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Expression of hCG-β in Head and Neck Squamous Cell Carcinomas: A systematic Review

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Abstract

Head and Neck Squamous Cell Carcinoma (HNSCC) is a major public health issue all around the world. Establishment of an early and reliable biomarker with high sensitivity and specificity will enable early diagnoses of cancer and the best way for patient survival and improved quality of life. Human Chorionic Gonadotropin (HCG) is a glycoprotein hormone normally produced by placental syncytiotrophoblast, which plays a critical role in implantation and maintenance of blastocyst. This hormone is known to be produced by neoplastic cells in tumors of trophoblastic origin. It has been widely studied tumor marker for ovarian tumors. The association of hCG-β in various head and neck tumors such as salivary gland, oral cavity, esophagus, thyroid and parathyroid has been reported. The current paper comprehensively studied the role of hCG-β in head and neck malignancies.

Introduction

Head and neck squamous cell carcinomas are amongst the most destructive tumors, with oral squamous cell carcinoma representing the vast majority. More than 11 million people are diagnosed with cancer every year. Five-year survival rates are reportedly as low as 9% for some parts of the oral cavity, largely due to late-stage diagnosis when tumor metastasis has occurred.[1] In India alone, 2.5 lakhs new patients are diagnosed of whom about three-fourths are in an advanced stage.[2] Among the HNSCCs, carcinoma of oral cavity and oropharynx predominates in Indian population. The prognosis of these patients depends upon various factors like age of patient, size of tumor, site of tumor, thickness of tumor, degree of differentiation and spread into regional lymph nodes. The spectrum of HNSCC varies from place to place within the country. [2]

Early detection also improves morbidity accompanying the treatment of HNSCC, with late-stage diagnosis associated with poorer prognosis. The carcinoma is commonly preceded by a range of tissue and cellular alterations consistent with carcinoma, yet restricted to the surface epithelial layer. These changes often manifest in a clinical mucosal lesion. Tumor markers are biochemical substances elaborated by tumor cells either due to the cause or effect of malignant process. A tumor marker produced by the tumor and when present in significant

amounts, indicates the presence of cancer. [3] hCG-β is normally produced in significant amounts during pregnancy. It is also ectopically produced by trophoblastic as well as non-trophoblastic (colon, prostate, bladder, breast and lung) carcinomas. hCG-β has therefore been proposed as a cancer marker of broad utility. [4]

Progression of Squamous Cell Carcinoma

Cancer results from the outgrowth of a clonal population of cells from tissue. Oral carcinogenesis is a molecular and histological process featuring genetic and phenotypic markers for each stage, which involves enhanced function of several oncogenes and/or the deactivation of tumor suppressor genes, resulting in the loss of cell cycle checkpoints.[5] The development of cancer, referred to as carcinogenesis, can be modeled and characterized in a number of ways. One way to describe this process is to illustrate the essential features of both cancer cells and tumors: the "hallmarks" of cancer. Cancer development requires the acquisition of six fundamental properties: self-sufficient proliferation, insensitivity to anti-proliferative signals, and evasion of apoptosis, unlimited replicative potential, the maintenance of vascularization, and, tissue invasion and metastasis. Cancer can also be considered with regard to a step-wise development functionally grouped into three phases: initiation, promotion and progression. Initiation is characterized by genomic changes within the "cancer cell", such as point mutations, gene deletion and amplification, and chromosomal rearrangements leading to irreversible cellular changes. Tumor development is promoted by the survival and clonal expansion of these "initiated" cells. Progression encompasses a substantial growth in tumor size and either growth-related or mutually exclusive metastasis. [6]

According to the histological model of oral carcinogenesis, cells chronically exposed to environmental carcinogens progress through the stages of reactive hyperkeratosis, epithelial hyperplasia, degrees of dysplasia and intraepithelial carcinoma leading to invasive carcinoma.[1]The degree of dysplasia is the best guide to potential progression of oral lesions. Severe epithelial dysplasia has an overall malignant transformation rate of about 16% but studies show a wide range of 7-50%.[7] Moderate dysplasia has a malignant transformation potential of 3-15%, whereas mild epithelial dysplasia shows a very low risk (<5%).[7] It is always assumed however that, there is a temporal progression of disease, analogous to multistage carcinogenesis and that mild dysplasia will progress to severe dysplasia and then to carcinoma.[7]

Oral cancers are mostly diagnosed between 50 to 79 years of age, 96.6% being over 40 years old as studied by Omar et al.[8] Despite the advances of therapeutic approaches, percentages of morbidity and mortality of OSCC have not improved significantly during the last 30 years. Percentages of morbidity and mortality in males are 6.6/100,000 and 3.1/100,000 respectively, while in females the same percentages are 2.9/100,000 and 1.4/100,000 respectively. [9]

Studies of Prabhu et al [10] have shown that the incidence and prognosis of OSCC differs based on the site of origin of the lesion. They found that in India, buccal mucosal oral squamous cell carcinomas are most commonly followed by tongue lesions and the least common cases of OSCC arise from floor of the mouth (0.2 to 0.6 per 10000 OSCC cases). [10] They also inferred that 25% of lip lesions, 75% of labial mucosal lesions, 78% of buccal mucosal lesions and 67% of tongue lesions showed lymph node metastasis. [10]

Human Chorionic Gonadotropin (HCG)

Human Chorionic Gonadotropin (HCG) is a glycoprotein hormone that biochemically consists of two polypeptide

subunits (alpha and beta chains) with attached carbohydrate side chains. The α subunit is shared by other glycoprotein hormones such as luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone and the β subunits are unique for each hormone.[11] The hormone is normally produced by a placental syncytiotrophoblast which plays a critical role in implantation and maintenance of blastocyst. It is mainly activated by another glycoprotein hormone Activin-A which is mainly produced by trophoblasts as well as circulating inflammatory cells. This hormone is also known to be produced by neoplastic cells in the tumors of trophoblastic origin.[12] Further, the hormone is also widely used for diagnosis of pregnancy, pregnancy-associated disorders and trophoblastic disease such as in gestational trophoblastic disease in which the serum and urine levels of hCG-β are almost always elevated. Similar findings were also reported by Guo et al [13] in trophoblastic malignancies.

The expression of hCG-β is mainly cytoplasmic and its production by tumor cells is explained by differentiation theory, according to which the retrodifferentiation of tumor cells into an invasive and highly proliferative tissue type resulted in the transformation of moderately differentiated primary tumor into poorly differentiated lesion.[4] hCG-β also appears to enhance the growth of tumor cells in culture by preventing apoptosis.[14] All these findings suggested that hCG-β is an aggressive tumor marker and its expression could be attributed to decreased survival rate and poor prognosis of the disease.

Role of Human Chronic Gonadotrpins on Tumors

Ectopic human chorionic gonadotropin expression by non-gestational tumors was noted as early as 1904 by De Jewitzi et al and it was reviewed by Iles & Chard in 1991. [15] Up to the late 1970s, the incidence of ectopic hCG expression by common epithelial cancers could only be gleaned from a number of case reports. However, since the 1980s publications describing the ectopic expression of hCG have grown exponentially, and such findings are now generally reported in terms of the percentage of hCG positive patients with a given type of epithelial cancer (reviewed by Iles and Butler, 1998).Extensive immunochemical characterization has shown that, whilst intact hCG is abundantly produced by the placenta and by germ cell tumors, it is the free β subunit (independently of the common glycoprotein hormone αsubunit [GPHα] that is predominantly produced by common epithelial tumors.[15] Ectopic production of free hCG-β by bladder carcinoma is well established and its expression has also been shown in a broad range of common epithelial cancers including breast, cervical, endometrial, prostate, lung, colon, oral/facial tissue and stomach. An association between hCG-β expression, anaplastic and advanced disease has been noted and it can be associated with the aggressive nature of hCG-β positive tumors.

Method of Collection Of Data

Literature was searched for key words "HNSCC, hCG-β, epithelial tumors" to include articles published on various studies conducted on hCG-β in Head and neck carcinomas in different databases such as PubMed, Liliacs, Embase etc. Only original research and case report which studied correlation of hCG-β and HNSCC were included in this study. Review articles and studies with insufficient data were excluded. The search yielded 45 relevant articles that had information on hCG-β in epithelial tumors. Only 8 articles were selected based on our inclusion and exclusion criteria; remaining 37 articles were excluded.

The Biological Action of Hcgβ On Epithelial Tumors

The hCG-β expressing epithelial cancers have a tendency for the tumor to resist radiotherapy and develop metastases. Thus hCG (and by association, hCG-β) expression has largely been regarded solely as a marker of

the presence of pluripotent stem/germ cells. Other studies showed that the increase in the cancer cell population in response to hCG-β was brought about by inhibition of apoptosis rather than by stimulation of cell replication. [16]

Iles RK et al (1990) studied the expression of hCG-β by non trophoblastic non endocrine normal and malignant epithelial cells. A total of 83 established and finite cell lines were examined and assayed using a radioimmunoassay directed against the specific beta-subunit. Immunoreactive hCG was detected in the culture medium of choriocarcinoma (3/3), bladder cancers (7/10), oral and genital squamous cell carcinoma and epidermoid carcinoma (6/12), lung carcinomas (4/5), normal urothelium (6/8) and normal oral mucosa (3/4). Low levels of hCG were also detected in the culture media of one of eight skin keratinocyte cell lines and a control culture of fetal fibroblasts. No hCG was detected in cell lines from testicular germ cell tumors, epithelial ovarian carcinomas, colorectal carcinomas and breast carcinomas. This study suggested that expression of the free beta subunit of hCG is characteristic of some neoplastic and normal epithelial cells from mucosal tissues. The epithelial tumor groups which did not secrete hCG-like material (breast, colorectum and ovary) were generally adenocarcinomas, while the secreting carcinomas (bladder, lung, etc.) had squamous metaplastic histology. [15]

Ectopic hCG-β Expression

It is well established that production of hCG-β is not restricted to trophoblastic tumors alone and this hormone is secreted by several non-trophoblastic neoplasms as reported by a study conducted by Marcillac et al. [17] They found that non-trophoblastic cancers demonstrated elevated levels of serum hCG-β in 30-72 % of tumors of pancreas, 9% of stomach cancers, 11% of tumor of liver and 35-47% of bladder cancers. The study of Marcillac et al [17] on tumors of pancreas and bladder cancer were consistent with studies of Alfthan et al [18] and Iles et al [19] who also demonstrated similar findings in tumors of pancreas and bladder cancer respectively. Yet other studies have demonstrated the prognostic significance of hCG-β in urothelial and ovarian cancers. The hCG-β expression in OSCC patients was also consistent with Crawford et al [20] (who demonstrated similar findings in cervical carcinomas). The studies of Murhekar et al [21], Li et al [22] and Venyo et al [23] demonstrated similar findings in gastric carcinomas, esophageal carcinomas and urothelial carcinomas respectively.

In salivary gland tumor: Salivary gland tumors account for almost 5% of the head and neck malignancies. The study by Meda S et al revealed that 12.5% of both MEC and ACC showed hCG-β immune reactivity in focal areas with moderate intensity and no reactivity in pleomorphic adenoma. The results indicate that hCG-β immunoexpression demonstrates the aggressiveness and possibly a poor prognosis. [24]

In anaplastic thyroid carcinoma (ATC): hCG-β is expressed in a minority of ATCs. In a study by Becker et al only a single case had diffuse immunohistochemical expression. The response it showed to aggressive multimodality therapy and the resulting favorable outcome suggests that hCG-β positive ATC may be a unique tumor subtype, or possibly even a unique entity. [25]

In parathyroid carcinoma (PtCa): Parathyroid carcinoma is a rare presentation of primary hyperparathyroidism. In most patients the disease is benign and asymptomatic. PtCa is still occasionally seen in the more classical form in which severe biochemical and clinical manifestations predominate. [14] In these patients, a high index of suspicion for parathyroid cancer (PtCa) is important, because the best chance for cure is associated with complete resection at the time of initial

surgery. Rubin et al in a study suggested that hCG levels, especially its hyperglycosylated isoform, might add diagnostic and prognostic information in parathyroid carcinoma. [14]

In esophageal SCC: Dao-Ming Li et al showed The positive rate of HCG expression in patients with lymph node metastasis was 85.71% (18/21), higher than that (57.14%, 12/21) in those without lymph node metastasis (P<0.05). Expression of HCG in esophageal squamous cell carcinoma is related to its infiltration and metastasis. [22]

Studies on Expression of hCG-β In Oral Squamous Cell Carcinoma

Scholl et al (1997) reported a 47-year-old white man with a T4N1M0 squamous cell carcinoma of the left maxilla who was treated with a maxillectomy and neck dissection for an N1 positive neck. After completing his planned radiotherapy, he developed distant metastases, which included an axillary node that stained positive for human hCG-β. This case history fits the aggressive nature of beta HCG producing tumors elsewhere in the body. [26]

Hedstrom et al (1999) studied the concentration of free hCG-β subunit in serum as prognostic marker for squamous cell carcinoma of oral cavity and oropharynx. They studied 59 cases of squamous cell carcinoma of oral cavity and oropharynx preoperatively. Elevated preoperative hCG-β levels were observed in 8 patients and these patients showed shorter recurrence free survival than those with normal hCG-β levels. Risk for recurrent disease in patients with preoperatively elevated hCG-β was 3.6 folds more than that of patients with normal hCG-β levels. [4]

Bhalang et al (2000) conducted an immunohistochemical study of the expression of hCG-β in Oral Squamous Cell Carcinomas in comparison with oral fibromas. hCG-β immunoreactivity was identified in 29 of 45 cases of oral squamous cell carcinomas and could not be demonstrated in any of the oral fibromas. hCG-β staining was positive in 5 of 15 cases of well differentiated oral squamous cell carcinomas, in 12 of 15 cases of moderately differentiated oral squamous cell carcinomas and 12 of 15 cases of moderately to poorly differentiated oral squamous cell carcinomas, thus concluding that the presence of hCG-β positive tumor cells appears potentially to reflect a malignant behavior. [3]

Turner et al (2010) presented a case of tongue base SCC with diffuse metastasis showing positive staining for hCG-β. The observed increase in hCG-β positivity in cells with poorly differentiated histopathology suggests that hCG-β secretion may be a marker for tumor aggressiveness. [27]

Conclusion

hCG-β is a marker for many trophoblastic and non-trophoblastic tumors. All reported cases of HCG-secreting SCC of the head and neck have been associated with distant metastasis and poor prognosis. We would therefore advocate further investigation into hCG-β secretion as a possible diagnostic and prognostic tool in this patient population. This review also highlights the possible diagnostic dilemma that may arise in a premenopausal woman with elevated hCG-β levels and underlying non-trophoblastic carcinoma. Thus, hCG-β can be used as a diagnostic and a prognostic marker for epithelial malignancies in HNSCC including Oral squamous cell carcinoma.

S. no.	Name of the Author	Year	Study design	Tissue	Sample size (n=)	Relevance
1.	Scholl et al	1997	Ectopic production of Beta-hCG by a maxillary squamous cell carcinoma.	SCC of left maxilla	1	The first case in the literature of a paraneoplastic syndrome with beta-HCG production in association with squamous cell carcinoma of the maxilla is presented.
2.	Bhalang K et al	1999	Immunohistochemical study of the expression of human chorionic gonadotropin-β in oral squamous cell carcinoma.	Oral squamous cell carcinoma	45	hCG-β immunoreactivity was identified in 29 of 45 OSCC (64%)
3.	Hedstrom J et al	1999	Concentration of free hCG β subunit in serum as a prognostic marker for squamous cell carcinoma of the oral cavity and oropharynx was done by time-resolved immunofluorometric assay (IFMA) and solid phase immunoenzymometric assay.	Squamous cell carcinoma of the oral cavity and oropharynx.	59	Elevated pre- operative hCG-β levels were observed in 8 out of 59 patients (14 %) and elevated SCCAg in 12 (20%) of the patients

4.	Li M et al	2005	Expression of human chorionic gonadotropin, CD44v6 and CD44v4/5 in esophageal squamous cell carcinoma by IHC.	Esophageal SCC	42	HCG, CD44v6 and CD44v4/5 are related with the infiltration and metastasis of esophageal squamous cell carcinoma
5.	Rubin R et al	2008	Human chorionic gonadotropin measurements in parathyroid carcinoma done by serial measurements of urinary and serum hCG.	Parathyroid gland	18	hCG, especially its hyperglycosylated isoform, might add diagnostic and prognostic information in PtCa.
6.	Turner et al	2010	Secretion of hCG-β from squamous cell carcinomas of the head and neck.	SCC of tongue base	1	The observed increase in hCG-β positivity in cells with poorly differentiated histopathology suggests that hCG-β secretion may be a marker for tumor aggressiveness.
7.	Becker et al	2014	Prognostic Significance of b-Human Chorionic Gonadotropin and PAX8 Expression in Anaplastic Thyroid Carcinoma.	Anaplastic thyroid carcinoma	30	hCG-β is expressed in a minority of ATCs (17%)
8.	Meda S et al	2018	Immunohistochemical study of the expression of human chorionic	Mucoepidermoid carcinoma and Adenoid cystic	21	The presence of hCG-β positive tumor cells appears to potentially reflect the aggressive behavior of MEC

			gonadotropin-β in salivary gland tumors.	carcinoma		and ACC.

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