Moderately Differentiated Neuroendocrine Carcinoma (Atypical Carcinoid) of the Parotid Gland: Report of Three Cases with Contemporary Review of Salivary Neuroendocrine Carcinomas

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Abstract Primary neuroendocrine carcinomas (NECs) of the salivary glands are rare. Most reported NECs in that region are small cell carcinomas with few cases of large cell undifferentiated carcinoma and typical carcinoid tumors. Only two moderately differentiated NECs (atypical carcinoid tumors) have been previously reported. In the current series, the authors report three additional moderately differentiated NECs (atypical carcinoid tumors) of the parotid gland; two occurred in women and one in a man. All patients were initially treated with parotidectomy, with selective lymph node excision in one, and radiation therapy in another. Follow-up was available for two cases (18 and 79 months). One patient had two local recurrences, developing lymph node and liver metastases requiring further surgery and chemotherapy. Currently, she is alive with disease, on supportive care. The second patient is alive with no signs of recurrence. Patients' work-up excluded the possibility of metastatic NECs to the salivary glands in all cases. Histologically, the tumors demonstrated infiltrating nests, cords and trabeculae of round, oval to

spindle shaped cells with moderate to focally abundant eosinophilic cytoplasm, small to prominent nucleoli and chromatin stippling. Scattered rosette-like structures were prominent in one tumor. The highest mitotic counts for the three tumors ranged from 5 to 8 mitotic figures/10hpf. Necrosis, focal but distinct, was noted in two tumors, vascular invasion in two tumors and perineural invasion in one tumor. Immunohistochemical staining was diagnostic of neuroendocrine carcinoma, showing uniform positive labeling with broad-spectrum cytokeratin (with a paranuclear punctuate pattern in one case), chromogranin and synaptophysin antibodies. CK20 was negative in two tumors and stained rare cells (<1 %) in the third.

Keywords Salivary gland · Neuroendocrine carcinoma · Atypical carcinoid tumor · Neuroendocrine tumor

Introduction

Neuroendocrine carcinomas (NEC) represent a diverse group of malignant epithelial neuroendocrine neoplasms, ranging from well differentiated to high-grade neoplasms [1–4]. The classification of neuroendocrine tumors has dynamically evolved with various opinions and in different directions, in different parts of the body including the gastrointestinal tract, pancreas, head and neck, skin and lung. The latter is important since many clinicians use the pulmonary World Health Organization (WHO) classification to classify extrapulmonary neuroendocrine carcinomas. The current WHO recognizes 4 major types of lung neuroendocrine tumors based on mitotic rate and the extent of necrosis, namely typical carcinoid, atypical carcinoid, small cell carcinoma and large cell neuroendocrine carcinoma [5]. The recognition of the various subtypes is of

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prognostic and therapeutic significance. The occurrence of neuroendocrine carcinoma in the head and neck area, including the salivary glands, is rare but well documented [1, 2, 6–13]. In the major salivary glands, these tumors are predominantly undifferentiated carcinomas [1, 8–11] and are usually defined as either small cell (SmCC) or large cell undifferentiated carcinomas (LCC) [1, 3, 8]. While well differentiated and poorly differentiated NEC have been previously described in this region, [14] only two examples of moderately differentiated salivary gland NEC have been documented to date [1, 15].

Considerable debate exists regarding the best practical approach when classifying these tumors in the head and neck area. Lewis et al. [16] recently reviewed the currently proposed/utilized classification systems for head and neck neuroendocrine carcinomas. Various terms have been used ranging from carcinoid, atypical carcinoid and small cell carcinoma to grade 1–3 NEC to well to poorly differentiated NEC. In the recent WHO classification of Head and Neck Tumors a 3-tiered system was utilized: typical carcinoid, atypical carcinoid and small cell carcinoma [17]. Since publication of the WHO classification, several papers have been published confirming the occurrence of a large cell variant of NEC in the head and neck area including the larynx [1, 3]. The authors in the current series have elected to utilize a 4 tiered system, similar to that in current use in the lung, although we prefer the synonymous terminology of well differentiated NEC = carcinoid tumor; moderately differentiated NEC = atypical carcinoid tumor; poorly differentiated NEC, small cell type = small cell carcinoma and poorly differentiated NEC, large cell type = large cell NEC as previously suggested [18].

Recently the WHO recommended a new classification system for gastrointestinal NEC in 2010 [19]. This classification has three grades based on tumor proliferation that were separated into two groups: well differentiated neuroendocrine tumors and the poorly differentiated neuroendocrine carcinomas. The former category was further divided into 2 subgroups with tumors having a proliferative index of <2 % (or mitotic counts of <2 per 10 high power fields; 1hpf = 2 mm²) classified as grade 1, which were equated with carcinoid tumor and those with proliferative indices ranging from 2 to 20 % (or mitotic counts of 2–20 per 10 high power fields) classified as grade 2 well differentiated neuroendocrine tumors; the grade 3 NEC had proliferative indices of >20 % (or mitotic counts of >20 per 10 high power fields) and were subclassified as large cell or small cell types. Using this system, the current cases would be classified as grade 2 neuroendocrine tumors. However, whether or not this classification scheme can be applied to head and neck NEC has yet to be determined. Therefore, we have utilized the pulmonary grading system as indicated previously.

This series reports three additional patients with primary salivary gland moderately differentiated neuroendocrine carcinomas, where the histomorphologic and immunohistochemical features are equivalent to atypical carcinoid tumor of pulmonary origin. The criteria used for pulmonary atypical carcinoid tumor, “A tumor with carcinoid morphology with 2–10 mitoses per 2 mm² (10 hpf) or necrosis (often punctate)” was utilized in this series [5].

Case Reports

Case 1

A 59 year old male presented with an asymptomatic right parotid gland swelling present for unknown duration. Past medical history was unremarkable. The patient underwent CT scan of the head and neck, which revealed a right parotid gland mass approximately 2 cm in greatest dimensions (the images were not available for review). Following a thorough metastatic workup, the patient underwent right parotidectomy and modified radical neck dissection as well as the right spinal accessory nerve and ipsilateral anterior triangle dissection.

Pathology

Grossly, the parotidectomy revealed a poorly circumscribed, yellow-orange mass that measured 1.3 cm in greatest dimension. Histomorphologically, this case displayed prominent nesting with areas displaying an organoid pattern, focal ductal differentiation, and markedly infiltrative growth with intraparotid and extraparotid lymph node involvement. Tumor cells exhibited slight nuclear pleomorphism, a moderate amount of eosinophilic cytoplasm, vesicular chromatin with nuclear clearing and prominent nucleoli. The maximum mitotic count was 6/10 high power fields and focal necrosis was noted. Vascular invasion was also present (Fig. 1); perineural invasion was not noted.

Immunohistochemical staining confirmed the neuroendocrine derivation with staining using cytokeratin cocktail AE1/AE3 (1:100 dilution, DAKO TRS) (showing a paranuclear punctate pattern (Fig. 2a1) and variable positive staining with chromogranin A (Fig. 2b1) (1:15 dilution, DAKO Cytomation, Carpinteria, CA, USA) and diffuse staining with synaptophysin (Fig. 2c1) (1:75 dilution, DAKO TRS), respectively. The tumor did not stain with Calponin (Ventana; predilute), Smooth Muscle Actin (Ventana; predilute) or Cytokeratin 20 (Ventana; predilute).

A thorough clinical and radiographic work-up excluded the presence of any tumors elsewhere, confirming the

Fig. 1 The tumor cells in case 1 demonstrated marked nesting with an organoid growth pattern with focal ductal differentiation. The cells also demonstrated slight nuclear pleomorphism, a moderate amount of eosinophilic cytoplasm, vesicular chromatin, prominent nucleoli, and up to 6 mitotic figures/10 HPF (arrow). Vascular invasion was also identified (insert). (Hematoxylin and eosin stain, original magnification $\times 100$, Insert $\times 40$)

diagnosis of primary salivary gland disease. The patient was followed briefly postoperatively but was lost to follow-up thereafter.

Case 2

A 57-year-old female presented with a painful tender right parotid gland swelling of approximately 6 months duration. Past medical history was non-contributory. The patient underwent advanced imaging of the head and neck, which revealed a right parotid gland mass approximately 1 cm in greatest dimension (the images were not available for review). Following a thorough multidisciplinary metastatic workup, the patient underwent a superficial parotidectomy, followed by an abbreviated course of radiotherapy.

Grossly, the excision demonstrated a well-circumscribed homogeneous, grey-tan mass measuring 1.0 cm in greatest dimension. Histomorphologic examination revealed a locally infiltrating neoplasm predominantly composed of spindle-shaped to polygonal cells, forming trabeculae, cords and rosette-like structures. The tumor cells had moderate to abundant cytoplasm with moderate nuclear pleomorphism, fine stippled chromatin and small nucleoli (Fig. 3). A maximum of five mitotic figures/10 high power fields was identified. Necrosis, neural or vascular invasion were not noted.

Immunohistochemistry staining of this case also confirmed its neuroendocrine derivation, showing diffuse positive staining with cytokeratin cocktail AE1/AE3 (Fig. 2a2) and diffuse positive staining with chromogranin A (Fig. 2b2)

Fig. 2 Immunohistochemistry staining of cases 1–3 showing characteristic paranuclear dot staining with cytokeratin in case 1 (a1) and areas with diffuse staining with cytokeratin in cases 2 {a2} and 3 {a3}, respectively. Tumor cells from all 3 cases reacted positively

with chromogranin (cases1 {b1}, 2 {b2} and 3 {b3}). Similarly, strong and diffuse positive staining with synaptophysin was seen in cases 1{c1}, 2 {c2}, and 3 {c3}, respectively

Fig. 3 The tumor cells in case 2 were predominantly organized in spindle and trabecular patterns. The cells have moderate to abundant amounts of cytoplasm and nuclei showed moderate pleomorphism with mitosis (arrow). Rosette-like structures were also appreciated (insert). (Hematoxylin and eosin stain, original magnification $\times 100$, Insert $\times 20$)

and synaptophysin (Fig. 2c2), respectively. Additionally, the tumor reacted negatively with Calponin, Smooth Muscle Actin, anti-S-100 protein and Cytokeratin 20.

A thorough clinical and radiographic workup did not show evidence of any other tumors, confirming the diagnosis of primary neuroendocrine carcinoma of the salivary glands. On post-operative follow-up, the patient presented with local recurrence at 2 years 10 months, which required a modified radical neck dissection and adjuvant carboplatin therapy. She was well until 2 years 4 months later, when she presented with a second local recurrence. Metastasis to the liver was found, requiring further treatment with cisplatin, VP-16, temozolomide, thalidomide, and Alimta, with disease progression. The patient was alive with disease, on supportive care, after follow-up of 6 years 7 months.

Case 3

An 82-year-old female presented with a painful tender right parotid gland swelling of approximately 6 months duration. A CT scan of the neck (Fig. 4) demonstrated an enhancing oval mass arising from the inferior aspect of the deep lobe of the parotid gland extending medially into the parapharyngeal space. The intratumoral enhancement pattern was somewhat heterogeneous, suggesting areas of central necrosis.

The patient was treated with a total parotidectomy. Grossly, the tumor consisted of a well-demarcated, pear-shaped, tan firm mass, measuring 5.5 cm $\times$ 2.0 cm in greatest dimension. Histomorphologic examination displayed an infiltrative growth pattern with prominent necrosis (Fig. 5). Tumor cells were arranged in solid cords

and nests with moderate amounts of eosinophilic cytoplasm, moderate nuclear pleomorphism with stippled chromatin and prominent nucleoli. Vascular and perineural invasion were evident and the highest mitotic count = 8 per 10 high power fields (Fig. 5b). Focal necrosis was also noted.

Immunohistochemistry staining showed similar results to the first 2 cases (Fig. 2a3–c3). Diffuse strong positive staining with cytokeratin cocktail AE1/AE3, chromogranin A and synaptophysin was seen. This tumor did not stain with Calponin and CK20 [with the exception of rare positive cytoplasmic staining of single cells (<1 %)]. Similarly, Smooth Muscle Actin and anti-S-100 protein did not stain the tumor.

A thorough clinical and radiographic work-up did not show evidence of another primary or metastatic disease, confirming the diagnosis of a primary salivary gland neuroendocrine carcinoma. The patient was alive, with no evidence of disease after 4 years of follow-up.

Discussion

Collectively, tumors of the neuroendocrine system are comprised of heterogeneous entities that vary in origin, nomenclature, classification, location, histological appearance, degree of differentiation, biological behavior, and functional activity, but share certain immunohistochemical and ultrastructural characteristics [20–22]. While some authorities favored a classification based on tumors' histogenesis, others relied on functional activity with less emphasis on the biological behavior and anatomic location [21, 22]. Meacham et al. [23] have extensively reviewed primary head and neck neuroendocrine carcinomas, noting the prevalence of these tumors for the parotid, paranasal sinuses and supraglottic regions. Previous reports highlighted the predominance of head and neck moderately differentiated neuroendocrine carcinomas (atypical carcinoids) in the larynx [2].

Salivary SmCCs are the most frequent type of salivary gland neuroendocrine carcinoma. They are rare and constitute 2.8 [24] and 1.85 % [9] of all major and minor salivary gland tumors, respectively. Histologically, these high-grade neoplasms are composed of sheets, ribbons, or nests of round, oval to fusiform cells measuring as large as or larger than (up to 2 times) lymphocyte diameter (normal small lymphocytes average 7–9 μ m in diameter). The cells are characterized by ill-defined cell boundaries, little eosinophilic cytoplasm and pyknotic nuclei with fine evenly distributed to clumped chromatin. Nuclear molding and crush artifact were also frequently observed. Nucleoli may be inconspicuous or even absent and mitotic figures are abundant, averaging 10 mitotic figures per 10 high

Fig. 4 Axial images from a contrast enhanced CT scan of the neck in case 3 (**a** is slightly cephalad to **b**), showing an enhancing oval mass arising from the inferior aspect of the deep lobe of the parotid gland (arrows) and extending medially into the parapharyngeal space,

bordered posteriorly by the sternocleidomastoid muscle and anteriorly by the mandible, with mass effect on the retromandibular vein. The intratumoral enhancement pattern is somewhat heterogeneous, suggesting areas of central necrosis

power fields [25]. Ductal differentiation [3, 17, 26], skeletal muscle differentiation [27], and squamous differentiation [28, 29], as well as the coexistence of conventional squamous and small-cell carcinomas may also be identified [24, 28, 29]. Additionally, vascular and perineural invasion are common findings. The tumor cells stain positively with broad-spectrum cytokeratin and they often display the characteristic punctate paranuclear dot staining [8, 28–31]. A major percentage of these tumors will also react with cytokeratins 7 and 20, respectively [25, 30, 32, 33]. These tumors will stain for one or more neuroendocrine markers [synaptophysin, chromogranin and CD56 neural cell adhesion molecule (NCAM)]. The majority of tumors also react positively with epithelial membrane antigen (EMA) [9] and neuron specific enolase (NSE) [25]. SmCC may also stain with neurofilament and CD57 (Leu-7) [25].

When compared to the SmCC, large cell undifferentiated carcinomas (LCC) are rare, comprising <1 % of malignant salivary gland malignancies [1, 3, 10, 11, 34–37]. The parotid gland is much more frequently involved than the minor salivary glands [10, 31, 37–39]. Patient's ages range from nine to 96 years with no racial predilection reported [40, 41]. Histologically, tumor cells demonstrate sheets, trabeculae or cords of large pleomorphic, polygonal or fusiform cells measuring >30 μ in diameter. The tumor cells have a well-defined cell border, abundant eosinophilic cytoplasm, and vesicular, round or fusiform nuclei with prominent nucleoli and coarse to

vesicular chromatin. Brisk mitotic activity is often seen which may exceed 15/10 high power fields. Perineural and/or vascular invasion and necrosis are frequently encountered as well [11, 42, 43]. Tumor cells may occasionally appear dyscohesive simulating a lymphoma. Spindle and anaplastic, bizarre or osteoclastic-like tumor giant cells with poorly formed ducts may be also identified [8, 43, 44]. Neuroendocrine differentiation is detected in a small percentage of LCC and is predominantly based on the occasional identification of neurosecretory granules ultrastructurally [10, 32, 38, 39] or by positive immunohistochemistry staining with one of the neuroendocrine markers such as chromogranin A, synaptophysin, CD57 and CD56 [32–45]. Typically, tumor cells do not stain with CK20, but show diffuse labeling with bcl-2 protein, p53, epidermal growth factor, Cyclin D1, EMA and carcinoembryonic antigen and greater than 50 % labeling with Ki-67 also may be detected [12, 32, 45, 46].

Well differentiated neuroendocrine carcinomas are extremely rare in the head and neck region [46–49]. Histomorphologically, these tumors demonstrate low-grade features where cells aggregate in cords and nests, with more cellular uniformity, more recognizable organoid to trabecular growth patterns, abundant eosinophilic cytoplasm and less cytologic atypia when compared to other types of neuroendocrine carcinoma. The cells exhibit a characteristic salt-and-pepper chromatin pattern; however, mitotic figures, pleomorphism, and necrosis are characteristically absent

Fig. 5 **a** A low power photomicrograph of case 3 showing lobules of small round blue tumor with prominent connective tissue necrosis identified in the background (*arrows*) (Hematoxylin and eosin stain, original magnification $\times 20$). **b** The tumor cells in case 3 were arranged in solid cords and nests and the cells displayed moderate amounts of eosinophilic cytoplasm with moderate nuclear pleomorphism and prominent nucleoli. Perineural invasion was noted as well (*insert*). (Hematoxylin and eosin stain, original magnification $\times 80$, *Insert* $\times 40$)

[49]. To date, there have been one and possibly a second primary well differentiated NEC (carcinoid tumor) reported in the major salivary glands [50, 51].

The moderately NECs appear to be just as rare as typical carcinoids. Including the three cases in this series, only five have been reported to date. One of the previously reported cases occurred in a 40-year-old male who presented with a parotid mass that was excised but went on to develop liver metastases at 6 years and was stable and asymptomatic at 10 years at last follow-up with disseminated liver disease. Light microscopic examination revealed nests of tightly cohesive cells, showing round uniform nuclei and a predominantly granular cytoplasm. Occasional more pleomorphic larger cells were detected as well. The cells exhibited numerous dense core neurosecretory granules with electron microscopic examination. Similarly, immunohistochemistry staining was confirmatory of the neuroendocrine lineage of the tumor [15]. The other case arose in the submandibular gland of a 53 year old female. This was a T1N0 tumor with a mitotic rate of 5/10 hpf. The tumor

was excised and the patient is alive and well at 27 months [1]. One may question the clinical necessity of separating MDNEC from the large cell variant of PDNEC. At this time, there are too few major salivary gland cases to know whether the MDNECs have a better prognosis than the poorly differentiated NECs, similar to other sites [16]. Additional cases will need to be studied to see if there is a difference in biologic behavior between these two groups.

We report three malignant parotid gland tumors with histomorphologic and immunohistochemical features diagnostic of neuroendocrine carcinoma with features that recapitulate the moderately differentiated subtype based on the overall cytomorphology, mitotic count and extent of necrosis. One tumor occurred in a male and two in females, with an average age of 66 years. One patient presented with an asymptomatic mass of unknown duration, while each of the other two cases presented with a painful, tender swelling of approximately 6 months duration. Metastatic work-up verified that all three tumors were primary parotid tumors, excluding metastatic neuroendocrine carcinoma to that region. Histological features and immunohistochemical stains were characteristic of moderately differentiated NEC. Maximum mitotic counts ranged from 5 to 8/10 high power fields. Necrosis was patchy and focal in two tumors; vascular and perineural invasion were identified in two and one tumor, respectively. Moderately differentiated neuroendocrine carcinoma should be managed aggressively with attempt to eradicate all of disease. The aggressive biologic behavior was evident in one of our two cases with follow-up and in one of the previously published reports [15].

Given their rarity in the salivary glands, it is essential to exclude metastatic tumors with neuroendocrine features to the parotid and other major as well as minor salivary glands from other regions in the body; especially from pulmonary and cutaneous origins, via thorough clinical and radiographic examination and work-up. This is especially significant since primary neuroendocrine salivary tumors share histomorphologic and immunohistochemical properties with other neuroendocrine tumors elsewhere in the body. This may be problematic at times due to the presence of well-documented reports of primary lung neuroendocrine tumors, which are initially discovered as metastatic disease to the parotid gland [52–58]. Salama et al. [57] reported two metastatic moderately differentiated neuroendocrine carcinomas of pulmonary origin to the parotid glands. One of the cases was detected more than 2 years following the diagnosis of the primary lung tumor in an 82 year old woman, while in the second case, the primary lung mass was discovered subsequent to the discovery of a 3 month duration left parotid gland swelling. Similarly, Gulati et al. [58] have described a metastatic moderately differentiated bronchopulmonary neuroendocrine carcinoma to the submandibular gland in a 56-year-old male,

nine years following the initial diagnosis of primary small cell carcinoma of the salivary glands. CK20+ staining is observed in both primary salivary and metastatic cutaneous neuroendocrine carcinomas and may help to exclude metastatic small cell carcinoma of pulmonary origin, which typically does not stain with CK20, with only rare exceptions [52, 53]. Similarly, the absence of detectable lung pathology would also aid in excluding a metastatic lung tumor.

Negative immunohistochemistry staining with S-100, HMB45 and Mart-1 help to distinguish MDNEC from malignant melanoma, especially since the nesting pattern of moderately differentiated NEC may be confused with clusters of melanoma cells, which is well known for mimicking several other tumors in the head and neck region [59]. The demonstration of neuroendocrine markers may also help to separate salivary gland moderately differentiated NEC from the solid variant of adenoid cystic carcinoma, where such distinction could be problematic at times, especially since both tumors may grow in sheets and nests and often display a brisk mitotic activity. The presence of focal areas of cribriform architecture, which is not a characteristic of a moderately-differentiated NEC, coupled with the identification of myoepithelial differentiation by positive immunohistochemical staining with actin and myosin, or other myoepithelial markers [60–62] and the co expression of vimentin and cytokeratin in a diffuse rather than a dot like pattern, as seen in neuroendocrine tumors [63], confirms the diagnosis of adenoid cystic carcinoma.

Salivary NEC may also be confused with an infiltrating basaloid squamous cell carcinoma (BSCC), since the latter may exhibit a peripheral palisading pattern [25]. The identification of areas of conventional squamous cell carcinoma within the basaloid tumor pattern and a cribriform growth pattern is helpful in differentiating between these two tumors. Furthermore, BSCC frequently demonstrates a greater degree of cytologic atypia and mitotic activity and, more importantly, does not typically stain positively with neuroendocrine markers [64–66].

Histological evidence of epithelial differentiation, as well as the identification of positive staining with leukocyte common antigen and other more specific T cell and B cell lymphoid markers (CD3, CD5 and CD20 and CD79a, respectively) among others, can help distinguish MDNEC from malignant lymphoma. Additionally, the growth patterns described previously may be distinguished from the rather diffuse pattern seen with many lymphomas. Neuroendocrine tumor cells also tend to be larger and contain nuclei with more uniform peripheral contours and more finely stippled chromatin.

In summary, we report 3 neuroendocrine carcinomas of the parotid gland with features that recapitulate moderately

differentiated NEC. This brings the total number of reported cases to five.

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