancer* 2001; **93**: 330–6.
4. Roh MS, Hong SH. Utility of thyroid transcription factor-1 and cytokeratin 20 in identifying the origin of metastatic carcinomas of cervical lymph nodes. *J Korean Med Sci* 2002; **17**: 512–7.
5. Alberini JL, Belhocine T, Hustinx R, Daenen F, Rigo P. Whole-body positron emission tomography using fluorodeoxyglucose in patients with metastases of unknown primary tumours (CUP syndrome). *Nucl Med Commun* 2003; **24**: 1081–6.
6. Stokkel MP, Terhaard CH, Hordijk GJ, van Rijk PP. The detection of unknown primary tumors in patients with cervical metastases by dual-head positron emission tomography. *Oral Oncol* 1999; **35**: 390–4.
7. AAssar OS, Fischbein NJ, Caputo GR, et al. Metastatic head and neck cancer: role and usefulness of FDG PET in locating occult primary tumors. *Radiology* 1999; **210**: 177–81.
8. Riquet M, Badoual C, le Pimpec BF, Dujon A, Danel C. metastatic thoracic lymph node carcinoma with unknown primary site. *Ann Thorac Surg* 2003; **75**: 244–9.
9. Gould VE, Warren WH, Faber LP, Kuhn C, Franke WW. Malignant cells of epithelial phenotype limited to thoracic lymph nodes. *Eur J Cancer* 1990; **26**: 1121–6.
10. Kaneko K, Yamanda T, Haniuda M, et al. Metastatic squamous cell carcinoma of hilar lymph node with unknown primary site. *Nihon Kokyuki Gakkai Zasshi* 2000; **38**: 39–44. (in Jpse. with Engl. abstr.)
11. Sakuraba M, Mae M, Oonuki T, Nitta S. Mediastinal and hilar lymph node of cancer unknown origin: 3 case reports. *Nihon Kokyuki Gakkai Zasshi* 1999; **37**: 72–7. (in Jpse. with Engl. abstr.)