Acta Med. Okayama, 2011
Vol. 65, No. 6, pp. 407–411

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

A Case of Mediastinal Lymph Node Carcinoma of Unknown Primary Site Treated with Docetaxel and Cisplatin with Concurrent Thoracic Radiation Therapy

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Mediastinal lymph node carcinoma of unknown primary site is rare and may have a better prognosis if extensive treatment is performed. Case, A 69-year-old-male presented with a persistent cough. Chest computed tomography (CT) demonstrated a large tumor 9.5 × 8.2 cm, in the mediastinum, compressing the right main bronchus, the right pulmonary artery, and the superior vena cava. Because fiberoptic bronchoscopy was insufficient for diagnosis, mediastinoscopic tumor biopsy under general anesthesia was undertaken. Histological examination revealed adenocarcinoma. Extensive examinations revealed no other neoplastic lesion except in the mediastinum. Mediastinal lymph node carcinoma of unknown primary site was diagnosed. The patient was treated with docetaxel and cisplatin with concurrent thoracic radiation therapy. A month after the start of chemoradiotherapy, the mediastinal tumor regressed markedly. The patient remained free of symptoms without regrowth of the primary site. Exploration of the body showed no further abnormalities 20 months after disease onset.

Key words: mediastinal lymph node, unknown primary site, chemoradiation

Mediastinal lymph node carcinoma of unknown primary site is a rare disorder. There are several case reports describing patients treated by surgical resection, but cases treated by chemoradiotherapy have seldom been reported. Therefore, the usefulness of chemoradiotherapy in this disease remains to be determined. We report here a patient with mediastinal lymph node carcinoma of unknown primary site successfully treated by chemoradiotherapy. The purpose of this report is to draw attention to the potential usefulness of chemoradiotherapy for its treatment.

Case Report

A 69-year-old Japanese man was referred to our hospital on March 14th 2008 because of an abnormal mass in the right pulmonary hilum. The patient described a persistent cough of 1 month duration and a chest pain of a week. He had a 94 pack-year smoking history. He had a 20-year history of hypertension, hemorrhoids at the age of 64, and disc herniation at 59.

Physical examination at his first visit showed no abnormalities in the chest and abdomen. The chest roentgenogram at his first visit showed a right hilar

Received February 21, 2011; accepted July 22, 2011.
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mass 9.2 × 2.5 cm. Computed tomography (CT) of the chest revealed a mediastinal tumor mass measuring 9.5 × 8.2 cm compressing the trachea, the right main bronchus, the pulmonary artery, and the superior vena cava (Fig. 1). Computed tomography-supported positron emission tomography showed increased fluorodeoxyglucose retention in the mediastinum (maximum standard uptake values (SUV max 13.8) and a right supraclavicular lymph node (SUV max 4.5) (Fig. 2). The serum examination showed an elevated level of carcinoembryonic antigen, 7.8 ng/ml.

Fiberoptic bronchoscopy showed extrinsic compression and deformity of the trachea and the right main bronchus. The bronchial mucosa was intact. No endoluminal mass was present. Transbronchial needle aspiration of the subcarina node was insufficient for diagnosis. The patient underwent mediastinoscopic examination, and a tumor biopsy was performed. Microscopically, the tumor cells replaced most of the lymph node, showing a solid growth pattern and occasionally formed palisading arrangements. The tumor cells have a slightly eosinophilic cytoplasm and eccentric round pleomorphic nuclei and small nucleoli. There was anisonucleosis (Fig. 3). No mucinous cells were detected by PAS or Alucian blue staining. In the immunohistochemical study, tumor cells stained positive for cytokeratin and AE1/AE3 and negative for chromogranin A or synaptophysin. A small number of cells were positive for CEA. Pathological diagnosis was adenocarcinoma of the thoracic lymph node.

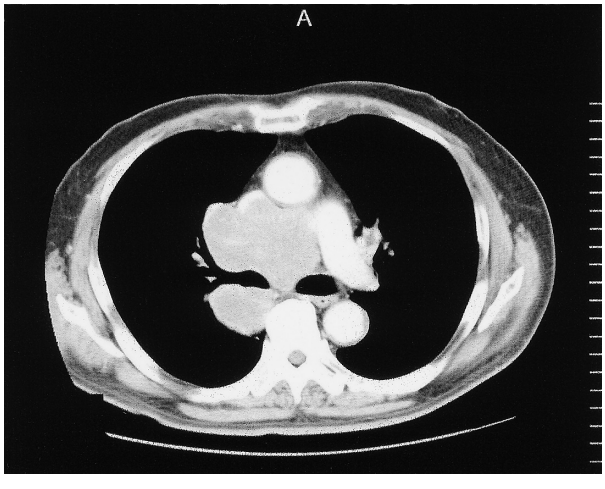

Fig. 1 Chest CT showing the mediastinal mass compressing superior vena cava, trachea, and main bronchi. Scale divisions represent 1 cm each.

The mediastinal mass had a clear margin separated from the lung parenchyma, and there was no sign of pleural effusion; it therefore seemed unlikely that lung cancer had invaded the adjacent mediastinum (T4N3M0).

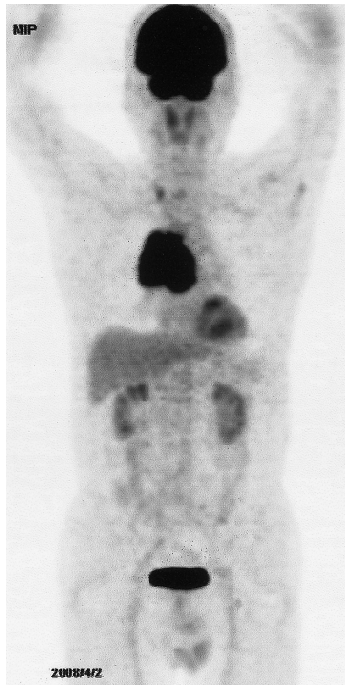

Fig. 2 An image of whole-body fluorodeoxyglucose-positron emission tomography demonstrating high uptake in the mediastinal region and a right supraclavicular lymph node.

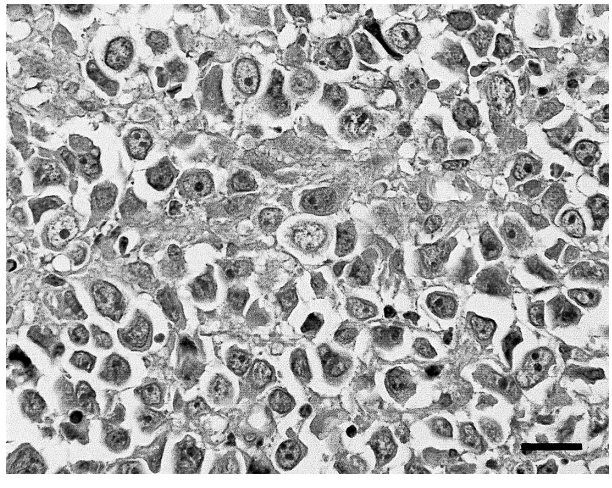

Fig. 3 Microscopic findings of resected mediastinal lymph node showing a solid growth pattern of tumor cells replacing the lymph node without recognizable gland formation. Adenocarcionoma was diagnosed. (hematoxylin-eosin; scale bar indicates 50 μm)

Despite the extensive diagnostic work-up, including gastroscopic and colonoscopic examinations, enhanced CT of the body, and PET/CT, no primary cancer site was detected. Mediastinal lymph node carcinoma of unknown primary site was diagnosed.

The patient had been treated with a protocol for lung cancer with external beam radiation to the thorax and chemotherapy with cisplatin and docetaxel [1]. Both docetaxel 40 mg/m^2 and cisplatin 40 mg/m^2 were given on days 1, 8, 29, and 36. Beginning on day 1 of chemotherapy, thoracic radiation therapy was given at a total dose of 61.4 Gy over 6 weeks. A month after the start of chemoradiotherapy, the mediastinal tumor regressed markedly (Fig. 4). Grade 3 granulocytopenia was observed on day 12, and recombinant human granulocyte colony stimulating factor was administered. Reticular shadow, compatible with radiation pneumonitis, was observed in the right upper lung field on chest CT 86 days after the start of chemoradiation therapy. Because the patient noted a high fever with elevated serum CRP levels, methylprednisolone, 500 mg/day, was administered for 3 days for the treatment of radiation pneumonitis and was tapered gradually.

The patient remained free of symptoms without regrowth of the primary site 22 months after disease onset, and exploration of the body with enhanced CT or PET showed no further abnormalities.

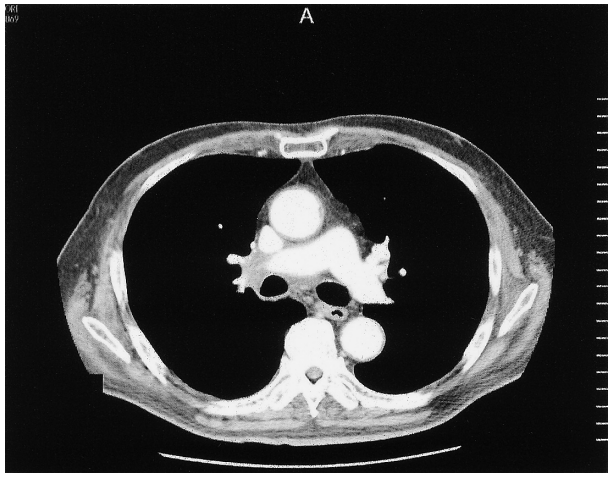

Fig. 4 Chest CT, a month after the start of chemotherapy, showing a markedly regressed mediastinal tumor. Scale divisions represent 1 cm each.

Discussion

It has been reported that metastatic cancers of unknown primary tumor comprise 0.6–6.7% of all cancers [2–4].

Greager *et al.* studied 286 cases of primary unknown cancer and reported that the major sites of metastasis are lymph nodes [5]. However, metastatic cancer in the thoracic lymph nodes from unknown primary site is a rare disorder [6] and has seldom been reported in English [7–11].

Several hypotheses regarding the development of primary unknown cancer are possible. One possibility is that the primary site of the cancer is the lymph node. It is a well-known fact that benign epithelial inclusions exist in cervical [12, 13], pelvic and peritoneal [14, 15], and axillary lymph nodes [16–18]. Neoplastic cells in lymph nodes may have resulted from the transformation of ectopic epithelial inclusions. In fact, there has been a report describing a carcinoma that originated from benign epithelial inclusion in an axillary lymph node [19]. The second hypothesis is that the primary is too small to be detected by our means of the clinical investigation. Recent advances in diagnostic techniques such as high-resolution CT or PET/CT enable us to detect very small cancer lesions, making the possibility of an occult primary site very low. However, the possibility of an occult primary site could not be denied even after an extensive radiological or endoscopical workup. The third hypothesis is that the spontaneous regression of primary cancer lesion occurred, while the metastatic lesion remained intact. The host immunologic mechanism might destroy a small primary tumor but fail to destroy an established metastatic tumor. It has been reported that spontaneous regression occurs no more than once in 60,000–100,000 cancer cases [20]. The incidence of spontaneous regression is extremely low compared to that of cancer of unknown primary site, 0.6–6.7% of all cancers, as described previously, and we could not explain the pathogenesis of cancer of unknown primary based on this hypothesis alone.

Although it is not widely accepted, the most probable hypothesis seems to be that neoplastic cells arise from endogenous epithelium in the lymph node.

The term T0N2M0 lung cancer has been used as a synonym of mediastinal lymph node carcinoma of unknown primary site. However, the possibility of the

endogenous cancer origin in the mediastinal node has not been ruled out, as described previously, and the most widely accepted term currently in use, and that we adopt here, is 'Mediastinal lymph node carcinoma of unknown primary site.'

Miyoshi has reported 70 cases of mediastinal lymph node carcinoma of an unknown primary site in Japan [21]. In the study group, a male predominance was seen. The age ranged from 5 to 85 years with a median age of 57.7 years. The most frequent histology type was adenocarcinoma in 41% of patients, followed by small cell carcinoma in 19%, large cell carcinoma in 17%, and squamous cell carcinoma in 16%.

In general, it appears that patients with cancer of an unknown primary site have a limited life expectancy with a median survival of 6–9 months [22]. However, when limiting such cases to mediastinal lymph node carcinoma, the survival period is far longer [11]. It is suggested that surgical resection of the mediastinal lymph node should be the first treatment of choice because the best survival benefit is obtained by complete dissection of the tumor [6, 11]. There are some papers suggesting that radical resection of mediastinal lymph node carcinoma either combined with chemotherapy or radiation therapy may offer a chance of cure and may increase long-term survival [6, 11, 21, 23, 24]. In our patient, complete excision of the mediastinal tumor was difficult, and supraclavicular involvement was prominent.

There have been only a few reports showing the effectiveness of chemoradiotherapy in the treatment of mediastinal lymph node carcinoma from an unknown origin. It has been reported that patients with mediastinal lymph node carcinoma from unknown origin do poorly when treated only medically [25]. On the other hand, Miwa *et al.* have reported two cases of mediastinal lymph node carcinoma treated by chemoradiotherapy. Both cases were alive 33 and 24 months, respectively [11]. Watanabe *et al.* also reported a case of carcinoma of unknown primary site with involvement of the mediastinal lymph node that was successfully treated by chemotherapy with carboplatin and paclitaxel followed by sequential radiation therapy [26]. This protocol is designed for nonsmall cell lung cancer. These reports suggest the potential usefulness of chemoradiation therapy for mediastinal lymph node carcinoma of unknown primary site. Kiura *et al.* have reported promising treatment results of docetaxel and cisplatin with radiation therapy for nonsmall cell lung cancer [1]. In the study, the overall response rate was 79% and the survival rate was 54% at 2 years. We have therefore chosen to treat the patient with this protocol, and he is still alive 22 months after the diagnosis.

In conclusion, it is suggested that appropriate chemoradiotherapy for mediastinal lymph node carcinoma of an unknown primary site may offer a chance of long-term survival in patients who are not eligible for radical exsection.

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