CLINICAL REPORT

Small Cell Neuroendocrine Carcinoma: A Rare Nasopharyngeal Malignancy with Aggressive Clinical Course

Nishu Bhardwaj¹ · Aanchal Kakkar¹ · David Victor Kumar Irugu²

Received: 18 March 2018 / Accepted: 4 April 2018 / Published online: 12 April 2018
© Association of Otolaryngologists of India 2018

Abstract Primary small cell neuroendocrine carcinoma is uncommon in head and neck region, with occasional cases in nasopharynx. Distinction from other round cell tumors is imperative to ensure optimal patient management. We present a case of a 30-year-old woman who presented with a rapidly growing nasopharyngeal mass.

Keywords Small cell carcinoma · Nasopharynx · Immunohistochemistry

Introduction

Small cell neuroendocrine carcinoma (SmNEC) is a distinct malignant neoplasm, most frequently arising in the lung. Extrapulmonary SmNECs account for approximately 5% of all SmNECs, and have been reported at various sites such as esophagus, and pancreas [1, 2]. In the head and neck, sporadic cases have been reported in larynx, and salivary glands [3]. SmNEC of nasopharynx is exceedingly rare, with only fourteen cases reported in literature (Table 1). Distinction of SmNEC from other small round cell tumors found here is vital, as they have a dismal clinical course and poor response to therapy; however, this is often a challenge due to overlapping pathology features [4]. We present a case of SmNEC presenting as a

nasopharyngeal mass, and discuss the differential diagnoses.

Case Report

A 30-year-old female presented with complaints of nasal obstruction for 4 months, and few episodes of epistaxis. On examination, a 6 × 5 cm mass was seen in the nasopharynx. Imaging showed an expansile, heterogeneous mass along the posterior nasopharyngeal wall, extending inferiorly into the oropharynx, anteriorly into the nasal cavity, and infiltrating the hard palate. Cystic spaces denoting necrosis were also seen. A biopsy was taken from the hard palate, following which the patient did not return to OPD. Three months later, she presented with increase in size of the mass, a new swelling on right side of neck which was associated with pain, hoarseness of voice, and difficulty in swallowing. On examination, the primary tumor had increased in size, and enlarged level II, III and IV cervical lymph nodes were identified. A second biopsy was performed from the nasopharyngeal mass. Microscopically, although the first biopsy was small, both biopsies showed similar morphological features (Figs. 1, 2). The tumor was composed of nests of small round cells, with large areas of necrosis, and marked crushing. Tumor cells had scant cytoplasm, hyperchromatic nuclei with stippled chromatin, and inconspicuous nuclei. Nuclear molding was noted. Many interspersed neutrophils were seen. Foci of perineural infiltration were identified.

On immunohistochemistry (IHC), the first biopsy (Fig. 1d–f) showed focal granular positivity for pancytokeratin (CK), while it was negative for leukocyte common antigen (LCA), chromogranin and synaptophysin. Further IHC could not be performed as the tumor tissue was

✉ Aanchal Kakkar
aanchalkakkar@gmail.com

¹ Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

² Department of Otorhinolaryngology and Head and Neck Surgery, All India Institute of Medical Sciences, New Delhi, India

Table 1 Reported cases of nasopharyngeal small cell carcinoma

No.	Authors	Age/sex	Treatment received	Follow-up
1	Galera-Ruiz et al. [19]	48 years/ female	Three biopsies followed by chemoradiotherapy	PD; DOD 4 months after completion of treatment
2	Lin et al. [1]	43 years/male	Chemoradiotherapy	CR, followed by PD (lymph node and lung metastases) after 6 months; DOD at 38 months
3	Mohebbi et al. [22]	74 years/ female	Complete resection followed by chemotherapy	CR; NED at 18 months
4	Deviprasad et al. [7]	40 years/male	Surgery	Local recurrence at 6 months; DOD at 11 months
5	Hatoum et al. [23]	66 years/ female	Chemoradiotherapy	Local recurrence; DOD at 15.2 months
6	Hatoum et al. [23]	80 years/male	Chemoradiotherapy	NED at 5.4 months
7	Lee et al. [16]	41 years/male	Chemoradiotherapy	CR; NED at 9 months
8	Subha et al. [9]	51 years/male	Radiotherapy	CR; local, nodal recurrence and liver metastases; DOD at 2 months
9	Shunyu et al. [2]	52 years/male	Not available	Not available
10	Nandi et al. [12]	5 years/male	Chemotherapy followed by radiotherapy	PR; brain metastasis at 3 months; AWD at 17 months on palliative treatment
11	Aguiar et al. [4]	43 years/ female	Chemoradiotherapy	Persistent disease; AWD at 10 months
12	Takahashi et al. [18]	54 years/male	Chemoradiotherapy	CR; Brain metastasis at 18 months, treated by STR, local RT, chemotherapy; recurrence of brain metastasis, spinal cord metastasis treated with palliative RT; DOD at 32 months
13	Azevedo et al. [24]	54 years/male	Chemoradiotherapy	NED at 6 months
14	Bellahammou et al. [3]	46 years/ female	Chemotherapy	DOD after third course of chemotherapy
15	Present case	30 years/ female	Two biopsies	DOD before treatment initiation

AWD alive with disease, CR complete remission, DOD dead of disease, NED no evidence of disease, PD progressive disease, PR partial remission, RT radiotherapy, STR sub-total resection

exhausted, and a diagnosis of poorly differentiated carcinoma was made. The second biopsy (Fig. 2d–f) revealed immunopositivity for CD56, CK, and chromogranin (focal); synaptophysin and p40 were negative. Ki-67 labelling index was high (90%). A diagnosis of SmNEC of the nasopharynx was made. However, the patient's condition deteriorated due to rapid progression of disease, and she expired before treatment could be initiated.

Discussion

Neuroendocrine carcinomas (NECs) of the head and neck can be classified into well-differentiated NEC (carcinoid), moderately-differentiated NEC (atypical carcinoid), and poorly-differentiated NECs, the latter being divided further into small cell and large cell neuroendocrine carcinomas

[5, 6]. The cell of origin of these tumors remains a subject for debate, with one hypothesis being that they arise from the cells of the dispersed neuroendocrine system, while another group believes that these tumors originate from pluripotent stem cells capable of dual epithelial and endocrine differentiation [7, 8].

SmNEC is infrequently encountered in extrapulmonary locations. In head and neck region, larynx is the most common site (0.5–1% of carcinomas), followed by salivary glands [3, 9]. Neuroendocrine tumors of the nasopharynx are extremely infrequent, and primary nasopharyngeal SmNEC remains a rare entity [10]. Majority of patients present in 5th–6th decades; occasional cases have been reported in younger patients, including in children [11]. Clinical presentation is non-specific, resembling other malignancies of this region. Common symptoms include nasal obstruction, rhinorrhea and epistaxis, with some

Fig. 1 Biopsy from the hard palate shows an infiltrating small round cell tumor (**a** HE, $\times 100$) whose cells have scant cytoplasm, and hyperchromatic nuclei with focal nuclear molding (arrows) (**b** HE, $\times 400$); perineural infiltration was present (**c** HE, $\times 200$).

Immunohistochemistry shows dot-like cytokeratin positivity (**d** IHC, $\times 400$) while chromogranin (**e** IHC, $\times 200$) is negative. Ki-67 labelling index is moderately high (**f** IHC, $\times 400$)

Fig. 2 Second biopsy shows a tumor beneath the nasal mucosal lining (**a** HE, $\times 100$) which is infiltrating the underlying bone (**b** HE, $\times 200$) and has histomorphological features similar to the previous

biopsy (**c** HE, $\times 400$). Diffuse cytokeratin (**d** IHC, $\times 200$), and focal chromogranin (**e** IHC, $\times 400$) and CD56 positivity (**f** IHC, $\times 200$) is seen

patients presenting with symptoms of local invasion such as hearing loss, tinnitus, exophthalmos, and restricted eye movements [10]. Paraneoplastic syndromes may also be associated, due to the secretion of various hormones [10]. SmNEC may occur as a second malignancy after radiotherapy for nasopharyngeal carcinoma [12]. Metastases to neck nodes have been reported in only few cases [11–13]. Our patient presented with nasal obstruction and epistaxis, and developed cervical lymphadenopathy rapidly in the course of the disease.

Histopathological diagnosis remains a challenge due to the overlapping morphological features with other small round cell tumors. Differential diagnosis includes nasopharyngeal carcinoma (NPC), basaloid squamous cell carcinoma (BSCC), ONB, malignant melanoma, rhabdomyosarcoma, malignant lymphoma, Ewing sarcoma, and SmNEC [14]. Immunohistochemistry plays an important part in distinguishing these entities which differ in their management and prognosis. Chapman-Fredricks et al. [15] found that CK alone could narrow down the diagnostic possibilities among nasopharyngeal malignancies by excluding melanoma, rhabdomyosarcoma and lymphoma. For epithelial tumors, this distinction was more difficult. However, a limited panel including CK (positive in all epithelial tumors, with dot-like positivity in SmNEC), CK5/6 (positive in NPC and BSCC; negative in SmNEC), p63 (positive in all epithelial tumors except SmNEC), and HLA-DR (positive in NPC), could discriminate between most cases. While staining with neuroendocrine markers helps identify SmNEC, it is often focal or of weak intensity, and may even be negative, as in the first biopsy from our patient [13, 15, 16]. In the second biopsy also, staining for neuroendocrine markers CD56 and chromogranin was seen only focally, and synaptophysin was completely negative. Another important differential diagnosis is the recently described NUT midline carcinoma (NMC), which frequently occurs in head and neck [17]. NMC shows strong nuclear positivity with p40 and NUT, aiding in its distinction. Lastly, another hurdle to arriving at the diagnosis of SmNEC is the paucity of viable tumor tissue in small biopsies, resulting in multiple biopsies being required before a final diagnosis is made. Unlike NPC, no convincing evidence establishing the pathogenetic role of Epstein Barr virus (EBV) in nasopharyngeal NECs has been found, suggesting that EBV EBER-ISH detection may be valuable in distinguishing SmNEC from NPC [16].

Owing to the scarcity of reported cases, no definite treatment protocols exist for nasopharyngeal SmNEC at present. Due to their aggressiveness, most patients require a combination of therapeutic modalities [18]. Surgery followed by chemo-radiotherapy achieved a better response than chemo-radiotherapy alone [19]. Initial complete

response to chemo-radiation, however, has been reported to be followed by development of distant metastasis [18].

Like its pulmonary counterpart, nasopharyngeal SmNEC behaves aggressively, and despite early detection and initial response to treatment, has poor prognosis [3, 16]. Mean survival for head and neck SmNEC is 14.5 months with estimated 5-year-survival rate being 13% [20]. Nasopharyngeal SmNEC has the shortest overall survival among all head and neck locations, with median survival of 15.1 months, as compared to 36.4 months for nasal cavity SmNECs [21]. Overall survival is significantly shorter for head and neck SmNEC patients with nodal involvement, averaging at 20.8 versus 43.9 months in those without lymph node disease [21].

Thus, SmNEC of the nasopharynx is a rare entity with an aggressive clinical course. Careful morphological evaluation and immunohistochemistry play a central role in diagnosing this neoplasm. Proper diagnostic criteria and treatment protocols need to be established to detect cases at an early stage and manage them appropriately, in order to limit morbidity and mortality.

Compliance with Ethical Standards

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

Ethical Approval This article is a case report and does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent was obtained from the patient included in the study.

References

1. Lin IH, Hwang CF, Huang HY (2007) Small cell carcinoma of the nasopharynx. *Acta Otolaryngol* 127:206–208
2. Shunyu N, Lynrah Z, Goyal A, Raphal V (2012) Small-cell neuroendocrine carcinoma of nasopharynx. *Clin Rhinol Int J* 5:130–131
3. Bellahammou K, Lakhdissi A, Akkar O, Kouhen F, Rais F, Dahraoui S, M'rabti H, Errihani H (2017) Small-cell neuroendocrine carcinoma of nasopharynx: a case report. *IJSM* 3:132–135
4. Aguiar A, Jacome M, Azevedo I, Monteiro E, Castro V (2015) Small-Cell neuroendocrine carcinoma originating from the nasopharynx: report of a rare case. *Rep Radiother Oncol* 2:E3814
5. Perez-Ordóñez B, Bishop JA, Gnepp DR, Hunt JL, Thompson LDR (2017) Neuroendocrine tumours. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ (eds) WHO classification of head and neck tumours. IARC, Lyon, pp 95–98
6. Mills SE (2002) Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. *Mod Pathol* 15:264–278
7. Deviprasad S, Rajeshwari A, Tahir M, Adarsha T, Gangadhara S (2008) Small cell neuroendocrine carcinoma originating from the lateral nasopharyngeal wall. *Ear Nose Throat J* 87:E1–E3

8. Wenig BL, Gnepp DR (1989) The spectrum of neuroendocrine carcinomas of the larynx. *Semin Diagn Pathol* 6:329–350
9. Subha S (2011) Neuroendocrine carcinoma of the nasopharynx: a case report. *Med Health Sci* 9:101–103
10. Mineta H, Miura K, Takebayashi S (2001) Immunohistochemical analysis of small cell carcinoma of the head and neck: a report of 4 patients and a review of sixteen patients in the literature with ectopic hormone production. *Ann Otol Rhinol Laryngol* 110:76–82
11. Nandi M, Arun I, Bhattacharya A, Sen S, Ray S, Mallick I (2014) Reporting of a primary sinonasal neuroendocrine small cell carcinoma in the paediatric age group. *Head Neck Oncol* 6:5
12. Chen C, Hsu M (2000) Second primary epithelial malignancy of nasopharynx and nasal cavity after successful curative radiation therapy of nasopharyngeal carcinoma. *Hum Pathol* 31:227–232
13. Sturgis C, Burkey B, Momin S, Hoschar A (2015) High grade (large cell) neuroendocrine carcinoma of the nasopharynx: novel case report with touch preparation cytology and positive EBV encoded early RNA. *Case Rep Pathol* 2015. <https://doi.org/10.1155/2015/231070>
14. Serrano MF, El-Mofty SK, Gnepp DR (2008) Utility of high molecular weight cytokeratins, but not p63, in the differential diagnosis of neuroendocrine and basaloid carcinomas of the head and neck. *Hum Pathol* 39:591–598
15. Chapman-Fredricks J, Jorda M, Gomez Fernandez C (2009) A limited Immunohistochemical panel helps differentiate small cell epithelial malignancies of the sinonasal cavity and nasopharynx. *Appl Immunohistochem Mol Morphol* 17:207–210
16. Lee LY, Chang KP, Hsu CL, Chen TC, Kuo TT (2011) Small-cell neuroendocrine carcinoma of the nasopharynx: report of a rare case lacking association with Epstein–Barr virus. *Int J Surg Pathol* 19:199–202
17. Kakkar A, Antony VM, Irugu DVK, Adhikari N, Jain D (2017) NUT midline carcinoma: a series of five cases, including one with unusual clinical course. *Head Neck Pathol*. <https://doi.org/10.1007/s12105-017-0858-2>
18. Takahashi S, Miyashita T, Hoshikawa H, Haba R, Togami T, Shibata T (2015) Accelerated hyperfractionated radiotherapy for small cell carcinoma of the nasopharynx. *Head Neck* 37:E63–E65
19. Galera-Ruiz H, Villar-Rodriguez JL, Sanchez-Calzado JA (2001) Sinonasal neuroendocrine carcinoma presenting as a nasopharyngeal mass. *Otolaryngol Head Neck Surg* 124:475–476
20. Galanis E, Frytak S, Lloyd RV (1997) Extrapulmonary small cell carcinoma. *Cancer* 79(1729–3):6
21. Pointer KB, Ko HC, Brower JV, Witek ME, Kimple RJ, Lloyd RV, Harari PM, Baschnagel AM (2017) Small cell carcinoma of the head and neck: an analysis of the National Cancer Database. *Oral Oncol* 69:92–98
22. Mohebbi A, Daneshi A, Emami AR (2008) Nasopharyngeal neuroendocrine carcinoma: A case report. *Ear Nose Throat J* 87:E4
23. Hatoum GF, Patton B, Takita C (2009) Small cell carcinoma of the head and neck: the university of Miami experience. *Int J Radiat Oncol Biol Phys* 74:477–481
24. Azevedo D, Rios E, Vendeira L, Sarmiento C (2017) Small cell neuroendocrine carcinoma of the nasopharynx: a rare case report. *Autopsy Case Rep* 7:31–35