Acinic cell carcinoma of the salivary glands: a literature review

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Acinic cell carcinoma (ACC) is a low-grade malignant salivary neoplasm that constitutes approximately 17% of primary salivary gland malignancies. In the head and neck region, the parotid gland is the predominant site of origin and women are usually more frequently diagnosed than men. Previous radiation exposure and familial predisposition are some of the risk factors for ACC. A slowly enlarging mass lesion in the tail of the parotid gland is the most frequent presentation. The diagnosis is usually confirmed with a fine needle aspiration biopsy, and surgical excision is the main treatment of this malignant neoplasm. Other treatment modalities such as radiotherapy may be indicated in some cases. ACC has a significant tendency to recur, to produce metastases (cervical lymph nodes and lungs), and may have an aggressive evolution. Therefore, long-term follow-up is mandatory after treatment.

According to The World Health Organization, acinic cell carcinoma (ACC) is a malignant epithelial neoplasm of the salivary glands in which at least some of the neoplastic cells demonstrate serous acinar cell differentiation characterized by cytoplasmic zymogen secretory granules. Salivary ductal cells can also be a component of this low-grade neoplasm that most often occurs in the parotid gland and presents at a relatively younger age than other salivary gland tumors. This malignant disease shows a female predilection.

ACC was referred to as an entity for the first time more than 50 years ago by Godwin et al.1 The terms “acinar” and “serous” refer to the histologic resemblance of tumor cells to the secretory parenchymatous cells of the parotid, grouped in grape-like clusters and hence given the latin name “acinus” (Figure 1). In the past, the malignant nature of this cancer had been disputed or gone unrecognized. In earlier literature, it was classified as an “acinic cell tumor” or benign “adenoma”. Recent literature detailing the high potential for recurrence, metastases and even death resulted in WHO re-classification as a “malignant carcinoma”, though with a more common low-grade behavior.

Epidemiology

Salivary gland cancers comprise about 0.6% of all cancers. ACCs constitute approximately 6% to 8% of all salivary gland neoplasms, and 17% of primary salivary gland malignancies, representing the third most common epithelial malignancy of the salivary glands in adults, following mucoepidermoid carcinoma and adenoid cystic carcinoma. In the pediatric age group, ACC is the second most common epithelial malignancy following mucoepidermoid carcinoma.

Women are more frequently diagnosed (58.8%) than men (41.2%). The median age at diagnosis is 52 years, younger than for most other salivary gland cancers. Slightly more than 16% of patients were under the age of 30 and women comprise a significantly larger proportion of cases in this younger age group (64.4%) than among those 30 years of age or older.

According to the National Cancer Data Base Report on cancer of the head and neck in the United States, the parotid gland was the predominant site of origin (86.3%) for reported ACCs. The median tumor size was 2 centimeters and slightly more than two-thirds of cases presented for treatment during the first stage of the disease. Regional and distant metastasis, high grade, and large tumor size were all more common among patients older than 30. No ethnic or racial predilection showed an association with ACC.
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Women are more apt to get this malignant neoplasm. The authors of this article recently noticed a chronological association between onset and recurrence of ACC and pregnancy, in one case.

Long-term follow-up studies of the survivors of the atomic bomb explosions in Hiroshima and Nagasaki show an increased relative risk of 3.5 for benign and 11 for malignant salivary neoplasms. Therapeutic radiation, particularly of the head and neck region, has been linked with a significantly increased risk of developing salivary gland cancers. There appears to be a risk from iodine 131 used in the treatment of thyroid disease, as the isotope is also concentrated in the salivary glands. Workers in a variety of industries have an increased incidence of salivary gland carcinomas in general. These industries include asbestos and rubber manufacturing, exposure to metal in the plumbing industry and nickel compounds, woodworking in the automobile industry and employment in hairdressing and beauty shops.

A number of viruses have been implicated in the pathogenesis of salivary gland tumors. There is a strong association between Epstein Barr Virus (EBV) and lymphoepithelial carcinomas, but EBV has not been shown in ACC or other salivary gland carcinomas.

Endogenous hormones have been reported in normal and neoplastic salivary glands, but some of the results have been conflicting. Estrogen receptors have been reported in a minority of cases of ACC, mucoepidermoid carcinoma, and salivary duct carcinoma. Progesterone receptors and androgen receptors were also seen in some cases of ACC. These findings raised suspicion that some of the salivary gland neoplasms including ACC might be hormonally dependent like breast carcinoma.

Clinical presentation
Parotid ACC typically presents with a slowly enlarging mass in the parotid region. Spiro et al found out that 34.3% to 50.8% were palpated in the tail of the parotid gland. Pain (7.5%) and facial nerve palsy (3.0%) were seldom reported. Most of the previously untreated patients had been aware of the lesion for less than one year and in about 7%, intervals of 5 to 10 years elapsed before a physician was consulted.

Presentation with lymph node or distant metastasis occurs rarely. At least one case was reported where a patient presented with a lymph node metastasis high in the jugular chain of nodes, without a palpable abnormality of the ipsilateral parotid gland. Distant lung metastasis have been reported to occur as the presenting finding from occult parotid primary ACC, which despite extensive clinical evaluation, only became apparent 1 year after initial diagnosis. Bilateral occurrence, familial cases, and presentation in children have also been reported.

Recurrence and metastasis
ACC has a significant tendency to recur, to produce metastases (cervical lymph nodes and lungs), and may have an aggressive evolution. The average recurrence rate among several studies is estimated to be around 35%. Late local recurrence was reported in many cases, up to 30 years from the initial presentation. Metastases tend to be hematogenous rather than lymphatic, with a propensity for lung and bone. Distant spread occurs in 12% of all patients during the course of ACC. Most common sites are cervical lymph nodes (16% of ACC...
Pathogenesis and pathology
Relatively large studies to identify the submicroscopic changes associated with the development and progression of salivary gland tumors have recently been conducted. The genetic alterations linked to ACC of the parotid gland included alterations at chromosomes 4p, 5q, 6p, and 17p, suggesting the association of tumor suppressor genes with the oncogenesis of these tumors. Moreover, deletions of chromosome 6q, loss of Y and trisomy 21 have been reported in association with ACC. Further molecular studies indicated that retinoblastoma pathways, which are common to most human tumors, might also be involved in the pathogenesis and etiology of ACC.

Acinic/acinar/acinous cell carcinoma belongs to the family of adenocarcinomas. Cancers with some similarities include adenoid cystic, muco-epidermoid, low-grade adenocarcinomas, and possibly some breast cancers. Secretory carcinoma of the breast may be an identical entity.

Histology
Untreated ACCs usually present as solitary, encapsulated, soft tumors of a grey-white color (Figure 1). In recurrent lesions, the tumor often appears lobulated, the capsule may be absent, and areas of necrosis may be evident.

ACC is histologically defined by serous acinar cell differentiation (Figure 2). However, several cell types and histomorphologic growth patterns are recognized. These include acinar, intercalated ductal, vacuolated, clear, and non-specific glandular and solid-lobular, microcystic, papillary-cystic, and follicular growth patterns.

The majority of tumor cells in ACC were described as having many ultrastructural features similar to those found in the normal serous acinar cells. These cells were round or polygonal with eccentrically placed nuclei and inconspicuous nucleoli. The lightly basophilic cytoplasm was usually finely or coarsely granular, but was clear focally in some cases. Occasionally, this clear, vacuolated cytoplasmic pattern was evident throughout the entire tumor. Numerous intercellular microcysts, cysts, crude acini, gland-like areas and large papillary cystic spaces have been described in some cases, and well developed glandular configurations occur rarely. Regardless of the cell pattern, appropriate sections often revealed microscopic invasion of the capsule and even nests of tumor cells outside of the capsule. Calcification may be prominent. Drut and Gimenez reported ACC of the salivary gland with massive deposits of globular amyloid.

Attempts at histological grading have been controversial and inconsistent. Features that are often associated with more aggressive tumors include frequent mitoses, focal necrosis, neural invasion, pleomorphism, infiltration, and stromal hyalinization. Occasional cases of dedifferentiation from a low-grade to a high-grade malignancy have been reported. These tumors are characterized by cytological pleomorphism, increased mitotic and proliferation indices and have a worse prognosis.

Diagnosis
The diagnosis of ACCs frequently presents difficulties, owing to its great radiological and cytological similarity with benign tumors and with normal acinar component of the salivary gland, respectively. The differential diagnosis is considered, fundamentally, with clear cell carcinomas, mucoepidermoid carcinomas, Warthin’s tumor, and oncocytes.

Fine Needle Aspiration Biopsy (FNAB)
FNAB has been well established in the diagnosis of salivary gland lesions as it provides essential information on the diagnostic/therapeutic management of these tumors; this methodology is highly sensitive in its diagnostic efficacy. The cytologic findings in fine-
needle aspiration (FNA) biopsies of ACCs are usually characterized by acinar differentiated tumor cells and by certain cytoarchitectural patterns. ACC is a common cause of false negative interpretation owing to the conspicuous absence of hallmark morphologic features of malignancy such as necrosis, cellular pleomorphism, and high mitotic activity. It is frequently mistaken for benign salivary gland tumors (e.g. oncocytoma) and even non-neoplastic parotid parenchyma.

**Radiological Studies**

In addition to FNAC and other ancillary diagnostic tests, imaging studies are usually used in the pretreatment assessment and management planning of ACC which might include ultrasonography, CT, MRI, and nuclear scans. Ultrasonography, which is an easy, non-invasive, and widely available test method, is useful in evaluating tumor size, location, and the nature of the tumor. In addition, it is also used to perform ultrasound-guided FNA biopsies. A CT scan usually demonstrates slight contrast enhancement and may be necessary for evaluation of tumor size, extension, relationship to facial nerve and other structures, and distant metastasis (Figure 3).

ACC usually demonstrates a nonspecific signal intensity pattern on MRI scan that can occasionally be somewhat similar to the signal produced by some benign salivary neoplasms. Low T1 and T2 signals can be detected on some images. The signals correlate with the histology, suggesting vascularity, haemosiderin deposition, fibrosis and calcification within the tumor itself.

**Management**

In general, management of ACC consists of complete surgical removal of the tumor, by total or subtotal parotidectomy. Postoperative radiotherapy may be useful for recurrent, undifferentiated cases of ACC, positive margins, and advanced tumors with cervical lymph node spread. A total parotidectomy with removal of the facial nerve might be necessary for some of the T3 and T4 cases, and neck dissection may also be indicated. Nerve grafting after total nerve resection is recommended for a better quality of life. Cervical lymphadenectomy was reported for 12.1% of cases. Nodes were confirmed as positive in 36.6% of patients who underwent neck dissection.

Incomplete excision is associated with a lower chance of survival so if complete and total tumor removal is not achievable, radiation should always be considered. Over the past three decades, radiation treatment alone, specifically with fast neutron beam radiation, has shown promising and effective results, especially for inoperable tumors. That means that it is a viable alternative to surgery, not just a postoperative adjunct. North et al concluded that radiotherapy is recommended for all cases of salivary gland cancer postoperatively except for those tumors staged as T1N0 or T2N0 with low-grade histology, which were excised with negative margins. It is the opinion of the Acinic Cell Carcinoma Information Centre at this time, that these are reasonable criteria and that fast neutron beam radiation should be strongly considered either instead of surgery, or post-operatively, in all the above described cases.

Weighing all the pros and cons, the Acinic Cell Carcinoma Information Centre currently recommends that fast neutrons are the first “treatment of choice” to consider in most ACC cases and that this treatment provides the best chance for long-term local control of disease. This is especially the case for inoperable or unresectable tumors, incomplete tumor removal, residual disease, and recurrences. Unfortunately, there are a very limited number of high energy fast neutron treatment centers worldwide, which sometimes provides a logistical challenge. If fast neutron treatment is not an option for the patient, accelerated hyperfractionated dosing of conventional beams should be considered. This method has also resulted in high rates of long-term loco-regional controls in salivary gland cancers.

Chemotherapy for ACC has largely been considered ineffective, except for pain-relief or partial responses.
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The use of chemotherapy for malignant salivary gland tumors in general remains under evaluation. ACC has been considered chemo-resistant, which is likely due to the (usually) slow metabolism of this cancer.

Predictive Factors and Prognosis
ACC of the salivary glands are distinctive neoplasms of individually unpredictable behavior. Contrary to the widely accepted notion that ACCs can be equated with favorable prognostic groups, such as low-grade mucoepidermoid carcinoma or low grade adenocarcinomas, recent studies are increasingly suggesting that there is a subset of ACCs with poor prognosis. Prolonged follow-up data are believed necessary to gauge the impact of treatment on survival. Aggressive tumors were treated three times as frequently with surgery and radiation compared with treatment patterns for less aggressive disease.4,5

Multiple recurrences and metastasis to cervical lymph nodes indicate a poor prognosis. Distant metastasis is associated with very poor survival. While tumors in the submandibular gland are more aggressive than those in the parotid gland, ACCs in minor salivary glands are less aggressive than those in the major salivary glands.1

The overall 5-year disease-specific survival is estimated to be around 91%, and 88% at 10 years. Significant association was noted between poor survival and high-grade disease, regional or distant metastasis at presentation, submandibular tumors, pain, male gender, and age older than 30 years.57 Short duration of symptoms, incomplete excision, frequent mitoses, focal necrosis, pleomorphism, neuromuscular infiltration, stromal hyalinization, large size and involvement of the deep lobe of the parotid gland have also been reported as poor prognostic factors.58 In other studies, the presence of a predominately solid architecture was strongly associated with a poor outcome.59,60 For high-grade tumors, the 5-year survival rate was only 33%.6

Surveillance
Although indolent in nature (slow-growing), ACCs are quite persistent in their potential for local recurrences and distant metastases, often many years later. Local and multiple recurrences may occur in up to half of patients. Recurrences and metastases after 3 to 10 years are common, especially after inadequate primary tumor removal. Recurrences more than 20 or 30 years after initial treatment are also noted in the literature.1 Due to the notably high tendency of ACC to recur and to produce latent metastasis, long-term follow-up is mandatory after treatment.4,6,26,27

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