Adenocystic Carcinoma of Salivary Gland: A Literature Review

Santosh Kumar Subudhi[1], Sthitaprajna Lenka[1], Kalyan Sundar Pal[2], Satchidananda Meher[2], Aditi Ava Rath[2]

[1]Professor, [2]Post Graduate Trainee, Department of Oral & Maxillofacial Surgery,Institute of Dental Sciences, Siksha O Anusandhan (Deemed to be University), Bhubaneswar, Odisha: 751003, India

Abstract

Adenoid cystic carcinoma is a rare salivary gland tumor that has a consistent slow growth rate and has destructive biological behavior because of its deep peripheral tissue invasion and higher recurrence rate and tendency of distant metastasis. The involvement of adjacent vital structures may lead to death. Its clinical presentation also causes difficulty in diagnosis. Surgical resection following radiotherapy is the main treatment modality of Adenoid cystic carcinoma. Even after successful therapy of the primary tumor, there is a high rate of local recurrence and in contrast to other epithelial malignancies, it has a very poor prognosis. The survival rate is good for the initial 5 years but it falls after 5 years follow up.

Keywords: *Adenoid cystic carcinoma, Malignant neoplasm, Distant metastases, Perineural invasion.*

Introduction

Robin, Lorain, and Laboulbene were first described Adenoid cystic carcinoma in two articles published in 1853 and 1854 reporting on two nasal tumors and one parotid.[1] Cribriform arrangement of the cells invasion of adjacent structure and spread through the nerve also described by them. ‘‘Cylindroma’’ was the term suggested by Billroth in 1856 suggested the for tumor and Spies coined the current name of ‘‘adenoid cystic carcinoma’’ in 1930. It comprises 1% of all malignancies of the head and neck region and about 10% of all salivary gland tumors. It is the most common malignant tumor of minor salivary glands and is also one of the most common cancers of the major salivary glands. ACC not only involves the salivary gland but also involve the lacrimal gland, ceruminous gland, paranasal air sinuses, larynx, and trachea. Initially,the tumor was described benign and mixed tumors. The layer was establishedas malignant. Currently, ACCis recognizedas an extremely difficult malignancy to treat. Conleyand Ding mandescribed it as one of the most biologically destructive and unpredictable tumors of the head and neck. It has a high, almost inevitable, predisposition torecur if a patient, lives long enough, and this occurs even when radical excision has been performed.[2]

Corresponding Author:
Dr. Aditi Ava Rath
Post Graduate Trainee, Department of Oral & Maxillofacial Surgery, Institute of Dental Sciences, Siksha O Anusandhan (Deemed to be University), Bhubaneswar, Odisha: 751003, India
e-mail: aditirath@rediffmail.com

Clinical presentation:

Location: Nearly 10% of all salivary gland neoplasm are adenoid cystic carcinoma which most commonly involves the minor salivary glands (in 60% cases). Whereas in the head and neck region the parotid gland is the single most common site for the tumor involvement. Minor salivary gland adenoid cystic carcinoma commonly affects the minor salivary gland present intraorally, most commonly the palate.

Age: There is no age predilection but more common in adults with a peak of incidence at the 4th to 6th decade of life. Sometimes children may also be affected. It is found that in children major salivary glands are common sites for the tumor whereas in adult minor salivary glands are commonly affects than the major salivary gland.[3-5]

Gender: There is slight female predilection (F:M = 1.2:1). Although other different study shows that there is no significant gender predilection for the tumor.

Clinical Features: 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".There are no distinct signs and symptom of ACC to identify it clinically exactly. Different studies revealed that ACC is a persistent slow-growing tumor with a recurrent growth pattern. It has a long clinical course and distant metastases occur at a late stage. On the advancement of the malignancy in an advanced stage, there are chances of involvement of adjacent nerve. Generally, 2nd division of the trigeminal nerve is involved causing paresthesia and pain along the distribution of the nerve. Radiological and histopathological study reports along with clinical reports are correlated for final diagnosis.[3-5]

There is multiple contradictory behavior of ACC. **First**, slow growth, but progressive, relentless course. **Second**, clearance of the margin is achievable but multiple local recurrences occur**. Third**, regional metastases to cervical lymphnodesareuncommon, but the incidence of distant metastasis to lung, live, bone is quite common, and **Forth**,survival rate is high for the first 5 years,but in case of 10-to 20-yearsurvivalrate, it is quite low. [3-5]

Histological features: Histopathological study of the tumor reveals it consists of a mixture of ductal and epithelial cells and they are arranged in three different patterns. They are namely 1.Cribriform, 2.tubular, and 3.solid. the cells having little cytoplasm with angulated and hyperchromatic nuclei. Mitotic figures are less present in the tubular and cribriform pattern and found more in the solid strand pattern which is associated with very poor prognosis. Huang et al. concluded in his study that the location of the tumor, clinical staging, and the histopathological variant are the factors that determine the prognosis and patient survival. [6]

Histopathologically adenoid cystic carcinoma can be graded as below

Grade I: The tumor consists only of cribriform and tubular

Grade II: A mixture of cribriform, tubular, and solid growth patterns, with a solid growth pattern of less than 30% of the tumor.

Grade III: Tumors with predominantly solid features (>30% or more of the tumor).

Immunohistochemically, ACC was consistently positive for cytokeratin [AE1/3, CK 34βE12, CK5/6, CK7, CK14, CK18] p63, CA19-9, c-KIT (CD117), PDGFRA, MUC1, and Ki-67. ACC was consistently negative for CK8, CK20, desmin, S100 protein, CD34, chromogranin, MUC2,MUC5AC, and MUC6. Some ACCs were positive for CK CAM5.2, CK19, EMA, CEA, vimentin, α-smooth muscle actin, p53, CD10, and synaptophysin.[7]

Perineural Invasion: Neoplastic invasion of nerves was reported first in 1842 by Cruveilheir. It is direct spread from the primary tumor and it is continuous microscopically though appears discontinuous macroscopical view. This invasion occurs at the level of perineural and endoneurial plane through the path of least resistance. Lymphatic channels in these tissue planes have very little to no role in this aspect. Most commonly involve the 2nd and 3rd division of the trigeminal nerve but may also involve the descending portion of the facial nerve and other smaller branches. It is considered that Gasserian ganglion is the most commonly affected site while the cavernous sinus is less commonly affected. As per different literature the latency between involvement of the nerve and onset of the neurological symptoms and diagnosis time ranges between months to 3 years. In the case of ACC of nasopharynx cranial nerve involvement is more common. It is considered as an indicator of poor prognosis as there is a chance of involvement of the cranial cavity, skull base, orbital cavity, and pterygopalatine fossa. The relationship between the distant metastases and perineural invasion is controversial sill now. Researchers considered perineural invasion as a significant factor for prognosis and distant metastases of the primary tumor. It is also supported by other studies.[8]

Distant Metastases: It is difficult to estimate the incidence of distant metastasis in ACC, but it usually ranges from 35 to 50%.Incidence of distance metastases employing hematogenous spread is quite common in ACC and creates challenges in successful treatment of the same. Distant hematogenous spread is quite common in the case of ACC in contrast to the regional lymph node spread of other types of malignancies. These metastases occur in a very unpredictable way and can involve the

lung, liver, bone, and other soft tissue. Pulmonary or lung metastasis is quite common. These metastatic of primary ACC remain asymptomatic for a longer period especially the pulmonary metastasis which has very slow progress. On the other hand metastases to the bone have a very rapid and fatal course. The successful treatment of an ACC with well-controlled local disease is not possible because of these distance metastases. As per Spiro "the incidence of distant metastasis at other sites is likely to be more frequent, as no further investigations are done once lung metastasis is detected. In 40-60% cases, distant metastases are most common in lung, bone, and soft tissues. distance metastases should be considered as a separate disease process and for the same, the effort to control the primary tumor control should not be hampered.[8-10]

Management: Optimal management of the ACC of the head-neck region is not well established. Management depends on the site of the involvement, staging of the tumor, histological grading, metastatic involvement, and biological behavior of the tumor. It is difficult to treat an ACC because of its unreliable behavior, multiple and late local recurrence. Generally, surgical resection with a clear margin along with radiotherapy is most commonly employed for the treatment of ACC. Before delivery of the treatment throughout the workup and complication of each treatment procedure should be evaluated. Care should be taken to preserve the normal function of different anatomical structures as far as possible. Indications for surgery are: 1.bony involvement, 2. Tumors that are not sensitive to radiotherapy, 3. Recurrent lesion at the primary site, 4.side effect is radiotherapy is greater. Radiotherapy for the treatment of ACC has not been used solely as these tumors are radiosensitive but not radiocurative. The primary response to the radiotherapy is assuring but in later stage recurrence rate is higher. As per a study "patients receiving radiation alone, 96% had tumor regression but 93% relapsed, and half of them relapsed in 18 months.[11]

The use of chemotherapeutic agents in the treatment of ACC is controversial because of its poorly defined and limited role. Generally administered for palliative care.[41,42,43-45] Few studies proved that the use of cyclophosphamide, doxorubicin, cisplatin are useful and have some activity as a single agent or in combination during surgical management of the ACC of the parotid gland, facial nerve should be preserved if there is no involvement of the nerve present. For that presurgical evaluation of the nerve function should be done when the submandibular gland involved supraomohyoid neck dissection to be done along with the resection of the tumor. Post-operative radiotherapy is given following surgery in both cases. Local radical excision and postoperative radiotherapy should be done in the case of minor salivary glands ACC. Postoperative radiotherapy reduces the chances of recurrence but survival benefits are not demonstrated.[12]

Prognosis: There are many prognostic factors of ACC. They are 1. Size 2. primary site, 3. involvement of adjacent structures, 4. lymphnode metastases, 5. clinical staging, 6. treatment modality, 7. positive margins of surgical resection, 8. perineural invasion, and 9. histological subtype. It has been noted that the prognosis of minor salivary gland ACC is worse than those ACC of the major salivary glands. In the case of minor salivary gland tumor, peripheral extra glandular soft tissue and bone are readily infiltrated by the tumor and cause increased dissemination of the tumor which makes the complete excision of the tumor more difficult. Again the cribriform subtype of ACC has the best prognosis whereas the solid subtype has the worst and the prognosis for tubular form is intermediate. Another study reported that there was no significant relationship between the morphologic type of ACC and locoregional control. But they found that there was a high rate of distant metastases in the case of cribriform and solid variety. "Authors found that positive margins did not influence survival, but are implicated in increased treatment failure. However, many others reported the presence of surgical positive margins as a parameter for survival and tumor control." Some authors describe a close relation between perineural invasion and the degree of extension of the primary tumor. While some others reported the perineural invasion as a negative survival predictor. Poor prognosis was often associated with perineural invasion. Ki-67 antigen expression, DNA ploidy, nucleolarorganizing regions, S-phase value are some tumor markers that are associate with poor prognosis.[8-12]

Conclusion

Adenoid cystic carcinoma is one hard to treat malignancy because of its aggressive clinical behavior. Early diagnosis is necessary to reduce the morbidity and successful management. Follow up at regular intervals is necessary to prevent the local and distant recurrence of the same. Surgical resection of the lesion along with radiotherapy proved to be beneficial for the management

of this type of malignancy. Radiotherapy helps to reduce recurrence.

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