Braz J Otorhinolaryngol. 2017;xxx(xx):xxx–xxx

Brazilian Journal of
OTORHINOLARYNGOLOGY
www.bjorl.org

ORIGINAL ARTICLE

The analysis of expression of p16 protein in group of 53 patients treated for sinonasal inverted papilloma☆

Roland Zydroń[a,*], Andrzej Marszałek[b,c], Magdalena Bodnar[b,d], Paweł Kosikowski[e], Grażyna Greczka[d], Małgorzata Wierzbicka[d]

[a] Poznan University of Medical Sciences, Department of Otolaryngology and Oncological Laryngology, Poznan, Poland
[b] Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Department of Clinical Pathomorphology, Torun, Poland
[c] Poznan University of Medical Sciences & Greater Poland Cancer, Oncologic Pathology and Prophylaxis, Poznan, Poland
[d] Poznan University of Medical Sciences, Department of Otolaryngology and Oncological Laryngology, Poznan, Poland
[e] Poznan University of Medical Sciences, Department of Clinical Pathomorphology, Poznan, Poland

Received 18 January 2017; accepted 28 March 2017

KEYWORDS
Inverted papilloma;
Sinonasal tumors;
p16;
HPV;
Malignant transformation;
Recurrences

Abstract
Introduction: Sinonasal Inverted Papilloma (IP) constitute relevant therapeutic problem due to destructive character of growth, tendency to recur and the possibility of malignant transformation. Therefore, many attempts to identify risk factors for IP occurrence have been undertaken, as well as research to find markers that would allow for the earlier detection of tumors and the application of adequate therapy. A widely known risk factor of IP is HPV infection. One of the markers of HPV infection and the ongoing effect of this change (although arousing some controversy) is the expression of the p16 protein.
Objective: The aim of the study was to analyze the correlation between the expression of p16 as a surrogate of HPV infection in analyzed histopathological material and epidemiological variables, recurrences or malignant transformation.
Methods: The retrospective study includes a group of 53 patients (18 women and 35 men) undergoing treatment for sinonasal IP in the period of 2002–2012. The intensity of the p16 protein in histopathological material was scored as: 0 – no expression, 1 – diffuse expression (borderline) and 2 – positive expression; or 0 – no expression/diffuse expression (borderline); 1 – positive expression. The Ethics Committee agreement was obtained (1089/12; 245/13).
Results and conclusion: There was no statistically significant relationship between the expression of p16 and the age of patients, cigarette smoking, tumor location, tumor staging

☆ Please cite this article as: Zydroń R, Marszałek A, Bodnar M, Kosikowski P, Greczka G, Wierzbicka M. The analysis of expression of p16 protein in group of 53 patients treated for sinonasal inverted papilloma. Braz J Otorhinolaryngol. 2017. http://dx.doi.org/10.1016/j.bjorl.2017.03.011

Peer Review under the responsibility of Associação Brasileira de Otorrinolaringologia e Cirurgia Cérvico-Facial.

* Corresponding author.
E-mail: rolandpoz@gmail.com (R. Zydroń).

http://dx.doi.org/10.1016/j.bjorl.2017.03.011

according to the Krouse and Cannady classification, the presence of dysplasia or the occurrence of relapse.

PALAVRAS-CHAVE
Papiloma invertido;
Tumores nasosinusais;
p16;
HPV;
Transformação maligna;
Recorrências

Análise da expressão da proteína p16 em um grupo de 53 pacientes tratados para papiloma invertido nasossinusal

Resumen
Introdução: Papiloma Invertido (PI) nasossinusal constitui um problema terapêutico relevante devido ao caráter destrutivo do crescimento, tendência à recorrência e a possibilidade de transformação maligna. Assim, muitas tentativas têm sido realizadas para identificar fatores de risco para ocorrência de PI, bem como pesquisas para encontrar marcadores que permitam a detecção precoce de tumores e a utilização de terapia adequada. Um fator de risco amplamente conhecido de PI é a infecção pelo HPV. Um dos marcadores da infecção por HPV e do efeito contínuo dessa alteração (embora suscitando alguma controvérsia) é a expressão da proteína p16.
Objetivo: O objetivo do estudo foi analisar a correlação entre a expressão de p16 como um substituto da infecção pelo HPV no material histopatológico analisado e as variáveis epidemiológicas, recorrências, ou transformação maligna.
Método: O estudo retrospectivo inclui um grupo de 53 pacientes (18 mulheres e 35 homens) submetidos a tratamento para PI nasossinusal no período de 2002 a 2012. A intensidade da proteína p16 no material histopatológico foi pontuada como: 0 - sem expressão, 1 - expressão difusa (limite) e 2 - expressão positiva; ou 0 - sem expressão/expressão difusa (limite); 1 - expressão positiva. O Comitê de Ética aprovou o estudo (1089/12; 245/13).
Resultados: e conclusão Não houve relação estatisticamente significante entre a expressão de p16 e a idade dos pacientes, tabagismo, localização tumoral, e estadiamento tumoral de acordo com a classificação de Krouse e Cannady, presença de displasia ou ocorrência de recidiva.

Introduction

Sinonasal Inverted Papillomas (IPs) are developed from the ciliated epithelium covering the nasal cavity and paranasal sinuses, called Schneiderian membrane. They constitute 0.4%–4.7% of sinonasal tumors.[1] The Schneiderian membrane is an epithelial lining similar in structure to the respiratory epithelium of the lower respiratory tract, but unlike that tissue, is derived from the ectoderm not the endoderm. Schneiderian epithelium is composed of a single layer of cylindrical ciliated cells, with a small amount of goblet cells. IPs are built with hyperplastic epithelium which grows endophytically into down-lying stroma. The epithelial growths are limited by the basement membrane. The epithelium forming the IP is formed from a few to several layers of cells of the type of squamous, transitional and/or ciliated columnar epithelium. Usually, an admixture of goblet cells is also visible. IP is characterized by a low number of mitoses (mainly located close to the base). Sometimes, superficial keratosis (10%–20% of cases) and intraepithelial dysplasia (5%–10% of cases) is observed.[2]

The most well-known IP risk factor is HPV infection.[3–6] The other considered risk factors for IP development are: inflammatory infiltration,[7] welding fumes and organic solvents.[8]

The maintenance of the transformed phenotype, dependent upon high-risk human papillomavirus (hrHPV) infection, is mainly caused by the expression of two viral oncogenes, E6 and E7. hrHPV E6 protein initiates carcinogenesis by its ability to target p53. The E6/UBE3A (E6-AP) ubiquitin ligase complex targets TP53 for ubiquitylation and proteasomal degradation. Moreover, hrHPV E6 activates telomerase (TERT) to regulate cellular adhesion, and uncontrolled proliferation.[9]

The hrHPV E7 protein initiates carcinogenesis by degradation and inactivation of the retinoblastoma tumor suppressor protein (RB1) by preventing it from binding to the transcription factor E2F, and thereby promoting cell cycle progression.[10] E2F activation by hrHPV E7 is thought to stimulate expression of the tumor suppressor p16 [INK4A]. The p16 [INK4A] tumor suppressor inhibits CDK4/CDK6 activity by recalling the complex formation with D-type cyclins (CCND). CDK4/6 inhibition causes accumulation of hypophosphorylated, active, RB1 tumor suppressor, which triggers G_1 cell cycle arrest by repressor complex formation with E2F/DP transcription factors.[10]