

Research Article

Adenoid Cystic Carcinoma of the Head and Neck– literature review

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ABSTRACT

Adenoid cystic carcinoma (ACC) is a rare salivary gland malignant neoplasm. Clinically it represents as an indolent yet a persistent lesion, which shows propensity for late distant metastases, involving vital tissues often leading to the death of the patient. Its innoceous clinical presentation remains a diagnostic challenge.

Till date surgery and radiotherapy still remain the main course of treatment. Despite advanced successful therapies these tumors are notoriously associated with loco regional recurrences. In contrast to other epithelial malignancies with poor prognosis, ACCs have a good five year survival rate. Nevertheless, overall survival rate drops after 5-year followup period.

This review paper attempts understanding ACC – it's clinical presentation, management and factors affecting prognosis.

Keywords: Adenoid cystic carcinoma; Malignant salivary gland neoplasm; Perineural invasion.

Key Messages : This review deals with recent concepts pertaining to clinical behaviour and management of ACC. It also provides an insight with respect to prognosis of ACC.

Introduction

Salivary gland neoplasms represent, one of the most morphologically and clinically diverse group of neoplasms which often clinicians, pathologists and surgeons are encountered with, considerable diagnostic and management challenges. Though uncommon, the salivary gland neoplasms represent about 3% of all head and neck neoplasms in toto and about 80% of these are benign and innocuous.[1,2] Thus malignancies of this variety are rarely encountered which may comprise about 0.5% of all malignancies and 5% of all of head and neck.[3]

ACC formally "cylindroma" is relatively uncommon salivary gland malignancy. It accounts for about 1% of all head and neck malignancies and fifth most common malignant tumor of salivary gland. ACC was first described by three Frenchmen (Robin, Lorain, and Laboulbene) subsequently published in 1853 and 1854.[4] However, Billroth in 1859 first described ACC as "Cylindroma" and having a great tendency to recur.[5,6,7] Spies later coined the term "ACC".[7] The malignant behavior and its ability to spread along nerve sheaths was described by Dockey and Mayo.[4, 8, 9] Foote and Frazell extensively described ACC in major and minor salivary glands with an incomplete capsule, its variation in history and propensity to perineural spread.[10] Although ACC commonly arise in major and minor salivary glands, it may also occur in other sites of body such as the breast, tracheobronchial tree, skin, lacrimal gland, female genital tract and prostrate.[8]

Given the aggressive nature of the lesion and its clinical presentation with the effect on overall survival rate, it is apparent that it has to be diagnosed at early stage and treated aggressively. This however remains a diagnostic dilemma clinically and histopathologically.

The following extensive review is an attempt to summerise the features of this malignant tumor of salivary gland origin, portraying a brief outline of new research directed towards it.

Clinical presentation

Demographics

Site: As mentioned earlier ACC can occur in any glandular tissue of the body. ACC was once considered as the most common malignant tumor affecting minor salivary glands.[2] However recent studies have shown that polymorphous low-grade adenocarcinoma and mucoepidermoid carcinoma are more common malignancies than ACC.[11] Intraorally, as much as 50% of ACCs occur on the palate followed by other less common sites of involvement such as lower lip, retromolar-tonsillar pillar region, sublingual gland, buccal mucosa, and the floor of the mouth.[1, 5, 13, 14] Issacson and Shear observed the pattern of neoplasm occurrences in decreasing order with palate at highest affinity followed by floor of the mouth, tongue and gingival.[15] Among the major salivary glands, the parotid and the submandibular glands are the two most common favored sites accounting to about 55% cases,[16] and also the parotid gland

being the most common site of occurrence.[16, 17] Issing PR et al, in their retrospective study comprising 56 patients reported, 16 ACC in parotid, 12 in submandibular and 16 involving skull base of which 13 in paranasal sinus and 3 in nasopharynx, 8 in oral cavity and 2 were in larynx.[18] Of extra-oral origin, the nose and paranasal sinus represent the most common site for minor gland ACC.[16] In an report by Spiro et al. of 242 salivary gland ACC cases, 171 patients presented lesions involving accessory glands, while 64 patients presented the palate as the most affected site, being tongue the second most affected area.[19] ACC arising centrally within the mandible is extremely rare and the most common site was the posterior body or the angle of the mandible.[20] Intracranial ACC, yet is more rare and has been reported as 4-22% of ACC.[21]

Age: ACC is not a tumor of certain age but predominantly occurring in adulthood with a definite peak incidence in fourth through sixth decade of life.[22-24, 25, 26] Sometimes even children are affected.[27] ACC of the major salivary glands has been shown to be in younger patients (mean 44 years) but with advanced age (mean 54 years) tumors of the minor glands are more frequent.[11]
Gender: Eveson et al.[26] and Greiner et al.[28] found that ACC is more common in women. Spiro et al.[19] and Stallmach I et al.[29] on the other hand reported that ACC is more frequent among men. By far there appears to be no significant sexual preferences.[6, 30- 32]

Clinical presentation: ACCs usually do not show any specific signs and symptoms. A review of literature pointed out that ACC routinely displays a slow, but persistent and recurrent growth pattern, long clinical course, and late onset of metastases.[16] A classic presentation is an asymptomatic mass. Over a period of time as the tumor grows it has a propensity for invading nerves, pain and numbness usually follows as the lesion advances. Conley and Dingman in 1974 mentioned that "any non-ulcerating tumor in a major or minor salivary gland recognized for months or years, causing mild discomfort or pain and associated with paresthesias, is highly suggestive of adenoid carcinoma until proven otherwise".[30] Lui et al. reported epistaxis, nasal obstruction and tinnitus as the most frequent symptoms associated with nasopharyngeal ACC.[33] Other symptoms associated with advanced stage of sinonasal ACCs were facial pain and numbness in the distribution of the second division of trigeminal nerve and frank oral swellings. Less frequent symptoms include facial swelling, loss of visual acuity and smell, epiphora and oral ulcerations.[18, 34] The typical clinical presentation coupled with radiographic and histopathological evidence helps in diagnosing of this disease.

Perineural invasion

Perineural invasion is a form of direct primary spread of neoplasia which is microscopically continuous, although may be macroscopically discontinuous with the main focus of the tumor.[35] Cruveilheir first reported neoplastic invasion of nerves in 1842.[36] This process occur wholly[35] or principally[37] in perineural or endoneural tissue planes along the path of least resistance. Spread through perineural lymphatic channel is considered either not to occur[35] or to be a minor component of this phenomenon.[37] The second and third division of the trigminal nerve are among the most common affected ones.[38] The descending portion of the seventh cranial nerve[38] and, smaller cranial branches may also be affected.[39, 40] Chummun et al.[17] and Bianchi et al.[14] reported perineural invasion in 51.1% and 58.2% cases respectively. Rapidis et al. documented histologically perineural invasion in 18 (81.81%) out of 22 patients, but observed no significant association with local recurrence.[25] The region of gasserian ganglion was also considered to be the most common site of involvement (35.8%),[21, 41-43] while cavernous sinus was involved in 15.1%.[21, 44-47] Literature also reveals that the time between onset of neurological signs and symptoms, and the time of diagnosis range between few months to 3 years.[21, 42, 43, 48] However a study suggested that the duration could be several years.[46] Clinical presentation such as facial pain and parasthesia in trigeminal distribution reflected the possibility of perineural spread. Nasopharyngeal ACC have a higher incidence of cranial nerve involvement (55%).[49]

Perineural invasion is considered an indicator of poor prognosis, because of the inherent risks of spread to the nasal and orbital cavity, pterygopalatine fossa, skull base, cranial cavity and local recurrences making surgical resection difficult.[33, 50, 51] Relationship between perineural invasion and distant metastases is still controversial. Vrielink et al[52] reported that 40% of tumors with perineural invasion subsequently metastasized in contrast to those without perineural invasion. However a study by Van der Waal et al[53] found no significant correlation between the two parameters. In contrast, Mendenhall et al[54] in their multivariate analysis, stated that perineural invasion was a significant prognostic factor for the development of distant metastases, which was further confirmed in a study by Rapidis AD et al.[25]

Metastases

The impact of distant metastasis is one of the most frustrating things in dealing with ACC. In contrast to other types of carcinomas, distant hematogenous metastases are far more frequent than regional lymphnode metastases. This occurs in an unpredictable manner. Mücke et al[55] found a higher incidence of lymphnode involvement, but a lower incidence of distant metastases at presentation. With follow-up, a further 17% of ACC cases developed distant metastases, though the primary tumor was completely resected. Similar findings were correlated by Umeda et al.[56] It is difficult to estimate the incidence of distant metastasis in ACC, but it usually ranges from 35 to 50%.[57] Spiro[58] suggested that the incidence of distant metastasis at other sites are likely to be more frequent, as no further investigations are done once lung metastasis are detected. In 40-60% cases, distant metastases are most common in lung, bone, and soft tissues.[11] Often distant metastases defeat successful treatment of patients with ACC, despite effective local control of the disease. Distant metastases was considered as an independent disease process and its presence should not reduce the effort for local disease control.[22, 59, 60] Late onset of distant disease spread is one more peculiarity of this tumor.[41, 61, 62]

Metastases from ACC primary can remain asymptomatic for a long period of time,[61, 63] particularly pulmonary metastases that seems to progress slowly[23, 56, 58, 63] sometimes apparently isolated, and frequently surgically resectable. While metastatic spread to the bones, the course is rapidly fatal. Sung et al[61] speculated that microscopic deposits to distant sites occurs early in the growth of the primary tumor.

Histopathology

There are three recognized histopathologic patterns of ACC – cribiform, tubular, and solid. Although, the cribiform and the solid subtypes were documented earlier, the tubular subtype was identified later.[64] The cribiform is the most common and easily recognized pattern whereas the solid variant, the least common histopathologic subtype. All three patterns of ACC consist of both ductal and myoepithelial cells. Quite often the cribiform subtype has been described as "swiss cheese-like". Characteristically it consists of pseudocystic spaces that either contain basophilic glycosaminoglycan or eosinophillic basal lamina material.

The tubular subtype represents more apparent ductal spaces and also the most differentiated microscopic pattern of ACC. The solid subtype usually contains no or occasional cyst like spaces and a much greater degree of nuclear and cellular pleomorphism and mitotic activity.[16] As polymorphism is a very common in ACC, one can see all the three subtypes in a single specimen. Thus, Anderson MD suggested pathological grading system which is now followed world-wide.[65] Grade I – tubular and cribiform only without any solid component. Grade II – mostly cribiform but less than 30% solid component. And Grade III – predominantly solid subtype.

Recently there are reported cases of dedifferentiated ACC. Dedifferentiation is an abrupt transformation or clonal evolution of a poorly differentiated or high-grade component arising within a low-grade carcinoma without histologic transition from original carcinoma.[66] Over expression of p53 protein, cyclin D1 and higher Ki67 index have been strongly correlated in the dedifferentiation process.[66]

Management

The main objective of treatment is to cure the patient of the disease. The optimal therapy for ACC has not been established. Radiation therapy and surgery are the most commonly employed for tis treatment. Management in such scenario depends on many factors some of which include cell type and degree of differentiation; the site, size, and location of the primary lesion; status of lymphnode and presence of bone involvement. Treatment delivery should also consider preservation of speech and swallowing function; and a through workup of the potential complications of each therapy. Treatment of ACC is exasperating due to its unreliable biologic behavior, multiple and late recurrences, though occasional long survival, but recurrent and metastatic nature. However a review of the literature showed that the best survival results were with combined surgery and radiation therapy.

Surgery may be considered the primary treatment or may be carried out in combination with radiotherapy. Usual indications for surgery include – tumors with bone involvement, tumors lacking sensitivity to radiation, recurrent tumors at the site of primary that received radiotherapy, and when side effects are expected less than radiotherapy. Often surgery is needed to reduce the bulk of the tumor mass there by for example aiding in drainage. Surgical failure has often been attributed to – incomplete excision, failure to obtain disease free margins, tumor seeding, unrecognized lymphatic or hematogenous spread, neural invasion or perineural spread.

Rarely radiation therapy has been used solely in the treatment of ACC. One must not forget, ACC though are radio sensitive, they are not radiocurative. Though the initial response is encouraging, these tumors were shown to recur.[67] Doses of 60 Gy or more were of benefit when minimal residual microscopic disease was evident.[6] Though the best results have been obtained with the combination of radical surgery and radiation, there are no randomized trials that prove the value of adjunctive radiation therapy.[68] In a follow-up study by Sloan-Kettering, among patients receiving radiation alone, 96% had tumor regression but 93% relapsed, and half of them relapsed in 18 months.[69] As a part of palliative care, radiation may provide symptomatic relief from pain, ulceration, bleeding and pharyngeal obstruction. For advanced tumors radiation therapy are rarely curative. In another follow-up study, recommended neutron radiotherapy was used for tumors that were unresectable, associated with high surgical morbidity and post-operative tumor burden after surgery.[70]

Chemotherapy use for ACC is controversial as it has shown limited and poorly defined role. It is often administered for palliation.[7, 32, 71-73] Few studies have shown cisplatin, 5-fluoruracil, doxorubicin, and cyclophosphamide, having some activity, either as single agents or in combination.[74, 75] An interesting alternative was involving a superselective intracranial application of cisplatin, resulting in complete local remission and also in pulmonary dissemination of tumor.[76] Some authors[47] account chemotherapy ineffective while others recommend it as palliative treatment in advance cases of ACC.[77]

Prognosis

Many factors have been reported to influence the prognosis of ACC, eg. the primary site,[65, 78] size, involvement of adjacent structures[19, 64, 65, 79, 80] lymphnode metastases,[19] clinical stage of disease,[19, 78, 80] treatment modality,[22, 62, 78] positive margins of surgical resection,[64, 65, 81] perineural invasion,[33, 50, 51] and histological subtype.[64, 82-84] However, the key prognostic factors has not been universal.

It has been observed, ACC of the minor salivary glands have a worse prognosis than those of the major salivary glands.[31, 78] An obvious fact is that tumors of the minor salivary glands can more readily infiltrate the extra glandular soft tissues and bone, thus allowing increased dissemination of the tumor rendering complete excision more difficult.[16]

The significance of tumor grading as a prognostic factor still remains controversial, as the quantitative classification of different subtypes are not standardized. It is mainly a subjective process, as a variety of histological patterns can be seen in any given tumor. The cribiform subtype is thought to have the best prognosis and the solid subtype the worst with the tubular form having an intermediate prognosis.[82-84] In an study, Blanchi et al[14] reported no significant correlation between morphologic type and locoregional control. However they did notice a higher rate of distant spread in the solid and the cribriform types.

Authors found that positive margins did not influence survival, but are implicated in increased treatment failure.[85, 86] However many others[12, 14] reported the presence of surgical positive margins as a parameter for survival and tumor control.

An association between perineural extension and degree of advancement of the primary tumor has been reported by

some authors.[87, 88] While some report the perineural invasion as a negative survival predictor because of higher incidence of distant metastases,[85, 86] though not significant, Cruz Perez et al[12] and Blanchi et al[14] observed the presence of perineural invasion associated to a poor prognosis.

Some of the markers implicated in the prognosis include DNA ploidy, Ki-67 antigen expression, S-phase value, and nucleolar-organizing regions.[86] Although a significant correlation between DNA ploidy and patient survival was reported in a study,[89] continuing analysis of DNA-related factors in ACC is needed.

Conclusion

The clinical behavior of ACC, and its late local and distant failures makes periodic examination obligatory for life time. Early diagnosis and treatment in a way minimize the chances of extensive morbidity associated with the treatment. Insight into the early diagnosis is necessary at any interval, considering the psychological issues associated with the treatment outcome. Newer treatment approach promise a better and successful outcome in dealing with these lesions in general.

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