Chapter

Adenoid Cystic Carcinoma of Larynx

Tarang Patel and Garima Anandani

Abstract

Salivary gland tumours are rare tumours of larynx, hypopharynx and parapharyngeal space. Adenoid cystic carcinoma (AdCC) is the most common malignant salivary gland tumour of larynx. Subglottic region is the most common site followed by supraglottic region. AdCC usually involves elderly patients. Etiology of AdCC is mostly unknown. Clinically patient presents with dysphagia, cough, dyspnoea, hoarseness and rarely haemoptysis. Indirect laryngoscopy shows submucosal laryngeal mass. On CT scan, there is a submucosal mass, which may show extra-laryngeal extension. Histopathological examination shows epithelial and myoepithelial cells arranged in cribriform pattern, which may present with perineural invasion in the periphery of the lesion. Patients usually present in a later course of the disease. Tumour may present with pulmonary metastasis. The surgical approach depends on the tumour stage.

Keywords: adenoid cystic carcinoma, larynx, minor salivary gland tumour, cribriform pattern, perineural invasion, local recurrence

1. Introduction

Adenoid cystic carcinoma (AdCC) was first described in 1853 and thereafter underwent multiple modifications of names before it was given the current name of AdCC in 1930 by Spies [1, 2]. AdCC is an epithelial malignant neoplasm predominantly involving minor and major salivary glands [3]. Malignant tumours involving minor salivary glands are rare and consists of 2–4% of all the head and neck malignancies [4]. Minor salivary gland tumours commonly occur in the oral cavity, peculiarly in the hard palate, with an occasional occurrence in the nasal cavity, paranasal sinuses, pharynx and larynx, correlating with the usual distribution of minor salivary glands in the head and neck region [4, 5]. AdCC is a rare tumour comprising of <1% of all cancers of head and neck. Out of all salivary gland tumours, AdCC accounts for 7.5–10% [6–10]. Minor salivary gland tumours of larynx are very rare, constituting less than 1% of laryngeal tumours [11].

Laryngeal AdCC accounts for 0.07–0.25% of all laryngeal tumours, and hypoglottis is the most common laryngeal site to be involved [5, 8, 12]. Laryngeal AdCC originates from subepithelial minor salivary glands [13]. There is usually no sexual predilection for laryngeal AdCC [10, 14]. Spread through perineural invasion is common [15].

Patients of laryngeal AdCC commonly present with a complaint of dyspnoea. Rarely do patients present with loco-regional metastasis. The average survival of patients is about eight years, and the evolution of prognosis depends on local recurrence and metastasis to lung, bones and brain [12, 16].

2. Discussion

The most common laryngeal malignancy is squamous cell carcinoma; however, other epithelial, mesenchymal and neuroendocrine tumours are rare in this location [16, 17]. Laryngeal salivary gland carcinomas are rare because density of minor salivary glands in larynx is very low, about 23–47 glands per cm^2. Laryngeal salivary gland malignancies comprise less than 1% of all laryngeal malignancies, the most common being AdCC [18, 19]. No definite risk factors have been identified for laryngeal AdCC [20]. Smoking affects laryngeal AdCC in the same way as it affects squamous cell carcinoma [21]. Sub-glottis (64%) is the most common site to be affected, followed by supra-glottis (25%), trans-glottic (6%) and glottic (5%) regions [22].

2.1 Etiopathogenesis and genetic profile

The definite aetiology of AdCC of larynx is not known to date. However, according to recent research, genomic changes are the cornerstone of aetiology for the development of malignant salivary gland tumours including AdCC. The most common genomic changes are a chromosomal translocation t(6;9) or very rarely a translocation t(8;9), which result in fusion of MYB or MYBL1 oncogenes with NFIB transcription factor gene [23]. Recent findings suggest that t(6;9) led to the fusion of MYB exon 14 to NFIB coding exon. This caused deletion of MYB exon 15, which contains many regulatory genes. The loss of MYB gene regulation leads to the overactivation of crucial MYB target genes involved in apoptosis, cell growth, cell cycle control and cell adhesion [24, 25]. West et al. suggested that MYB-NFIB translocation is specific for AdCC and it is not present in any other salivary gland tumour [26]. Cytogenetic studies have demonstrated that AdCC tumour is derived from various differentiated salivary gland tissues undergoing dedifferentiation and lead to early developmental gene profile [27, 28]. Microarray study found that AdCC is associated with genes of myoepithelial differentiation and high levels of SOX4 transcription factor along with overexpression of casein kinase-1 epsilon and frizzled-7 involved in the Wnt/β-catenin pathway [29–31].

2.2 Clinical features

These tumours often occur in elderly patients usually in 6th or 7th decades. However, they can occur at any age ranging from 10 to 96 years [21, 32]. There is generally no gender predilection [10, 14]; however, according to a few researchers, there is a slight preponderance in females [21, 32]. It is clinically characterized by indolent and slow growth [1]. Mostly tumour goes undetected, until the involvement of local structures and local nerves, which may cause variable symptoms depending on the site involved [33]. Clinical features correlate with tumour size and location. Patients with glottic tumours present with dyspnoea or hoarseness, whereas supraglottic tumours present with dysphagia. Patients with glottic and supraglottic tumours are diagnosed at an early stage due to the early detection of

symptoms [4, 5]. Subglottic tumours often present with difficulty in breathing, cough and stridor at a later stage. Due to the submucosal spread of laryngeal AdCC, it is often tough to diagnose AdCC at an early stage [5, 16, 21]. Hence, most of the patients are diagnosed at a later stage of the disease [20]. There is neurological involvement along with local infiltrative growth penetrating the nerve, lymphatics, blood vessels, muscle and bone [34]. AdCC metastasis to cervical lymph nodes is rare, seen only in about 10–15% of cases of head and neck AdCC [35]. Previous reports suggest that AdCC presents with distant metastasis in 35–50% of cases, lung being the most common site followed by bone and liver [4, 14, 36, 37].

2.3 Radiological findings

If dyspnoea persists even after adequate therapy, radiological examination such as computerized tomography (CT) scan is necessary for an exact assessment of the tumour [16, 38]. CT scan is also of crucial importance in accurate pre-operative evaluation. It can assess the primary tumour site, extra-luminal spread, local spread and distant metastasis. However, sometimes AdCC may be difficult to be diagnosed on CT scan because of submucosal spread of laryngeal AdCC in absence of any apparent mass. CT scan with contrast medium can be used in difficult cases [21]. FDG-PET scan shows variable uptake in case of AdCC depending on the differentiation and grade as compared to squamous cell carcinoma, which usually shows high uptake [39]. FDG-PET scan expresses high sensitivity in cases of residual/recurrent tumour or local metastasis of AdCC (**Figure 1**) [40, 41].

2.4 Pathological findings

2.4.1 Gross examination

Grossly tumour is usually firm and poorly circumscribed. Tumour size ranges from 1 to 8 cm. Tumour size more than 3 cm is usually related to increased rate of distal metastasis [42]. Cut surface is grey-white, firm to soft, and very rarely haemorrhage and necrosis which may suggest high-grade variant of tumour or dedifferentiated AdCC (**Figure 2**) [1, 43].

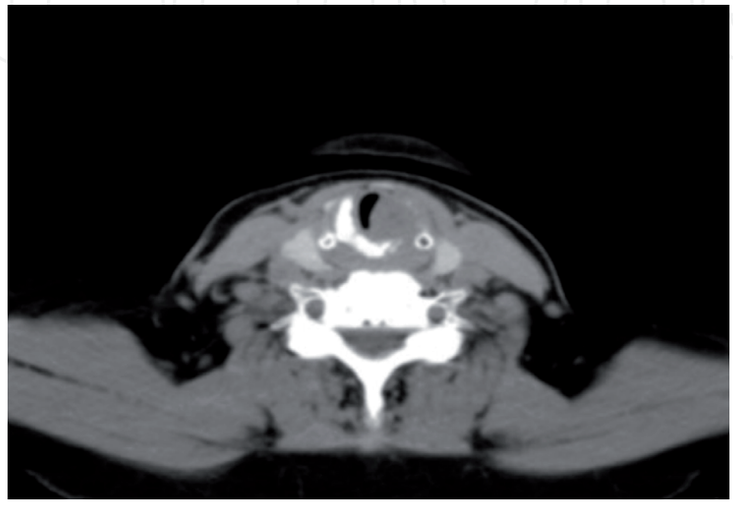

Figure 1.
CT scan of larynx showing a mass involving the left vocal cord along with infiltration of adjacent cartilage.

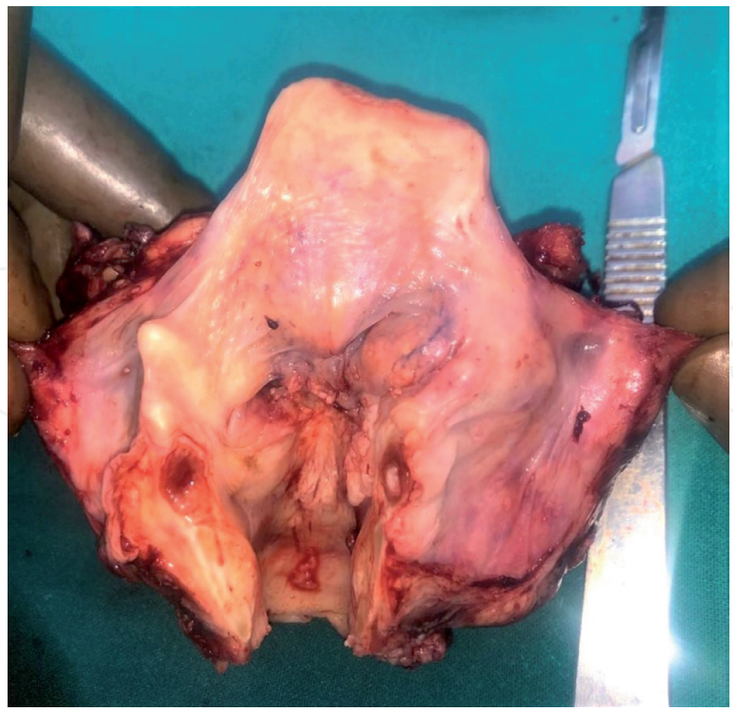

Figure 2.
Specimen of total laryngectomy showing right-sided glottic mass on gross examination.

2.4.2 Microscopic examination

Microscopy shows basaloid malignant tumour encompassing a mixture of epithelial and myoepithelial cells. Histopathological classification is mainly divided into three types: solid, cribriform and tubular [44–46]. Cribriform pattern is the most common histological pattern characterized by islands or nests of basaloid cells interrupted by punched out spaces, which form 'sieve-like' or 'swiss-cheese' pattern [47, 48]. These cystic spaces are not true glandular lumina and they are continuous with the stroma surrounding them. The characteristic eosinophilic periodic-acid-schiff (PAS) positive basement membrane material is present in the pseudocyst [1, 47, 48]. Some tumour cells show true glandular lumina along with pseudocysts. Tumour cytology shows relatively uniform basaloid appearing cells with hyperchromatic angulated nuclei and scant cytoplasm [1]. AdCC is notorious for increased tendency for perineural invasion (PNI). AdCC showing perineural invasion is so common that in absence of invasion of perineurial spaces, diagnosis of AdCC is doubtful [49].

Some AdCC show mainly tubular growth, some may have predominantly solid patterns, and very rarely sclerosing pattern may be seen [50–52]. Solid variant is characterized by tumour cells arranged in sheets without the formation of lumen or pseudocysts and may consist of admixture of epithelial and myoepithelial cells. A solid component may show increased mitosis and cytological atypia along with foci of necrosis [23, 53]. Dedifferentiated or high-grade transformation of AdCC may be rarely seen, which consists of conventional AdCC along with dedifferentiated components in the form of poorly differentiated adenocarcinoma or undifferentiated carcinoma. High-grade components lack any ductal or myoepithelial differentiation and show increased mitosis (>5/HPF), comedo-necrosis and focal squamoid growth (**Figure 3** and **4**) [43].

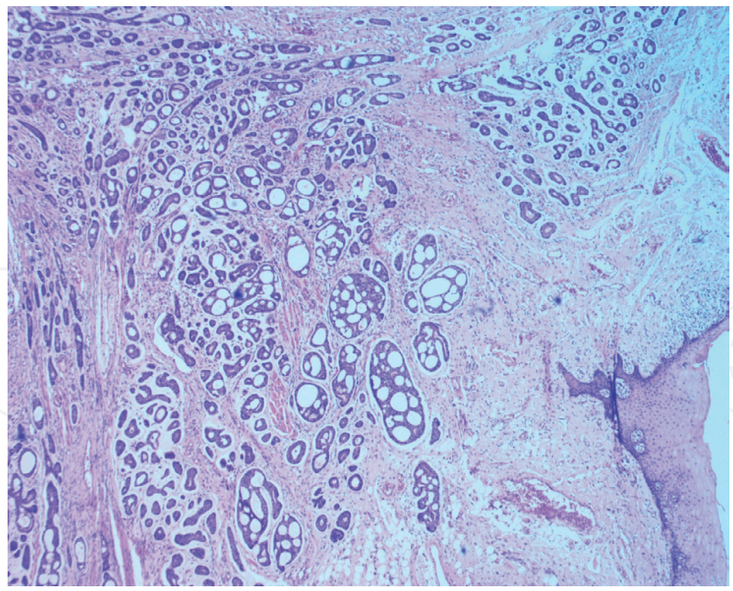

Figure 3.
H&E stained sections from the excision biopsy showing submucosal proliferation of tumour cells arranged predominantly in cribriform and tubular pattern (100×).

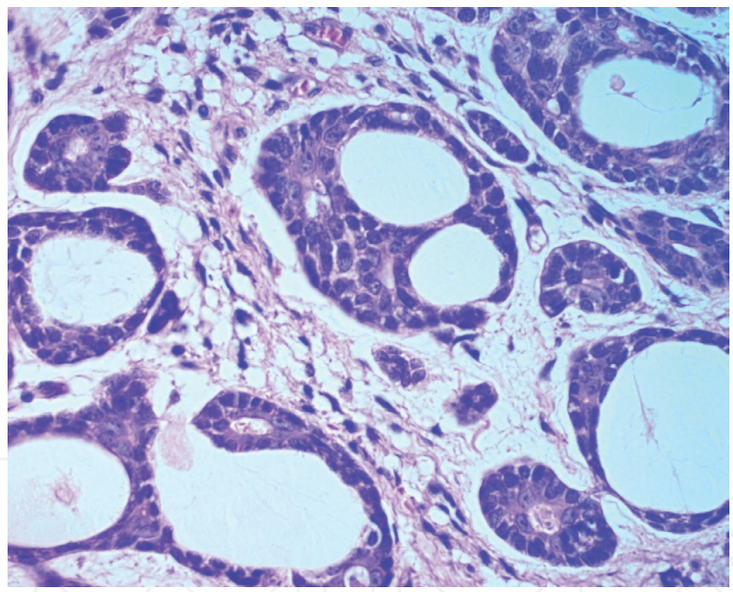

Figure 4.
H&E stained sections from the excision biopsy showing basaloid cells having angulated hyperchromatic nuclei with punched out spaces containing basement membrane material (400×).

Immunohistochemistry (IHC) or electron microscopy study revealed that tumour cells of AdCC depict either myoepithelial or intercalated ductal differentiation [54]. Tumour cells in the region of ductal cells express markers of intercalated duct phenotype, showing positivity for CD117 (c-kit), CEA, keratin and lysosome. Tumour cells adjacent to cystic spaces show myoepithelial markers in form of immunopositivity for p63, S-100 and actin [54–56]. Cytogenetics studies demonstrate loss of heterozygosity at chromosome 6q23-35 [57]. TP53 mutations are very rare except in a few cases of dedifferentiated AdCC [58].

Major diagnostic entities need to be differentiated from AdCC, including polymorphous adenocarcinoma, pleomorphic adenoma and basal cell adenoma/

adenocarcinoma. Polymorphous adenocarcinoma is also common in minor salivary gland, but it is negative or only focal positive for c-KIT. Pleomorphic adenoma is a benign encapsulated tumour with frequent chondromyxoid stroma, whereas AdCC is invasive tumour with foci of PNI [56]. Basal cell adenoma and basal cell adenocarcinoma predominantly arise in major salivary glands [1].

AdCC is graded in accordance with the percentage of solid components seen microscopically. Grade I tumour is composed of predominantly tubular and cribriform patterns. Grade II tumour shows cribriform and tubular pattern with less than 30% solid component and Grade III tumour consists of more than 30% solid tumour area [59]. Solid component of AdCC usually acts as a predictor of poor prognosis [33, 60]. However, grading can be difficult as a single tumour may be composed of variable patterns of more than one subtype. According to few reports, staging using American Joint Committee on Cancer (AJCC) is more useful to predict prognosis and distant metastasis [32, 61]. During staging, documentation of PNI is crucial because infiltration of major nerve has been associated with a poorer prognosis compared to infiltration of minor nerve [62, 63].

2.5 Treatment

Surgical excision in form of total laryngectomy is the preferred treatment for localized AdCC, which ultimately results in complete resection of the tumour with negative surgical margins, without compromising the function of the affected organ [64–66]. Modified radical neck dissection is performed only in cases of positive cervical lymph nodes [64]. Post-operative recurrence rates usually range from 30 to 75% [67].

To minimize the risk of relapse or recurrence, post-operative radiotherapy (PORT) may be administered [63, 68, 69]. Five-year and ten-year local control rates are higher in patients treated with surgery and PORT compared to those patients treated only with surgery [67, 70, 71]. After complete resection in T1 and T2 tumours, radiotherapy (RT) is recommended in intermediate or high-grade AdCC. Cases of T3 and T4 tumours in presence of clinically positive lymph nodes, PNI and positive surgical margins are treated with adjuvant RT. The dose recommended in PORT is >60 Gy in high-risk patients and >44 Gy in low- to intermediate-risk patients [72]. Primary definitive RT is recommended in patients with unresectable tumour mass [68, 72]. Chemotherapy is useful along with surgery in cases of high-grade tumours or to prevent metastasis. It is also recommended in advanced cases of distant metastasis [16, 21, 72].

It is hypothesized that vascular endothelial growth factor receptor (VEGFR) plays an important role in tumour angiogenesis and AdCC pathogenesis of AdCC. The expression of VEGF by the tumour cells correlates with tumour size, staging, invasion of blood vessels, risk of recurrence and distant metastasis. VEGF-A also acts as a downstream regulator of MYB expression. So VEGFR signal inhibition in the tumour may be useful in suppressing the tumour growth and blood flow [29, 73, 74]. Anlotinib, a tyrosine kinase inhibitor against VEGFR-1,-2,-3, and Lenvatinib, a multiple kinase inhibitor against VEGFR-1,-2,-3 kinases have shown effective results as a molecular target therapy for AdCC [72, 75, 76].

Definitive tumour grading and TNM staging along with reporting of perineural invasion and status of surgical margins are the principal prognostic factors. Ki-67 and p53 markers further add details regarding tumour grade and prognosis. Post-therapy close and long-term follow-up are required to ascertain any tumour relapse or distant metastasis [77].

3. Conclusions

Laryngeal minor salivary gland carcinomas are very rare, comprising <1% of all the malignancies of larynx. Laryngeal AdCC should be kept in mind in cases of locally aggressive laryngeal tumours, particularly when a patient is not at risk for the development of squamous cell carcinoma. Most of the patients are diagnosed at a later stage of the disease. Pre-operative diagnosis is usually confirmed by microscopy. Surgical excision with clear margins with or without RT is recommended for management. Recurrence or distant metastasis of laryngeal AdCC can be detected by regular post-operative follow-up. Identification and study of new molecular markers underlying AdCC pathogenesis, such as c-KIT and VEGFR may help in the development of targeted therapy.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

AdCC	Adenoid cystic carcinoma
MYB	Myeloblastosis
MYBL1	MYB Proto-Oncogene Like 1
NFIB	Nuclear factor 1 B-type
SOX4	SRY-related HMG-box
CT	Computerized Tomography
FDG	Fluorodeoxyglucose
PET	Positron Emission Tomography
PAS	Periodic-acid- Schiff
PNI	Perineural invasion
HPF	High power field
IHC	Immunohistochemistry
CD117	Cluster of differentiation 117
CEA	Carcino-embryonic antigen
p63	Protein 63
TP53	Tumor Protein 53
AJCC	American Joint Committee on Cancer
H & E	Hematoxylin and Eosin
RT	Radiotherapy
PORT	Post-operative radiotherap
Gy	Gray
VEGFR	Vascular endothelial growth factor receptor

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