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Case Report

Extensive Focal Epithelial Hyperplasia

Maryam Alsadat Hashemipour DDS MSc•*, Ali Shoryabi DDS MSc*,
Shahrzad Adhami DDS MSc**, Hoda Mehrabizadeh Honarmand***

Heck's disease or focal epithelial hyperplasia is a benign contagious disease caused by human papillomavirus types 13 or 32. It occurs with low frequency in the Iranian population. This condition is characterized by the occurrence of multiple, small papules or nodules in the oral cavity, especially on the labial and buccal mucosa and tongue. In some populations, up to 39% of children are affected. Conservative surgical excision of lesions may be performed for diagnostic or aesthetic purposes. The risk of recurrence after this therapy is minimal, and there seems to be no malignant transformation potential. In the present work, we presented the clinical case of a 12-year-old Iranian girl with oral lesions that clinically and histologically correspond to Heck's disease.

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Keywords: Focal epithelial hyperplasia • Heck's disease • Papillomavirus

Introduction

Heck's disease or focal epithelial hyperplasia (FEH) is a relatively rare condition that is seen predominantly in children. It is more common in Native Americans and certain other ethnic groups than in those of western European origin.[1–6] The condition is noted to produce multiple, relatively small, raised plaques or papules on the mucosal surface of lips, buccal mucosa, tongue, and other sites. Lesions may be the color of surrounding mucosa or whiter. The lesions are asymptomatic and can be found by routine examination.[5–9] The frequency of this disease is variable with a wide range from 0.002 to 35% depending on the population studied and geographic region.[4,10] The condition seems to remit spontaneously in most cases.[6,11] Biopsy reveals epithelial hyperplasia acanthoses, bullous extension of rete ridges and focal or diffuse ballooning degeneration of spinous layer. Virus-like particles have been observed in lesional keratinocytes, and viral antigens have been detected by immunohistochemistry.[5,6] The etiologic agent of Heck's disease was first characterized in 1983 and was designated as HPV 13, which has a relation with HPV6 and HPV11.[12] Later, another type of HPV was isolated from this disease and referred to as HPV 32.[13–15] No treatment is required, but lesions may be conservatively excised or treated with laser or cryotherapy if necessary.[15–17] This paper reports the case of an Iranian girl with FEH and demonstrates the association with HPV 13 through polymerase chain reaction (PCR).

Case Report

A 12-year-old girl attended the Oral Medicine Department of Kerman Dental School with a "feeling of lumps throughout the mouth and throat." Her mother reported that the lesions, which were painless to palpation, appeared spontaneously about 8 years ago. The patient had taken several drugs, with no success. The results of serological tests performed on this patient were unremarkable. Oral examination revealed multiple

Authors' affiliations: *Member of Kerman Oral and Dental Disease Research Center, Department of Oral Medicine, Kerman University of Medical Sciences, **Department of Pathology Dentistry Faculty, ***Dental Student, Kerman University of Medical Sciences, Kerman, Iran.

•**Corresponding author and reprints:** Maryam Alsadat Hashemipour DDS MSc, Oral Disease and Dental Research Center, Department of Oral Medicine, Faulty of Dentistry, Kerman University of Medical Sciences, Shafa Street, Kerman, Iran.
Tel: +98-341-223-1196
E-mail: m_s_hashemipour@yahoo.com
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lesions with a wide range of size (5 to 10 mm). These lesions were found on the retrocommisural area, mucosa of the lower lip and buccal mucosa. The color of these lesions was the same as mucosa, with no inflammatory appearance (Figure 1). The surface of these lesions was soft with firm consistency and pediculated. The clinical diagnosis was FEH, and incisional biopsy was performed on the cheek and lip mucosa. Histopathological study revealed a squamous epithelium with prominent acanthosis and broad elongated rete ridges (Figure 2). Epithelial dysplasia was not detected, but there were very isolated mitosoid cells (Figure 3). Due to esthetic problem and also lesion biting, these lesions were removed under local anesthesia with a CO_2 laser set operated at 5 – 7 Watt during a continuous mode. The procedure was carried out with no bleeding, sutures or dressing. After two weeks, all lesions healed with no scarring. There have been no recurrences after 12 months (Figure 4).

PCR analysis and DNA sequencing

DNA was extracted from 5 µM paraffin sections. Sections were deparaffinized and placed in 200 µL of digestion buffer (50 mM Tris, pH 8.5, 1 Mm EDTA, 0.5% Tween 20) containing 200 µg/mL proteinase K and incubated overnight at 37°C.[18] The lysate was extracted twice with phenol:chloroform (1:1), and precipitated by ethanol. DNA was dissolved in 100 µL TE buffer. The extracted DNA was stored at 4°C until analysis. DNA quality was evaluated in all specimens by PCR using primers PCO3/PCO4 (PCO3: 5′ ACA CAA CTG TGT TCA CTA GC /PCO4: 5′ CAA CTT CAT CCA CGT TCA CC), that amplified a 110 base pair product from the human M-globin gene. HPV consensus primers, MY09 and MY11 which cover a broad spectrum of HPV types, were used in the PCR assay to amplify an approximately 450 bp fragment.[19] The sequences of the primers were MY09: 5' CGT CCM ARR GGA WAC TGA TC 3' and MY11: 5' GCM CAG GGW CAT AAY AAT GG 3'. PCR amplification was carried out in a DNA thermal cycler and involved an initial denaturation, followed by 38 cycles at 95°C for 60 second (sec), 55°C for 60 sec, and 72°C for 120 sec with an additional final cycle at 95°C for 60 sec, 55°C for 60 sec, and 72°C for 5 min. PCR experiment was run in parallel with a negative control and a DNA sample known to be positive for HPV. Extracted DNA from the HeLa cell line was used as HPV positive control. No DNA was added for negative controls. Material of the positive HPV sample was used for determination of HPV type 13 using the PCR method. The product was analyzed in 1.5% agarose gel electrophoresis. The fragment of 450bp corresponded to the amplification of L1 region of the HPV viral capsid with consensus primers MY09 and MY11. Analysis by PCR detected HPV13 (Figure 5).

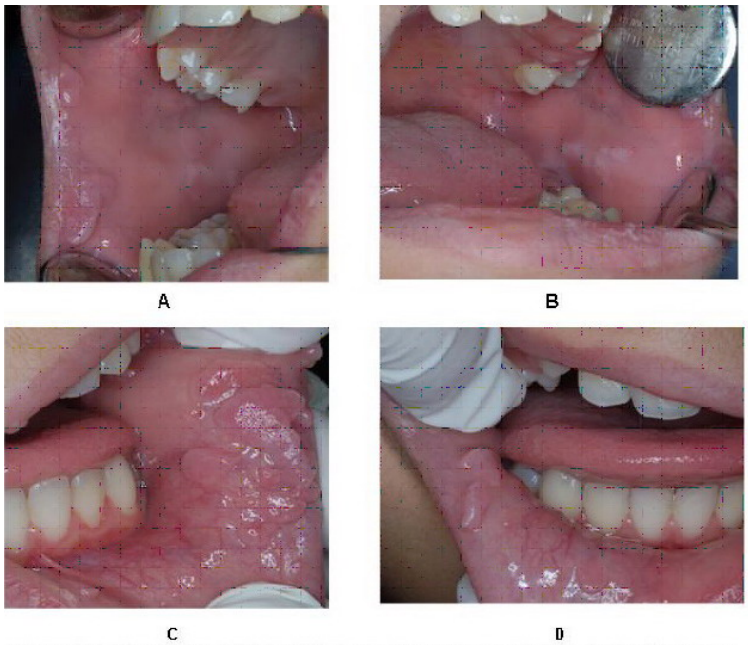

Figure 1. Clinical appearance of the lesion: **A)** Elevated, well-defined lesions in commissure, **B)** Multiple lesions in buccal mucosa, **C & D)** Multiple pink papules in lower lip

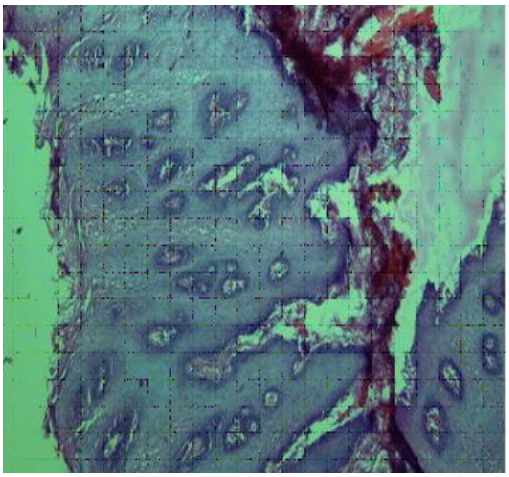

Figure 2. Prominent acanthosis of the epithelium with broad and elongated rete ridges ×100

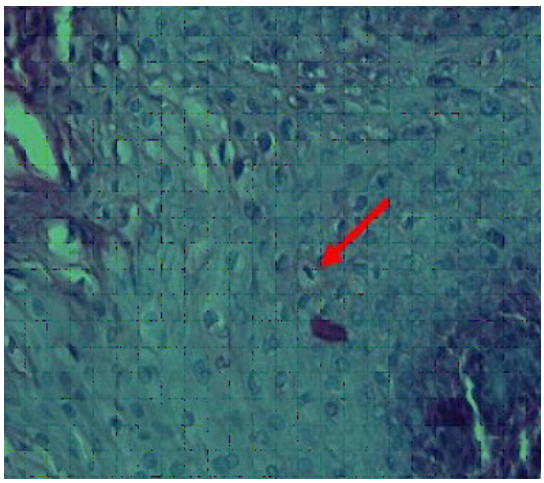

Figure 3. Mitosoid cell ×400

Discussion

Focal epithelial hyperplasia is a rare virus-induced and localized proliferation of oral squamous epithelial that was first described in Native Americans and Inuit's (Eskimos).[3–5,11] Currently, it is known to exist in many populations and ethic groups and is apparently produced by HPV type 13 and possibly type 32.[5,20,21] In many studies it has been shown that malnutrition, poor hygiene, and social conditions have also been associated with this disease. FEH has a wide range of frequency from one geographic region to another (from 0.002 to 35%).[4] In Iran, this disease seems to be rare. A literature survey by the authors show that there are only two studies of Heck's disease by Iranian investigators.[22,23] In the study by Moussavi, two cases of FEH were reported. The patients were both white females. Multiple nodular lesions were seen on the upper and lower labial and buccal mucosa. No further treatment was undertaken for the lesions.[22] FEH was also reported by Namazi in 2007.[23]

This disease occasionally affects young and middle-aged adults. Multiple papillary lesions similar to focal epithelial hyperplasia arise with increased frequency in AIDS patients.[5,8]

Sites of involvement in the oral cavity include the labial, buccal, and lingual mucosa. Gingival and tonsillar lesions have also been reported. Clinically, this disease appears as multiple soft, nontender, flattened or rounded papules, which are usually clustered and the same color as normal mucosa, although they may be scattered and pale. Rarely, occasional lesions show a slight papillary surface change. Individual lesions are small (3 to 10 mm), discrete and well demarcated, but they frequently may be clustered so closely together that the entire area takes on a cobblestone or fissured appearance.[5–9]

The histological hallmark of focal epithelial hyperplasia is an abrupt with considerable acanthosis of the oral epithelium. Others occasionally demonstrate an altered nucleus that resembles a mitotic figure (mitosoid cell). Virus-like particles have been noted ultrastructurally within both the cytoplasm and the nuclei of cells, in the prickle cell layer. The presence of HPV has

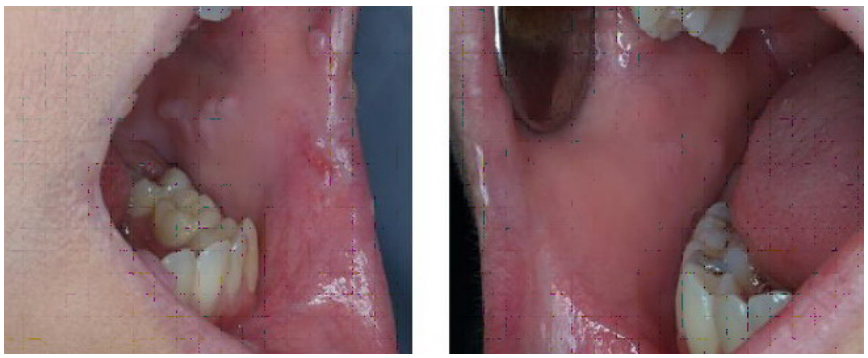

Figure 4. Clinical appearance of the lesion after Co_2 laser therapy

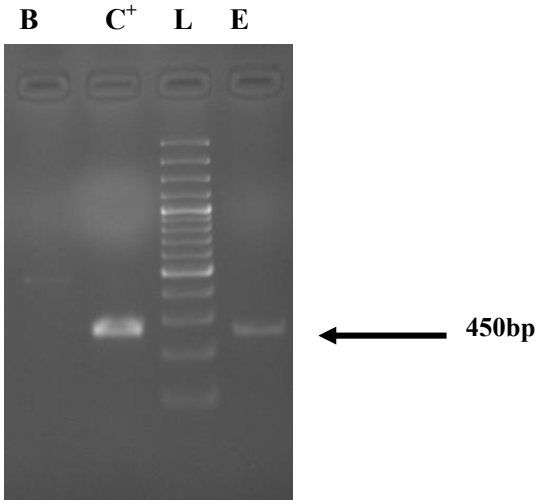

Figure 5. Agarose gel electrophoresis of PCR product obtained from biopsy of oral mucosa lesions. The fragment of 450bp corresponds to the amplification of L1 region of HPV viral capsid with consensus primers MY09 and MY11. L=ladder; C^+=positive control; B=negative control; E=sample

been demonstrated with both DNA in situ hybridization and immunohistochemical analysis.[5–7]

The diagnosing Heck's disease is very important because many differential diagnosis such as: inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, verruciforme xanthoma, verrucous carcinoma, Cowden's disease, condyloma acuminatum, and Goltz-Gorlin syndrome are needed.[8] The first three lesions mentioned above are reactive lesions and an irritating agent can be identified in most cases. Verrucous carcinoma may occur in different age groups, along with epidemiological features which are typically found in oral carcinomas. Cowden's disease, which is characteristic of an older age group, causes fibroepithelial polyps. These polyps are less mobile and more consistent and have different intra-oral topographies. A differential diagnosis with condyloma acuminatum is needed and important because the clinical appearance of isolated lesions in both diseases are similar, as they are both caused by HPV. FEH lesions tend to be flatter and more numerous. In addition, the location of FEH lesions which are mostly limited to the lip, tongue and buccal mucosa is very specific.[15]

PCR is a useful tool to identify the viral etiology of FEH lesions because it is a rapid and sensitive method.[7] The presence of HPV detected in the case presented in this paper and HPV-13 were found by PCR. Thus, the differential diagnosis of condyloma acuminatum is rejected.[11]

Heck's disease tends to regress spontaneously although it can persist for many years, with cases having been described in the elderly.[10,11] Surgical treatment is necessary only in the case of lip involvement by aesthetic problems or lesions that are constantly traumatized by biting.[15,16] Many methods of treatment have been proposed for FEH: scalpel surgery, cryotherapy, laser ablation, electrocoagulation, and topical treatments with retinoic acids or interferon.[15,17] Between different therapeutic procedures that have been reported, CO_2 laser surgery seems to be one of the best. Advantages of this method are its haemostatic effect, healing without scarring, lesser risks of bleeding and infection and patient compliance. Our patient has been followed for 12 months without recurrence.[24] We believe that our patient had FEH, based on age at onset, absence of sexual contact, clinical and histological symptoms consistent with the condition and detection of serotype 13 as shown in the PCR study. Based on the data, the patient was diagnosed with FEH. These patients must be followed up for investigation of treatment success.[15] In present report, the patient's lesions were removed by laser therapy and the patient was under follow-up for 12 months, after which a new lesion was not seen. It is not known whether recurrence of the lesions is related to latent infection, changes in immune response or new infection.[24]

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