THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2018.04935
Med Bull Sisli Etfal Hosp 2020;54(1):88–93

Original Research

Oncocytic Lesions of Salivary Glands with Morphological and Immunohistochemical Findings

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Abstract

Objectives: Salivary gland neoplasms are less than 5% of all head and neck neoplasms (1). Although there are morphological similarities between different neoplasms, there may be catchy morphological differences in a single tumour. According to the World Health Organization (WHO), 4th Head and Neck Tumours Classification oncocytic salivary gland lesions are classified as nodular oncocytic hyperplasia, oncocytoma and oncocytic carcinoma. Oncocytic cells may be a component of other salivary gland neoplasms and metastatic malignities.

Methods: In this study, salivary gland oncocytic lesions diagnosed in 2016-2017 were evaluated with Haematoxylin and Eosin (H&E) sections and PAS, diastase resistance PAS, p63, DOG1, cytokeratin7 (CK7), androgen receptor (AR) and PAX8 stains.

Results: Nineteen cases were benign, two cases were malignant. Eighteen of the benign lesions were Warthin tumour (WT), one case was oncocytoma with nodular oncocytic hyperplasia. Acinic cell carcinoma (AciCCA) with oncocytic cells predominant was one of the malignant cases. The other case was high-grade salivary duct carcinoma (SDCA).

Conclusion: The rarity and heterogeneity of this group of lesions may cause difficulties in diagnosis. We present histochemical and immunohistochemical findings of these lesions in light of the literature.

Keywords: Neoplasm; oncocytic; salivary gland.

Please cite this article as "Özakkoyunlu Hasçiçek S, Tunçel D, Ünsal Ö, Kabukcuoğlu F. Oncocytic Lesions of Salivary Glands with Morphological and Immunohistochemical Findings. Med Bull Sisli Etfal Hosp 2020;54(1):88–93".

Salivary gland tumors (SGTs) make up less than 5% of all head and neck tumors.[1] 4. According to the 4. Edition of the World Health Organization (WHO) Classification of Head and Neck Tumors, 31 different types of salivary gland epithelial neoplasms have been identified.[2] They may exhibit benign, low-, or high- grade malignant behavior. There may be evident morphological similarities between tumor types and remarkable morphological diversities within a single tumor. Hybrid lesions, dedifferentiation and malignant transformation bring on difficulties in the morphological evaluation. Although hematoxylin eosin sections are the basis for diagnosis in most lesions, immunohistochemical markers are important in defining cellular differentiation. Parotid, submandibular and sublingual glands are major salivary glands located in the upper respiratory system. They consist of serous, mucous and mixed acinies, and intercalar, striped and excretory ducts. Epithelial cells are surrounded by myoepithelial cells in acinies and inter-

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Submitted Date: April 11, 2018 **Accepted Date:** July 16, 2018 **Available Online Date:** March 24, 2020

calar channels surround in the ducts, while basal cells are located in the striped and excretory ducts. Most neoplasia originates from acinar/ductal epithelial cells (luminal cells) and/or myoepithelial/basal cells (abluminal cells).

Monophasic tumors (myoepithelioma, acinic cell carcinoma and salivary gland duct carcinoma) contain only one cellular component, while tumors originated from luminal and abluminal cells (pleomorphic adenoma, epithelial–myoepithelial carcinoma, adenoid cystic carcinoma) are biphasic.

Oncocytic cells with large granular eosinophilic cytoplasm rich in mitochondria are seen in many reactive and neoplastic salivary gland lesions. The 4th Edition of WHO Classification of Head and Neck Tumors addresses the oncocytic lesions of the salivary gland under headings of nodular oncocytic hyperplasia, oncocytoma and oncocytic carcinoma. Nodular oncocytic hyperplasia is a nonneoplastic epithelial lesion. It is most often seen in the parotid, and in the 5th, and 6th decades of life. Nodular oncocytic hyperplasia is a proliferation of oncocytic cells in multiple capsule-free solid – tubule-trabecular pattern. It is often accompanied by clear cell changes.[3]

Oncocytoma is a rare tumor seen in the elderly and most commonly involves the superficial lobe of the parotid gland. Oncocytoma is an encapsulated lesion and includes monotonous oncocytic cell proliferation. Atypia, increased mitotic activity, perineural-vascular-soft tissue invasion, and lack of capsule indicate malignancy in oncocytes.[4]

Local invasion, destruction of surrounding tissues and regional lymphatic infiltration are necessary for the diagnosis of oncocytic carcinoma.[5-7] Other monomorphic oncocytic neoplasms that cause difficulty in diagnosis include WT, oncocytic cystadenoma, mucoepidermoid carcinoma (MEC), acinic cell carcinoma (AciCCA), breast analogue secretory carcinoma (BASC) and metastatic renal cell carcinoma. Pleomorphic oncocytic neoplasms are salivary gland duct carcinoma (SDCA), high- grade MEC, metastatic squamous cell carcinoma (SCC), metastatic adenocarcinoma and metastatic melanoma.[8] In the parotid gland, there are many lymph nodes draining from the scalp, the upper half of the face, nose, oral cavity, nasopharynx and oropharynx. Cutaneous SCC and melanoma metastases should be kept in mind. At the same time, intraparotid lymph node spread with the retrograde flow is seen in hypopharyngeal and laryngeal carcinomas.[9]

The evaluation of this group of lesions with the help of the last classification and literature findings is a guiding tool in creating a diagnostic algorithm. The patients diagnosed in our center were presented in this study.

Methods

Oncocytic lesions of the salivary gland diagnosed in our clinic between 2016 and 2017 were reevaluated. Since this study had a retrospective design, local ethics committee approval was not obtained. The hematoxylin-eosin stained sections prepared from fixated materials in 10% formaldehyde were stained with histochemical and immunohistochemical dyes were histopathologically classified according to the 4th Edition of WHO Classification of Head and Neck Tumors, apart from cases diagnosed as WT, immunohistochemical analyses with periodic acid Schiff (PAS), diastase- resistant periodic acid shiff (D-PAS) and p63 (mouse mab, 7JUL clone: Leica biosystems, UK), DOG1 (mouse mab, K9 clone: Leica biosystems, UK), CK7 (mouse mab, RN7 clone: Leica biosystems, UK), androgen receptor (AR) (mouse mab, EP267 clone: EPCAM, USA), PAX8 (mouse mab, MRQ-50 clone: Cell Marque, America), CD10 (mouse mab (56C6 clone: Leica biosystems, UK) were performed in Leica Bond Max automated staining device using Leica Bond Polymer Refine Detection kit.

Any statistical method was not used while evaluating the study data. The data were presented as mean (±SD), frequencies and ratios.

Results

Nineteen of 21 cases were in the benign and two cases in the malignant group. Eighteen of the benign lesions were evaluated as WT and the remaining lession was diagnosed as oncocytoma accompanied by noduler oncocytic hyperplasia (Fig. 1). All lesions were located in the parotid gland. In four cases diagnosed with WT, the lesions were ipsilateral and multiple. The average age of patients with benign

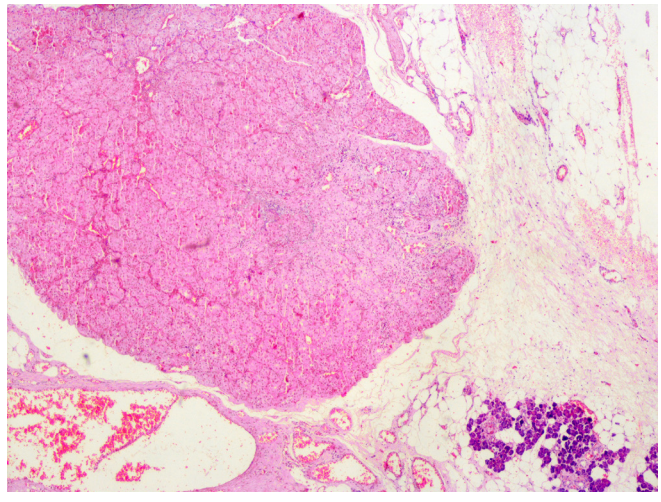

Figure 1. Non-encapsulated, nodular focus of microcytosis with regular contours H.E.X100.

lesions was 54.3, while of malignant cases, it was 61. Three female and 16 male patients had benign lesions, both malignant cases were male. One of them was predominantly diagnosed with AciCCA markedly rich in oncocytic cells, and the other case received the diagnosis of SDCA (Figs. 2, 3).

In the case diagnosed as AciCCA predominantly rich in oncocytic cells, there were PAS- positive, diastase- resistant cytoplasmic granules (Fig. 4). Widespread cytoplasmic staining was observed with CK7, while the Ki67 proliferation index was 40%. Cells could not be stained for DOG1, PAX8, CD10, p63. In the case diagnosed as SDCA, there was widespread nuclear positivity with AR and cytoplasmic staining with CK7, 34βE12, GCDFP15 (Fig. 5). Ki67 proliferation index was 70% (Table 1).

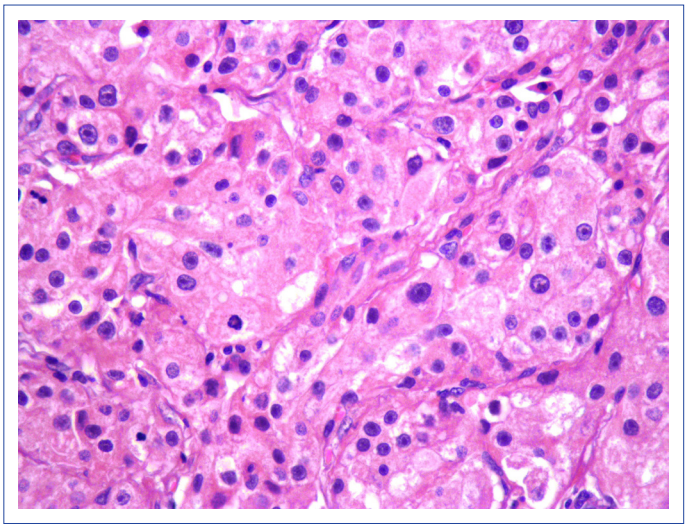

Figure 2. Acinic cell carcinoma consisting dominantly of oncocytic cells. H.EX200.

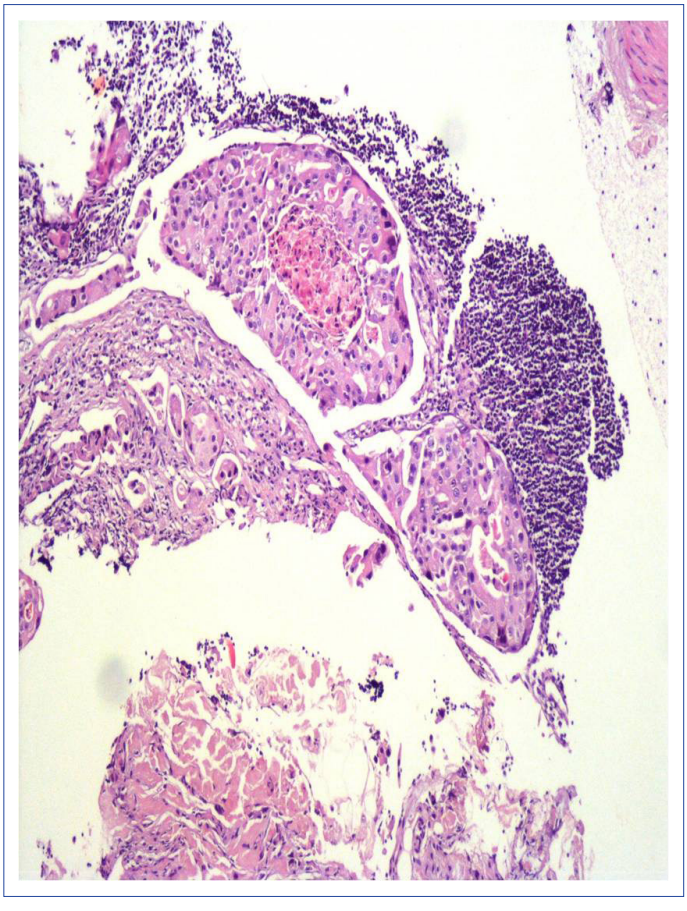

Figure 3. Widespread areas of comedo necrosis in the carcinoma of salivary gland duct. H.E.X100

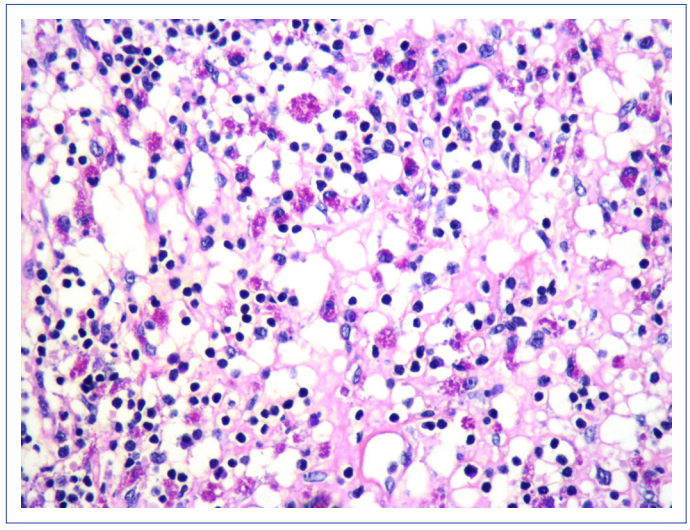

Figure 4. PAS- positive cytoplasmic granules in acinic cell carcinoma. PASX100.

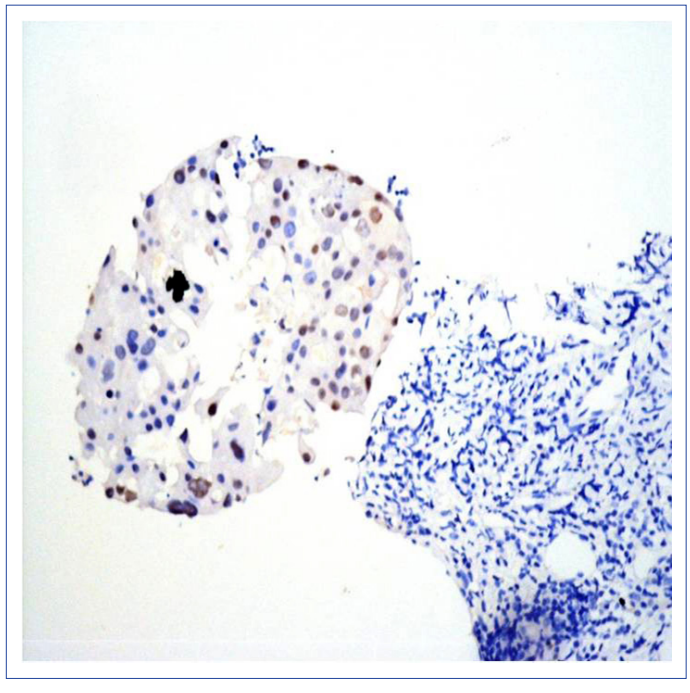

Figure 5. Nuclear staining with androgen receptor in the carcinoma of salivary gland duct ARX200.

Table 1. Demographic, morphologic and immunohistological characteristics of the cases

Gender	Age	Location Dia meter (mm)	Multifocality	Pathologic diagnosis	Histochemical, immunohistochemical markers aiding in diagnosis	
					Positive	Negative
M	69	Parotid 40	-	W.T		
M	55	Parotid 25	-	W.T		
E	58	Parotid 32	-	W.T		
M	53	Parotid 30	-	W.T		
M	46	Parotid 28-5	+	W.T		
M	58	Parotid 30	-	W.T		
F	60	Parotid 25	-	W.T		
M	47	Parotid 23	-	W.T		
M	52	Parotid 35-20	+	W.T		
M	63	Parotid 28-15	+	W.T		
K	68	Parotid 30	-	W.T		
M	58	Parotid	-	W.T		
K	62	Parotid 28	-	W.T		
M	56	Parotid 25-10	+	W.T		
M	57	Parotid 30	-	W.T		
M	57	Parotid 28	-	W.T		
M	48	Parotid 34	-	W.T		
M	54	Parotid 25	-	W.T		
M	69	Parotid 45	-	Oncocytoma	p63, CK7	PAS/DPAS AR, DOG1, CD10, PAX8
M	53	Parotid 25	-	AciCCA	CK7 PAS/DPAS	DOG1, p63 CD10, PAX8 AR
M	69	Parotid 45	-	SDCA	PAS/DPAS AR, CK7 34βE12, GCDFP15	DOG1, p63 CD10, PAX8

Discussion

Salivary gland tumors include a group of 11 benign and 20 malignant types of epithelial tumors, and also morphological variations, as well as evident morphological similarities in a single tumor type pose diagnostic difficulties for pathologists. Oncocytic cells appear in many lesions and cause diagnostic difficulties. WT, oncocytoma, MEC, AciCCA and MASC are monocytic oncocytic neoplasms, while metastatic renal cell carcinoma, SDCA, metastatic SCC, metastatic adenoCA, metastatic melanoma, and high- grade MEC are oncocytic neoplasias in pleomorphic morphology. To arrive at a definitive diagnosis, existing morphological and macroscopic findings should be evaluated all together, and patterns of differential diagnosis should be formed, considering different types of cells, and commonly seen patterns in the lesion, besides, histochemical and immunohistochemical studies should be used for this purpose.

WT is the most common oncocytic tumor of the salivary glands. In the parotid gland, it is more common in the 6th and 7th decades of life and in males. Smoking is a predisposing factor. Sometimes synchronous-metachronous multiple lesions appear in the same or both salivary glands. Macroscopically, it contains well-rounded, oval-round, solid, large and small cystic structures. The lymphoid stroma, which is also noted by the germinal centers, and papillary projections lined by double-row oncocytic columnar cells supported by basal cells, are observed. WT constitutes 85.7% of our cases, while 22.2% of them are multiple lesions. Double-row oncocytic columnar cell papillary projections accompanying lymphoid stroma have been the main finding which made us arrive at the diagnosis.

Nodular oncocytic hyperplasia is a nonneoplastic salivary

gland lesion, more commonly known as oncocytosis, with no malignant potential. Almost always, the lesion peaks at 5th and 6th decades of life. It contains nodules formed by oncocytic cells in the solid and tubule-trabecular pattern, separated by a sharp border from the surrounding salivary gland parenchyma. Morphology plays a key role in diagnosis due to the lack of both specific information and studies on its molecular and immunohistochemical profile.[10] Clear cell changes are frequently seen and are called clear cell oncocytosis.

Clear cell changes are more common in bilateral lesions and indicate an increased risk of recurrence.[11] The lesions where clear cell changes are common bring to mind metastases from renal cell carcinoma. Renal cell carcinoma metastases are hemorrhagic, and the vascular network is specific.[12] PAX8 positivity is helpful in the differential diagnosis. Oncocytoma is surrounded by an intact capsule, while 7% of the cases are bilateral, and 1/3 cases are synchronous. In our case, in a 69-year-old male patient, an oncocytoma 4.5 cm in diameter, and multiple nodular oncocytic hyperplasia nodules in the surrounding parenchyma were detected. The appearance of more than one oncocytic lesion in the same gland is associated with a "transition concept that starts with oncocytic metaplasia and explains that oncocytic lesions develop by transition between each other".[6]

While all oncocytic neoplasias show histochemical reactivity with phosphotungstic acid hematoxylin (PTAH), basal cells are stained with p63 in oncocytoma. It is not stained with SOX10 and DOG1.[13] Oncocytoma and WT show excretory and striped channel differentiation. AciCCA shows serous acini and intercalar channel differentiation.[14,15] Thus, it has different immunohistochemical profiles.[16] SOX10 (SRY-associated HMG-box10) is known to play an important role in the development of the neural crystal and has a strong expression in Schwannomas and melanocytic tumors.[17,18] Normal major salivary glands are transcription factors that are usually expressed in acinar and intercalar duct SOX10 positivity is primarily helpful in differentiating AciCCA from oncocytoma and WT in cytology materials. Indeed, oncocytoma and WT are SOX10 -negative tumors.[9,20] As SOX10, DOG1-positivity is detected in especially in AciCCA, in salivary gland tumors that show differentiation of acinar and intercalar channels, while DOG-1 negativity is observed in oncocytoma and WT.[16] In AciCCA, cells are generally rich in PAS-positive, diastase- resistant zymogen granules. It is used to differentiate AciCCA from MASC together with strong, diffuse DOG1 -positivity, PAS positivity and diastasis resistance.[20]

As defined in the latest WHO classification, MASC is a histologically, immunohistochemically and genetically similar to the secretory carcinoma of the breast.[21] Macrocystis, microcystic, lobular, papillary, cribriform, tubular and solid microcystic growth patterns can be seen. Tumor cells have a low nuclear grade, multivacuoles and eosinophilic granular cytoplasm. In the past, it received mostly the diagnoses of zymogen-poor AciCCA, mucin-producing signet-ring cell adenocarcinoma, or MEC. Strong co-expression of S100 and mammaglobin together with morphology, supports the diagnosis and is especially helpful in differentiating it from AciCCA. It should be kept in mind that adenoid cystic carcinoma (ACC) may show similar immunophenotype.[8] While staining with ACC p63, staining with GCDFP15 is not observed.[22] MASC is not stained with p63, while widespread staining is observed with GCDFP15.[20]

p63 is a valuable determinant in differentiating AciCCA from MEC. Sams et al. evaluated p63 expression in 31 AciCC and 24 MEC cases, and demonstrated p63-negativity in all AciCCAs, and strong p63-positivity in all MEC cases.[23] p63 helps to differentiate oncocytic MEC from oncocytoma and oncocytic carcinoma. It has been reported that in oncocytic MEC, more than 50% of the cells in tumor wells are p63 positive, while in oncocytoma and oncocytic carcinoma, only occasionally stained peripheral cells in tumor wells have been observed.[24]

SDCA is an aggressive malignant epithelial tumor that develops from intralobular and interlobular excretory ducts. Ductal, papillary, solid and cribriform growth patterns with comedo necrosis similar to MASC are observed. Generally, AR, GCDFP15, CK7, 34βE12, CEA, AE1/AE3 and EMA are positive.[25] AR is more frequently expressed in male patients with SDC than in female patients.[26] AR and GCDFP15 -positivity and estrogen receptor (ER), progesterone receptor (PR) negativities are characteristic. Staining with GATA3, a new determinant for breast carcinoma is also observed in SDCA.[26]

Conclusion

Despite a scarce number of our cases, this study was presented in this group of lesions with many different tumors since we thought that reviewing the present morphological findings and histochemical and immunohistochemical findings in the light of literature may be beneficial considering difficulties encountered in differential diagnosis based on histopathological findings.

Disclosures

Ethics Committee Approval: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – Ö.H.S., T.D., Ü.Ö., K.F.; Design – Ö.H.S., T.D., Ü.Ö., K.F.; Supervision – Ö.H.S., T.D., Ü.Ö., K.F.; Ma-

terials – Ö.H.S., T.D., Ü.Ö.; Data collection &/or processing – Ö.H.S., T.D., Ü.Ö.; Analysis and/or interpretation – Ö.H.S., T.D., Ü.Ö., K.F.; Literature search – Ö.H.S., T.D., Ü.Ö.; Writing – Ö.H.S.; Critical review – Ö.H.S., K.F.

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