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ORIGINAL PAPER

Oncocytic Lipoadenoma of the Salivary Gland: A Clinicopathologic Analysis of 7 Cases and Review of the Literature

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Abstract Oncocytic lipoadenoma is an exceedingly uncommon neoplasm of the salivary gland composed of oncocytic epithelium and adipose tissue. Retrospective. Seven cases of oncocytic lipoadenoma were analyzed in order to further characterize the clinical and pathologic features of this rare tumor. The patients included six males and one female who ranged from 40 to 83 years of age (mean 62 years) at presentation. All tumors arose in the parotid gland. Grossly, the tumors were solitary, well circumscribed and had light brown to yellow cut surfaces. Histologically, the tumors were composed of an admixed population of oncocytes and adipocytes in varying proportions, with the lipomatous component ranging from 5 to 70 %. Other common features included the presence of serous acini, ductal elements, sebaceous glands, and a patchy chronic inflammation. Clinical follow up information, available in all cases, with a duration of 3–148 months (mean 57 months), showed no evidence of tumor recurrence. Due to its rarity, oncocytic lipoadenoma can pose problems in diagnosis, although the distinctive morphologic features of this neoplasm allow for separation from more commonly recognized oncocytic neoplasms of the salivary glands.

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Introduction

Oncocytic neoplasms of the salivary glands consist of a wide array of morphologically diverse tumors, all of which are characterized histologically by a predominance of oncocytes. With the exception of papillary cystadenoma lymphomatosum (Warthin tumor), salivary gland tumors with prominent oncocytic features are uncommon, and include oncocytoma, oncocytic carcinoma, and oncocytic cystadenoma, as well as oncocytic variants of pleomorphic adenoma, myoepithelioma, mucoepidermoid carcinoma, and epithelial-myoepithelial carcinoma [1–11].

Another recently characterized oncocytic neoplasm arising in the salivary gland has been termed *oncocytic lipoadenoma*. First described in 1998, oncocytic lipoadenoma is a histologically distinctive tumor composed of oncocytic cells and mature adipocytes [12]. The tumor is decidedly rare; with only a few examples in the literature, mostly as case reports [13–24]. With scant published data, we analyzed seven new cases of oncocytic lipoadenoma in order to further delineate the clinicopathologic features of this unusual salivary gland neoplasm, combined with a thorough review of the literature.

Materials and Methods

Seven cases of oncocytic lipoadenoma were identified from the files of the Departments of Pathology within Southern California Permanente Medical Group. Hematoxylin and eosin stained slides from all cases were reviewed, with a

Table 1 Clinicopathologic features of seven cases of oncocytic lipoadenoma

Case no.	Age (years)	Sex	Symptom duration	Anatomic site and side	Size (cm)	% Fat component	Treatment	Follow-up (months)
1	61	Male	15 years	Left parotid gland	2.0	20	Superficial parotidectomy	ANED (42)
2	83	Male	3 months	Right parotid gland	2.5	15	Superficial parotidectomy	ANED (12)
3	67	Male	6 months	Right parotid gland	4.0	5	Superficial parotidectomy	ANED (3)
4	40	Female	9 months	Right parotid gland	4.0	50	Superficial parotidectomy	ANED (148)
5	56	Male	"Years"	Left parotid gland	3.5	70	Superficial parotidectomy	ANED (110)
6	65	Male	24 months	Left parotid gland	1.9	50	Superficial parotidectomy	ANED (57)
7	65	Male	24 months	Right parotid gland	3.5	50	Superficial parotidectomy	ANED (26)

ANED alive with no evidence of disease

range of 1–9 slides (mean 4 slides) per case available for analysis. Clinical data, treatment, and follow-up information were obtained from electronic medical records. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of an Internal Review Board authorization (#5968) performed under the direction of Southern California Permanente Medical Group and the Code of Federal Regulations, Title 45, Part 46.

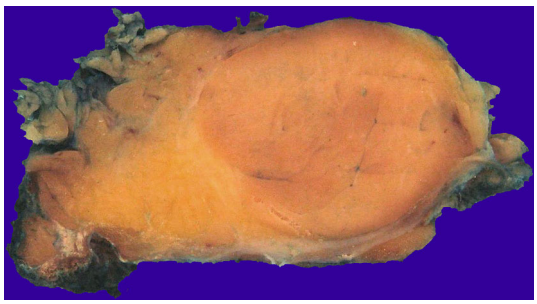

Fig. 1 Macroscopically oncocytic lipoadenoma is represented by a well circumscribed nodule with a light brown cut surface

Results

Clinical Features

Clinical data are summarized in Table 1. The patients included six men and one woman. Their ages at presentation ranged from 40 to 83 years of age, with a mean age of 62 years (median 65 years). A description of clinical symptoms was available for all patients. Six patients presented with a painless, slow growing neck mass, while one patient complained of headache and ear pain. The duration of symptoms ranged from 3 to 180 months (mean 41 months). All tumors were located in the parotid gland (4 right, 3 left). Preoperative fine needle aspiration of the tumor was performed in six patients, with diagnoses of pleomorphic adenoma (n = 2), Warthin tumor (n = 1), oncocytic lesion (n = 1), and nondiagnostic (n = 2).

Pathologic Features

On gross examination, the tumors were well circumscribed and limited to the parotid gland, with solid homogeneous, light brown or yellow cut surfaces (Fig. 1). The tumors ranged from 1.9 to 4.0 cm in greatest dimension (mean 3.1 cm).

Microscopically all tumors were surrounded by a thin, fibrous capsule (Fig. 2a). In three cases, the capsule was poorly formed and incomplete, with areas of uninvolved salivary gland parenchyma directly adjacent to tumor. The tumors were composed of a mixed population of oncocytes and adipocytes in varying proportions (Fig. 2b). The oncocytes were round to polygonal with distinct cell borders and abundant granular, eosinophilic cytoplasm. Nuclei were centrally located, with a vesicular to pyknotic appearance, and contained small, variably prominent nucleoli. The oncocytes were arranged in compact nests and small acini. The adipocytic component of the tumors ranged from 5 to 70 %. The adipocytes had the appearance of mature fat, with mild variability in size and peripherally located hyperchromatic, small nuclei. In some tumors, the adipocytes were relatively evenly dispersed between the

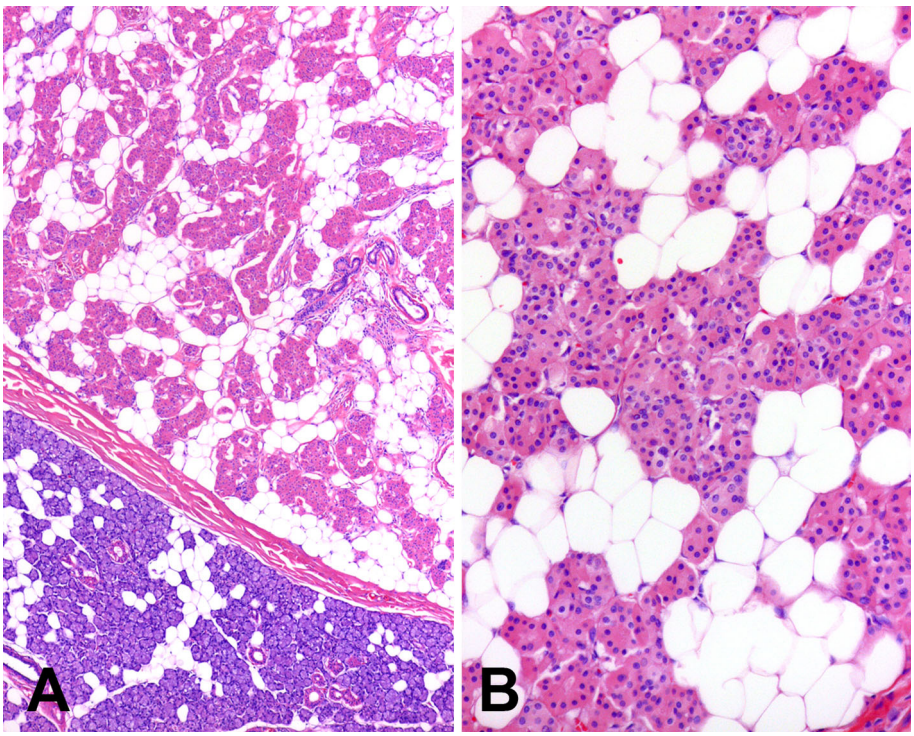

Fig. 2 Microscopically oncocytic lipoadenomas are (**a**) surrounded by a fibrous capsule and (**b**) composed of oncocytes and adipocytes

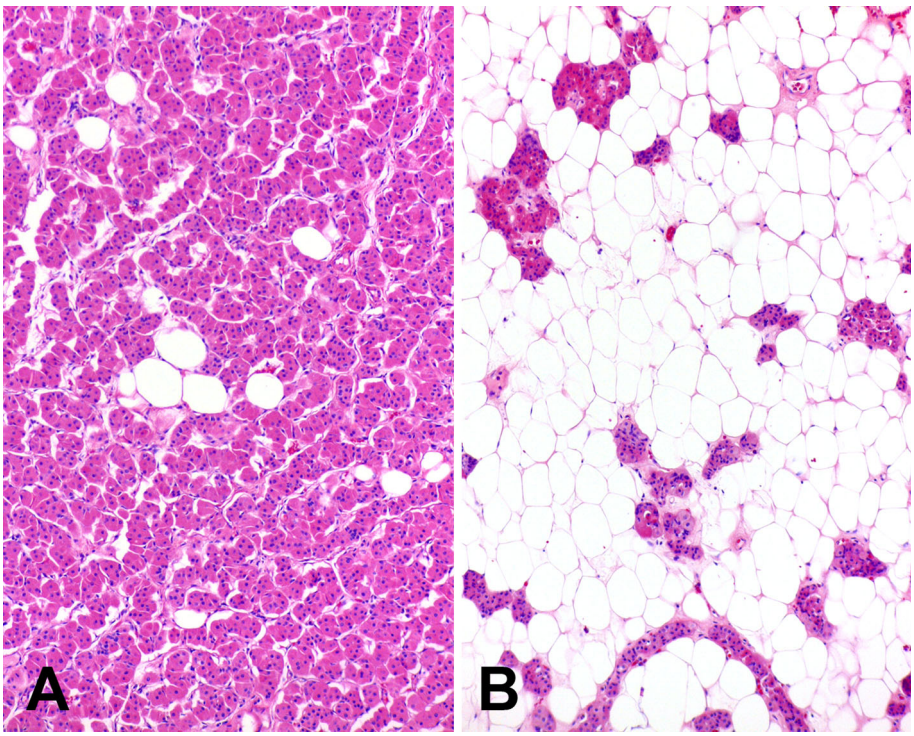

Fig. 3 Oncocytic lipoadenomas may have a variable appearance with either the (**a**) oncocytic or (**b**) lipomatous components of the tumor predominating

nests of oncocytes, while in others they were irregularly distributed, resulting in areas dominated by adipose tissue with scant oncocytes or a prominent oncocytic component with a paucity of fat cells (Fig. 3). Neither the oncocytic nor the lipomatous components of the tumors showed any cellular pleomorphism or mitoses.

Scattered ductal elements were observed as a minor feature in all cases (Fig. 4a). These consisted of collections of striated ducts as well as larger interlobular ducts, often with periductal fibrosis. Conspicuous serous acini were present in four tumors (Fig. 4b) and rare sebaceous glands were identified in six tumors (Fig. 4c). Six tumors

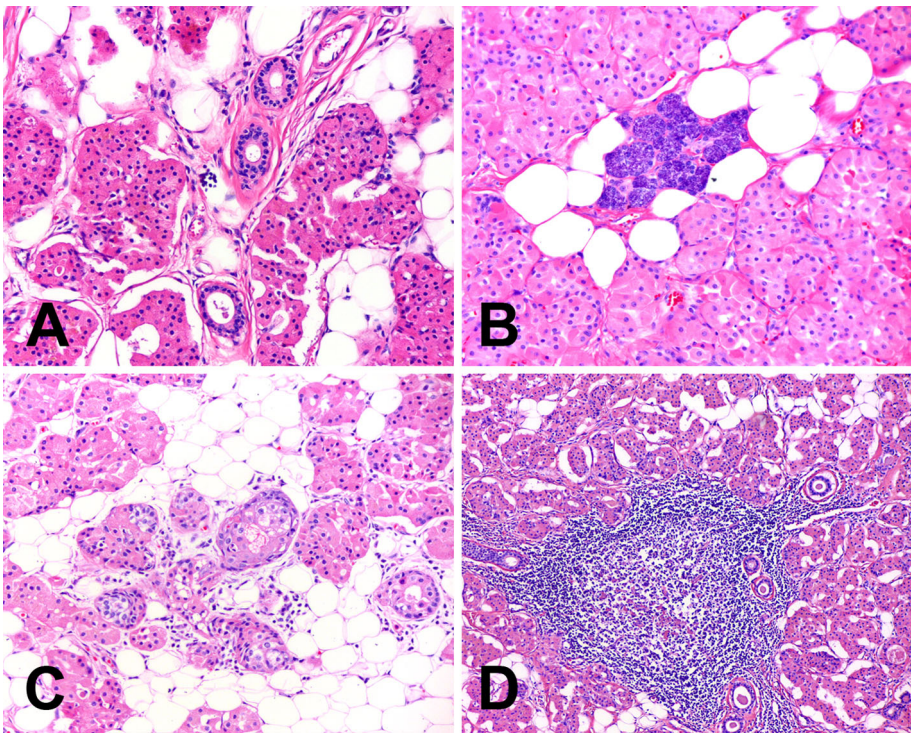

Fig. 4 Other microscopic findings often seen in oncocytic lipoadenomas include (**a**) ductal elements, (**b**) serous acini, (**c**) sebaceous glands, and (**d**) chronic inflammation

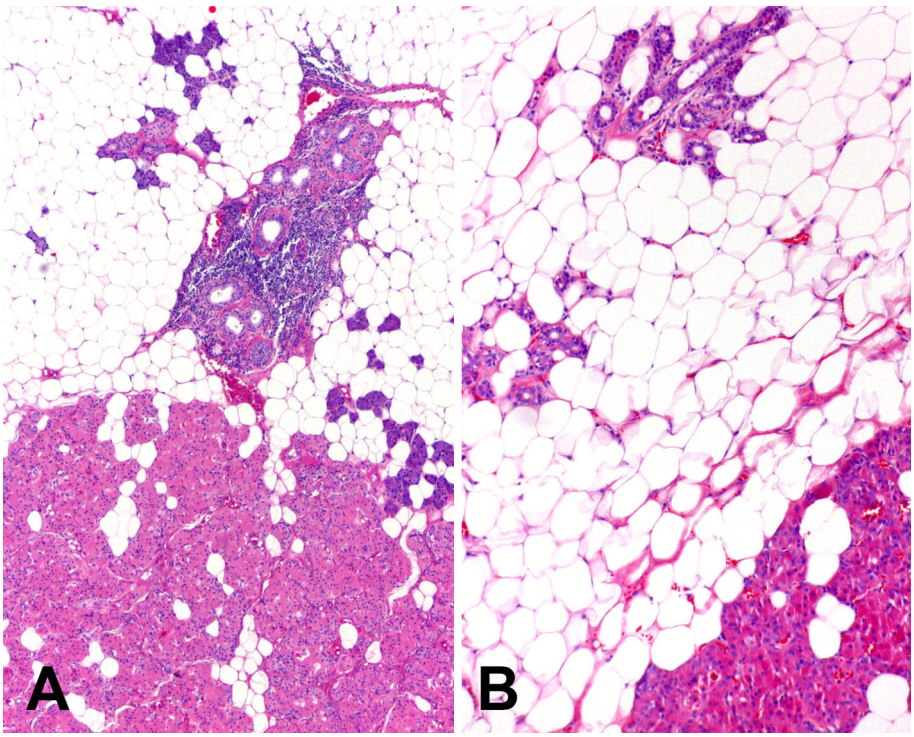

Fig. 5 (**a**) Low and (**b**) intermediate magnification images of an example of oncocytic lipoadenoma with an area resembling sialolipoma. The *lower aspects* of the images show the typical microscopic appearance of oncocytic lipoadenoma while the *upper aspects* show a predominance of mature adipose tissue with scattered normal salivary gland ducts and acini similar to that observed in sialolipoma

displayed a patchy inflammatory infiltrate composed predominantly of small lymphocytes and occasional plasma cells. The lymphocytic infiltrate was particularly prominent in one case with well formed germinal centers (Fig. 4d). Stromal alteration characterized by dense fibrocollagenous tissue was seen in one case.

One unusual tumor, in addition to admixed oncocytic and lipomatous components, contained a well delineated area composed of predominantly adipose tissue with islands of salivary gland duct-acinar units resembling sialolipoma (Fig. 5). None of the tumors exhibited necrosis, vascular invasion, perineural invasion, capsular invasion, or extraglandular extension.

Table 2 Previously reported cases of oncocytic lipoadenoma of the salivary glands

References	Age (years)	Sex	Anatomic site	Size (cm)	% Fat component	Follow-up (months)
Hirokawa et al. [12]	66	F	Submandibular gland	11.0	50	ANED (30)
Kato and Korie [13]	57	F	Parotid gland	4.4	40	NR
Klieb and Perez-Ordoñez [14]	46	F	Parotid gland	3.0	30–40	ANED (6)
Aouad et al. [15]	38	M	Parotid gland	4.0	NR	NR
Pusiol et al. [16]	73	M	Submandibular gland	9.0	80	ANED (NR)
Chahwala et al. [17]	50	F	Parotid gland	13.5	NR	NR
Ilie et al. [18]	64	M	Parotid gland	5.0	70	ANED (24)
Tokyol et al. [19]	56	M	Parotid gland	7.0	40	ANED (6)
McNeil et al. [20]	70	M	Parotid gland	4.2	40	NR
Mitsimponas et al. [21]	55	F	Parotid gland	2.4	10	ANED (12)
Casadei et al. [22]	NR	M	NR	NR	30	ANED (NR)
Casadei et al. [22]	NR	F	Submandibular gland	NR	30	ANED (NR)
Casadei et al. [22]	NR	F	Parotid gland	NR	30	ANED (NR)
Devadoss et al. [23]	50	F	Parotid gland	13.5	50–60	ANED (24)
Agaimy et al. [24]	63	M	Parotid gland	4.5	10	ANED (6)
Agaimy et al. [24]	29	M	Parotid gland	4.5	20	ANED (141)
Agaimy et al. [24]	54	F	Parotid gland	2.9	10	ANED (18)
Agaimy et al. [24]	55	M	Parotid gland	2.7	70	ANED (13)
Agaimy et al. [24]	7	F	Parotid gland	NR	50	NR
Agaimy et al. [24]	89	M	Parotid gland	4.2	80	NR

M male, *F* female, *NR* not reported, *ANED* alive with no evidence of disease

Treatment and Follow-up

Treatment consisted of superficial parotidectomy in all cases. Clinical follow up information was available for all patients with a mean duration of 57 months (range 3–148 months). None of the patients developed local recurrence and all are alive with no evidence of disease.

Discussion

Lipoadenoma and adenolipoma are designations used to refer to neoplasms composed of epithelial and lipomatous elements. They have been described in many anatomic sites, including the skin, breast, parathyroid, thyroid, and salivary gland [24–31]. Mixed lipomatous and epithelial tumors where the latter component is comprised of oncocytes have been termed oncocytic lipoadenoma, which appear to be unique to salivary glands. Oncocytic lipoadenoma is rare; to date twenty cases have been reported in the literature (Table 2) [12–24]. The "adenoma" designation highlights the predominance of the epithelial component, rather than sialolipoma which emphasizes the fatty component. Combining the cases from the present clinical series with those previously described shows a wide age range at presentation (7–89 years) with a mean age of 57.7 years. The tumor occurs slightly more frequently in men than women, with a male to female ratio of 1.5:1. Patients typically present with a painless, slowly growing mass or swelling that has not uncommonly been present for an extended duration of time (mean 34.5 months; range 2–180 months) [12, 14, 15, 17–21, 23]. The vast majority of oncocytic lipoadenomas have originated in the parotid gland, with only few reports of submandibular gland involvement [12, 16, 22]. The tumor has thus far not been documented in minor salivary glands. Based on present data and other reports, oncocytic lipoadenoma appears to be a benign tumor with no risk or recurrence or aggressive behavior (mean follow up 40 months) [12, 14, 18, 19, 22–24].

On gross examination, oncocytic lipoadenomas are well circumscribed neoplasms with pushing borders. The cut surface may vary from tan to brown to yellow, depending on the amount of adipose tissue present. Histologically there is typically evidence of a thin fibrous capsule separating the tumor from the surrounding salivary gland parenchyma. The neoplasm has a morphologically distinctive appearance characterized by the presence of two distinct cell populations: oncocytes and adipocytes. The oncocytes are usually arranged in nests and acini with a microscopic appearance resembling a conventional oncocytoma. The lipomatous component of the tumor has the

appearance of mature adipose tissue and can comprise as little as 5 % to as much as 80 % of the tumor volume [12–24]. The adipocytes may be relatively evenly dispersed among the oncocytes, or may be irregularly distributed with either the oncocytic or lipomatous component predominating in a given area of the tumor. This should be taken into consideration when rendering a diagnosis on core needle biopsy or fine needle aspiration material, where sampling is limited.

Although not typically emphasized, foci of normal salivary gland elements including ducts, serous acini, and sebaceous glands, are a frequent finding in oncocytic lipoadenomas [14, 16, 18–21, 24]. A mild tumor associated lymphocytic inflammatory infiltrate, seen in the majority of the cases in the present series and similarly observed by others, is also a common feature [12, 14, 18–21, 24].

The histologic appearance of oncocytic lipoadenoma is sufficiently distinctive to be recognizable on routine hematoxylin and eosin stained sections. Immunohistochemical studies are not usually required for diagnosis, though the immunophenotype of oncocytic lipoadenoma has been previously elucidated. The lesional oncocytes express AE1/AE3, CK7, and EMA [13, 14, 18–20, 23], with p63, CK5/6, CK14, CK19, and high molecular weight keratin positivity observed in a basal cell distribution [14, 18, 20]. The tumor cells are negative for muscle specific actin, smooth muscle actin, and calponin [14, 18–20, 23].

The principle differential diagnostic considerations of oncocytic lipoadenoma include other oncocytic neoplasms of the salivary gland. Among the various salivary gland tumors exhibiting a prominent oncocytic component, oncocytic lipoadenoma is most likely to be mistaken for oncocytoma. Both are well circumscribed tumors comprised of classical eosinophilic oncocytic cells. Oncocytomas, however, are composed exclusively of oncocytes and lack the lipomatous component characteristic of oncocytic lipoadenoma. The presence of adipose tissue similarly allows for separation of oncocytic lipoadenoma from stroma poor Warthin tumor, Warthin tumor with nodular oncocytic proliferation, and oncocytic pleomorphic adenoma. Nodular oncocytic hyperplasia shows multifocal nests of oncocytes intermixed with adipocytes and normal acinar cells, perhaps simulating the appearance of oncocytic lipoadenoma. Oncocytic lipoadenoma, however, is at least partially surrounded by a fibrous connective tissue capsule, while nodular oncocytic hyperplasia represents an unencapsulated proliferation of oncocytes frequently with multifocal distribution.

The differential diagnosis also includes sialolipoma. Sialolipoma is characteristically composed predominantly of adipose tissue with admixed islands of salivary gland acini, ductal, myoepithelial and basal cells [32]. The epithelial/myoepithelial elements may show focal oncocytic change in some cases [32–35], but unlike oncocytic lipoadenoma, sialolipoma in general lacks a prominent oncocytic component. The tumor tends to show lobulation with evenly distributed salivary gland elements within the fat.

In the present series we did observe one case that showed a discrete area resembling sialolipoma within an otherwise typical oncocytic lipoadenoma. Similar salivary gland tumors exhibiting features of both oncocytic lipoadenoma and sialolipoma have been illustrated by other investigators, one of which was described using the term "oncocytic sialolipoma" [16, 24]. Whether to classify such lesions as oncocytic lipoadenoma, oncocytic sialolipoma, or as a hybrid lipoepithelial salivary gland tumor remains to be determined. Nonetheless, the existence of these phenotypically mixed cases suggests a possible histogenetic relationship between oncocytic lipoadenoma and sialolipoma.

The pathogenetic mechanisms underlying the development of oncocytic lipoadenoma remain elusive. It could be argued that the neoplasm represents an oncocytoma with lipomatous metaplasia. Adipocytic differentiation in salivary gland tumors such as pleomorphic adenoma has been attributed to transdifferentiation of constituent myoepithelial cells resulting in metaplastic transition to adipocytes [36, 37]. However, ultrastructural and immunohistochemical studies have not demonstrated a definite myoepithelial cell population in oncocytic lipoadenoma [13, 14, 18–20, 23]. A subset of cells immunoreactive for p63 and basal type keratins have been observed in oncocytic lipoadenomas in a peripheral basal cell type distribution, though the exact nature of this particular cell population is unclear [14, 18, 20]. These could represent pluripotent basal or stem cells capable of lipomatous metaplastic change, though this remains speculative.

From a molecular genetics perspective, cytogenetic analysis has been performed on a single case of oncocytic lipoadenoma which demonstrated a t(12;14) translocation involving the high mobility group AT-hook 2 (*HMGA2*) gene on chromosome 12 [18]. *HMGA2* encodes a protein belonging to the non-histone high mobility group protein family. The protein influences an array of cellular processes through regulation of gene transcription [38]. In addition to oncocytic lipoadenoma, *HMGA2* gene rearrangements have also been recognized in a number of other neoplasms, including soft tissue lipomas and a subset of salivary gland pleomorphic adenomas [39, 40]. Further molecular analyses may yield more definitive evidence as to the significance of *HMGA2* gene disruption in the development of oncocytic lipoadenoma.

Oncocytic lipoadenoma is a unique salivary gland neoplasm. The current 7 cases serves to further characterize the clinical and pathologic features of this rare tumor. Oncocytic lipoadenomas have a distinctive morphologic

appearance that permits accurate diagnosis and separation from other salivary gland neoplasms with a prominent oncocytic component. Clinically, the tumor behaves in a benign fashion, with no risk of recurrence following surgical excision.

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