

Focal Epithelial Hyperplasia—Presentation, Diagnosis, and Management

a report by

Tommaso Lombardi, MD and Med Dent, PhD

Laboratory of Oral and Maxillofacial Pathology, Division of Stomatology and Oral Surgery, School of Dental Medicine, Faculty of Medicine, Geneva

Focal epithelial hyperplasia (FEH) (see *Figure 1*), also known as Heck's disease, was described in 1965 by Archard et al.¹ and Witkop and Niswander² in patients from North American and South American Indian populations. However, the disease had apparently already been recognized in Caramanta and Katio Indians from Colombia, in Venezuelan Indian children, and in Guatemalan Indians.³ This condition is often designated in Latin America as multifocal papillomavirus epithelial hyperplasia or multifocal epithelial hyperplasia, which are considered to be more accurate terms.^{3,4} Cases have also been reported to occur worldwide, including in Caucasians.

FEH is a benign, localized oral squamous epithelium proliferation induced by human papillomaviruses (HPV), most commonly by the HPV 13 or HPV 32 subtypes.⁵ A communal lifestyle with characteristic sharing of food and personal objects, poor hygiene, and extreme poverty have been associated with this disease. Genetic predisposition seems to be important, and the HLADR4 (DRB1*0404) allele in particular is thought to play a major role in vulnerability to HPV 13 or 32 viruses.⁶

An association between FEH and immunodeficiency has been reported to exist. In one case, FEH developed after immunosuppressive treatment.⁷ FEH has also been described in two siblings with leukocyte adhesion deficiency.⁸ There are some reports of FEH in association with HIV infection.⁹⁻¹¹

Usually, FEH is a condition that affects children and, occasionally, young and middle-aged adults with frequent manifestation in the same family. The incidence of the disease varies according to the different studies, but it has been found to occur in about 35% of individuals in some tribes.¹² Some authors found a male predilection,⁶ while others have reported that the disease is more frequent in females.³

Clinical Features

Typically, FEH presents as asymptomatic, multiple, well-demarcated, round or ovoid flat papular lesions ranging in size from a few millimeters up to 1cm. They are usually sessile, rarely pedunculated, soft or firm in consistency with a smooth or papillary surface. They usually have the color of the surrounding normal mucosa and may disappear when stretched. Occasionally, the lesion may appear pale or even white. Typically, these lesions are clustered with a tendency to confluence, presenting sometimes with a cobblestone or fissured aspect, or they may be scattered over the oral mucosa. The most frequently affected anatomical sites are, in order of frequency, lower lip, buccal mucosa, labial commissures, upper lip, tongue, gingivae, alveolar mucosa, palate, anterior faucial pillars, and posterior pharyngeal wall.¹³

FEH must be clinically differentiated from mainly verruca vulgaris and condyloma acuminatum. Usually, these two diseases occur as solitary lesions or are few in number compared with FEH, and arise in a completely different clinical setting. It may be difficult to distinguish between these lesions on the basis of histopathology alone. However, the demonstration of specific subtypes of HPV virus (i.e. 13 and 32) allows a definitive diagnosis. Other lesions that could be considered in some cases are Cowden's disease (multiple hamartoma syndrome) and Crohn's disease, but the histological aspect of the lesions and the clinical setting usually allow such diseases to be ruled out. Other common conditions affecting the oral mucosa such as squamous papilloma and fibroepithelial hyperplasia may infrequently show clinical manifestations similar to those of FEH. Generally, however, these show no evidence of koilocytic nuclear or cytoplasmic changes, and a search for HPV DNA sequences will be negative.

Other lesions may also be included in the differential diagnosis, but these occur in a different age group, with epidemiological features and histopathological patterns diverse to FEH.

Histopathological Features

A biopsy of representative lesions is recommended to confirm the clinical diagnosis. FEH shows a spectrum of pathological changes. Distinct features include an epithelial hyperplasia of varying degrees, resulting in the elongation of the rete ridges and acanthosis (see *Figure 2*). The rete ridges are at same depth as the adjacent normal rete ridges. This phenomenon results from the upward but not the downward mucosal extension. There is often clubbing and anastomosis of rete ridges. The surface is covered by a layer of parakeratosis, and some superficial epithelial cells show marked vacuolization or koilocytosis similar to that found in other HPV-induced lesions (see *Figure 3*). Occasionally, keratinocytes show an abnormal nucleus with coarse clumped heterochromatin resembling a mitotic figure (see *Figures 4 and 5*). These cells are called mitosoid cells, mitosoid bodies, or mitosoid figures. Other findings occasionally include binucleated cells and an increased number of mitoses.



Tommaso Lombardi, MD, is Head of the Laboratory of Oral and Maxillofacial Pathology in the Division of Stomatology and Oral Surgery at the Faculty of Medicine in Geneva. He has published many scientific and clinical articles in peer-reviewed journals, and has presented many continuing education courses nationally and internationally. His main interests lie in oral mucosal diseases. Dr Lombardi received a Privat Docent from the University of Geneva, Switzerland.

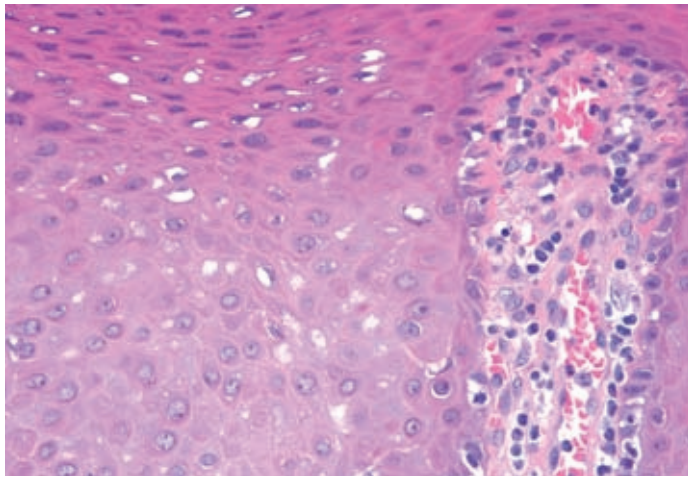
E: Tommaso.Lombardi@medecine.unige.ch

Figure 1: Clinical Appearance of Focal Epthelial Hyperplasia Lesions



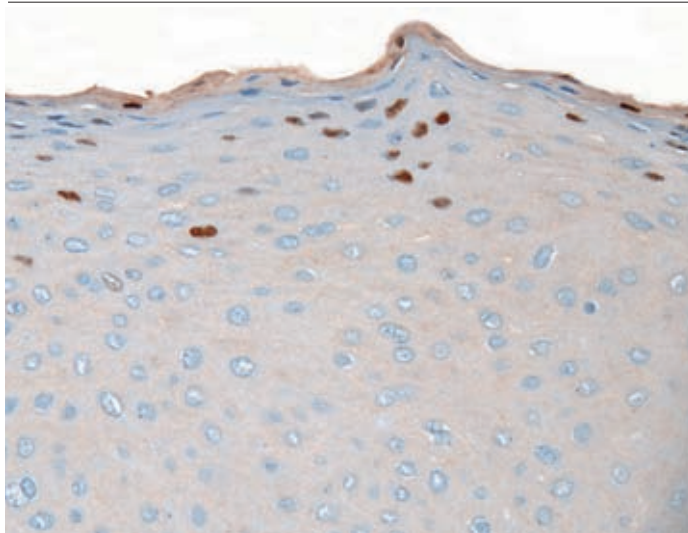
Picture courtesy of Professor J Samson.

Figure 3: Koilocytic Cells in the Upper Epithelial Layer



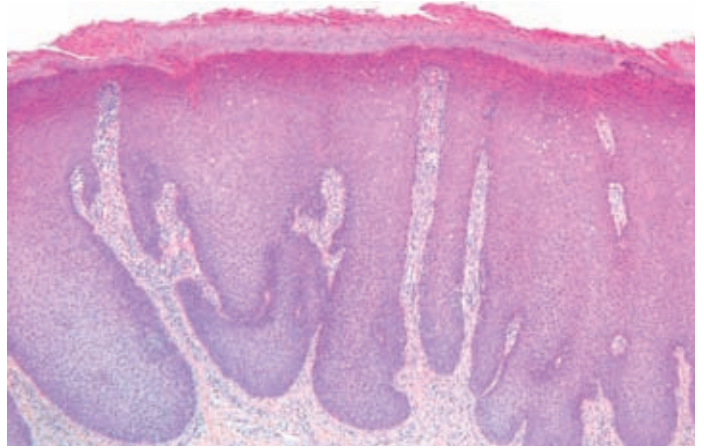
Hemalun eosin safran = x40.

Figure 5: Keratinocytes Immunolabeled by an Anti-human Papillomavirus Antibody



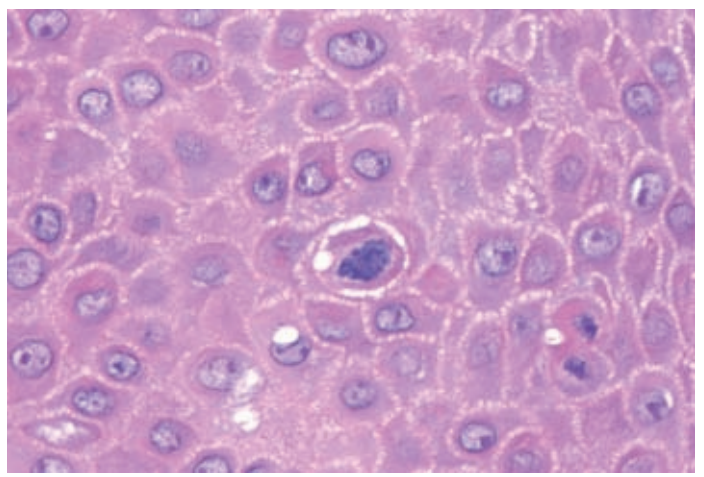
Hemalun eosin safran = x40.

Figure 2: Microphotograph Showing Hyperplasia, Acanthosis, and Clubbing of the Rete Ridges of the Oral Epithelium



Hemalun eosin safran = x8.

Figure 4: Mitosoid Cell



Hemalun eosin safran = x40.

Early works have shown papillomavirus particles within the cytoplasm and the nuclei of the affected cells. DNA *in situ* hybridization and immunohistochemistry techniques have further demonstrated the presence of HPV. Polymerase chain reaction (PCR) and DNA sequencing enable a confirmation of the histopathological diagnosis in doubtful cases and the identification of the HPV subtype responsible for the lesion.

Treatment

Treatment of FEH is not always required because in most cases lesions resolve spontaneously. Some cases may persist for several years, but, although worrisome for the patient, the lesions do not become malignant. In the presence of functional (e.g. lesions that are constantly traumatized on biting) or aesthetic impairment (lesions visible because they are located on the lip), treatment may be necessary. Several treatment modalities have been proposed for FEH, such as scalpel surgery, cryotherapy, laser ablation, cauterization for localized lesions,^{14,15} and interferon- $\alpha 2$ for extensive lesions.¹⁶ Topical treatments such as interferon- $\beta^{17,18}$ and imiquimod¹⁹ have also been proposed and these should be preferred, especially in non-compliant children. Follow-up of the patients is important for the evaluation of treatment outcomes because recurrences are not infrequent.

Conclusion

FEH is an uncommon condition in European countries, but should be included in the differential diagnosis of multiple papular and/or nodular lesions, particularly for those thought to be induced by HPV because of increasing immigration from high-FEH-prevalent countries. Its

course is benign and the condition is associated with serotypes of HPV with no carcinogenic risk. The differential diagnosis should include condylomas, particularly in children, in order to avoid wrong sexual- or abuse-related implications. Adult cases may be associated with HIV infection. ■

1. Archard HO, Heck JW, Stanley HR, Focal epithelial hyperplasia: an unusual oral mucosal lesion found in Indian children, *Oral Surg*, 1965;20:201–12.
2. Witkop CJ, Niswander JD, Focal epithelial hyperplasia in Central and South American Indians and Latinos, *Oral Surg Oral Med Oral Pathol*, 1965;20:213–17.
3. Ledesma-Montes C, Garcés-Ortiz M, Hernández-Guerrero JC, Clinicopathological and immunocytochemical study of multifocal epithelial hyperplasia, *J Oral Maxillofac Surg*, 2007;65:2211–17.
4. Carlos BR, Sedano HE, Multifocal papilloma virus epithelial hyperplasia, *Oral Surg Oral Med Oral Pathol*, 1994;77:631–5.
5. Syrjänen S, Human papillomavirus infections and oral tumors, *Med Microbiol Immunol*, 2003;192:123–8.
6. García-Corona C, Vega-Memije E, Mosqueda-Taylor A, et al., Association of HLA-DR4 (DRB1*0404) with human papilloma virus infection in patients with focal epithelial hyperplasia, *Arch Dermatol*, 2004;140:1227–31.
7. Tan KN, Medak H, Cohen L, Burlahou P, Focal epithelial hyperplasia in a Mexican Indian, *Arch Dermatol*, 1969;100:474–7.
8. Mealey BL, Hallmon WW, Waldrop TC, Occurrence and resolution of focal epithelial hyperplasia in two siblings with leukocyte adhesion deficiency, *J Periodontol*, 1993;64:149–52.
9. Vilmer C, Cavellier-Balloy B, Pinquier L, et al., Focal epithelial hyperplasia and multifocal human papillomavirus infection in an HIV-seropositive man, *J Am Acad Dermatol*, 1994;30:497–8.
10. Viraben R, Aquilina C, Brousset P, Bazex J, Focal epithelial hyperplasia (Heck's disease) associated with AIDS, *Dermatology*, 1996;193:261–2.
11. Moerman M, Danielides VG, Nousia C, Van Wanz F, Recurrent focal epithelial hyperplasia due to HPV13 in an HIV-positive patient, *Dermatology*, 2001;203:339–41.
12. Clausen FP, Geographical aspects of oral focal epithelial hyperplasia, *Phat Microbio*, 1975;39:204–13.
13. Jaramillo F, Rodriguez G, Multiple oral papules in a native South American girl, *Arch Dermatol*, 1991;127:888–992.
14. Luomanen M, Oral focal epithelial hyperplasia removed with CO₂ laser, *Int J Oral Maxillofac Surg*, 1990;19:205–7.
15. Bassioulas K, Danielides V, Georgiou I, Photos E, et al., Oral focal epithelial hyperplasia, *Eur J Dermatol*, 2000;10:395–7.
16. Köse O, Akar A, Safali M, et al., Focal epithelial hyperplasia treated with interferon alpha-2a, *J Dermatolog Treat*, 2001;12:111–13.
17. Steinhoff M, Metzke D, Stockfleth E, et al., Successful topical treatment of focal epithelial hyperplasia (Heck's disease) with interferon-β, *Br J Dermatol*, 2001;144:1067–9.
18. Akyol A, Anadolu R, Anadolu Y, et al., Multifocal papillomavirus epithelial hyperplasia: successful treatment with CO₂ laser therapy combined with interferon alpha-2b, *Int J Dermatol*, 2003;42:733–5.
19. Maschke J, Brauns TC, Goos M, Imiquimod for the topical treatment of focal epithelial hyperplasia (Heck disease) in a child, *J Dtsch Dermatol Ges*, 2004;2:848–50.

Associated Articles

Imiquimod for the Topical Treatment of Focal Epithelial Hyperplasia (Heck Disease) in a Child

Maschke J, et al.

J Dtsch Dermatol Ges, 2004;2:848–50.

Focal epithelial hyperplasia (FEH) or Heck disease is a rare skin disease caused by human papillomaviruses (HPV). The case of a nine-year old boy is presented to demonstrate the successful treatment of massive FEH with 5% imiquimod cream. Initially, the patient had noticed several separate papules, which spread and developed into multiple peri- and intraoral papillomatous nodules. The lesions were treated with carbon dioxide laser destruction. However, multiple skin-colored papillomatous nodules were found on the tongue, buccal mucosa, and lips 1.5 years later. Treatment with imiquimod was initiated, because the patient suffered tremendously from the disease. Five percent imiquimod cream was applied three times per week. Regression of lesions was obvious after one month of treatment. Complete clearance was achieved after two additional months of treatment and no recurrence was detected over a follow-up period of five months. The cases highlight the clinical value of imiquimod for the non-traumatic and almost painless therapy of HPV-induced skin diseases in children. ■

Multifocal Papillomavirus Epithelial Hyperplasia: Successful Treatment with CO₂ Laser Therapy Combined with Interferon Alpha-2b

Akyol A, et al.

Int J Dermatol, 2003;42:733–5.

Human papillomavirus (HPV) infections of the oral mucosa present with various clinical and histopathological features in relation to the causative HPV type and chronicity and the extent of the infection. The entity is known by several names based on histopathological variations

such as focal epithelial hyperplasia, oral florid papillomatosis, verrucous hyperplasia, oral florid verrucosis, and Ackerman's tumor. In recent years, the term multifocal papillomavirus epithelial hyperplasia (MPVEH) has been proposed to define the variant that usually occurs in childhood and is characterized by diffuse confluent papillomatous lesions in the oral mucosa. Despite the lesions' benign appearance, early diagnosis and therapy of MPVEH is essential because of its high capacity for progression and its tendency for malign degeneration. ■

Association of HLA-DR4 (DRB1*0404) with Human Papillomavirus Infection in Patients with Focal Epithelial Hyperplasia

García-Corona C, et al.

Arch Dermatol, 2004;140:1227–31.

The study's objective was to determine gene frequencies of HLA-DR alleles in 22 Mexican patients with focal epithelial hyperplasia and compare them with those present in ethnically matched healthy subjects, as well as to determine the types of human papillomavirus (HPV) present in the lesions. The study was prospective and retrospective observational, and was set in a dermatology outpatient clinic in a general hospital. The study consisted of twenty-two patients with clinically and histologically confirmed focal epithelial hyperplasia seen within a 10-year period. The main outcome measures were results of high-resolution DNA typing for HLA-DR alleles and biopsy for viral typing. Results showed HLA-DR4 (DRB1*0404) was significantly increased ($p < 0.001$; odds ratio 3.9; 95% confidence interval 1.86–8.03). Seventeen (85%) of 20 patients had HPV subtype 13. The data on HPV differed from reports elsewhere that described association with HPV type 32. The HLA-DRB1*0404 allele suggests that Amerindian populations are at risk, and in this group, the Mexican population studied was affected only by HPV type 13. ■