Poorly Differentiated Neuroendocrine Carcinoma of the Nasal Cavity

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Poorly differentiated neuroendocrine carcinoma of the nasal cavity is a rare and aggressive neoplasm. We report a 47-year-old woman with poorly differentiated neuroendocrine carcinoma of the nasal cavity. Despite treatment with radical surgery, adjuvant radiotherapy and palliative chemotherapy, the patient died due to multiple distant metastases to lungs, bone and liver. **(Mid Taiwan J Med 2009;14:41-5)**

Key words

head and neck, nasal cavity, neuroendocrine carcinoma, sinus, small cell carcinoma

INTRODUCTION

Patients with sinonasal malignancies of neuroendocrine origin usually present with locally advanced disease. These neoplasms cannot generally be distinguished based on clinical or radiologic criteria and hence require expert pathologic diagnosis [1]. The most common site of head and neck neuroendorcine carcinoma is the larynx. Carcinoid tumors are commonly considered to be well-differentiated neuroendocrine carcinoma, whereas atypical carcinoid tumors are regarded as moderately differentiated neuroendocrine carcinoma. Small cell neuroendocrine carcinomas are classified as poorly differentiated neuroendocrine carcinoma, small cell carcinoma or small cell undifferentiated (neuroendocrine) carcinoma [1,2]. Primary poorly differentiated neuroendocrine carcinoma of the nasal cavity is a rare and aggressive neoplasm. It has a high recurrence rate, and a tendency to metastasize to other sites via the lymphatic system and blood stream [3]. The 5-year survival rate is only 13% [3]. Treatment includes surgery, radiation and chemotherapy. Progress in understanding and improving outcomes in this uncommon sinonasal malignancy has been hampered by difficulties in pathologic diagnosis and the rarity of this malignancy. The poor outcome of poorly differentiated neuroendocrine carcinoma of the sinonasal tract is consistent with the expected outcome of small cell carcinoma arising at other sites [1]. We report a rare case of primary neuroendocrine carcinoma of the nasal cavity.

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CASE REPORT

A 47-year-old women presented to our outpatient clinic at the China Medical University Hospital on 1 June, 2005 with a one-month history of left-sided nasal obstruction and yellowish bloody discharge from the left nostril. The patient was a non-smoker and had not been exposed to radiation or environmental irritants. The patient's medical history was noncontributory. Physical examination revealed an erosive tumor arising from the left inferior turbinate. Computed tomography (CT) revealed a homogeneous tumor in the left inferior turbinate (Fig. 1).

The patient underwent incision biopsy of the tumor on 2 June, 2005. Histologic examination revealed a highly cellular tumor exhibiting a trabecular growth pattern and a focal rosette formation of undifferentiated cells with a high mitotic rate and extensive necrosis (Fig. 2). The tumor had invaded the underlying minor salivary glands and bone. The section margin was free of tumor. There was no definite lymphovascular or perineural permeation. Immunohistochemical staining was positive for cytokeratin, chromogranin A and synaptophysin (Fig. 3), and negative for protein S-100 and neurofibriliar protein (NFP). Based on these findings, poorly differentiated neuroendocrine carcinoma was diagnosed. Systemic workup, including abdominal sonography and bone scan, showed no evidence of distant metastasis. The clinical stage of this tumor was T1N0M0, stage I.

After consulting with a medical oncologist and a radiation oncologist, surgical resection of the tumor and post-operative radiotherapy were planned. We approached the tumor via a trans-oral partial left medial maxillectomy. The neoplasm was a granular cell tumor extending from the left inferior pole of the left inferior turbinate to the lateral wall of the inferior meatus. There was no involvement of the left maxillary sinus mucosa or left middle turbinate. The left inferior turbinate and the left medial maxillary wall were completely excised. The patient then underwent local radiotherapy. A total of 54.9 Gy were fractionated into 36 sessions and radiotherapy was completed on 2 August, 2005. No local or regional recurrence was found during routine follow-up from August 2005 to October 2005. On 22 November, 2005, however, the patient presented to the outpatient clinic with a mass on the left side of her neck. T1- and T2-weighted magnetic resonance images showed an enhanced mass in the left carotid space with a greatest diameter of 1.3 cm. Pathological

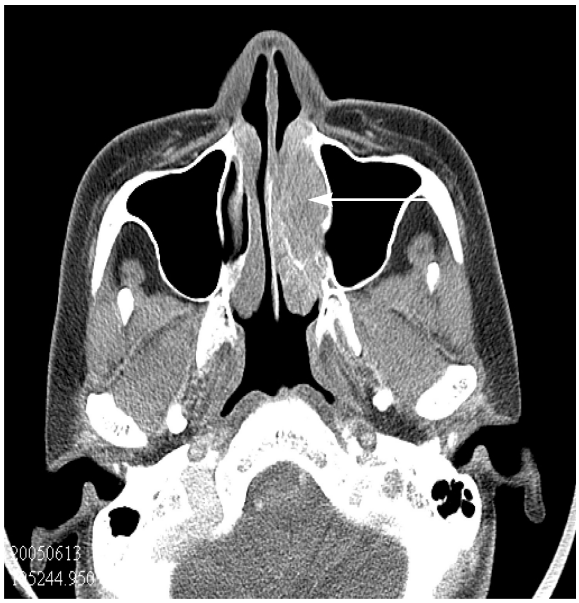

Fig. 1. CT scan with contrast of the head and neck reveals disproportionate hypertrophy of the left inferior nasal turbinate (axial view).

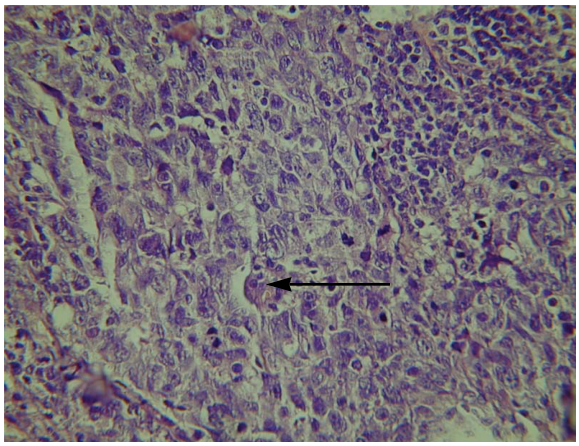

Fig. 2. Photomicrograph shows undifferentiated tumor cells arranged in a trabecular pattern with focal rosette formation. (H & E, original magnification × 200)

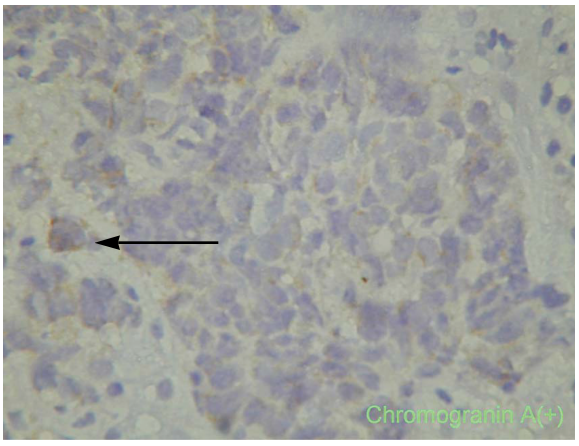

Fig. 3. Immunohistochemical staining reveals positive staining for cytokeratin, chromogranin A and synaptophysin. (original magnification × 400)

study confirmed regional recurrence. An ^{18}F-fluorodeoxyglucose (FDG) positron emission tomographic scan revealed multiple foci of increased FDG uptake in the left side of the neck, the right lateral chest wall, both lungs, and liver. Abdominal sonography revealed 4 tumors in both lobes of the liver. The patient received 5 courses of salvage chemotherapy (Etoposide 26.32 mg/m^2 qd $\times$ 3 days + Cisplatin 105.28 mg/m^2 qd $\times$ 3 days). As the disease progressed, the regimen was changed to Doxorubicin (52.64 mg/m^2 qd $\times$ 1 day), Vincristine (1.32 mg/m^2 qd $\times$ 1 day), Filgrastim (0.20 mg/m^2 qd $\times$ 3 days), and Topotecan (2.63 mg/m^2 qd $\times$ 5 days) in May 2006. On 2 October 2006, she was sent to our emergency department because of a 2-day history of progressive dyspnea. She died on 4 October, 2006 due to progressive disease, lung metastasis and respiratory failure induced by the enlarging neck mass.

DISCUSSION

Primary neuroendocrine carcinoma of the nasal cavity is rare. The most common site for this tumor in the head and neck region is the larynx.

The presentation of neuroendocrine carcionoma depends on the site of origin. Most patients with neuroendocrine carcinomas of the head and neck present with epistaxis and facial pain. Other symptoms can include facial swelling, nasal obstruction, proptosis, paresthesia, and anosmia. The most frequent sites for distant metastases are the lungs, liver, and bone. Neuroendocrine carcinomas may produce ectopic hormones, but clinical manifestations of hormone production are uncommon in these tumors when arising in the head and neck.

Microscopically, poorly differentiated neuroendocrine carcinomas arising in the head and neck are indistinguishable from those of bronchogenic origin. Typically there are sheets, cords, and ribbons of small cells with little or no cytoplasm that appear undifferentiated under light microscopy. The nuclei have a uniformly stippled chromatin pattern. Mitotic figures are frequent. Necrosis varies from scattered, individual cell death to irregular zones of infarct-like change. Intravascular and perineural invasion are common.

Conventional microscopy is generally insufficient for the diagnosis of neuroendocrine carcinoma, as it shares histological features with other neoplasms, such as lymphomas, sinonasal undifferentiated carcinoma, and olfactory neuroblastoma [3]. Immunohistochemical findings are generally useful in differentiating between small cell tumors of different histogenetic origins. The pattern of immunostaining in paranasal poorly differentiated neuroendocrine carcinoma is similar to that in pulmonary small cell carcinoma. Typically there is reactivity for cytokeratins, often with a punctuate perinuclear pattern, a feature noted in small cell carcinoma. Neuroendocrine markers such as chromogranin, synaptophysin, and neuron-specific enolase are also frequently expressed. Microscopically, the differential diagnosis includes olfactory neuroblastoma and malignant lymphoma. In these cases, olfactory neruoblastoma is excluded by negative staining for S100 and the presence of extensive necrosis, which is usually absent or minimal in olfactory neuroblastoma. Negative staining for leukocyte common antigen can exclude malignant lymphoma [4].

The treatment of poorly differentiated neuroendocrine carcinoma has not been clearly defined. Depending on clinical condition and tumor staging, surgical excision of localized disease, radiation therapy to the primary site, multiple-drug chemotherapy, or a combination of these modalities may be appropriate [5]. Treatment of poorly differentiated neuroendocrine carcinoma has varied over time [2]. In the 1980s, surgery followed by radiotherapy was favored [6]. In the late 1990s, neoadjuvant chemotherapy and high-dose proton-photon radiotherapy, with or without surgery, produced encouraging results at 45 months for poorly differentiated neuroendocrine carcinoma of the nasal and paranasal cavities [7]. Commonly used adjuvant agents include cyclophosphamide, cisplatin, doxorubicin, vincristine, and methotrexate [8].

Extrapulmonary poorly differentiated neuroendocrine carcinoma is a highly aggressive neoplasm with a poor prognosis. The reported 5-year overall survival rate is 13% [9]. Duration of survival from onset of symptoms to death for patients with poorly differentiated neuroendocrine carcinoma of the head and neck is only about 13 months [2]. The causes of death include failure to control local disease and distant tumor metastasis.

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鼻腔神經分泌性癌

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鼻腔神經分泌性癌爲一罕見疾病，本院於2005年5月經歷一位47歲女性病患，主訴爲最近一個月的左側鼻腔黃稠帶血分泌物，伴隨漸歇性的鼻塞而至本院求診。理學檢查發現左側下鼻甲充血性腫大，並有些許潰爛，與右側下鼻甲相較顯著不同。影像學檢查發現左側下鼻甲腫大。爲排除惡性病變之可能，先予切片檢查，病理報告爲分化不良的神經分泌性癌。經由左側內側部分上頷骨切除手術切除腫瘤。病患於術後接受放射治療。由於疾病持續進展，病患於2006年5月接受共六次化學治療。病患由於呼吸困難於2006年10月2日被送至本院急診。於2006年10月4日因呼吸衰竭而死亡。分化不良的神經分泌性癌只在免疫染色或電子顯微鏡下才可鑑別診斷。此疾病臨床表現類似末期腫瘤，常有多發性的轉移。目前治療方式無共識。手術、化學治療或放射治療皆有報導。病患五年存活率約爲13%。（**中台灣醫誌 2009;14:41-5**）

關鍵詞

頭頸部，鼻，神經內分泌癌，鼻竇，小細胞惡性腫瘤

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