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Proceedings of the NASHNP Companion Meeting, March 18th, 2018, Vancouver, BC, Canada: Salivary Neuroendocrine Carcinoma—An Overview of a Rare Disease with an Emphasis on Determining Tumor Origin

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Abstract
Salivary neuroendocrine carcinomas are rare and the overwhelming majority is high-grade. The parotid gland is the most commonly involved site followed by the submandibular gland. Most arise de novo but rare examples occurring as a high-grade transformation of another type of salivary gland neoplasm exist. There is significant morphologic and immunophenotypic overlap with neuroendocrine carcinomas of other sites, especially the skin. Like cutaneous neuroendocrine (or Merkel cell) carcinomas, approximately three-fourths are cytokeratin 20 positive. Cytokeratin 20 positive salivary neuroendocrine carcinomas are often referred to as being of the 'Merkel cell type' since most other non-cutaneous neuroendocrine carcinomas are cytokeratin 20 negative. Salivary neuroendocrine carcinomas may be challenging to separate from Merkel cell carcinomas of the head and neck on pathologic grounds because the latter often metastasize to the parotid gland. Clinical history is often relied upon to separate primary salivary tumors from cutaneous metastases but may not be helpful in all cases. Here we review the clinical, pathologic and molecular features of salivary neuroendocrine carcinomas focusing on high-grade major salivary gland tumors. The difficulty in separating salivary tumors from metastatic Merkel cell carcinoma will be highlighted.

Keywords Salivary · Neuroendocrine carcinoma · Small cell carcinoma · Large cell neuroendocrine carcinoma · Merkel cell polyomavirus · Merkel cell carcinoma

Introduction

Primary neuroendocrine carcinomas (NECs) of the salivary glands are uncommon, accounting for 1–3% or less of major salivary gland malignancies, with existing literature limited to case reports and a few larger case series [1, 2]. About three-fourths arise in the parotid with nearly all remaining tumors located in the submandibular gland [1–18]. Sublingual and minor salivary gland carcinomas likely exist but are difficult to distinguish from morphologically identical NECs derived from the overlying surface mucosa of the upper aerodigestive tract.

There is no established grading system for salivary NECs but lung criteria and terminology are generally applied. The overwhelming majority are high-grade with the small cell type out numbering large cell carcinomas by a factor of about 5:1 [1–18]. Well and moderately-differentiated NECs are exceedingly rare with < 10 cases described in the literature [19–22]. This includes an interesting example of a hereditary well-differentiated neuroendocrine neoplasm of the salivary glands with unique morphology and association with sensorineural hearing loss and enamel hypoplasia that was described in a family from the Isle of Man [21].

One major controversy is the ability to distinguish primary salivary NECs from metastases to the salivary glands. The parotid gland is unique among the salivary glands because it is rich in lymph nodes, which may be

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located within the parenchyma itself and closely intermingle with salivary tissue. These parotid lymph nodes are a favored site for metastasis from cutaneous malignancies of the head and neck to deposit, including NECs (known as Merkel cell carcinomas in the skin) [23]. Morphologic features between cutaneous and salivary NECs may be indistinguishable. As a result, metastatic Merkel cell carcinomas are not easily separable from primary salivary tumors on pathologic grounds.

Here, we review the clinical, pathologic and molecular features of high-grade NECs of the major salivary glands with emphasis on the difficulty of separating primary tumors from metastases. Given their rarity, well and moderately-differentiated NECs (carcinoid and atypical carcinoid tumors), and minor salivary gland tumors will not be considered.

Clinical Features

Salivary high-grade NEC is a disease of adulthood with only exceedingly rare examples occurring in the pediatric population [2]. Although the reported age range is quite broad (5–91 years), the majority of patients are in the 6th to 8th decade of life with very few patients younger than 40 years of age [2, 24]. Men are more commonly affected than women with a male to female ratio of approximately 2–3 to 1 [1–18]. The most common clinical presentation is of a rapidly growing neck mass in the region of the parotid gland or, less commonly, in the submandibular gland (neck level IB). While most tumors measure > 2 cm at presentation, a minority are smaller, likely owing to their superficial, and thus easily detectable, location.

Morphology and Immunophenotype

Small cell and large cell NECs of the salivary glands are morphologically similar to those of other sites, including the lungs (Fig. 1). Small cell carcinomas are composed of sheets, trabeculae or nests of small, 'blue' tumor cells. The nuclear to cytoplasmic ratios are high with scant cytoplasm and hyperchromatic, finely granular chromatin. Nuclear molding and crush artifact are common features. Rosettes may be identified occasionally. Large cell NECs have more abundant cytoplasm, larger nuclei with more course chromatin and often prominent nucleoli. Palisading at the periphery of tumor nests may be seen and rosettes can be encountered in the large cell type as well. Both large and small cell types have brisk mitotic activity (> 10 mitoses per 10 high power fields). Apoptotic debris is usually present in the background and there may be areas of geographic necrosis.

A minority of cases may have an associated non-neuroendocrine component, which is usually epithelial and described as ductal but may be squamous [2]. Ueo et al. described an unusual and clinically aggressive parotid carcinosarcoma in which a high-grade large cell NEC predominated [13]. Rhabdomyosarcoma, myxosarcoma, sarcoma not otherwise specified (NOS), adenocarcinoma NOS, and squamous cell carcinoma were also present within the tumor. Although salivary carcinosarcomas may arise from a pre-existing pleomorphic adenoma, background pleomorphic adenoma was not seen in this case. The patient died of disease at 8 months.

There are also very rare examples of high-grade NEC arising from a lower grade salivary neoplasm as a form of high-grade transformation. Cimino-Mathews et al.

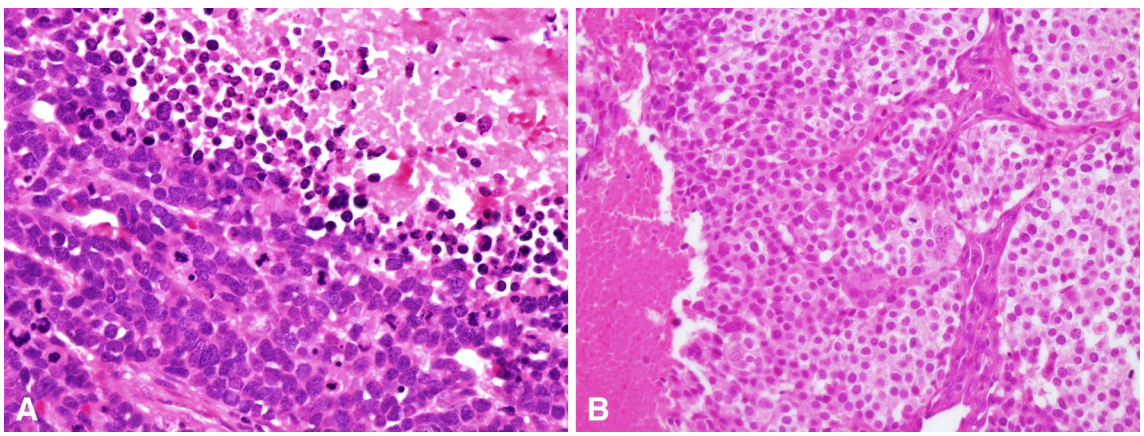

Fig. 1 Examples of small and large cell salivary neuroendocrine carcinomas. Small cell carcinoma (**a**, ×600 magnification) is composed of sheets, nest and trabeculae of cells that have high nuclear to cytoplasmic ratios, finely granular chromatin, scant cytoplasm and often nuclear molding. Necrosis is present (top) and mitotic activity is brisk. Large cell neuroendocrine carcinoma (**b**, ×400 magnification) contains larger cells with more abundant cytoplasm and in some case prominent nucleoli

reported a mixed small cell carcinoma/adenocarcinoma that was ex pleomorphic adenoma of the parotid gland [9]. A case of small cell carcinoma associated with acinic cell carcinoma has also been described (Fig. 2) [25]. It may be that additional cases of high-grade NECs represent transformed salivary neoplasms in which the lower grade component has been completely replaced or went un-sampled.

The immunophenotype of salivary high-grade NECs overlaps with neuroendocrine tumors from other sites (Fig. 3). Neuroendocrine marker positivity is a hallmark of all neuroendocrine tumors, although individual tumors may not stain with every antibody. Thus, a panel of neuroendocrine markers is typically performed. Cytokeratins (CKs) often display perinuclear 'dot-like' positivity, especially in the small cell type. Among high-grade NECs, CK20 positivity, often in a perinuclear 'dot-like' pattern, is considered sensitive (~95%) and fairly specific for cutaneous Merkel cell carcinomas, as <5% of lung small cell carcinomas are CK20 positive [26, 27]. However, CK20 positivity is also present in about 3/4 small cell and some large cell NECs of salivary origin (Fig. 3) [1]. CK20-positive salivary NECs are often referred to as 'Merkel cell type' due to the shared morphology and immunophenotype with cutaneous Merkel cell carcinomas. In contrast, thyroid transcription factor-1 (TTF-1) is only occasionally positive in salivary NECs, even though it stains the majority (70–90%) of pulmonary and many other extra-pulmonary small cell carcinomas [1, 28]. CK7 is also negative in the majority of tumors.

Molecular Genetics

Limited genetic studies have been performed on a small number of salivary high-grade NECs. We previously performed next-generation sequencing of 151 cancer-related genes in 4 high-grade salivary NECs (3 small cell and 1 large cell type) [29]. *Retinoblastoma* (*RB1*) deletions were found in 2 of 3 small cell carcinomas and the 1 large cell NEC with loss of retinoblastoma protein (pRB) expression in all 4 cases (Fig. 3) [29]. Other common genetic

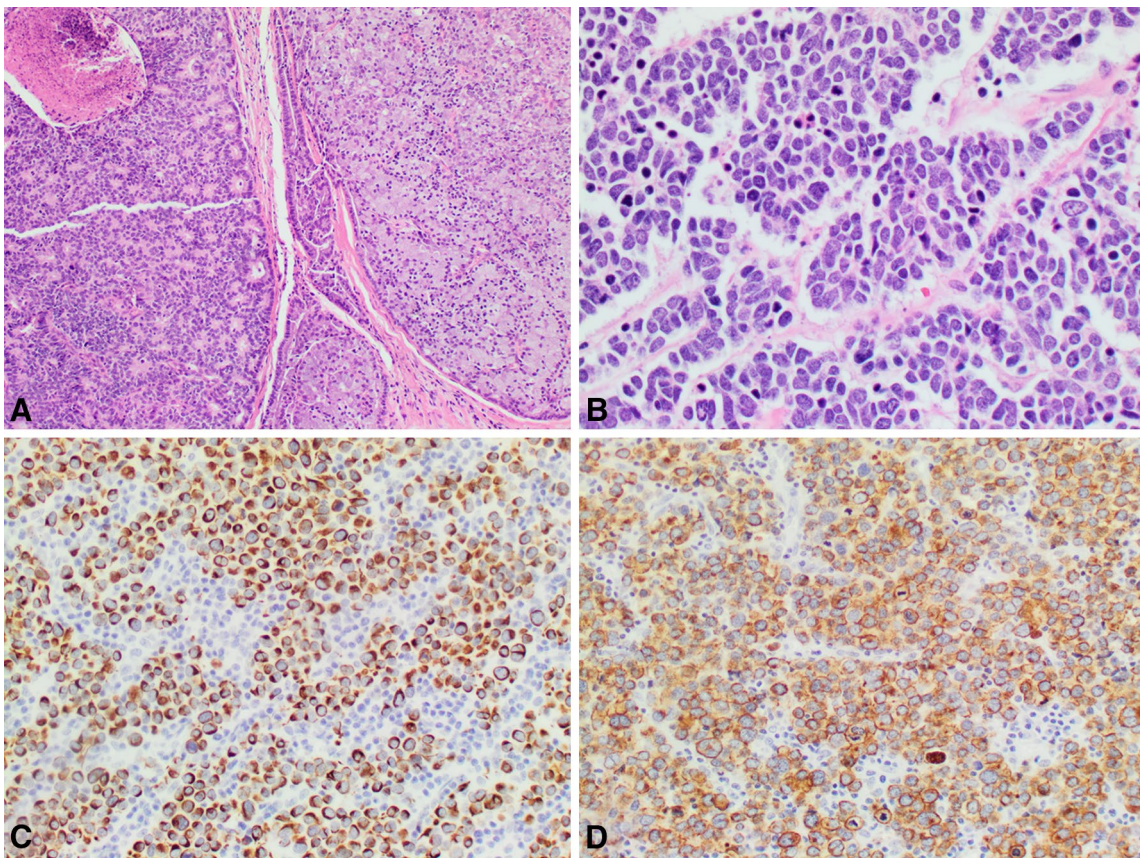

Fig. 2 Small cell carcinoma arising from acinic cell carcinoma as a form of high grade transformation. A high grade component is present (left) with necrosis adjacent to the low grade acinic cell carcinoma (right, **a**, ×100 magnification). Typical features of small cell carcinoma including hyperchromatic nuclei, high nuclear to cytoplasmic ratios, nuclear molding and apoptotic debris are seen in the high grade component (**b**, ×400 magnification). The tumor cells are positive for cytokeratin 20 (**c**, ×200 magnification) and chromogranin (**d**, ×200 magnification). Images courtesy of Dr. Lester D. Thompson

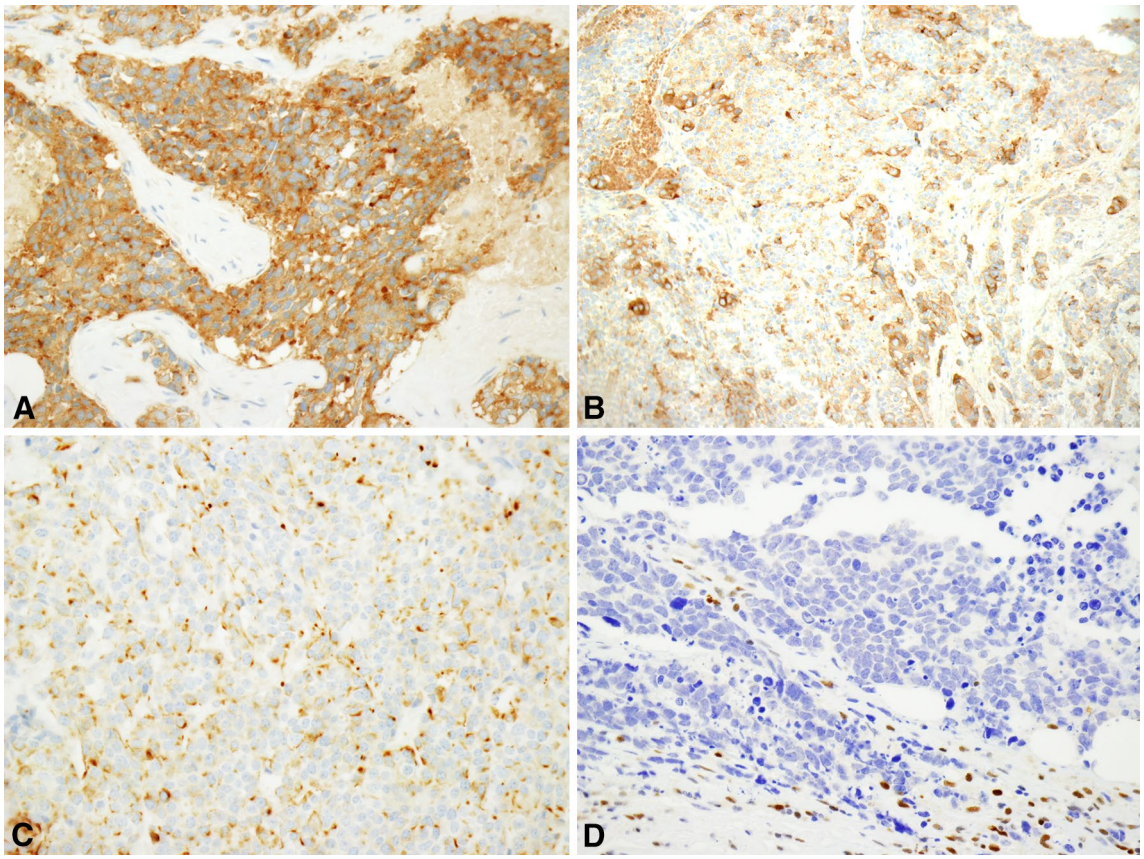

Fig. 3 Immunophenotype of salivary neuroendocrine carcinomas. One or more neuroendocrine markers (**a**, synaptophysin; **b**, chromogranin, ×200 magnification) are typically positive. Cytokeratin 20 positivity (**c**, ×200 magnification) is frequently observed, akin to cutaneous Merkel cell carcinomas, and pRB expression is often lost (**d**, ×400 magnification)

alterations included *TP53* mutations and activation of the mTOR pathway (*PTEN* mutations; *mTOR, AKT* or *PIK3CA* amplification) [29].

Review of the literature yields only two additional molecular studies. Andreasen et al. performed comparative genomic hybridization on a single case of combined large cell neuroendocrine and squamous cell carcinoma of the submandibular gland [12]. A hypodiploid genome was found with whole or partial chromosomal loss of 3p, 4, 7q, 10, 11, 13, 16q and gains of 3q and 16p [12]. The 16p gain included the *NIFB* gene, which interestingly is also involved in recurrent gene fusions with *HMGA2* in pleomorphic adenomas and with *MYB* in adenoid cystic carcinomas. Nagao et al. also performed limited loss of heterozygosity (LOH) assessment of TP53 and p16 loci in 2 large cell NECs of the parotid gland [30]. One case showed LOH of *TP53* and both showed LOH of p16 (encoded by the *CDKN2A* gene), although p16 was strongly and paradoxically overexpressed by immunohistochemistry [30]. p16 overexpression could have been explained by pRB loss because pRB is a negative regulator of p16. pRB loss is a well-known cause of p16 overexpression in both cell lines and other tumor types [8]. This possibility was not investigated.

Up to 80% of cutaneous Merkel cell carcinomas harbor Merkel cell polyomavirus (MCPyV) and clonal integration of the virus into the host genome along with frequent deletions of the viral large T antigen are involved in oncogenesis [31–33]. MCPyV is generally not found in high-grade NECs from other sites [34]. However, given the morphologic and immunophenotypic similarity between Merkel cell carcinoma and salivary high-grade NEC, one may wonder whether CK20-positive salivary high-grade NECs of the 'Merkel cell type' also carry the virus. It appears that a subset of salivary high-grade NECs may be MCPyV-positive, albeit less frequently than cutaneous tumors. We previously found no MCPyV-positive salivary high-grade NECs by immunohistochemistry and PCR among 7 parotid tumors [11]. However, subsequent reports have found MCPyV in a few salivary tumors. Two additional studies have examined salivary NECs for MCPyV by PCR and collectively found 3 out of 4 tumors to be MCPyV-positive [6, 10]. Combining these studies with ours, MCPyV has been found in a total of 3 out of 11 or 27.3% of salivary high-grade NECs,

a much lower rate than for cutaneous Merkel cell carcinomas. One additional study reported MCPyV positivity by immunohistochemistry in a CK20-negative submandibular NEC but the staining pattern reported was unusual (nuclear dot rather than diffuse staining) and the presence of the virus was not confirmed with molecular studies [8]. We also note that MCPyV infection is common in the general population and occurs early in childhood with potential reactivation and detection in immunocompromised states [35, 36]. It is therefore unclear whether all of the reported cases of MCPyV-positive salivary high-grade NECs represent a viral passenger effect or are causative; in only one case was a viral genomic deletion characteristic of viral integration in Merkel cell carcinoma reported [6]. Further, there is no way to completely eliminate the possibility that MCPyV-positive salivary high-grade NECs actually represent occult primary Merkel cell carcinomas of the skin.

In summary, the predominant molecular changes in salivary high-grade NEC appear to involve loss of pRB with associated overexpression of p16, *TP53* mutations and activation of the mTOR pathway. These molecular alterations are similar to those observed in high-grade NECs from a variety of other sites, including the lung and skin. Most lung small and large cell NECs (68 and 87%, respectively) show absence of pRB expression with corresponding p16 overexpression [37]. pRB loss is also frequent among MCPyV-negative Merkel cell carcinomas [38]. Further, p53 mutations and mTOR pathway activation are common in pulmonary NECs [39]. Unlike cutaneous Merkel cell carcinomas, only a minority of salivary high-grade NECs appears to be MCPyV-positive.

Treatment and Prognosis

There is little data in the literature to guide treatment with management strategies generally extrapolated from other tumor types, especially cutaneous Merkel cell carcinoma. Surgery is the mainstay of therapy with most patients undergoing local resection and neck dissection [1, 2]. The majority receive adjuvant radiation and a subset chemotherapy [1, 2]. While PD-L1 inhibitors have shown disease response in Merkel cell carcinomas, their efficacy in salivary NECs is unknown [40].

There are two large case series that examined clinical outcomes of salivary small cell carcinomas [1, 2]. Gnepp and Wick reported 2- and 5-year survivals of 55.6 and 33.3%, respectively, among 9 patients [2]. Nagao et al. found significantly worse survival rates at 2 and 5 years (38 and 13%, respectively) among 12 patients [1]. Factors that negatively impacted survival were tumor size > 3 cm, CK20 negativity and fewer number of positive neuroendocrine markers by immunohistochemistry [1]. In our experience with 5 cases of salivary small cell carcinoma, the 2- and 5-year survival rates were 80.0 and 75.0%, respectively [11]. Combining the data from these 3 studies yields a 2-year survival rate of 50% among 26 patients and a 5-year survival rate of 29.2% among 24 patients [1, 2, 11].

In summary, the 5-year survival for salivary small cell carcinoma appears better than the dismal < 10% survival of small cell carcinoma of the lung and may be slightly worse than the 39% 5-year survival rate of regionally metastatic Merkel cell carcinoma [41, 42]. Interestingly, unknown primary Merkel cell carcinomas appear to have an even better prognosis than either salivary high-grade NEC or known primary regionally metastatic Merkel cell carcinoma. There is so little outcome data for salivary large cell NECs in the literature that it is difficult to draw conclusions about patient survival. Although immunosuppression has been associated with more aggressive disease in cutaneous Merkel cell carcinomas, there is no existing literature regarding immunosuppression in salivary NECs. Anecdotally, one of our 4 salivary high-grade NEC patients was immunosuppressed secondary to a renal transplant. This patient had a large cell NEC and died of disease.

Distinguishing Primary Tumors from Metastases

As mentioned above, the parotid gland contains many lymph nodes, which are a favored site of metastasis from cutaneous head and neck cancers. When faced with a parotid gland malignancy, the pathologist is often asked whether the tumor is a metastasis from the skin or a salivary primary. Presence or absence of nodal involvement is not particularly useful. Parotid lymph nodes are unique in that they are intimately associated with the salivary tissue and often contain benign salivary inclusions beneath the capsule (Fig. 4). Thus, salivary gland neoplasms can quite easily directly extend into the lymph nodes and in some cases may even arise from salivary inclusions in a lymph node. On the flip side, absence of nodal involvement in the parotid gland does not rule out a metastasis as high-grade malignancies grow rapidly and can quickly efface an involved intraparotid lymph node. Distinguishing primary from metastasis is less of a concern in the submandibular gland, which generally lacks lymph nodes within its substance.

Histologic tumor type is helpful to differentiate metastases from primary tumors. For example, squamous cell carcinomas are usually, but not always, metastases, while salivary type adenocarcinomas (mucoepidermoid carcinoma, adenoid cystic carcinoma, etc.) are almost always primary. Unfortunately, in the case of high-grade NECs, histologic type is not particularly useful as NECs can arise from either the skin or salivary glands, although the small cell type (Merkel

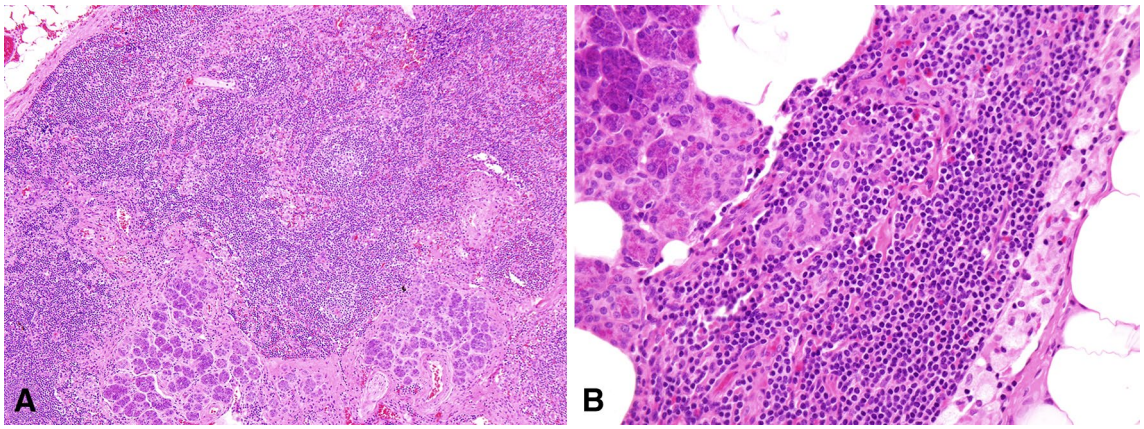

Fig. 4 Salivary inclusions in parotid lymph nodes. Parotid lymph nodes frequently contain intranodal salivary tissue (**a**, ×100 magnification; **b**, ×400 magnification) that may be intraparenchymal or subcapsular

cell carcinoma) is more common in the skin. Immunohistochemistry also does not discriminate between cutaneous and salivary NECs as both are often CK20 positive [1, 27, 33].

The clinical context, including history of prior malignancy and imaging, is important and often relied upon to rule out metastatic disease. However, patients may not recall details of past skin cancer diagnoses and not all skin lesions are even sent for pathology. Furthermore, rare Merkel cell carcinomas occur as primary nodal disease without an identifiable skin tumor and, exceptionally, primary tumor regression has also been described in Merkel cell carcinomas [33, 43]. Thus, documentation of a skin primary may not be possible in all Merkel cell carcinomas.

Are there any additional pathological or molecular features that can be used in clinical practice to separate salivary high-grade NECs from metastatic Merkel cell carcinoma, especially when the latter is of unknown primary? MCPyV, present in many Merkel cell carcinomas, can be assessed by clinically available immunohistochemistry, which is sensitive and specific for high viral copy number in cells, or PCR [44, 45]. Subtle morphologic features including round nuclei with a lack of nuclear molding also suggest a MCPyV-related tumor but are not reliable [45]. However, determining viral status may not be helpful, as a subset of salivary high-grade NECs may also be virus-positive.

Other molecular studies could yield diagnostically relevant information. Many salivary type tumors harbor recurrent translocations. *EWSR1, ETV6* and *MAML2* rearrangements are characteristic of clear cell, secretory and mucoepidermoid carcinomas, respectively [46]. *MYB* rearrangements are common in adenoid cystic carcinoma. Approximately 65% of pleomorphic adenomas contain rearrangements of *PLAG1* or *HMGA2* [46]. One may wonder whether recurrent translocations are present in a subset of salivary high-grade NECs, indicating origin from a lower grade salivary neoplasm. However, we found no canonical gene fusions among 4 salivary high-grade NECs (unpublished data), consistent with the literature that most salivary high-grade NECs arise de novo.

Evaluation of UV-signature mutations may be more promising. Recently, a high prevalence of UV-signature mutations has been detected in virus-negative Merkel cell carcinomas including those of unknown primary origin [47, 48]. Thus, UV-signature mutations, as evidence of a sun-damage induced mechanism of pathogenesis, is a potential means of distinguishing virus-negative cutaneous from salivary NECs, as that latter should not be related to sun exposure. Morphologic, immunohistochemical and molecular comparison of salivary and cutaneous, as well as pulmonary, high-grade neuroendocrine carcinomas is given in Table 1.

Summary

Salivary high-grade NEC is a rare malignancy with histologic and immunophenotypic overlap with more common cutaneous NECs (Merkel cell carcinomas). Clinical history is often relied upon to separate the two but it is not helpful in all cases. Therefore, at present it is difficult to reliably separate the two tumor types.

This lack of clarity in the separation of salivary and cutaneous high-grade NECs has likely led to cross-contamination of the two entities in the literature. It is probable that some salivary high-grade NECs have been classified as unknown primary Merkel cell carcinoma, especially when CK20 positive, and vice versa. A high percentage (50%) of unknown primary Merkel cell carcinomas occur in the cervical region; it is possible that a subset of these cases are actually salivary primaries [49]. On the other hand, some tumors classified as salivary high-grade NECs may truly be Merkel cell carcinomas for which the primary tumor went unrecognized as such or regressed. One wonders if this is the

Table 1 Morphologic, immunohistochemical and molecular comparison of salivary, cutaneous and pulmonary high-grade neuroendocrine carcinomas

Feature	Salivary	Cutaneous (Merkel cell carcinoma)	Pulmonary
Morphology			
Small cell	85%	>99%[a]	~80%
Large cell	15%	<1%	~20%
Non-neuroendocrine component	Yes (rarely salivary type)	Yes	Yes
Immunophenotype			
TTF-1	~15%	<5%	~70–90%
CK20	~75%	>90%	<5%
MCPyV status[a]			
Positive	~25–30%	~75–80%	No
Molecular			
RB1 mutations	Yes	Yes (MCPyV-tumors)	Yes
UV-signature mutations[b]	No	Yes (MCPyV-tumors)	NA
Recurrent translocations, salivary type	No[c]	NA	NA

TTF-1 thyroid transcription factor-1, *CK20* cytokeratin 20, *MCPyV* Merkel cell polyomavirus, *RB1* retinoblastoma, *NA* not applicable

[a]MCPyV+ tumors may have distinct histologic features

[b]UV-signature mutations may be diagnostically useful in separating MCPyV-negative Merkel cell carcinoma from salivary high-grade NEC

[c]No recurrent translocations have been identified to date in salivary high-grade NEC (limited number of cases tested)

case for some of the MCPyV-positive tumors. The distinction is important as primary salivary high-grade NEC may be more clinically aggressive than unknown primary Merkel cell carcinoma [49].

Additional biomarkers to separate salivary high-grade NECs from cutaneous metastases are needed. For MCPyV negative cases, UV-signature mutations may be a means of distinguishing cutaneous from non-cutaneous (salivary) origin in the future. A clearer definition of salivary high-grade NEC will lead to a better understanding of the pathogenesis and biological behavior of this rare tumor type.

Compliance with Ethical Standards

Conflict of interest The authors have no sources of funding or conflicts of interest to disclose.

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