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## RESEARCH ARTICLE

### ADENOID CYSTIC CARCINOMA OF MINOR SALIVARY GLANDS AND RARE SITES

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#### ABSTRACT

**Objectives:** Adenoid cystic carcinomas (ACCs) are rare malignant tumours of salivary glands. Their occurrence at numerous other body sites is rare and poorly described. Frequent local recurrences, late distant metastasis and perineural invasion are commonly seen in these tumours. The aim of this study was to analyse the array of these tumours at various body sites. **Materials and Methods:** A single centre retrospective search over two years revealed 18 cases whose clinical, epidemiological, histomorphological and immunohistochemical findings were evaluated. **Results:** Tumour sites in decreasing order of frequency were minor salivary glands of the oral cavity, nasal cavity, maxillary sinus, larynx, bronchus and one each from the breast and cervix. The mean age of presentation was 50 years and it was more frequently seen in females. The most common histological patterns were tubular and cribriform. Solid pattern was seen predominantly in ACCs of floor of mouth, maxillary sinus and upper gingivobuccal sulcus (GBS). Perineural invasion was seen in tumours of minor salivary glands of oral cavity and maxillary sinus. Local invasion was seen in ACC of oral cavity, maxillary sinus and larynx. **Conclusion:** Although ACCs occur most frequently in the major salivary glands, more than one third of cases occur in minor salivary glands in the head and neck and lower respiratory tract, and other sites more rarely. These have a characteristic histomorphology pattern which can be identified easily. Immunohistochemistry plays a limited role in diagnosis on small biopsy specimens. Radical surgical excision with or without post-operative radiation therapy is the treatment of choice.

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## INTRODUCTION

Adenoid cystic carcinoma, formerly called "cylindroma", is a slow growing and relentless salivary gland malignancy. In the head and neck region, it accounts for less than 10% of all epithelial salivary neoplasms (El-Naggar et al., 2017). They comprise more than one third of minor salivary gland tumours. It was first described by three Frenchmen (Robin, Lorain, and Laboulbène) in 1853 and 1854 (Robin Charles and Laboulbène, 1853; Lorain M. and Robin, 1854). Spies later coined the term adenoid cystic carcinoma (Spies, 1930). Until the 1940s, the tumour was thought to be benign but Dockerty and Mayo in 1943 emphasized the malignant nature of this tumour and also explained that it can spread along peripheral nerves (Dockerty, 1943). Among the major salivary glands, parotid is the most commonly involved (Bradley, 2004). Intraorally, the most common site is the palate and extraorally, nose and paranasal sinus represent the commonest site for minor salivary gland ACCs (Pinakapani, 2015). These tumours can also occur at various body sites, for example, the

lung (Hu, 2015), breast (Kim et al., 2014), lacrimal gland (Bradley, 2013), nasopharynx (Yan-Fang Liang et al., 2014), paranasal sinuses (Michel, 2013), larynx (Marchiano et al., 2015), cervix (Jamal, 2016), external auditory canal (Nayak, 2009), skin (Cacchi, 2011), vulva (Pellizzon, 2018) and prostate (Shong-San, 1984). They are classically characterised by slow growth, frequent recurrences, late distant metastasis with a poor long term survival (Ouyang et al., 2017). The purpose of this two year study was to analyse the spectrum of adenoid cystic carcinomas at various sites.

## MATERIALS AND METHODS

We analysed 18 adenoid cystic carcinoma cases at varying retrospectively sites (excluding major salivary gland tumours). Out of these 18 cases, 8 were identified on small biopsy and surgical specimens were received in the remaining 10 cases. Detailed information on clinical parameters were obtained from the patients' case files. The major clinical parameters studied were age, sex, site and size of tumour, surgery performed and presence of lymphadenopathy. Histological (H and E) and immunohistochemistry (IHC) findings of all cases were analysed.

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All cases were diagnosed in accordance with the WHO Classification of Head and Neck tumours, 2017, 4<sup>th</sup> edition (El-Naggar *et al.*, 2017). Immunohistochemistry for CD 117 antibody (GIVE DILUTION, Clone for CD117 (EP 10) was performed by immunoperoxidase staining on formalin fixed paraffin embedded (FFPE) tissue sections of biopsy specimens in three cases. Other immunostains, used in two cases, were site-specific- TTF1 for lung and ER, PR and HER2 for breast.

## RESULTS

Out of 18 adenoid cystic carcinomas excluding the major salivary gland tumours, 5 arose from minor salivary glands in the oral cavity, 4 from the nasal cavity, 2 from the maxillary sinus, 1 with maxillary sinus involvement and orbital extension, 2 from larynx (glottis and subglottis); 2 from the bronchus, and one each from the breast and cervix. Minor salivary gland sites in the oral cavity included two cases of floor of mouth, and one each of buccal mucosa, tongue and upper GBS. The distribution of ACCs according to site is given in Table 1. The mean age (range) was 51(29-68) years and was more commonly seen in females. Male to female ratio was 1:6.10 were surgically resected and 8 were biopsy specimens. In the surgically resected specimens, all tumours were located submucosally with the largest dimension of the tumour varying from 7.5 to 2.5 cm. They were well circumscribed, solid and grey white to brown in colour. Histologically, the most common patterns seen were tubular and cribriform (Figure 1). Solid pattern was seen predominantly in ACCs of three cases of floor of mouth, maxillary sinus and upper GBS (Figure 2). Of these three cases, perineural invasion, infiltration into adjacent structures (Figure 3) and lymph node involvement was seen in ACC of maxillary sinus and floor of mouth.

Perineural invasion was seen in three tumours (Figure 4). Adjacent tissue involvement and lymph node metastasis was seen in upper GBS carcinoma, however, perineural invasion was not seen. In the other case of floor of mouth and glottic ACC, adjacent structures were invaded by the tumour (Figure 5) but lymph nodes were not involved. Immunohistochemistry using CD 117 antibody was done in ACC involving breast, bronchus and cervix and was positive in all the three cases (Figure 6). IHC for ER/PR/HER2 was negative in breast ACC and TTF-1 was negative in ACC lung. All patients are alive, with recurrence seen in a single case of ACC of left buccal mucosa.

## DISCUSSION

Adenoid cystic carcinomas may be encountered in various body sites as primary tumours or representing metastatic disease. There are many studies which have reported extra-major salivary gland ACC in the literature including the oral cavity (Pinakapani, 2015; Shum, 2016), nasal cavity (Michel *et al.*, 2013), maxillary antrum (Michel *et al.*, 2013; Rahmani *et al.*, 2017), tracheobronchial tree (Hu *et al.*, 2015), larynx (Marchiano *et al.*, 2015), breast (Kim *et al.*, 2014), cervix (Jamal, 2016), external auditory canal (Nayak *et al.*, 2009), skin (Cacchi *et al.*, 2011), vulva (Pellizzon, 2018), prostate (Shong-San, 1984). In our series, of 18 adenoid cystic carcinomas, 5 arose in the oral cavity, 3 in the maxillary antrum (one with orbital extension), 4 in the nasal cavity, 2 each in the larynx and bronchus and one each from the breast and cervix.

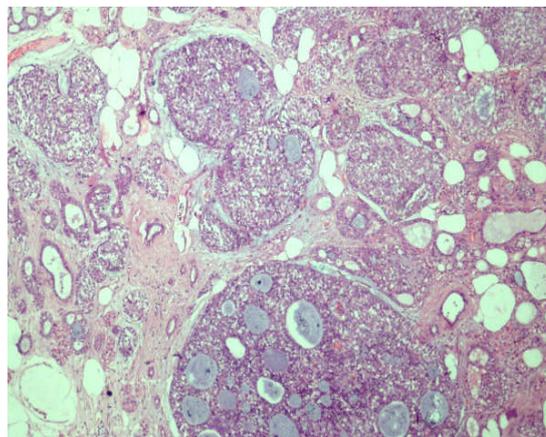


Figure 1. Photomicrograph showing tumour cells in tubular and cribriform pattern infiltrating breast parenchyma (40) (H & E x 40)

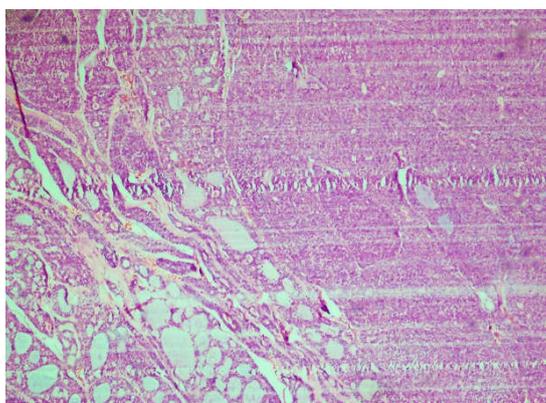


Figure 2. Photomicrograph showing tumour cells in cribriform and solid pattern (H & E)

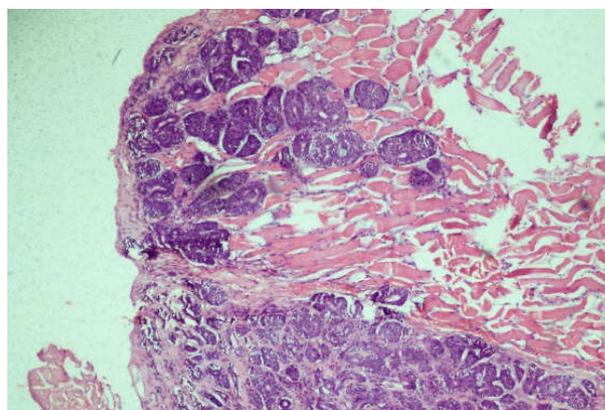


Figure 3: Photomicrograph showing tumour cells in tubular and cribriform patterns infiltrating the adjacent muscle (H & E x 100)

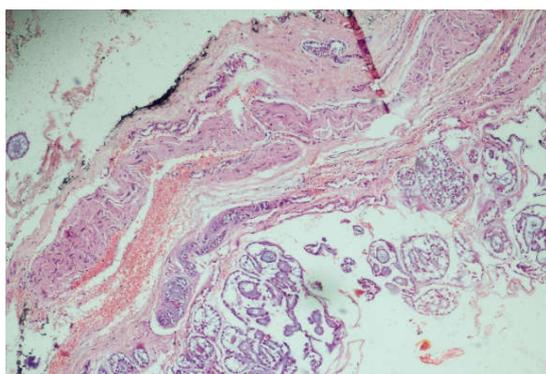
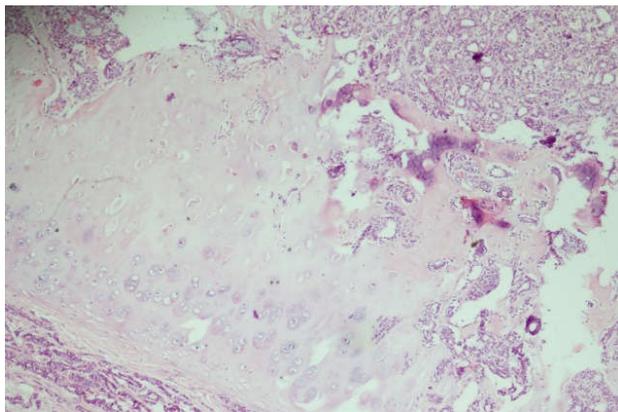


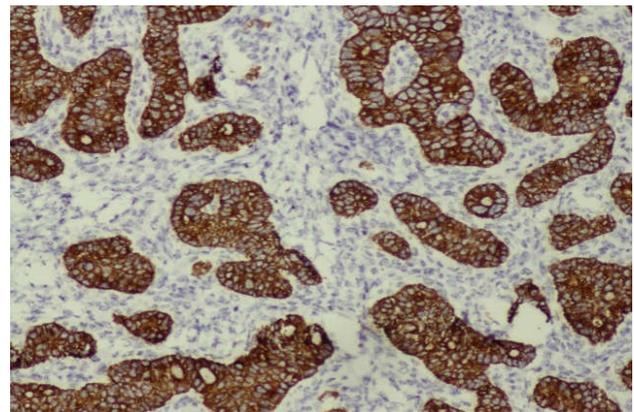
Figure 4. Photomicrograph showing perineural invasion (H & E x 40)

**Table 1. Distribution of 18 ACCs carcinomas according to site, perineural invasion, lymphnode involvement and recurrence**

Primary site	N	Perineural invasion	Infiltration into adjacent structures	Lymphnode involvement	Recurrence
Oral Cavity					
Left buccal mucosa	1				+
Floor of mouth	2	1/2	2/2	1/2	
Tongue	1	1/1			
Upper GBS	1		1/1	1/1	
Maxillary sinus	2	1/2	½	1/2	
Maxillary sinus with orbit extension	1				
Nasal cavity	4				
Larynx	2		½		
Bronchus	2				
Breast	1				
Cervix	1				



**Figure 5. Photomicrograph showing ACC positive of larynx with tumour cells infiltrating cartilage (H & E x 40)100**



**Figure 6. Photomicrograph showing immunostaining with CD 117 (H & E x)**

Oral cavity subsites included two cases of floor of mouth, and one each of buccal mucosa, tongue and upper GBS. These tumours are more commonly seen in females and are tumours of adulthood, seen most commonly between the 4<sup>th</sup> to 6<sup>th</sup> decades of life (Hu *et al.*, 2015; Kim *et al.*, 2014; Bradley, 2013; Yan-Fang Liang *et al.*, 2014; Michel *et al.*, 2013; Marchiano *et al.*, 2015; Jamal, 2016; Nayak, 2009). In our study also, they were more commonly seen in females with a median age of presentation at 51 years and a submucosal location<sup>23</sup>. The commonest histomorphological patterns described in various studies are tubular and cribriform which are similar to our study (Hu *et al.*, 2015; Kim *et al.*, 2014; Bradley, 2013; Yan-Fang Liang *et al.*, 2014; Michel *et al.*, 2013; Marchiano *et al.*, 2015; Jamal, 2016). A correlation between the histological pattern and distant metastasis has been suggested, with solid patterns being associated with distant metastasis (Michel *et al.*, 2013). In our study also, solid pattern was predominantly seen in the most aggressive tumours which involved the GBS, maxillary sinus and floor of mouth and glottis. ACC is associated with late onset of metastasis<sup>19</sup> and late death and since this is a two-year study, these parameters could not be studied. Although association with perineural invasion is ubiquitous (Hu *et al.*, 2015; Kim *et al.*, 2014; Bradley, 2013; Yan-Fang Liang *et al.*, 2014; Michel *et al.*, 2013; Marchiano *et al.*, 2015; Jamal, 2016), in our study perineural invasion was seen in three of 18 cases-ACC in the maxillary sinus, floor of mouth and tongue. This might be an under-representation since only limited biopsy specimens were available in 8/18 cases. ACCs are also locally infiltrative tumours and while lymph node metastasis is uncommon, 10% of cases do metastasize to lymphnodes (Patil *et al.*, 2016). These tumours are likely to recur.

In our study, tumours from upper GBS, maxillary sinus, glottis and floor of mouth were locally aggressive and ACCs from upper GBS, maxillary sinus and floor of mouth had also spread to lymphnodes. Strong diffuse cytoplasmic reactivity of CD 117 is seen in more than 50% of the tumor cells of ACC.<sup>24</sup> In our study, CD 117 was done in only three cases, on small biopsy specimens, mainly to rule out other differential diagnoses on those limited samples. Although surgical resection is the mainstay of treatment in these tumours, postoperative radiotherapy is offered to reduce local recurrence in T3-T4 tumours, close resection margins, bone invasion, perineural invasion and lymphnode positive tumours. Radiotherapy is also given in unresected tumours (Sharma *et al.*, 2010). ACC of cervix is said to be radiosensitive (Jamal, 2016). However, the role of chemotherapy and Imatinib is controversial (Sharma *et al.*, 2010; Hans-jochim *et al.*, 2005).

### Conclusion

Adenoid cystic carcinomas are slow growing, locally aggressive tumours, which are prone to recurrence, and can occur at any body site. They account for < 1% of all head and neck cancers and do not have a propensity to metastasize to regional lymphnodes. Although a longer follow-up is required for our series, the 10 year survival rate is reportedly 50 -70% and the local recurrence rate is highly variable.

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