

Title: Paratracheal middle mediastinal thymic carcinomas

Ryo Nakanobo, M.D.¹, Masatsugu Hamaji, M.D., PhD¹, Akihiro Ohsumi, M.D., PhD¹, Sho Koyasu, M.D., PhD², Hironori Yoshida, M.D., PhD³, Hiroaki Ozasa, M.D., PhD³, Masahide Isowa, M.D.¹, Naoki Nakajima, M.D., PhD⁴, Akihiko Yoshizawa, M.D., PhD⁴, Hiroshi Date, M.D., PhD¹

¹Department of Thoracic Surgery, ²Department of Diagnostic Radiology, ³Department of Pulmonary Medicine, and ⁴Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan

Word count: 1448 words

Key words: thymic carcinoma, middle mediastinum

Conflict of interest: none declared

Funding: no funding

Ryo Nakanobo and Masatsugu Hamaji equally contributed to this work.

Corresponding author:

Masatsugu Hamaji, M.D., PhD

Department of Thoracic Surgery, Kyoto University Hospital, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan

Ph: +81-75-751-4975

Fax: +81-75-751-4974

E-mail address: mhamaji@kuhp.kyoto-u.ac.jp

Abstract

Herein, we describe case studies of two patients who underwent resection of paratracheal middle mediastinal thymic carcinomas. In both patients, complete resection of these masses via right thoracotomy was performed using three dimensional computed tomography. Final pathological diagnoses were thymic squamous cell carcinoma and thymic atypical carcinoid tumor, respectively. Challenges and debates in preoperative, intraoperative, and postoperative management are discussed in this article.

Introduction

Management of isolated and fluorodeoxyglucose (FDG)-avid paratracheal mass or lymphadenopathy represents a diagnostic and therapeutic challenge. Typical differential diagnoses include ectopic thyroid, isolated mediastinal lymph node metastasis, lymphoma, and thymoma [1]. Herein, we describe two patients who underwent a diagnostic and therapeutic resection of paratracheal middle mediastinal masses. There is no standard approach or specific guideline for the management of middle mediastinal masses, therefore, their management requires detailed examination of individual cases.

Case report

Patient A

A 74-year-old man, who had a smoking history of 34 pack-years and a history of myocardial infarction from 4 years ago, was referred to us with abnormal tumor markers (carcinoembryonantigen: 80 ng/ml) and asymptomatic 7.1 cm mass in the paratracheal area of the middle mediastinum (Figure 1A and 1B). Esophagogastroduodenoscopy and colonoscopy results were negative for malignant lesions. Computed tomography (CT) did not suggest any primary lesion that could possibly have metastasized to the large paratracheal mass, whose maximal standard uptake value was 16.7 as determined using positron emission tomography (PET) (Supplemental Figure 1). Endobronchial ultrasound guided needle biopsy of the mass suggested non-small cell lung cancer with programmed cell death protein one being strongly positive ($= > 75\%$). After the multidisciplinary tumor board, we proceeded with a diagnostic and therapeutic resection.

We performed an antero-axillary skin incision and performed a fourth intercostal thoracotomy. The tumor was found to compress the superior vena cava and required careful and meticulous dissection (supplemental video). The phrenic nerve was preserved, whereas, the vagus nerve and the azygos vein had to be resected because both appeared to be incorporated into the tumor. The tumor was found to be involved in the right lobe of the thymus. Hilar lymph nodes were also resected along with the paratracheal mass.

Pathology showed poorly differentiated 8.0 cm squamous cell carcinoma of thymic origin with negative

surgical margins (Figure 3A). All the resected lymph nodes were found to be negative for tumor growth. Eight weeks after surgery, postoperative radiotherapy with 50 Gy was administered as adjuvant treatment[洋至 1] [京都大学 2] . After adjuvant radiotherapy, carcinoembryoantigen levels were reduced to 2.3 ng/ml.

Patient B

A 77-year-old man with a 15 pack-year smoking history presented to us with an asymptomatic 5.0 cm mass in the paratracheal area of the middle mediastinum (Figure 2A and 2B). His comorbidities included hypertension and diabetes mellitus, both of which were controlled using oral medication. Computed tomography did not show any primary lesion that could possibly have metastasized to the large paratracheal mass or lymph node whose maximal standard uptake value was 4.9 as determined using FDG-PET (Supplemental Figure 2). We proceeded with a diagnostic and therapeutic resection.

We began by performing video-assisted thoracoscopic surgery however, we performed a fourth intercostal thoracotomy for a safer dissection. The azygos vein had to be resected due to its adhesion to the tumor mass. The tumor was found to be involved in the right lobe of the thymus. Intraoperative lymph node dissection[洋至 3] (station 3a) was performed for staging

Pathology results showed a 4.5 cm atypical carcinoid tumor (Figure 3B). All of the sampled lymph nodes (station 3a) were positive for tumor. Seven weeks after surgery, postoperative chemotherapy using **four cycles of** carboplatin and etoposide was performed as adjuvant treatment.

Comment

We report cases of these two patients as there is little data upon preoperative, intraoperative, and postoperative management of middle mediastinal thymic carcinomas. In general, ectopic thymomas account for 4% of all thymomas [1] and patients with middle mediastinal thymoma were previously reported [2], whereas, no information is available upon thymic carcinoma or neuroendocrine carcinoma.

As preoperative management for a potential mediastinal lymphadenopathy, it is necessary to identify

occult primary tumors using chest to pelvic CT, as recommended by the The National Comprehensive Cancer Network (NCCN) in their guidelines [3]. There is no standard approach for management of an isolated paratracheal mass or mediastinal lymph node. In case CT scan and PET-CT results are not helpful for identification of any potential primary lesions, a diagnostic and therapeutic resection might benefit relatively healthy patients.

Intraoperative considerations include a surgical approach, preservation of mediastinal structures, appropriate staging, and extent of resection. Three dimensional images provided us with the entire picture of the relatively complex anatomical location of the tumor in the middle mediastinum. An open approach (lateral thoracotomy), rather than a minimally invasive approach, appears to be suitable given the possibility of involvement of surrounding structures, and the requirement of meticulous dissection of affected tissues. **Right-sided robotic approach may be a potential alternative, whereas median sternotomy would not be an alternative, considering the anatomical location of the tumor.** The necessity of total thymectomy is unclear owing to lack of relevant data. We did not perform a total thymectomy given the negative margins and no signs or symptoms of myasthenia gravis. Evaluation of lymph nodes was recommended for a staging purpose [4] and was performed in both of our patients.

Adjuvant treatment in our patients required extensive discussion with our multidisciplinary tumor board. Generally, postoperative radiotherapy (PORT) is recommended for stage II or more advanced thymic carcinoma [4]. As the tumor size significantly indicates poor prognosis [5], we proceeded with PORT for Patient A, who had a stage I, although 8.0 cm thymic carcinoma. NCCN guidelines recommend PORT with or without postoperative chemotherapy as adjuvant treatment for patients with thymic neuroendocrine tumors [6], whereas, in Patient B, we found extensive metastases to anterior mediastinal lymph nodes from the middle mediastinal carcinoid, which are considered to be more than locoregional diseases, therefore, our multidisciplinary tumor board recommended postoperative chemotherapy.

In conclusion, we report two patients with paratracheal middle mediastinal thymic carcinomas. Preoperative, intraoperative, and postoperative management should be tailored, attaining balance between existing NCCN guidelines and opinions of the multidisciplinary tumor board. However, further

investigation is required to elucidate optimal management of middle mediastinal thymic carcinomas.

Figure legends

Figure 1. Chest computed tomography with contrast for the paratracheal mass (A) and three dimensional reconstruction of the paratracheal mass (B) in Patient A. **The mass was indicated by arrows.**

Figure 2. Chest computed tomography with contrast for the paratracheal mass (A) and three dimensional reconstruction of the paratracheal mass (B) in Patient B. **The mass was indicated by arrows.**

Figure 3. Histopathological findings (haematoxylin and eosin staining, 40 x magnification) for specimens from Patient A (A) and Patient B (B). Remarkable nuclear enlargement, anisokaryosis, and nuclear mitosis (A) and Salt-and-pepper chromatin and eosinophilic cytoplasm with a proliferation rate of 2 10 mitoses per high-power field (B). **Mitoses were indicated by arrows.**

References

- [1] Weissferdt A, Moran CA. The spectrum of ectopic thymomas. *Virchows Arch.* 2016;469(3):245–54
- [2] Fukui T, Sumitomo R, Otake Y, Huang CL. Middle Mediastinal Thymoma. *Ann Thorac Surg.* 2018;106:e189-e191
- [3] NCCN clinical practice guidelines in Oncology. NCCN Occult primary, Available at, <https://www2.tri-kobe.org/nccn/guideline/occult/english/occult.pdf> accessed on 16th Jun 2019
- [4] NCCN clinical practice guidelines in Oncology. NCCN Thymoma and Thymic carcinoma, Available at, <https://www2.tri-kobe.org/nccn/guideline/archive/lung2015-2017/english/thymic.pdf> accessed on 12th Jul 2019
- [5] Hishida T, Nomura S, Yano M, et al. Long-term outcome and prognostic factors of surgically treated thymic carcinoma: results of 306 cases from a Japanese Nationwide Database Study. *Eur J Cardiothorac Surg.* 2016;49:835-41.
- [6] NCCN clinical practice guidelines in Oncology. Neuroendocrine tumors, Available at https://gialvalis.gr/wp-content/uploads/2015/03/NCCN_neuroendocrine.pdf accessed on 16th Jun 2019.

Supplemental figure legends

Figure 1. The paratracheal mass that was fluorodeoxyglucose-avid on Positron Emission Tomography for Patient A.

Figure 2. The paratracheal mass that was fluorodeoxyglucose-avid on Positron Emission Tomography for Patient B.

Supplemental video legend

We performed a fourth intercostal thoracotomy on patient A. The mediastinal pleura was opened and the tumor was found to be adhered to the superior vena cava and required careful and meticulous dissection. The phrenic nerve was preserved, whereas, the vagus nerve and the azygos vein had to be resected because both appeared to be incorporated into the tumor.