VALUE OF IMMUNOHISTOCHEMICAL EXPRESSION OF P16^{INK4A} IN VARIOUS FORMS OF CERVICAL NEOPLASIA

Essay

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List of Abbreviations

Abb.	Full term
ANOVA	Analysis of variance test
CIN	Cervical intraepithelial neoplasia
DAB	Diaminobenzidine
ECRC	endometrial carcinoma reaching to the cervix
ICSC	invasive cervical squamous cell carcinoma
IECC	invasive endocervical carcinoma
HGSIL	high grade squamous intraepithelial lesions
LGSIL	low grade squamous intraepithelial lesions
PBS	phosphate buffer solution
SIL	Squamous intraepithelial lesion
TBS	Tris buffer saline

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Abstract

Title: Value of immunohistochemical expression of P16 INK4A in various form of cervical neoplasia

Background: Cervical carcinoma represents a major public health problem particularly in developing countries with an age adjusted cancer mortality rate up to 10/10 000. HPV is detected in 99% of cervical tumors.P16 diffuse immunohistochemical expression has been established as a surrogate marker for high risk HPV strains identification. Squamous cell carcinoma accounts for 70-80% of cancer cervix whereas, adenocarcinoma accounts for 10-15%. Cervical intraepithelial neoplasia/ lesions (CIN/CIL) are considered risk factors for cancer cervix. Whilst HGSIL represent an absolute precursor lesion, LSIL only progresses to cancer in 10-15% of cases. The trend of progress to cancer still represents a zone of ambiguity especially among LSIL. Another zone of confusion in diagnosing cervical carcinoma is its putative morphological overlap with endometrial adenocarcinoma, a pitfall that has important management consequences.

Aim: The aim of this study is to evaluate the possible role of immunohistochemical expression of p16INK4A in improving the diagnostic performance of different grades of cervical neoplasia (cervical intraepithelial neoplasia and cervical carcinomas). Further, correlation between p16INK4A expression will be done with the various clincopathologic parameters.

Materials and methods: Immunohistochemical expression of P16INK4A was investigated in 42 cases of cervical neoplasia. These included 7 cases of LGSIL, 4 cases of HGSIL, 17 cases of cervical squamous cell carcinoma, 5 cases of endocervical carcinoma and 9 cases of endometrial carcinoma reaching to the cervix. Semi quantitative assessment using a combined (intensity/percentage) score was interpreted to evaluate expression. Statistical correlation of immunohistochemical results to medical data and microscopic diagnosis was done.

Results: P16INK4A expression showed a highly significant difference between groups as regard overall score with highest score among HGSIL cases (10.5± 3.0) and lowest among Endometrial Carcinoma (3.1 ±3.48),

(P value 0.002) . Also, there was a highly significant difference between groups as regard overall marker result (P value 0.009).Moreover, upon comparing lesions of cervical origin to endometrial carcinomas there was a highly significant difference between the two groups as regard overall score (P value 0.002) and marker result (P value 0.003) with higher score and more positive results among lesions of cervical origin. There was no significant statistical correlation between age or parity of patients and P16INK4A expression.

Conclusion: P16INK4A is a useful conjunction prognostic marker in CIL lesions refining morphological detection of high risk groups. Furthermore, it offers additional diagnostic benefit in verifying cervical origin of adenocarcinoma extending to the endometrium when the clinical/microscopic evaluation is non conclusive.

INTRODUCTION

Cervical cancer has been the main cause for cancer related morbidity and mortality for females worldwide, accounting for 6% of all malignancies in women. About 470,000 new cases are diagnosed annually with nearly 230,000 related deaths **(Parkin et al, 2001)**. It is estimated that it occurs in 0.0015-0.012 % of all pregnancies **(Morimura et al, 2002)**. Moreover 3% of newly diagnosed cervical cancers occurs in pregnant women **(Mcintyre-Seltman and Lesnock, 2008).**

Although several factors that contribute to cancer cervix development have been identified—mainly intrinsic factors (genetic), and extrinsic factors belonging to the Human Papillomavirus (HPV)—genetic factors show great potential for use as susceptibility or prognosis factors **(Torres-Poveda et al, 2016, Audirac-Chalifour et al, 2016).**

Low-grade cervical intraepithelial neoplasia LSIL may progress to high-grade HSIL. However, both mild and moderate cervical dysplasias are more likely to regress than to progress. **Howaty et al, (1999)** estimated the risk of mild dysplasia progressing to cancer as 1% per year, and that of

moderate dysplasia as 16% within 2 years and 25% within 5 years.

Trimble et al (2005) reported that CIN2/3 lesions associated with human papilloma virus HPV16 are significantly less likely to resolve spontaneously than those caused by other types of HPV.

The direct precursor of cervical cancer is represented by Cervical Intraepithelial Neoplasia (CIN) that is usually detected and managed through the Papanicolaou (Pap) test cytological screening and/or high risk Human Papillomavirus DNA testing **(Trimble et al, 2005).**

Etiological role of papilloma viruses in cervical cancer is established while its role in cellular gene alterations along the course of tumor progression is less clear **(Karcheva et al, 2007).** The conceptual advances and development of an effective vaccine in the past twenty-five years have made it possible to envision a long-term reduction in mortality and morbidity for HPV related tumors of the lower female genital tract **(Wigle et al, 2013).**

Tumour suppressor genes code for proteins that restrict the proliferative and survival capacity of a cell. Such genes may be rendered dysfunctional through multiple mechanisms