Primary Small Cell Carcinoma of the Larynx

Toshio Yoshihara, Ichiyo Kubota, Nanami Narita and Tetsuo Ishii

Introduction

Small cell carcinoma (oat cell carcinoma) of the lung is a relatively common neoplasm. On the other hand, small cell carcinoma of the larynx is an extremely rare tumor. Both tumors are histologically very similar and are highly malignant. There have been approximately 70 cases reported since this tumor, arising in the larynx, was first described by Olofosson and van Nosstran in 1972. Because of its rarity, only a few cases have been reported in Japanese literature. A review of 104 patients in our hospital with laryngeal cancer revealed no cases of small cell carcinoma. It is known that small cell carcinoma also arise in the nasal cavity, oral cavity, salivary gland and esophagus. In the present study, we describe the immunohistochemical and ultrastructural features of small cell carcinoma of the larynx which we recently encountered. The histogenesis, clinical features and the treatment of this tumor are also discussed.

Case History

The patient was a 76-year-old man who noticed a heartburn in March of 1989. He had no history of smoking cigarettes, and had undergone an operation for stomach and duodenal ulcer 10 years ago. Endoscopic examination of the esophagus at the clinic of general surgery showed a tumor at the right arytenoid and aryepiglottic fold (Fig.1). The initial biopsy specimen showed that small cell carcinoma was most suspected. He was treated with 5-FU, Mitomycin C and Toyomycin and the tumor mass disappeared endoscopically. Follow up examination had been done by general surgeons. He developed sore throat in August of 1990, and was introduced to our department. On admission, physical examination of the larynx revealed a tumor at the right arytenoid area, but both vocal cords were mobile. Both esophagoscopy and esophagography revealed no abnormalities. The neck was free of lymphadenopathy. Blood count and blood serum tests including calcitonin, neuron specific enolase (NSE), carcinoembryonic antigen (CEA), adencorticotrophic hormone (ACTH), dopamine, adrenalin and antiuuriotic hormone (ADH) levels were within normal ranges. On October 30, 1990, laryngomicrosurgery was done (Fig.2). Biopsy revealed small cell carcinoma. Chest X-ray showed a nodular shadow in the left middle lung field (Fig. 3). Bronchoscopic and cytologic examinations of bronchial washings revealed acid-fast bacilli, but the tumor cells were not found.
He was transferred from our hospital to another hospital for the examinations and treatment of pulmonary tuberculosis. The final diagnosis was atypical mycobacteriosis, and INH, RFP and EB were given to him.

He received a total of 600 rad of radiation therapy at both hospitals. The swelling of arytenoid area disappeared endoscopically. However, the patient complained of hemorrhoidal bleeding and was examined by general surgeons in our hospital. Biopsy revealed rectum cancer (adenocarcinoma). Before rectum operation we treated him with 1 course of 150mg carboplatin (JM-8, CBDCA) and 300mg etoposide (VP-16). On February 14, he underwent an operation for rectum cancer. Follow up examination is being continued at both departments.

**Histological Examinations**

Tissues obtained by laryngeal biopsy were fixed in 10% formaline and embedded in paraffin. The sections were stained with hematoxylin and eosin (H-E). In addition, immunohistochemical studies were performed using the avidin-biotin-peroxidase complex (ABC) techniques. The following antibodies were employed: cytokeratin (KL-1), vimentin, NSE, CEA, ACTH and leucocyte common antigen (LCA). Tissues for electron microscopy were fixed in 2.5% glutaraldehyde and postfixed in 0.1% osmium tetroxide, dehydrated in graded ethanols, and embedded in Epok 812. Ultrathin sections were stained with uranyl acetate and lead citrate, and were examined with a H-7000 electron microscope.

1. **Lightmicroscopic findings (H-E staining)**

   The tumor was composed of small round cells with high nucleocytoplasmic ratios. They were arranged in irregular sheets or nests. The nuclei were hyperchromatic without prominent nucleoli. Glandular structures were not found (Fig. 4).

2. **Immunohistochemical findings**

   Most of the tumor cells were immunoreactive for NSE (Fig. 5). Cytokeratin (KL-1) was also positive in some tumor cells (Fig. 6). All other antibodies used: ACTH, CEA, LCA and vimentin, revealed negative results.

3. **Electronmicroscopic findings**

   The tumor cells were polygonal in shape and the nuclei were pleomorphic with small nucleoli. The cytoplasm contained well developed mitochondria,
Golgi complex, and both smooth and rough endoplasmic reticulum (Fig. 7, 8). Cytoplasmic processes were also well developed and they were interdigitated with each other (Fig. 9). Many dense core granules (neurosecretory granules) were found (Fig. 7, 8, 9). These granules were surrounded by a limiting membrane and were approximately 100-500nm in diameter (Fig. 9). These cores showed various degrees of densities low to high (Fig. 8, 9). Tonofilaments in the cytoplasm or desmosome-like structures were not clearly identified.

Fig.4 The tumor was composed of uniform small round cells, which were arranged in irregular sheats or nests. X 70

Fig.5 Most of the tumor cells were positively staind with NSE. X190.

Fig.6 Cytokeratin (KL-1) was partly positive. X 190.

Fig.7 The tumor cells were polygonal in shape with pleomorphic nuclei. N : nucleus
Fig. 8 Cytoplasmic organelles were well developed. 
G: Golgi complex, m: mitochondria, N: nucleus. Dense core granules (arrow) and granules showing lower densities (arrowheads).

Fig. 9 Dense core granules (neurosecretory granules) were approximately 100-500 nm in diameter. Cytoplasmic processes (arrow). Granules showing lower dense cores (arrowheads).
Discussion

Small cell carcinoma is often referred to as oat cell carcinoma, anaplastic carcinoma, undifferentiated carcinoma, neuroendocrine carcinoma or Kulchitsky cell carcinoma etc.

Friedman and Ferlito\textsuperscript{13} described that neuroendocrine carcinomas of the larynx are subclassified into three types: typical carcinoid tumor, atypical carcinoid tumor and small cell neuroendocrine carcinoma. Furthermore, they divided small cell neuroendocrine carcinomas of the larynx into oat cell carcinoma which is composed of small cells with sparse cytoplasm, intermediate cell type and combined small cell carcinoma\textsuperscript{14}. The combined type is a tumor which consists of small cell carcinoma intermixing with adenocarcinoma and/or squamous cell carcinoma. The present case showed neither glandular nor epithelial differentiation although some tumor cells were cytokeratin positive, and was considered to be an oat cell type rather than the other two types.

Histologically, the small cell neuroendocrine carcinoma was characterized by the uniform small cells with hyperchromatic nuclei and scanty cytoplasm. Immunohistochemical studies have showed that the tumor cells may be positively stained with several antibodies such as NSE, ACTH, calcitonin, serotonin, CEA, somatostatin and keratin\textsuperscript{5, 15–17}. Most of the tumor cells of the present case were uniformly stained with NSE and partly stained with cytokeratin. Electronmicroscopically, the tumor cells contained membrane-bound, electron dense neurosecretory granules in their cytoplasm. These granules are also found in oat cell carcinoma of the lung\textsuperscript{18}, carcinoid of the larynx\textsuperscript{16} and glomus jugulare tumor\textsuperscript{19}. It has been suggested that these tumors originated from Kulchitsky cell or amine precursor uptake decarboxylation (APUD) cell system\textsuperscript{18, 20, 21}. Embryologically, both the larynx and lung arise from the medial diverticulum of the foregut\textsuperscript{22}. On the other hand, several authors\textsuperscript{4, 23} postulated that they arise from pluripotential endodermal stem cells because the small cell carcinoma of the larynx sometimes showed coexistence of squamous, adenomatous or sarcomatous differentiation.

It is well known that small cell carcinoma of the larynx may be associated with some hormone-secreting syndromes such as Schwartz-Barter syndrome (hypersecretion of ADH)\textsuperscript{25} and the Eaton-Lambert syndrome (myasthenic syndrome)\textsuperscript{26}. Bishop et al.\textsuperscript{27} reported a case of laryngeal small cell carcinoma with ectopic ACTH syndrome. Our case showed no abnormalities and normal values in blood serum tests of calcitonin, NSE, CEA, ACTH, catecholamine and ADH.

Although the larynx is an infrequent site of metastasis from other regions such as the kidney, lung, breast, prostate and colon, we must differentiate it from metastatic small cell carcinoma. According to a report of the Mayo Clinic, metastasis to the larynx revealed to be 0.2\% of all laryngeal neoplasms\textsuperscript{28}. In our case rectum cancer (adenocarcinoma) is considered to have no histological relation to laryngeal carcinoma. Immunohistochemical electron microscopic studies are also important in distinguishing small cell carcinoma from undifferentiated squamous cell carcinoma.

Generally, the supraglottic area is the most common primary site in this tumor. According to the world literature reviewed by Giddings\textsuperscript{6}, twenty-three patients had supraglottic lesions out of 51 patients. Small cell carcinoma of the larynx is known to show poor prognosis as compared with squamous cell carcinoma. At initial examination twenty-nine patients of 53 patients had metastasis in the cervical lymph node, parotis or brain\textsuperscript{6}.

There have been many reports concerning the treatment for this disease. Surgical procedures alone have failed in the majority of cases reported\textsuperscript{4}. Radiotherapy is possibly effective in controlling limited small cell carcinoma of the larynx, however, only radiotherapy has failed in many cases because of the distant metastasis\textsuperscript{4}. It is well established that chemotherapy is effective in small cell carcinoma of the lung. Combination chemotherapy had been done for oat cell carcinoma of the lung using cyclophosphamide, doxorubicine, methotorexate, vincristine etc. Recently, etoposide (VP-16) and cisplatin (CDDP) or carboplatin (CBDCA) have also been used, and revealed good results. Thus, radiotherapy combined with systemic chemotherapy is recommended. In our case, 5-FU, Mitomycin C and Toyomycin were given initially by the general surgeon before admittance to our hospital and they also seemed to be effective because the tumor disappeared.

Giddings\textsuperscript{6} described that out of twenty patients who were free of metastatic disease at initial examination, nine patients were alive at the time of each report. The average survival length for patients with...
metastasis was 12 months. In our case, as far as the laryngeal region is concerned, no recurrence has been found to the present. Postoperative course of rectum cancer has also been good, and systemic chemotherapies will be undertaken several times.

Summary

Histological and ultrastructural features of a primary small cell carcinoma of the larynx were presented. Lightmicroscopically, the tumor was composed of small round cells with high nucleocytoplasm ratios. They were arranged in irregular sheets or nests. Immunohistochemically, most of the tumor cells were stained with antibodies to neuron specific enolase (NSE), and some were stained with antibodies to cytokeratin. Ultrastructurally, the tumor cells contained spherical dense core granules (neurosecretory granules), approximately 100-500nm in diameter. The other cytoplasmic organelles were also well developed. Small cell carcinoma of the larynx must be differentiated from metastatic small cell carcinoma from other sites or undifferentiated squamous cell carcinoma. In our case there was no evidence of primary lesion in other regions. Furthermore, immunohistochemical and ultrastructural examinations were useful for differential diagnosis.

Acknowledgements

We are grateful to associate Professor Motohiko Aiba, Department of Pathology, Tokyo Women's Medical College for his valuable advice. We also thank Miss Naoko Abo for technical assistance. This work was supported in part by a Grant-in-Aid for Scientific Research, No. 02670776, from the Ministry for Education, Science and Culture of Japan.

References

22) Benisch BM et al : Primary oat cell carcinoma