What's New in the AFIP Fascicle on Salivary Gland Tumors: A Few Highlights from the 4th Series Atlas

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Abstract After a 12 year interval from the previous fascicle, a new fascicle on Tumors of the Salivary Glands in the new fourth series of the AFIP Atlas of Tumor Pathology was published in 2008. The data, presentation, illustrations, tables, and physical characteristics of the newest fascicle have been updated and improved. There have only been a few alterations and additions to the classification of tumors and tumor-like non-neoplastic conditions of salivary gland. Three of the most significant are discussed in this paper. Sialoblastoma has been reclassified as malignant; inflammatory pseudotumor has been reclassified as neoplastic and re-identified as inflammatory myofibroblastic tumor; and sclerosing polycystic adenosis is a new entity among tumor-like conditions.

Keywords Salivary gland · Neoplasia · Tumors · Neoplasms · Malignant · Benign · Statistics · Prevalence · Incidence · Clinical · Radiographic · Molecular · Immunohistochemistry · Prognosis · Management · Differential diagnoses

Introduction

Fascicle 17 in The 3rd Series of the AFIP Atlas of Tumor Pathology on Tumors of the Salivary Glands [1] was published in 1996. After a 12 year interval, a revised and updated *Tumors of the Salivary Glands* was recently published in 2008 in the AFIP Series 4 Atlas of Tumor Pathology, fascicle 9 [2]. This new fascicle includes

updated data, new illustrations, new graphs, revised and new tables, and better binding. In addition to these changes in presentation format and physical changes, there are some revisions to the classification of neoplasms and non-neoplastic tumor-like diseases. Unlike the classifications of tumors of some other organ systems, such as lymphoid and soft tissue tumors, which seem to undergo rapid and frequent modification, changes to the classification of salivary gland tumors is more incremental and evolutionary. Thus, there are only a few changes in the new fascicle from the tumors presented in the previous fascicle. This review will direct its attention to three of the more significant changes: sialoblastoma, inflammatory myofibroblastic tumor, and sclerosing polycystic adenosis.

Discussion

Sialoblastoma

In the second edition of the World Health Organization (WHO) Histologic Typing of Salivary Gland Tumours that was published in 1991 [3], there was no neoplasm identified as *sialoblastoma*. Under the section called *Other Carcinomas*, there was a two-sentence description of an entity called *embryonal carcinoma*, but the very limited histopathological description and absence of photomicrographs and clinical data do not allow comparison of this tumor to what is currently classified as sialoblastoma. Tumors believed to be consistent with sialoblastoma have been reported using terms such as embryoma, congenital carcinomas, congenital basal cell adenoma, adenoid cystic carcinoma, hybrid basal cell adenoma-adenoid cystic carcinoma, and low-grade basaloid adenocarcinoma [2, 4]. The term *sialoblastoma* appears to have been first used by

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Taylor [4] in 1988. The Third Series of the AFIP Atlas of Tumor Pathology, fascicle 17 on Tumors of the Salivary Glands, published in 1996, included and described sialoblastoma among the group of benign epithelial neoplasms [1]. However, because of the few reported cases and limited understanding of the biologic behavior of this tumor at that time, that publication expressed equivocation by stating, “Sialoblastoma is a rare, congenital or perinatal, aggressive and potentially low-grade malignant” neoplasm. Due to reports of multiple recurrences, aggressive growth, and metastasis, the WHO Classification of Tumours: Pathology and Genetics of Head and Neck Tumours published in 2005 [5] and the AFIP Series 4 Atlas of Tumor Pathology, fascicle 9, Tumors of the Salivary Glands published in 2008 [2] have included sialoblastoma among malignant epithelial salivary gland neoplasms.

Among the approximately forty cases that have been described in the literature [4, 6, 7], at least four patients experienced metastases and one patient died because of her tumor. Among the patients with metastases, three had pulmonary metastases [4, 8, 9] and one had lymph node metastases [10]. The patient that died experienced multiple recurrences and died of respiratory insufficiency and deterioration of her general health [11].

Sialoblastomas are congenital neoplasms, and most are evident at birth or shortly thereafter. Some tumors are identified by prenatal sonography. The simultaneous occurrence of hepatoblastoma has been reported [6]. The majority of tumors develop in the parotid glands as masses in the cheek or over the angle of the mandible. Som [12] reported a tumor anterior to the masseter muscle, which may indicate origin in accessory parotid gland tissue. Fewer tumors, but still a significant number, have occurred in the submandibular gland. There is no significant gender predilection. Tumors have ranged from 1.5 cm to as large as 15 cm. Tumors are usually firm and nodular and fixed to underlying structures and/or overlying skin. Nearly all patients appear to be asymptomatic, but one infant had facial paralysis at birth [10]. There is limited information on imaging studies, but the MRI signal intensity is similar to muscle on T1-weighted images and similar to fat on T2-weighted images [7, 12].

Because of the limited number of reported cases, it is still controversial whether morphologic variations in sialoblastomas are predictive of biologic behavior and allow categorization into benign and malignant types. It has been suggested that perineural invasion, vascular invasion, necrosis, and cytologic atypia beyond that expected for embryonic epithelium indicate aggressive behavior [13]. Williams et al. [4] have reported the largest series of cases and divided seven sialoblastomas into four with favorable histomorphology and three with unfavorable histomorphology that correlated with more aggressive behavior by

the three tumors with unfavorable histomorphology. However, the report by Brandwein et al. [14] indicates that caution may be warranted in trying to designate aggressive (malignant) and non-aggressive (benign) sialoblastomas on the basis of histomorphology alone. They reported the case of a 21-month old toddler that experienced recurrences or persistence of a sialoblastoma that required numerous procedures over a ten month period. The tumor demonstrated markedly increased features of malignancy in the last specimen compared to the initial surgical specimen.

Although there is histologic variability, characteristically, sialoblastomas are composed of numerous small, individual, and solid hypercellular islands of primitive, basaloid epithelial cells separated by fibrous or fibromyxomatous stroma (Fig. 1). Tumor cells have large, round to ovoid, vesicular nuclei and abundant, eosinophilic cytoplasm with indistinct cell borders. In some tumors, cells in solid areas have a high nuclear/cytoplasmic ratio and large basophilic nucleoli. In some areas, only thin fibrovascular septa separate the islands of tumor from one another, resulting in large, solid sheets of tumor. Within some epithelial islands, small ducts with distinct lumina are lined by cuboidal or low columnar cells. The lumina commonly contain a basophilic secretory product. The peripheral layer of cells in some tumors demonstrates palisading of nuclei. Cribriform spaces are sometimes focally evident. The proliferation of ductal and solid islands of epithelium mimics the developing fetal salivary gland. Acinar, squamous, and sebaceous differentiation are evident in some individual cases. Rarely, there are calcifications. Among tumors there is variation in cytomorphologic atypia, mitotic rate, necrosis, and frank infiltration [10].

Fig. 1 Sialoblastoma. Nests of basaloid cells have round, vesicular nuclei and poorly demarcated eosinophilic cytoplasm. Collagenous tissue of varying thickness separates tumor aggregates. There are foci of necrosis (*top center*) with dystrophic calcification

The immunoreactivity of sialoblastomas with antibodies to cytokeratin, smooth muscle actin, p63, and S-100 protein is similar to that of basal cell adenomas and basal cell adenocarcinomas and suggests that many of the non-luminal tumor cells have a basal or myoepithelial phenotype [4].

Although some tumors appear well circumscribed, there is often focal extension into surrounding tissues. Other tumors are markedly infiltrative, and the facial nerve is sometimes infiltrated by tumor. Necrosis, nuclear pleomorphism, mitotic rate, and the MiB1 proliferative index are variable among tumors. As noted above, one tumor exhibited increasing features of cytologic malignancy over time [14].

Williams et al. [4] associated semi-encapsulation of cytologically benign basaloid tumor cells in intervening stroma with a favorable prognosis and anaplastic basaloid tumor cells, minimal stroma, and broad pushing to infiltrative periphery with unfavorable prognosis. They also found that Ki-67 was expressed at 3% in one tumor with favorable histology and 15 and 50% in two tumors with unfavorable histology.

Other basaloid tumors are the primary consideration in the differential diagnosis and include basal cell adenoma, basal cell adenocarcinoma, and adenoid cystic carcinoma. All of these other tumors are remarkably rare in patients under 5 years of age, and a basaloid salivary gland tumor that occurs in an infant almost certainly would be more appropriately classified as sialoblastoma. In contrast to basal cell adenoma and basal cell adenocarcinoma, sialoblastoma is typically composed of more primitive cells that have less peripheral palisading of nuclei and demonstrates significant cytomorphologic atypia. The hyperchromatic, angular nuclei and pale to clear cytoplasm that characterizes the cytomorphology of many tumor cells in adenoid cystic carcinoma are usually absent in sialoblastoma.

Enucleation is probably inadequate treatment, even if the tumor appears well-circumscribed [7], and surgical excision with tumor-free margins is recommended therapy. Chemotherapy has had a role in some cases, but limited number of cases makes it difficult to meaningfully assess the efficacy of both chemotherapy and radiotherapy [4, 8–10].

Inflammatory Myofibroblastic Tumor

In the Third Series of the AFIP Atlas of Tumor Pathology, fascicle 17 on Tumors of the Salivary Glands [1], published in 1996, a lesion classified as *inflammatory pseudotumor* was identified as a reactive, mass-producing lesion in the chapter on *Tumor-like Conditions*. The term *pseudotumor* suffers from ambiguity and imprecise and inconsistent application of the diagnosis. In the past, in general, it has been used to identify non-neoplastic lesions whose clinical presentations suggested neoplasia. Williams et al. [15]

described six cases of inflammatory pseudotumor from the AFIP's files that involved the parotid glands. Similar lesions occur throughout the body but most often involve lung, mesentery, and omentum. Other terms that have been used to describe lesions with similar histology include *plasma cell granuloma*, *plasma cell pseudotumor*, and *inflammatory myofibrohistiocytic proliferation* [16]. Today, many of these lesions are considered neoplastic and preferentially classified as *inflammatory myofibroblastic tumors* [16]. A closely related term is *inflammatory fibrosarcoma* [16]. Thus, in the AFIP Series 4 Atlas of Tumor Pathology, fascicle 9, Tumors of the Salivary Glands published in 2008 [2], *inflammatory pseudotumor* has been reclassified as *inflammatory myofibroblastic tumor* (IMT) and included in the chapter on *Nonlymphoid Mesenchymal Neoplasms*.

IMTs affect patients of all ages but are predominantly tumors of children and young adults. Tumors in the parotid gland, however, have only occurred in older adults [15, 17, 18].

IMTs are circumscribed but unencapsulated tumors with infiltrative growth at their periphery. They are composed of spindle shaped myofibroblasts accompanied by an inflammatory infiltrate (Fig. 2). The spindle and stellate-shaped cells are often arranged in a storiform or fascicular pattern in a myxoid to hyaline stroma that typically contains focal to diffuse collections of lymphocytes, plasma cells, histiocytes, and scattered eosinophils.

The spindled cells are nearly universally immunoreactive for vimentin. While immunoreactivity for smooth muscle actin (SMA) and muscle specific actin in spindled cells is evident in nearly all tumors, reactivity varies from

Fig. 2 Inflammatory myofibroblastic tumor. There are numerous inflammatory cells scattered among a nodular mass of spindled cells, which have a haphazard arrangement. *Insert:* The inflammatory cell infiltrate is composed of plasma cells, lymphocytes, histiocytes, and eosinophils

Fig. 3 Inflammatory myofibroblastic tumor. An immunostain for smooth muscle actin reacts with many of the spindled cells

diffuse to only focal (Fig. 3). Desmin and cytokeratin reactivity are less frequent. About half of the tumors demonstrate immunoreactivity for anaplastic lymphoma kinase 1 (ALK) [16]. ALK gene rearrangements are frequent in tumors from children and young adults but infrequent in tumors of older adult patients.

In support of their classification as neoplasms, clonal abnormalities at 2p22-24 have been reported [16].

Principal considerations in the differential diagnosis include leiomyoma, leiomyosarcoma, myofibroma, and nodular fasciitis, all of which typically demonstrate immunoreactivity for SMA in spindled cells. All of these entities lack the conspicuous, diffuse inflammatory cell components of IMT. While inflammatory cells are a characteristic element of nodular fasciitis, they are typically fewer than in IMT, are more prominent along the periphery of the lesion, and lymphocytes, rather than plasma cells, predominate. Extravasated erythrocytes and a feathery, myxoid matrix also distinguish nodular fasciitis from IMT.

IMT are regarded as tumors with an indeterminate or low malignant potential [19]. Considering tumors from all sites, about one-fourth to one half recur, and a few tumors have metastasized, which has been related to tumor size [16, 20]. A few patients have died because of their disease, mostly due to local growth [20]. It has been suggested that tumors with cytologic atypia, p53 expression, ganglion-like cells and aneuploidy are more aggressive tumors [21]. In the parotid gland, surgery has been curative [15, 18].

Sclerosing Polycystic Adenosis

Sclerosing polycystic adenosis (SPA) was first described by Smith et al. [22] in 1996. Thus, it was an entity not included in the Third Series of the AFIP Atlas of Tumor

Pathology, fascicle 17 on Tumors of the Salivary Glands [1], published in the same year. Several subsequent cases have been reported [23], and it has been added to the chapter on Tumor-like Conditions of the AFIP Series 4 Atlas of Tumor Pathology, fascicle 9, Tumors of the Salivary Glands [2].

Smith et al. [22] considered SPA to be a rare, nodular, sclerotic and inflammatory lesion with some features similar to fibrocystic disease of the breast. Recently, controversy has arisen as to whether this lesion is a benign reactive lesion or a neoplasm [24]. Skalova et al. [24] reported lesions from six female patients that demonstrated a non-random pattern of X-chromosome inactivation using analysis of human androgen receptor (HUMARA) locus polymorphism. This non-random inactivation implies clonality. Reports of cytologic atypia or dysplasia within some tumors have added to the perplexing nature of this lesion [25]. However, no lesions with invasive carcinoma have been identified. While some lesions have recurred, none has metastasized and no patients have died.

Most lesions have occurred in the parotid gland with infrequent involvement of the submandibular and minor salivary glands. A slight majority of women have been affected. Children to elderly adults have been affected. Lesions are typically slow-growing and asymptomatic [22, 25].

The lesions are circumscribed but encapsulated nodules that range from 1 to 12 cm in diameter. The characteristic histologic features are hyalinized collagenous sclerosis, foci of ductal and acinar proliferation, cystic ducts, and chronic inflammation (Fig. 4). The prominent fibrosis often

Fig. 4 Sclerosing polycystic adenosis. There are many cystically dilated ducts as well as enlarged ducts with intraluminal epithelial hyperplasia (adenosis) within a sclerotic collagenous stroma. Note the area of nodular sclerosis on the right and the cystic duct with degenerating enlarged ductal cells with foamy cytoplasm on the left. *Inset:* acinar-like cells have enlarged eosinophilic cytoplasmic granules

contains rounded, hyalinized nodules, which sometimes surrounds aggregates of foamy histiocytes. The tubuloacinar hyperplasia has an indistinctly lobular pattern. Some cystic ducts have apocrine-like epithelium while others have a cribriform pattern of transluminal epithelial hyperplasia, which sometimes resembles collagenous spherulosis. In some cysts, the ductal epithelium has prominently foamy cytoplasm and appears to be degenerating. Foamy histiocytes are often associated with the areas of epithelial degeneration. Some acinar-like cells have large, eosinophilic, PAS-positive, cytoplasmic granules. Within the lesion is a chronic inflammatory cell infiltrate.

The differential diagnosis includes pleomorphic adenoma, cystadenoma, salivary duct carcinoma, and polycystic disease. SPA lacks the myxoid to chondroid component and myoepithelial proliferation of pleomorphic adenoma, and pleomorphic adenoma lacks the nodular sclerosis, xanthomatous infiltrate, inflammatory cells, and acinar-type cells with reddish granules that characterized SPA. Likewise, cystadenoma lacks these features. Salivary duct carcinoma is characterized by cellular pleomorphism, mitotic figures, comedonecrosis, and invasive growth and lack of nodular sclerosis, xanthomatous infiltrate, acinar-type cells, and foamy degeneration of cyst-lining epithelial cells. Polycystic disease is a diffuse rather than circumscribed disease process, and nodular sclerosis, xanthomatous infiltrate, acinar-type cells with eosinophilic granules, and foamy degeneration of cyst-lining epithelial cells are absent.

Local excision appears to be appropriate therapy.

Conclusion

While there have been additions to the data, presentation, illustrations, tables, and physical characteristics of the newest AFIP fascicle on salivary gland tumors from the previous fascicle published 12 years before, there has only been minimal change to the classification and the entities discussed in the new fascicle. Three of the most significant are: sialoblastoma has been reclassified as malignant rather than benign; inflammatory pseudotumor has been reclassified as neoplastic rather than reactive and called inflammatory myofibroblastic tumor; and sclerosing polycystic adenosis is a new entity among tumor-like conditions but remains ambiguous as to its reactive or neoplastic nature.

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