CASE REPORT 4

Oral multiple virally induced lesions in a child -shall we be concerned?

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Abstract

Human papilloma viruses (HPVs) are a group of DNA viruses from the papilloma virus family. There are more than 200 known genotypes of papilloma virus, out of which 40 types can affect human and are mainly transmitted via direct contact. HPVs can cause a wide range of clinical manifestations that may affect the skin, genital, anal and oral mucosa [(1)].

Introduction

HPVs are a large and diverse group of viruses that are classified based on either their DNA sequence, tissue preference, or their carcinogenic potential. Based on DNA sequence, five major HPV genera can be identified, these include Alpha papillomavirus, Beta papillomavirus, Gamma papilloma virus, Mu papilloma virus and Nu papilloma virus [(2)]. Different genotypes have different life-cycle characteristics and disease associations [(3)]. For example, Alpha group primarily infects mucosal surfaces while cutaneous surfaces can be affected by any other group [(3, 4)]. Due to their association with cervical cancer, there are 12 mucosal HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) that have been classified as carcinogenic to human. HPVs are a group of a double stranded DNA, circular, non-enveloped, icosahedral, measuring approximately 55 nm in diameter viruses. They selectively infect the actively dividing basal epithelial layers, where they alter cellular gene expression and abrogate keratinocytes differentiation to cause thickened disorganised basal cell layer relevant in HPV infections [(5)].

HPV infection is the most common sexually transmitted infection worldwide, with up to 80% of adult population experience HPV anogenital infection during their lifetime [(5-7)]. HPV infection is common in young sexually active individuals, with the majority of subjects (80–90%) clearing the infection over a period of two years without clinical symptoms [(8)]. In healthy individuals, the prevalence of oral infection with any type of HPV has been estimated to be 7.7% (men 9.3%, women 5.5%) with 1.4% prevalence for high risk HPV-16 [(9)]. The incidence was found to be of 4.38 cases per 1000 person-months, and the clearance of the infection has been reported to happen in up to 80% of cases over a period ranging from 3.7 to 20.7 months [(9, 10)]. Over the last 20 years, rates of HPV detection in oropharyngeal cancers have increased over three-folds, and HPV-positive oropharyngeal cancer is projected to become the most common HPV-caused cancer in the United States by 2020 [(11)].

Transmission of HPV is primarily through sexual contact, with the risk of infection directly related to number of sexual partners and early onset of sexual activity. Risk of oropharyngeal HPV infection is also directly related to increased number of lifetime vaginal and oral sex partners, and open-mouthed kissing partners in both men and women [12]. Non-sexual routes of genital HPV infection may happen, such as from a mother to the infant at the time of birth. This vertical pattern of transmission can cause oral HPV in 18% of neonates born to vaginally infected mothers [13]. HPV detection in children may raise suspicions of sexual abuse, however infection can be caused by other non-sexual routes such as autoinoculation from cutaneous lesions, through physical contact with other family members and those in close contact with the child, and possibly indirect transmission via fomites [14]. Moreover HPV subtyping using molecular techniques is insufficient to determine the source of HPV infection and pursue the possibility of sexual abuse [15].

Oral HPV infections

Different HPV genotypes can present in different forms in the oral cavity reflecting the specific genotype of the causative HPV, the mode of transmission, host predisposing factors and host response to the infection.

Benign HPV related infections in the oral cavity comprise *Squamous papilloma (SP), Veruuca Vulgaris (VV), Condyloma Acuminatum (CA), and Multifocal Epithelial Hyperplasia (MEH)* or Heck's disease. These lesions can present as exophytic, papillary, verrucous, or smooth with pink or white keratotic surfaces, single or multiple. The lesions can appear in any part of the oral mucosa, but the tongue, soft palate, and lips are the most frequently affected sites where the low-risk genotypes are identified in the majority of cases [4].

Oral squamous papilloma (SP) appears as exophytic sessile or pedunculated growth with pink papillary surface texture or white keratinised surface, and they are most commonly caused by low risk 6 and 11 genotypes. On the other hand, *Verruca Vulgaris* (VV) is less common in the oral cavity, it appears as a well circumscribed, white, cauliflower-like, exophytic growth with prominent keratosis. It is caused by HPV 2 and 4 subtypes and can clinically mimic other HPV oral infections. Oral VV lesions can also resemble skin lesion and this suggests autoinoculation as a possible pathway of infection [16, 17].

Condyloma Accuminatum (CA) presents mostly in the anogenital area but can also be manifested intraorally. They are considered as sexually transmitted infections caused by HPV 6, 11 genotypes and sometimes may harbour the high-risk genotypes 16 and 18. Oral

condylomas are more common in adolescents and young adults, but they still can happen in any age. They generally affect the tongue and palate and appear as several small or coalesced larger growths, soft and exophytic papules, with keratotic or normal surface texture. The lesions can also affect the lips and be of verrucous appearance [16, 18].

Multifocal epithelial hyperplasia (MEH) is a condition that can generally be differentiated from other HPV lesions based on the characteristic clinical appearance. It affects the buccal and labial mucosae and characteristically appear as multiple papules or papillomas which are slightly raised, sessile and have smooth normal mucosal surface. Lesions may appear as white coalescing large plaques as well [19]. The surface can be corrugated but with no changes to the surrounding mucosa. Lesions typically disappear upon stretching the mucosa and return to their normal appearance when the pressure is released [20], and they are asymptomatic unless traumatised by mastication. The most commonly isolated genotypes are HPV 13,32, but other types such as HPV 55, 1, 6, 11, 16, 18 are also implicated, and it is possible to isolate more than one type from the same patient [21] [22]. MEH is most common in the early childhood and is endemic to the first nation people of North America, Canada, Greenland, and descendant of Khoi-San in South Africa where it can affect up to 36% of population [22]. It is also common in small enclosed communities and in people with crowded living conditions and low socioeconomic statuses [23]. The increased prevalence of MEH in certain ethnic populations suggest a possible underlying genetic predisposition to the condition [24, 25]. In one study, up to 92% of affected individuals reported presence of similar lesions in other relative individuals [20].

Histopathological features are generally shared among different presentations of oral HPV lesions with slight differences, but these are not usually pathognomonic. Histopathologically, lesions appear as polypoid or papillary squamous epithelium with various degrees of para-keratinisation [21] . The epithelium appears acanthotic with widened anastomosing rete ridges that have a classical shape of bronze age battle axe. Koilocytes, cells reflecting the viral cytopathic effect, are characterized by shrunken eccentrically placed nucleus with a vacuolated cytoplasmic halo. Koilocytes are typically seen in the spinous cell layer [20]. In addition to that, mitotic figures may be present and slightly increased in the basal cell layer. The presence of mitosiod bodies is characteristic of MEH and has been found in 100% of cases [21], however their absence in the histopathological exam does not rule out MEH [22].

Case report

A 12-year old boy was referred to the Oral Medicine Clinic of the Royal Dental Hospital of Melbourne in September 2017 by a school outreach dentist for a review of multiple warts on the left buccal mucosa that has persisted for approximately 4 months, which was the period between his two most recent dental visits. Patient was asymptomatic, and he reported being aware of these lesions for a period close to two years with no remarkable changes in the size, shape, colour or anatomical distribution of the lesions. However, the growths had been aesthetically concerning and were often traumatised during mastication. In the medical history, patient reported allergy to Ibuprofen, otherwise no significant medical history or underlying diseases were mentioned. The patient was from a Syrian descent, his father migrated to Australia in 1987 and he has two elder brothers. They live in the metropolitan area and he attends private local school.

Extra-oral examination was within normal limits, there was no regional lymphadenopathy, swelling or asymmetry. There was no evidence of cutaneous pathology and no obvious signs of neglect or poor socioeconomic status and the general personal hygiene was unremarkable. Intra-oral examination was significant for multiple soft sessile papillomatous papules ranging from 3-6 mm in diameter, with normal mucosal color and distribution over the left buccal mucosa anteriorly and left lower labial mucosa *(Fig.1)*. Our differential diagnosis was that of HPV induced lesions, and due to the characteristic multifocal involvement of multiple lesions, MEH was on top of the list of differential diagnosis. Excision of an isolated papule from the left lower labial mucosa was performed on the day to confirm diagnosis. Histopathological exam showed polypoid papillary lesion consisting of fibrovascular core and surrounded by hyperplastic epithelium with occasional koilocytes, and no mitosiod bodies were seen *(Fig.2 &3)*. Due to the non-specificity of the histopathological diagnosis, multiple condyloma acuminate lesions as a possible diagnosis was not ruled out. We subsequently referred the patient for wider excision with oral and maxillofacial team at the Royal Children's Hospital of Melbourne due to the expressed aesthetic concerns on one hand. And on the other hand, the inability to rule out multiple condyloma accuminatum lesions based on histopathological examination alone requested further investigations and viral subtyping. Although we had a very low suspicion of neglect or sexual abuse and regardless of the fact that non-sexual routes of HPV transmission are possible [14, 15] , we referred the patient for further viral genotyping and counselling to be done in the children's hospital with qualified healthcare providers as recommended by The American Academy of Paediatrics [4]. In June 2018, patient underwent

wider local excision under local anaesthesia with the oral maxillofacial team. Unexpectedly, the lesion did not show viral cytopathic features upon histopathological examination. The patient developed some tightness in mouth opening over the 2 months post-surgery, and this was found to be completely resolved 3 months later with no evidence of recurrence of the lesions. Consequently, patient was discharged from the Children's Hospital. Patient was reviewed in our department after 12 months, and there was no relevant oral mucosal pathology. Therefore, he was discharged from the Oral Medicine Department back to his community dental clinic.

Discussion

Reports of MEH first appeared in literature as early as 1881[26]. Since then, there have been multiple case reports describing similar disease processes using different names. In 1965, Archard et al. published 19 cases found in different Indian tribes and they named this disease as *Focal Epithelial Hyperplasia* (FEH) or *Heck's disease* [27]. However, the name *Multifocal Epithelial Hyperplasia* (MEH) has been recently suggested and has been widely used in Latin America [28].

MEH in children could be a distressful condition for both patients and caregivers, partly due to the insufficient knowledge about the disease and its natural history, fear of serious pathology or contagious infection, and when there are multiple large lesions which could interfere with aesthetics and function. The disease is common in certain ethnic groups and in families with low socioeconomic statuses, and up to 100% of patients in studied cohorts reported monthly income of less than $200 USD [20, 29].

The presence of familial cases and the fact that MEH is endemic to certain communities suggest an infective and genetic underlying risk factors of the disease, respectively [20, 22, 26]. In a study by García-Corona et.al, the *HLA-DRB1*0404* allele was found to be significantly associated with HPV 13 infection in 22 Mexican patients with MEH [30].

HPV virus infects epithelial cells exclusively, it gains access to the actively dividing basal epithelial cells through surface micro-abrasion where it attaches to the cell membrane receptors and enters the cytoplasm via endocytosis. The virus travels through the cytoplasm of the infected cell and enters the nucleus via micro pores or after breakdown of the nuclear membrane during mitosis. Soon after that, the virus DNA goes initial replication and amplification keeping low number of virus per infected cell, by this mechanism the virus

succeeds to evade the host immune system and avoids initiating an inflammatory response. Once the infected basal keratinocytes start to divide and differentiate, they carry the viral genomes with them as they move through the upper epithelial layers. Consequently, a massive upregulation of viral gene expression and viral DNA replication, with amplification of the viral copy number to many thousands of copies per cell occurs. Further viral replication and cell cycle disruption leads to the appearance of clinical manifestations [5].

MEH is not known to be a premalignant condition and treatment is not always necessary [29]. There have been reports of spontaneous remission over variable periods of time up to two years [31]. On the other hand, variable treatment options have been suggested, such as cryotherapy, electrosurgery, surgical removal, laser therapy, Imiquimod, retinoic acid , interferon and trichloroacetic acid [22, 29, 32].

Viral genotyping is not always necessary and has not been done in the case presented as it has been decided by the Children's Hospital team that no further management is necessary. Similarly, we did not investigate the condition any further as we had a very low suspicion of sexual abuse initially, and because the presence of sexually transmitted HPV genotypes is not always confirmatory of sexual abuse. Currently, the evidence for HPV genotyping is not strong and it is usually advised against. Firstly, because HPV DNA has been detected in various sites in non-abused children, and secondly, because viral subtype alone cannot determine mode of transmission, and the presence of HPV DNA alone without visible disease or cytological abnormality does not warrant any management [33].

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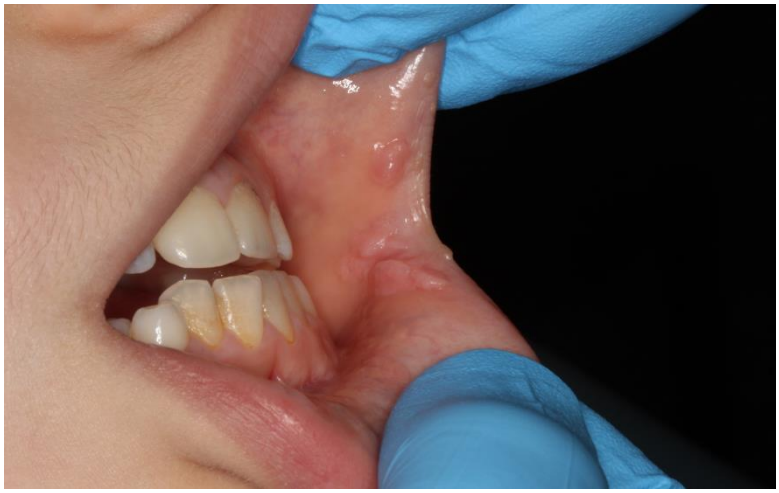
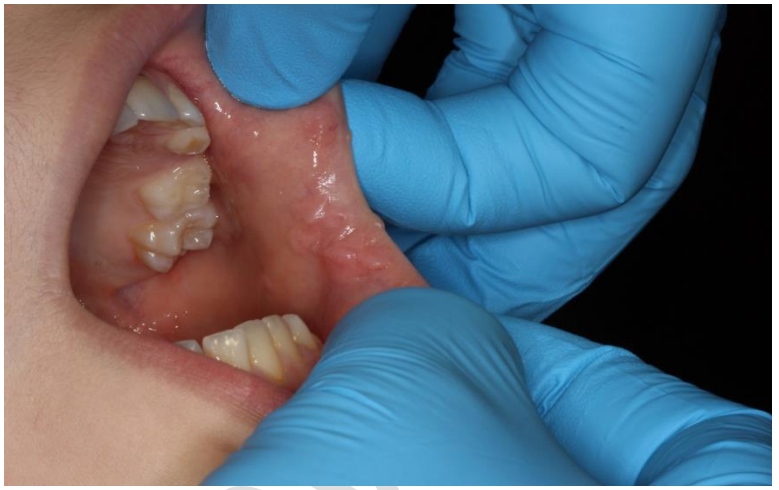
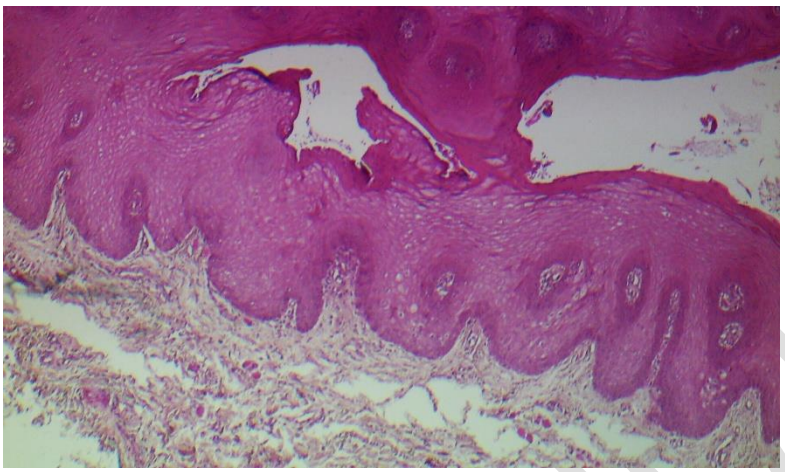
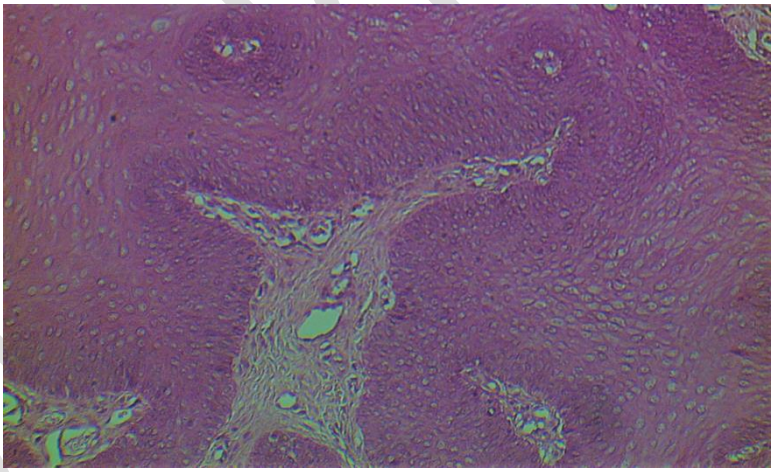
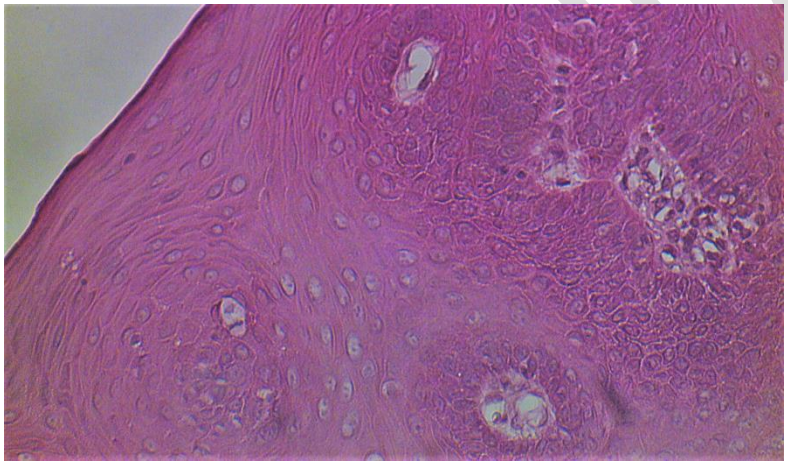



Figure 1. Clinical appearance of multiple papules affecting the left buccal commissure area.

Figures 2 & 3. High power photomicrograph showing the characteristic papillary lesion with parakeratosis, wide rete ridges and fibrovascular cores. Low power showing epithelial hyperplasia and typical Koilocytes. Bottom, histopathology report.

MACROSCOPIC:
Unlabelled as to site. Rubbery, white, sessile tissue with cauliflower-like projections on the surface. 6x3x3mm Resection margin inked. All in. ST 20.11.17

MICROSCOPIC:
The sections show a polypoid and papillary lesion consisting of a fibrovascular branching core covered by hyperplastic squamous epithelium with a papillomatous surface and occasional vaguely koilocytic cells. No mitosoid cells are seen.

CONCLUSION:
Features most consistent with a viral wart

Dr Christopher M Angel 21/11/2017