CASE SERIES

Small cell neuroendocrine carcinoma of nose and paranasal sinuses: The Shaukat Khanum Memorial Cancer Hospital experience and review of literature

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Abstract

Small cell neuroendocrine carcinoma (SCNEC) is a rare disease of nose and paranasal sinuses. In contrast to other regions SCNEC of this region has been reported to be recurrent and locally aggressive. No definite treatment has been established till date because of rarity of this disease. The purpose of this descriptive study is to present the series of 8 cases with SNEC of nose and paranasal sinuses.

Retrospective review of 8 patients presenting with Small cell neuroendocrine carcinoma of nose and paranasal sinuses, from January, 2005 to December, 2014 treated at Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore was performed to determine the clinical characteristics and outcome of this disease.

The subjects were 7 males and 1 female with a mean age of 45±15 years (range 24 to 59 years). Tumours were present in nasal cavity (n=4), ethmoid sinus (n=3) and maxillary sinus (n=1). Almost 50% of patients presented with AJCC stage IV-A. All patients had immunohistochemistry proven diagnosis. All patients (08) received radiotherapy with mean doses 58±Gy (Range 54-66Gy). Surgery was performed in 2 while chemotherapy was administered in 4 patients. Recurrence occurred in 3 patients, one each with loco-regional, distant and both. At a median follow up of 38 months, 5 patients were alive with no evidence of disease.

SCNEC is a rare but aggressive neoplasm. Current standard of care varies but multi-modality approach should be the cornerstone in management of SCNEC. Early diagnosis and intervention improve the final outcome.

Keywords: SCNEC: Small cell neuroendocrine carcinoma, Gy: Grey, APUD: Amine precursor uptake and decarboxylase System.

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Introduction

Small cell neuroendocrine carcinoma has been recognized as a distinct, relatively infrequent pathological entity that occurs at multiple sites in head and neck regions. It is more commonly seen in Larynx, paranasal sinuses and salivary glands. It was first described in the sinonasal region by Chowdhuri and his colleagues in 1965[1] and later in 1972 Oloffson et al.[2] reported a laryngeal SCNEC. It has been postulated that outside lung, the tumour arises from the neuroendocrine APUD (amine precursor uptake and decarboxylation) cells, which are widely distributed in the body.[3] Histologically, it is undistinguishable from the pulmonary tumour. Immunohistochemical study is essential to make an adequate differential diagnosis from other malignant tumours such as lymphoma, rhabdomyosarcoma, undifferentiated nasopharyngeal carcinoma, and undifferentiated sinonasal carcinoma.[4] Small Cell neuroendocrine carcinoma that originate in the head and neck have a tendency for aggressive local invasion and a strong propensity for both regional and distant metastases. Treatment may include surgical resection, radiotherapy, chemotherapy, or combination of these modalities.[5]

Case Series

Records of eight patients were retrieved from January, 2005 to December, 2014 using Cancer Registry Database of Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, who have been histologically diagnosed with sinonasal neuroendocrine carcinoma. Demographic data for each individual including age at diagnosis, sex, risk factors, grade, stage, geographic location were all obtained from the same database. The Registry used the American Joint Committee on Cancer (AJCC 7th edition) staging manual for staging all available cancer sites.

The patients were scheduled for follow-up visits every 3 months after the initial surgery during first year followed by 4 months in second year, 6 months in third year and then annually. Follow-up consisted of a routine physical examination and a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the primary

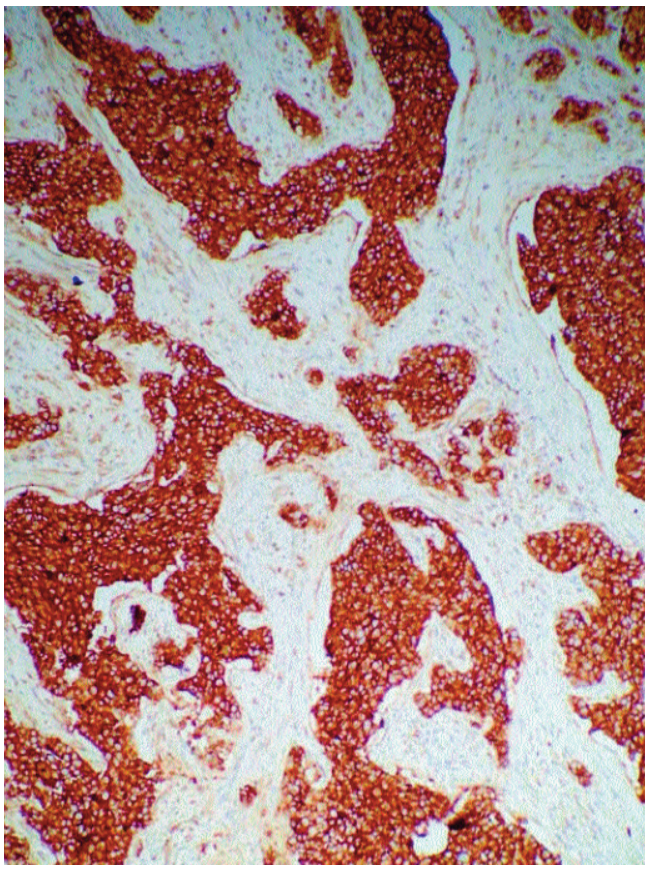

Figure-1: Synaptophysin and CD56 staining.

site. Patient follow-up was reported up to the date they were last seen in the clinic.

Seven (7) of the patients were male and one was female. The mean age at presentation was 45±15 years (range: 24 -59 years). Primary site of involvement in four (4) patients was nasal cavity, ethmoid sinus in three (3) and maxillary sinus in one (1) patient. Half of the patients presented with AJCC stage IV-A. All these eight cases showed almost similar histological features. Immunohistochemical studies showed staining for CD 56, Synaptophysin, Chromogranin, Cytokeratin and Enolase Neuron. Seven cases were positive for cytokeratin, 5 for chromogranin, 2 with CD56 and one each with synaptophysin and neuron specific Enolase. Surgical excision of primary tumour was performed in 2 patients only. All patients (08) received radiotherapy with mean doses 58Gy (Range 54-66Gy). Chemotherapy was administered in neoadjuvant setting in 04 patients and one received in concurrent setting. Induction chemotherapy was offered with regimens including platinum (75mg/m2 every 21 days) while etoposide (120 mg/m2 on day1/D1 and day2/D2) was given in combination for distant metastasis. Recurrence

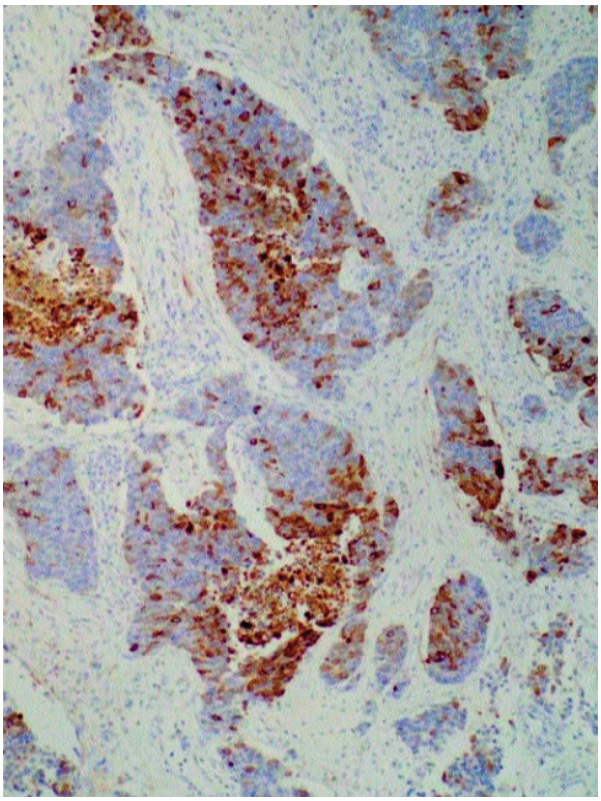

Figure-2: Cytokeratin staining.

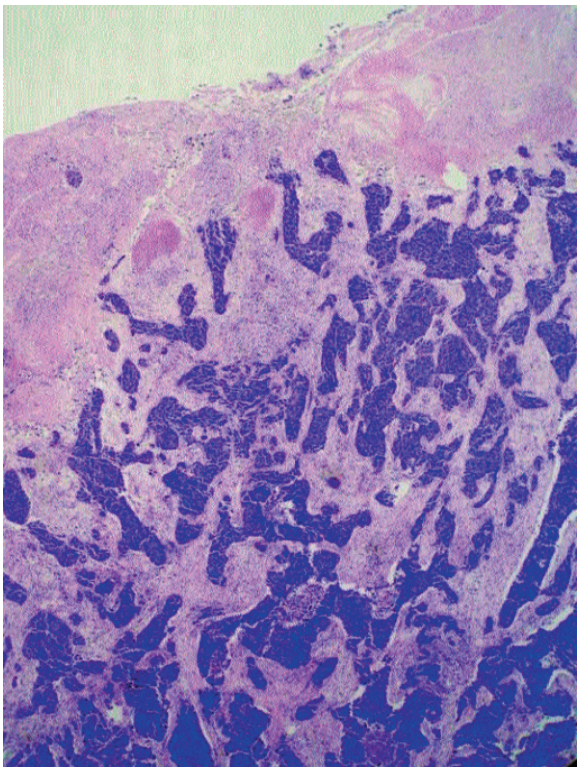

Figure-3: Tumor arranged in nests with overlying ulceration.

occurred in 3 patients, one each with loco regional, distant and both. At a median follow up of 38 months, 5 patients were alive with no evidence of disease.

Discussion

Neuroendocrine tumours have been previously classified by the World Health Organization by tissue of origin; neural or epidermoid. Tumours of neural origin include paragangliomas and Merkel cell carcinoma of the integument. Epidermoid tumours include large cell (carcinoid), atypical and small cell carcinomas. Neuroendocrine carcinoma (NEC) of the head and neck are thought to be derived from the APUD cell family (amine precursor uptake and decarboxylase system), more specifically the Kulchitsky's cells. Merkel cell carcinoma, however, is thought to be derived from a type I mechanoreceptor located at the dermal-epidermal junction

Small Cell Neuroendocrine carcinoma in Head and Neck regions is uncommon with only 180 cases of larynx and 75 of Paranasal sinuses being reported in English literature so far. Most of them are males as is obvious in our findings, approximately 50 years of age and heavy smokers.[7-9] Likhacheva et al. reviewed 20 patients treated for neuroendocrine carcinoma of the nasal cavity or paranasal sinuses from 1992 to 2008 at MD Anderson Cancer Centre; 11 were male and 9 female with a median age of 49.2 years.[10]

Unlike Squamous cell carcinoma which is most commonly seen in Maxillary sinus, Paranasal Neuroendocrine Carcinomas are mostly observed in ethmoid sinus.[9]

Extra-pulmonary SCNEC has proven to be a fatal disease having poor prognosis with a 13% five year survival rate.[11] Five patients in our study are alive without disease at a median follow up of 38 months.

Immunohistochemical markers are used to further sub-classify and avoid misdiagnosis among epithelial neuroendocrine tumours. Neurone-specific enolase, chromogranin, CD56, immunoperoxidase, synaptophysin, epithelial membrane antigen, calcitonin, and bombesin stains may be useful to establish the diagnosis.[12]

Surgery and Radiotherapy has the primary role in treating paranasal sinus SCNECs while Chemotherapy can be used in the adjuvant setting but in laryngeal tumours, radiotherapy and chemotherapy has served better role for laryngeal SCNECs.[13]

In our series, we used a radiation dose ranging from 50-60 Gy with good local control as compared to 60-70 Gy which has been accepted as standard protocol in other centers.[14-16] In the 1980s, surgery followed by radiotherapy was the routine approach to treat small cell tumours. Perez-Ordonez et al.[17] have emphasized the use of combined-modality therapy for these neoplasms. In the late 1990s, Fitzek et al.[18] and Bhattacharyya et al.[19] showed promising results of chemotherapy followed by radiation with surgery reserved for non-responders as treatment protocol for sinonasal neuroendocrine carcinomas. A few recent studies have shown that surgery as an initial treatment followed by postoperative chemo-radiotherapy is associated with better disease control and overall survival in treatment of sinonasal neuroendocrine carcinoma even in poorly differentiated small cell neuroendocrine carcinoma.

Conclusion

SNEC is a rare entity with strong propensity for loco-regional recurrence and distant metastasis. Surgery, if tumour is resectable with clear margins or radiotherapy otherwise should be the main modalities of treatment but chemotherapy has a role in an adjuvant setting. This study has its limitations due to small sample size as the disease is very rare and more studies need to be done for developing treatment guidelines.

Disclaimer: The study has been presented as a poster at Shaukat Khanum Memorial Cancer symposium held in 2015.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Consent: A written informed consent has been taken from the patient for the publication of this case report and any accompanying images. Approval was provided by the Institutional Review Board.

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