




BRIEF REPORT

Virus-Induced Cancers of the Skin and Mucosa: Are We Dealing with “Smoking Guns” or “Smoke and Mirrors” in the Operating Theatre?

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ABSTRACT

Introduction: Human papillomavirus (HPV) alone is thought to cause ~610,000 cases of cancer per year, and is the dominant aetiological agent for ano-genital (esp. cervical) and head and neck cancers (esp. oropharyngeal). Merkel cell polyomavirus (MCV) is a more recently discovered virus which causes Merkel cell carcinoma, a rare but highly aggressive skin malignancy.

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Methods: We explored the available published evidence to see if transmission of live HPV or MCV virus in smoke generated by laser or diathermy was feasible, and would pose an infection risk. Long-term infection with such carcinogenic viruses would then pose an increased risk for the development of virus-induced cancers in medical personnel.

Results: The morphological structures of both HPV and MCV are very similar, and the size, external capsids and genomic structures show striking similarity. Both viruses have a non-enveloped external protein capsid consisting of 72 capsomeres, and a double-stranded DNA core. Sizes of both viruses range from 50 to 60 nm. There are now recent data demonstrating live and infectious HPV in smoke, and that these viruses can be used to infect cells in vitro. Further, anecdotal reports of virus transmission leading to disease causation in the production of respiratory airway viral warts (benign disease), and, finally, reports of HPV-induced oropharyngeal carcinoma (malignant disease) in two gynaecological surgeons as an occupational health hazard have been published recently.

Conclusion: There is now sufficient evidence to support the hypotheses that live infectious carcinogenic viruses can be transmitted via smoke generated from surgical procedures, and, in rare instances, actually cause significant disease. Protective measures such as smoke extraction and airway protection should be instituted for

all healthcare personnel, particularly those with multiple repeated exposures such as gynaecological surgeons.

Keywords: Benign tumours; HPV; Human papillomavirus; Malignant tumours; MCV; Merkel cell polyomavirus; Smoke

INTRODUCTION

Virus-induced cancers of the skin and mucosa are important causes of total cancer in the world. For instance, human papillomavirus (HPV) is thought to account for ~4.8% of total world cancers each year, and these cancers include ano-genital cancers, and head and neck cancers [5]. In 2006, the WHO classified HPV as a Class I carcinogen. This was in recognition of the worldwide importance of HPV in causing several different types of cancers in different anatomical locations and systems. Alpha group HPV (which tend to infect the genital skin and mucosae) are the dominant group of HPV involved in the ano-genital cancers, and head and neck cancer epidemics currently seen worldwide.

Mutations in skin cell DNA due to ionising UV radiation is by far the most important risk factor for development of skin cancers. Other important risk factors for squamous cell carcinoma (SCC) of skin are white skin, increased age, male sex, and decreased immune status [14]. The link between HPV and SCC skin was initially noted in a specific cohort of patients with epidermodysplasia verruciformis (EV). EV is a rare genetic disorder, most commonly autosomal recessive in its Mendelian inheritance, characterised by decreased cell-mediated immunity and infection by beta group HPV which leads to widespread plaques and papillomas/wart-like lesions, and a high risk of SCC of skin. Beta group HPV 5 and 8 are the types most commonly associated with SCC of skin in these patients [8]. The lifetime risk of developing skin SCC in the USA is thought to range from 7% to 11%, and is estimated to be even higher in Australia [3]. Accurate data on the incidence of skin SCC in the UK is not readily available due to inefficiencies in data collection

and the cancer registry system, but is thought to also be increasing [10].

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumour of the skin with highly aggressive behaviour and increasing incidence, and its viral causation has recently been elucidated. MCC has high metastatic potential regardless of the size of the primary tumour and a 5 year disease associated mortality of 46% [12]. MCV was first described in causal association with Merkel cell carcinoma in 2008 by the group led by Patrick Moore at the University of Pittsburgh [4]. Since then, others have confirmed their findings, that infection of susceptible cells in the skin (possibly Merkel cells or dermal stem cells) can lead to viral DNA integration with subsequent clonal replication of infected cells, and this leads to tumour formation.

The annual estimated age standardised incidence rate of MCC in the UK is between 0.1 and 0.2 per 100,000 (1999–2008) and is thought to be increasing [9] (http://www.ncin.org.uk/publications/data_briefings/rareskincancer).

In the East of England, the age standardised incidence rates for MCC in males and females are 0.19 and 0.24 per 100 000 person-years, respectively. The total age standardised incidence rate was 0.21 per 100 000 person-years and represents a threefold increase in this region from 2004 to 2013 [9]. The main risk factors for MCC development are high UV exposure, white race (the significance of melanin protection appears important), elderly age (median age at diagnosis is 76.2 years for women, and 73.6 years for men), and immunosuppression.

The prevalence of MCV in the community is extremely common, with 80% of healthy North American adult (blood donors) found to be seropositive for past MCV exposure [16]. Also consistent with this, MCV was detected in 80% of skin swabs from healthy volunteers, and this suggests that it may be a common inhabitant of human skin microflora [6]. The pathogenesis of MCC is clearly not a simple one. Infection with MCV is clearly not sufficient to cause MCC, as demonstrated by the markedly differing incidence with prevalence rates in the population. Therefore, additional cellular and molecular

events must occur, probably with viral integration into the cellular genome and loss of immunosurveillance before tumour pathogenesis finally occurs. In this regard, MCV encodes a large T tumour antigen (LT) and a small tumour antigen (sT) which play a role in pathogenesis by targeting several tumour suppressor genes [2].

In this article, we have sought to understand if laser or diathermy smoke is able to transmit virus from skin or mucosa to attending medical personnel, and whether virus transmitted in this way is able to infect and cause cancer in the longer term. We directly review the morphological structure of HPV and MCV, and searched for published evidence whether these viruses are able to persist in smoke and remain viable. We then looked for reports of benign and malignant tumours associated with chronic infection with these viruses.

METHODS

We undertook a literature search through PubMed Central using different combinations of the words “HPV, human papillomavirus, Merkel cell polyomavirus, MCV, lasers, laser smoke, diathermy, diathermy smoke, plume(s)”. We have preferentially included publications since 2000 to ensure more up-to-date data unless the article found was highly relevant for smoke or diathermy. Exclusion criteria included non-English and non-German articles. Further cross-referencing from the reference lists of these papers and the end results of the search for laser and diathermy smoke publications involving HPV and MCV are discussed below. This article does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS AND DISCUSSION

Structural Analysis

We have summarised below the useful morphological comparisons between HPV and MCV in Table 1.

Both MCV (family Polyomaviridae) and HPV (family Papillomaviridae) were classified within the family Papovaviridae (now obsolete) because of their structural similarities. Both viruses consist of a double-stranded (ds) DNA core, surrounded by non-enveloped capsid.

The MCV icosahedral capsid is formed of 72 capsomeres, each consisting of 5 VP1 proteins associating with a VP2 and a VP3 protein. The DS-DNS genome is approximately 5.4 kb in length.

The HPV icosahedral capsid is also formed of 72 capsomeres, which consist of 5 L1 proteins encasing an L2 core each. The DS-DNA genome is approximately 8 kb in length.

It is clear that HPV and MCV are structurally very similar. EM images of both viruses are essentially identical.

Aerosolization of Viruses in Laser or Diathermy Smoke

Although published data on MCV in electrocautery or laser smoke are not available, numerous published studies looking at HPV (a virus very similar in structure and size) in exactly this situation, are available. A previous study for HPV DNA detection in electrocautery smoke yielded positive identification of intact HPV virions, and demonstrated infectivity of these virions [15].

Further, there are anecdotal reports of HPV transmission from patient to surgeon via laser smoke. In one case, a surgeon contracted laryngeal papillomatosis after treating anogenital condylomata by ablation with laser [11]. The 44-year-old surgeon stated categorically that there were no other (i.e. sexually transmitted) methods in which he could have contacted HPV types 6 and 11 apart from the operating theatre. In another case (published in German), a 28-year-old gynaecological theatre nurse who assisted in laser ablation of anogenital condylomata developed laryngeal papillomatosis [1]. Her case was thoroughly investigated by a prestigious virology institute in Germany and hers was deemed to be a case of occupational disease.

Table 1 Structural comparisons between human papillomavirus and Merkel cell polyomavirus

Virus	HPV (human papillomavirus)	MCV (human polyomavirus 5)
Family (prev. both in Papovaviridae—obsolete term)	Papillomaviridae	Polyomaviridae
Group	1 (ds-DNA)	1 (ds-DNA)
Genera	Alpha-, Beta-, Gamma-, Mu-, Nu-Papillomaviridae	Polyomaviridae
Size (nanometers)	~ 55–60	~ 50–60
Genome length (kb)	~ 8	~ 5.4
Genome structure	Circular double-stranded DNA	Circular double-stranded DNA
Envelope	No	No
Icosahedral capsid exterior	Yes	Yes
Capsomeres	72	72
Capsomere structure	5L1 with 1L2	5VP1 with 1VP2 and 1VP3

There has also been a study to isolate bovine papillomavirus (BPV) from laser smoke in controlled laboratory conditions, and the authors succeeded in demonstrating infectivity by inoculation of the extracted virions onto bovine skin and mucosa, with subsequent growth of papillomas [7].

Papillomaviridae and Polyomaviridae are structurally very similar and share very similar morphology, and therefore data from one suggest that it could possibly be extrapolated to the other.

Finally, there are now recent anecdotal reports of HPV + oropharyngeal carcinoma occurring in gynaecological surgeons who have performed thousands of cases of laser surgery. These two cases in surgeons appear to confirm that the risk of contracting HPV from laser smoke is a real one, and, what is more concerning, the transmission of high-risk HPV appears to be responsible for these cases of head and neck carcinoma [13]. One of us, (R.A.F.C.), a senior gynaecological surgeon, has been a proponent of smoke extraction for CO₂ lasering of the cervix since the 1990s. Furthermore, the adoption of large loop diathermy excision of

the transformation zone by UK gynaecological oncology centres as the main treatment modality (as part of a single see and treat strategy) for the cervical screening programme has been useful, as it generates much less smoke compared to the CO₂ laser.

Limitations of Study and Learning Points

The available published literature on viruses in smoke is small, and the case reports of virus-associated tumours are few and anecdotal. There is no direct evidence in terms of long-term follow-up studies. However, despite the circumstantial evidence, there is now sufficient evidence to emphasise that all health-care personnel should be taking all available safety precautions in their daily work in seeing and treating patients, as the consequences of developing a malignancy is potentially life-threatening. The learning points are summarised below:

- Human papillomavirus (HPV) and Merkel cell polyomavirus (MCV) are viruses that cause cancers of the skin and mucosae.

- These cancers appear to increasing steadily in frequency across the world.
- Healthcare personnel are exposed to smoke from laser or diathermy plumes when treating patients.
- Viable infectious viruses have been isolated from smoke.
- Case reports of both benign and malignant tumours occurring in healthcare personnel with no other risk factors have now been reported.

CONCLUSIONS

The available evidence appears to suggest that there is a possibility that transmission of viruses such as HPV or MCV from patient to surgeon or other theatre staff is a real risk, particularly for repeated laser operations on high-risk sites such as the anogenital area; therefore, it remains prudent to recommend that all available options, such as efficient smoke extraction systems, respirator filtration masks, surgical face masks with particulate filtration, etc., to minimise or prevent surgeon exposure to laser or diathermy smoke should be utilised. Evidence of the development of subsequent malignancies in these gynaecological surgeons is now available. The multifactorial oncogenesis process which leads to malignancy must be fulfilled for cancer to develop, and this is a reason for positivity, because it ensures that the actual risk of developing cancer is low.

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K.Y. Goon, Holger Sudhoff and Robin A.F. Crawford participated in the discussions around the evidence and helped to draft the manuscript. Eunice K.H. Tan and Nick J. Levell helped conceive the study, and participated in its design and helped to draft the manuscript. All authors read and approved the final manuscript.

Disclosures. Peter . C. Goon, Patrick K Y. Goon, Eunice K H. Tan, Robin A F. Crawford, Nick J. Levell and Holger Sudhoff have nothing to disclose.

Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

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