Case Report

Small cell neuroendocrine carcinoma of the paranasal sinus

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ABSTRACT

Small cell neuroendocrine carcinoma (SNEC) is an uncommon tumor. This tumor usually occurs in the lungs, the extra-pulmonary form accounts for only about 4% of all cases. Primary SNEC of the paranasal sinuses is extremely rare; only about 76 cases have been reported in literature. Unfortunately due to the rarity of this neoplasm, there are no specific recommendations pertaining to the management, treatment options are generally extrapolated from similar tumors of pulmonary origin. While Surgery was used in the past, upfront chemoradiation now seems to be evolving as the treatment of choice. We report a case of sinonasal SNEC who had undergone definitive concurrent chemoradiation and is currently disease-free for close to 2 years. The clinical presentation, imaging studies, histopathological diagnosis with immunohistochemistry correlation, management protocols, and a brief review of literature of this rare tumor is discussed.

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Introduction

Small cell neuroendocrine carcinoma (SNEC) is an uncommon tumor. This tumor usually occurs in the lungs and the extra-pulmonary form accounts for only 4% of all cases.[1] Primary SNEC of the paranasal sinuses is extremely rare and was first described by Ray Chowdhuri in 1965.[2] Since then, only about 76 cases have been reported in literature. Treatment approaches to these rare tumors has been controversial, with the trend changing from surgery in the past to chemoradiation. We report a case of sinonasal SNEC, who, despite having presented in an advanced stage, is currently free of disease.

Case Report

A 22-year-old female was referred to our center with a complaint of painless swelling on the left side of the face for 6 weeks duration. Extra-oral examination revealed the presence of an expansile swelling in the left maxillary region, extending into the peri-orbital region. There was stretching of the skin on the left face over the swelling. On intra-oral examination, a proliferative growth was noted in the left maxillary gingivo-buccal sulcus extending downwards till the level of the oral commissure [Figure 1a and b]. Computerized tomography (CT) scan demonstrated a large destructive soft tissue lesion in the left maxillary sinus with extensions into the left nasal cavity, ethmoid and sphenoid sinus, left alveolus, and hard palate. Extensions were also noted into the infra temporal fossa, soft tissues of the cheek, masticator spaces, and the inferior orbital fissure [Figure 1c and d]. An intra-oral biopsy of the lesion was done which on microscopy revealed a poorly differentiated neoplasm composed of monotonous sheets of small round blue cells with scanty cytoplasm and hyperchromatic nuclei, the cells were arranged in a rosettoid manner. The tumor cells were seen infiltrating the fibrocollagenous connective tissue with areas of necrosis; the mitotic activity was not clearly made out. Immunohistochemical profile showed tumor cell positivity for Epithelial Membrane Antigen (EMA), keratin, Neuron Specific Enolase (NSE), chromogranin, synaptophysin, and CD 57. The tumor cells were negative for vimentin, desmin, Leukocyte Common Antigen (LCA), CD 99, Human Melanoma Black (HMB 45), and Thyroid Transcription Factor-1 (TTF1). The tumor cells

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that showed strong nuclear positivity to Ki 67 was 50%. The final histopathology on immunohistochemistry correlation [Figures 2a-d and 3a-d] favored a diagnosis of SNEC. CT scan of the brain, thorax, and abdomen were normal. A bone marrow aspiration and biopsy did not show any atypical cells.

A combination of concurrent chemotherapy and radiotherapy was planned. The patient received a total of 60 Grey of external beam radiotherapy along with four cycles of concurrent cisplatin and etoposide. There was a clinical complete response, a post-therapy CT scan (after 6 months) showed only residual thickening of the left maxillary antrum. The patient did not wish to undergo any further investigations/biopsy to confirm remission; she is being followed up with a combination of clinical examination and imaging and is presently symptom-free with no evidence of recurrence for close to 2 years now [Figures 4a and b].

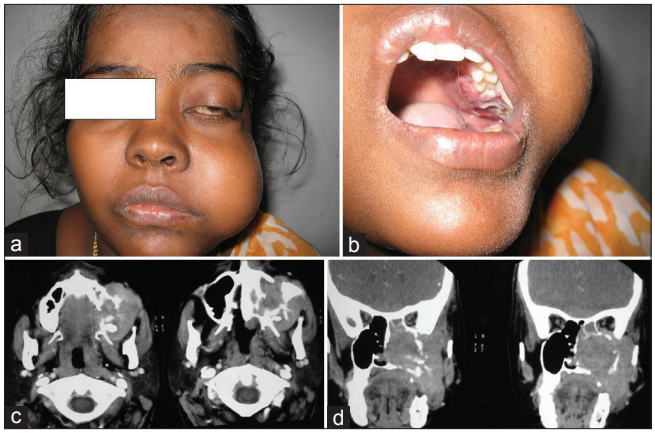

Figure 1: (a and b) Clinical photograph at presentation. (c, axial) and (d, coronal): CT scan showing a large destructive soft tissue lesion in the left maxillary sinus with extensions into the left nasal cavity, ethmoid and sphenoid sinus, left alveolus and hard palate. Extensions were also noted into the temporal fossa, soft tissues of the cheek, masticator spaces and inferior orbit

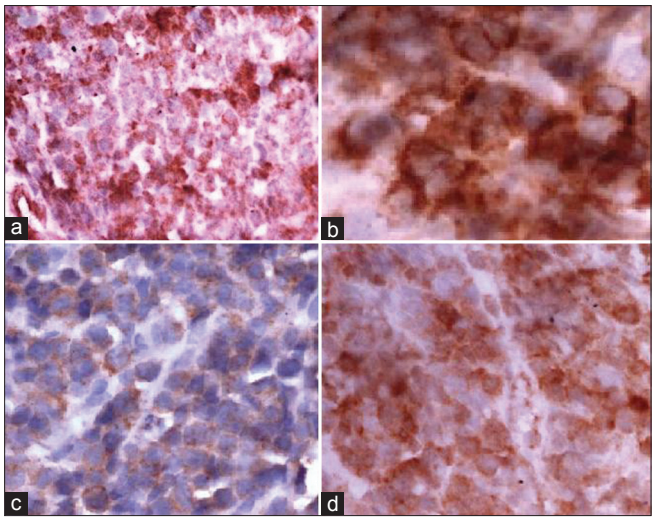

Figure 3: (a) Tumor cells showing immunopositivity to CD 57 (IHC, ×100). (b) Tumor cells showing immunopositivity to chromogranin (IHC, ×100). (c) Tumor cells showing immunopositivity to synaptophysin (IHC, ×100). (d) Tumor cells showing immunopositivity to NSE (IHC, ×100)

Discussion

Neuroendocrine carcinomas have been classified into from low grade to high grade into four types – carcinoid, atypical carcinoid, large cell neuroendocrine carcinomas, and SNECs.[3]

Extra-pulmonary primary small cell neuroendocrine carcinomas (EPSNECs) are uncommon malignant

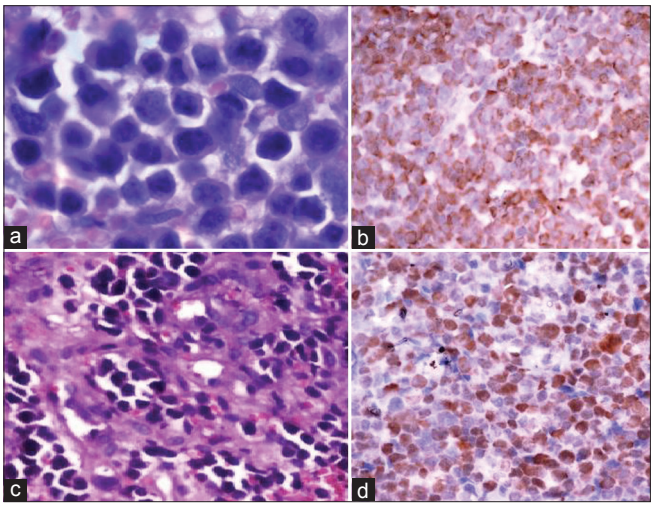

Figure 2: (a and c) Light microscopy showed the presence of bits of fibrocollagenous tissue infiltrated by small round cells with scanty cytoplasm and hyperchromatic nuclei. At places the cells were arranged in rosettoid manner. Mitotic activity was not well made out. (b) Tumor cells showing immunopositivity to keratin (IHC, ×100). (d) 50% of tumor cells showing nuclear positivity to Ki-67 (IHC, ×100)

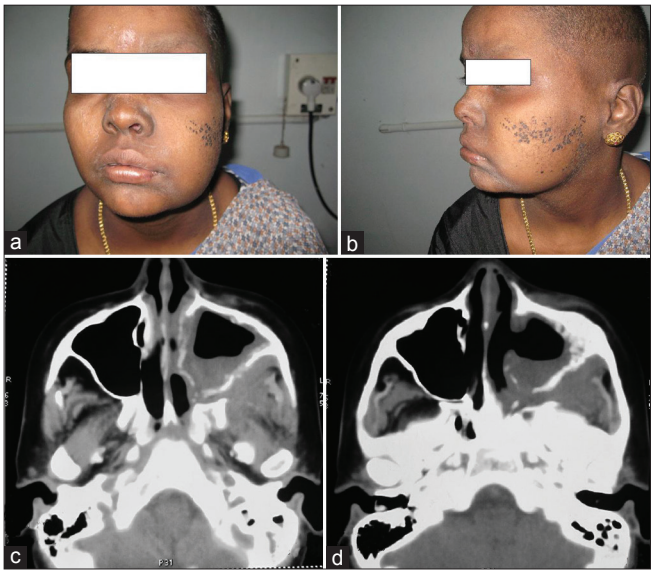

Figure 4: (a and b) Clinical photograph post-chemoradiation. (c and d) A post-therapy CT scan (after 6 months) showing only residual thickening of the left maxillary antrum

neoplasms, whereas primary sites documented may include esophagus, salivary glands, gastrointestinal tract (including small intestine and large intestine), pancreas, larynx, cervix uteri, uterus, urinary bladder, prostate, breast, and lacrimal gland. Primary sinonasal SNECs are extremely rare.

EPSNECs are thought to arise from a multi-potential stem cell. However, there is recent molecular evidence that small cell elements may arise as a late-stage phenomenon in the genetic progression of more organ-typical carcinomas. The morphologic, immunohistochemical, and ultra structural features are similar to those described in pulmonary SNECs. SNEC is a histological sub-type among a broad group of sinonasal malignancies together known as sinonasal neuroendocrine tumors. Other sub-types include sinonasal undifferentiated carcinoma and esthesioneuroblastoma.

The initial presentation of nasal obstruction, nasal discharge, and recurrent epistaxis is practically indistinguishable from that of more benign diseases and hence is likely to result in delay in presentation. Occasionally, the presenting complaint may be swelling of the maxilla and expohthalmos. The aggressiveness coupled with the complex anatomy of this region, ensures that most patients present in an advanced stage of disease. The association between the paraneoplastic endocrine syndrome and SNEC is well documented. However, review of literature showed only in five cases of SNECs of nasal and paranasal sinuses with endocrine syndromes.[4] Our patient did not have any endocrine syndrome.

Diagnosis by histological examination is challenging. It is indistinguishable from its pulmonary counterpart. Both consist of small-sized cells arranged in sheets, nests, or cords, with moderate to scanty cytoplasm and hyperchromatic nuclei. It is important to differentiate this tumor from olfactory neuroblastoma, which is a low grade tumor. Definitive diagnosis is made by correlation with immunohistochemistry and/or electron microscopy.[5,6]

Unfortunately due to the rarity of this neoplasm, there is no specific recommendation on management guidelines, treatment options are generally extrapolated from similar tumors of pulmonary origin. Treatment approaches to this aggressive tumor has varied over the years. Previously, surgery followed by radiotherapy or chemotherapy was preferred.[7,8] In general, these patients usually present in advanced stages, surgery can be extremely disfiguring and may not be curative. Chemotherapy using cisplatin and etoposide followed by high dose proton-photon radiotherapy has been proven by some authors to be an effective line of treatment.[9,10] Surgery is now reserved for non-responders. Despite presenting in an advanced stage, our patient responded well to a standard combination of chemotherapy and radiotherapy and continues to be in remission.

SNECs are aggressive tumors with high potential for local invasion as well as distant metastasis. As most patients present in advanced stages, the prognosis is extremely poor. A recent review of literature by Han *et al*.[7] stated that local recurrence rate was 33% and rate of distant metastasis was 31%. Metastatic deposits occur in the brain, bones, lungs, and skin. The 1 and 5-year survival rates were about 57% and 10%, respectively.

Our understanding of the disease biology is evolving; clearly more extensive studies are required to assess malignant potential and to better device personalized treatments for this rare but aggressive tumor.

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