Case Description
A 17-year-old girl from Ecuador with no relevant personal or family history consulted for asymptomatic lesions on the upper and lower lips, present since age 11, that had spread slowly and progressively. The physical examination revealed numerous, well-defined papules between 3 and 7 mm, of the same color as the adjacent mucosa or pinkish-white, with a smooth surface, and located only on the upper and lower lips (Figures 1 and 2).

Introduction
Human papilloma virus (HPV) can cause various conditions in the oral mucosa that are characterized by epithelial growths, most of them benign. The most common include papillomas, condylomas, and viral warts, and more rarely focal epithelial hyperplasia (FEH) or Heck disease. It is sometimes implicated in premalignant or malignant diseases, such as leukoplasia or epidermoid carcinoma. Benign oral lesions have been associated with HPV 2, 4, 6, 11, 13, and 32, and malignant lesions with HPV 16 and 18.1

FEH is a rare disease of the oral mucosa, of benign course, that normally appears in childhood and is clearly associated with HPV serotypes 13 and 32.

We describe a 17-year-old Ecuadorian girl with FEH who was seen in our department.

Figure 1. Flat, smooth, mucosa-colored papules.
The patient had no lesions on the skin or other mucous membranes and denied any high-risk sexual contact or family history of these lesions.

The histological study showed epidermal hyperplasia, acanthosis, mild parakeratosis, and papillary projections with areas of horizontal anastomosis (Figure 3). The superficial layers of the epidermis contained koilocytes and apoptotic or dyskeratotic cells with an apparently mitotic appearance (Figure 4).

Analysis by polymerase chain reaction (PCR) detected HPV 13.

Imiquimod therapy 3 times a week was initiated for 3 weeks, without response. The patient did not come for further follow-up.

Discussion

FEH is a benign proliferative disease of the oral mucosa that is rare among white individuals, but with a highly variable prevalence according to geographic area, being as high as 35% in certain ethnic groups. There is a clear predominance among Native Americans, Eskimos, and in some African communities.

Onset usually occurs in childhood and adolescence, mainly between 3 and 18 years of age, and the condition is more common among women. It is caused by HPV and 90% of cases are associated with serotypes 13 and 32, more often serotype 13.

This entity has distinctive clinical and histological characteristics. Clinically, it is characterized by multiple flesh-colored papules of 3 to 10 mm that tend toward confluence and produce a cobblestone appearance in the mucosa. The most common site is the lower lip, and to a lesser extent, the upper lip, tongue, and buccal mucosa. Involvement of the palate, floor of the mouth, and oropharynx is rare.

The histological characteristics include epithelial hyperplasia, elongation and anastomosis of the interpapillary
ridges, parakeratosis, focal acanthosis, focal koilocytosis, and the presence of structures resembling mitotic figures in superficial keratinocytes (cells that show nuclear degenerative changes and simulate mitosis).

Although the pathogenesis is unknown, host factors such as the immune system, malnutrition, and genetic factors, are key aspects of the etiology of this entity. Some adult cases associated with human immunodeficiency virus have been reported. A clear family history and association with certain HLAs has been observed, suggesting that individuals can be genetically predisposed to the disease. A Mexican study found a significant association with HLA DR4. This allele is relatively common in indigenous populations from Mexico, Guatemala, and Colombia. There appears to be a genetic susceptibility that leads to a specific immunological abnormality in the response to certain HPV types.

The differential diagnosis should consider multiple diseases of the oral cavity, mainly condyloma, viral warts, mucosal neuroma, white sponge nevus, papilloma due to a disease of the oral cavity, mainly condyloma, viral warts, abnormality in the response to certain HPV types. The immune system, malnutrition, and genetic factors, are key aspects of the etiology of this entity. Some adult cases associated with human immunodeficiency virus have been reported. A clear family history and association with certain HLAs has been observed, suggesting that individuals can be genetically predisposed to the disease. A Mexican study found a significant association with HLA DR4. This allele is relatively common in indigenous populations from Mexico, Guatemala, and Colombia. There appears to be a genetic susceptibility that leads to a specific immunological abnormality in the response to certain HPV types.

The differential diagnosis should consider multiple diseases of the oral cavity, mainly condyloma, viral warts, mucosal neuroma, white sponge nevus, papilloma due to a bite, florid oral papillomatosis, and diffuse epithelial hyperplasia in tobacco chewers.

Knowing the serotype may differentiate the condition from other HPV infections of the oral mucosa, since FEH is the only one with specificity between serotypes and pathology, being associated with HPV 13 and 32. Certain diseases are more often associated with certain serotypes, for example, papilloma with HPV 6, 11, 13, 16, and 32 (most often 6 and 11), verruca vulgaris with HPV 2 and 4, and condylyoma with HPV 2, 6, 11, 16, and 32 (most often 6 and 11).

The course of FEH is benign, with resolution often occurring spontaneously within months or a few years, but sometimes taking longer. Treatment is not therefore necessary and none have been shown to be truly effective, although good response has been reported with destructive methods such as CO₂ laser, podophyllum resin, and interferon.

We believe that our patient had FEH, based on her ethnic origin, age at onset, absence of sexual contact, clinical and histological symptoms consistent with the condition, and serotype 13 detected in the PCR study. Based on the data, the patient was diagnosed with FEH.

**Conclusion**

FEH is an uncommon, relatively unknown condition in America, it is now more likely for physicians to encounter this condition in Spain. The course is benign and associated with serotypes of HPV with little or no carcinogenic risk; therefore, aggressive therapy should not be undertaken. The differential diagnosis should include condylomas, particularly in young patients, in order to avoid inaccurate sexual or abuse-related implications.

**Conflicts of Interest**

The authors declare no conflicts of interest.

**References**


**Actas Dermosifiliogr. 2007;98:621-3**

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