Tokai J Exp Clin Med., Vol. 43, No. 4, pp. 148-152, 2018

A Case of Mediastinal Lymph Node Carcinoma of Unknown Primary Site

Takayuki NAKANO, Hajime WATANABE, Haruka TAKEICHI, Tomoki NAKAGAWA, Mitsutomo KOHNO, Ryota MASUDA and Masayuki IWAZAKI

Division of General Thoracic Surgery, Department of Surgery, Tokai University School of Medicine

(Received August 15, 2018; Accepted September 20, 2018)

A 63-year-old man was pointed out with a mediastinal tumor on chest computed tomography (CT). On positron emission tomography-CT, fluorodeoxyglucose accumulation with a maximum standardized uptake value of 12.70 was seen in this tumor. Scar-like nodule was found in the apex of the right lung, but no abnormal accumulation was observed in this nodule. The level of carcinoembryonic antigen was abnormally elevated. We performed mediastinal tumorectomy under thoracoscopic surgery. Since arterial oxygen saturation fell during intraoperative one-lung ventilation, we finished the surgery without resection of right apex nodule. Histologically, mediastinal tumor was diagnosed as metastatic adenocarcinoma in lymph node. Because immunohistochemical staining suggested lung adenocarcinoma as the primary site, the right apex nodule was resected. Pathological diagnosis of this nodule was scar fibrosis. No other malignant lesions were detected, and therefore we finally diagnosed this tumor as mediastinal lymph node carcinoma of unknown primary site. The patient was given adjuvant chemotherapy, and at present, 37 months after surgery, the patient remains free of the disease.

Key words: carcinoma of unknown primary site, mediastinal lymph node carcinoma

INTRODUCTION

An entity in which carcinoma is recognized only in the mediastinal lymph node but the primary site can not be identified is called mediastinal lymph node carcinoma of unknown primary site (CUP) [1, 2]. Mediastinal lymph node CUP is rare, and its pathogenesis and many other aspects remain unknown. We herein report, along with a literature review, our experience with a case of mediastinal lymph node CUP.

CASE REPORT

A 63-year-old man visited a neighborhood clinic with a chief complaint of coughing. Chest radiography revealed a band-like shadow in the left middle lung field, and chest computed tomography (CT) revealed that the shadow was a pulmonary cyst. However, because an additional mass was detected in the superior mediastinum, he was referred to our hospital.

The patient had comorbidities of hypertension, dyslipidemia, and hyperuricemia, and was a current smoker who had been smoking 30 cigarettes per day for 45 years (smoking index, 1350). He was 167 cm tall and weighed 67 kg. His family history showed that his father had lung cancer and his brother had combined pulmonary fibrosis and emphysema.

No abnormalities were seen in physical findings, and the coughing was already relieved at first visit to our hospital. Although routine laboratory data was within normal limits, the level of carcinoembryonic antigen, a tumor marker, was abnormally high at 79.8 ng/mL. Chest CT revealed a solid mass (a maximum diameter of 41 mm) that was inhomogeneously enhanced with a smooth margin at a site corresponding to the right superior mediastinal lymph node #4R, as well as a scar-like nodule with a maximum diameter of 14 mm that was accompanied by fine calcification of the interior at the apex of the right lung. The surrounding lung tissue appeared emphysematous. No significant lymphadenopathy was observed (Fig. 1a). Positron emission tomography (PET)-CT revealed fluorodeoxyglucose (FDG) accumulation with a maximum standardized uptake value (SUVmax) of 12.70 in the mediastinal mass; however, no abnormal accumulation was observed in any other areas, including the right apex nodule (Fig. 1b). Because the patient refused bronchoscopy, which we recommended, surgery was performed for diagnosis and treatment.

Thoracoscopic resection of the mediastinal tumor was performed. Because there was no sign of invasion to the surrounding tissue, complete resection of the tumor was possible. Although intraoperative rapid pathologic examination led to a diagnosis of suspected carcinoma, lymph node metastasis of lung cancer could not be diagnosed. As arterial oxygen saturation (SpO_2) continued to decrease during intraoperative one-lung ventilation, we decided not to resect the right apex nodule and wait for the final pathologic diagnosis of the mediastinal tumor.

The tumor was a yellowish-white, well-circumscribed nodule measuring 40 × 35 × 32 mm that was grossly covered with a capsule and accompanied by necrosis (Fig. 2a). Histologically, poorly-differentiated adenocarcinoma tissue was found in lymphoid tissue, leading to a diagnosis of metastatic adenocarcinoma in the lymph node (Fig. 2b). Immunohistochemical staining revealed

Takayuki NAKANO, Division of General Thoracic Surgery, Department of Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan Tel: +81-463-93-1121 Fax: +81-463-95-7567 E-mail: nakanot11299119@yahoo.co.jp

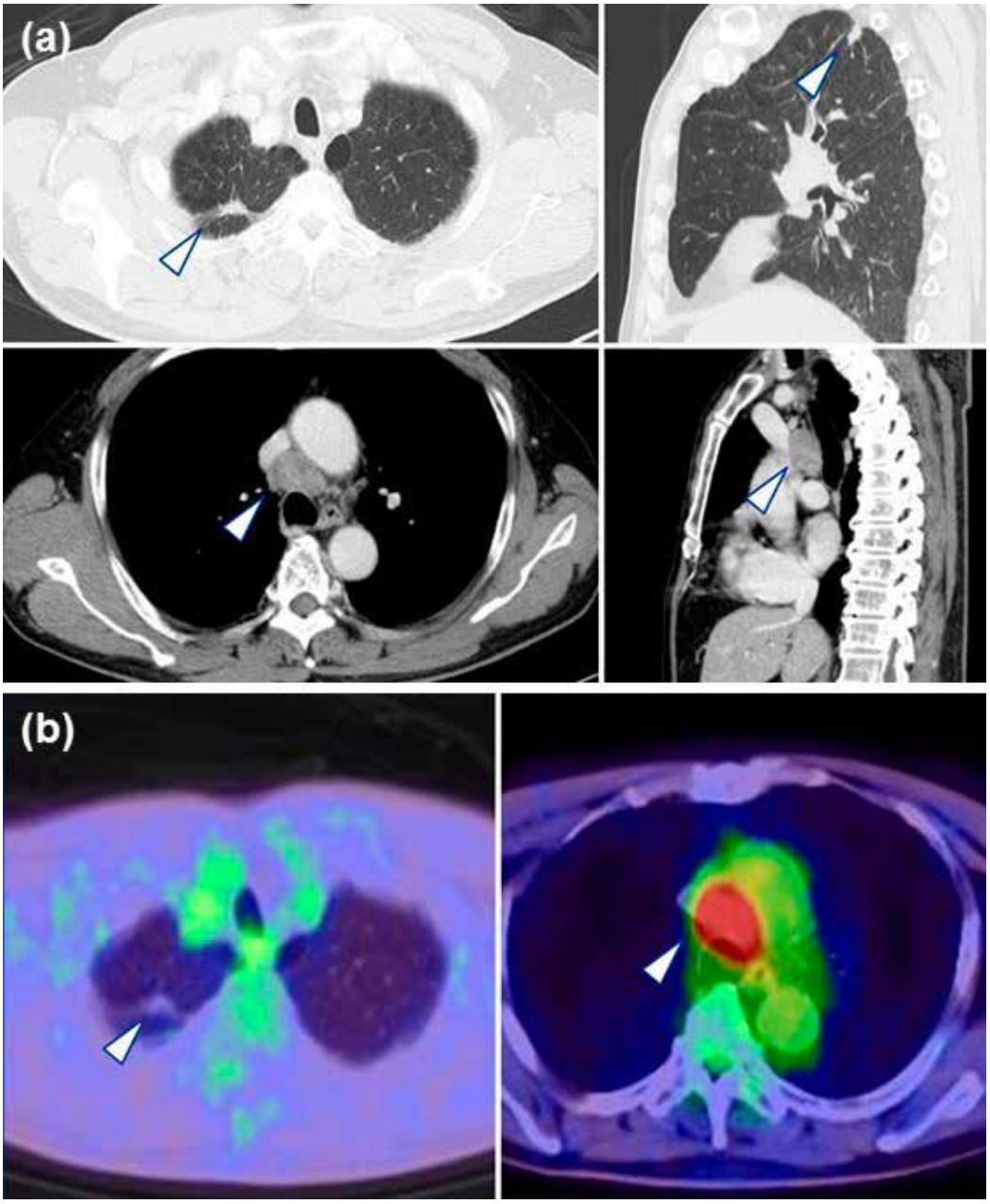

Fig. 1 Imaging findings
Chest CT revealed a mediastinal mass, as well as a scar-like nodule at the apex of the right lung (a). PET-CT revealed FDG accumulation with SUVmax of 12.70 in the mediastinal mass; however, no abnormal accumulation was observed in the right apex nodule (b).

that thyroid transcription factor (TTF)-1 and cytokeratin (CK) 7 were positive, but CK20 was negative (Fig. 3), suggesting lung adenocarcinoma as the primary site. Both the epidermal growth factor receptor gene mutation and the anaplastic lymphoma kinase fusion gene were negative.

The postoperative course was uneventful, and the patient was discharged on postoperative day 6. Subsequently, upper and lower gastrointestinal endoscopy was performed to locate the primary site, but no malignant findings were observed. Because immunohistochemical staining of the mediastinal lesion suggested primary lung adenocarcinoma, surgery was performed to exclude the possibility of the right apex nodule being the primary site.

Partial resection of right upper lobe was performed 3 weeks after the initial surgery. After thoracoscopic approach was performed through ports placed in the previous surgical wounds, SpO_2 again decreased during one-lung ventilation. The procedure was converted to mini-thoracotomy, and the right apex nodule was resected. Intraoperative rapid pathologic examination revealed no malignant findings. Although poor oxygenation persisted even after surgery, respiratory rehabilitation allowed the patient to withdraw from oxygen inhalation on postoperative day 4, and he was discharged on postoperative day 10. The final pathologic diagnosis for the right apex nodule was scar fibrosis, and no malignant findings were observed.

Because no apparent primary site was found, we ultimately diagnosed the mediastinal lesion as mediastinal lymph node CUP. Postoperative adjuvant chemotherapy was administered according to the treatment for lung cancer. At present, 37 months after initial

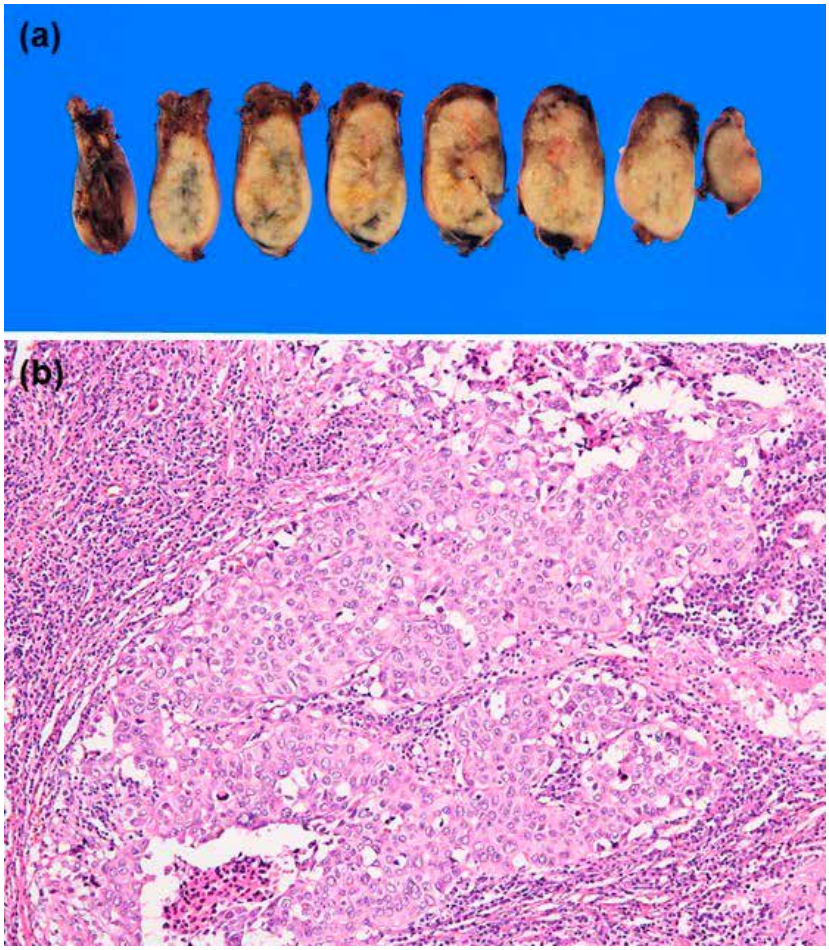

Fig. 2 Gross findings of the resected specimen of the mediastinal lesion (a) and histopathologic findings (hematoxylin-eosin staining) (b)
The tumor was a yellowish-white well-circumscribed nodule measuring 40 × 35 × 32 mm that was grossly covered with a capsule (a). Histologically, a sheet-like proliferation of atypical cells and irregular ductal structures were observed in the lymphoid tissue, which are features of poorly-differentiated adenocarcinoma (b).

surgery, the patient remains free of the disease.

DISCUSSION

CUP accounts for 3–5% of all cancer cases [1, 2]. The most common site of CUP is the lymph nodes. The majority of cases occur in the cervical lymph nodes [1, 3], and those occurring in the mediastinal lymph nodes are rare [4]. In a study of 617 cases of CUP, Holmes *et al.* reported that there were 9 cases of mediastinal lymph node CUP, accounting for only 1.5% of all patients [1]. In Japan, according to a study conducted on 102 cases of hilar or mediastinal lymph node CUP by Fukushima *et al.* [5], this carcinoma is more common in men (85.3%) and smokers (94.4%). The mean patient age in that study was 61.5 years. Fukushima *et al.* reported that the histologic types were adenocarcinoma (40.2%), squamous cell carcinoma (17.6%), small cell carcinoma (14.7%), and large cell carcinoma (12.7%) [5].

Immunohistochemical staining and PET-CT have been reported to be useful in determining the primary site [4, 6–8]. TTF-1–positive adenocarcinoma that is also positive for CK7 and negative for CK20 is strongly suggested to be of pulmonary origin [6, 7].

Regarding treatment, many reports indicate that surgical resection is the first choice for mediastinal lymph node carcinoma [9, 10], and there are many cases in which CUP is diagnosed only after surgery has been performed. However, no consensus on surgical procedures has been reached. One report indicates that aggressive lobectomy is necessary for cases in which clinical involvement as the primary site is suspected [11], while another report indicates that lung resection is unnecessary because there is no difference in prognosis with or without lung resection [9]. In addition, there are reports indicating the need for systematic lymph node dissection [9, 11], while others state that it is unclear which procedure, lymph node resection or systematic lymph node dissection, is better, because of no consistent tendency for local reccurence [12]. Postoperative chemotherapy is considered useful [9, 10], while there is a report that postoperative radiotherapy does not contribute to the prevention of recurrence [9].

As the mean survival time is generally considered to be 6 to 10 months [2, 3], overall prognosis for CUP is poor. In contrast, the prognosis for hilar or mediastinal lymph node CUP is often reported to be relatively favorable, as Fukushima *et al.* reported a 5-year survival rate of 75.1% and a mean survival time of 97.3 ± 7.8 months in cases of resected hilar or mediastinal lymph node CUP [5]. This survival rate is better than the prognosis for N1 or N2 lung cancer.

It has been proposed that hilar or mediastinal lymph node CUP is not metastatic lesion but primary

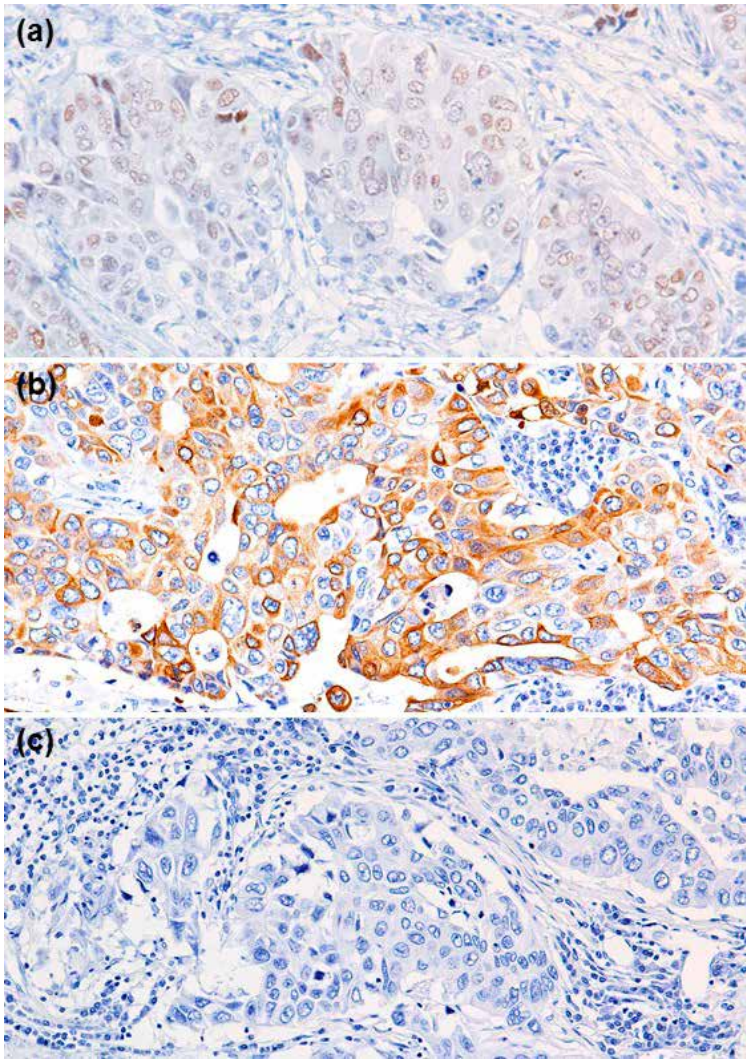

Fig. 3 Immunohistochemical findings of the mediastinal lesion
The adenocarcinomatous tissue was positive for thyroid transcription factor 1 (a) and cytokeratin 7 (b), but negative for cytokeratin 20 (c).

tumor arising in the lymph nodes [13]. In other words, this carcinoma is hypothesized to result from malignant transformation of epithelium migrating into the lymph nodes. This hypothesis can explain cases in which a favorable outcome is achieved by lymph node resection alone. However, although there are reports of histologically demonstrated migration of epithelial tissue into the hilar or mediastinal lymph nodes [4, 14], malignant transformation of such tissue may be difficult to prove. Another possible mechanism in the pathogenesis of hilar or mediastinal lymph node CUP is lymph node metastasis of T0 lung cancer [5]. This theory is supported by the report that lung lesions considered as the primary site became evident later [15]. And the reports that primary lung cancer has spontaneously regressed but the metastatic hilar lymph node grew larger [16, 17] are also supportive for this theory. Moreover, 71% of the cases reported by Fukushima *et al.* [5] in which immunohistochemical staining was performed showed results suggestive of primary lung cancer, which also appears to support T0 lung cancer theory.

In our case, the immunohistochemical staining results suggested primary lung cancer, and we cannot exclude the possibility that the right apex nodule was a primary site that spontaneously regressed, as reported by Kawasaki *et al.* [17]. However, it seems difficult to prove this histologically. At present, 37 months after surgery, the patient remains free of the disease, however careful follow-up is needed.

CONCLUSION

We experienced a case of mediastinal lymph node CUP. This disease is considered to have a relatively favorable prognosis. But, because this disease is rare, careful follow up is necessary. Its pathogenesis needs to be elucidated by further accumulation of cases.

ACKNOWLEDGMENT

We would like to express our sincere appreciation to Dr. Shingo Sato in the Department of Pathology at Tokai University Oiso hospital for his guidance regarding the histopathological findings in our case.

The authors declare no conflicts of interest.

REFERENCES

1) Holmes FF, Fouts TL. Metastatic cancer of unknown primary site. Cancer 1970; 26: 816–20.
2) Pavlidis N, Fizazi K. Carcinoma of unknown primary (CUP). Crit Rev Oncol Hematol 2009; 69: 271–8.
3) Greager JA, Wood D, Gupta TKD. Meatastatic cancer from an undetermined primary site. J Surg Oncol 1983; 23: 73–6.
4) Riquet M, Badual C, le Pimpec BF, Dujon A, Daniel C. Metastatic thoracic lymph node carcinoma with unknown primary site. Ann Thorac Surg 2003; 75: 244–9.
5) Fukushima K, Shibuya H, Shimizu I, Kameda Y. A case of metastatic thoracic lymph node carcinoma of unknown origin. Jpn J

Lung Cancer 2013; 53:35–41. (in Japanese with English abstract)
6) 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.
7) Yoshino N, Yamauchi S, Hino M, Ohaki Y, Koizumi K, Shimizu K. Metastatic thoracic lymph node carcinoma of unknown origin on which we performed two kinds of immunohistochemical examinations. Ann Thorac Cardiovasc Surg 2006; 12: 283–6.
8) Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. Eur Radiol 2009; 19: 731–44.
9) Morio A, Miyamoto H, Izumi H, Ohu T, Yamazaki A, Hosoda Y. A case report of adenocarcinoma of unknown origin metastatic to the mediastinal lymph nodes with a review of 21 cases reported in Japan. Jpn J Lung Cancer 2001; 41: 73–8. (in Japanese with English abstract)
10) Miwa K, Fujioka S, Adachi Y, Haruki T, Taniguchi Y, Nakamura H. Mediastinal lymph node carcinoma of an unknown primary site: clinicopathological examination. Gen Thorac Cardiovasc Surg 2009; 57: 239–43.
11) Kawano R, Hata E, Sakaguchi H, Ikeda S, Yokota T. Two Cases of T0 lung cancer with hilar and mediastinal lymph node metastasis. Jpn J Chest Surg 2003; 17: 117–22. (in Japanese with English abstract)
12) Ueshima Y, Kurioka H, Takumi C, Hiraoka N, Ono S. Two cases of cancer of unknown origin affecting the hilar and mediastinal lymph nodes. Jpn J Lung Cancer 2004; 44: 245–9. (in Japanese with English abstract)
13) Masaki Y, Gomibuchi M, Tanaka S, Sasai T. Mediastinal lymph-node carcinoma with no apparent primary lesion. Kyobu Geka 1997; 50: 743–7. (in Japanese with English abstract)
14) Morita M, Nakai Y, Kakimoto S, Isida K. Mediastinal lymph-node carcinoma with no apparent primary lesion; report of a case. Kyobu Geka 2003; 56: 1154–7. (in Japanese with English abstract)
15) Kawasaki H, Arakaki K, Taira N, Furugen T, Ichi T, Yohena T, *et al*. 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. Ann Thorac Cardiovasc Surg 2016; 22: 116–21.
16) Kohdono S, Ishida T, Fukuyama Y, Hamatake M, Takenoyama M, Tateishi M, *et al*. Lymph node cancer of the mediastinal or hilar region with an unknown primary site. J Surg Oncol 1995; 58: 196–200.
17) Kawasaki H, Yoshida J, Yokose T, Suzuki K, Nagai K, Hojo F, *et al*. Primary unknown cancer in pulmonary hilar lymph node with spontaneous transient regression: report of a case. Jpn J Clin Oncol 1998; 28: 405–9.