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Role Of Viruses In Odontogenic Tumors – A Systematic Review

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Abstract:

Introduction: Odontogenic tumours are neoplasm of the cells or tissues that initiate odontogenic processes. Odontogenic tumours constitute less than 1% of all jaw tumours. Odontogenic tumors are derived from tooth forming tissues, either the epithelial or the ectomesenchymal or both. Viruses such as Epstein Barr virus (EBV), Polyoma virus, Human papilloma virus (HPV), HTLV- 1 may have a role in pathogenesis and aggressiveness of odontogenic tumours.

Aims & Objectives: To review the possible relation of viruses with the odontogenic tumours and to update the evidence on the role of viruses in the etiopathogenesis of odontogenic tumours.

Materials & methods: Search strategy– For this systematic review the data were obtained from electronic search engines like PUBMED, GOOGLE J-GATE from 1966 -2017.

Results: This systematic review found that onco viruses especially HPV and EBV viruses play a major role in causation of odontogenic tumors by enhancing the pathology by altering the genetic and molecular mechanism.

Conclusion: Oncoviruses play a major role in enhancing the pathology of odontogenic tumors.

Keywords: Viruses, Oncoviruses, Odontogenic tumour, EBV, HPV, HTLV-1, Polyoma virus.

I. INTRODUCTION

Odontogenic lesions can be divided discretely into cysts (an epithelial lined pathological cavity) and tumors (a solid tissue mass, not necessarily neoplastic). They are derived from tooth forming tissues, either the epithelial or the ectomesenchymal or both. They form a heterogeneous group of hamartomatous lesions, benign and malign tumors. According to their origins, they are divided into epithelial, ectomesenchymal, and mesenchymal. Among the most frequent OTs are Keratocystic Odontogenic Tumors (KCOTs), ameloblastomas, and odontomas. Odontogenic tumors are quite rare and constituteless than 1% of all jaw tumors. The KCOT arises from the dental lamina and other sources of odontogenic epithelium. This lesion tends to be more aggressive in its growth pattern, providing a higher recurrence rate than other odontogenic pathoses. Ameloblastomas can be derived from any odontogenic epithelium ranging from the dental lamina (pre-odontogenesis), to reduced enamel epithelium (post-odontogenesis), to epithelial rests of Malassez and Serres (post-eruption), and possibly the basal layer of the overlying epithelium (The primitive source of dental lamina during embryogenesis and pre-odontogenesis). Odontogenic myxomais an intraosseous neoplasm consisting of myxomatous fibrous extracellular matrix originating from mesenchymal remnants. Adenomatoid odontogenic tumors arise from the dental lamina in the gubernacular cord of developing permanent teeth. Ameloblastic fibromas are similar

in origin to ameloblastomas, being derived from the enamel organ or dental lamina, except there is a lack of dental hard tissue in the specimen. (Viruses such as Human papilloma virus (HPV), Epstein Barr virus (EBV), Polyoma virus, may have a role in pathogenesis and aggressiveness of odontogenic tumours.

The aim of the study was to review the possible relation of viruses with the odontogenic tumours and to update the evidence on the role of viruses in the etiopathogenesis of odontogenic tumours.

II. MATERIALS & METHODS

Search strategy: For this systematic review the data was obtained from electronic search engines like PUBMED, GOOGLE J-GATE, from 1966-2017. Key words that were used are viruses, Oncoviruses, Odontogenic tumour, EBV, HPV, Polyoma virus.

Review methodology: Review of full texts, abstracts, review articles and case reports of relevant studies were selected and evaluated to match our inclusion criteria of etiopathogenesis of odontogenic tumours and its association with viruses.

Data collection & Extraction: The articles were collected and evaluated independently by a single reviewer. The data was captured and analysed for the number of studies reported in the literature based on our inclusion criteria.

Evaluation of articles: The articles selected as per inclusion criteria were evaluated for the type of study and the presence of viruses & their role in the etiopathogenesis of odontogenic tumors and a focus on the management of virus induced odontogenic tumors.

III. RESULTS

The systematic review was done to know the possible relation of viruses with odontogenic tumors as well as the etiopathogenesis of virus induced odontogenic tumors.Total 15 articles was selected. Among these 15 articles, 9 articles were related to prospective studies, 5 articles were retrospective studies, 1 case report. From the literature review, and following authors have put forward the etiopathogenesis related to viruses and odontogenic tumors. In prospective studies, most of the authors have concluded the presence of viruses and their role in the etiopathogenesis of the odontogenic tumors. In two articles the authors have concluded that there is no specific role of viruses in the etiopathoenesis of odontogenic tumors (Vanheerden WFP 1993 & Migaldi M 2005). None of the authors have focused on the management of virus induced odontogenic tumors. The inference of these studies is quoted in table 1.

IV. DISCUSSION

ETIOPATHOGENESIS

Odontogenic tumors are lesions derived from the epithelial and/or mesenchymal elements of the tooth forming apparatus and are therefore found exclusively within the jawbones. A series of genetic and molecular alterations appear to promote the development and progression of tumors via multiple steps. Although the etiology and pathogenesis of odontogenic tumors remain unknown. Recent studies have identified various molecular alterations responsible for their development and progression.

Oncogenic viruses can contribute to different steps of thecarcinogenic process, and the association of a virus with a given cancer can be anywhere from 15% to 100%.

In addition to elucidating the etiology of several human cancers, the study of oncogenic viruses has been invaluable to the discovery and analysis of key cellular pathways that are commonly rendered dysfunctional during carcinogenesis in general.

Factors such as trauma, tooth extraction, infection, a past history of endodontically treated tooth and genetic causes or contamination from the surface mucosal epithelium induced by the surgical manipulation will contribute to the pathogenesis. Virus may also enter into vascular system and may represent the possible route for viral transmission and eventually lead to odontogenic tumour formation. Through any one /multiple etiological factors as mentioned above, virus may enter in to the bone and infect the odontogenic epithelium.

In our systematic review, a prospective study done by sand et al stated that surgical manipulation is suggested to be one of the reasons for HPV presence and also attributable to contamination from the surface mucosal epithelium in odontogenic tumors.

Bodaghi et al in their prospective study concluded that, peripheral blood mononuclear cells may be regarded as HPV carriers and might spread the virus through blood, suggesting that those cells may migrate to sites of HPV infection and take up HPV from tissues or the bloodstream as they do for many other viral infections.

A retrospective study done by Kahn et al have given inference that, possibility of HPV to be acquired in utero or at parturition and involves the invaginating primitive enamel organ, then at a later date, the virus stimulates growth factors or reduces the growth factor's natural inhibitory control.[16]

Viruses encode proteins that reprogram host cellular signaling pathways that control proliferation, differentiation, cell death, genomic integrity and recognition by the immune system.

In our systematic review, Kumamoto et al. Investigated the role of the expression of stem cell‐related molecules in oncogenesis and cytodifferentiation of odontogenic tumors, expression of CD 133, Bmi‐1 and ATP‐binding cassettesubfamily G member 2 (ABCG2) in ameloblastic tumors and tooth germs. CD 133, prominin‐1, a product of single copy gene on chromosome 4 (4p 15.33) in humans has been found to have a role in cell growth, development and tumor biology. It is expressed in the differentiated epithelia of

various organs, and lack of expression of this marker could initiate tumors. Kumamoto in their retrospective study have concluded that human odontogenic tumor pathology is enhanced by viruses such as HPV, EBV and HTLV -1. Many DNA and RNA viruses are oncogenic in a wide variety of animals, and increasing evidence suggests that certain types of human tumors are caused by viruses, such as human papilloma virus (HPV), Epstein–Barr virus (EBV), and human T-cell leukemia virus type 1 (HTLV-1).

In our review, several studies done by Eisenberg E et al, Tsuchia H et al.Nameen AK et al, Alsaegh et al, have detected the presence of HPV in ameloblastoma. A study done by Clyde J et al on mice, confirmed the presence of polyoma virus and stated that polyoma virus plays a role in induction of odontogenic tumors.

This systematic review provides a contemporary outline of our understanding of the molecular and genetic events associated with virus induced odontogenic tumors.

A. HUMAN PAPILLOMAVIRUS (HPV)

Papillomaviruses (PVs) are a group of small, non-enveloped, double-stranded DNA viruses that constitute the Papilloma viridae family. These viruses infect squamous epithelia of a variety of species. They can be further divided into low and high-risk, depending on the associated lesion's propensity for malignant progression. High-risk mucosal HPVs, such as HPV16 and HPV18, cause squamous intraepithelial lesions that can lead to the formation of tumors. During carcinogenic progression the HPV genome frequently integrates into a host cell chromosome and, as a result, the viral oncoproteins, E6 and E7, are the only viral proteins that are consistently expressed in HPV positive tumors.

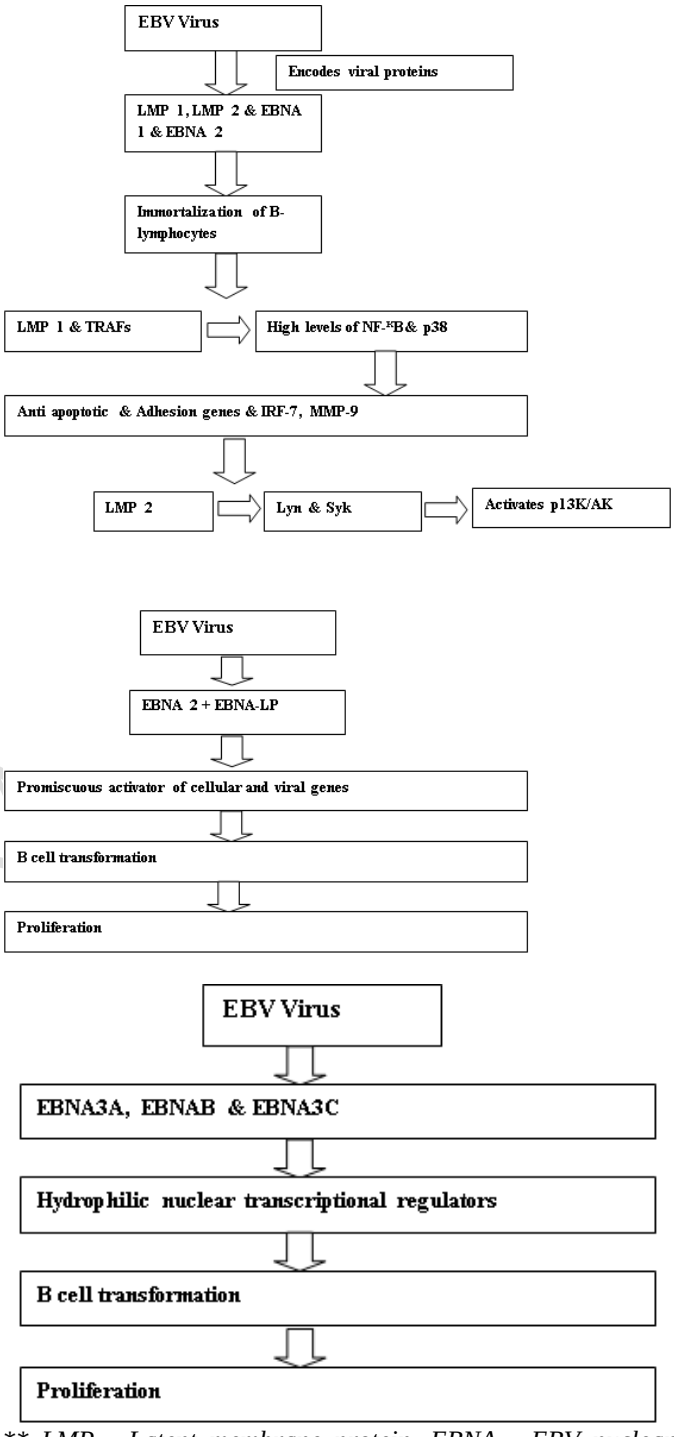
PATHOGENESIS OF HPV INDUCED ODONTOGENIC TUMORS

HPV genome integrates into host cell chromosome results in expression of E6 &E7 oncoproteins causes immortalization of primary human keratinocytes and dysregulation of p53 & pRB genes which leads to irreparable DNA damage and also because of evasion of apoptosis leads to tumor formation.

B. EPSTEIN-BARR VIRUS (EBV)

EBV is a ubiquitous double-stranded DNA virus of the γ herpesviruses subfamily of the Lymphocryptovirus (LCV) genus. Worldwide, more than 95% of the population is infected with EBV.EBV infects and replicates in the oral epithelium, and resting B lymphocytes trafficking through the oral pharynx become latently infected. Infected B-lymphocytes resemble antigen activated B cells, and EBV gene expression in these cells is limited to a B cell growth program, termed Latency III, that includes LMP1, LMP2a/b, EBNAs -1, -2, -3a-3b,-3c and -LP, miRNAs, BARTs, and EBERs. In immunocompromised individuals, infected cells increase in number and eventually B cell growth control pathways are activated, inducing transformation and leading to malignancies.

PATHOGENESIS OF EBV INDUCED ODONTOGENIC TUMORS



** *LMP - Latent membrane protein, EBNA - EBV nuclear antigen, TRAF TNF receptor associated factors, NFKB - Nuclear factor kappa B, IRF - Interferon registration factor, MMP- Matrix Metaloprotinase*

Flowchart 1: Major biological activities that contribute in pathogenesis of EBV induced odontogenic tumors

C. POLYOMAVIRUS

The Polyomaviridae family is a group of non-enveloped, small double-stranded DNA viruses that have been isolated

from humans, monkeys, rodents and birds. Like SV40, a role for BKV and JCV in human tumors has been suggested, however, no conclusive proof exists that either virus directly causes or acts as a cofactor in human cancers. However, the association of these polyomaviruses with human malignancy remains controversial. Dawe CJ et al (1966) Prospective Study on mice concluded that Polyoma virus plays a role in induction of odontogenic tumor.

D. HUMAN T-CELL LEUKEMIA VIRUS (HTLV-1)

HTLV-1, the first human retrovirus to be discovered that is clearly associated with a human malignancy. Approximately 20 million people worldwide are infected with HTLV-1. A number of studies indicate that the multifunctional viral accessory protein Tax is the major transforming protein of HTLV- 1. Tax modulates expression of viral genes Tax is also able to functionally inactivate p53, p16INK4A. Unlike other well-established DNA tumor viruses, which generally require continuous expression of viral oncoproteins to sustain transformation Tax may be needed to initiate transformation, but may not be necessary for maintenance of the transformed phenotype. HBZ gene promotes the proliferation of a human T-cell line. It appears that HBZ may have a bimodal function at the mRNA and protein levels, as the RNA form of HBZ supports T-cell proliferation through regulation of the E2F1 pathway, whereas HBZ protein suppresses Tax-mediated viral transcription through the 5′-LTR.

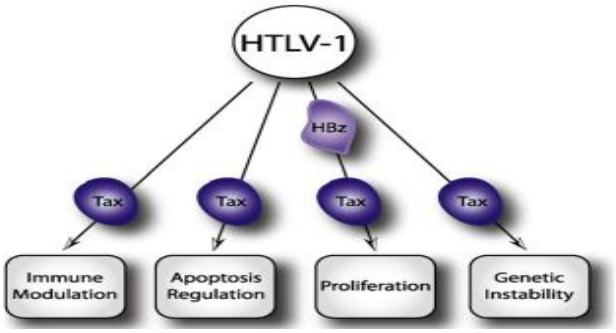


Figure 1: Schematic depiction of major biological activities that contribute to the transforming activities of HTLV-1

III. CONCLUSION

The development and progression of odontogenic tumors are affected by viruses because of the alterations of many kinds of genes and molecules. A better understanding of underlying molecular mechasnism will help to predict the course of odontogenic tumors and lead to the development of new therapeutic applications, such as molecular targeted treatment and patient tailored therapy, for odontogenic tumors.

S. no	Author	Year	Study Design	Inference
1.	Dawe CJ et al	1966	Prospective Study on mices	Polyoma virus plays a role in induction of odontogenic tumor.
2.	Kahn et al	1989	Retrospective Study	Possibility of HPV to be acquired in utero or at parturition and involves the invaginating primitive enamel organ, then at a later date, the virus stimulates growth factors or reduces the growth factor's natural inhibitory control
3.	Tsuchia H et al	1991	Retrospective Study	Detected the presence of HPV in head and neck tumors
4.	Van heerden WFP et al	1993	Case report	HPV is not considered to be an etiological factor in the pathogenesis of ameloblastoma.
5.	Fujita S e.t al	1997	Prospective Study	EBV participates as one of the transforming factors in the occurrence of ameloblastoma.
6.	Sand et al	2000	Prospective Study	Surgical manipulation is suggested to be one of the reasons for HPV presence and also attributable to contamination from the surface mucosal epithelium in odontogenic tumors.
7.	Eisenberg E et al.	2000	Prospective Study	Confirmed the presence of HPV in intraosseus Ameloblastoma.
8.	Nameen AK et al.	2003	Prospective Study	Concluded the positive relationship between Ameloblastoma and HPV.
9.	Kumamoto et al.	2004		Concluded that human odontogenic
10.	Bodaghi et al	2005	Prospective Study	Peripheral blood mononuclear cells may regarded as HPV carriers and might spread the virus through blood, suggesting that those cells may migrate to sites of HPV infection and take up HPV from tissues or the bloodstream as they do for many other viral infections
11.	Migaldi M et al	2005	Prospective Study	The data did not support an etiopathogenic evidence for role of HPV virus in odontogenic tumors. Tumors are caused by HPV, EBV and HTLV-1
12.	Margaret E. McLaughlin-Drubin et al	2009	Retrospective Study	Oncogenic viruses helps to investigate cellular network including discovery of oncogenes, tumor suppressors and identification of regulatory networks
13.	Feller L et al	2009	Retrospective Study	HPV can cause latent infection in basal cells with low HPV DNA copy number insufficient for transmission of

S. no	Author	Year	Study Design	Inference
				infection.
14.	Correnti M	2010	PROSPECTIVE STUDY	Concluded that HPV low and high risk was detected in intraosseous ameloblastoma.
15.	Alsaegh M A et al	2014	Prospective Study	Presence of HPV DNA in Ameloblastomas indicates the possible relation of HPV with odontogenic tumors

Table 1: Summary of prospective studies, retrospective studies & case reports of role of viruses in Odontogenic tumors

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