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Epithelial-myoepithelial carcinoma of intercalated duct origin: Review literature

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Abstract

The epithelial-myoepithelial carcinoma of intercalated duct origin is a rare, low-grade salivary gland neoplasm that exhibits a dual composition of both the epithelial and myoepithelial cells. This tumor can manifest a spectrum of cytomorphologic and structural features, but it classically shows duct-like structures consisting of inner cuboidal, eosinophilic, epithelial cells surrounded by clear myoepithelial cells. This review article describes the clinical features, the histopathology, the immunohistochemistry, the treatment of this tumor and the in-depth discussion on the differential diagnosis.

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Keywords: epithelial, myoepithelial, epithelial-myoepithelial carcinoma of intercalated duct origin

Introduction

Epithelial-myoepithelial carcinoma of intercalated duct origin was first coined by Donath and co-workers[1] in 1972 to describe a distinctive but rare tumor of salivary gland. It accounted for less than 1% of salivary gland carcinomas[1]. Epithelial-myoepithelial carcinoma of intercalated duct origin has been referred to by various names; tubular solid adenoma, cystic adenoma, clear cell adenoma[2], clear cell myoepithelial adenoma[3], adenomyoepithelioma[4], clear cell carcinoma[5,6], glycogen-rich adenoma[7], and glycogen-rich adenocarcinoma[8].

Clinical features

The epithelial-myoepithelial carcinoma of intercalated duct origin is found mostly in the major salivary glands with the parotid parotid gland as the preponderant site of involvement. It may occur in the minor salivary glands of the mouth and has also been described in the maxillary sinus[9], trachea[10] or the lacrimal gland.[11] The incidence in parotid gland has been reported from 71.5 to 88.89%.[12-15] The age of the patients ranges from 13 to 91 years[14,16] with the peak incidence in the seventh and the eighth decades of life.[14] There is a marked female preponderance over male. In one series, the ratio of female to male is as high as 1.7:1.[9] Patients with epithelial-myoepithelial carcinoma of intercalated duct origin may be asymptomatic or complain of long-standing salivary gland swelling[2,17] or the progressive enlarging mass over a period of months to years. Features typifying malignancy such as pain and facial nerve palsy rarely occur.[18] The overlying skin usually appears intact.[15] This tumor possesses high recurrence rate ranging from 23.5% to 55.56%.[9,12,14,16] Some patients even suffer from multiple recurrences.[12] The incidence of recurrence is higher in tumors larger than 4 cm.[14] Occasional spread to regional lymph nodes or distant metastases have been documented.[9] Some reports, although in small amount, showed deaths resulting from this neoplasm.[9,12,14,16] Epithelial-myoepi-

thelial carcinoma of intercalated duct origin is a tumor of low-grade malignancy, showing relatively low mortality and locoregional aggressiveness.[19]

Histopathology

Macroscopically, the tumor is well circumscribed and is well demarcated from adjacent healthy tissues. It has a multilobular appearance.[15,17,20] The tumor size ranges from 1.5to 8.0 cm. in maximum dimension.[16] Under low-power light microscopy, the epithelial-myoepithelial carcinoma can be seen to have a multinodular nodules separated by vascular and fibrous connective tissue.[9] This salivary gland carcinoma is capable of a spectrum of histopathologic appearances. The tumor may exhibit the classical biphasic pattern or there may be varying degree of clear cells, epithelial cells, or stromal predominance within each tumor.[16,18] The classic bicellular form is unmistakable with hematoxylin and eosin stains and light microscopy.[9] The histologic appearance of the epithelial-myoepithelial carcinoma of intercalated duct origin varies not only between neoplasms, but also within the same neoplasm.[12] The tumor is usually composed of a collection of duct-like structures with variable dimension (figure 1). The most striking feature of this tumor is its biphasic appearance. The duct-like structures are lined by cuboidal, eosinophilic, epithelial cells which abut the lumina. These cells are surrounded by clear myoepithelial cells. The cuboidal cells have finely granular, dense eosinophilic cytoplasm and centrally or basally located, round nuclei. The clear cells are polyhedral with well-defined cell borders and slightly eccentric, vesicular nuclei. The clear cells are then surrounded by prominent, periodic acid Schiff-positive material.[12,21] Simpson RH et al[15] described the histopathologic pattern of the epithelial-myoepithelial carcinoma into 3 distinctive types. In the first or classic pattern, the two layers lining the ducts were easily discernible, as well as the surrounding basement membrane. In the second or clear cell predominant pattern, sheets of clear cells resembling the outer layer of the classic pattern were divided into alveolar structures by thin strands of stroma. An inner layer of cells was present, but was often difficult to identify. The third or sclerotic pattern consisted of abundant hyalinized stroma separating relatively sparse double-layered ducts. Fonseca and colleagues[22] classified the cellular organization of this tumor into 4 distinct architectural types: solid, tubular, cribriform and papillary. Some ductal lumina contain homogeneous eosinophilic secretory material.[12,19] Perineural and periarterial invasion and coagulative necrosis which is characteristically located within the center of the tumor may be seen, but nuclear pleomorphism and mitoses are rare.[2,18,19,21,23] The lesion may be encapsulated, but the capsule is frequently incomplete and tumor nodules often extend through it.[23] Special stains demonstrate that the cytoplasm of clear cells contains periodic acid Schiff-positive, diastase-digestible material indicating the presence of glycogen (figure 2). Intracytoplasmic mucin is not present in both the clear and the ductal cells.[9,12,19]

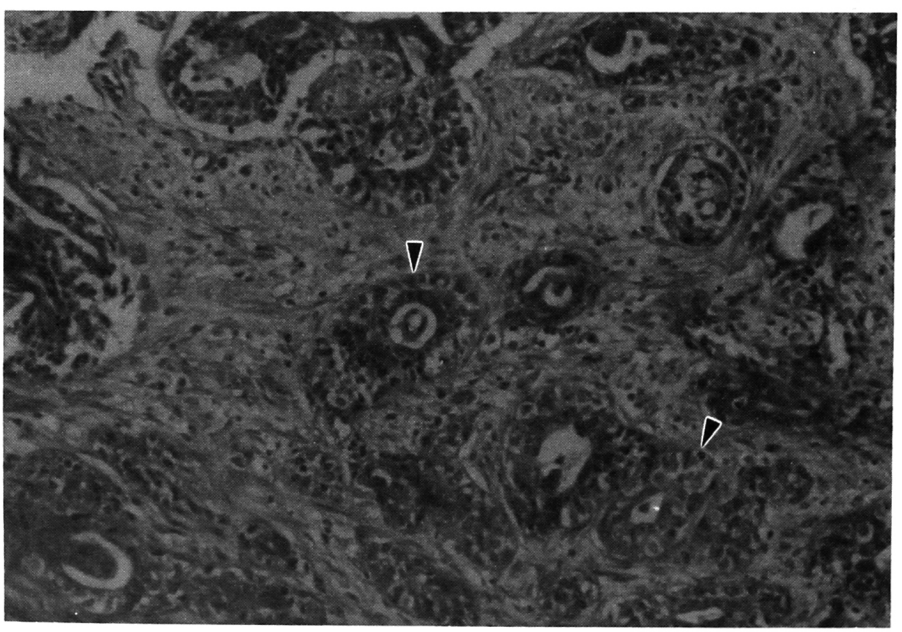

Figure 1 Photomicrograph showing duct-like structures (arrowheads) consisting of inner epithelial cells and outer myoepithelial cells. Hematoxylin and eosin stain. X 180

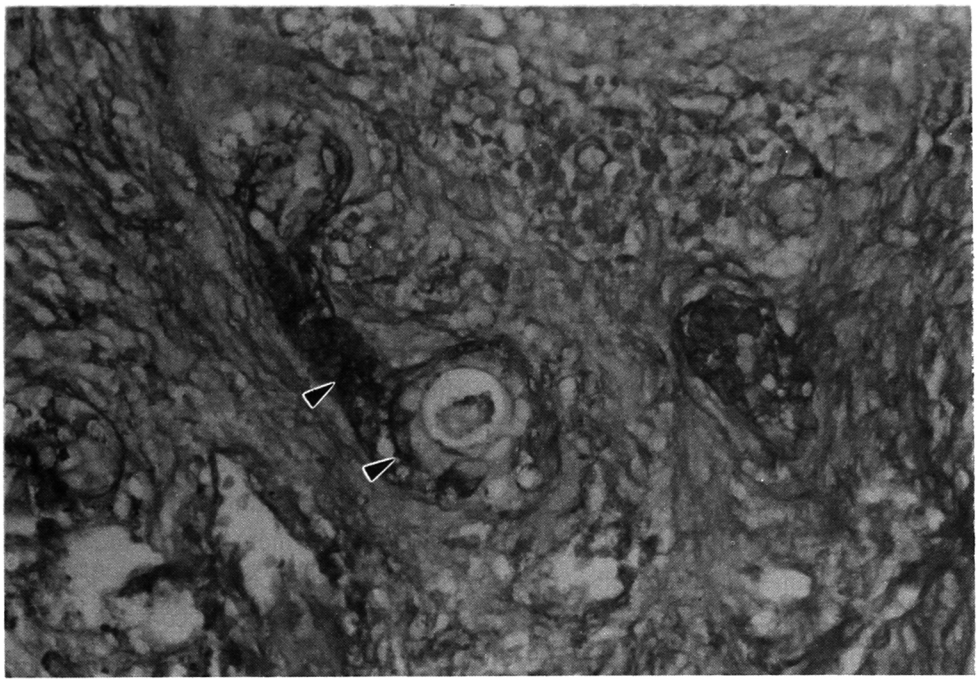

Figure 2 Photomicrograph showing positive periodic acid Schiff staining in the myoepithelial cells (arrows) surrounding the inner epithelial cells. Periodic acid Schiff stain counterstained with light green. X 360

Immunohistochemistry

Antibody to S-100 protein shows positive staining reaction in both the nuclei and the cytoplasm of the clear cells.[9,20] In the solid pattern composed almost exclusively of clear cells, the reaction tends to be diffuse while the reaction is limited to peripheral clear cells in the biphasic areas.[12] Besides the S-100 protein positive staining reaction, the clear cells also exhibit positive staining reaction to smooth muscle actin, myosin and vimentin, whereas they are constanly negative for keratin.[19,24,25,26]

Immunohistochemical staining of the inner layer of cells demonstrates positive staining reactions to epithelial membrane antigen (EMA) and low molecular weight cytokeratin.[15,26] Some of the ductal cells show focal areas of immunoreactivity for amylase. Positive staining for amylase is also observed in secretory material present in the lumina of some ducts.[12] Basement membrane outlining the ductal structures is stained with the anti-type IV collagen.[25]

DNA ploidy

DNA ploidy has been shown to be a valuable prognostic indicator in various types of neoplasms, including salivary gland tumors.[27] The result of the ploidy study by CHO et al[16] showed that most epithelial-myoepithelial carcinoma of intercalated duct origin demonstrated diploidy and the primary tumor revealed diploidy, whereas the recurrence showed aneuploidy. The low incidence of aneuploidy together with the near-diploidy in epithelial-myoepithelial carcinoma of intercalated duct origin are consistent with the low-grade malignancy of this disease.

Electron microscopy

Electron microscopy has confirmed the dual cellular composition. The cells bordering the lumens are more or less cuboidal showing an irregular array of atypical microvilli, and many similar peripheral projections into slender clefts between adjacent cells. The round nuclei have evenly dispersed chromatin and inconspicuous nucleoli. The organelles found include a moderate number of mitochondria, varying quantities of granular endoplasmic reticulum forming dilated cisternae, a prominent golgi complex and the small, smooth, clear vesicles present toward the apical or luminal aspect of the cells. In addition, they show intracytoplasmic tonofilament bundles and well-formed desmosomes around the cell periphery.

Immature or primitive myoepithelial cells lie outside the inner row of cells. They contain electron-lucent or finely granular lakes of glycogen, band of microfilaments with interspersed densities, typical of smooth muscle myofilaments. These cells assume a narrow, elongated

profile with a basal lamina at the stromal-epithelial interface. This basal lamina is often multilayered and rather complex in arrangement. Extensive, dilated, rough endoplasmic reticulum are also a prominent feature of these cells.[2,12,21]

Treatment

Surgical excision is considered the treatment of choice. Wide excison margin has been recommended as the tumor has a high rate of local recurrence which may relate to the locally infiltrative growth pattern.[18] The possibiliy of multiple tumor foci within the gland has been proposed[28] and this may provide an explanation for the high recurrence rate despite adequate surgical excision.[12,21] The tumors arising in the parotid gland have mainly been managed by superficial or total parotidectomy with the facial nerve or its branches being sacrificed only if macroscopically infiltrated, those in the submandilbular gland by gland excision and those in minor salivary glands by wide local resection. Raddiotherapy has been restricted to patients with either extensive of recurrent disease and only in combination with surgery(reviewed by Mamek M and Grant)[20]

Discussion

Clear cells are most often resulted from artifacts or fixation, but in some instances, they may be a reflection of peculiar functional state of the tumor cells. A scarcity of organelles in clear salivary duct cells, glycogen storage in myoepithelial cells, accumulation of mucin in mucous cells, lipid in sebaceous cells, tonofilaments in epidermal clear cells and immature zymogen granules in clear acinar cells may also account for this appearance.[17]

Although clear cells may be encountered frequently in a number of salivary gland tumors such as acinic cell carcinoma and mucoepidermoid carcinoma, it is rare for them to form the bulk of the tumor.[24] The major differential diagnoses for epithelial-myoepithelial carcinoma of intercalated duct origin are mucoepidermoid carcinoma, acinic cell carcinoma, pleomorphic adenoma, clear cell oncocytoma, sebaceous carcinoma and metastatic renal cell carcinoma.

Mucoepidermoid carcinoma variant which shows a large amount of clear cells can be mistaken for epithelial-myoepithelial carcinoma of intercalated duct origin. In mucoepidermoid carcinoma, clear cells are epidermoid cells which undergo vacuolar degeneration[29] so that they do not contain glycogen as in the clear cells of epithelial-myoepithelial carcinoma of intercalated duct origin and the arrangement of both typical epidermoid cells and the clear cells type of the epidermoid cells does not conform to the normal anatomical arrangement observed in the epithelial-myoepithelial carcinoma of intercalated duct origin : inner ductal cells surrounded by outer myoepithelial cells. The mucous secreting cells are found only in mucoepidermoid carcinoma, not in epithelial-myoepithelial carcinoma of intercalated duct origin. The mucous secreting cells in mucoepidermoid carcinoma usually line the cystic spaces and not surrounding the ductal cells as in epithelial-myoepithelial carcinoma of intercalated duct origin and it is imperative that mucin be demonstrated in the mucous secreting cells in order to diagnose the tumor as mucoepidermoid carcinoma.[9] The mucin which is acid mucopolysaccharide stains positively with periodic acid Schiff with and without diastase digestion.[17] In contrast to glycogen of the clear myoepithelial cells in epithelial-myoepithelial carcinoma of intercalated duct origin which are periodic acid Schiff-positive, but diastase digestible.[30]

In sebaceous carcinoma, only the sebaceous cells are found. In the contrary, epithelial-myoepithelial carcinoma of intercalated duct origin shows not only ductal cells, but also clear myoepithelial cells. In addition, the cytoplasm of the sebaceous cells is foamy, lipid-rich and does not contain glycogen while the cytoplasm of the myoepithelial cell of epithelial-myoepithelial carcinoma of intercalated duct origin is clear and does contain glycogen.[15] In addition, the sebaceous carcinoma also stains positively for cytoplasmic lipid material which is not present in epithelial-myoepithelial carcinoma of intercalated duct origin.[21]

In the variant of acinic cell carcinoma that shows numerous clear cells can be confused with epithelial-myoepithelial carcinoma of intercalated duct origin. After a careful search, there may be collections of basophilic or even granulated cells resembling normal acinar cells.[29] The secretory granules of acinic cell carcinoma contain a mucopolysaccharide that is periodic acid Schiff-positive, diastase resistant.[31,32] These findings may help in the identification of this variant. In the electron microscopy, the acinic cell carcinoma contains proenzyme or zymogen granules within the cytoplasm of the tumor cells, but does not demonstrate the presence of organized myofilaments as in the epithelial-myoepithelial carcinoma of intercalated duct origin.[21]

Pleomorphic adenoma can be differentiated from epithelial-myoepithelial carcinoma of intercalated duct

origin in that the former contains very distinctive pattern of stroma such as myxoid, chondroid, mucoid, and hyaline matrix which is not present in the latter.

Clear cell oncocytoma can be differentiated from epithelial-myoepithelial carcinoma of intercalated duct origin by the presence of cytoplasmic granules which show the positive staining reaction to phosphotungstic acid hematoxylin (PTAH), and the negative immunohistochemical stains for S-100 and muscle specific actin and positive immunohistochemical stain for cytokeratin.[33] Even though most of the tumor cells are completely clear, some contains variable amounts of eosinophilic granular cytoplasm. Transition from typical eosinophilic oncocytes to clear cell form is sometimes seen.[34]

The definite ductal component surrounded by clear cells is typical of epithelial-myoepithelial carcinoma of intercalated duct origin and not seen in metastatic renal cell carcinoma.[15] The presence of thick septa composed of periodic acid Schiff-positive basement membrane material between nests of clear cells is not seen in metastatic renal cell carcinoma. According to Ellis and Gnepp[35], the most useful feature in distinguishing epithelial-myoepithelial carcinoma of intercalated duct origin from metastatic renal cell carcinoma is the rich vascularity, often accompanied by deposits of hemosiderin in metastatic renal cell carcinoma. Metastatic renal cell carcinoma may sometimes be distinguished by positive cytoplasmic staining with Sudan Black or Oil Red O; however, frozen section must be available.[36]

Conclusion

Epithelial-myoepithelial carcinoma of intercalated duct origin is a rare salivary gland tumor. Parotid gland is the most commonly affected site. It has the peak incidence in the seventh and the eighth decades of life with the predilection for women. Classically, it shows duct-like structures with inner darkly staining, cuboidal cells and an outer mantle of clear cells surrounded by a basement membrane. From the results of the histopathology, the immunohistochemistry, and the electron microscopy, it is concluded that the inner darkly staining cells represent the epithelial component and the clear cells represent the myoepithelium. These cells appear clear because of the accumulated glycogen. The differential diagnoses for this tumor include, mucoepidermoid carcinoma, acinic cell carcinoma, pleomorphic adenoma, clear cell oncocytoma, sebaceous carcinoma and metastatic renal cell carcinoma. Despite its bland histopathologic features, it is considered to be a low-grade malignancy because of its local infiltrative growth pattern, high recurrence rate, periarterial or perineural invasion and its capacity to metastasize.

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เอ็พพิธีเลียมไมโอเอ็พพิธีเลียมคาร์ซิโนมาที่มีต้นกำเนิดมาจากท่ออินเตอร์คาเลทเตด : บทความปริทัศน์

บทคัดย่อ

เอ็พพิธีเลียลไมโอเอ็พพิธีเลียลคาร์ซิโนมาที่มีต้นกำเนิดมาจากท่ออินเตอร์คาเลทเตดเป็นเนื้องอกของต่อมน้ำลายที่พบได้น้อยและมีความรุนแรงต่ำ เนื้องอกชนิดนี้มีส่วนประกอบของเซลล์เนื้องอก 2 ชนิดคือเซลล์เยื่อบุผิวและเซลล์ไมโอเอ็พพิธีเลียลโดยสามารถแสดงลักษณะของเซลล์และการเรียงตัวของเซลล์เป็นรูปร่างต่าง ๆ ได้หลายแบบ แต่ลักษณะต้นแบบคือจะพบโครงสร้างที่มีรูปร่างคล้ายท่อซึ่งประกอบด้วยเซลล์เยื่อบุผิวที่ย้อมติดสีชมพู รูปร่างลูกบาศก์บุอยู่ภายในล้อมรอบด้วยเซลล์ไมโอเอ็พพิธีเลียลที่มีลักษณะใส บทความปริทัศน์นี้เป็นการบรรยายถึงลักษณะทางคลินิก ลักษณะทางจุลพยาธิวิทยา ลักษณะของอิมมูโนฮิสโตเคมี การรักษาของเนื้องอกชนิดนี้และอภิปรายอย่างลึกซึ้งในเรื่องการวินิจฉัยแยกโรค

(ว.ทันต. จุฬาฯ. 2542;22:117-122)

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