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Fat-Containing Salivary Gland Tumors: A Review

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Abstract Fat-containing tumors of the salivary glands are uncommon. Their wide histological spectrum varies from pure lipomatous neoplasms similar to their cutaneous and soft tissue counterparts to mixed lipoepithelial lesions specific to the salivary glands. With few exceptions, these uncommon lesions affect mainly the elderly, with a mean age at presentation of $\geq$50 years and show a predilection for males. A few cases occur in childhood; some of them represent congenital lesions. In decreasing order of frequency, ordinary (soft-tissue type) lipoma, oncocytic lipoadenoma, non-oncocytic sialolipoma, and pleomorphic adenoma/myoepithelioma with extensive lipometaplasia are the main variants of fat containing tumors encountered in the salivary glands. While pleomorphic adenoma/myoepithelioma with lipometaplasia behave in the same way as their non-fat-containing counterparts, other lipomatous salivary gland tumors listed above are cured with simple excision and do not carry a risk of recurrence. Other lipoma variants (spindle cell lipoma, osteolipoma, fibrolipoma, angiolipoma, pleomorphic lipoma, lipoblastoma and hibernoma) are exceptionally rare in the salivary gland. Atypical lipomatous tumors/liposarcoma have been only rarely reported in the salivary gland and they behave in a similar fashion to their soft-tissue counterparts. Diffuse lipomatosis and lobular fatty atrophy are the two tumor-like lesions that might closely mimic sialolipoma, particularly in limited biopsy material without knowledge of the gross findings. This review summarizes the clinicopathological features of the main types of salivary fat-containing lesions and discusses their differential diagnoses.

Keywords Sialolipoma · Lipoma · Adenolipoma · Oncocytic lipoadenoma · Lipometaplasia · Salivary gland

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Introduction

Fat-containing tumors of the salivary glands are uncommon. Their histomorphological spectrum varies greatly and ranges from minor scattered adipocytic elements within otherwise typical epithelial or mixed salivary gland tumors to predominantly lipogenic mixed tumors and pure lipomatous mesenchymal lesions indistinguishable from soft tissue adipocytic neoplasms [1, 2] (Table 1). Due to their rarity, there is no general agreement on the histogenetic classification and nomenclature of these lesions and a few lesions are not included in the current world health organisation (WHO) Classification of Head and Neck Tumours [2]. Based on their histological composition, fat-containing salivary gland lesions can be divided into monophasic true adipocytic neoplasms (lipoma and its variants and atypical lipomatous tumor/liposarcoma) and hybrid lipoepithelial lesions composed of epithelial derivatives admixed with a variable fatty component. The latter group can be further classified based on the nature of the epithelial component which may fit one of the well characterised salivary gland tumors such as pleomorphic adenoma and myoepithelioma. In addition, rare salivary gland tumors may display a fatty component associated with an epithelial component distinct from the above entities (sialolipomas and lipoadenomas). This review summarizes the main types of fat-containing salivary gland lesions and discusses their pertinent differential diagnoses.

Table 1 Fat-containing tumors and tumor-like lesions of salivary glands

1. Fat-containing epithelial/myoepithelial tumors
Pleomorphic adenoma with lipometaplasia
Myoepithelioma with lipometaplasia
2. Mixed lipoepithelial tumors
Sialolipoma (=non-oncocytic)
Oncocytic lipoadenoma
Unclassified polycystic lipoadenomatous lesions
3. True adipose tissue neoplasms
Ordinary lipoma
Rare lipoma variants (spindle cell lipoma, osteolipoma, fibrolipoma, angiolipoma, lipoblastoma, hibernoma, pleomorphic lipoma)
Atypical lipomatous tumor/liposarcoma
4. Fat-containing tumor-like salivary gland lesions
Diffuse/interstitial lipomatosis
Lipomatous lobular atrophy

Fat-Containing Epithelial/Myoepithelial Salivary Gland Tumors

Pleomorphic Adenoma and Myoepithelioma with Lipometaplasia

Although scattered, isolated adipocytes might be encountered in classical pleomorphic adenomas more commonly if thoroughly searched for, pleomorphic adenomas and myoepitheliomas with extensive lipometaplasia comprising ≥20 % of the tumor is exceedingly uncommon with less than 15 reported cases in the English literature to date (10 pleomorphic adenomas and 5 myoepitheliomas) [3–10]. Approximately 80 % of tumors involved major salivary glands (11/12 in the parotid) with only three cases in minor glands. The mean age of patients with myoepithelioma was higher than for pleomorphic adenoma (55 vs. 41 years). All of these tumors showed unequivocal areas of typical pleomorphic adenoma or myoepithelioma. However, the adipocytic component was usually more closely admixed with the epithelial/myoepithelial component in a manner that may closely mimic a mesenchymal lipomatous neoplasm (Fig. 1). Immunohistochemical examination confirms the epithelial (ductal and basal) or myoepithelial line of differentiation in these tumors. Prominent areas of hyaline cartilage and trabecular bone were seen in one case [8]. The fatty component and the occasional heterologous differentiation in these lesions probably represent the well known capacity of neoplastic myoepithelium to show pluriform mesenchymal transdifferentiation [11]. The adipocytic components comprised 20–90 % of the tumor mass in most cases. None of the reported case recurred after surgical excision.

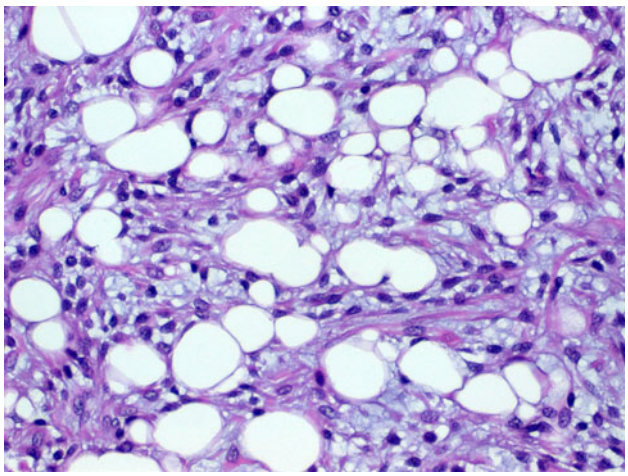

Fig. 1 Parotid gland myoepithelioma with extensive lipometaplasia closely mimicking a mesenchymal lipomatous neoplasm

Sialolipoma (Non-Oncocytic Adenolipoma)

The term *sialolipoma* was coined by Nagao et al. [12] in 2001 for biphasic salivary gland tumors that contain normal looking salivary gland elements (serous acini and ductal, myoepithelial and basal cells) admixed with a variable but usually prominent fatty tissue component. Although a few foci of oncocytic cells might be encountered in some cases, this variant generally lacks a significant oncocytic component. Close resemblance of sialolipoma to normal salivary gland architecture and its occasional occurrence in childhood allowed some authors to suggest a hamartomatous origin [13–18]. The term sialolipoma was included in the most recent 2005 world health organization (WHO) Classification of Head and Neck Tumors [2]. Since the series of Nagao et al. [12], approximately 35 cases of sialolipoma have been reported under diverse names in the English literature [reviewed in reference 19–21].

Sialolipoma is basically a non-oncocytic tumor that displays prominent lobulation and is predominantly composed of mature adipose tissue admixed with evenly distributed normal salivary tissue elements [2, 12]. The fatty component predominates over the epithelial elements (≥20–90 %) (Fig. 2). Foci of sebaceous metaplasia commonly associated with variable periductal inflammation and fibrosis represent a common finding in sialolipoma, but oncocytes are usually absent. Sialolipoma with prominent sclerotic change [22] should be distinguished from sclerosing polycystic adenosis of the salivary glands [23]. The latter represents a clonal disease associated with variable sclerosis, acinar cell hyperplasia and cystic ductal changes that have been likened to fibrocystic disease of the breast [24, 25]. In sharp contrast to the bland histology of sialolipoma, sclerosing polycystic disease may on occasion feature clear-cut epithelial dysplasia indistinguishable from in situ carcinoma of the breast [25, 26].

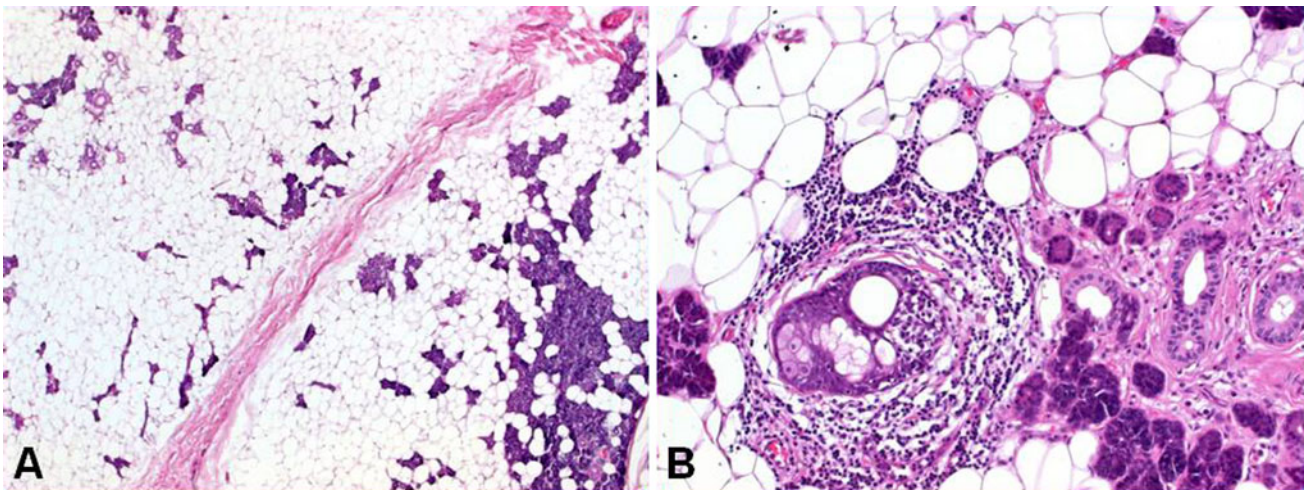

Fig. 2 **a** Sialolipoma showed lobules with a predominance of fat entrapping normal looking salivary elements. **b** Sebaceous metaplasia involving a duct with periductal lymphoid reaction. Note normal salivary tissue within the lesion on the right

The term *sialolipoma* seems more appropriate for this variant and is in line with the nomenclature used for similar lesions in other organs, such as thymolipoma and thyrolipoma. The histological appearance of sialolipoma and similar lesions in other organs clearly suggest that the epithelial component is not neoplastic but rather represents entrapped parenchymal cells. Thus this finding makes the alternative term *adenolipoma* inappropriate. Likewise, the designation lipoadenoma is inaccurate as the epithelial component is not adenomatous and this term would otherwise under-appreciate the predominant fatty component. The occasional presence of minor oncocytic foci should not justify the designation oncocytic sialolipoma.

Oncocytic Lipoadenoma

Salivary gland lesions composed predominantly of oncocytoma-like epithelial component admixed with variable adipocytic tissue remained poorly classified and were not included in the 2005 WHO classification [2]. These lesions have been published in the recent literature as single case reports under different names (oncocytic sialolipoma, oncocytic lipoadenoma and adenolipoma) [21, 27, 28]. To date, around 15 cases of oncocytic lipoadenomas have been reported; a majority of them featured foci of sebaceous differentiation [19–21].

Different from the fat-dominated sialolipoma, oncocytic lipoepithelial lesions (oncocytic lipoadenomas) tend to be predominantly epithelial thus meriting the designation lipoadenoma to emphasize the predominance of the epithelial component. The oncocytic component closely resembles oncocytoma and oncocytic adenoma [19–21]. The oncocytes either show close intermingling with the fatty cells or they may form discrete circumscribed oncocytic nodules within a lipoma-like background (Fig. 3). Scattered residual serous acini are commonly detectable between the oncocytic cells [21]. Foci of sebaceous metaplasia associated with variable periductal chronic inflammation and sclerosis is a common feature of both sialolipoma and oncocytic lipoadenoma suggesting relationship in some of the cases. Indeed, we previously have observed lesions with overlapping features of both variants [21]. Consistent with this view, cytogenetic studies on mammary adenolipoma (mammary analogue of sialolipoma) and oncocytic lipoadenoma of the parotid gland showed similar molecular alterations as soft tissue lipomas and pleomorphic adenoma (rearrangements of 12q13-15), suggesting that the fatty component is neoplastic and that the two variant of salivary tumors might be closely related genetically [29, 30]. Studies on the keratin profile and p63 expression in oncocytic

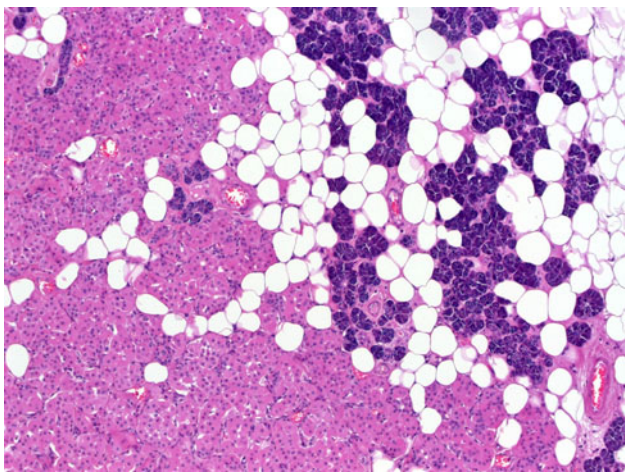

Fig. 3 Oncocytic lipoadenoma featured compact oncocytes resembling oncocytic adenoma with adjacent serous acini and fat cells

lipoadenoma demonstrated dual cell population similar to salivary oncocytomas [31].

Both sialolipoma and oncocytic lipoadenoma present at a wider age range than ordinary lipoma and may rarely occur in children. In one series, sialolipoma and oncocytic lipoadenoma were the only variants that occurred in patients <20 years old [21]. Due to congenital occurrence in some patients, a hamartomatous origin was suggested by some authors [13, 15, 16, 18]. Unlike salivary lipomas, sialolipoma and oncocytic lipoadenoma do not show a predilection for males. The main sites of origin for both variants are the parotid gland, the intraoral glands and the submandibular gland in decreasing order of frequency [19–21]. Both pursue a benign course and they are cured by simple excision [19–21].

Unclassified Polycystic Lipoadenomatous Lesions

Four cases of polycystic lipoepithelial salivary gland lesions having in common microcystic ductal structures have been reported under the designations *striated duct adenoma* [32], *lipoadenoma with probable striated duct differentiation* [33], *parotid lipoadenoma with sclerotic and polycystic changes* [22] and *microcystic lipoadenoma* [21] (Fig. 4). These four lesions were composed of variably cystic and solid ductal structures containing inspissated secretions and intermingled fatty cells. Some of these lesions displayed cystic changes that might suggest a diagnosis of sclerosing polycystic adenosis [25]. However, they lacked the prominent sclerosis, acinar hyperplasia and lobular pattern of sclerosing polycystic adenosis and they contained adipose tissue which is not a feature of sclerosing polycystic adenosis [25]. One lesion showed clear-cut basal cells and myoepithelial layer by immunohistochemistry, distinctly different from striated duct adenoma [21].

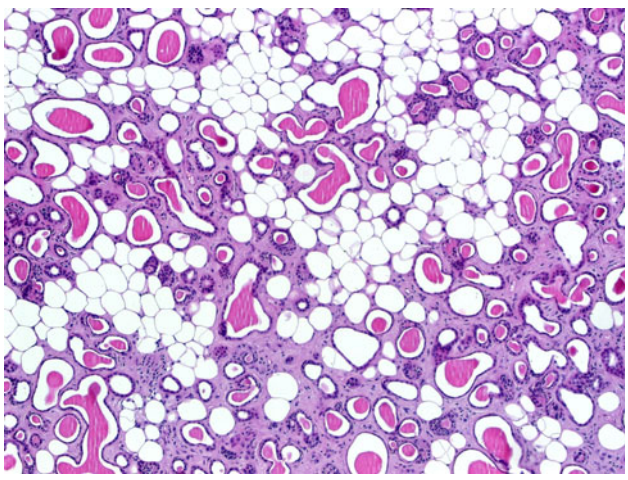

Fig. 4 This encapsulated nodule showed equal amount of adipocytes and cystic ducts within fibrous stroma. Microcystic lipoadenoma was suggested as a descriptive term for this unclassified rare lesion

True Adipose Tissue Neoplasms of Salivary Glands

Ordinary Lipoma

Ordinary lipoma represents the most common adipocytic lesion of the salivary glands. Lipomas represented 0.2–0.8 % of major salivary gland tumors and 22.5 % of all benign mesenchymal salivary neoplasms in large series [34–36]. Mainly adults are affected with a mean age of approximately 55 years and a clear-cut predilection for males (2–4:1) [21, 34]. Most salivary gland lipomas present as a slowly growing mass for months to several years. If patients with systemic fatty disorders (Madelung disease) are excluded, salivary gland lipoma occurs exclusively as a unilateral lesion [21]. The mean tumor size is 3.3 cm. ordinary lipoma of salivary gland is histologically indistinguishable from cutaneous and soft tissue lipomas except for their strict localization within the parenchyma of salivary gland (Fig. 5). Only rare lesions contain residual atrophic serous acini, but evenly distributed salivary gland structures are definitionally absent, a feature important in distinguishing ordinary lipoma from sialolipoma. Foci of sebaceous differentiation or oncocytic cells are not a feature of ordinary lipoma of salivary gland. Fatty lobular atrophy may occasionally be seen in the surrounding parenchyma [21]. Salivary lipomas are cured by simple excision. To date no recurrences have been reported.

Rare Lipoma Variants

The literature contains rare isolated case reports of uncommon lipoma variants that presented in the salivary glands. Spindle cell lipoma [37], osteolipoma [38], fibrolipoma [39], angiolipoma [40], lipoblastoma [41], hibernoma [42], and pleomorphic lipoma [43] are the main subtypes reported. Of these, spindle cell lipoma may mimic myoepithelioma with extensive lipometaplasia. Thus, encountering such a lesion should alert to this rare differential diagnosis and warrant use of specific markers (spindle cell lipoma is CD34 and may be desmin positive, but keratin negative while lipomatous myoepithelioma shows the inverse). Osteolipoma may closely mimic pleomorphic adenoma with bone and cartilage formation. Similarly, pleomorphic adenoma composed predominantly of chondroid matrix with admixed metaplastic fat thus mimicking chondroid lipoma. In summary, all these uncommon lipoma variants represent a diagnosis of exclusion and the diagnosis should be rendered only after a pleomorphic adenoma and myoepithelioma are carefully ruled out on the basis of histological and, if necessary, immunohistochemical analysis.

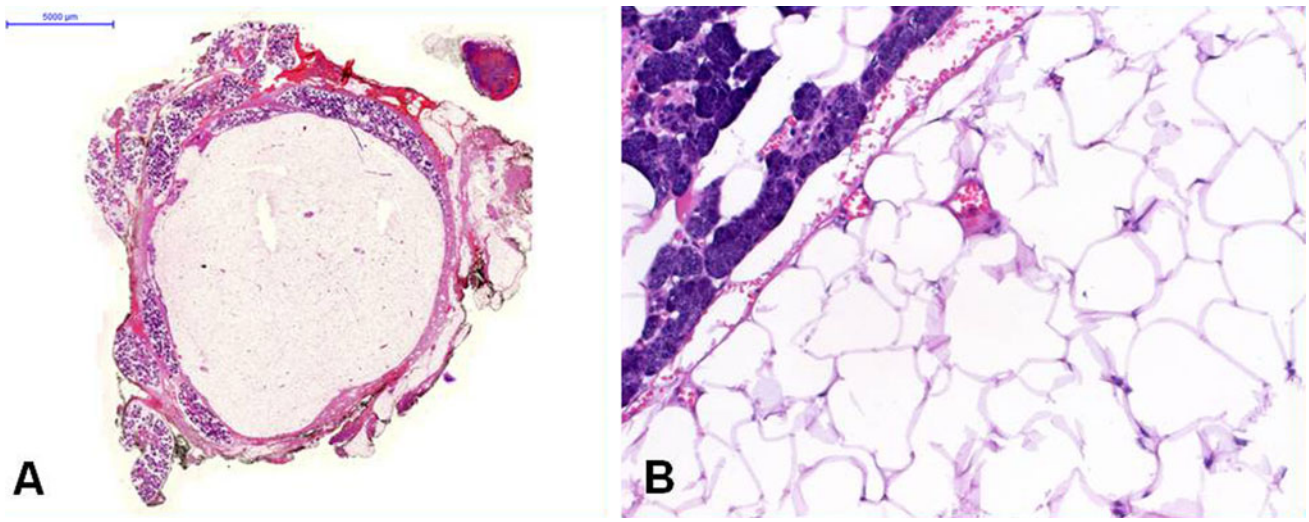

Fig. 5 **a** whole mount section of ordinary lipoma of parotid gland showed complete intraglandular location and encapsulation. **b** bland adipocytes are seen at higher magnification

Atypical Lipomatous Tumor/Liposarcoma

Liposarcoma is exceptionally rare in the salivary glands. Among two series of non-lymphoid mesenchymal salivary neoplasms reported from large centers or registries, liposarcoma was represented by a single case in the two studies (one myxoid liposarcoma and one pleomorphic liposarcoma) [34, 44]. However, the parotid gland was the third most common site for liposarcoma of the oral and salivary gland region in the AFIP series of 18 patients reported by Fanburg-Smith et al. [45] Histological subtypes of the four patients included in this latter study were well differentiated/lipoma-like (2), myxoid (1) and dedifferentiated (1) liposarcoma [45]. Rare cases of liposarcoma metastatic to the parotid gland have been reported and should be included in the differential diagnosis of liposarcoma at this unusual location [46]. Bilateral atypical lipomatous tumors of the neck may coexist with bilateral lipomatous changes of the parotid in patients with Madelung disease [21]. Another differential diagnosis of liposarcoma in the salivary gland is the rare occurrence of liposarcoma as a component of true malignant mixed tumor (carcinosarcoma) with heterologous differentiation [47].

Fat-Containing Tumor-Like Lesions of Salivary Gland

Interstitial Lipomatosis and Lipomatous Atrophy

Interstitial lipomatosis (diffuse lipomatosis) is an uncommon condition that affects the major salivary glands and rarely also the intraoral glands. However, diffuse lipomatosis leading to clinical swelling of the gland or even necessitating surgery in some cases is strictly uncommon [35]. A variable degree of increased interstitial fat may be occasionally observed in the parotid glands of patients with several underlying disease conditions including those with alcoholic liver cirrhosis [48] and rarely HIV patients managed with HAART treatment [49]. The condition features diffuse fatty infiltration resulting in diffuse swelling of the gland but without forming a discrete tumor mass or a capsule. Although mostly a disease of the elderly, diffuse lipomatosis rarely occur in children [50]. Presence of normal salivary duct structures intermixed with mature adipose tissue may mimic sialolipoma in fine needle aspiration or limited biopsy material, particularly if one is not aware of the gross and imaging findings (absence of a circumscribed gross mass). Thus, judgment of the presence or absence of a circumscribed mass grossly or as illustrated by imaging modalities is mandatory for correct biopsy interpretation. Lobular lipomatous atrophy (lipomatosis limited to one lobule of the gland) may closely mimic a mass and resemble sialolipoma [51]. However, the affected lobule is contiguous with other lobules of the salivary parenchyma (lacking a capsule) and the multilobular pattern of sialolipoma is absent. Furthermore, lobular lipomatous atrophy is usually associated with underlying obstructive, inflammatory or other diseases of the gland and displays other features related to atrophic changes including thick-walled vessels and ductular hyperplasia with periductal fibrosis.

Other Rare Mimics of Fat-Containing Salivary Gland Lesions

Several rare neoplastic lesions of the neck may closely mimic lipomatous salivary gland tumors. Ectopic hamartomatous

thymoma is a rare tumor often occurring within the lateral lower neck in close proximity to the sternoclavicular joint [52, 53]. This uncommon entity, described initially by Rosai et al. in 1984, features epithelial cells forming cords, solid nests and cysts admixed with plump spindle cell areas, islands of fatty tissue and lymphoid aggregates. The fatty component comprise up to 50 % of the tumor. The plump spindle cell component shows unequivocal myoepithelial differentiation [53]. Thus some ectopic hamartomatous thymomas with a prominence of spindle cells and fat might closely mimic and be difficult to distinguish from fat-containing myoepithelioma of parotid gland. Furthermore, one case in the original series by Rosai et al. contained a cluster of serous acini. Indeed, a salivary line of differentiation has been suggested by Michal et al. [54]. In contrast to sialolipoma, a prominent component of evenly distributed serous acini is lacking in ectopic hamartomatous thymoma. On the other hand, the characteristic corded, nested and cystic pattern of the epithelial islands and the presence of other typical constituents should make distinction from fat-containing salivary gland myoepithelioma possible. Fat-forming solitary fibrous tumor (SFT) is another uncommon neoplasm that may rarely present in the head and neck and mimic fat-containing myoepithelioma [55]. This tumor usually displays areas of conventional SFT associated with a variably adipocytic component. By immunohistochemistry, lipomatous SFT lack myoepithelial markers and express CD34, bcl-2 and CD99 [55].

In summary, fat-containing salivary gland tumors and lesions are heterogeneous in their histogenesis and morphological appearances with great overlap between some lesions. They encompass well defined salivary gland tumor entities (pleomorphic adenoma and myoepithelioma with lipometaplasia), tumors with oncocytic and lipomatous components (oncocytic lipoadenoma), tumors that recapitulate the architecture of normal parotid tissue (sialolipoma), true adipocytic neoplasms indistinguishable from cutaneous and soft tissue fatty tumors (lipoma and liposarcoma and their variants) and miscellaneous functional, metabolic or atrophic changes (lipomatosis, lobular atrophy). Careful analysis of both the overall architecture and the cellular constituents of a given lesion are mandatory for appropriate classification of these uncommon conditions.

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