Basal Cell Adenocarcinoma and Basal Cell Adenoma of the Salivary Glands: A Clinicopathological Review of Seventy Tumors with Comparison of Morphologic Features and Growth Control Indices

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Abstract Basal cell adenoma and basal cell adenocarcinoma represent uncommon basaloid salivary gland neoplasms that show marked morphologic similarity. We wished to compare clinical outcome and morphologic features as well as growth and proliferation associated markers for both neoplasms. We reviewed the pathologic features of 70 neoplasms diagnosed as basal cell adenoma or basal cell adenocarcinoma. Observations included maximum mitotic activity and presence or absence of invasion into surrounding normal tissues as well as immunohistochemical studies for Ki-67, caspase 3, p53, and bcl-2. Establishing malignancy on the basis of invasion into surrounding benign tissues, 41 basal cell adenomas and 29 basal cell adenocarcinomas were identified. For tumors with follow-up, recurrence rates were 6.7 % for basal cell adenoma and 16.7 % for basal cell adenocarcinoma. One patient with basal cell adenocarcinoma had distant metastases and died of disease. Overall basal cell adenocarcinomas showed significantly higher values for growth and proliferation markers compared to basal cell adenomas. Salivary gland basal cell adenoma and basal cell adenocarcinoma show morphologic similarity. Basal cell adenocarcinoma can exhibit a locally aggressive behavior and has potential metastatic behavior. The overall mitotic rate and Ki-67 expression were higher in basal cell adenocarcinoma compared to basal cell adenoma, but overlap between the results of these observations in each tumor did not allow for accurate diagnosis or prediction of outcome in individual cases. We conclude that morphologic observation of local tissue invasion is

the best marker for separating basal cell adenoma from basal cell adenocarcinoma.

Keywords Basal cell adenoma · Basal cell adenocarcinoma · Salivary gland neoplasms

Introduction

Basal cell adenoma and basal cell adenocarcinoma both represent salivary gland neoplasms with basaloid cell proliferation. Basal cell adenoma is not common, representing approximately 1–3 % of salivary gland neoplasms [1, 2] and basal cell adenocarcinoma is even less common, representing approximately 1–2 % of salivary gland neoplasms [2]. While basal cell adenocarcinoma has been reported to rarely arise from an underlying basal cell adenoma, it is thought that most basal cell adenocarcinomas arise de novo [3–7].

The two tumors have many similar morphologic attributes and separation can at times be difficult, particularly based only on cytomorphology. In addition, separation from other salivary gland tumors with abundant basaloid cells, such as adenoid cystic carcinoma, can be difficult. While both basal cell adenoma and basal cell adenocarcinoma can recur, basal cell adenocarcinoma is defined by many as having distinctive morphologic features of malignancy including local invasion of surrounding tissues [2, 8–10]. Biologically, basal cell adenocarcinoma has distinct malignant potential, evidenced by metastasis, albeit low, and rarely death due to disease [6, 8]. Basal cell adenocarcinomas are risk stratified as low histologic grade [11]. We wished to correlate clinical outcome and morphologic features with growth and proliferation associated markers between both entities to determine if we could

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Table 1 Patient demographics

	Basal cell adenoma	Basal cell adenocarcinoma
Tumors (N)*	41	29
Men	17	12
Women	24	17
Age (years)	14–86 (mean 58)	40–90 (mean 67)
Cases with follow-up (months)	30 (1–342 months; mean 75, median 48)	18 (1–170 months; mean 59, median 70)
Site		
Parotid	33	22
Submandibular	1	1
Sublingual	0	1
Oral cavity**	6	3
Parapharyngeal***	1	2

* 70 Tumors in 69 patients; one man with basal cell adenoma and subsequent contralateral basal cell adenocarcinoma

** Sites of oral cavity basal cell adenomas included lip (3), buccal mucosa (1), maxillary mucosa (1), and palate (1). Sites of oral cavity basal cell adenocarcinomas included lip (2) and buccal mucosa (1)

*** The authors have maintained the parapharyngeal sites as the primary site although it is possible that these sites actually represented extensions from a parotid gland primary. No additional clinical or pathology data could lend support to a parotid origin

further refine separation of the two and better predict indicators of behavior.

Materials and Methods

We reviewed the clinical outcomes and pathologic features of 70 neoplasms diagnosed as basal cell adenoma or basal cell adenocarcinoma gathered from our institution and consultative practice. These 70 neoplasms were found in 69 patients, with one patient presenting initially with a basal cell adenoma in the parotid gland and subsequently presenting with a basal cell adenocarcinoma in the contralateral parotid gland (Table 1). The study was approved by the Institutional Review Board. Cases were selected by search of our departmental laboratory information system using terms that would encompass basal cell adenoma and basal cell adenocarcinoma. For those patients having primary surgery originating in other institutions, the original slides were reviewed along with clinical and demographic data when available. Tissue blocks were requested when available.

Histologic observations using hematoxylin and eosin stained slides included architectural pattern, perineural invasion, lymphovascular space invasion and presence or absence of invasion into the surrounding normal tissues. Mitoses were counted in areas of ‘hot spots’ where the

maximum number of mitotic figures were found and reported as the number per 10 high-power fields (hpf) (40X objective with field diameter of 55 μ m). Regardless of other findings, basal cell adenocarcinomas were separated from basal cell adenomas as those tumors having unequivocal invasion into the surrounding normal tissues, which included surrounding salivary gland or periglandular tissue for salivary gland tumors or destructive local invasion in mucosal tumors. Although vascular/lymphatic invasion or perineural invasion qualified for a designation of malignancy, all tumors that exhibited either of these two features also showed destructive invasion into surrounding tissues. No features of intercalated duct lesions were seen in the salivary gland tissues of our cases nor were any features of adenoid cystic carcinoma, such as cribriform growth pattern. Of note, to our knowledge, no patients in our series had a history of skin adnexal tumors.

Immunohistochemistry

Tissue blocks were available for 36 cases of basal cell adenoma and 18 cases of basal cell adenocarcinoma. We chose common markers, which could be studied by immunohistochemistry, that relate to cell survival including bcl-2, a protein that is ‘pro-survival’ and caspase 3, an effector of apoptosis. We also chose to study p53, an important regulator of cell growth control. To judge cell proliferation, we assayed Ki-67.

Tissue sections of 4 microns were sectioned from the formalin fixed paraffin embedded tissue for immunohistochemistry. Sections were deparaffinized and then brought through xylenes and alcohols to distilled water. Heat epitope induced retrieval (Biocare Decloaking Chamber, Concord, CA) was carried out for all antibodies. The antibodies (sources and catalog number), dilutions and incubation times were as follows: Ki-67 antigen (Mib-1 antibody, Dako, M7240, Glostrup, Denmark; 1:100, 15 min at room temperature); caspase 3 (Cell Signaling 9661, Danvers, MA; 1:100 for 60 min at room temperature); p53 (Dako M7001; 1:100 for 15 min at room temperature); bcl-2 (Dako M0887; 1:100 for 30 min at room temperature). After exposure to antibody, the slides were washed in buffer and then Dako Mouse Envision System HRP (Dako) was applied for 30 min at room temperature. After washing with buffer, Dako DAB Plus (Dako) was applied followed by Dako DAB enhancer (Dako). After washing in buffer, the slides were counterstained with hematoxylin.

All immunohistochemical staining was assessed manually by the following methods: for Ki-67, at least 1,000 cells were counted to establish a percentage (proliferation index). For an estimation of apoptosis, caspase 3 immunohistochemical staining was performed and interpreted as

Table 2 Gross and microscopic data

	Basal cell adenoma	Basal cell adenocarcinoma
Tumors (N =)	41	29
Size (cm)	0.2–5.5 (mean 1.9, median 1.5)	0.9–8.5 (mean 2.9, median 2.5)
Primary architectural pattern		
Trabecular	25	8
Solid	5	15
Membranous	6	4
Tubular	5	2

the number of cells staining per 10 hpf in areas of maximum activity. p53 was considered overexpressed with >10 % neoplastic cells staining. If more than 5 % of the neoplastic cells expressed bcl-2, the result was considered as positive.

Statistical analysis was performed using Stata software, Version 12 (Stata, College Station, TX).

Results

Basal Cell Adenomas

Seventeen tumors occurred in men and 24 in women. The patient ages ranged from 14 to 86 years (mean 58 years). The parotid gland accounted for 33 cases (80.5 %) and the submandibular gland for 1 case. Other sites included lip (3), buccal mucosa (1), maxillary mucosa (1), parapharyngeal space (1) and palate (1). The clinical and radiographic data for the parapharyngeal space tumor could not confirm that this tumor had originated in the parotid and thus the location as originally reported by the clinicians was maintained. Twenty tumors were on the right, 20 tumors were on the left and 1 (lip) was located centrally. No basal cell adenomas occurred in the sublingual glands. The basal cell adenomas ranged from 0.2 to 5.5 cm (mean 1.9 cm).

The basal cell adenomas were characterized morphologically as having relatively uniform basal-like cells that were consistently seen throughout the tumor. Although these tumors had an overall basaloid appearance, the individual cells could vary from having scant, minimally discernable cytoplasm, to having slightly increased cytoplasm that was paler in appearance. No spindle cell elements were present. The nuclei of either type were small and round but those with less cytoplasm were more dense. The cells often formed small nests and there was distinct peripheral palisading of cells. Membranous patterns, i.e., those with abundant hyaline-like material, were present as

Table 3 Comparison of growth and proliferation-related markers of basal cell adenoma and basal cell adenocarcinoma

	Basal cell adenoma	Basal cell adenocarcinoma	p value
Available tissue (N)	36	18	
Maximum mitotic rate (per 10 HPF)	0–5 (mean 0.7)	1–43 (mean 8.6)	<.001****
Ki-67 index*	0.1–10.5 % (mean 3.3)	0.4–53.3 % (mean 15.5)	<.001****
Apoptotic index**	0–9 (mean 1.0)	0–37 (mean 10.1)	<.001****
p53 overexpression	3 (8.3 %)	8 (44.4 %)	.004***
Loss of bcl-2 Expression	4 (11.1 %)	3 (16.7 %)	.429***

* Proliferation index calculated by number of cells with Ki-67 expression per at least 1,000 cells. Areas of greatest Ki-67 (hot spots) were selected for counting

** Apoptotic Index calculated by counting maximum number of cells positive for caspase 3 per 10 high power fields

*** χ^2 , Fisher exact

**** *t* test, unpaired

were those patterns that formed tubules, trabeculae or solid areas.

The majority of the tumors showed mixed architectural patterns and subtypes were classified based on the predominant pattern. Twenty-five were trabecular, 6 membranous, 5 solid and 5 tubular. While several tumors showed focal (<5 %) hyaline-like material, those that were classified as membranous type were characterized by extensive (>75 %) hyalinization throughout the tumor. No cribriform patterns were observed. No areas of intercalated duct hyperplasia (IDH) were identified in the salivary gland tissues surrounding the tumors as all tumors showed distinct bilayering of cells (Table 2).

In the basal cell adenomas, the maximum mitotic rates ranged from 0 to 5 mitoses per 10 hpf (mean = 0.7). The basal cell adenoma with 5 mitoses/10 hpf presented in the parotid tail of a 70-year-old man. The tumor was characterized by focal nuclear atypia, had a membranous pattern and overexpressed p53. However, this tumor has not recurred in 10.2 years of follow-up.

Proliferation indices (Ki-67 antigen expression as measured by Mib-1 antibody) ranged from 0.1 to 10.5 % (mean = 3.3 %). Apoptotic rates (maximum number of caspase 3 positive cells per 10 hpf) ranged from 0 to 9 (mean = 1.0, median = 0). p53 was overexpressed in 3/36 cases (8.3 %) and bcl-2 expression was lost in 4/36 cases (11.1 %) (Table 3).

Follow-up data was available in 30 of 41 patients, ranging from 1 to 342 months (mean 75 months). In cases with follow-up, 2/30 recurred (6.7 %). Four cases of membranous pattern had follow-up and one of these

recurred. The other recurrent tumor had a trabecular pattern. The recurrent tumor with a membranous pattern occurred in a 14 year old male. The Ki-67 index was 6.2 % for the recurrent tumor although the primary tumor's proliferation index was 10.5 %.

Basal Cell Adenocarcinomas

Hematoxylin and eosin stained slides were reviewed encompassing tumors in 29 patients. Twelve tumors occurred in men and 17 in women. The patient ages ranged from 40 to 90 years (mean 67 years). The parotid gland accounted for 22 tumors (75.9 %), the submandibular gland for 1 and the sublingual gland for 1 tumor. Other sites included lip (2), buccal mucosa (1) and parapharyngeal space (1). Fifteen tumors were on the right and 14 on the left. As was the case for the basal cell adenomas, the tumor located in the parapharyngeal space could not be confirmed to be located in the parotid and the location as reported clinically was maintained. The tumor sizes ranged from 0.9 to 8.5 cm (mean = 2.9 cm).

Cytologically and to a large extent, histologically, these tumors were very similar to that of basal cell adenoma. They were characterized as having tumor cells with basophilic vesicular nuclei with minimal cytoplasm and often prominent peripheral palisading. The tumor cells were often arranged in nests with cells in the center of the nests being somewhat larger and having slightly paler nuclei. Rare cases had increased nuclear atypia and the tumor that metastasized had higher nuclear grade features. A thick hyalinized membrane was seen at least focally in many of the cases and was extensive in 3 tumors. As in basal cell adenoma, many of the tumors showed mixed architectural patterns and subtypes were classified based on the predominant pattern. Fifteen were solid, 8 trabecular, 4 membranous and 2 tubular (Table 2).

Maximum mitotic rates ranged from 1 to 43 mitoses per 10 hpf (mean = 8.6) (Table 3). Proliferation indices (Ki-67 antigen expression as measured by Mib-1 antibody) ranged from 0.4 to 53.3 % (mean = 15.5 %). Apoptotic rates (maximum number of caspase 3 positive cells per 10 hpf) ranged from 0 to 37 (mean = 10.1). p53 was over-expressed in 8/18 cases (44.4 %) and bcl-2 expression was lost in 3/18 cases (16.7 %) (Table 3).

Two basal cell adenocarcinomas arose in pre-existing pleomorphic adenomas, so-called basal cell adenocarcinoma ex-pleomorphic adenoma. One basal cell adenocarcinoma arose in a site in which many years previously a diagnosis of basal cell adenoma had been rendered. We could not confirm if this malignancy arose in a basal cell adenoma or was an adenocarcinoma misdiagnosed as basal cell adenoma originally.

Fig. 1 Basal cell adenoma with solid and tubular patterns. Two cell layers are evident in tubular areas

Of the 29 cases, 5 showed perineural invasion and 6 exhibited lymphovascular invasion. However, each of these tumors showed invasion into the surrounding normal tissues in other areas as did all of the other cases of adenocarcinoma. Seventeen of the carcinomas had positive margins on their primary surgical excision.

We were able to find follow-up data on 18 of 29 patients with basal cell adenocarcinoma, ranging from 1 to 170 months (Mean = 59 months). There were 3 recurrences in these 18 patients (3/18 = 16.7 %). One of the patients with recurrent disease had distant metastases and died due to disease. This patient had initially presented with a tumor in the right submandibular gland 13 months previously and had distant metastasis to the manubrium identified at the time of diagnosis. A history of right neck swelling had been present for 4–5 years prior to the initial presentation.

Discussion

Basal cell adenoma and basal cell adenocarcinoma represent basaloid neoplasms which primarily occur in the parotid gland of older individuals. Intra-oral locations of minor mucosal salivary gland origin are also well described [12, 13]. Following the description of Kleinsasser and Klein in 1967, basal cell adenomas were increasingly being

reported as neoplasms having features distinguishing them from pleomorphic adenomas by their lack of myxochondroid stroma [13–15]. The histologic hallmark of these tumors is the essentially pure population of basaloid cells with small round nuclei showing no atypia with individual cells having either scant cytoplasm or those with slightly more pale cytoplasm. Distinct peripheral palisading of the cells is present with tumor cells arranged in a relatively few specific patterns including trabecular, tubular, solid and membranous. Cribriform patterns have also been described [16, 17]. Some tumors have a relatively pure composition of one of these patterns but a mixture of at least two is common. Mitoses are typically absent to rare (Fig. 1).

In our series of basal cell adenomas, 17 tumors occurred in men and 24 in women. The patient ages ranged from 14 to 86 years (mean 58 years). The youngest patient in our series, 14 years, is one of the youngest reported. This patient's tumor did recur 3 years after initial diagnosis and had a membranous pattern. While the literature suggests that basal cell adenomas with greater than 50 % membranous pattern should be designated as membranous type, all of our cases had over 75 % membranous pattern. Any membranous area seen in the other tumors was <5 %. None of our patients had a history of skin adnexal tumors such as cylindroma, although this finding has been reported by others [8, 18, 19]. One of our patients presented with a basal cell adenoma in the parotid gland and subsequently presented with a basal cell adenocarcinoma in the contralateral parotid gland.

The etiology of basal cell adenoma has been suggested to be from intercalated duct lesions. These proliferations of cells with morphologic and immunohistochemical appearances matching those of intercalated duct cells can be divided into IDH and intercalated duct adenoma (IDA). These proliferations of intercalated cells resemble basal cell adenomas [20, 21]. Further, Montalli et al. [22] have suggested that intercalated duct lesions, tubular basal cell adenoma and non-tubular basal cell adenoma form a continuum of lesions. Intercalated duct lesions are generally much smaller than basal cell adenomas, with average sizes of <0.5 cm versus >1.0 cm for basal cell adenomas [20]. In general, findings that suggest intercalated duct lesion over basal cell adenoma are the absence of spindle cell stromal components, minimal bilayering and common presence of acinic cells, all of which are uncommon or not seen in basal cell adenoma. All of the basal cell adenomas in our study, even the smallest at 0.2 cm, did not show these features (Fig. 2). Likely, more observation is required to assign the biologic significance of separating intercalated ductal adenomas from small basal cell adenomas or even basal cell adenocarcinomas. In the work of Ellis and Wiscovitch [8], the authors found a 0.7 cm basal cell

Fig. 2 Membranous basal cell adenoma. This tumor was 0.2 cm in size but showed two cell types and hyaline material surrounding the tumor cells nests as well as appearing as hyaline droplets within the nests

adenocarcinoma of the buccal mucosa that exhibited lymph node metastasis.

Recurrence in basal cell adenoma is rare with the exception of membranous subtype, which has been reported to recur in up to 25 % of cases [2]. In our tumors in which we had follow-up, basal cell adenoma had an overall recurrence rate of 6.7 % (2/30). One of 26 (3.8 %) non-membranous basal cell adenomas recurred, whereas 1 of the 4 membranous basal cell adenomas recurred.

Klima et al. [23] are credited for the first report of basal cell adenocarcinoma, the malignant counterpart of the basal cell adenoma. Their description was that of a parotid gland neoplasm that appeared to be similar to basal cell adenoma but showed necrosis and mitoses. Basal cell adenocarcinoma shows similar histologic patterns to those of basal cell adenoma, including solid, trabecular, tubular and membranous patterns. In our series, the solid pattern was the most common, making up 15/29 cases (52 %). None of our basal cell adenocarcinomas exhibited a cribriform pattern, although this pattern has been reported in these carcinomas by others [16, 17].

One of the largest series of basal cell adenocarcinomas was reported by Ellis and Wiscovitch [8] from the Armed Forces Institute of Pathology in which they reported on 29 cases. All of their cases were found in major salivary

glands. Similarly, our study showed a strong preponderance of basal cell adenocarcinomas occurring in the parotid (22/29) with the submandibular and sublingual glands each showing a single case. Our series showed 76 % of lesions arising in the parotid gland and 3 % each in the submandibular and sublingual glands. However, we also found 4 intra-oral tumors and 2 tumors in a parapharyngeal location. Overall, the literature supports that the number of cases of basal cell adenocarcinoma arising in the minor salivary glands is relatively small, most commonly seen in buccal mucosa and palate with fewer in the tongue and lip [24, 25].

The literature notes recurrence rates in basal cell adenocarcinoma from 28 % to 50 % [6, 8, 26]. In our series, basal cell adenocarcinoma recurred at a rate of 16.7 % (3/18). Basal cell adenocarcinoma uncommonly metastasizes and rarely even causes death. In their review, Muller et al. reported metastases to cervical lymph nodes in 4 patients (8 %) and distant metastases in 2 patients (4 %) [6]. The sites of distant metastases included skin and lung [6, 8]. Additionally, according to their review, 1 case of basal cell adenocarcinoma has resulted in death (2 % of cases) [6]. In our series, only 1 of 18 patients with follow-up data had distant metastasis to the manubrium and this same patient also died of disease (5.6 %). To our knowledge, this is only the third reported case of basal cell adenocarcinoma with distant metastases and only the second reported case of death due to disease.

There was a female predominance in our patients with basal cell adenocarcinomas but the sex predilection is variable in the literature [6]. Ellis and Wiscovitch [8] reported a slight male predominance in their series from the AFIP. The youngest patient with basal cell adenocarcinoma in our series was 40 and the oldest was 90, with a mean of 67 years, slightly less than a decade older than the mean of patients presenting with basal cell adenoma (58 years), roughly in line with other reports [5, 6, 8]. Jung et al. [27] reported a predilection for basal cell adenocarcinoma to occur on the left side; however, in our series there was no predilection noted for either side in basal cell adenoma and basal cell adenocarcinoma.

Whether or not basal cell adenocarcinoma arises de novo or from a pre-existing basal cell adenoma has been discussed in the literature with reports documenting a progression from adenoma to carcinoma [5–7]. While none of our cases of basal cell adenocarcinoma could be documented by the authors to be associated with basal cell adenoma, one adenocarcinoma was found in a site in which a basal cell adenoma had been diagnosed many years previously. We did, however, find two basal cell adenocarcinomas arising in pleomorphic adenomas, basal cell adenocarcinoma-ex pleomorphic adenoma.

Basal cell adenoma and basal cell adenocarcinoma are difficult to separate by cytomorphology alone, as both are composed of basaloid cells with minimal atypia. From a cytologic view point, the cells of each are essentially indistinguishable, a finding that makes fine needle aspiration separation of the two lesions impossible in most cases [28, 29].

The differential diagnosis of basal cell adenoma as well as basal cell adenocarcinoma includes adenoid cystic carcinoma. The solid variant of adenoid cystic, a tumor which shows abundant solid areas devoid of cribriforming patterns is more likely to be confused with a solid basal cell adenoma or basal cell adenocarcinoma. In addition, the tubular patterns of basal cell adenoma could be misidentified as a tubular predominant adenoid cystic carcinoma. Cribriform variants of basal cell adenomas and basal cell adenocarcinomas have been described as well [16, 17, 30]. Of note, hybrid tumors that show adenoid cystic carcinoma and basal cell adenoma or basal cell adenocarcinoma are described [31].

Separation of adenoid cystic carcinoma from basal cell adenoma and basal cell adenocarcinoma may best be accomplished using cytomorphologic criteria. Basal cell adenoma and basal cell adenocarcinoma have nested cells with peripheral palisaded patterns and a distinct arrangement of cells with paler cytoplasm in the center of the nests with smaller and darker cells at the periphery. The nuclei of adenoid cystic carcinoma are angular rather than rounded and the cell arrangements are not palisaded [28].

The morphologic separation of basal cell adenoma from basal cell adenocarcinoma can be difficult. Invasion of the surrounding gland and soft tissues is widely held to be the most critical feature distinguishing basal cell adenocarcinoma from basal cell adenoma. Similar to Ellis and Wiscovitch [8], we defined malignancy in our cases as tumors showing basic morphologic and cytologic features of basal cell adenoma, but with invasive and locally destructive features such as invasive destruction of adjacent tissues. This invasion was destructive in that it pushed or split apart normal salivary gland parenchyma or adipose tissue. It was sometimes associated with a desmoplastic reaction, but not always (Figs. 3, 4). It is of interest that separating the tumors on the basis of invasion correlated with the measurement of mitotic activity, proliferation marker (Ki-67 antigen expression) and apoptosis marker (caspase 3 expression) (see below).

Perineural invasion was seen in 5 of our cases and lymphovascular invasion in 6 of our cases. In the series of Ellis and Wiscovitch [8], perineural invasion was seen in 10 and lymphovascular invasion in 7 of their 29 cases. The study of 11 cases by Nagao et al. [26] revealed that 8 had vascular invasion and 4 had perineural invasion. While

Fig. 3 Basal cell adenocarcinoma. Nests of basaloid cells with minimal atypia invade into the adjacent salivary gland tissue

Fig. 4 Basal cell adenocarcinoma, membranous pattern with invasion into the surrounding periparotid gland soft tissue

perineural and lymphovascular invasion alone are grounds for rendering the diagnosis of basal cell adenocarcinoma, all cases in our series with either of these findings also showed invasion into the surrounding tissues.

Mitoses are also recognized to be increased in basal cell adenocarcinoma as compared to basal cell adenoma. While mitotic activity cannot completely differentiate basal cell adenoma from basal cell adenocarcinoma, overall, mitoses are increased in basal cell adenocarcinoma compared to basal cell adenoma and represent a useful tool to point to a correct pathway for diagnosis. In our practice, finding mitotic figures in a basaloid salivary gland neoplasm in which a diagnosis of basal cell adenoma is entertained, particular attention should be paid to the overall mitotic rate and a thorough search for tumor invasion should be performed. In this setting, we recommend submitting the entire lesion for histologic evaluation. The average maximum mitotic rate for basal cell adenomas in our study was 0.7 per 10 hpf while the average maximum mitotic rate for basal cell adenocarcinomas was 8.6 per 10 hpf. Ellis and Auclair [32] have noted that a mitotic rate of >4 –5 per 10 hpf is correlated with a diagnosis of basal cell adenocarcinoma over basal cell adenoma. Nagao et al. [26] found that >4 mitoses per 10 hpf were associated only with basal cell adenocarcinomas. Our study also suggests that in general, mitotic rates above 3 per 10 hpf are correlated with malignancy. However, the mitotic count cannot be

substituted for an evaluation of the local biologic behavior of the tumor, such as local destructive invasion, perineural or vascular invasion, or metastases. One case that we classified as basal cell adenoma had 5 mitoses per 10 hpf, presenting in the parotid tail of a 70 years old man, and was characterized by focal nuclear atypia and a membranous pattern. It overexpressed p53 but did not exhibit a locally invasive pattern. This tumor has not recurred in 10.2 years of follow-up (Fig. 5).

Markers of growth control and cell turnover showed differences between benign and malignant lesions for some but not all of the markers in our study. In our series the average proliferation index was 3.3 and 15.5 % for basal cell adenoma and basal cell adenocarcinoma, respectively. The average proliferation index, as measured by Ki-67, has been reported to be 2.1 % in basal cell adenoma and 21 % in basal cell adenocarcinoma [26] and <5 % in a smaller series that investigated basal cell adenocarcinoma alone [33].

As a marker of apoptosis, we utilized caspase 3, a ubiquitously distributed neo-epitope that is the main effector of the apoptotic cascade [34]. In our series, basal cell adenomas had an average apoptotic rate of 1.0 per 10 hpf while the rate in basal cell adenocarcinomas was 10.1 per 10 hpf. To our knowledge, caspase 3 has not been previously evaluated in basal cell neoplasms of the salivary gland, though other apoptotic markers have been used. The

Fig. 5 This membranous basal cell adenoma showed up to 5 mitoses per high power field. No invasion was present and the patient has had no recurrence after 10 years of follow-up

TUNEL method has been used as an assessment of apoptotic activity to predict the prognosis of salivary gland malignancies in general [35] as well as to help differentiate basal cell adenoma from basal cell adenocarcinoma [26], wherein apoptotic rates were increased in basal cell adenocarcinoma (0.58 %) compared to basal cell adenoma (0.07 %).

p53, a transcription factor that regulates cellular response to varying insults, is an integral component in biochemical pathways central to human carcinogenesis. In our study, p53 overexpression (Table 3) was seen in both basal cell adenomas and basal cell adenocarcinomas but it was relatively uncommon. In one study, 0 of 9 basal cell adenomas had significant overexpression (defined as >10 % of cells expressing), while in basal cell adenocarcinoma it was overexpressed in 55 % of cases [26]. Another study showed no overexpression in 3 cases of basal cell adenocarcinoma [33]. In our series, 8 % of basal cell adenomas showed p53 overexpression compared to 44 % of basal cell adenocarcinomas.

Bcl-2 expression has been reported only rarely in basal cell adenomas and basal cell adenocarcinomas. One study showed increased loss of bcl-2 expression in basal cell adenocarcinoma with retained expression in basal cell adenoma [26]. In our series loss of bcl-2 expression was seen in 11 and 17 % of basal cell adenoma and basal cell adenocarcinoma, respectively.

While there was a tendency for higher Ki-67, p53 overexpression, caspase 3, and loss of bcl-2 expression, no unequivocal expression or staining pattern confirmed benign versus malignant morphology or accurately predicted behavior. Of note, the tumor of the one patient with distant metastases and death due to disease did show a markedly increased mitotic rate (43/10 hpf), proliferation index (25 %), and apoptotic rate (31/10 hpf).

While both basal cell adenoma and basal cell adenocarcinoma are low grade neoplasms, basal cell adenocarcinomas can exhibit a locally aggressive behavior and have potential metastatic behavior. In this study, we conclude that separating basal cell adenoma from basal cell adenocarcinoma based on invasion into the surrounding gland and/or soft tissues is valid. Ancillary observations, such as increased mitotic rate or elevated Ki-67 indices can alert the pathologist to the possibility of basal cell adenocarcinoma but do not supplant the morphologic observation of tumor and local tissue interaction.

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Conflicts of interest No conflicts of interest declared.

References

1. de Araujo VC. Basal cell adenoma. In: Barnes EL, Eveson JW, Reichart P, et al., editors. World health organization classification of tumors: pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005. p. 261.
2. Ellis GL, Auclair PL. Tumors of the salivary glands. Atlas of Tumor Pathology, 4th series, Fascicle 9. Silver Spring: ARP Press; 2008. 71–85; 269–281.
3. Chen KTK. Carcinoma arising in monomorphic adenoma of the salivary gland. *Am J Otolaryngol*. 1985;6:39–41.
4. Ellis GL, Gnepp DR. Unusual salivary gland tumours. In: Gnepp DR, editor. Pathology of the head and neck. New York: Churchill Livingstone; 1988. p. 617–23.
5. Luna MA, Batsakis JG, Tortoledo E, et al. Carcinoma ex monomorphic adenoma of salivary glands. *J Laryngol Otol*. 1989;103:756–9.
6. Muller S, Barnes L. Basal cell adenocarcinoma of the salivary glands. Report of seven cases and review of the literature. *Cancer*. 1996;78:2471–7.
7. Nagao T, Sugano I, Ishida Y, et al. Carcinoma in basal cell adenoma of the parotid gland. *Pathol Res Pract*. 1997;193:171–8.
8. Ellis GL, Wiscovitch JG. Basal cell adenocarcinomas of the major salivary glands. *Oral Surg Oral Med Oral Pathol*. 1990;69:461–9.
9. Akiyama K, Karaki M, Hosikawa H, Mori N. A massive basal cell adenocarcinoma of the palatal minor salivary gland that progressed into the pterygopalatine fossa. *Int J Oral Maxillofac Surg*. 2012;41:444–7.
10. Ellis G. Basal cell adenocarcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. World health organization classification of tumors: pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005. p. 229–30.

11. Seethala RR. An update on grading of salivary gland carcinomas. *Head Neck Pathol.* 2009;3:69–77.
12. Veeresh M, Bavle RM, Vinay KN, et al. Basal cell adenoma of the submandibular gland. *J Maxillofac Oral Surg.* 2010;9:289–91.
13. Fantasia JE, Neville BW. Basal cell adenomas of the minor salivary glands. A clinicopathologic study of seventeen new cases and a review of the literature. *Oral Surg Oral Med Oral Pathol.* 1980;50:433–40.
14. Kleinsasser O, Klein HJ. Basalzelladenome der speicheldrüsen. *Arch Klin Exp Ohr Nas Kehlkopfsheilk.* 1967;189:302–16.
15. Nagao K, Matsuzaki O, Saiga H, et al. Histopathologic studies of basal cell adenoma of the parotid gland. *Cancer.* 1982;50:736–45.
16. Dardick I, Lytwyn A, Bourne AJ, et al. Trabecular and solid-ciribiform types of basal cell adenoma. A morphologic study of two cases of an unusual variant of monomorphic adenoma. *Oral Surg Oral Med Oral Pathol.* 1992;73:75–83.
17. Tian Z, Hu Y, Wang L, et al. An unusual ciribiform variant of salivary basal cell tumours: a clinicopathological study of 22 cases. *Histopathology.* 2012;61:921–9.
18. Headington JT, Batsakis JG, Beals TF, et al. Membranous basal cell adenoma of parotid gland, dermal cylindromas, and trichoepitheliomas. Comparative histochemistry and ultrastructure. *Cancer.* 1977;39:2460–9.
19. Reingold IM, Keasbey LE, Graham JH. Multicentric dermal-type cylindromas of the parotid glands in a patient with florid turban tumor. *Cancer.* 1977;40:1702–10.
20. Weinreb I, Seethala RR, Hunt JL, et al. Intercalated duct lesions of salivary gland: a morphologic spectrum from hyperplasia to adenoma. *Am J Surg Pathol.* 2009;33:1322–9.
21. Naunheim MR, Lin HW, Faquin WC, et al. Intercalated duct lesion of the parotid. *Head Neck Pathol.* 2012;6:373–6.
22. Montalli VA, Martinez E, Tincani A et al. Tubular variant of basal cell adenoma shares immunophenotypical features with normal intercalated ducts and is closely related to intercalated duct lesions of salivary gland. *Histopathology.* 2013. doi:10.1111/his.12339. (Epub ahead of print).
23. Klima M, Wolfe K, Johnson PE. Basal cell tumor of the parotid gland. *Arch Otolaryngol Head Neck Surg.* 1978;104:111–6.
24. Ward BK, Seethala RR, Barnes EL, et al. Basal cell adenocarcinoma of a hard palate minor salivary gland: case report and review of the literature. *Head Neck Oncol.* 2009;1:41–4.
25. Gross M, Maly B, Goldfarb A, et al. Basal cell adenocarcinoma in a buccal minor salivary gland. *Acta Otolaryngol.* 2004;124:213–6.
26. Nagao T, Sugano I, Ishida Y, et al. Basal cell adenocarcinoma of the salivary glands: comparison with basal cell adenoma through assessment of cell proliferation, apoptosis, and expression of p53 and bcl-2. *Cancer.* 1998;82:439–47.
27. Jung MJ, Roh JL, Choi SH, et al. Basal cell adenocarcinoma of the salivary gland: a morphological and immunohistochemical comparison with basal cell adenoma with and without capsular invasion. *Diagn Pathol.* 2013;8:171.
28. Chhieng DC, Paulino AF. Basaloid tumors of the salivary glands. *Ann Diagn Pathol.* 2002;6:364–72.
29. Robinson RA. *Head and neck pathology atlas for histologic and cytologic diagnosis.* Philadelphia: Lippincott Williams & Wilkins; 2010.
30. Li BB, Zhou CX, Jia SN. Basal cell adenoma of salivary glands with a focal ciribiform pattern: clinicopathologic and immunohistochemical study of 19 cases of a potential pitfall for diagnosis. *Ann Diagn Pathol.* 2014;18:5–9.
31. Murphy JG, Lonsdale R, Premachandra D, et al. Salivary hybrid tumour: adenoid cystic carcinoma and basal cell adenocarcinoma. *Virchows Arch.* 2006;448:236–8.
32. Ellis GL, Auclair PL. Basal cell adenocarcinoma. In: Ellis GL, Auclair PL, Gnepp DR, editors. *Surgical Pathology of the Salivary Glands.* Philadelphia: W.B. Saunders Co. 1991. p. 441–54.
33. Quddus MR, Henley JD, Affify AM, et al. Basal cell adenocarcinoma of the salivary gland: an ultrastructural and immunohistochemical study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1999;87:485–92.
34. Gown AM, Willingham MC. Improved detection of apoptotic cells in archival paraffin sections: immunohistochemistry using antibodies to cleaved caspase 3. *J Histochem Cytochem.* 2002;50:449–54.
35. Ben-Izhak O, Laster Z, Araidy S, et al. TUNEL—an efficient prognosis predictor of salivary malignancies. *Br J Cancer.* 2007;96:110–6.