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Case Report Open Access

First Report of Three Major Oncogenic Viruses: Human Papillomavirus, Epstein-Barr Virus And Merkel Cell Polyomavirus in Penile Cancer

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Abstract

We report here in first hand a case of triple infection caused by oncogenic viruses: HPV16, EBV-2 and MCPyV, in a squamous cell carcinoma of penis with an unfavorable outcome. Although reports on multiple viral infections in tumors are increasing, we do not know whether they are simply co-detected in the tissue or playing a synergistic role in the tumorigenesis. Studies addressing a putative co-stimulatory effect among these agents are needed in order to improve our comprehension of cell transformation.

Keywords: Human papillomavirus; Merkel cell polyomavirus; Epstein-Barr virus; Penile cancer

Introduction

The penile carcinoma is a rare, potentially mutilating disease with undefined etiology, derived from the squamous epithelium of the foreskin or the glans of the penis, with increasing incidence worldwide and associated with several risk factors [1,2]. The human papillomavirus (HPV) is the well-known cause of benign lesions as genital warts. HPV high risk subtypes have also been associated with 30 to 90% of penile malignancies, with a higher prevalence of HPV16 and 18 [3-5].

It has been assumed that cofactors, such as infections caused by other DNA virus presenting oncogenic potential may play a role in the progression of penile neoplasia. Of interest, Epstein-Barr virus (EBV) is among the sexually transmitted viruses that might be a cofactor in cancer development [6] and also Merkel cell polyomavirus (MCPyV), the agent of a subset of Merkel cell carcinoma, a rare and aggressive neoplasia, which has been frequently detected in squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Recent studies found HPV-positive SCC cervical cancers and adenocarcinomas to be also positive for MCPyV [7,8]. Nevertheless, the occurrence of MCPyV in other genital cancers is unknown, as well as in co-infection with other viruses. Herein, we report the first detection of HPV, EBV and MCPyV in penile cancer.

Case Report

An 85-years old patient with a penile flat and ulcerative lesion extending along the body of the penis was admitted to the National Institute of Cancer Hospital, Rio de Janeiro, Brazil, in December 2013. He underwent surgical local excision and the histopatological examination revealed a moderately differentiated squamous cell carcinoma (MDSCC) with pT3N3Mx TNM staging. The patient died six months after the surgical procedure.

Viral testing was performed after DNA extraction from the surgical specimen. HPV DNA was detected by using of MY09/11 polymerase chain reaction (PCR) [9]. Type-specific PCR and restriction fragment length polymorphism analysis, showed HPV16 genotype. For the detection and typing of EBV, a nested-PCR was conducted [10], showing EBV-2 genotype. MCPyV molecular detection was performed through nested-PCR using primers for the LT3 region [11]. For analysis confirmation, the 183bp amplicon produced in the nested-PCR was sequenced and revealed 100% homology with MCPyV through a BLAST query.

The methylation pattern of p16 INK4A gene was also investigated through MSP-PCR [12], due to its relation to malignant transformation but no hipermethylation was observed.

Discussion

MCPyV was discovered in 2008 and is the only known polyomavirus etiologically involved in tumorigenesis in humans, therefore leading to several studies on MCPyV in diverse tumoral samples. Particularly, non-melanoma skin cancers have been studied, especially squamous cell carcinoma and basal cell carcinoma. The prevalence of MCPyV in SCC ranges from 13% to 38% [13-15].

Other studies have found both HPV and MCPyV in skin cancers. Falchook and colleagues (2013) [16] reported the presence of HPV-MCPyV in a SCC from a patient with melanoma treated with the BRAF inhibitor dabrafenib. In another study involving SCC, Dworkin and colleagues (2009) [13] demonstrated a higher proportion of HPV DNA among the MCPyV-positive group (87%) in comparison to the MCPyV-negative group (57%), although a clear correlation between these two viruses could not be established. Mittledorf and colleagues (2012) [17] reported HPV6 and MCPyV DNA in a combined MCC-invasive SCC. Furthermore, two recent studies have already demonstrated MCPyV DNA in 19 to 37% cervical carcinomas, and one study reported a combined MCC-SCC involving HPV-MCPyV detection in the vulva [18] suggesting that MCPyV might play a role as cofactor to HPV-related cancers [7,8].

It has been suggested that oncoviruses co-infections in tumors might be genetically predisposed. In addition, HPV and MCPyV may cooperate for the development of nonmelanoma skin cancer [14]. Although both hypothesis are possible, a synergic tumorigenic effect is likely due to similarities in genome organization and protein structures of polyomaviruses and papillomaviruses.

On the other hand, the association between HPV and EBV is well established. EBV has been frequently found in the genital mucosa, urethral discharges and genital ulcers [19,20] and, as the cause of approximately 50% of human penile cancers is still unknown, some studies have proposed the role of EBV as a cofactor in HPV integration and induction of malignant transformation [21,22]. Although epigenetic alterations involving hipermethylation of tumor suppressor genes were proposed as additional co-factors favoring oncogenesis [23], we did not observe an altered pattern on p16 methylation status of the studied sample, suggesting that other oncogenic pathways are involved. No reports addressing MCPyV and EBV co-infections in skin are available.

In conclusion, this is the first report on MCPyV in a MDSCC penile cancer, and the first to detect MCPyV, HPV and EBV in the same lesion. As proposed for other skin regions, MCPyV could eventually be involved in the carcinogenesis, acting along with other known risk factors to initiate and/or continue the complex malignant transformation process. However, as a first description, other studies are necessary to elucidate the role of viral co-infections and if MCPyV plays an important role in penile SCC.

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