Moderately Differentiated Neuroendocrine Carcinoma (Atypical Carcinoid) of the Larynx

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Abstract

A moderately differentiated neuroendocrine carcinoma or atypical carcinoid of the larynx occurred in a 68-year-old woman who developed rapidly progressive dysphagia, hoarseness and a neck mass. Immunohistochemical and electron microscopic studies verified the nature of this tumor. Local invasion and distant metastases are common. It is suggested that cigarette smoking could increase the risk of developing this neoplasm.

Squamous cell carcinoma is the most common primary malignancy of the larynx while neuroendocrine (NE) carcinoma is an unusual entity. The nomenclature of the latter neoplasms is confusing due to a spectrum in their differentiation and histological features. Various classifications have been proposed[1-3]. For example, Woodruff et al divided such tumors into two main types : small cell NE carcinoma and large cell NE carcinoma[3]. Other authors have classified into well-differentiated NE carcinoma (typical carcinoid), moderately differentiated NE carcinoma (atypical carcinoid) and poorly differentiated NE carcinoma to include oat cell and undifferentiated cells with NE features[1,2]. Despite such taxonomic confusion, the term NE carcinoma is preferable because it offers a unifying pathological diagnosis. It also reflects the fact that this tumor is essentially a carcinoma that displays NE differentiation. We report herein a case of moderately differentiated NE carcinoma of the larynx which appears to be the first case in this country.

CASE REPORT

A 68-year-old woman complained of increasing dysphagia, hoarseness, and occasional hemoptysis for two weeks before hospitalization. She also noticed progressive growing mass of the neck bilaterally. The patient had smoked one pack of cigarettes a day for 30 years. Physical examination revealed a 3 cm firm mobile right jugulodigastric node and a 2 cm of enlarged node on the

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left cervical region. An indirect laryngoscopy showed a 2 cm supraglottic mass with intact mucosa. Direct laryngoscopy and biopsy were performed. The pathological diagnosis of the biopsy specimen was "poorly differentiated squamous cell carcinoma." She, then underwent total laryngectomy with modified radical neck dissection. The bone scan disclosed abnormal uptake of radiotracer involving lumbar vertebrae (L-3 and L-5). Hence postoperative radiation totaling 5,500 rads was given. The patient was sent home 50 days after admission. She was doing well when seen four months later. However, she developed progressive weakness of both legs. The patient denied further medical treatment. She died at home six months after initial therapy.

Grossly, a well circumscribed tumor in the supraglottic submucosal region was noted showing gray white in color and firm in consistency (Fig. 1). The tumor was composed of polygonal or columnar cells with varying pleomorphism. The nuclei were vesicular, occasionally hyperchromatic. Mitoses were infrequently observed. The neoplastic cells were often arranged in trabecular, and acinar patterns as well as rosette-like appearance (Fig. 2). Four cervical nodes showed metastatic foci of tumor cells. Immunohistochemically, chromogranin A, calcitonin and cytokeratin were expressed in neoplastic cells (Fig. 3).

A portion of the tumor was washed, refixed in glutaraldehyde, and prepared for electron microscopy by the standard procedure. Ultrastructurally, the tumor cells contained distinct membrane-bounded electron-dense secretory granules of variable size ranging from 100 to 270 nm in diameter (Fig. 4). Mitochondria were relatively abundant but endoplasmic reticulum and Golgi apparatus were not prominent. Desmosomes were identified occasionally.

The final pathological diagnosis was moderately differentiated neuroendocrine carcinoma (atypical carcinoid) of the larynx with metastasis to cervical nodes, bilaterally.

DISCUSSION

The diagnosis of NE carcinoma reported here is warranted on the basis of its histological, immunohistochemical and ultrastructural findings[2]. Initially, such diagnosis was not entertained preoperatively in our case because a biopsy previous to laryngectomy was interpreted as poorly differentiated squamous cell carcinoma. In retrospect, the biopsy specimen was reexamined with the use of immunohistochemical stainings showing positive reaction with chromogranin and cytokeratin. It is thus necessary for surgical pathologists to be aware of this entity since their misinterpretations as squamous cell carcinoma, amelanotic

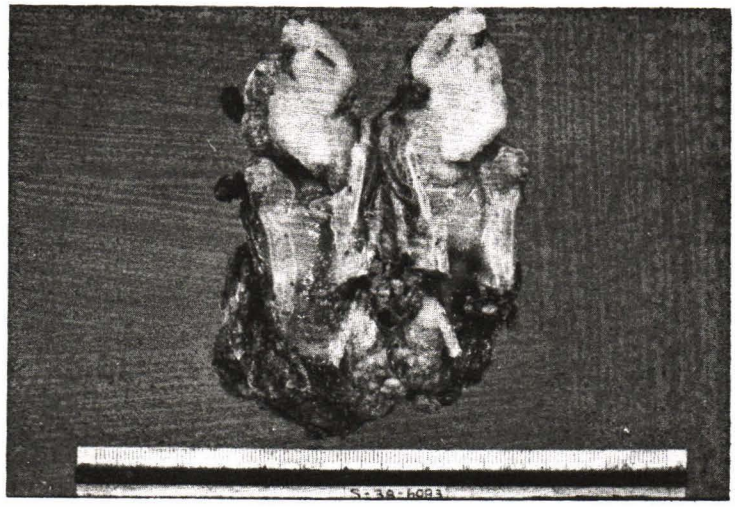

Fig. 1. Gross specimen showing a large supraglottic mass.

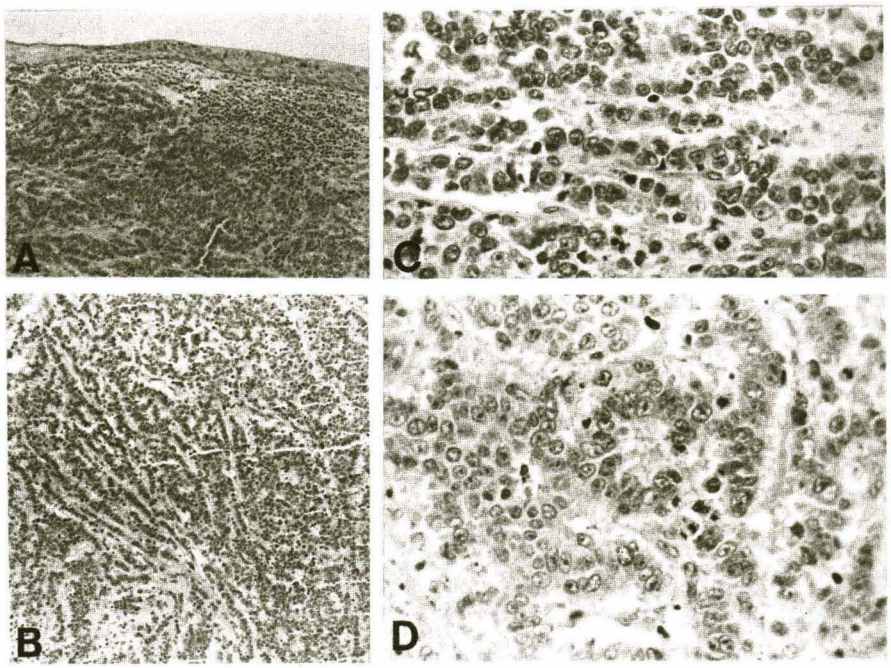

Fig. 2. Photomicrographs of the lesion.
(A) Infiltrating submucosal tumor beneath intact squamous epithelium (H & E x 40)
(B) Tumor cells in trabecular and acinar patterns (H & E x 100)
(C) Higher-power view showing nuclear pleomorphism (H & E x 400)
(D) Formation of rosettes (H & E x 400)

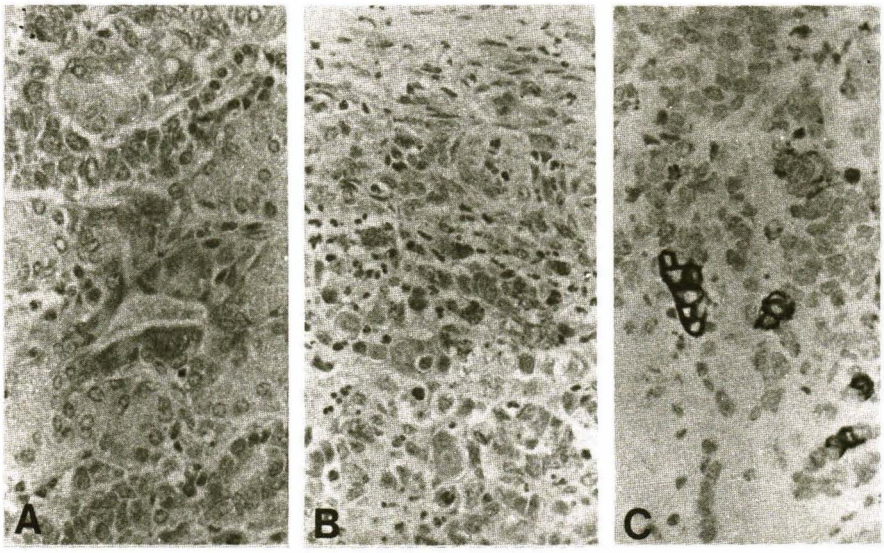

Fig. 3. Positive immunoreactivity for chromogranin, calcitonin and keratin (Immunoperoxidase stain x 400)

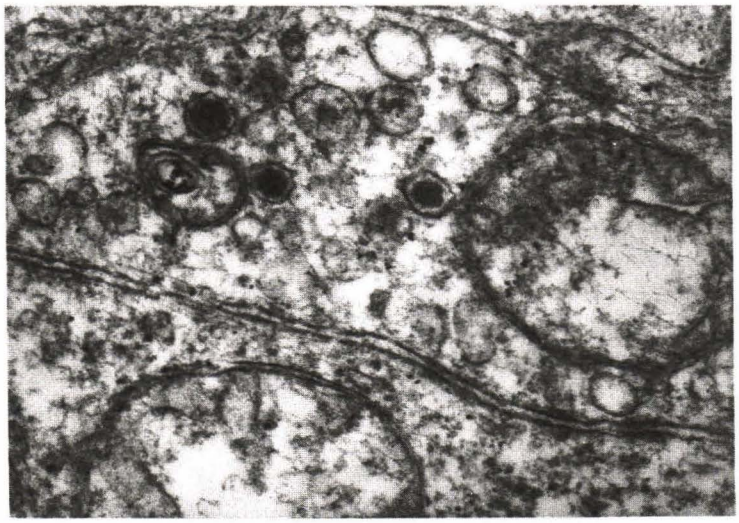

Fig. 4. Electron micrograph of neoplastic cells showing membrane-bound neurosecretory granules and junctional complexes (x 108,000).

melanoma or anaplastic carcinoma, etc. are common[4-6]. Both immunohistochemistry and electron microscopy are useful in the differential diagnosis[1,4,6]. Immunoreactivity with chromogranin and the presence of neurosecretory type granules in the cytoplasm as seen in our case indicate the neuroendocrine cells[1,7].

NE carcinomas of the larynx may not be as rare as formerly believed. Since Goldman et al described the first convincing case of primary laryngeal carcinoid, the number of case reports now amounts to 200 cases and it probably forms the largest group of nonepidermoid carcinoma of the larynx[1,8]. Athough the incidence of this neoplasm is difficult to access, Ferlito and Friedmann found 18 cases (0.5%) of laryngeal NE carcinomas in a series of 3,647 primary and secondary laryngeal neoplasms[1]. Wenig et al reported 54 cases (0.6%) of moderately differentiated NE carcinoma in a series of 8,469 cases of primary malignant tumors of the larynx[2]. In most series, NE carcinomas affected predominantly in men ranging from 2:1 to 4:1[2-4,9-11]. Of the 54 cases reported by Wenig et al, the ages of the patients varied from 37 to 83 years and the peak incidence were sixth and seventh decades of life[2]. Other series had a similar pattern in age distribution[3-4,9-11].

A definitive smoking history in our patient is of interest because such positive history for tobacco has been recorded in cases with NE carcinoma of the larynx ranging from 63 per cent to 71 per cent[2,3,12,13]. It should be noted that cigarette smoking has been shown to be an etiologic factor of epidermoid carcinomas of the lung and larynx. These data then suggest a relationship between cigarette smoking and the risk for developing NE carcinoma of the larynx.

The most common clinical manifestations including hoarseness, dysphagia, hemoptysis and complaints of neck mass as noted in our patient are reasonably related to the supraglottic location of the tumors and the fact that cervical nodes are the most common regional metastases[4,5,9-12]. The duration of illness may vary from a few weeks to several years. None of the reported cases including ours had symptoms suggestive of the carcinoid syndrome or other hormonal abnormalities although reports of elevated urinary 5-hydroxyindoleacetic acid have been described in two patients[6,9]. The reason for lack of such clinical features remains unclear[6,14].

Pathologically, laryngeal NE carcinomas often exhibit different degrees of differentiation. Most reported cases including our lesion belong to moderately differentiated NE carcinoma[2,3,5,6].

It is thus necessary to distinguish such lesions from the typical carcinoid because of the difference in growth pattern, therapy and outcome of the patients. Either moderately differentiated NE carcinomas or poorly differentiated NE carcinomas are likely to be locally infiltrative or spread extensively *via* the lymphatic and blood stream as clearly demonstrated in our case while well-differentiated NE carcinomas are not[1,5]. The most common sites of distant metastases are liver, lungs, bone and bone marrow, breast in addition to cervical lymph nodes [1,2,4,10]. Brain metastases are rare and occur usually as a terminal event[1].

Regarding therapeutic measures, surgery is recommended by most authors because radiation and chemotherapy have been disappointing in controlling the lesion[2,4,6,9,15]. Surgical treatment has consisted of partial and total laryngectomy with or without an associated neck dissection depending on the extent of the tumor. Conservative laryngeal excision is indicated if the tumor can be resected adequately[6,15]. A large neoplasm with cervical node metastases may require total laryngectomy with radical neck dissection as noted in our case[4,10].

Long-term follow-up is necessary to permit evaluations for recurrence as well as metastatic disease. It should be noted that the tumor can recur after prolonged disease-free intervals. Generally the prognosis of moderately differentiated NE carcinoma of larynx is poor due to its aggressive behavior, early development of local and distant metastases and rapidly fatal clinical course as observed in our case and the majority of case reports[1,2,15].

SUMMARY

A case of moderately differentiated neuroendocrine carcinoma of larynx in a 68-year-old Thai woman is described. Immunoreactivity with chromogranin, calcitonin, keratin and the presence of neurosecretory granules are useful in distinguish this tumor from other neoplasms because misinterpretation of this tumor is common. A review of the literature showed supraglottic region was the most common site. About two-thirds of the patients developed metastases. Surgery is the treatment of choice.

ACKNOWLEDGEMENT

This work was supported by Bangkok General Hospital Dr. Vira Kasantikul is currently in receipt of financial support from Chulalongkorn Faculty of Medicine-China Medical Board Scholar Development Fund.

(Received for publication on May 10, 1996)

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นิวโรเอนโดไครน์คาร์ซิโนมาของกล่องเสียง†

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ได้รายงานผู้ป่วยหญิงไทย อายุ 68 ปี ด้วยก้อนเนื้องอกนิวโรเอนโดไครน์ คาร์ซิโนมาชนิดพัฒนาปานกลางของกล่องเสียง ผลบวกต่อโครโมแกรนิน คัลซิโตนิน และซัยโตเคอราติน ด้วยกรรมวิธีอิมมูโนฮิสโตเคมีร่วมกับการพบ neuro-secretory granules **ด้วยกล้องจุลทรรศน์อิเลคตรอน ช่วยในการวินิจฉัยแยกจากเนื้องอกชนิดอื่น ๆ** จากการทบทวนวารสารพบว่ามะเร็งชนิดนี้เกิดที่บริเวณ supraglottis บ่อยที่สุด และ 2 ใน 3 ของผู้ป่วยมีการลุกลามไปยังเนื้อเยื่อข้างเคียงหรือแพร่กระจายของเนื้องอกไปยังอวัยวะอื่น ๆ การผ่าตัดยังเป็นวิธีการรักษาที่ได้ผลดี

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