Case Report

Adenoid cystic carcinoma: A case report and review of literature

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Abstract

Adenoid cystic carcinoma (ADCC) is an uncommon tumor of head and neck, whose clinical patterns are characterized by slow growth, perineural invasion and distant metastasis. Cribriform, tubular and solid are the three recognized histopathological patterns which are seen in ADCC. We report a case of ADCC involving palate with an update on the current understanding of its clinical behavior, molecular biology, pathogenesis, histopathological aspect, treatment and prognosis.

Keywords: Adenoid cystic carcinoma, head and neck, salivary gland neoplasm

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INTRODUCTION

Malignancies of salivary glands are rare and accounts for 2%–7% of all neoplasms of head and neck,[1] yet they represent most morphologically and clinically diverse group of neoplasms and they often lead to considerable diagnostic and management challenges. They may arise in the major salivary glands (parotid, submandibular and sublingual) or the so-called minor salivary glands, which are small, predominantly mucus secreting glands located beneath the mucosal lining of the upper aerodigestive tract.[2]

Adenoid cystic carcinoma (ADCC) represents about 10% of salivary gland tumors and about 1% of all head-and-neck malignant neoplasms. Although ADCC is rare, it can be considered the most common malignant neoplasm of the submandibular and minor salivary glands.[3] Among the major glands, the parotid is the most common site of occurrence. Intraorally, 50% of ADCCs occur on the palate. ADCC accounts for 8.3% of all palatal salivary gland tumors and 17.7% of malignant palatal salivary gland tumors (Armed Force Institute of Pathology series).[4]

The other less common sites are lower lip, retromolar tonsillar pillar area, sublingual gland, buccal mucosa and floor of the mouth. The nose and paranasal sinuses represent the next most common sites for minor gland ADCCs.[4] ADCC has been described as a tumor with indolent, but persistent and recurrent, growth and late onset of metastases, which eventually leads to death. It commonly presents with delayed metastases to the lungs, bone and liver.[5]

Histologically, ADCC can be categorized into three histological subtypes based on the growth pattern: tubular, cribriform and solid.[5] They may occur either separately or together in the same tumor, and the solid subtype is the

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most aggressive. A unique feature of ACC is the propensity for perineural invasion, even with early-stage tumors.[6] Tumor is graded according to Szanto *et al*.[7] cribriform or tubular (Grade I), <30% solid (Grade II) or >30% solid (Grade III). Tubular pattern (well differentiated) is believed to have the best prognosis compared to the cribriform pattern (moderately differentiated) and solid pattern (poorly differentiated).[4]

We report a case of ADCC of palate associated with a carious tooth with a brief literature review on its clinical, histopathological, molecular and therapeutic aspects.

CASE REPORT

A 46-year-old male patient reported to the college with a chief complaint of pain in his upper left back tooth region of the jaw since 1 month. According to the patient pain was persistent for 1 month before our consultation and was associated with a swelling. The extraoral examination was within normal limits with no evidence of lymphadenopathy. His medical history was noncontributory. The patient has smoking habit since a couple of years.

On intraoral examination, deep mesio-occlusal caries with respect to 26 was seen associated with a solitary erythematous swelling with clear borders involving the left posterior portion of hard palate. The swelling was small initially and gradually increased to the present size and was seen extending from mesial aspect of canine to 2 cm anterior to tuberosity on left side, involving the palatal area but not crossing the midline. The mucosa over the swelling was smooth and was continuous with the adjacent mucosa. Over the swelling, a small punctum was also seen with no surface discharge [Figure 1]. On palpation, the inspectory findings were confirmed. There was no mobility of the involved teeth but was tender on palpation. The swelling was nontender, nonfluctuant, firm in consistency and immobile. Furthermore, there was a grayish patch seen over anterior part of soft palate with wrinkled surface, which was nontender and non scrappable on palpation. Based on the clinical examination, provisional diagnosis of mesio-occlusal caries with palatal abscess with respect to 26 was made.

The clinical differential diagnosis included a benign or malignant neoplasm of minor salivary glands. Routine blood investigations were found to be normal. Cone-beam computerized tomography revealed a well-circumscribed soft-tissue density lesion measuring about 20.5 mm × 17.1 mm on left palatal region adjacent to premolars and molars [Figure 2]. An incisional biopsy of palate was performed. Histopathological examination revealed fibrovascular connective tissue stroma with mild chronic inflammatory cell infiltrate consisting predominantly of lymphocytes. There was the presence of numerous islands of small cuboidal to polygonal-shaped cells with little cytoplasm and hyperchromatic nuclie resembling basaloid epithelial cells along with multiple cylindrical cyst-like spaces filled with eosinophilic material [Figure 3]. There was no evidence of perineural invasion even on serial sectioning.

Based on histopathology, diagnosis of ADCC (cribriform pattern) was established. The patient was treated by wide surgical excision with clear margins and hemi-maxillectomy of left maxillary region with postradiotherapy. The present case was staged as $T_3N_0M_0$ based on the American Joint Committee on cancer as a guide to prognosis. The patient is under regular follow-up.

DISCUSSION

In 1853, Robin, Lorain and Laboulbene first described two cases of an uncommon epithelial tumor of the nose and the parotid gland, which was named "cylindroma" by Billroth in 1856. Only in 1930, Spies introduced the term "ADCC", and until 1940s, ADCC was considered a benign variant of the mixed salivary gland tumor. The malignant nature of this neoplasm was finally explained by Dockerty and Mayo in 1943.[3]

ADCC accounts for ~1% of all malignancies of the head-and-neck region and mainly encountered in secretory glands, especially the salivary glands. Although ADCCs are usually slow growing, local recurrences and distant metastases often occur, resulting in a poorer long-term prognosis.[8] The 5-year survival rate is relatively high, however, the 10- to 20-year survival rates are dismally low. Therefore, further understanding of the characteristic biological behavior and molecular genetics of ADCC may provide new insights into the novel treatment of the disease.[5]

ADCC is thought to arise from the mucous-secreting glands. It arises specifically from the intercalated ducts, and electron microscopy shows that it arises from cells that can differentiate into epithelial and myoepithelial cells.[6]

The molecular pathogenesis of ACC is still poorly understood. However, significant progress is recently made. Persson *et al*.[9] first to report that the ACC-specific t(6;9)(q22-23;p23-24) translocation results in a fusion of

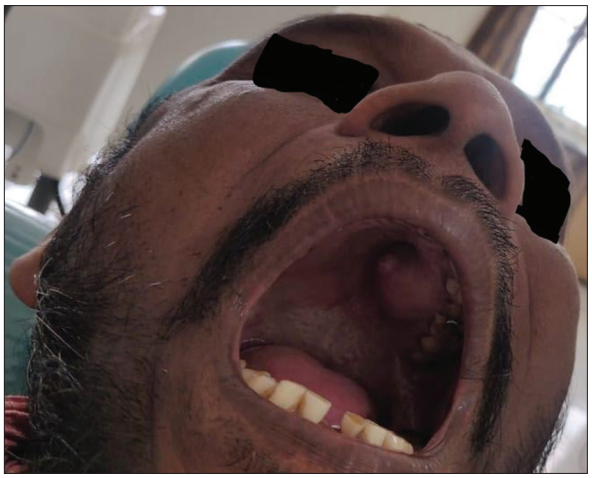

Figure 1: Intraoral Swelling of approximately 2.5 cm, 2.0 cm on the left palatal area

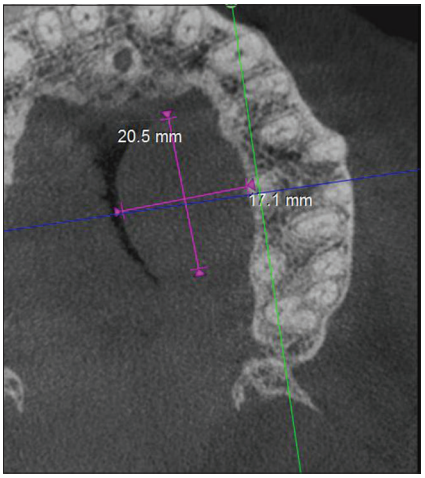

Figure 2: Cone-beam computerized tomography image

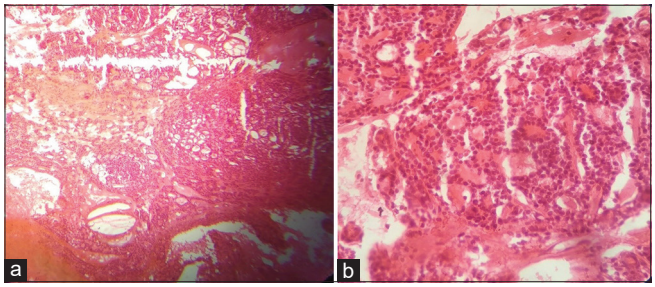

Figure 3: (a and b) Photomicrographs showing islands of small cuboidal to polygonal shaped cells resembling basaloid epithelial cells along with multiple cylindrical cyst-like spaces (H&E, [a] ×10, [b] ×45)

the MYB oncogene to the transcription factor gene NFIB. The chromosomal translocation t (6;9)(q22-23;p23-24) produced chimeric transcripts containing MYB and NFIB and caused deregulation of the MYB gene. As a result, genes targeted by MYB were activated constitutively, resulting in downstream dysregulation of critical cellular mechanisms involved in apoptosis, cell adhesion and cell cycle regulation.[10]

ADCCs express genes associated with myoepithelial differentiation along with high levels of the transcription factor Sox4. The latter normally regulates embryonic development and is also a candidate human oncogene. Other overexpressed genes include casein kinase 1-epsilon and frizzled-7, which are implicated in the Wnt/b-catenin signaling pathway and in tumorigenesis. They frequently produce high levels of the receptor tyrosine kinase c-KIT and variably overexpress other growth factor receptors including fibroblast growth factor receptor 1 (FGFR1), epidermal growth factor receptor and/or human epidermal receptor-2.[11]

The clinical behavior of ADCC is a paradox: First, tumor growth is slow, but its clinical course is relentless and progressive. Second, operative intervention is usually feasible, but multiple local recurrences are the rule. Third, metastatic spread to regional lymph nodes is uncommon, but distant spread to the lungs and bones is frequent.[12]

Gross pathology of an adenoid cystic tumor has been described as a hard unencapsulated mass. A sagittal slice of the tumor would reveal a gray–white-colored mass, with hemorrhage and necrosis indicative of high-grade transformation.[13]

Microscopically, ADCC is composed of small basaloid epithelial, nonluminal, hematoxyphilic cells, with small or moderate cytoplasm which are arranged in three growth patterns: cribriform, tubular and solid as described earlier. Generally, nuclei are not so pleomorphic, with small or bland nucleoli. This type of tumor shows a predominant myoepithelial differentiation. Cribriform pattern is the most frequent and is composed of basaloid cells organized in oval/rounded masses of variable size, punched out by rigid, oval, cyst-like spaces (pseudolumina) that may contain "cylinders" (i.e., globules of hyaline material and/or myxoid glycosaminoglycans) and occasionally, small "true lumina" lined by luminal cells, composing a "swiss cheese"-named model.[3] Billroth, in 1859, first described ADCC under the name "cylindroma," for its cribriform appearance formed by tumor cells with cylindrical pseudolumina or pseudospaces and described that ACC had a "great tendency to recur. [6] Tubular pattern is characterized by tubules lined of luminal cells enclosed by nonluminal cells with, usually, clear cytoplasm. Solid pattern is composed of basaloid cells growing in sheets without lumina formation. Commonly, ADCC is composed of cribriform and tubular patterns.[3] Our case showed predominantly cribriform pattern of ADCC.

Fine-needle aspiration cytology (FNAC) can be used for diagnostic purposes. The finding of large globules of extracellular matrix, partially surrounded by

basaloid cells, suggests ADCC. However, diagnosis of salivary cancers by FNAC is notoriously difficult and is often compromised by false-negative evaluations. Histopathological diagnosis remains the "gold standard" and is especially necessary when the planned therapeutic intervention involves radical surgery and possible sacrifice of the facial nerve.[14]

ADCCs express a characteristic immunohistochemical pattern, and therefore immunohistochemistry represents an essential diagnostic for the diagnosis of ADCCs.

Immunohistochemical studies demonstrated that the pseudocysts are positive for periodic acid Schiff reagent and Alcian blue and contain basement membrane components such as Type IV collagen, heparin sulfate and laminin isoforms. Epithelial cells are positive for carcinoembryonic antigen and epithelial membrane antigen. Duct lining cells are positive for C-kit (CD117) and myoepithelial cells are positive for S-100 protein, calponin, p63, smooth muscle actin and myosin. Expression of S-100, glial fibrillary acidic protein and neural cell adhesion molecule have been correlated with the presence of perineural invasion. P53 mutations appear to be involved with tumor progression and recurrence.[4]

Treatment of ADCC is influenced by location of the tumor, stage at diagnosis and biologic behavior as reflected in histologic grade. The "gold standard" treatment for ADCCs that is deemed as potentially resectable after extensive workup is radical surgical resection, ensuring free margins and postoperative radiotherapy.[14]

Parotid ACC should be treated by the preservation of the facial nerve if not paralyzed preoperatively and not involved intimately by tumors at the time of surgery, followed by postoperative radiotherapy. Submandibular ACC should be treated by a supraomohyoid neck dissection followed by postoperative radiotherapy. ACC of the minor salivary glands should be treated by local radical excision and postoperative radiotherapy.[12]

The adenoid cystic carcinoma research foundation has suggested a combination of magnetic resonance imaging and CT to check for, and to track, any residual disease or potential recurrence.[15] Long-term follow-up is required in view of propensity for recurrence and distant metastasis.

CONCLUSION

Salivary gland neoplasms should always be considered as differential diagnosis, especially when the lesion is involving palate. ADCC of head and neck is a common malignant tumor of minor salivary glands and has a tendency of perineural invasion and distant metastatis and therefore early diagnosis and long-term follow-up of patient is mandatory.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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