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Advance in the Studies on Small Cell Neuroendocrine Carcinoma of the Paranasal Sinuses

Changsheng Cong
Yonghua Yu
Shuanghu Yuan
Dongwei Gao

Department of Radiotherapy, Shandong Tumor Hospital, Jinan 250117, Shandong Province, China.

Correspondence to: Yonghua Yu
E-mail: sdwufx@163.com

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CJCO http://www.cjco.cn
E-mail: 2008cocr@gmail.com
Tel (Fax): 86-22-2352 2919

ABSTRACT Small cell neuroendocrine carcinoma (SCNEC) of the paranasal sinuses is extremely rare, with an unclear pathogenesis. The presence of neuroendocrine granules is suggestive of neuroendocrine differentiation. It was reported that this disease relates to the presence of accessory salivary glands, and some basic research has shown that it might originate from the multi-potent stem cells. There are no specific clinical symptoms but rhinal and ophthalmological symptoms are found in most cases. Diagnosis mainly depends on histopathological manifestations, immunohistochemical results and features of the electron microscopic ultra-structure. Pathological differentiation from poorly differentiated squamous carcinoma, melanoma, esthesioneuroblastoma and neuroglioma etc. is needed. No unified regimen has been employed in treating the disease. At present, combined therapy has a manifest therapeutic effect, such as success with the 2003 French regimen. Tumor relapse is common and prognosis is poor. A complete combined treatment plan will be helpful to improve the prognosis.

KEY WORDS: small cell, neuroendocrine carcinoma, accessory nasal cavity/paranasal sinuses.

Introduction

Small cell neuroendocrine carcinoma (SCNEC) was mentioned in the literature of lung cancer in the 19th century. The SCNEC of the paranasal sinuses (SCNECPS) was first reported by Raychowdhuri in 1965, i.e., a case with SCNEC of the ethmoidal sinus was found by an autopsy[1]. Since the case is rare and pathohistological diagnosis complicated, understanding of the SCNEC's patho-mechanism remains difficult. In our study, the pathogenesis, clinical features, differential diagnosis, treatment, and prognosis of the SCNECPS reported and investigated in the literature both in China and overseas were reviewed.

Pathogenesis

The histogenesis of SCNECPS is still unclear. It was reported in 1972 that SCNEC of the nasal cavity and paranasal sinuses was related to presence of the intracavity accessory salivary glands[2]. Presence of neuroendocrine granules and argentophilic character of the tumor cells suggested the features of neuroendocrine differentiation. SCNEC of the head and neck have been classified in a tumor series characterized by amine precursor uptake and decarboxylation (APUD). This concept of histogenesis applies to all neuroendocrine cells (NECs) and tumors, which usually have the same cytological chemical characteristic and function. NECs represent the common features of the APUD cells and tumor. APUD cells which are usually

comprised of pyknotic nucleargranules, produce biogenic amines, neuron-specific enolase (NSE) and other specific proteins. APUD tumors often secrete ectopic hormones. However, a homologous clinical symptom, such as paraneoplastic syndrome, was seldom found in neuroendocrine carcinoma of the head and neck, which was obviously different from that of the lung, and pancreas, etc.[3] Of course, detection of ectopic hormones does help to diagnose and establish a prognosis.

It has been suggested in some reports that neuroendocrine carcinoma of the nasal cavity and paranasal sinuses may produce serum mucoprotein, and all SCNECs of the head and neck (except for skin Merkel cellular carcinoma) are related to the glands. These glandular epithelia (GE) are exocrine glands, and the tumor originates from the GE[4]. However, the relationship has not been generally recognized by histopathological examination and previous literature. Noguchi et al.[5] have conducted eteroplastic transplantation of the excised tumor tissue in nude mice in order to set up a nude mouse SCNEC-transplanting cell line, and to detect the NSE and progastrin releasing peptide (pro-GRP) in the serum, using histopathological and immunohistochemical methods. The results showed that the NSE and pro-GRP in the serum are the available tumor markers for extrapulmonary SCNEC. Noguchi et al.[6] established a new SCNEC cell line from the maxillary sinus SCNEC tissue, so as to understand the biological features and interpret the histogeneous mechanism. They investigated the character of neural cell differentiation and neuroendocrine features by administering dibutyryl cyclic AMP (db-cAMP). The findings showed that the cell line took a globular, or fusiform shape in the monolayer culture dish, and with positive NSE and nerve cell adhesion molecules (N-CAM, CD56, GRP). There was NSE expression in the culture dish, and the ultrastructural dense-core neuroendocrine granules could be detected in the cytoplasm. The db-cAMP induced nerve cell development and extension, forming a reticulate arrangement. This reveals a strong immunoreactivity of the PKase, with the presence of neurofilaments of high molecular weight. The time-dependent microtubule-2 was found in the lysate, which indicated that the cell line had the ability to differentiate into the neuroblasts, thus validating the hypothesis that extra-pulmonary SCNEC may come from multipotent stem cells.

Clinical and Pathological Features

Clinical features

SCNECPS is an uncommon tumor that has rarely been reported in China. In the world there are only reports of less than 50 cases. The median age of onset is 53 years, without sexual differentiation. No reports on whether the disease is related to smoking, or a vocation were found in the literature. The characteristics of the disease are local recurrence and invasion, sometimes with metastasis. Clinical symptoms include the following: regional occupying symptoms, such as the rhinal symptoms (nasal obstruction, thick nasal mucus and rhinorrhagia, etc.), eye symptoms (exophthalmos, dacryorrhea, diplopia and vision extinction, etc.), local infiltration causing post-influenza-like hyposmia and hypogeusia and facial numbness and tumescence, basicranial destruction syndrome such as headache and cranial nerve infiltration, etc., lymph node metastasis of the neck, regional pains and functional disturbance resulting from distant metastasis, and the neuroendocrine syndrome. The latter 2 symptoms are rare, but they are also the key factors of an unfavourable prognosis. More attention should be paid to initial symptoms, since the site is occult and the disease in the advanced stage can only be found at an onset of the symptoms. A general physical checkup is one of the key steps for early discovery of the tumors.

Pathologcal features

Microscopic findings show that the tumor is greyish-white, with a fragile texture and frequent hemorrhage. The result of H&E staining reveals that the tumor cells have a cord-like, nest-like, and trabecular change, with an extensive hemorrhage and necrosis. The size of the cells is small, having less cytoplasm, with big, round or oval-shape nuclei and strong basophilia. The nucleolus is absent or inconspicuous, the degree and distribution of the staining trachychromatic, with polymorphic changes, and common caryomitotic figures. The tumor invasion mainly reflects the infiltration around the lymph and blood vessels and surrounding nerves. H&E staining is not sufficient to diagnose small cell neuroendocrine carcinomas, and argentophilic and argentaffin staining show a positive change in 80% of the cases. Though the immunohistochemical method has no specificity for diagnosing SCNEC, neuroendocrine markers, such as the NSE, chromaffin granule A (CgA), synapsin (SYN), Leu7 (HNK-1), serotonin, cytokeratin (CK), etc., are still helpful to identify the NEC in the tumor. Aggregate analysis with at least 2 or more stains is usually recommended, and a final diagnosis can be made if the result is positive. Microscopic examination shows there are neuroendocrine granules with a size of 50-200 nm in the cytoplasm, which is a common feature of neuroendocrine tumors.

Classification of neuroendocrine carcinomas is usually difficult. Based on WHO TNM staging, carcinoid is a well-differentiated neuroendocrine carcinoma, while untypical carcinoid is a moderately differentiated neuroendocrine carcinoma. Small cell cellular carcinoma is a poorly differentiated neuroendocrine carcinoma.

Differential Diagnosis

The common symptoms of tumors of the paranasal sinuses include headaches, visual disorders and rhinal obstructions to various degrees. Concerning the clinical

diagnosis of the disease, the tumor is usually first misdiagnosed as a nasosinusitis or ophthalmic disease, as well as a dental disease. Georgiou et al.[7] reported a case with small cell neuroendocrine carcinoma of the maxillary sinus. The patient visited a physician because of a feeling of facial tumescence, resulting in a first diagnosis of a dental disease. The symptoms were not significantly relieved after an extraction of the left premolar and molar teeth. Other symptoms occurred, such as diplopia, epistaxis, abnormality of the ophthalmic branch of the trigeminal nerve, and paraesthesia of the ramus maxillaris, etc. CT and pathological diagnosis indicated it was a maxillary sinus SCNEC.

The histological differential diagnosis of SCNEC should be separated from poorly differentiated squamous carcinoma, melanoma and esthesioneuroblastoma etc.[8] Electron microscopic observation of melanoma reveals that there are melanosomes in the cytoplasm, and an esthesioneuroblastoma tumor presents with an orbicular-ovate, or small and round shape, and a lamellar, cord-like or trabecular arrangement. The tumor cells are few, with a round or orbicular-ovate nucleus and chrysanthemum-like conglomerate structure. An immunohistochemical assay shows a positive change in the NSE, CgA, Cyn and Keratin, making these tumors difficult to differentiate from SCNEC. However it is clear that, after comparing an esthesioneuroblastoma with a SCNEC, the former has a lobular structure and vascular mesenchyma in the tumor, with internuclear small fibers within the tumor.

Microscopic findings of the support cells in the tumor cells, and these changes are insufficient in SCNEC. In addition, further discrimination from an esthesioneuroblastoma should be conducted[9]: Homogeneous round nucleated cells can be seen in the former tumor, with dendritic processes of various quantities, and a large amount of dense granules. The size of the granules ranges from 150 to 350 nm. The dendritic processes include length-wise distributed neurotubules. A synaptic junction is occasionally found, and the supporting cells and Sertoli's cells are frequently seen. The cells of a SCNEC are round, compactly arranged and distributed, with the characteristics of very little cytoplasm and insufficient neuroblasts. Most of these tumor cells are epithelioid cells, CK and NSE etc. The immunohistochemical results are also positive, further confirming their neuroepithelial characteristics. The major difference between the esthesioneuroblastoma cells and the SCNEC cells is that the SCENC cells lack supporting Sertoli's cells. Microscopic examination shows that the 2 tumors are quite similar. Therefore, immunohistochemical assays and electron microscopy are very important for differential diagnosis.

Treatment and Prognosis

There is no single therapeutic regimen for the treatment of SCNECPS. Reports from the literature propose a single chemotherapy, a single surgery[10], a single radiotherapy[11], postoperative radiotherapy and chemotherapy, chemotherapy in combination with radiotherapy[12], as well as a therapeutic combination of surgery, chemotherapy and radiotherapy. In the 1980s, postoperative radiotherapy was highly recommended, and presently that treatment is even accepted more. At end of the 1990s, chemotherapy plus radiotherapy (concurrent with surgery in some cases) achieved a satisfactory result. The survival time of patients was extended to 45 months. For chemotherapeutic regimens, cisplatin, vincristine, cyclophosphamide, flurouracil, etoposide, adriamycin and methotrexate etc.[13] have all been used.

In November, 2003, a therapeutic regimen was recommended at the 35th Meeting of French Head and Neck Cancer Society[1]: First a 2-cycle chemotherapy of a CE regimen was conducted (Carboplatin 33 mg/m^2, etoposide 100 mg/m^2, d 1~3), over an interval of 15 days. The curative effect was evaluated based on imaging results, i.e. a comparison of the size of the tumor before and after the CE-drug treatment. If, after the drug treatment, the chemotherapeutic results were more than 50%, or in some cases less than 50% but the tumor still could not be excised, an irradiation dose of 68 Gy was given to the patients. Then the curative effect was assessed based on imaging results. It was suggested that surgery should be conducted if the chemotherapeutic effect was less than 50%, and the tumescent lymph node lump could be excised. Then a 68-Gy radiation therapy could be performed. A CE regimen was given at the end of all therapies so as to insure a curative effect.

Bhattacharyya et al.[14] were successful in treating esthesioneuroblastoma and SCNEC by chemotherapy in combination with proton therapy, i.e. 2 cycles of CE chemotherapy were given to patients following histological and imaging diagnosis, and patients with a sensitivity to the chemotherapeutic regimen were administered a combined treatment of proton and photon therapy. The radiotherapeutic dose was 68 Gy. Surgery and postoperative radiotherapy were conducted in the patients without a chemotherapeutic response. A 20.5-month follow-up was performed, and the results showed that there was a significant chemotherapeutic effect in 8 cases, with an obvious disappearance of the lump without surgical excision, and in 1 case surgery and postoperative radiotherapy were carried out. No recurrence (median disease-free survival time: 10.4 months) was found at the end of the follow-up, and complications were rare, usually being a transient episode. This therapeutic regimen offers a good preliminary success, and the incidence of complications was acceptable. The rate of mortality was lower compared to that of craniofacial resection and conventional radiotherapy.

Huang et al.[15] performed combined chemotherapy (cisplatin 20 mg/d and 5-fluorouracil 0.5 g/d, i.v. drip for 5 d each), surgical treatment (rhinal tumorectomy by

paranasal incision and tumorectomy by coronal-incision craniotomy with bilateral frontal bone flap+ anterior basicranial reconstruction) and postoperative radiotherapy (bilateral preauricular-field radiotherapy by linear accelerator, with a tumor dose of 54 Gy, and the treatment plan for anterior ethmoidal sinus was in accordance with the anterior nasal field, and the electronic irradiation dose was 40 Gy) to treat a patient with the carcinoma of the maxillary sinus and ethmoidal sinus invading the skull base and frontal cerebrum. No recurrence was found after 3, 6, 9 and 18 months.

Kin et al.[16] reported on a 66-year patient with SCNECPS, having diffuse infiltration in his eye sockets and left cerebral hemisphere, and an obvious cerebral edema. A neuroimaging examination showed that the tumor at the left paranasal sinuses invaded the skull and the frontal bone. Radical excision of the lumps and intraorbicular contents were conducted by combined surgical therapy, and the musculocutaneous flap was used to reconstruct the anterior basion. Postoperative pathological results showed a "undifferentiated neuroendocrine carcinoma of the paranasal sinus," and the patients received chemotherapy after surgery. The postoperative survival time was 2 years, with a slight hemiparalysis and moderate logopathy.

Opinion varies as to the prognosis of this disease. From the literature, prognosis for SCNECPSs is extremely poor, mainly because of its malignant biological behavior and difficult early diagnosis. Babin et al.[1] had reported 21 cases with SCNEC of the nasal cavity and the paranasal sinus, and recurrence or metastasis occurred in 17 of these cases within 2 years. The median survival time was 37 months. In addition, single therapeutic methods in early cases failed to bring about a satisfactory therapeutic result, but development of a combined treatment regimen has significantly improved the prognosis over recent years.

References

1 Babin E, Rouleau V, Vedrine PO, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. J Laryngol Otol 2006; 120: 289–297.

2 Koss LG, Spiro RH, Hajdu S. Small cell (oat cell) carcinoma of minor salivary gland origin. Cancer 1972; 30: 737–741.

3 Baugh RF, Wolf GT, McClatchey KD. Small cell carcinoma of the head and neck. Head & Neck 1986; 8: 343–354.

4 Silva EG, Butler JJ, Mackay B, et al. Neuroblastoma and neuroendocrine carcinomas of the nasal cavity. A proposed new classification. Cancer 1982; 50: 2388–2405.

5 Noguchi K, Urade M, Sakurai K, et al. Small cell neuroendocrine carcinoma of the maxillary sinus--a case report and nude mouse transplantable mode l. Head Neck 2002; 24: 491–496.

6 Noguchi K, Urade M, Kishimoto H, et al. Establishment of a new cell line with neuronal differentiation derived from small cell neuroendocrine carcinoma of the maxillary sinus. Oncology 2004; 66: 234–243.

7 Georgiou AF, Walker DM, Collins AP et al. Primary small cell undifferentiated (neuroendocrine) carcinoma of the maxillary sinus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004; 98: 572–578.

8 Zhang J and Chen XP. Small cell neuroendocrine carcinoma of the nasal cavity: a report of two cases. Chongqing Xi Xue 2005; 34: 632–633 (Chinese).

9 Min KW. Usefulness of electron microscopy in the diagnosis of "small" round cell tumors of the sinonasal region. Ultrastruct Pathol 1995; 19: 347–363.

10 Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. Cancer 1997; 79: 1729–1736.

11 Chaudhry MR, Akhtar S, Kim DS. Neuroendocrine carcinoma of the ethmoid sinus. Eur Arch Otorhinolaryngol 1994; 251: 461–463.

12 Rischin D, Porceddu S, Peters L, et al. Promising results with chemoradiation in patients with sinonasal undifferentiated carcinoma. Head Neck 2004; 26: 435–441.

13 Hu M. Neuroendocrine carcinoma of the maxillofacial region. Kou Qiang He Mian Wai Ke Za Zhi 2003; 13: 95–97 (Chinese).

14 Bhattacharyya N, Thornton AF, Joseph MP, et al. Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation. Results in 9 cases. Arch Otolaryngol Head Neck Surg 1997; 123: 34–40.

15 Huang B, Si YF, Li B, et al. A case report of carcinoma of maxillary sinus and ethmoidal sinus invading skull base and frontal cerebrum. Chin J Otorhinolaryngol Head Neck 2005; 40: 44.

16 Kin S, Wanibuchi M, Minamida Y, et al. A case of sinonasal carcinoma with intracranial invasion treated by a multidisciplinary team. No Shinkei Geka 2003; 31: 677–682.