



TTF-1 in the Diagnosis of Metastatic Small Cell Carcinoma of the Esophagus from the Lung

Hsiu-Lung Fan, Hung Chang*, and Shih-Chun Lee

*Division of Thoracic Surgery, Department of Surgery,
Tri-service General Hospital, National Defense Medical Center,
Taipei, Taiwan, Republic of China*

Esophageal cancer is one of the most common cancers worldwide. All patients present with dysphagia, weight loss, or chest pain. There are many methods to establish a definite diagnosis and tumor staging, including computed tomography, an upper gastrointestinal series, and panendoscopy. An intramural tumor of the esophagus was strongly suspected in our patient based on radiological findings and panendoscopy. However, the final diagnosis, based on positive histopathology for TTF-1, was of a metastatic small cell carcinoma originating in the lung.

Key words: esophageal carcinoma, primary small cell carcinoma, secondary small cell carcinoma

INTRODUCTION

Esophageal carcinoma is one of the most common malignancies worldwide. Small cell carcinoma of the esophagus is a rare and aggressive tumor with early dissemination. It is necessary to establish the original source of a small cell carcinoma of the esophagus. There have been many investigations of the use of thyroid transcription factor 1 (TTF-1) to distinguish primary small cell carcinomas of the esophagus from metastatic tumors. However, the value of TTF-1 immunostaining has not been established. The goal of this article is to review the relevant literature to understand the new developments in investigations to distinguish between primary small cell carcinoma of the esophagus and metastatic small cell carcinoma from the lung.

CASE REPORT

A 66-year-old woman was admitted to our hospital with poor food intake, choking, and nausea over 4 weeks. Three years earlier, the patient could not swallow solid foods and ate only a soft diet. The patient had not visited any doctor

previously. During the previous years, the patient could not eat a soft diet, and drank only milk. A weight loss of about 6-7 kg was noted over a 6 month period. A systemic review identified general weakness and a productive cough with a little sputum, which had been present for one year. The patient had type 2 diabetes mellitus, hypertension, and glaucoma, but no history of smoking, alcohol abuse, or contact with chemicals.

The patient's temperature was 37°C, her pulse rate 78 beats per minute, her respiratory rate 20 breaths per minute, and her blood pressure 130/70 mmHg. The patient was in a state of acute distress. She appeared weak and pale. No palpable neck nodes were found. Her breathing sounds were normal. Her bowel sounds were normal, but there was mild tenderness in the epigastric region without rebound or guarding. The remainder of the examination revealed no abnormalities. A chest radiograph showed a mild increase in interstitial infiltration in both lung fields.

Abdominal computed tomography (CT) after the oral and intravenous administration of contrast material showed a long segment (> 8 cm) of asymmetric wall thickening and a soft-tissue mass (> 4 cm in the axial dimension) over the esophagus, extending downward from the level of the subcarina for more than 8 cm, with significant dilatation of the esophageal lumen. The boundary between the soft-tissue mass and the posterior wall of the left mainstem bronchus was unclear. The esophageal lesion also had an extraluminal extension, with a smooth indentation over the left atrium. Enlarged nodes, with a maximal size of about 2.7 cm, in the subcarinal space, the AP window, and the surrounding region of the esophagus were noted. Nodal metastases were strongly suspected (Fig. 1).

Received: May 16, 2006; Revised: August 18, 2006;
Accepted: August 30, 2006

*Corresponding author: Hung Chang, Division of Thoracic Surgery, Department of Surgery, Tri-Service General Hospital, No. 325, Sec. 2, Cheng-Gong Road, Taipei 114, Taiwan, Republic of China. Tel: +886-2-8792-3311 ext 18593; Fax: +886-2-8792-3311; E-mail: hung@ndmctsgh.edu.tw



Fig. 1 A long segment (> 8 cm) of asymmetrical wall thickening and soft-tissue mass (> 4 cm in the axial dimension) over the esophagus, extending downward from the level of the subcarina for more than 8 cm, with significant dilatation of the esophageal lumen.

An upper gastrointestinal barium study showed a large segmental polypoid intraluminal mass, about 5 cm in axial length, in the lower third of the esophagus, with the proximal end just below the level of the carina. It also showed focal esophageal expansion and mild obstruction (Fig. 2).

An upper gastrointestinal panendoscopic study showed an ulcerative mass in the middle to lower third of the esophagus. Five tiny pieces of esophageal tissue were taken for pathological biopsy. The results indicated a small cell carcinoma characterized by areas of small crushed round blue cells with salt-and-pepper chromatin, scattered cytoplasm, and abnormal mitoses. The tumor cells were infiltrating the desmoplastic submucosa of the esophageal tissue, associated with squamous epithelial ulceration and focal necrosis. Immunohistochemical staining was positive for TTF-1. The pathology report indicated that a pulmonary origin should be considered.

DISCUSSION

We strongly suspected that the tumor in our patient was a primary esophageal tumor, especially on the basis of the panendoscopic findings and CT scan. Ultimately, the pathology report indicated a small cell carcinoma derived from the lung, based on immunohistochemical data. Therefore, it was interesting to establish the original source of this small cell carcinoma of the esophagus.

Primary small cell carcinomas constitute approximately 0.8%-2.4% of all esophageal malignancies¹. The ratio of male to female patients is about 1.57². Primary small cell

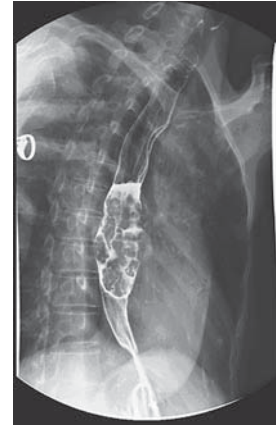


Fig. 2 A large segmental polypoid intraluminal mass, about 5 cm in axial length, in the lower third of the esophagus (with the proximal end just below the level of the carina).

carcinomas are commonly located in the middle or lower third of the esophagus. In contrast, small cell carcinomas derived from the lung often arise as secondary extensions from metastatic lung cancers within the mediastinal lymph nodes. Small cell lung cancer accounts for approximately 15%-20% of all cases of lung cancer. However, no data are available on the incidence of direct extensions of the metastases to the esophagus from the mediastinal lymph nodes.

Primary small cell carcinomas of the esophagus most commonly present with symptoms of rapidly progressing dysphagia, weight loss, and chest pain. The mean period from the onset of symptoms to diagnosis is about 4.4 months². Lung cancer usually presents with bronchopulmonary symptoms, including cough, hemoptysis, wheezing or stridor, dyspnea, postobstructive infectious symptoms, or nonbronchopulmonary symptoms of chest pain or pancoast tumors. Dysphagia is a very rare symptom of lung cancer. No study has reported a case in which dysphagia was the only symptom of lung cancer. In our patient, the main problem was dysphagia, not bronchopulmonary symptoms. This caused us to make an incorrect diagnosis before the pathology report was available.

Based on the findings of the upper gastrointestinal series, which indicated a large polypoid intraluminal mass in the lower third of the esophagus, a fungating-type squamous cell carcinoma of the esophagus was first considered. Other differential diagnoses included spindle cell squamous cell carcinoma. A fibrovascular polyp seemed less likely because its most common location is in the upper third of the esophagus and its incidence is relatively low in Taiwan. Therefore, we could not make an accurate diagnosis based on imaging findings.

A definite diagnosis of esophageal carcinoma was based on an esophageal biopsy. It is very hard to distinguish morphologically between pulmonary and extrapulmonary small cell carcinomas. Immunohistochemical studies have recently provided a way to make this distinction because small cell carcinomas of the esophagus display characteristic neuroendocrine differentiation. About 50% of small cell carcinomas of the esophagus are accompanied by squamous cell or glandular differentiation^{3,4}. This phenomenon is more common in the esophagus than in the lung. Ho et al.³ reported that a pluripotent primitive cell is the common precursor of adenocarcinomas, squamous cell carcinomas, and small cell carcinomas. Tennvall et al.⁵ also reported that primary small cell carcinomas of the esophagus coexist with adenocarcinomas and/or squamous cell carcinomas.

Unfortunately, the presence of neurosecretory granules is not definitive for a diagnosis of small cell carcinoma. Only 27% of patients display neurosecretory granules on electron microscopy². This may be one method with which to differentiate the site of origin of a small cell carcinoma, but further studies are required to evaluate the usefulness of this method.

TTF-1 is a popular marker with which to distinguish small cell lung carcinoma from nonpulmonary small cell carcinoma. TTF-1 is expressed in the follicular epithelial cells of the thyroid, lung, and certain areas of the brain: anterior pituitary, parathyroid gland, and parafollicular C cells⁶⁻¹⁰. Fabbro et al.¹¹ have reported that TTF-1 is present in all types of lung carcinomas¹¹. About 83% — 100% of small cell lung carcinomas exhibited TTF-1 positivity^{11,12}. These investigations indicated that TTF-1 is a highly sensitive marker for small cell lung carcinoma. Clinically, TTF-1 staining has been used to differentiate small cell lung carcinomas from small cell carcinomas of the esophagus. In contrast, Chang et al.¹³ reported that only 19/36 (53%) small cell carcinomas were positive for TTF-1. Ordonez et al.¹⁴ reported that only 4/54 (7%) nonpulmonary small cell carcinomas were positive. That investigation showed that TTF-1 staining is not an absolutely specific diagnostic method for small cell lung carcinoma. Therefore, the real role of TTF-1 must be investigated in future research and another marker found that defines the origins of small cell carcinomas.

There are many treatment options for patients with small cell carcinoma of the esophagus, including surgical resection, radiation therapy, and chemotherapy, used alone or in combination. Surgery alone is not recommended because of potential rapid systemic recurrence. Surgery after induction chemotherapy or chemoradiotherapy is

used in patients with limited-stage disease. Many clinical studies have shown that surgical resection is associated with improved long-term disease-free survival. However, surgery plays a minor role in the treatment of extensive-stage small cell carcinoma of the esophagus.

Because the carcinoma is radiosensitive, radiotherapy is used for local control. However, many clinical trials have shown that radiotherapy alone is of little benefit because of the dissemination of the malignancy. Therefore, radiotherapy is not recommended as the sole treatment modality^{15,16}. Radiotherapy combined with chemotherapy can result in a pathologically complete response and better long-term survival^{17,18}.

Because of its similarity to small cell carcinoma of the lung, chemotherapy is used in patients with small cell carcinoma of the esophagus, as first described in 1980¹⁹. Casas et al.² reported that chemotherapy was strongly associated with an improvement in survival rate. Many other clinical trials have confirmed this relationship between chemotherapy and survival^{16,20}. However, the limitations of chemotherapy are the short duration of the response and a poor long-term survival rate. Therefore, many clinicians consider combined therapies. McCullen et al.²¹ first reported the use of high-dose chemotherapy, autologous bone-marrow transplantation, and adjuvant chemotherapy, with a survival rate of 37 months. Van der Gaast et al.²² reported that a combination of chemotherapy and radiotherapy improved the long-term survival rate. Complete pathological regression was also achieved with combined chemoradiotherapy^{17,23}. Casas et al.² noted that chemotherapy plus radiotherapy is the standard approach for limited-stage disease. Nishimaki et al.¹⁸ reported that preoperative cisplatin followed by radical esophagectomy and postoperative radiotherapy achieved a survival rate of 106 months. Law et al.²⁴ showed improved long-term survival after esophagectomy followed by adjuvant chemotherapy and radiotherapy. In the future, combined therapies will still play a very important role in the treatment of small cell carcinoma of the esophagus. Theoretically, radiolabeled somatostatin analogues may be of benefit because small cell carcinoma of the esophagus has neuroendocrine characteristics. This warrants further investigation.

In conclusion, it is very difficult to distinguish primary small cell carcinoma of the esophagus from metastatic tumor based on symptoms, signs, or radiological findings. Pathological investigations give useful information with which to identify the original source and select the direction of optimal treatment. It is a challenge to discriminate between a diagnosis of primary small cell carcinoma of the

esophagus and metastatic small cell carcinoma from the lung.

REFERENCES

1. Beyer KL, Marshall JB, Diaz-Arias AA, Loy TS. Primary small cell carcinoma of the esophagus. Report of 11 cases and review of the literature. *J Clin Gastroenterol* 1991;13:135-141.
2. Casas F, Ferrer F, Farrus B, Casals J, Biete A. Primary small cell carcinoma of the esophagus: A review of the literature with emphasis on therapy and prognosis. *Cancer* 1997;80:1366-1372.
3. Ho KJ, Herrera GA, Jones JM. Small cell carcinoma of the esophagus: Evidence for a unified histogenesis. *Hum Pathol* 1984;77:460-468.
4. Takubo K, Nakamura K, Sawabe M. Primary undifferentiated small cell carcinoma of the esophagus. *Hum Pathol* 1999;30:216-221.
5. Tennvall J, Johansson L, Albertsson M. Small cell carcinoma of the oesophagus: A clinical and immunohistopathological review. *Eur J Surg Oncol* 1990;16:109-115.
6. Ghaffari M, Zeng X, Whitsett JA, Yan C. Nuclear localization domain of thyroid transcription factor-1 in respiratory epithelial cells. *Biochem J* 1997;328:757-761.
7. Lazzaro D, Price M, De Felice M, Di Lauro R. The transcription factor TTF-1 is expressed at the onset of thyroid and lung morphogenesis and in restricted regions of the fetal brain. *Development* 1991;113:1093-1104.
8. Kimura S, Hara Y, Pineau T. The T/ebp null mouse: Thyroid-specific enhancer-binding protein is essential for the organogenesis of the thyroid, lung, ventral forebrain, and pituitary. *Genes Dev* 1996;10:60-69.
9. Suzuki K, Kobayashi Y, Katoh R, Kohn LD, Kawaoi A. Identification of thyroid transcription factor-1 in C cells and parathyroid cells. *Endocrinology* 1998;139:3014-3017.
10. Suzuki K, Lavaroni S, Mori A. Thyroid transcription factor 1 is calcium modulated and coordinately regulates genes involved in calcium homeostasis in C cells. *Mol Cell Biol* 1998;18:7410-7422.
11. Fabbro D, Di Loreto C, Stamerra O, Beltrami CA, Lonigro R, Damante G. TTF-1 gene expression in human lung tumors. *Eur J Cancer* 1996;32A:512-517.
12. Folpe AL, Gown AM, Lamps LW. Thyroid transcription factor-1: Immunohistochemical evaluation in pulmonary neuroendocrine tumors. *Mod Pathol* 1999;12:5-8.
13. Chang YL, Lee YC, Liao WY, Wu CT. The utility and limitation of thyroid transcription factor-1 protein in primary and metastatic pulmonary neoplasms. *Lung Cancer* 2004;44:149-157.
14. Ordonez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. *Am J Surg Pathol* 2000;24:1217-1223.
15. Doherty MA, McIntyre M, Arnott SJ. Oat cell carcinoma of the esophagus: A report of six British patients with a review of the literature. *Int J Radiat Oncol Biol Phys* 1984;10:147-152.
16. Huncharek M, Muscat J. Small cell carcinoma of the esophagus. The Massachusetts General Hospital experience, 1978-1993. *Chest* 1995;107:179-181.
17. Casas F, Farrus B, Daniels M, Reyes MG, Campo E, Estape J, Biete A. Six-year follow-up of primary small cell carcinoma of the esophagus showing a complete response: A case report. *Jpn J Clin Oncol* 1996;26:180-184.
18. Nishimaki T, Suzuki T, Nakagawa S, Watanabe K, Aizawa K, Hatakeyama K. Tumor spread and outcome of treatment in primary esophageal small cell carcinoma. *J Surg Oncol* 1997;64:130-134.
19. Kelsen DP, Weston E, Kurtz R, Cvikovic E, Lieberman E, Golbey RB. Small-cell carcinoma of the esophagus: Treatment by chemotherapy alone. *Cancer* 1980;45:1558-1561.
20. Nichols GL, Kelsen DP. Small cell carcinoma of the esophagus: The Memorial Hospital experience 1970 to 1987. *Cancer* 1989;64:1531-1533.
21. McCullen M, Vyas SK, Winwood PJ, Loehry CA, Parham DM, Hambling T. Long-term survival associated with metastatic small cell carcinoma of the esophagus treated by chemotherapy, autologous bone marrow transplantation and adjuvant radiation therapy. *Cancer* 1994;73:1-4.
22. Van Der Gaast A, Verwey J, Prins E, Splinter TA. Chemotherapy as treatment of choice in extrapulmonary undifferentiated small cell carcinomas. *Cancer* 1990;65:422-424.
23. Jereczek-Fossa B, Airoidi M, Vasario E, Redda MG, Valente G, Orecchia R. Small cell carcinoma of the esophagus: A case report and review of the literature. *Tumori* 2000;86:174-177.
24. Law SY, Fok M, Lam KY, Loke SL, Ma LT, Wong J. Small cell carcinoma of the esophagus. *Cancer* 1994;73:2894-2899.