SHORT COMMUNICATION

Salivary Gland Tumors: An Etiological Appraisal

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ABSTRACT

Salivary gland neoplasms are relatively rare, yet they represent a wide variety of both benign and malignant histologic subtypes. These tumors constitute a heterogeneous group of lesions of great morphological variation. While the clinical presentation of a salivary gland neoplasm is usually an asymptomatic mass that may occasionally be ulcerated or cause pain, the histological presentation is far more complex. The tumor spectrum is vast, and yet repetitive features may be seen in a variety of neoplasms with different biological behavior. This paper attempts to revisit this relatively less common yet an important aspect of the maxillofacial discipline.

KEYWORDS: Salivary gland, benign, tumor, pleomorphic adenoma, malignant, neoplasm, imaging.

INTRODUCTION

Salivary gland neoplasms make up about 3% of all the head and neck tumors,[1] appearing mostly in the fourth to sixth decade of the patient's life. Although the malignant variety typically presents after 60 years, the benign lesions are normally seen after an age of 40 years. Additionally, the benign tumors occur more frequently in women, whereas the malignant tumors are almost equally distributed between both the sexes.[2-5]

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The salivary glands, as such, are divided into two groups: the major salivary glands and the minor salivary glands.[4] Whereas, the major salivary glands constitute of the parotid gland, submandibular gland, and the sublingual gland, the minor salivary glands comprise of about 600-1000 small glands distributed throughout the upper aero digestive tract. It is, therefore, important to recognize that these tumors may arise not only in the major salivary gland but also from any of the numerous, diffused intraoral minor salivary glands and thus in any discussion, the general features described for any histological tumor will hold true for both major and minor salivary gland tumors.

ETIOLOGY OF SALIVARY GLAND NEOPLASMS

Although the exact etiology of salivary gland neoplasms is not yet completely clear, two theories worth mentioning here are the bicellular stem cell theory and the multicellular theory.[6]

Bicellular Stem Cell Theory: This theory states that the tumors arise from one of the two types of

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undifferentiated stem cells: the excretory duct reserve cell or the intercalated duct reserve cell. The excretory stem cells are believed to give rise to squamous cell carcinoma and mucoepidermoid carcinomas, and the intercalated stem cells are stated to be responsible for both benign tumors like pleomorphic adenoma, oncocytoma as well as malignant tumors like adenocarcinoma, adenoid cystic carcinoma, and acinic cell carcinoma.

Multicellular Theory: This theory believes that every tumor type is associated with a specific differentiated cell of origin within the salivary gland. For, e.g., pleomorphic adenomas are thought to arise from the intercalated duct cells, squamous cell carcinomas from excretory duct cells, and the oncocytomas from the striated duct cells.

As per the available literature, the bicellular stem cell theory is considered to be a more probable etiology in the development of salivary gland tumors than the multicellular one as the former more clearly explains certain neoplasms that contain multiple discrete cell types such as the pleomorphic adenoma or the within tumor. Tobacco, alcohol, and low dose radiotherapy have also been associated with the development of the salivary gland tumors.

PATHOPHYSIOLOGY

Although it is very difficult to understand the molecular events that lead to the formation of salivary gland neoplasms most of the studies have been investigating the role that tumor suppressor genes, especially the p53 family,[6,7]to understand the development of salivary gland neoplasms. Some literature suggests p53 mutations are important in the development of both benign and malignant salivary gland neoplasms and that most mutations occurred in the fifth and eighth exons of the gene. While the over expression of p53 has been seen mostly in the carcinomas arising from pleomorphic adenomas, benign salivary neoplasms, like pleomorphic adenomas have been understood to express increased levels of transactivation-incompetent truncated isoforms of p63 and p73, while lower levels of normal forms have been found in normal salivary tissue.

The function of oncogenes is also being studied. Murine double minute 2 (MDM2), a cellular protooncogene, which is capable of causing tumor genesis by inactivating the p53 tumor-suppressor gene, has been found to be overexpressed in certain types of benign and malignant salivary gland neoplasms. The overexpression of MDM2 along with high-mobility group protein gene (HMGIC) has also been believed to lead to malignant changes resulting in carcinoma ex-pleomorphic adenoma.[6]

Some studies that look at the neovascularization in salivary gland neoplasms have revealed few factors that increase angiogenesis and are important in the development of salivary gland neoplasms. High levels of nitric oxide synthase and vascular endothelial growth factor are correlated with the stage and size, tumor recurrence, vascular invasion, poor prognosis, and biological behavior of these tumors.

Additionally, recurrent translocations that involve PLAG1, a zinc-finger gene located on band 8q12, have been reported in pleomorphic adenomas. The evidence also suggests that the effects of these translocations can occur without gross rearrangements but with gene over expression due to radiation exposure. Overexpression of PLAG1 is correlated with over expressed levels of beta-catenin levels that translocate to the nucleus, a process associated with other cancers, such as colorectal cancer and melanomas. Few salivary gland neoplasms have also been associated with over expressed beta-catenin through abnormal signaling like an adenoid cystic carcinoma with mutations in CTNNB1 (one of the b-catenin gene) which show tumorigenesis with this process.

Promoter methylation, chromosomal loss (like an allelic loss of chromosomal arm 19q) and mutations that cause hypermethylation and downregulation of 14-3-3ó (a target gene for p53 in the Gap2/mitosis cell cycle check point) are also being implicated in the tumorigenesis in salivary gland neoplasms apart from multiple other genes

IMPORTANCE OF HISTORY TAKING & CLINICAL EXAMINATION

The importance of comprehensive history taking and clinical examination can never be overemphasized as a critical first step in treating patients with suspected salivary gland neoplasms.[3] Tumor size, shape, location, growth rate, associated symptoms with food intake, facial weakness and/ or facial asymmetry and associated pain shall all be duly observed and carefully

noted in the case sheet. A loco regional and head and neck examination along with general physical examination shall be carried out for the patients with such pathologies.

DIAGNOSTIC IMAGING AND PROCEDURES

Diagnostic imaging has proven to be indispensable in the diagnostic approach of salivary gland disorders. Conventional radiography, ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI), fine-needle aspiration cytology (FNAC) and flow cytometry[8] examinations are traditionally used to assist the clinician in tabulating the diagnosis of such tumors of the salivary glands.

Table 1: Table showing historical classifications to salivary gland tumors

Year	Authors	Significant Features of the Classification
1954	Foote &Frazell	Classifies tumors into3 categories; Benign, Malignant and Unclassified tumors
1970	Evans & Cruickshank	Classifies tumors into 4 categories; Epithelial, Connective Tissue, Miscellaneous and Metastatic tumors
1972	WHO	Classifies tumors into 4 categories; Epithelial, Non Epithelial, Unclassified tumors and Allied conditions
1974	Thackray& Lucas	Classifies tumors into 4 categories; Adenomas, Carcinomas, Connective tissue & other tumors and Metastatic tumors
1979	Batsakis	Classifies tumors into 2 categories; Benign and Malignant tumors
1986	Seiferi & Colleagues	Classifies tumors into 4 categories; Adenomas, Malignant epithelial, Non epithelial and metastatic tumors,
1990	Ellis & Auclair,	Armed Force Institute of Pathology (AFIP) Morphologic Classification of Salivary Gland Neoplasm Classifies tumors into 2 categories; Primary Epithelial (Benign &Malignant) and Non Epithelial (Benign mesenchymal, Sarcomas, Lymphomas, Metastatic) tumors
1991	World Health Organization	Histologic Classification of Salivary Gland Tumors Classifies tumors into 7 categories; Adenomas, Carcinomas, Non Epithelial tumors, Malignant Lymphomas, Secondary tumors, Unclassified tumors and tumor like lesions

Numerous classifications have been put forward by many authors over a period (Table1) to categorize such complex pathologies. The World Health Organization (WHO) classification is mostly followed. According to International Classification of Diseases for Oncology (ICD-O) {821} and the Systematized Nomenclature of Medicine (http://snomed.org) Morphology codehas been given. Behaviour is coded '0' for benign tumours, '3' for malignant tumours, and '1' for borderline or uncertain behaviour. Also, a help e-desk for specific questions about the TNM classification of salivary gland tumor is available at http://www.uicc.org.[9]

CONCLUSION

Although a detailed review of each type of tumor is beyond the scope of this paper, it is important for oneto recognize that neoplasms may arise not only fromone of the major salivary glands but also from any of the numerous, diffused intraoral minor salivary glands. Also there appears to be no truly specific, recognized tumor native only to a particular gland. Although researchers have learned much from the study of this diverse group of tumors over the years, but still, the diagnosis and treatment of salivary gland neoplasms remain a complex and challenging problems for the

surgeon.Successful diagnosis and comprehensive treatment of this complex group of pathologiesis, oriented arounda thorough understanding of the clinical nature and biological behavior of these tumors.

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REFERENCES

1. Shafer WG, Hine MK, Levy BM. Textbook of Oral Pathology. 4th ed. Philadelphia (PA): W. B. Saunders Company; 1993. p. 230-57.
2. Marx RE, Stern D. Oral and maxillofacial pathology - a rationale for diagnosis and treatment. 1st ed. Illinois (IL): Quintessence Publishing Co, Inc; 2003. p. 528-72.
3. Greenberg MS, Glick M. Burket's Oral Medicine -Diagnosis and Treatment. 10th ed. Ontario (NY): BC Decker Inc; 2003. p. 235-70.
4. Subhashraj K. Salivary gland tumors: a single institution experience in India. Br J Oral MaxillofacSurg 2008;46: 635-38.
5. Al-Khateeb TA, Ababneh KT, Irbid J. Salivary tumors in north Jordanians: A descriptive study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:e53-e59.
6. Johns MM,Harri PA. Salivary Gland Neoplasms. Medscape 2007. [Available online fromURL: http://emedicine.medscape.com/article/852373]
7. Levine AJ. The common mechanisms of transformation by the small DNA tumor viruses: The inactivation of tumor suppressor gene products: p53. Virology 2009;384: 285-93.
8. Yuasa K, Nakhyama E, Ban S, Kawazu T, Chikui T, Shimizu M,*et al*. Submandibular gland duct endoscopy - Diagnostic value for salivary duct disorders in comparison to conventional radiography, sialography, and ultrasonography. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 1997; 84:578-81.
9. Available online on: https://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb9/bb9-chap5.pdf