A Case Report of Focal Epithelial Hyperplasia (Heck's disease) with PCR Detection of Human Papillomavirus

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Abstract Focal epithelial hyperplasia or Heck's disease, is a rare viral infection of the oral mucosa caused by human papillomavirus. The frequency of this disease varies widely from one geographic region to another. In Caucasians there have been only few cases reported. This paper reports a case of focal epithelial hyperplasia and demonstrates the association with HPV subtype 32 through polymerase chain reaction (PCR) and sequencing of PCR products. A 7-year-old Caucasian girl was admitted to our clinic for investigation of multiple oral mucosal lesions in the mouth. Lesion was excised under local anesthesia without any complication. The lesion was diagnosed as focal epithelial hyperplasia according to both clinical and histopathological features. Dental staff should be aware of these kind of lesions and histopathological examination together with a careful clinical observation should be carried out for a definitive diagnosis.

Keywords Focal epithelial hyperplasia · Human papillomavirus · Polymerase chain reaction

Introduction

Focal epithelial hyperplasia (FEH) which is also known as Heck's disease or multifocal papilloma [1, 2], is a rare benign lesion of the oral mucosa produced by the subtypes 13 or 32 of human papillomavirus (HPV) [2–4]. A site-specific predilection for keratinized and non-keratinized surfaces has been observed in these two types of HPV, respectively. Moreover, the subtype 32 of HPV tends to cause the disease in the older age groups while the subtype 13 of HPV seems to be equally involved in the development of the disease in both young and old patients. It was first described in Native Americans in 1965 by Archard et al. [1]. The frequency of this disease varies widely from one geographic region to another. The majority of cases published since 1965 have described this entity in various ethnic groups in Eskimos and North, South and Central American Indians [1, 2, 5, 6]. In Caucasians there have been only few cases reported [2, 6]. The lesion is consistent with the patients' communal way of life [6].

Focal epithelial hyperplasia primarily occurs in children with no gender predilection. This condition is characterized by the occurrence of multiple or unique whitish or normal in color small papules or nodules in oral cavity, especially on labial and buccal mucosa, lower lip and tongue, and less often on the upper lip, gingiva and palate [1].

This paper reports a case of focal epithelial hyperplasia and demonstrates the association with HPV subtype 32 through polymerase chain reaction (PCR) and sequencing of PCR products.

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Case Report

A 7-year-old Caucasian girl was admitted to Oral Diagnosis and Radiology Department, Samsun, Turkey for multiple oral mucosal lesions in the mouth. The patient was otherwise healthy and her physical examination showed no significant abnormality. Intraoral examination revealed multiple or unique soft, sessile papules and nodules involving upper labial mucosa and left buccal mucosa (Figs. 1, 2). The lesions were not ulcerated nor inflamed. The size of the lesions ranged from 2 to 10 mm. The lesions had been present for six months and were asymptomatic. However the lesion on the left cheek had sometimes interfered with mastication.

A general physician was consulted who confirmed routine laboratory parameters as well as immune parameters (B cells, T cells, CD41, CD81 and HLA activated T cells, natural killer cells, IgE, immunoglobulins, skin test for recall antigens) which were within normal values.

Based on her history, we decided to carry out a biopsy in order to discount either a papillomatosis or a verrucal infection of the oral mucosa. To check this further, largest lesion on the buccal and upper labial mucosa were excised under local anesthesia without any complication and submitted for histopathological examination and PCR analysis.

The histopathological study revealed a squamous epithelium with focal parakeratosis, hyperkeratosis, acanthosis, verrucous proliferation and marked papillomatosis (Fig. 3), hyperplasia of basal cells, and isolated perinuclear cellular vacuolization (koilocytosis), cellular binucleation and nuclear irregularities. The presence of epithelial dysplasia was not detected. There were well isolated mitosoid cells. (Fig. 4).

Fig. 2 Labial mucosa of the patient shows slightly elevated papulonodular lesion

Fig. 3 Squamous epithelium with parakeratosis, acanthosis and marked papillomatosis ($\times 100$)

Fig. 1 Clinical photograph to show the multiple lesions of focal epithelial hyperplasia on the left buccal mucosa of the 7-year-old girl patient

Fig. 4 Typical nuclear changes produced by human papillomavirus in focal epithelial hyperplasia (mitosoid bodies) are seen in this microscopic field ($\times 400$)

Human papillomavirus subtype 32 DNA was clearly detected in biopsy material by using polymerase chain reaction (PCR). HPV-PCR and subsequent sequencing was performed for the detection and typing of HPV-DNA. The β -globin gene was used as an internal control for PCR amplification with the RS40/RS42 primer pair resulting in a 188-bp amplicon. All samples were subjected to GP-PCR with the HPV-consensus CPIIG/CPI primer pair to amplify a 188-bp fragment in the highly conserved E1 ORF region, 13 the MY09/MY11 primer pair to amplify a 450-bp fragment in the L1 open reading frame, and the GP5/6 primer pair to amplify a 152-bp fragment in the L1 open reading frame. To determine the HPV subtype, PCR products were subjected to direct sequence analysis. Briefly, after purification of the PCR products using a Microspin G50-column (Amersham Pharmacia Biotech, Treiburg, Germany), the products were sequenced directly with the Big Dye Terminator kit (Applied Biosystems) using the PCR primers and a ABI Prism 377 automated sequencer. For nucleotide sequence analysis and comparisons, the programs Seqed, Fasta, and MAP of the Wisconsin Genetics Computer Group (version 9.1) sequence analysis software package were used. All available sequences of HPV types were retrieved from GenBank and complemented with sequences stored in a local HPV nucleotide sequence database.

The clinical and histopathological features, and the molecular detection of HPV subtype 32 were typical of FEH. Considering the diagnosis and the benign nature of the disease no treatment was attempted and this was explained to the patient. The patient was followed for 18 months, during which no clinical alteration occurred at the excised sites.

Discussion

FEH is a rare but potentially serious disease of the mucosa. In 1965, Archard et al. [1], described Inuit and Indian children from North and South America suffering from verruciform papules and nodules on the oral mucosa, sometimes also affecting the anal and/or genital mucosa. Today it is known to exist in numerous populations and ethnic groups such as Eskimos, North, South, and Central American Indians [1, 2, 5, 6]. Although people of other races may be affected, there are relatively few reports of Caucasians with FEH [2, 6]. A comprehensive study was conducted in Sweden [5] and a total of 17 cases (0.11% of the population) were found, with uncertain geographical or familial distribution. A series of 17 cases in Norwegian Caucasians had also been described [3].

FEH is clinically characterized by multiple circumscribed, sessile, soft elevated nodules of the oral mucosa

which sometimes form clusters. They are reddish or whitish or like the adjoining oral mucosa [1]. In our case the clinical manifestations were similar to those usually reported. The condition usually occurs in children and has familial predilection, may last for several months, or years, before running its course [1]. There is not a certain explanation for this feature but some authors proposed that the less developed immunologic system in children can be related with the beginning of the disease and later, developing of immunity is responsible for vanishing of the lesions. This may explain why no lesions are found in adults.

Setting the diagnosis of FEH is extremely important because of the need for the differential diagnosis with other conditions, namely inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, verruciform xanthoma, verrucous carcinoma, Cowden's disease, condyloma acuminatum, and focal dermal hypoplasia syndrome (Goltz–Gorlin syndrome) [2]. The diagnosis of FEH can be made on the basis of clinical observations, but histological examination may show characteristics of viral infection, as reported here. Microscopically epithelial hyperplasia in FEH presents as an abrupt and considerable focal acanthosis. Koilocyte changes and mitosoid bodies are present in the superficial keratinocytes. Histopathologically, FEH was differentiated from papilloma and viral warts by its lack of pronounced surface projections and presence of mitosoid bodies [4].

PCR is a rapid, sensitive and useful tool to identify the viral etiology of FEH lesions [7]. An additional advantage of PCR using consensus primers to HPV detection is the range of viral diversity that can be identified. Once the presence of HPV was detected in the case presented in this paper, sequencing of PCR products was important to establish which viral type was actually the etiologic agent of FEH (in this case, HPV subtype 32).

FEH is described in the literature as a benign condition that heals spontaneously and therefore requires no treatment, except in some cases of functional (e.g., lesions that are constantly traumatized on biting) or aesthetic impairment [8]. Several treatment modalities have been proposed for FEH like cryotherapy, electrocoagulation, treatment with carbon dioxide laser or systemic treatment with interferon- α or topical treatment of interferon- β and retinoic acid [9]. In the case presented, the lesion on the left buccal mucosa was traumatized on biting and excised under local anaesthesia to arrive at a definitive diagnosis. Recurrence and the site of new lesions are unpredictable, and continued review of the patient is often necessary. The patient described here has been followed for 18 months without recurrences or changes in the aspect of the remaining lesions.

Hyperplasias are often mistaken in clinical experiences. There are many underlying factors for FEH such as genetic

predisposition and a viral factor may be pointed out. Recent reports have indicated the presence of FEH in HIV infected patients. Suppression of the immune system leaves the patient vulnerable to opportunistic infections, including HPV infections [9]. The early detection of associated oral disease should, in many cases result in earlier diagnosis of HIV infection. Although many immunocompromised patients do develop many HPV lesions, some of which are caused by HPV subtypes with so called high-risk for malignancy (such as 18, 31, 33, 35 and 51). Recent research has shown no malignant potential for HPV 13 and 32 subtypes [10].

There are many underlying factors for FEH such as genetic predisposition and a viral factor may be pointed out. The early detection of associated oral disease should, in many cases result in earlier diagnosis of HIV infection. Dental staff should be aware of these kind of lesions and histopathological examination together with a careful clinical observation should be carried out for a definitive diagnosis.

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