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Histopathological and Immunohistochemical Analysis of Intraductal Carcinoma of the Salivary Gland: A Case Series

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MAYO CLINIC

Introduction

Intraductal carcinoma (IDC) of the salivary glands, initially described as "low-grade salivary duct carcinoma" represents a rare, recently described neoplastic entity with distinct histopathological features. Recognized subtypes include the intercalated duct type, apocrine type, hybrid/mixed type, and an Oncocytic variant. These subtypes exhibit unique morphological and immunohistochemical profiles, which are crucial for accurate diagnosis and classification. This study presents a case series of four cases of IDC, with a comparative analysis of the histomorphology, immunohistochemical profile (IHC) and molecular findings.

Methods

A database search found four histologically confirmed cases of IDC of the salivary glands, diagnosed at Mayo Clinic over the past two years. The histology, IHC profile and molecular findings (if available), were reviewed.

Results

This study analyzed four cases of IDC in the salivary glands, all located in the parotid gland. Patients ranged from ages 40-80 years, with M:F ratio of 1:1. Histology showed a well delineated lesion and a cystic proliferation with variable degrees of papillary and micropapillary architecture in all four cases, with prominent lymphoid stroma in 3/4 cases. The cellular constitution was highly variable with mixed intercalated duct type cells and Oncocytic cells in one case, pure Oncocytic and intercalated morphology in one case each, and intercalated duct morphology with focal apocrine differentiation in the last case (Figure 1). Notably, there was absence of marked cytologic atypia or increased mitotic activity, with only one case (Oncocytic type, Case# 3) showing focal evidence of single cell invasion into the stroma suggestive of early invasion. Interestingly, we noted focal evidence of Bonafide acinar differentiation in the mixed-type IDC case, characterized by large cells with basophilic granular cytoplasm, further supported by DOG-1 staining (Figure 1).

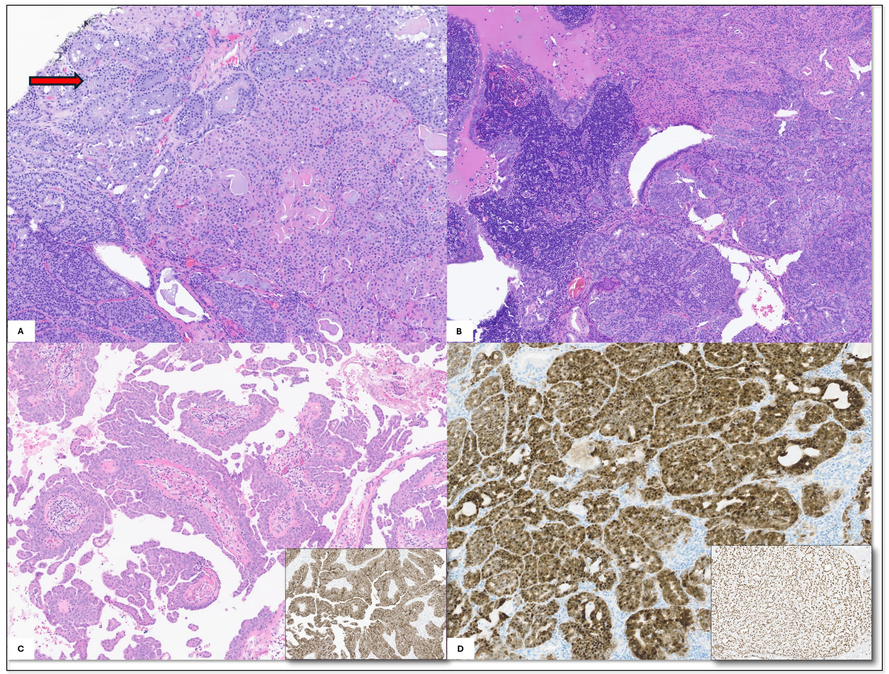

Figure 1: **A) Focal acinar differentiation in mixed type IDC (Case#1, red arrow). B) Mixed Intercalated and Oncocytic morphology. C) Oncocytic type IDC (Case# 3), Inset shows BRAF V600e expression. D) S-100 (diffuse expression), Inset shows SOX-10 IHC**

	Case 1	Case 2	Case 3	Case 4
IDC subtype	Mixed type with Bonafide acinar differentiation	Intercalated duct type	Oncocytic type	Intercalated duct type with apocrine features
S100	+	+	+	+
SOX-10	+	+	+	+
GATA-3	+	NP	NP	NP
Mammaglobin	+	+	+	+ (focal)
CK7	NP	+	NP	NP
DOG-1	+ (focal)	-	NP	NP
p40	+	+	NP	NP
p63	+	+	+	+
Actin	NP	+ (focal)		
BRAF- V600e	NP	NP	+	-
AR	NP	NP	+ (focal)	NP
Molecular studies	Negative for ETV6-NTRK3 and NR4A3 mutations	NCOA4::RET gene fusion	BRAFV600e	BRAFV600e

Table1 : Comparative morphology and Immuno-histochemistry profile of the IDC cases

Results (Cont.)

To the best of our knowledge, acinar differentiation has not been previously described in IDCs, and this is the first case to show such differentiation.

Immunohistochemical (IHC) analysis (comparative analysis shown in table 1), consistently showed strong and diffuse expression of S100 and SOX-10 in all four cases. Mammaglobin expression was observed in all cases, though it was focal in one. P63 showed intact myoepithelial cell layer in all four cases.

Molecular studies were available in two cases; one showed a NCOA4::RET gene fusion (Case 2, pure intercalated duct type). BRAF V600E IHC was performed in two cases, of which the Oncocytic type showed positive expression.

Differential diagnosis includes lymphoepithelial cyst, Warthin tumor, mucoepidermoid carcinoma, acinic cell carcinoma and secretory carcinoma. Comprehensive IHC work up should help in ruling out majority of the differentials. However, FISH studies might be necessary in neoplasms with acinar differentiation, as seen in Case 1 of this series, to rule out acinar cell carcinoma. Molecular studies ruled out the possibility of acinic cell carcinoma and secretory carcinoma in case 1 in the form of negative NR4A3 and ETV6-NTRK3 mutations, respectively.

Conclusions

The findings in this case series highlight the histological, immunohistochemical and molecular diversity of intraductal carcinomas and emphasize the need to utilize a comprehensive panel for classification and differential diagnosis of this rare evolving entity from benign salivary gland entities, correctly characterize these rare neoplasms as malignant, and guide clinical management.

References

- *Emilija Todorovic, Ilan Weinreb, Intraductal Carcinomas of the Salivary Gland, Surgical Pathology Clinics, Volume 14, Issue 1, 2021, Pages 1-15, ISSN 1875-9181, ISBN 9780323776301*
- *Fisch AS, Laklouk I, Nakaguro M, Nosé V, Wirth LJ, Deschler DG, Faquin WC, Dias-Santagata D, Sadow PM. Intraductal carcinoma of the salivary gland with NCOA4-RET: expanding the morphologic spectrum and an algorithmic diagnostic approach. Hum Pathol. 2021 Aug;114:74-89. doi: 10.1016/j.humpath.2021.05.004. Epub 2021 May 12. PMID: 33991527; PMCID: PMC9377626.*
- *Vered M, Wright JM. Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Odontogenic and Maxillofacial Bone Tumours. Head Neck Pathol. 2022 Mar;16(1):63-75. doi: 10.1007/s12105-021-01404-7. Epub 2022 Mar 21. PMID: 35312978; PMCID: PMC9019005.*
- *Thompson LDR, Bishop JA. Salivary Gland Intraductal Carcinoma: How Do 183 Reported Cases Fit Into a Developing Classification. Adv Anat Pathol. 2023 Mar 1;30(2):112-129. doi: 10.1097/PAP.0000000000000362. Epub 2022 Aug 30. PMID: 36040027.*