



## Intercalated, Secretary, Salivary: Acinic Cell Carcinoma

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### Preface

An exceptional malignant epithelial tumour, which is an estimated 1-6 % of the salivary gland neoplasm, is the scripted Acinic Cell Carcinoma (ACC) [1]. The parotid gland is a frequent locus of the low grade neoplasm, which delineates a female preponderance and a predilection for young individuals, in contrast to the adjunct salivary gland neoplasm. Acinic Cell Carcinoma may reoccur and elucidate localized and distant metastasis to the regional cervical lymph nodes and lungs. The tumour may be clinically aggressive and may exemplify a mortality ranging from 1.3 % to 26% [1,2]. The malignant transformation of the terminal duct cells (intercalated duct cells) or the serous acinar cells [1,3] may account for the genesis of the neoplasm. A previous irradiation or a familial predisposition or a contingent hormonal exposure (akin to a breast carcinoma), may induce the tumour [1,4].

### Analysis and Attributes

Acinic Cell Carcinoma was initially chronicled in 1892 [5]. Distinctively termed as “Acinic Cell Tumour”, a debate followed on the malignant potential for this neoplasm, Further categorization as a malignant, infiltrative neoplasm and a nomenclature of an “acinic cell adeno-carcinoma” was developed [6,7]. Subsequent to this description, emerged the revised classification of the salivary gland tumours by the World Health Organization in 1991 [1,2] with the contemporary designation of “Acinic Cell Carcinoma”. Though Acinic Cell Carcinoma may appear at any age, the tumour prevalence is roughly denoted to be at 45.75 years with an extent of 40-49 years [8]. The preponderantly female neoplasm elucidates a female to male incidence at an estimated 1.4:1 [8]. Acinic Cell Carcinoma comprises of 6-37% of the childhood parotid malignancies [1]. An estimated 80% of the neoplasm emanates in the parotid salivary gland as a solitary, well circumscribed nodule. The intraoral minor salivary glands may be incriminated (17%) followed by the submandibular glands (4%) and the sublingual glands (less than 1%), besides the intra-parotid lymph nodes [1,2,4]. Approximately 3 % of the tumours may delineate a bilateral, parotid salivary gland lesion [1].

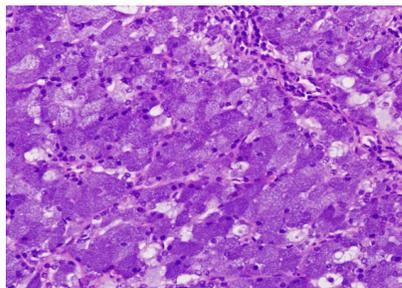
### Macroscopic Aspects

Describe the tumour as an encapsulated, solid to fragile, spherical lump with a greyish/ white cut surface, generally measuring less than 3 cm in diameter. Cystic degeneration may ensue.

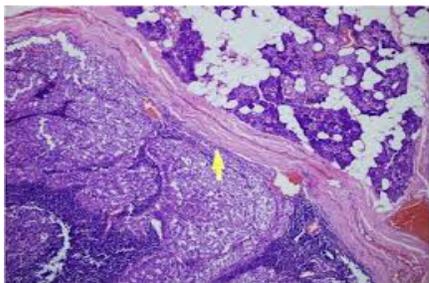
### Microscopic Morphology

May be predominantly variable. Solid, micro-cystic, papillary –cystic or follicular configurations may be demonstrated [1,3]. The tumour cells may manifest variously. The classic acinic cell may illustrate a granular and basophilic cytoplasm, with an ultra-structure and a secretory nature simulating a typical acinic cell of the normal salivary gland [1,3]. Intercalated duct cells, clear cells, vacuolated cells and non-specific glandular cells may be associated with the neoplasm. The architectural deviation and the cytology defines the neoplasm to be akin to the terminal duct –acinar unit of the salivary gland with the participation of the secretory (luminal) cells, intercalated duct cells, pluripotent reserve (basal)cells and the myoepithelial cells [1,3]. Acinic Cell Carcinoma may elucidate seven diverse morphologic patterns, as the acinar- lobular, micro-cystic, follicular, papillary- cystic, medullary, ducto- glandular and primitive- tubular [1,2]. The tumour may also be graded. The grading ranges from Grade I being the least infiltrative and Grade III as the most infiltrative neoplasm [1,2]. In addition, three major categories, the cystic- papillary, follicular and solid may be characterized [1]. Therefore, four principal varieties, as designated in the last three decades, the solid, micro-cystic, papillary –cystic and follicular, are currently employed [9]. Nevertheless, the tumour sub categories may not describe the particular sub-class of the Acinic Cell Carcinoma, as applicable for the clinical, therapeutic or prognostic determination. The solid and the micro-cystic configurations are the major morphologies of the neoplasm, with admixed tumour configurations being common [1,3]. In approximately half the cases (42%) the solid/ lobular or a solid/micro-cystic or a dual pattern may be exhibited [1]. The solid variant (33.3%) or papillary- cystic (16.6%) type or the micro-cystic (8.3%) kind of tumour may also be enunciated [1]. Well defined acinar cells with a predominantly basophilic or a greyish granular cytoplasm, intermixed with focal

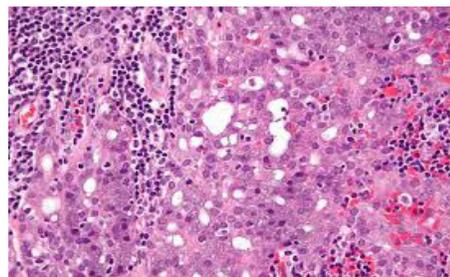
aggregates of nonspecific glandular epithelium depicting an eosinophilic or amphophilic cytoplasm is demonstrated in the solid category [3]. The micro-cystic proliferation simulates the terminal (intercalated) duct acinar unit [3], rather than a purely acinar evolution of the solid sub-type. Innumerable, miniscule spaces lined with cuboidal cells with amphophilic or eosinophilic cytoplasm, the cell perimeter exhibiting fenestrations or a lattice like configuration, may be depicted [8]. The follicular variant is the least common, inducing the major and minor salivary gland [1] lesions. An augmented acinar or micro-cystic architecture is delineated, the distended acini may be lined by a flattened epithelium, constituting of a colloid like or amorphous eosinophilic material [1]. The papillary-cystic theme comprises of cystic spaces with abundant papillary projections and a variable cellular lining such as the acinic cells, vacuolated cells, intercalated cells, non-specific glandular cells or clear cells [1]. Acinic Cell Carcinoma with dedifferentiation may exhibit foci of a low grade tumour intermixed with foci of poorly differentiated, high grade neoplasm or an undifferentiated carcinoma [8]. Lymphoid follicles with germinal centres may encroach upon the tumour margin. Laminated, concentric bodies, identical to the psammoma bodies, may occupy the glandular lumen (Figure 1-10).



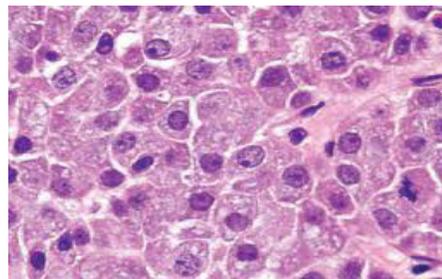
**Figure 1:** Acinic Cell Carcinoma with basophilic, granular acinar cells.



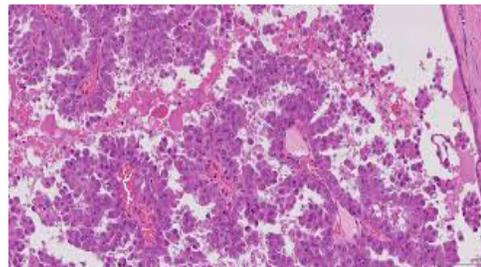
**Figure 2:** Acinic cell carcinoma with encapsulation and tumour localization.



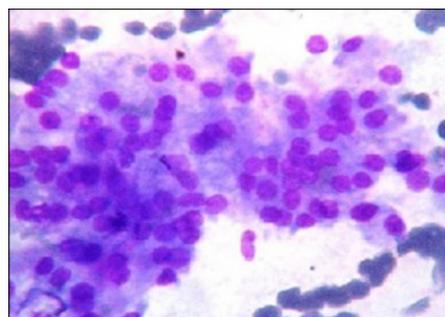
**Figure 3:** Acinar cell proliferation with a mild lymphoid infiltration.



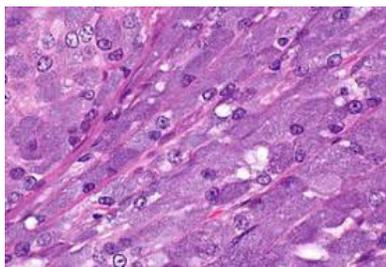
**Figure 4:** Acinar cell propagation with secretory vacuoles and prominent nuclei.



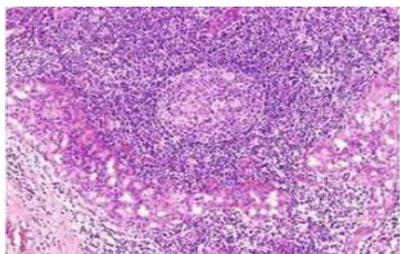
**Figure 5:** Acinic cell carcinoma with numerous papillary projections.



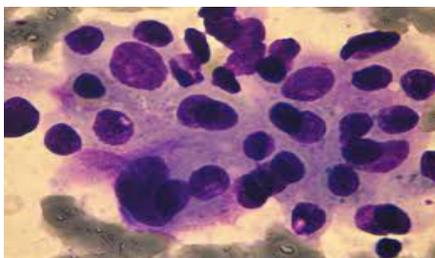
**Figure 6:** Acinic cell carcinoma with fine vacuolation-aspiration cytology.



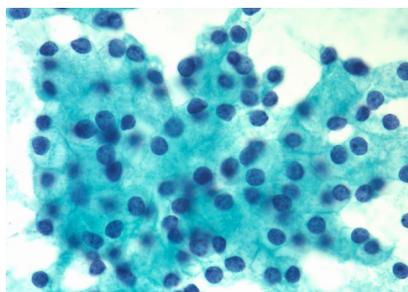
**Figure 7:** Basophilic acinar cells with prominent nucleie.



**Figure 8:** Acinic cell carcinoma with a predominant lymphoid stroma.



**Figure 9:** Acinic cell carcinoma with basophilic cytoplasm and mild anisonucleosis- aspiration cytology.



**Figure 10:** Acinic cell carcinoma with mono-layered sheets of acinar cells- aspiration cytology.

Well differentiated tumours with an extensive lymphoid stroma may elucidate a definite circumscription and a solid to micro-cystic configuration in which the tumour cells are enveloped by and intermixed with a predominant lymphoid infiltrate [1]. Hybrid tumours [1,3] or neoplasm with an abundant neuro-endocrine element [10] are adjunctive morphologic variations. The variant histology along with the infrequency of the lesion may compound the diagnostic dilemmas, especially if the acinar cells are inad-

equately discerned. Thus histochemical stains such as a Periodic Acid Schiff-Diastase (PAS-D) or Anti amylase antibodies may be pivotal to the interpretation [1]. Thyroid follicular carcinoma may characteristically simulate an Acinic Cell Carcinoma, which may be discriminated by employing an Anti Thyro-globulin immune stain. A papillary cystic tumour necessitates a distinction from a cyst-adenocarcinoma, (analyzed by a mucicarmine stain) or a muco-epidermoid carcinoma (with epidermoid cells, intensely mucicarmophilic mucocytes and a lack of serous acinar cells) [1]. A polymorphous low grade carcinoma may also require a distinction in the minor salivary glands, though a low grade papillary cystic carcinoma may not commonly appear as a predominant variant, the morphology is inclined towards a perineural invasion, a uniform cell population and a propensity for a single file infiltration at the tumour perimeter, in contrast to the acinic cell carcinoma [1]. Occurrence of clear cells in the Acinic Cell Carcinoma composed of a clear cell component may mandate a distinction from adjunctive Clear cell carcinomas such a mucoepidermoid cell carcinoma, epithelial-myoeplithelial cell carcinoma, clear cell adenocarcinoma, clear cell oncocytoma and metastatic renal cell carcinoma (tumour cells being reactive for glycogen stains) [1,3]. The preponderant clear cell configuration delineates a hyper-nephroid morphology (identical to the renal cell carcinoma with a glycogen quantification and an absence of mucin or lipid vacuoles.

### Immune Histochemical Reactions

Reactivity for Keratin, Amylase (focal reaction), Alpha1 Anti-chymotrypsin, Transferrin, Lactoferrin, IgA secretory component and a Proline rich protein may be expressed [3]. A miniscule neuro-endocrine element, displaying argyrophilia, dense core neurosecretory granules on electron microscopy and immune reactivity for Vasoactive Intestinal Peptide (VIP) may be demonstrated [1,3]. The morphological aspects may not be able to clearly define the prognostic implications of the neoplasm [9]. A solid sub-category of tumour elucidates a poorer prognosis. A papillary cystic sub-class may depict a 100% mortality rate [1]. The dedifferentiated variant of the carcinoma may be accompanied with a worse clinical culmination as the entire parotid gland, the facial nerve, the blood and lymphatic vessels may be incriminated along with the metastasis in the regional lymph nodes [1]. The lack of consistent benchmarks may determine incompetent and ambiguous grading classifications, established solely on the histology. The tumour location and magnitude may participate in the histological grading paradigm [8] although these may actually be prototypes of the clinical tumour staging. Clinical staging may frequently be a superior prognosticator of the tumour consequence, in contrast to the histological grading. Highly destructive tumours delineate frequent mitosis, focal necrosis, neural invasion, pleomorphism, infiltration with a lack of circumscription and stromal hyalinization [3]. Inadequate resection, massive dimensions, incrimination of the submandibular gland and the deep lobe of the parotid gland

are aspects which augment the invasiveness of the neoplasm [3,8]. Practically two-thirds (67%) of the detected Acinic Cell Carcinomas may depict infiltration in the abutting uninvolved tissues. Tumour dispersal in the lymph nodes may be exemplified in one-fourth (25%) instances and perineural or vascular invasion may be absent. The definitive year continuance is at an estimated 89% and may decline to 56% beyond 20 years [3].

The regional lymph nodes may be the frequent metastatic location. Features of prognostic significance are pain, tumour fixation, gross infiltration of the tumour, desmoplasia, atypia on cytology, augmented mitotic activity and a competent preliminary surgical resection [3]. A localized, insurgent lesion or a metastatic disease may amplify the possibility of a local reoccurrence. Radiation therapy as a therapeutic modality, is of questionable efficacy. The mortality due to the neoplasm may extend from 1.3% to 26%, localized reoccurrences from 8.3% to 45%, implicated regional lymph nodes in 3.8% to 16% and distant metastasis from 2.6 % to 14% [1,9]. Acinic Cell Carcinoma frequently disseminates to the cervical lymph nodes, pulmonary and hepatic sites, contra-lateral orbits and bones (thoracic spine) [11,12]. An anaplastic (dedifferentiated) element, interpreted as a high grade adenocarcinoma, a poorly differentiated or an undifferentiated carcinoma may emerge. Flow cytometry may depict aneuploidy and an accelerated clinical outcome. TP53 gene mutation and HER2 gene amplification may not be encountered in the dedifferentiated Acinic Cell Carcinoma [13,14]. The analogous mammary secretory carcinoma may be accompanied by a t (12;15) (p13; q25) translocation resulting in an ETV 6 and NTRK3 gene fusion [3]. Therefore, a Mammary Analogue Secretory Carcinoma of the salivary gland (MASC) requires a segregation from the true Acinic Cell Carcinoma. Mammary Analogue Secretory Carcinoma of the salivary gland (MASC) may exhibit micro-cystic and glandular spaces with abundant eosinophilic secretion and a reactivity for Periodic Acid Schiff (PAS) stain, Mucicarmine, MUC 1, MUC 4 and Mammaglobulin [3,15].

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