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CASE REPORT

ADENOID CYSTIC CARCINOMA OF SUBMANDIBULAR GLAND: A CASE REPORT

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ABSTRACT

Adenoid Cystic Carcinoma (ACC) is a relatively rare tumor that accounts for 1% of all head and neck malignancies and 10% of all salivary neoplasms, according to the World Health Organization (WHO) classification of head and neck tumors. Most ACCs originate from the major and minor salivary glands, and a minority called salivary gland–type carcinomas, arise from glands in the nasal, paranasal, and external spaces. ACC has classically been described as having an indolent but persistent and recurrent course, with the delayed onset of distant metastases and eventual death of affected patients. Therefore, although uncommon, ACC is one of the most aggressive of the salivary gland tumors.

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INTRODUCTION

Adenoid cystic carcinoma is a basaloid tumour consisting of epithelial and myoepithelial cells in variable morphologic configurations, including tubular, cribriform and solid patterns. It has a relentless clinical course and usually a fatal outcome. Adenoid cystic carcinoma is the most common malignancy of the minor salivary glands. Its biological behaviour is slow and indolent growth; rare involvement of regional lymph nodes; likelihood of perineural invasion; multiple or delayed recurrences (Stijn van Weert *et al.,* 2013). Adenoid cystic carcinoma (ACC) was first described by three Frenchmen *(Robin, Lorain, and Laboulbene)* in two articles published in 1853 and 1854 (Stell, 1986). They described the cylindrical appearance of this tumor**.** *Billroth* in 1859, first described ACC under the name cylindroma and also described that ACC had a "great tendency to recur." *Spies* in 1930, is credited with the term adenoid cystic carcinoma, in a discussion of tumors, cutaneous and noncutaneous, of the basal cell variety (Tauxe *et al.,* 1962).

Epidemiology: Adenoid cystic carcinomas comprise approximately 10% of all epithelial salivary neoplasms and most frequently involve the parotid, submandibular and minor salivary glands. They comprise 30% of epithelial minor salivary gland tumors with the highest frequency in the palate, followed by the tongue, buccal mucosa, lip and floor of mouth. The tumor occurs in all age groups with a high frequency in middle-aged and older patients. There is no apparent sex predilection except for a high incidence in women with submandibular tumors. Occasionally it arises in sites other than the salivary glands, such as the lacrymal glands, the ceruminal glands of the external auditory canal, the nose, the paranasal sinuses, and the palate, the nasophaynx, or the larynx. Outside the head and neck region it may arise in the uterine cervix, the Cowper's gland, the Bartholin's gland, vulva, esophagus, breast, and trachea (Stijn van Weert *et al.,* 2013; Alfio José Tincani *et al.*).

CASE REPORT

A 50 year old female patient came to the Oral and Maxillofacial Surgery Department, Career Post Garaduate Institute of Dental Science and Hospital, Lucknow (U.P) with a chief complaint of pain and extraoral swelling in left submandibular region since 1year (Fig. 1). She described the initiation of pain 1 year back as an intermittent, dull ache in the left lower jaw region that becomes worse after meals. The pain was relieved with over-the-counter analgesics. Pain did not radiate to any other site. Swelling gradually increased over a period of time and from last 2 months it rapidally increased in size. Clinical examination revealed a 5cm X 3cm enlarged tender, hard, well circumscribed swelling of left submandibular gland extended from left mandibular molar

region to angle of mandible. The gland was bimanually palpated. No saliva or discharge was seen after milking of the gland. Swelling was not fixed to the overlying skin and freely movable over the underlying structures. The overlying skin was non pulsatile, and of normal color and temperature. No other regional lymph nodes were palpable. There was no altered sensation over tongue and paresthesia on lower lip with no sign of deviation of tongue. FNAC and ultrasonographic examination revealed a submandibular salivary gland neoplasm. With contrast CT examination showed a well circumscribed radiopaque mass of left submandibular salivary gland with no regional lymph node involvement (Fig. 2). Incisional biopsy done.

Histopathologial findings: Microscopic study showed an infiltrative malignant tumor composed of cells arranged predominantly in bilayered, tubules with focal cribiform pattern along with sheets of undifferentiated tumor cells. The cells appeared as basaloid and were disposed in a fibrous and hyalinizedstroma. Tumor cells had ovoid to angulated nuclei with moderate atypia and coarse cromatin with clear to eosinophilic cytoplasm. Mitosis were seen. Interspersed hyaline stromal materials were also noted with evidence of Perineural infiltration of tumor. All these findings were consistent with Adenoid cystic carcinoma.

Immunohistochemistry analysis: Case was found positive for epithelial marker PAN-CK (Pan cytokeratin), which is mainly used for differential diagnosis between myoepithelioma/ myoepithelial carcinoma or "undifferentiated carcinoma" and non-epithelial tumors).

P-63 positive were found which is one of the most sensitive myoepithelial marker

CD 117 was also found positive with Ki-67 proliferation index40% (Cell proliferation marker; differential diagnosis between benign and malignant tumors; prognostic factor)

All these findings were consistent with Adenoid cystic carcinoma. Patients was planned and taken up for complete surgical excision of the submandibular gland. All investigations were within the normal limits. Surgery was performed under general anesthesia. Patient was painted and draped in complete aseptic condition. Left submandibular incision was given approximately 4 cm below the lower border of mandible, extending from left mandibular first molar upto the angle. After incising skin, muscle and fascial layers exposure of submandibular gland done. Gradually detaching the encapsulated mass from lower border of the mandible and preserving underlying vital structures, complete excision of submandibular gland with wharton's duct performed (Fig. 3). Surgical site cleaned and inspected for any other metastatic growth. Surgical drain placed and closure done. Due to poor socioeconomic status patient refused for radiotherapy treatment. Patient was on follow up for almost 5 years and no recurrence seen (Fig. 4).

DISCUSSION

Adenoid cystic adenomas (or cylindromas) are rare, and account for less than 1% of all head and neck cancers and 20–25% of all salivary cancers (Spiro *et al.,* 1974; Luksi´c *et al.,* 2012). They develop mainly in the intraoral salivary glands,

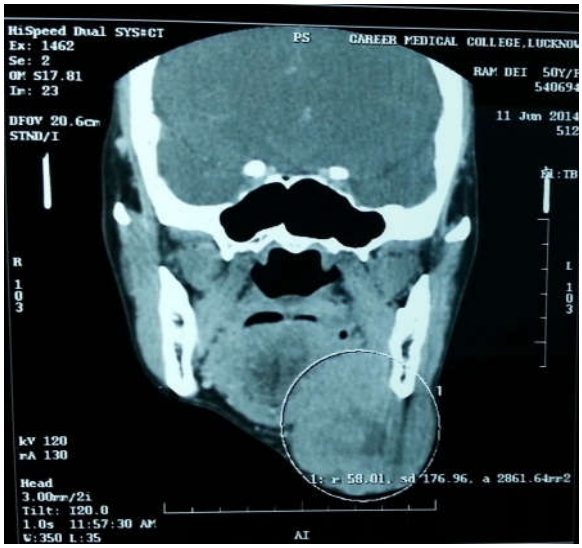

Fig. 1. Coronal view of face in contarst CT

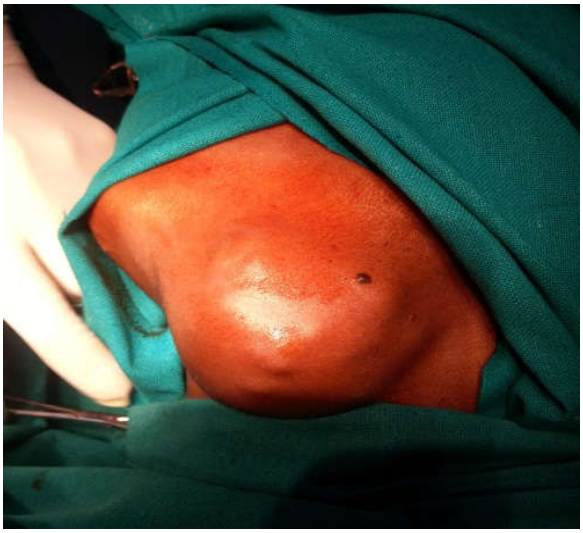

Fig. 2. Preoperative Picture

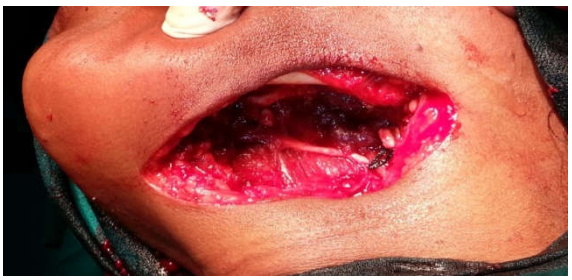

Fig. 3. Immediate Post Operative Picture before closure

Fig. 4. Follow up picture after 4.5 years

particularly the palate and the parotid, followed by submandibular and sublingual salivary glands (Da Cruz Perez *et al.,* 2006). Several authors have retrospectively analysed their clinicopathological features to try to identify significant prognostic factors, but the findings are still controversial. The age of the patient, size of the tumour, type and duration of symptoms, clinical stage, treatment, histological subtype, perineural or vascular invasion, and the histological state of the surgical margins have all been considered (Da Cruz Perez *et al.,* 2006; Van der Wal *et al.,* 2009; Agarwal *et al.,* 2008; Matsuba *et al.,* 1986; IvicaLukˇsi *et al.,* 2014). The tumour is most common during the fifth and sixth decades of life with female predilection. However, some authors have identified a slight male predilection (Da Cruz Perez *et al.,* 2006; Van der Wal *et al.,* 2009; Agarwal *et al.,* 2008). *IvicaLukˇsi´c, Petar Suton, Darko Macan, Kristijan Dinjar* (IvicaLukˇsi *et al.,* 2014) found perineural invasion in half of the resection specimens and this was similar to previous reports, which vary between 15% and 72% (Van der Wal *et al.,* 1990; Bianchi *et al.,* 2008; Mücke *et al.,* 2010; Howard *et al.,* 1985). A similar occurrence of perineural invasion has also been reported in squamous cell carcinoma of the oral cavity (Ellington *et al.,* 2012). However, in contrast to oral squamous cell carcinoma, adenoid cystic carcinoma has good 5-year survival that ranges from 78% to 90%, while 10 and 20 year survival are much worse because of the adverse impact of delayed recurrence (range 32–74%) (Da Cruz Perez *et al.,* 2006; Bianchi *et al.,* 2008; Mücke *et al.,* 2010; Ciccolallo *et al.,* 2009; Ellington *et al.,* 2012).

IvicaLukˇsi´c, PetarSuton, DarkoMacan, KristijanDinjar (2014) found no significant association between perineural invasion and the size of the primary tumour, unlike (Van der Wal *et al.,* 1990) who found that the difference was significant. *Vrienlick et al.* (1988) also found an increased incidence of invasion associated with a more advanced stage of the primary tumour.In the multivariate analysis, *Yoon Ho Ko et al.* (2007) found that histological grade was associated with disease-free survival, whereas lymph node metastasis had a significant relationship with an unfavorable overall survival. *Le et al.* (1999) found that the presence of involved lymph nodes on admission was associated with an increased risk of distant metastasis and reduced survival and they observed that 75% of their patients with initial nodal involvement eventually developed distant metastases. Grade may also play a role as a prognostic factor in ACC. In addition, some studies have emphasized the importance of histological subtype. Most have reported that ACC patients with solid type are more likely to have a worse prognosis, resulting from the development of distant metastasis (Matsuba *et al.,* 1986; Khan *et al.,* 2001). Several reports have also found a strong correlation between the site of origin and prognosis. Nevertheless, it is still unclear whether the major or minor salivary glands have a poorer clinical outcome (Khan *et al.,* 2001; Chummun *et al.,* 2001; Nascimento *et al.,* 1986; Sung *et al.,* 2003). The univariate analysis showed that tumors of the minor salivary glands, including the sinonasal cavity, tended to recur. This finding supports the fact that patients with ACC arising from a site near the cranial base (nasal cavity and maxilla sinus) have an increased risk of recurrence (Zhang *et al.,* 2005). A review of published papers showed a significant association between invaded surgical margins and perineural invasion. This association can be explained by more aggressive and infiltrating tumours, which make it difficult to obtain clear margins (Van der Wal *et al.,* 1990; Agarwal *et al.,* 2008). Local and distant recurrences are common in adenoid cystic adenocarcinoma, and lead to poor long-term survival. Total failure rates vary from 43% to 70%, with local and distant failures ranging from 13% to 52% and 8% to 52%, respectively (Da Cruz Perez *et al.,* 2006; Matsuba *et al.,* 1986; Khan *et al.,* 2001; Kokemueller *et al.,* 2004; Prokopakis *et al.,* 1999). Some authors found that distant metastases were significantly influenced by perineural invasion (Vrielinck *et al.,* 1998; 29. Rapidis *et al.,* 2005). Some authors have found a significant association between perineural invasion and local control, and in most of the series, involvement of the nerve predicted poor local control (Agarwal *et al.,* 2008; Kokemueller *et al.,* 2004). *Sur et al.,* found that perineural invasion lost its significance as an independent prognostic factor when local control was considered (Sur *et al.,* 1997). Currently, ACC remains an extremely difficult disease to treat. Regarding the general treatment strategies for ACC in the head and neck, surgery and radiotherapy are considered effective treatment modalities. There are conflicting reports about the role of postoperative adjuvant radiotherapy. Some authors have shown that it improves local control when adverse prognostic factors are present (invaded resection margins, advanced stage disease, or deep infiltration) (Matsuba *et al.,* 1986; Miglianico *et al.,* 1987). However, several studies failed to show any survival benefit or improvement in local control with the addition of postoperative radiotherapy (Da Cruz Perez *et al.,* 2006; Khan *et al.,* 2001). Yoon Ho Ko *et al.* (2007) studied the series of 28 patients with positive surgical margins had adjunctive radiation therapy with a median 58.1 Gy as adjuvant treatment. ACC is relatively radiosensitive and may have a dose–response relationship with radiation (Spiro *et al.,* 1974; Chen *et al.,* 2006), but positive surgical margins may represent resistant disease (Haddad *et al.,* 1995). Indeed, (Kreitner *et al.,* 1988) reported that radiotherapy with a total dose of 70–80 Gy achieved good local control in all patients with ACC. However, it generally considered difficult to deliver 70 Gy or more with conventional radiotherapy. Avery *et al.* (2000) reported that post-operative radiotherapy with a maximum dose of 65 Gy successfully achieved local control. Despite aggressive therapy, loco regional recurrence occurs at a rate of 20–50% and may present as early as 2 years after primary treatment (Da Cruz Perez *et al.,* 2006; Chummun *et al.,* 2001). Despite aggressive treatment, including surgery and radiation therapy, it seems to be impossible to prevent the development of distant metastasis. Therefore, much more research is needed to identify molecular biomarkers that will predict the clinical outcome and to develop an effective treatment for patients with ACC.

Conclusion

Adenoid cystic carcinoma is an indolent tumor with locally aggressive behavior and a high rate of local recurrence, especially when perineural invasion is present. Radiotherapy is mandatory when disease-free margins cannot be obtained surgically and when there is locally advanced disease or high-grade histological findings. Long-term follow-up is needed because local recurrence and distant metastasis may occur late in the course of disease, especially among high-risk patients.

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