Clinical Perspective

Oncocytoma of the Parotid Gland and its Mimickers: A Comprehensive Review

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Abstract

Oncocytomas are benign neoplasms composed of oncocytes; the large eosinophilic   cuboidal to columnar cells with more than 60% of their cytoplasm occupied by mitochondria. Oncocytomas represent less than 1% of the salivary gland neoplasms and 82% to 90% of them occur in the parotid gland. Salivary gland oncocytomas constitute 2.5% of the parotid gland tumors. Despite the well-recognized morphology of this tumor, there is a wide range of neoplasms that may mimic oncocytoma and hence need to be considered in its differential diagnosis. A predominantly clear cell variant of oncocytoma may resemble a number of salivary gland neoplasms where clear cells may be prominent. In addition, oncocytic metaplasia may be a focal or an extensive component of other distinct salivary gland neoplasms. An awareness of all the possible "mimickers" of clear cell oncocytoma becomes more significant in view of the fact that most are malignant neoplasms with a poor prognosis.

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Salivary gland neoplasms comprise 2 to 3% of all head and neck tumors and oncocytomas account for less than 1% of all the salivary gland neoplasms.[1] Oncocytomas are benign salivary gland tumors composed of oncocytes, cuboidal to columnar epithelial cells with abundant eosinophilic cytoplasm secondary to the accumulation of excessive number of mitochondria. The German pathologist Hurthle was the first to describe oncocytes as constituents of normal canine thyroid glands in 1894. Oncocytes were also recognized by Schaffer in 1897 and were fully described by Hamperl in 1931 who coined the term "Oncocyte". The word oncocyte is derived from the Greek word 'onkousthai' which means – to swell or become larger. Tandler et al in 1964 revealed with electron microscopy that oncocytes contained unusually high numbers of mitochondria.[2]

Oncocytes have been found to arise in various glandular and secretory epithelia. In the Head and Neck area, oncocytic change has been noted in numerous organs such as: the salivary glands, pituitary, thyroid, parathyroid, nasal cavities, sinuses, ocular caruncle, lacrimal glands, buccal mucosa, Eustachian tube and the larynx. They have also been called oxyphilic cells, Askanazy cells and Hurthle cells in the thyroid gland.

The parotid gland is the most common site where oncocytic changes may occur, usually at the ductal or acinar cell level.[3] Oncocytes are one to two times the size of normal acinar cells, display abundant granular eosinophilic cytoplasm and a central pyknotic nucleus.[4] The cytoplasmic granularity is due to the accumulation of mitochondria that may occupy up to 60% of the cytoplasm. In contrast, mitochondria occupy only 5.2% of the cytoplasm of normal acinar cells.[5,6] The increased concentration of mitochondria is accompanied by a

gradual disappearance from the cytoplasm of other cytoplasmic membrane systems and loss of plasmalemmar specializations.[2]

Oncocytes may be seen in normal glands or may be part of a neoplastic process. Since oncocytes are capable of undergoing mitotic division, a supervening neoplastic change is possible.[7] The World Health Organization (WHO) classification of Salivary gland neoplasms recognizes three oncocytic entities: oncocytosis, oncocytoma and oncocytic carcinoma.[8] Oncocytosis is considered to be a hyperplastic change and may present with generalized enlargement of the glands whereas oncocytoma and oncocytic carcinoma represent neoplastic processes. Oncocytosis can further be categorized as diffuse hyperplastic oncocytosis (DHO), or multifocal nodular oncocytic hyperplasia (MNOH).[3] Oncocytomas are more common than oncocytosis and oncocytic carcinomas. Oncocytic carcinomas are the rarest of the oncocytic lesions.

Oncocytic changes are noted with increasing age and are almost a universal finding in individuals around the seventh decade of life. Diffuse hyperplastic oncocytosis affects the entire gland and the extent of oncocytic change is variable, although in some cases it may be marked. It is usually an incidental finding and there is no associated tissue response to this change such as fibrosis or inflammation.[4] Occasionally foci of oncocytosis may become quite proliferative and form small to moderately sized nodules that are usually only microscopically evident. These nodules may occasionally show a vague organoid pattern and some nodules may show peripheral fibrosis.[4] This presentation of oncocytosis is classified as multifocal nodular oncocytic hyperplasia. Although the distinction is arbitrary, the presence of a clinically evident, well-circumscribed and encapsulated mass favors the diagnosis of oncocytoma while multiple, unencapsulated nodules favors nodular oncocytosis. Oncocytomas have an apparent organoid histologic pattern associated with a thin capillary network, and produce compression of the surrounding tissues; these features are suggestive of a neoplastic process.[4]

There has been a long standing controversy on whether oncocytomas are hyperplastic responses or true neoplasms. Although the presence of oncocytes in normal salivary glands and the increased propensity of these cells with age imply that it might be a degenerative process, the large dimensions and the growth pattern of many oncocytomas favor a neoplastic process.[9] Also, the existence of malignant forms of oncocytoma favors the existence of a true neoplastic entity.

Oncocytoma
Etiology and pathogenesis
Oncocytic changes of secretory epithelia are thought to be metaplastic, a protective phenomenon against adverse change. Hamperl considered oncocytes to be burnt out cells as they lost their original specialization and increased in

number with age.[7] Bonikos DS et al suggest that oncocytic change may be the result of compensatory mitochondrial hyperplasia in normal cells caused by mitochondrial damage or the exhaustion of one or more mitochondrial enzymes.[10] Aging is also thought to cause a functional exhaustion of the mitochondrial enzymes and a compensatory mitochondrial hyperplasia to overcome an energy deficient condition.[11] In 1989, Linnane et al advocated that aging caused the accumulation of mtDNA errors leading to "mitochondrial respiratory failure" and multisystem degeneration.[12] Sunmunn et al state that oncocytic change could be a regressive alteration of previously hypertrophic or hyperplastic ductal epithelium with the appearance of a mitochondriopathy.[13] In early oncocytic change there is an increase in the number of mitochondria and later these organelles undergo striking modifications in form and size, become pleomorphic and are biochemically deficient, causing defective cellular metabolism. Capone et al in a study of 18 cases of salivary gland oncocytomas were able to demonstrate mitochondrial DNA mutations in the control region in only 1 case.[11] Although head and neck radiation has been reported in 20% of patients with oncocytomas, no clear etiological factors have yet been identified.[4]

Clinical and pathological features
Oncocytomas of salivary glands most commonly involve the parotid gland (82%) and the rest are located at the submandibular gland and minor salivary glands. They are typically tumors of older adults with a peak incidence at the 8th decade. However, they may rarely present in children. A slight female predominance is noted for the conventional oncocytoma and a more marked preponderance for females in the clear cell variant of oncocytomas.

Oncocytomas most often occur as asymptomatic, well-circumscribed, solitary, painless masses usually measuring 3 to 4 cm but may reach up to 7 cm in diameter. Rarely, they may present with pain or discomfort. They may also occur as multifocal or bilateral neoplasms.

Grossly oncocytomas are solid, well-circumscribed, tan to red-brown, nodular or multinodular lesions. Fibrous encapsulation has been a criterion used to distinguish oncocytoma from oncocytic hyperplasia, although in some oncocytomas it may be minimal.[4]

Microscopically the tumor is seen as solid clusters or cords of tightly packed oncocytes separated by thin strands of fibrovascular stroma (**Figure 1A**) with scattered lumina of variable sizes, some with associated eosinophilic intraluminal secretions. The cells are large cuboidal to columnar and arranged in an organoid pattern with prominent eosinophilic, finely granular cytoplasm and uniform round, centrally placed nuclei (**Figure 1B**). The eosinophilia is variable and hence there may be an admixture of light and dark stained cells. Oncocytomas may occasionally show extensive cystic change.
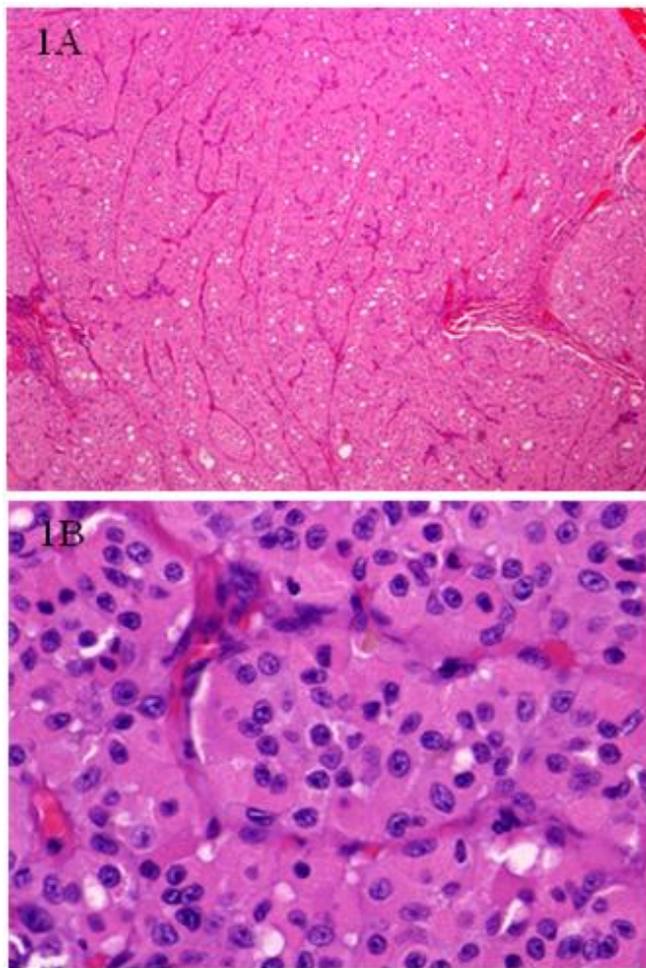
Figure 1. Morphological features of oncocytoma of the parotid gland. **1A.** Oxyphilic tumor cells forming cords and clusters, separated by thin strands of fibrovascular stroma (hematoxylin-eosin stain; original magnification x100). **1B.** Oncocytoma presenting the typical organoid pattern composed of eosinophilic cells with finely granular cytoplasm and uniform round, centrally placed nuclei (hematoxylin-eosin stain, original magnification x400).

The clear cell variant of oncocytoma has the same architectural pattern as that of conventional oncocytoma. The clear cell change in oncocytomas may range from forming a minor component to being the predominant cell type of the tumor. In this variant, the clear cytoplasm is due to the accumulation of cytoplasmic glycogen with margination of mitochondria in the oncocytes. These clear cells are positive for glycogen with PAS staining. Conventional eosinophilic oncocytes are often evident among the clear cells. An accurate recognition of the clear cell predominant oncocytomas is essential since other clear cell malignancies can closely resemble this benign tumor.

Ultrastructure

Electron microscopy is an invaluable tool for the demonstration of mitochondria in the cytoplasm of oncocytes. According to Gavriel C et al, electron microscopy of the oncocytes showed numerous tightly packed mitochondria of varying size and shape filling most of the cytoplasmic compartment.[15]

The characteristic acidophilia of oncocytes is due to the dense accumulation of mitochondria and should be distinguished from acidophilia that is secondary to the accumulation of lysosomes, neurosecretory granules, cytofilaments, smooth endoplasmic reticulum, or a combination of these. Tandler B et al suggested certain criteria to confirm that the cytoplasmic acidophilia of oncocytes is due to mitochondrial hyperplasia and not other causes. The features are high levels of oxidative activity, mitochondrial pleomorphism, absence of dense granules in the intra-mitochondrial matrix, and loss of electron microscopic features such as brush borders and basal-infoldings.[16] He also noted two types of oncocytes often in the same tumor; one form contained variably sized mitochondria with closely aligned stacks of cristae and the other had excessive numbers of normal appearing mitochondria virtually filling the cytoplasm.

Kim et al state that at the ultrastructural level, mitochondria are seen to be crammed together with virtually no cytoplasmic interstices except for some scattered lysosomes and bundles of cytokeratin filaments without the intervention of other organelles.[17] Riva et al conducted a scanning electron microscopic study of oncocytes from various anatomical sites and found that the mitochondria in oncocytes were quite pleomorphic. They hypothesized that the heterogeneity might be due to the deletion of specific segments of mitochondrial DNA in oncocytes situated in different sites. Whether these variations in mitochondrial shape, number, and disposition of their cristae play a role in the biology of oncocytes is unknown.[18] Müller-Höcker et al based on his study, suggests that development of respiratory chain defects is not always a concomitant of oncocytic transformation.[19]

Ancillary studies

In addition to electron microscopy, histochemical stains like phosphotungstic acid-hematoxylin (PTAH), Novelli, Cresylecht violet V and Kluver-Barrera Luxol fast blue reveal the mitochondria in the cytoplasm of the oncocytes.[4] Other suitable staining methods for mitochondria are the Champy-Kull method and Altmann acid-fuschin picric acid method. Enzyme histochemistry can also be used to demonstrate mitochondria.

Barnes and Bedetti reported that immunohistochemistry using an anti-mitochondrial antibody against cytochrome c oxidase was a very sensitive and specific method for identifying mitochondria within the cytoplasm of oncocytes by light microscopy.[20] This method can be used in paraffin

embedded tissues. Oncocytomas are positive for cytokeratin and basal cells stain with p63. These basal cells are not identifiable with routine light microscopy. Oncocytomas are negative for some myoepithelial markers like smooth muscle actin, calponin, S-100 protein and GFAP (Glial fibrillary acidic protein).[4] Strong reactivity for prostate-specific antigen has been reported in one case.[4]

The scintigraphic findings of oncocytoma are similar to those of Warthin tumor,[21] where a marked uptake and accumulation of 99Tcm -pertechnetate with prolonged retention helps to distinguish these tumors from other benign salivary gland tumors where a "cold pattern" is observed.[4]

Biological behavior

The prognosis for oncocytoma is excellent and the mainstay of treatment is complete surgical excision. Recurrence rates range from 0 - 30% usually between 0.5 – 13 years after initial diagnosis. Multifocal tumors and incomplete excisions are associated with increased risk of recurrence.[4]
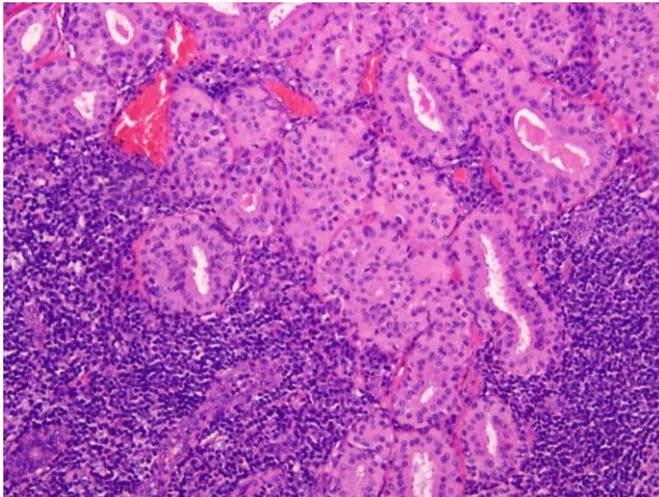
Figure 2. Oncocytoma showing areas with central lumen formation along with a dense peripheral lymphocytic infiltrate that may closely resemble a Warthin's tumor (hematoxylin-eosin stain, original magnification x200).

Differential Diagnosis of Oncocytoma

The differential diagnosis for oncocytic lesions in the parotid gland include; papillary cystadenoma lymphomatosum (Warthin tumor), acinic cell carcinoma, clear cell carcinoma, oncocytic carcinoma and mucoepidermoid carcinoma (**Table 1**). Oncocytomas with extensive cystic changes need to be differentiated from oncocytic cystadenoma. Of the above, Warthin tumor is the closest mimicker of oncocytomas as cystic change and lymphocytic infiltrates seen in Warthin tumor may often be a component of oncocytomas (**Figure 2**). Also, Warthin tumor may show focal areas of oncocytic hyperplasia that may resemble oncocytoma. In addition to the above stated lesions, many other salivary gland tumors like pleomorphic adenoma, myoepithelioma, basal cell adenoma,

cystadenoma, canalicular adenoma, polymorphous low grade adenocarcinoma and acinic cell carcinoma may show areas of oncocytic metaplasia. However, this oncocytic change is usually not extensive enough to be confused with an oncocytoma.[4]

Warthin tumor

Warthin tumor accounts for 4 to 25% of salivary gland neoplasms and has a predilection for the parotid gland. It has been suggested that oncocytic neoplasms may be the result of an acquired mitochondriopathy due to mtDNA errors.[11] There have been over 200 acquired mtDNA rearrangements described in the literature, and 1 rearrangement has been linked specifically to parotid tumorigenesis.[11] Lewis et al reported that concentration of a 'common' 4977-bp mitochondrial DNA deletion was significantly higher in Warthin tumor cells than in normal parotid tissue.[22] This finding has not been substantiated in oncocytoma. There is a strong association between smoking and the development of Warthin tumor with different studies stating that smokers have an eight fold to a forty fold risk of developing Warthin tumor as compared to non smokers.[4] There has been no association between smoking and development of oncocytomas of the salivary glands.

Warthin tumor has a thin capsule and is well demarcated from the surrounding tissue. Histopathologically, Warthin tumor is composed of cystic spaces lined by papillary proliferations of bilayered oncocytic epithelial cells with a supporting stroma (**Figure 3A**). Typically, lymphoid tissue with germinal centers of various diameters surrounds the oncocytic cystic lining. The cytoplasmic granularity and eosinophilia of the epithelial cells are due to the presence of abundant mitochondria (**Figure 3B**). The diagnosis of Warthin tumor is often quite straightforward but may be sometimes confused with other parotid lesions that show oncocytic, cystic changes or papillary structures. For instance, oncocytomas may display extensive cystic change and some areas may have a focal prominent lymphoid element bearing an overall close resemblance to Warthin tumor. However, the distinguishing features of Warthin tumor are its classical bilayered cystic oncocytic epithelium with papillary fronds, and the presence of extensive and consistent lymphoid tissue with germinal centers, features that are mostly absent in oncocytomas. Variations from characteristic microscopic features are seen in Warthin tumors that exhibit squamous and mucous metaplasia which occasionally may be extensive. Squamous metaplasia is a rare finding in oncocytomas and is usually associated with previous FNAB procedures.[4]

Oncocytic carcinoma

Oncocytic carcinoma was first described in 1953 by Bauer and Bauer and represents the rarest form of oncocytic lesions.[23] There are only few cases that have been reported arising in the parotid and submandibular salivary glands. Rarely, oncocytic carcinoma has been reported in intra-oral
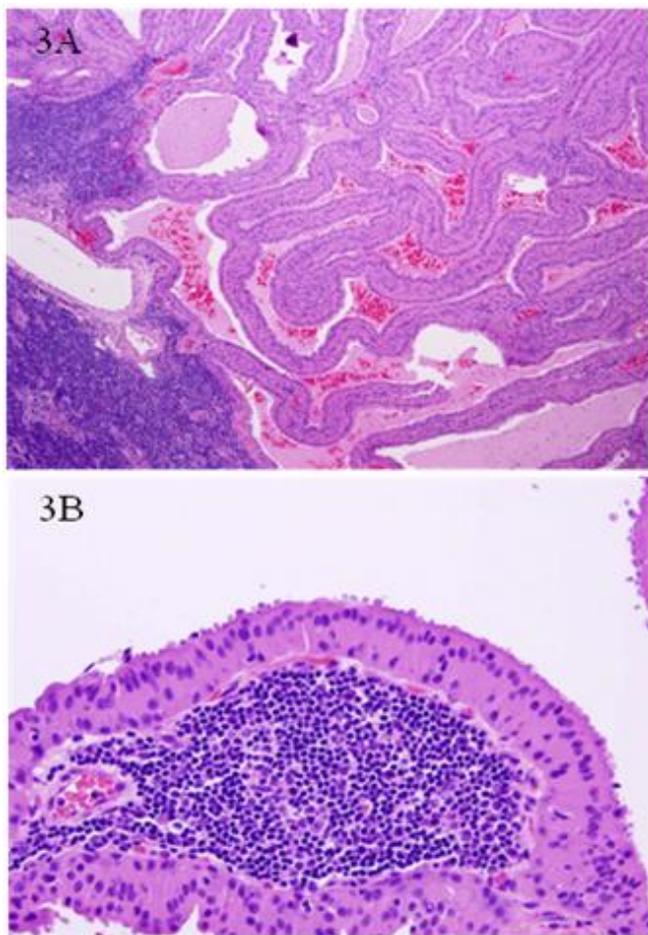
Figure 3. Morphological features of Warthin's tumor. **3A.** Warthin's tumor showing cystic spaces lined by oncocytic epithelial cells displaying a tenuous intraluminal papillary architecture with lymphoid infiltrate in the supporting stroma (hematoxylin-eosin stain, original magnification, x100). **3B.** Warthin's tumor with the characteristic bilayered oncocytic epithelium exhibiting cytoplasmic granularity and eosinophilia due to the presence of abundant mitochondria (hematoxylin-eosin stain, original magnification x 400).

minor salivary glands. The diagnostic criteria for oncocytic carcinoma dictate first that the tumor cells be identified as oncocytes. Secondly, the diagnosis of malignancy should be based not only on cellular and nuclear pleomorphism, but also on local infiltration, increased mitotic activity, vascular or perineural infiltration (**Figure 4A** and **Figure 4A**) and metastasis.[24] In cases where the histological and ultrastructural investigations are not sufficient to distinguish between oncocytoma and oncocytic carcinoma, the clinical findings become essential.[25] Clinically, recurrences and lymphatic involvement raise suspicion of a malignancy. Necrosis is present in 20% of oncocytic carcinomas.[26] Some cases of benign oncocytoma are not well encapsulated and may appear diffusely infiltrative[18] due to extensive oncocytic

change or multifocal involvement with small nodules. The lack of malignant histological features, such as perineural infiltration, vascular permeation and absence of lymphatic metastasis, could help differentiate between benign and malignant oncocytic tumors.
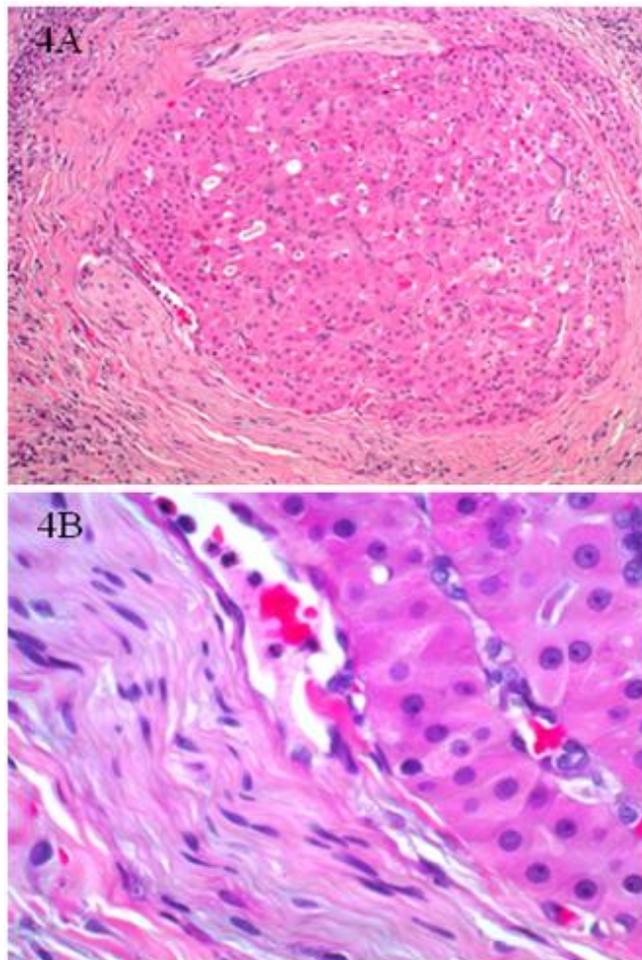
Figure 4. Morphological features of oncocytic carcinoma. **4A.** Oncocytic carcinoma showing perineural invasion (hematoxylin-eosin stain, original magnification x100). **4B.** High magnification of oncocytic carcinoma displaying a deceptively bland appearance of the cells, closely resembling benign oncocytes (hematoxylin-eosin stain, original magnification, x400).

Mucoepidermoid carcinoma
Sometimes the distinction between mucoepidermoid carcinoma (MEC) and oncocytoma may be obscured by metaplastic changes or the presence of clear cells. For instance, MEC may present with oncocytic metaplasia. Conversely, oncocytomas may exhibit squamous metaplasia resembling the epidermoid differentiation seen in mucoepidermoid carcinomas, especially after FNAC (Fine Needle Aspiration Cytology) procedures. Clear cells are seen quite often in mucoepidermoid carcinomas and may be a

predominant cell type (**Figure 5A; 5B**). This feature may lead to confusion with clear cell oncocytomas. However, the clear cells of oncocytoma show focal positivity with PTAH whereas the clear cells of mucoepidermoid carcinomas are PTAH negative.[4] In addition, the clear cells of mucoepidermoid carcinoma are mucicarmine positive while the clear cells of oncocytoma are mucicarmine negative. Furthermore, the organoid pattern of oncocytoma is uncharacteristic of mucoepidermoid carcinoma.
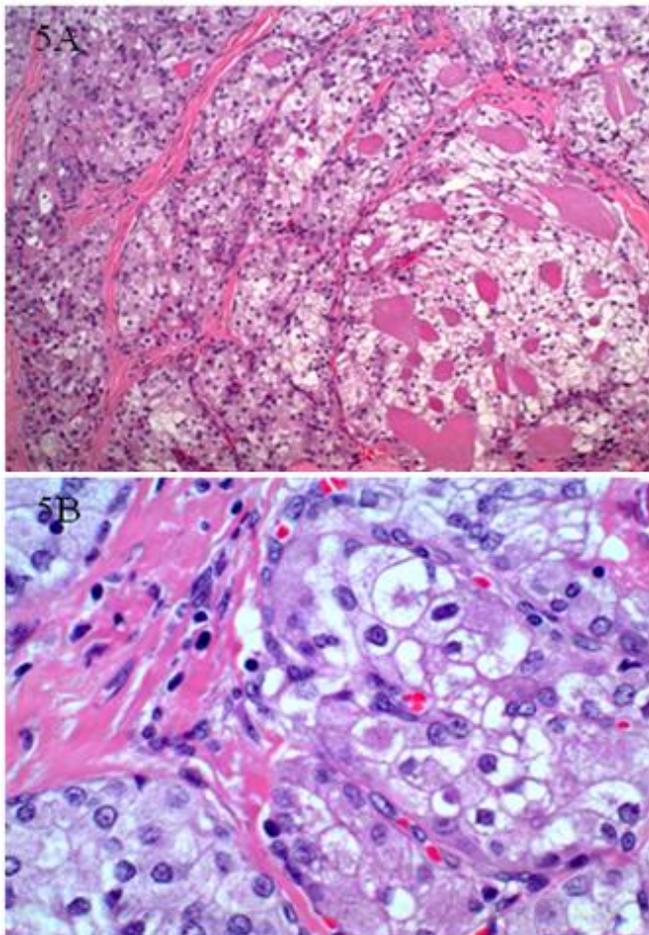
Figure 5. Morphological features of mucoepidermoid carcinoma. **5A.** Mucoepidermoid Carcinoma with a predominant clear cell component (hematoxylin-eosin stain original magnification x100). **5B.** Clear cell change in a mucoepidermoid carcinoma showing the clear cells admixed among cells with an epidermoid differentiation (hematoxylin-eosin stain, original magnification x400).

Recently, a chimeric gene *MECT1-MAML2 (mucoepidermoid carcinoma translocated 1- mastermind-like gene family)* has been described in up to 70% of mucoepidermoid carcinomas. This chimeric gene results from a translocation of the MECT1 and MAMLG2 genes at t(11;19)(q21;p13), respectively.[27] Although there were some

prior reports on the presence of t(11;19) in Warthin's tumour; a recent study using in situ hybridization and RT-PCR has failed to demonstrate the presence of MECT1–MAML2 fusion gene in seven cases of Warthin's tumour.[29] Hence identification of this chimeric gene may aid in the diagnosis of mucoepidermoid carcinomas.
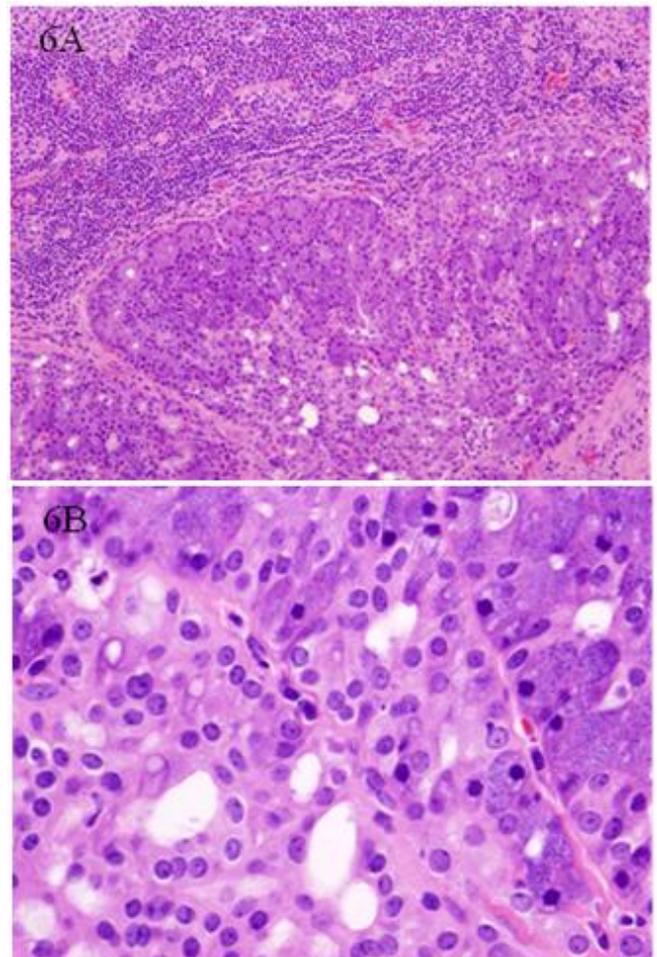
Figure 6. Morphological features of acinic cell carcinoma. **6A.** Acinic cell carcinoma with the cells arranged in a solid-lobular pattern (hematoxylin-eosin stain, original magnification x100).
6B. Acinic cell carcinoma composed of polyhedral cells containing abundant finely granular cytoplasm and an eccentrically placed nucleus (hematoxylin-eosin stain, original magnification x400).

Acinic cell carcinoma
Acinic cell carcinoma makes up 2.5 to 7% of all parotid gland tumors. The tumor is composed of many different cell types: acinar cells, vacuolated cells, intercalated cells, non-specific glandular cells and clear cells. Acinic cell carcinomas have multiple architectural patterns such as solid, solid-lobular (**Figure 6A**), acinar-microcystic, papillary

cystic, tubuloductal, follicular or macrocystic and dedifferentiated. Neoplastic acinar cells resemble the polyhedral cells of normal acini and contain abundant finely granular cytoplasm, which may be amphophilic, pale eosinophilic or basophilic with an eccentrically placed nucleus (**Figure 6B**). Solid and pseudoglandular growth patterns as well as clear cells may be seen in both acinic cell carcinomas and oncocytomas. Although clear cells are an infrequent finding in acinic cell carcinoma, their presence may cause a histological overlap with the clear cell variants of oncocytoma.[30] The clear cells in acinic cell carcinoma are negative for glycogen and PTAH in contrast to oncocytoma, where the clear cells are glycogen and focally PTAH positive. In addition, it has been reported that there are no basal or myoepithelial cells in acinic cell carcinomas. Recent studies using p63 as a marker have demonstrated the existence of basal cells in salivary gland oncocytic lesions.[31,32,33] According to Weiler et al[30] the presence of a diffuse distribution of basal cell component, stained by both p63 and CK5/6 antibodies favors a diagnosis of oncocytoma, since acinic cell carcinoma is completely devoid of basal cells. This basal cell component cannot be identified in routine H&E sections and thus, immunostains have to be used to make the distinction between these two lesions.

Neoplasms with clear cell changes

It is well known that clear cell change may be a component although rare, of conventional oncocytomas (**Figure 7A; 7B**).[34,35,36] However, in case of bilateral oncocytomas a significantly higher percentage of cases are associated with an abundance of clear cells.[34] The clear cells seen in oncocytomas are the result of intracytoplasmic accumulation of glycogen. Zhou et al demonstrated with electron microscopy that glycogen granules are present in oncocytes.[9] An increased accumulation of these glycogen granules with margination of organelles to the periphery may result in the clear cell variant of oncocytoma. The cytoplasmic clearing may also be secondary to cystic dilations of mitochondria as demonstrated by ultrastructural studies.[37]

Clear cell neoplasms of the salivary gland are almost always malignant with the rare exception of the clear cell variant of oncocytomas and myoepitheliomas. Clear cell (hyalinizing) carcinomas of the salivary gland are hence part of the differential diagnosis of oncocytomas when oncocytomas present a predominance of clear cells. Clear cell dominant oncocytomas can be identified as they retain the organoid architecture of conventional oncocytomas, are well-circumscribed and are usually not infiltrative. There are often some foci of intensely eosinophilic oncocytes identifiable among the clear cells. These foci react with PTAH stain and electron microscopy demonstrates the excessive mitochondrial accumulation.[38] Some of the clear cells in oncocytomas may reveal many small granules with PTAH staining that represent mitochondria.[18]
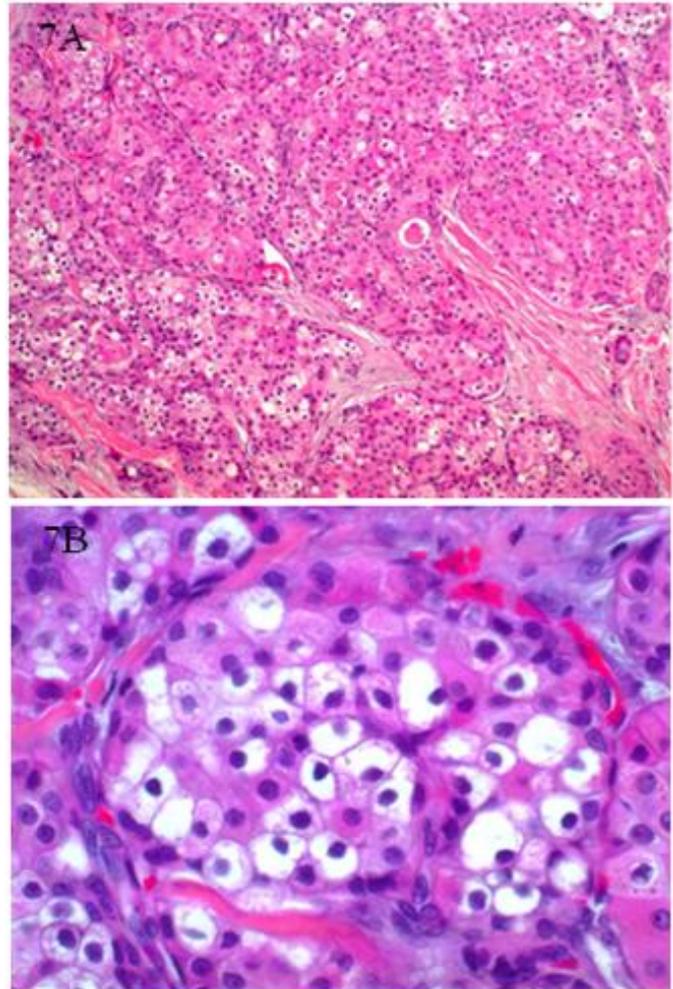
Figure 7. Morphological features of clear cell oncocytoma. **7A.** Oncocytoma with focal areas showing clusters of clear cells (hematoxylin-eosin stain, original magnification x100). **7B.** Oncocytoma with the clear cells interspersed among the oxyphilic oncocytes (hematoxylin-eosin stain, original magnification x400).

A majority of the clear cell adenocarcinomas of the salivary gland have a conspicuously hyalinized collagenous stroma (**Figure 8A; 8B**), which is not a feature of clear cell oncocytomas. Clear cell adenocarcinomas are poorly circumscribed, and show a conspicuous infiltrative growth pattern with involvement of peripheral nerves. Clear cell dominant oncocytomas, however, retain the organoid architecture of conventional oncocytomas, have some foci of characteristic eosinophilic cells, are circumscribed and not infiltrative.[4] Other clear cell neoplasms that need to be distinguished from the clear cell oncocytomas include epithelial-myoepithelial carcinoma, metastatic renal cell carcinoma and clear cell myoepithelioma.
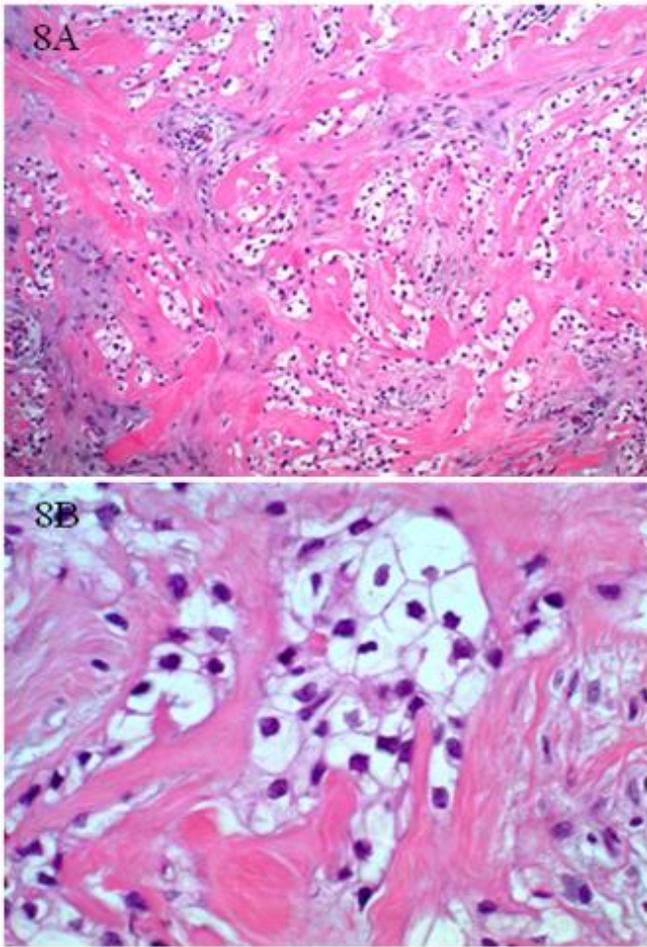
Figure 8. Morphological features of Hyalinizing clear cell carcinoma. **8A.** Hyalinizing clear cell carcinoma with the dense hyaline bands of connective tissue surrounding the clear cells (hematoxylin-eosin stain, original magnification x100). **8B.** High magnification of hyalinizing clear cell carcinoma showing congeries of clear cells (hematoxylin-eosin stain, original magnification x400).

Although rare it is very important to include metastatic renal cell carcinoma(RCC) in the differential diagnosis. Metastatic renal cell carcinoma to the salivary glands is difficult to differentiate from clear cell oncocytoma on the basis of histopathologic features alone. Renal cell carcinomas have a compact-alveolar or nested architectural pattern (**Figure 9A; 9B**) that closely resembles the architecture of oncocytomas. Both tumors have a clear cell component and stain with PTAH.[4] The clear cytoplasm of clear cell renal cell carcinoma results from accumulated droplets of glycogen, phospholipids, and neutral lipids, in particular cholesterol ester. Glycogen can be demonstrated by periodic acid -Schiff (PAS) stain, whereas neutral lipids can be identified using the Oil red O stain on fresh frozen tissue, as lipids are usually lost with routine histological processing. Clear cell RCC may also contain a variable proportion of cells with granular

eosinophilic cytoplasm, and in rare tumors these granular cells are the predominant or only cell type. An infiltrative growth, cellular and nuclear pleomorphism (in high grade lesions) and in particular, a prominent stromal vascularity, favor a diagnosis of clear cell renal cell carcinoma over oncocytoma.[4] Furthermore, blood lakes (pseudolumina filled with fresh red blood cells) were only identified in cases of metastatic RCC.[39]
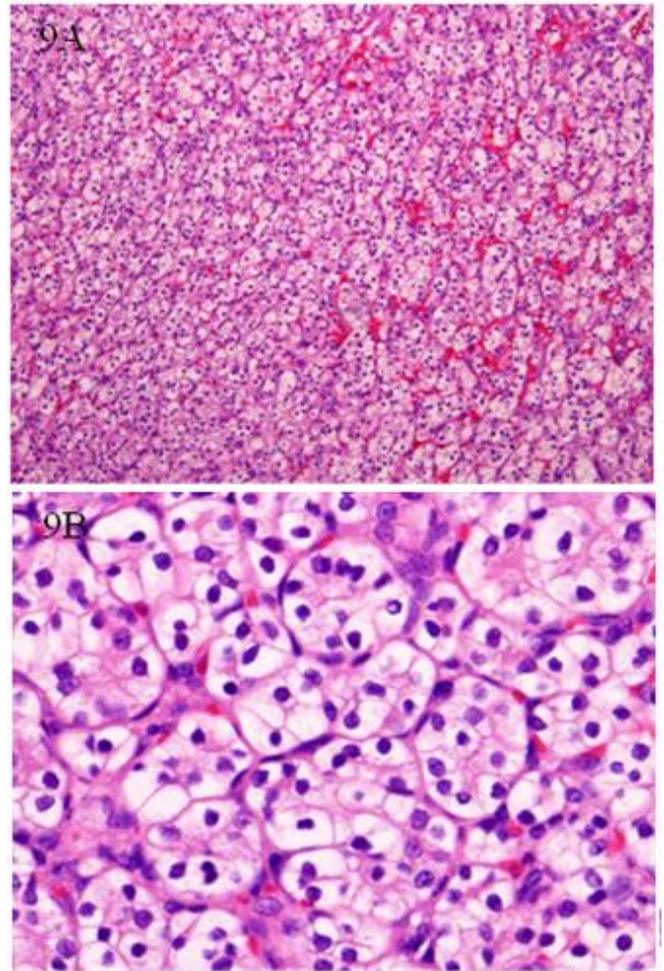
Figure 9. Morphological features of clear cell renal cell carcinoma. **9A.** Clear cell renal cell carcinoma with the characteristic vascular pattern and clear cells arranged in closely packed clusters (hematoxylin-eosin stain, original magnification x100). **9B.** Clear cell renal cell carcinoma showing cells with clear cytoplasm arranged in an alveolar pattern with prominent vascularity in the scant stroma (hematoxylin-eosin stain, original magnification x400).

Immunohistochemical staining for p63 has been proven to be a reliable marker for differentiating salivary gland oncocytic tumors from metastatic renal cell carcinoma.[36] In a study conducted by McHugh.J.B. et al all benign oncocytic tumors and oncocytic carcinomas demonstrated diffuse p63 nuclear

positivity of the basal cells located predominantly towards the periphery of the tumor cell nests. This staining pattern was found to be in distinct contrast to metastatic RCC in which none of the tumor cells stained positive for p63.[39] In addition, clear cell renal cell carcinoma displays immunoreactivity for CD10 and the renal cell carcinoma antigen. When in doubt, clinical and imaging studies are warranted to rule out a primary renal tumor.

Summary

Oncocytic lesions of the parotid gland demonstrate a spectrum of changes ranging from oncocytosis, to benign oncocytomas and oncocytic carcinomas. There have been reports of the coexistence of these oncocytic entities. This raises the concept of a progression model with a progressive transition between these oncocytic lesions.[11] This theory suggests that mitochondrial dysfunction may set the stage for a supervening oncocytic neoplastic proliferation.

In most cases oncocytomas are diagnosed without any difficulties. However, a diagnostic challenge can arise when extensive oncocytic metaplasia occurs in other salivary gland tumors such as pleomorphic adenoma, myoepithelioma, basal cell adenoma, cystadenoma, canalicular adenoma, and polymorphous low grade adenocarcinoma. More importantly, the existence of clear cell oncocytomas may create diagnostic quandaries with malignancies such as mucoepidermoid carcinoma, acinic cell carcinoma and metastatic renal cell carcinoma because all of them can present extensive clear cell populations. Awareness of the fine microscopic details of these lesions coupled to the utilization of ancillary procedures may avoid misdiagnosis.

Table 1. Comparing oncocytoma with its mimickers.

Lesion	Key features	Ancillary studies
Oncocytoma	Fibrous encapsulation, soild clusters or cords of oncocytic/clear cells in an organoid pattern. Fibrovascular septa with thin walled blood capillaries. Compression of the surrounding stroma.	Electron microscopy for mitochondria. PTAH positivity of the conventional oncocytic cells and focal positivity of the clear oncocytic cells. Positive IHC with anti-mitochondrial antibody and cytochrome c oxidase. P63 positivity in the basal cells. Positive scintigraphy with 99Tcm.
Warthin Tumor	Cystic cavity with bilayered papillary oncocytic proliferation. Prominent lymphoid component with germinal centre formation. Association with smoking.	4977 bp mitochondrial DNA deletion. Positive scintigraphy with 99Tcm.
Oncocytic Carcinoma	Cellular and nuclear pleomorphism. Perineural and perivascular invasion. Necrosis, increased mitotic activity, destructive invasion of adjacent tissue and metastasis.	p63 positive basal cells.
Mucoepidermoid Carcinoma	Epidermoid, intermediate and mucous cell differentiation. Clear cells if predominant are often associated with areas that show epidermoid differentiation.	Mucicarmine positivity of mucous cells. Clear cells are negative for PTAH. t(11;19)(q21;p13) translocation is present in 70% of Mucoepidermoid carcinomas.
Acinic cell carcinoma	Presence of acinar differentiation. Classic patterns of acinic cell carcinoma like soild, microcystic, papillary cystic, follicular and macrocystic.	No basal or myoepithelial cells are present in acinic cell carcinomas and hence the tumors are negative for p63.
Clear cell Adenocarcinoma	Conspicuous hyalinized collagenous stroma. Poorly circumscribed with an infiltrative growth pattern.	PAS positive clear cells. The tumor is negative for p63.
Metastatic Renal cell Carcinoma	Organoid pattern of arrangement. Blood lakes and prominent stromal vascularity. Nuclear pleomorphism in high grade tumors. Infiltrative growth pattern.	Positive for CD10, RCC antigen. Negative for p63. Cytokeratin and Vimentin positivity. Imaging studies to rule out a renal primary.

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