Locally advanced stage high-grade mucoepidermoid carcinoma of salivary gland in a 9-year-old girl: the controversy of adjuvant therapy

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Abstract

Malignant salivary gland tumors are rare in children, mostly represented by low-grade mucoepidermoid carcinomas. For these patients, long-term survival rates above 95% are reported after surgical resection. Here we report a case of a 9-year-old girl with a high grade locally advanced mucoepidermoid carcinoma undergoing adjuvant radiotherapy and chemotherapy after surgery. We emphasize the controversy and lack of evidence-based indication for these highly toxic adjuvant therapy modalities in children.

Introduction

Salivary gland malignancies account for approximately 1% of all cancers, and 3-6% of cancers of the head and neck region in the general population. Less than 5% of all salivary gland cancer cases occur during childhood, most of them are diagnosed over the age of 10 years and are histologically low or intermediate-grade.[1-5] Girls are mostly affected.[1,2] Salivary gland cancers are divided into those arising in major salivary glands (the parotid glands followed by the submandibular glands and sublingual glands) and minor salivary glands.[6] Mucoepidermoid carcinoma (MEC) is the most common malignant lesion and represents around 35-50% of all salivary gland malignant tumors in childhood.[6,7]

Most patients present with a slow growing and painless mass although some patients may complain of pain and this has been related to worse prognosis.[3,6,8]

Most cases of MEC in children are low or intermediate-grade and for this group of patients the prognosis is generally favorable after surgical resection with adequate margins with 5-year survival rates above 95%.[5,6] However, for high-grade tumors, 5-year overall survival rates as low as 40% are reported after surgery and radiotherapy in children, and the role of adjuvant therapy for this subgroup of patients is not well established being supported only by previous experience in adults.[9]

Case Report

A 9-year-old girl with a 2 months asymptomatic growing right submandibular mass was transferred to our hospital. A 5×3 cm in size, firm, non-tender right submandibular mass with local regional lymph node involvement was evident on physical examination. Neck ultrasound and magnetic resonance imaging (MRI) showed diffuse involvement and enlargement of the right submandibular gland with alteration of adjacent soft tissues and atypical loco-regional lymph nodes features, all suggesting malignant etiology (Figure 1). Fluorodeoxyglucose-positron emission tomography/computed tomography (CT) findings were consistent with MRI results.

Cytological examination of fine needle aspiration (FNA) material revealed an epithelial neoplasm composed of intermediate-sized cells with polygonal and well-defined boundary cytoplasms and low-grade nuclear atypia, all compatible with a diagnosis of MEC. She underwent surgical resection consisting of supraomohyoid neck dissection with preservation of spinal nerve and cervical plexus. Infiltration of the right lingual nerve as well as the right mylohyoid muscle was noted.

The pathological report described a submandibular gland (3×2.5×2.5 cm) extensively infiltrated by a high-grade mucoepidermoid carcinoma (score of 10 according to AFIP classification),[10] with lymphatic and perineural invasion (Figure 2). There were three ipsilateral metastatic lymph nodes. TNM classification was T2 N2b M0 (Stage IV-A). [11]

Assuming the diagnosis of a locally advanced stage malignant salivary gland tumor and according to our institution local guidelines for the management of adult head and neck cancer, a decision was made to give adjuvant therapy consisting of local radiotherapy in combination with cisplatin (100 mg/m^2 every three weeks during radiotherapy).

Radiation treatment was delivered in two phases. First, the patient received 45 Gy in 25 fractions with 3D conformal radiotherapy to tumor bed and ipsilateral neck with photons. During the second phase, up to 66.6 Gy were delivered to tumor bed and the affected nodal region in 12 fractions with intensity-modulated technique. Treatment was well tolerated without interruption for toxicity.

Mild facial nerve palsy and local dysestesia spontaneously regressed after surgery. Twenty-one months after surgical excision the patient is alive and well with no evidence of residual tumor. It will be important to address long-term outcome for this patient.

Discussion

Most salivary gland tumors in children and adolescents are benign but may be malignant, especially in young children under the age of 10 years.[3] A 25-year experience of 122 children with epithelial salivary gland tumors revealed that pleomorphic adenoma was the most frequent histological type in the benign group.[12] In the malignant group the most common was MEC which represents around 35-50% of all

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malignant tumors, followed by acinic cell carcinoma and adenocarcinoma.[3,12]

The majority of major salivary gland malignancies arise in the parotid glands (80%), followed by the submandibular glands and sublingual glands.[4,6,13] Local lymph node involvement and the distant metastases are rare in pediatric MEC patients.[5]

The most common cytogenetic and molecular finding in MEC is the specific chromosomal translocation t(11;19) (q21; p13) which results in the fusion gene *MECT1-MAML2*.[5,14] Several environmental exposures, viral infections and genetic patterns had been investigated as possible risk factors but only radiation exposure is consistently associated with an increased risk of salivary gland tumors. Epstein-Barr virus has been proposed as a possible risk factor although reviewed literature yields controversial results.[1,3]

The presence of symptoms like pain, dysphagia, trismus, tethering skin, facial or lingual palsy or lymphadenopathy in association with a growing mass should alert about malignant ethiology.[8,13] Diagnostic imaging studies are used in staging and can facilitate preoperative surgical planning.[13] MRI offers advantages over CT with better spatial resolution, superior soft tissue contrast and better identification of nerve involvement signs.[3,8] FNA can be used to distinguish between inflammatory benign and malignant processes. Incisional biopsy is not recommended because of the risk of tumor spillage and facial nerve injury.[13] Histologic grading is based on the presence of intracystic component, nuclear atypia, perineural and angio-lymphatic invasion, necrosis, mitotic activity and pattern of infiltration.[10] In children under the age of 10 it is more likely to find high-grade features and this is associated with a poorer prognosis.[3]

Complete surgical resection with adequate margins is currently the primary treatment for salivary gland malignancies in children.[6,7,15] Neck dissection should be considered when there is clinical evidence of high TNM stage, high histological grade and involvement of regional nodes.[5,13] The role of radiation therapy and/or adjuvant chemotherapy continues to evolve over time and no definitive guidelines have been established.[7,15,16] Postoperative radiation therapy is usually recommended both in adults and children for high grade tumors, lymph node metastasis, positive margins, perineural invasion and T3-T4 stage.[3,5,7,8,15,17] The role of chemotherapy for the management of salivary gland tumors have been limited to treatment of metastatic disease and to circumstances of palliation of loco-regional disease not amenable to either salvage surgery or radiation therapy.[4,15,18] Cisplatin, either alone or in combination with other agents such as 5-fluorouracil, cyclophosphamide and/or doxorubicin, is the chemotherapeutic agent most commonly reported but without overwhelming response rates or sustained clinical benefits.[4,18,19] Thus, for high grade and unresectable tumors the common recommendation is offering radiation with or without chemotherapy as adjuvant therapy. However, most treatment strategies are based on experience with adults and given that both irradiation and chemotherapy are clearly associated with substantial risk of long-term sequelae in children, further studies are needed to determine the indications and benefits of such treatment modalities.[1,13]

Finally, an association between several biologic markers and salivary gland tumors has been targeted as possible prognostic factors, and a correlation between high-grade MEC and expression of cell proliferation markers (PCNA and Ki-67) has been reported.[1,3,20]

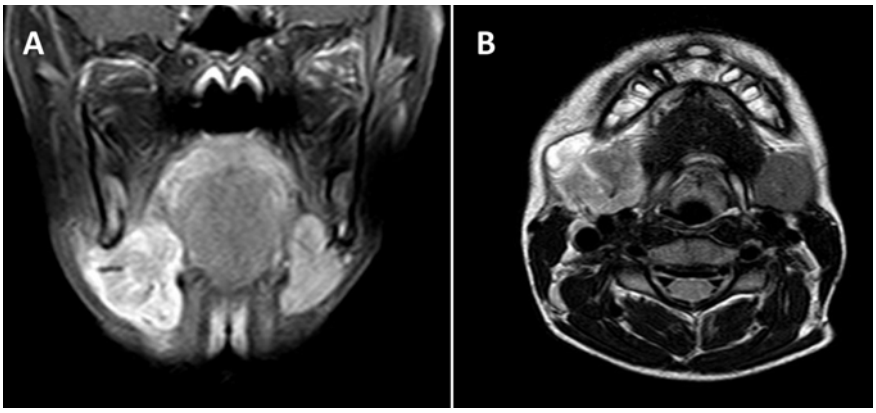

Figure 1. Coronal (A) and axial (B) magnetic resonance imaging images showing enlargement of the right submandibular gland.

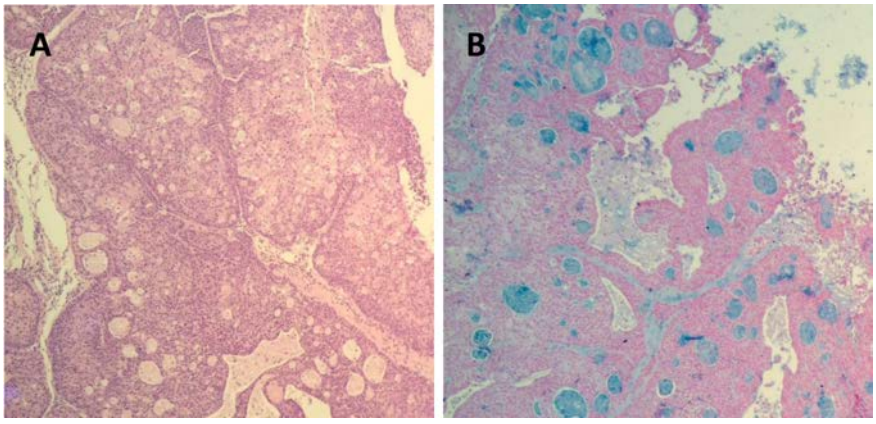

Figure 2. A) An epithelial proliferation growing in solid nests composed with squamous cells, other cells with clear cytoplasm, and mucus-secreting glandular cells (hematoxylin and eosin, magnification ×10); B) alcian blue staining for mucus within glandular lumens.

Conclusions

In summary, although overall survival rates of malignant salivary gland tumors in children and adolescents are generally favorable, the prognosis of children with locally advanced stage (lymph node metastasis), incompletely resected and high-grade histology (score 10/14) tumors is poor after surgery alone. However, the role of potentially toxic adjuvant therapies such radio- and/or chemotherapy are not clearly established in children and further studies are needed to determine the molecular pathogenesis as well as optimal treatment approaches for this high-risk subset of patients.

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