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Oncocytic Tumors in the Salivary Gland: A Tri-Focal Review – Integrated Cytopathological, Pathological, and Molecular Features

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Abstract

Background: Primary oncocytic salivary gland tumors and oncocytic subtypes of traditionally non-oncocytic salivary gland neoplasms are occasionally encountered in fine needle aspiration specimens, biopsies, and resections. Oncocytes are cells, either non-neoplastic or neoplastic, containing increased numbers of mitochondria resulting in cells with abundant eosinophilic cytoplasm and a low N/C ratio. ***Summary:*** A broad range of salivary gland tumors can be oncocytic including oncocytoma, Warthin tumor, mucoepidermoid carcinoma, salivary duct carcinoma, and others, especially those tumors where the oncocytic pattern represents a subtype of neoplasm; the oncocytic pattern can create a diagnostic challenge due to marked similarities in the oncocytic pattern of cells. ***Key Messages:*** While their microscopic cytologic and histologic features may be similar, these tumors differ intrinsically at the molecular level. Ancillary studies such as immunologic (e.g., androgen receptor for salivary duct carcinoma) and molecular analysis, e.g., FISH for detecting the *MAML2* or *PLAG1/HMGA2* gene alterations in mucoepidermoid carcinoma and pleomorphic adenoma, respectively, can be used to classify these oncocytic tumors in difficult cases.

Introduction

Oncocytic cells represent a special phenotype of neoplastic cells, reflecting a unique biologic process characterized by a prominent proliferation of morphologically abnormal mitochondria in the cytoplasm. This phenotype is driven by specific molecular mechanisms that interfere with mitochondrial function and metabolism [1]. The exact mechanisms of oncocytic transformation in salivary gland tumors have not been fully established, although mutations in mtDNA genes and alterations in nuclear DNA genes encoding mitochondrial proteins have been described. In 1931, Hamperl coined the term oncocyte (Onkocyten) to describe cells having abundant eosinophilic granular cytoplasm and a centrally located hyperchromatic nucleus [2]. In some cases, secondary to condensation of the cytoplasmic

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mitochondrial contents, oncocytic tumors can exhibit a clear cell appearance.

Oncocytic tumors composed entirely of oncocytes are by no means rare and have been reported, with different frequencies, in virtually every organ. In normal salivary glands, oncocytic metaplasia of ductal and acinar cells is commonly encountered, especially in older adults, but primary, pure oncocytic neoplasms, except for Warthin tumor, are comparatively rare.

In the salivary glands, the presence of oncocytic change in >75% can be observed in numerous histological subtypes of originally *non-oncocytic tumors*. Oncocytic metaplasia has been reported in mucoepidermoid carcinoma (MEC), cystadenoma, myoepithelioma (ME)/pleomorphic adenoma (PA), intraductal carcinoma (IC), and many other tumors. As a minor component, oncocytic change in salivary gland tumors is not uncommon, and it does not cause significant difficulties in the differential diagnosis and classification of these neoplasms in histologic or cytologic specimens. A critical issue to remember, however, is that some tumors can be diffusely or almost completely oncocytic without a well-defined non-oncocytic component.

There is no consensus about the existence of *salivary oncocytic carcinoma.* In the past, carcinomas consisting entirely of oncocytes were frequently diagnosed as oncocytic carcinoma. Oncocytic appearance is, however, a common change encountered in many different salivary gland tumors. Moreover, molecular studies have shown that many such tumors are oncocytic variants of other specific salivary carcinomas. As such, oncocytic carcinoma was not included in the recent WHO Classification of Head and Neck Tumors, 5th edition as an independent entity [3].

Primary Oncocytic Salivary Gland Tumors

Histopathology

Oncocytoma is a benign-encapsulated neoplasm composed of large epithelial cells with abundant eosinophilic granular cytoplasm due to the accumulation of mitochondria. Over 80% of cases occur in the parotid gland, approximately 10% in the submandibular gland, and the rest in the minor salivary glands and sublingual gland. Oncocytoma may arise in a background of *multinodular oncocytic hyperplasia*. Oncocytomas are characterized by polygonal cells with abundant granular eosinophilic cytoplasm and relatively uniform nuclei (Fig. 1a). Though uncommon, oncocytic and clear cell subtypes of malignant tumors may histologically mimic oncocytomas and identification of their distinguishing features is essential.

Nodular oncocytic hyperplasia may present as a clinically relevant mass, like an oncocytoma, and it may be very difficult to reliably differentiate between the two even through histological evaluation. In this scenario, the presence of a well-developed capsule, and unifocality of the oncocytic proliferation, is suggestive of an oncocytoma (Fig. 1b).

Warthin tumor is a benign salivary gland tumor composed of oncocytic epithelial cells lining ductal, papillary and cystic structures in a lymphoid stroma. Tumors are almost exclusively restricted to parotid glands, especially the inferior pole, and peri-parotid lymph nodes. Warthin tumor accounts for 5–20% of all salivary gland tumors. The cyst lining of Warthin tumor is composed of a double layer of oncocytes (Fig. 2a).

Cytopathology

Fine-needle aspiration (FNA) of *oncocytoma* yields cellular aspirates containing a population of large, polygonal-shaped cells with abundant dense, homogenously granular oncocytic cytoplasm (Fig. 1c, d). Nuclei are uniform, enlarged and round, and contain a distinct nucleolus. The cytologic features are bland; mitotic activity, nuclear pleomorphism, and a necrotic background are absent. The cells are arranged in dyshesive sheets and some crowded clusters. Small capillaries may be present with tumor cells surrounding them. The background lacks stripped nuclei, mucin, and proteinaceous material. The cytologic interpretation of these aspirates in combination with clinical and radiologic findings will usually favor an oncocytoma, and it may not be possible to entirely exclude other oncocytic salivary gland tumors due to the overlapping cytoplasmic oncocytic features [4–6]. Aspirates with oncocytic nodules within *nodular oncocytic hyperplasia* (Fig. 1e) are cytologically indistinguishable from aspirates of oncocytoma, although imaging findings may suggest the diagnosis [7].

Most FNAs of *Warthin tumor* exhibit characteristic cytologic features such that a specific classification of Warthin tumor can be made [8]. Aspirates are cystic and display a trilogy of features: (1) cohesive clusters of oncocytes, (2) scattered small lymphocytes, and (3) dirty proteinaceous background debris (Fig. 2b, c). The oncocytes are uniform and present in small cohesive groups with well-defined cell borders. Background lymphocytes are polymorphous with a predominance of small mature lymphocytes. The background debris is often granular and may

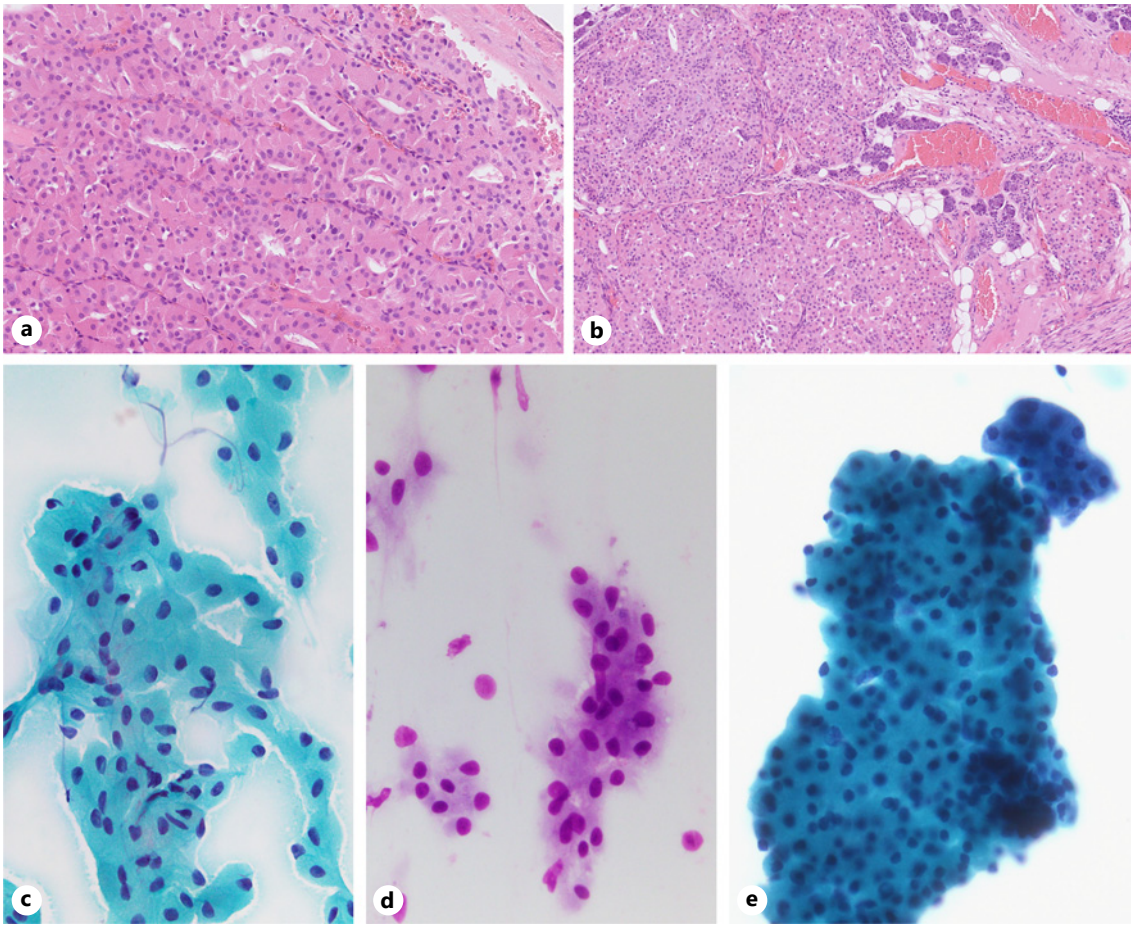

Fig. 1. a Oncocytoma is a well-circumscribed benign tumor composed of large cells with abundant eosinophilic, granular, mitochondria-rich cytoplasm, arranged in nests/sheets or small tubule-like structures separated by thin fibrovascular stroma. **b** Nodular oncocytic hyperplasia is a mass-like lesion composed of multiple unencapsulated nodules, often intermingled within the salivary gland. **c**, **d** FNA of oncocytoma showing large polygonal cells with abundant dense cytoplasm and small uniform round nuclei (Papanicolaou stain [**c**]; Diff-Quik stain [**d**]). **e** FNA of nodular oncocytic hyperplasia. The aspirate contains a cohesive group of cytologically bland oncocytes with abundant dense cytoplasm (Papanicolaou stain).

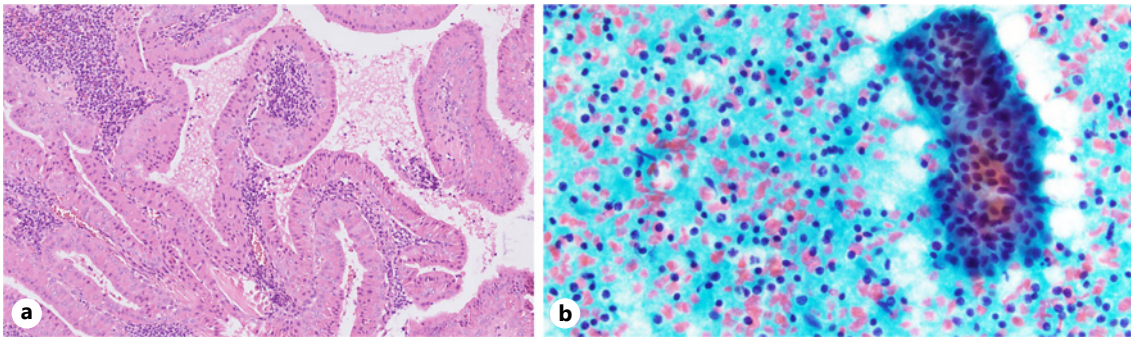

Fig. 2. a Warthin tumor is another benign oncocytic salivary gland neoplasm composed of a double layer of oncocytic epithelial cells lining ductal, papillary, and cystic structures surrounded by lymphoid stroma. **b** FNA of Warthin tumor demonstrating the classic cytologic pattern of flat cohesive groups of oncocytes within a background of small lymphocytes and proteinaceous debris (Papanicolaou stain [**b**]; Diff-Quik stain).

also contain very small orangeophilic fragments, and amylase crystalloids can also be present in some cases [9]. A subset of Warthin tumor can present a diagnostic challenge when infarction or metaplastic changes, especially squamous metaplastic changes, are present [8]. In addition, the frequent presence of degenerated or apoptotic oncocytes within the background debris and lymphocytes can be a diagnostic pitfall when misinterpreted as squamous cell carcinoma [10–13].

Molecular Pathology

Although next-generation sequencing (NGS) technologies have been crucial in the understanding of the molecular features underpinning salivary gland neoplasms, little is known about the genetic landscape of primary oncocytic salivary gland tumors. Immunohistochemical studies have demonstrated that both oncocytomas and Warthin tumors are positive for P63 and negative for P40, S100, Mammaglobin, SOX10, DOG1, GATA3, and AR [14–17]. In addition, oncocytomas do not generally show positive staining for specific myoepithelial markers such as smooth muscle actin, calponin, S100 protein, and glial fibrillary acidic protein [18, 19].

A recent study measuring the expression levels of FOXI1 and POU2F3 (master regulators of ionocytes and tuft cells) [20, 21] by IHC in salivary neoplasms, revealed the presence of a marked and consistent expression of these two proteins in Warthin tumors, as opposed to oncocytomas, which showed negativity for FOXI1 in the tumor cells [22]. Besides the well-established morphological and immunohistochemical features of primary oncocytic salivary gland tumors, additional studies devoted to the identification of genetic alterations responsible for the tumorigenesis of such entities are warranted. Immunohistochemical and molecular findings have been summarized in Table 1.

Oncocytic Change in Primary Non-Oncocytic Salivary Gland Tumors

Oncocytic Benign ME and PA

Histopathology

Extensive oncocytic metaplasia of PA and ME can be diagnostically challenging and may camouflage the correct diagnosis [18]. Grossly, the tumors are well-circumscribed and enclosed by a fibrous thin capsule. They may be either multilobular or comprised a single nodule.

These tumors should be treated more carefully compared with oncocytoma, given the risk of frequent recurrences and the possibility of malignant transformation. Oncocytic PA/ME consists of sheets and clusters of large polygonal cells with abundant eosinophilic cytoplasm with prominent granularity and well-defined cell borders (Fig. 3a). Numerous intracytoplasmic vacuoles can be seen in the cytoplasm of some tumor cells. Oncocytic myoepithelial cells have polymorphic and hyperchromatic nuclei (Fig. 3b). Immunohistochemically, the neoplastic cells show intense, granular cytoplasmic reactivity for anti-mitochondrial antibodies. Nuclear staining for PLAG1 may also be present (Fig. 3c). In contrast to oncocytomas, oncocytic myoepithelial PA and MEs are SOX10 and S100 positive (Fig. 3d).

Cytopathology

Aspirates of oncocytic PA/ME may lack the characteristic fibrillar matrix of conventional non-oncocytic PAs, and in those cases, they create a diagnostic challenge. FNA samples are cellular and contain cohesive sheets and clusters of large polygonal oncocytic cells with densely granular cytoplasm (Fig. 3e, f). The cytologic features overlap those of oncocytoma except that the oncocytic cells may contain cytoplasmic vacuoles and nuclei can show variable degrees of hyperchromasia and polymorphism. Some cases of oncocytic PA have been reported as a pitfall for carcinoma ex PA due to the large nuclear size; however, oncocytic PA lacks the nuclear pleomorphism, mitotic activity, and necrosis often seen in carcinoma ex PA [23]. When the characteristic fibrillar, metachromatic matrix of PA is present within oncocytic forms of PA, the cytologic interpretation is more straightforward [24–26].

Oncocytic MEC

Histopathology

Oncocytic mucoepidermoid carcinoma (OMEC) is a rare but diagnostically challenging subtype of MEC [27]. OMEC is notable for differential diagnostic considerations that are raised as a result of overlap with benign and low-grade oncocytic salivary gland tumors. Diffuse and strong immunoreactivity of p63 protein may be useful in distinguishing OMEC from its mimics. However, focal p63 staining can be present in benign oncocytomas. The presence of mucin containing cells, mucinous cystic formation, and foci of extravasated mucin are considered a hallmark of MEC. True mucocytes may be, however, very few and hardly discernible in OMECs. Recent evidence has shown that most MECs harbor gene fusions involving *MAML2*.

Cytologically, the individual tumor cells show a low nuclear-cytoplasmic ratio, centrally placed nuclei, and

Table 1. Primary oncocytic neoplasms of salivary glands – immunohistochemical and molecular findings

	Immunohistochemistry	Molecular genetics	Chromosomal region
Nodular oncocytic hyperplasia	CK7, Pan-CK, MIA	Not defined	
Oncocytoma	CK7, Pan-CK basal cells: p63, p40	Not defined	
Warthin tumor	• Inner epithelial layer: CK7, EMA • Outer epithelial layer: p63, p40	*KRAS* codon 12 mutations	12p12.1
Oncocytic PA/ME	PLAG1, HMGA2 SOX10, p63	*PLAG1* rearrangements *HMGA2* rearrangements	8q12 12q13-15
OMEC	p63, p40, mucicarmine, AMP	*CRTC1::MAML2* *CRTC3::MAML2* *EWSR1::POU5F1*	*t*(11;19)(q21;p13) *t*(11;15)(q21;q26) *t*(6;22)(p21;q12)
Oncocytic SDC	AR, CK7, HER2, GATA3	*HER2* amplification *FGFR1* amplification *TP53* mutations *PIK3CA* mutations *HRAS* mutations *AR* copy gain *PTEN* loss *CDKN2A* loss *PLAG1* rearrangements* *HMGA2* rearrangements*	17q21.1 8p11.23 17p13.1 3q26.32 11p15.5 Xq12 10q23.31 9p21.3 8q12 12q13-15
Oncocytic EMCa	• Biphasic pattern – Epithelial cells: CK7, Pan-CK – Myoepithelial cells: SMA, calponin, p63, and p40 – AR in oncocytic variant – RAS Q61R – membranous antibody	*HRAS* mutations (*codon 61*)	11p15.5
Oncocytic IC	S100, mammaglobin, peripheral p63/p40	*TRIM33::RET* *NCOA4::RET* *BRAF p.V600E* mutations	*t*(1;10)(p13;q11) *t*(10;10)(q11.21; q11.21) 7q34

AR, androgen receptors; MIA, mitochondrial antigen; Pan-CK, pancytokeratins.

abundant granular eosinophilic cytoplasm due to abundant mitochondria. The tumor cells are bland looking in most cases, but a moderate degree of nuclear atypia with enlarged and irregular nuclei and a clear cell phenotype with tumor cells having watery clear cytoplasm and distinct small nuclei can be sometimes encountered [27]. Our experience suggests that ancillary studies for the detection of *MAML2* rearrangement may provide useful evidence in difficult cases (Fig. 4a).

Cytopathology

The FNA diagnosis of MEC based upon cytologic features can range from definitive classification of MEC to atypical and descriptive depending upon the quality of the sample and degree of cyst contents present. OMEC, in particular, creates a diagnostic challenge, especially in the absence of material for ancillary studies [28–30]. Aspirates of OMEC contain crowded clusters of cells with moderate amounts of densely granular oncocytic cytoplasm and round to oval nuclei (Fig. 4b–d). Conventional epidermoid cells, mucinous goblet-type cells, and mucinous cyst contents are usually absent. As in histologic specimens, FISH analysis for *MAML2* gene rearrangement has proven to be especially useful for definitive classification of OMEC in FNA samples.

Salivary Duct Carcinoma

Histopathology

Salivary duct carcinoma (SDC) is an aggressive carcinoma resembling mammary ductal carcinoma, most typically with an apocrine (immuno) phenotype. Oncocytic SDC is defined by abundant granular eosinophilic

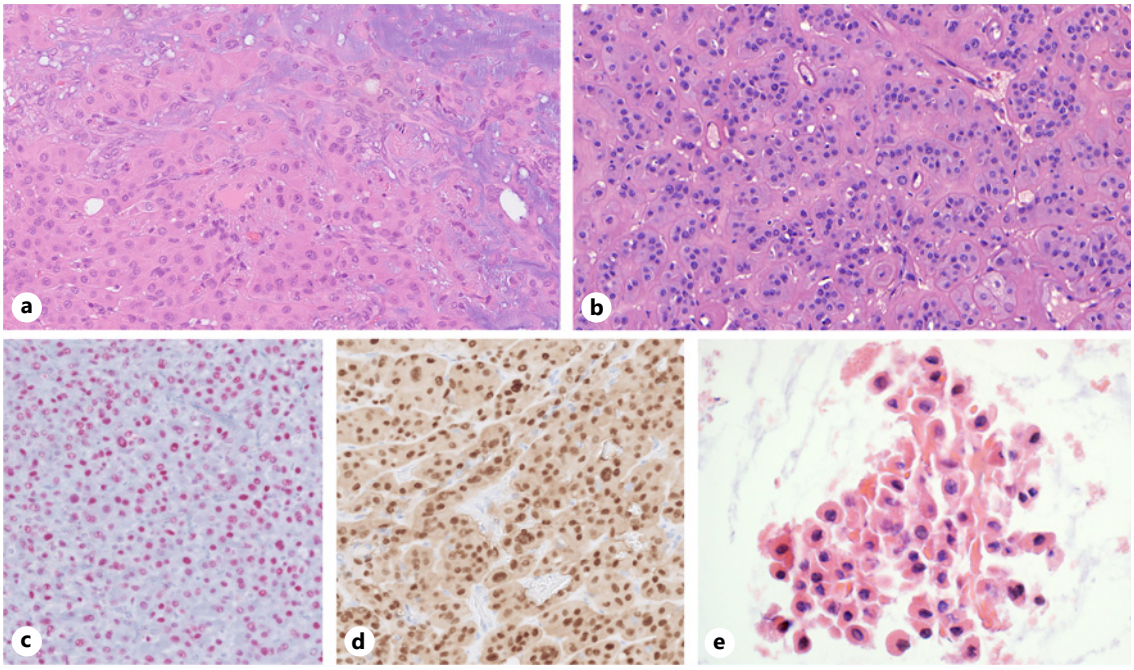

Fig. 3. a Oncocytic PA can be predominantly composed of oncocytes, with little or no chondromyxoid stroma, or just a minimal amount, typically located at the periphery. **b** Oncocytic ME is composed of nests of large polygonal oncocytic cells with numerous intracytoplasmic vacuoles and variability in the size and shape of the nuclei. **c** Nuclear staining for PLAG1 may also be present. **d** In contrast to oncocytomas, oncocytic myoepithelial PAs, and MEs are SOX10-positive. **e** FNA of cellular myoepithelial-predominant PA with prominent oncocytic metaplastic features (cell block, H&E [**e**]; Diff-Quik).

cytoplasm. The proportion of such cells required to establish a diagnosis of oncocytic SDC is arbitrary, but it should exceed 50% (Fig. 5a, b).

Cytopathology

FNAs of SDC are readily classified as malignant as well as high-grade [31]. The cells in conventional cases of SDC can be described cytologically as "oncocytoid" owing to their moderate amounts of eosinophilic cytoplasm. In the less common case of oncocytic SDC, the malignant tumor cells have even more pronounced eosinophilic cytoplasm which is densely granular. Still, nuclei are large, round to oval, and pleomorphic with a prominent nucleolus (Fig. 5c, d). Occasional mitoses as well as background necrotic debris may also be present. The cytologic features of SDC, even in oncocytic cases, are overtly malignant and usually suggestive of SDC, but for difficult cases, a cell block and staining of the androgen receptor can be useful for definitive classification [31–33]. The cytologic differential diagnosis for SDC includes metastatic carcinomas to the salivary gland. Among the most common oncocytic secondary cancers in the salivary gland is metastatic renal cell carcinoma which can pose a diagnostic pitfall [34–36].

Salivary Gland IC

Histopathology

Salivary gland IC is a complex ductal neoplasm surrounded by a layer of myoepithelial cells. Recent insights have shown that there are three different types: intercalated duct-like, with frequent *NCOA4::RET* fusions; apocrine, with SDC-like mutations; and mixed intercalated duct-like/apocrine, with *RET* fusions, including *TRIM27::RET*. Oncocytic IC shares similarities with intercalated duct-like IDC and can harbor *TRIM33::RET* fusions or *BRAF* V600E mutations [37] (Fig. 6a, b). Because of its indolent nature, oncocytic IC should be distinguished from histological mimics. In 2018, Nakaguro et al. [38] reported a form of low-grade IC with oncocytic features. Although these authors believed that it represented a unique form of IC, at the time it was difficult to exclude the possibility of oncocytic metaplastic change in intercalated duct-like ICs.

Cytopathology

Cytologic specimens of IC are diagnostically challenging to classify [37], especially given the different subtypes of IC and range of cytologic features that can be seen. FNA samples of all subtypes of IC are moderately cellular.

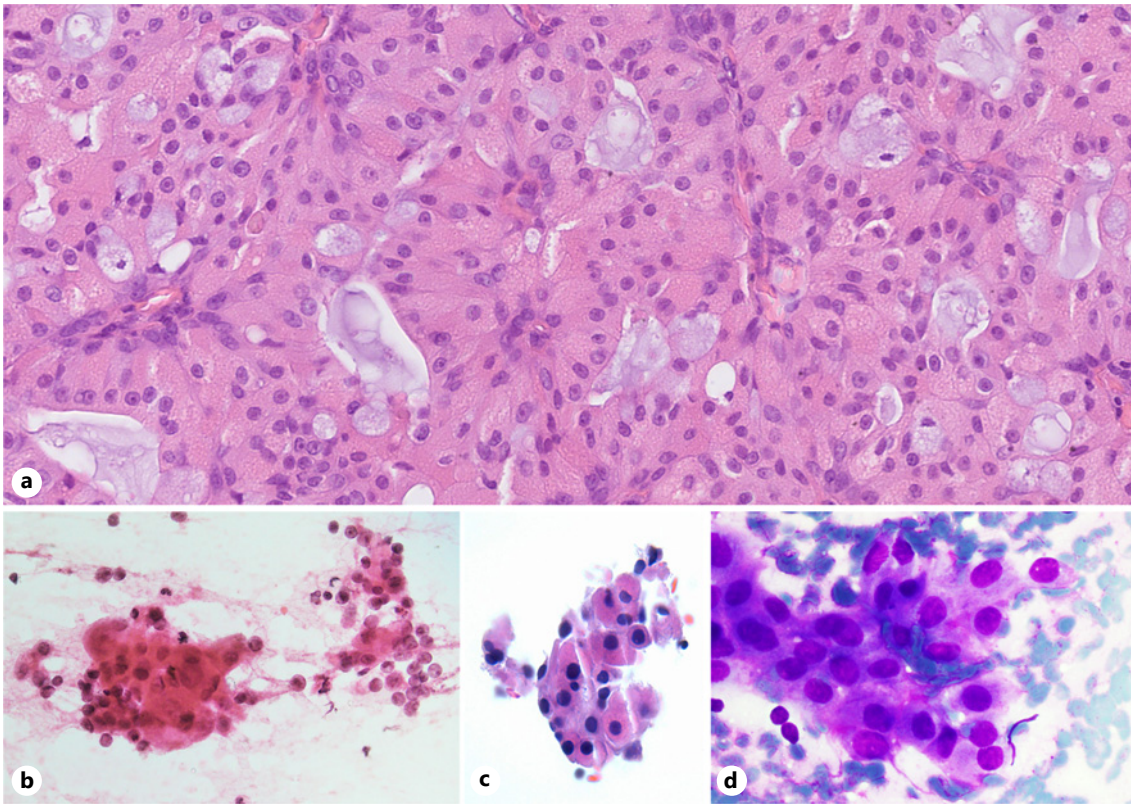

Fig. 4. a OMEC is composed of solid-growing oncocytic cells with mild to intermediate nuclear pleomorphism and eosinophilic nuclei. Mucoid cells are sparsely distributed throughout the tumor. **b**, **d** FNA of OMEC. These 2 aspirates contain variable numbers of cells with abundant granular oncocytic cytoplasm; mucinous cells are not apparent (Papanicolaou stain [**b**, **c**]; Diff-Quik [**d**]).

Aspirates of oncocytic IC contain small groups of crowded, mildly atypical cells with variable amounts of granular oncocytic cytoplasm [37]. The cytologic differential diagnosis is broad and includes a range of other low- and high-grade carcinomas with oncocytic features [37, 39, 40]. Even with immunohistochemical staining of cell blocks, definitive classification of these FNA specimens requires molecular analysis using cell block material.

Epithelial-Myoepithelial Carcinoma

Histopathology

Oncocytic low-grade epithelial-myoepithelial carcinoma (EMCa) is a salivary gland malignancy characterized by biphasic tubular structures, usually composed of tightly coupled inner ductal and prominent outer myoepithelial cells. Oncocytic and apocrine EMCa are uncommon subtypes that constitute up to 8% of all EMCa (Fig. 7a). The tumors show intact abluminal layers of myoepithelial cells positive for p63 and demonstrate an *HRAS* gene mutation [38].

Cytopathology

FNA samples of oncocytic EMCa demonstrate the same biphasic pattern of small tubules containing cohesive inner ductal cells and abundant outer myoepithelial cells with moderate amounts of oncocytic to clear cytoplasm (Fig. 7b, c) seen in histology. The myoepithelial cells may also be present as dispersed cells within the background. Nuclei are oval and show limited atypia including very mild nuclear irregularities, but overall, aspirates of these tumors are cytologically bland. The prominent biphasic nature of the tumor and abundant large oncocytic myoepithelial cells will suggest the diagnosis of EMCa, but ancillary studies are needed to distinguish this tumor from other primary low-grade salivary gland neoplasms with oncocytic or oncocytoid features [41–44]. In a subset of EMCa cases, the FNA may only contain a single population of cells, most often myoepithelial cells, and such cases can be difficult to distinguish from other myoepithelial-predominant salivary gland neoplasms [41, 42].

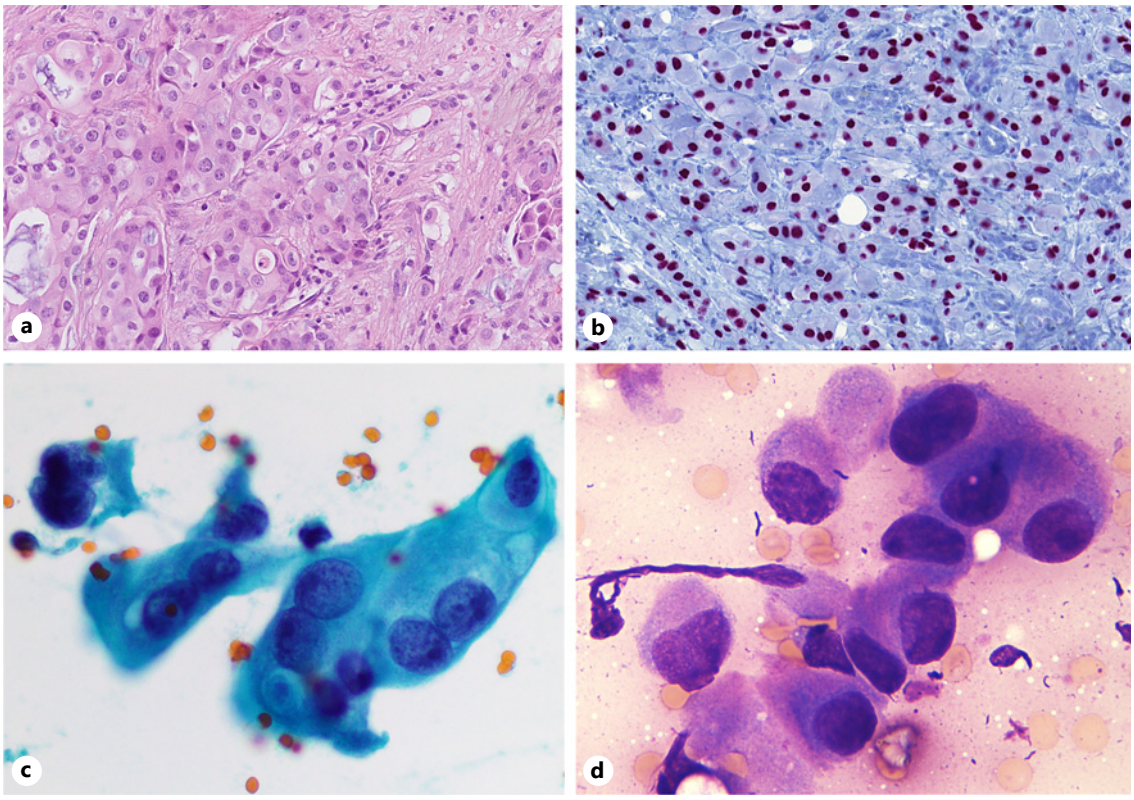

Fig. 5. a SDC, oncocytic subtype, is composed of solid-growing pleomorphic tumor cells with atypical nuclei, large granular eosinophilic cytoplasm, and apocrine differentiation. **b** Positivity for androgen receptors highlights the apocrine immunophenotype of this tumor. **c**, **d** FNA of oncocytic SDC consisting of large tumor cells with abundant oncocytic cytoplasm and large round, hyperchromatic nuclei (Papanicolaou stain [**c**]; Diff-Quik [**d**]).

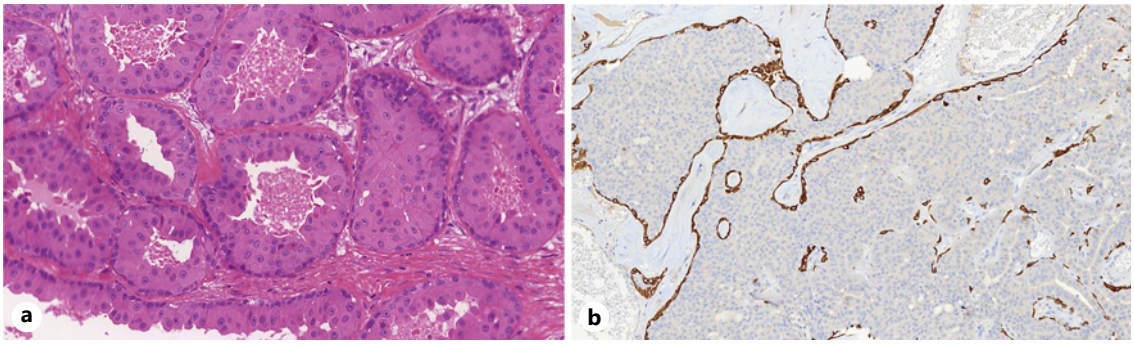

Fig. 6. a Oncocytic IC shows multiple lobules and ducts consisting of two epithelial cell layers, with the inner layer displaying focal hobnail cellular morphology. **b** The rim of myoepithelial cells surrounding tumor lobules is highlighted with CK14.

Molecular Pathology

Unlike primary oncocytic salivary gland tumors, the genetic landscape of the majority of the primary non-oncocytic salivary gland tumors with oncocytic change is well known. In fact, the application of molecular genetic testing has emerged as an additional ancillary diagnostic for the detection of PA and ME. The vast majority of PAs (>50%) are characterized by gene rearrangements that result in chimeric transcripts comprising *PLAG1* on chromosome 8q12 or *HMGA2* on chromosome 12q14-15

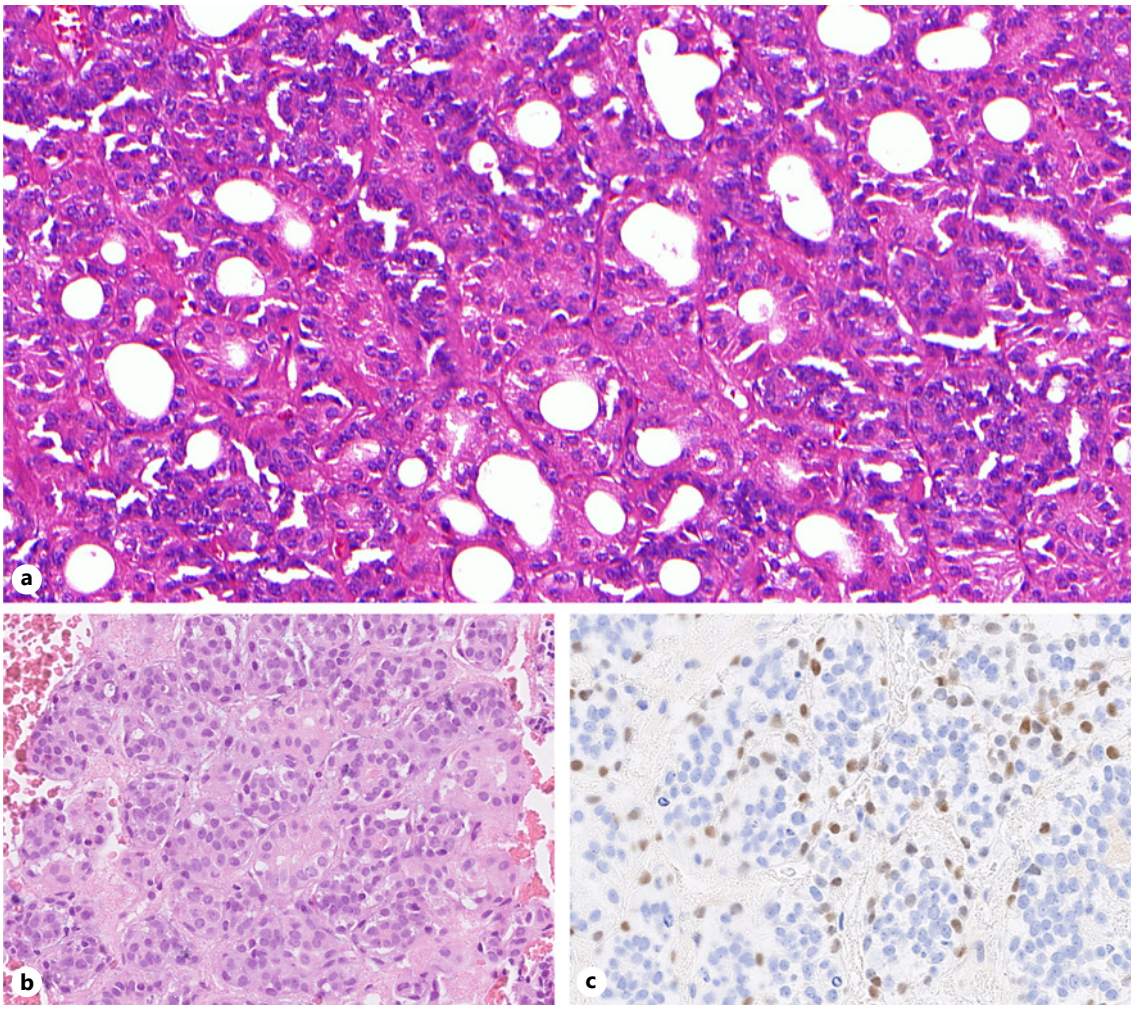

Fig. 7. a EMCa with focal oncocytic change in some tubular structures. **b** The same tumor but cytological specimen (cell block, H&E). **c** Abluminal myoepithelial cells are positive for p63 (cell block).

[18, 45, 46]. The most common *PLAG1* gene fusion affecting PA results in a promoter swap between *PLAG1* and *CTNNB1*, which have a role in cell-cell adhesion and the Wnt signaling pathway [47]. Another common partner in *PLAG1* gene fusions involves *LIFR* [47]. Other reported fusion partners are *FGFR1*, *TCEA1*, *CHCHD7*, *TGFBR3*, *GEM*, *ACTA2*, and *ND4* [47]. These translocations result in PLAG1 overexpression, which ultimately activates RAS and Wnt pathways [48, 49]. Although the molecular background of salivary MEs is less commonly known, one case of ME harboring 12q alteration was reported [50], and novel findings have detected rearrangements of *PLAG1* in half of these neoplasms, including gene fusions comprising *CHCHD7::PLAG1*, *GEM::PLAG1*, *NTF3::PLAG1*, *CHCHD7::PLAG1*, and *FBXO32::PLAG1* [18].

Recent studies have shown that a large proportion of OMECs harbor *CRTC1::MAML2* gene fusions [27, 51] The gene fusion *CRTC3::MAML2* was also found in a minor subset of OMECs [27]. These findings comprising *MAML2* rearrangements are considered to be extremely useful in distinguishing OMECs from other oncocyte-rich neoplasms such as oncocytomas and oncocytic carcinomas [27].

SDCs were found to harbor specific genomic alterations. Indeed, recent NGS studies focused on SDCs have reported the existence of numerous genetic alterations such as *PIK3CA* and *HRAS* hotspot mutations, gene amplifications, and homozygous deletions affecting *ERBB2* and *CDKN2A*, respectively, and rearrangements involving *MYB* and *PLAG1* [32, 52, 53]. Few case reports have identified rare translocations in SDC like *NCOA4::*

RET, *ETV6::NTRK3*, *BCL6::TRADD*, and *ABL1::PPP2R2C* [54]. Such findings emphasize the important roles for PI3K/AKT/mTOR signaling pathways in the tumorigenesis of SDC [53, 55–57].

As described above, recent studies investigating the molecular genetics of IC showed recurrent rearrangements affecting *RET* with a predominant *NCOA4::RET* fusion in the intercalated duct-type IC [58, 59] and a *TRIM27::RET* fusion in the apocrine-type IC [59, 60]. Recurrent rearrangements involving *RET* have been identified in 47% of cases of low-grade IC with intercalated duct phenotype [58, 59]; *NCOA4::RET* fusion was described in noninvasive IC, and the *RET* gene was identified as an early oncogenic driver [58, 59]. In addition, rare but well-documented cases of IC with focal or widespread invasive growth have been reported [59, 61]. In fact, the first case of S100 protein-positive and AR-negative intercalated duct-type IC harboring *NCOA4::RET* gene fusion and an invasive component was described recently by Weinreb et al. [58].

Akin to the oncocytic MEs, the genetic repertoire of oncocytic EMCa is poorly known. Nonetheless, the majority of EMCas were found to harbor *HRAS* mutations primarily affecting codon 61, followed by *PIK3CA* and *AKT1* mutations [38, 62, 63]. Of note, the *HRAS* p.Q61R hotspot mutation was not identified in any salivary gland tumors manifesting EMCa-like features such as adenoid cystic carcinomas, PAs, and myoepithelial carcinomas [38, 62], thus recognizing such hotspot mutation as a genetic marker in the diagnosis of EMCa.

Conclusion

Oncocytic variants of various salivary gland neoplasms can create a diagnostic challenge, especially in cytologic samples. In particular, oncocytic malignant tumors may histologically and cytologically mimic benign oncocytomas and identification of their distinguishing features is essential for proper patient management. In many of these cases, analysis of immunophenotypic and molecular alterations can provide the critical evidence for the correct classification of these oncocytic tumors.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors (A.S., M.B., A.D.C.P., and W.C.F.) contributed equally to this manuscript, and each was involved in the following roles: design and development of the work, writing of the manuscript, editing, and production of figures.

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