Focal epithelial hyperplasia associated with human papillomavirus-13 in a healthy Haitian adult

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Key words: Caribbean; focal epithelial hyperplasia; Haiti; Heck disease; Heck's disease; high risk; HPV; HPV13; HPV-13; HPV32; HPV-32; human papillomavirus; in situ hybridization; low risk; multifocal epithelial hyperplasia; oral; test.

INTRODUCTION

Focal epithelial hyperplasia (FEH), also known as Heck disease or multifocal epithelial hyperplasia, is a rare, benign mucosal proliferation associated with human papillomavirus (HPV) infection, most commonly with the low-risk, nononcogenic subtypes HPV-13 and HPV-32.[1] FEH is characterized by multiple asymptomatic exophytic white to mucosal-colored papules or nodules on the oral mucosa, gingiva, tongue, and lips and histopathologically by epithelial hyperplasia with parakeratosis and acanthosis, ballooning degeneration, mitosoid bodies, koilocytosis, and thickened and widened rete ridges.[1,2] FEH is common in some indigenous populations in North, South, and Central America and South Africa but is otherwise rare.[3] Cases commonly occur in children or immunocompromised adults.[3]

Herein, we present a case of FEH associated with HPV-13 in a healthy Haitian adult. Initial testing was negative as HPV-13 and HPV-32 are not typically included in low-risk HPV panels. Only 5 cases of FEH have been reported in Caribbean individuals, including 1 other case in an Haitian individual, and none were associated with HPV-13.[2,4-7]

Abbreviations used:

FEH: focal epithelial hyperplasia
HPV: human papillomavirus
ISH: in situ hybridization

CASE REPORT

A 30-year-old male of North Haitian descent with a past medical history of eczema and cheilitis presented for evaluation of white papules on the lips. The lesions were present for 1 year and were asymptomatic; however, associated dyspigmentation and texture were bothersome to the patient. He admitted to picking the lesions and also reported a papule on the right third digit, present for many years. He did not take any medications, did not have a history of immunosuppression, and denied similar family history. He reported recent negative sexually transmitted disease testing, including negative

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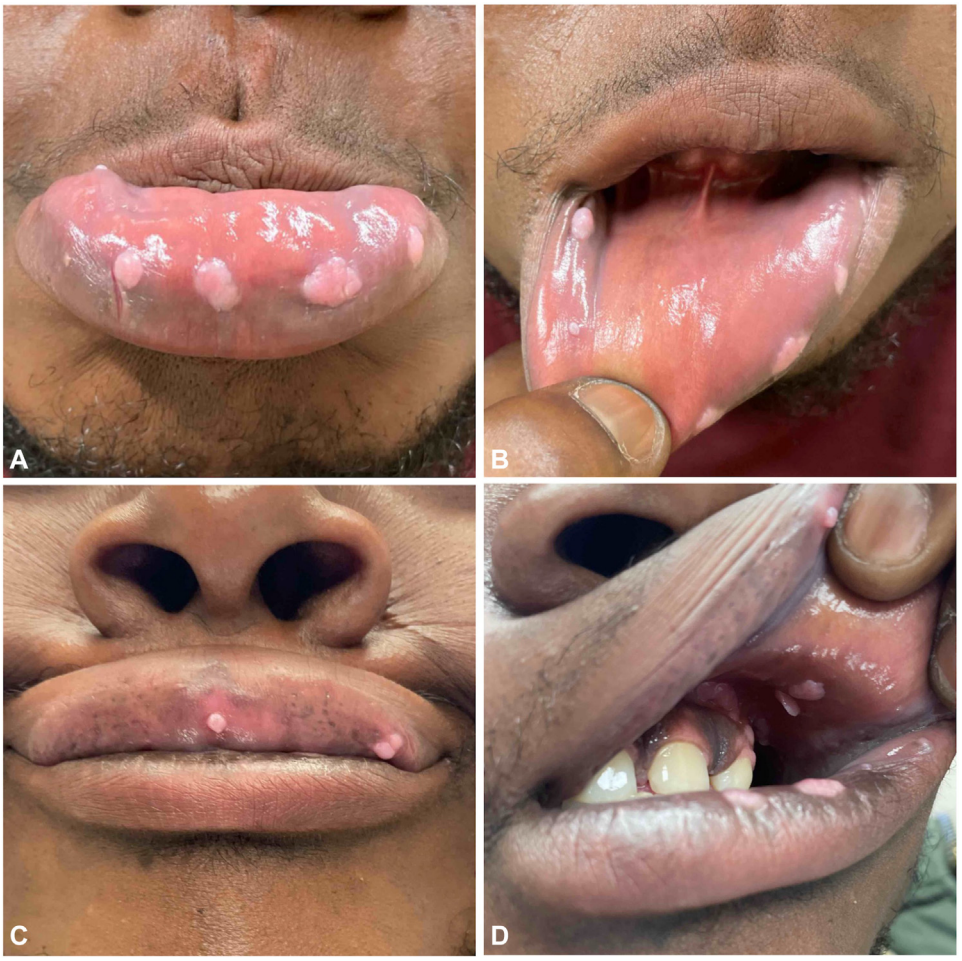

Fig 1. Multiple *light pink* to hypopigmented verrucous, exophytic papules on the lower lip mucosa (**A**, **B**, and **D**), upper lip mucosa (**C** and **D**), and gingival mucosa (**D**).

human immunodeficiency virus testing, and he declined additional testing.

Physical examination was notable for multiple soft, light pink to hypopigmented verrucous, exophytic papules on the upper and lower lip mucosa and gingival mucosa (Fig 1). On the right third digit, there was a firm, skin-colored hypertrophic papule, consistent with verruca vulgaris.

Biopsies of the left lower lip mucosa (punch), right lower lip mucosa (shave), midline lower lip mucosa (shave), and left lower lip mucosa (ellipse) demonstrated similar histopathology characterized by parakeratosis and epithelial hyperplasia forming long rete ridges with many koilocytes and karyorrhectic cells (mitosoid bodies) present (Fig 2).

Commercially available in situ hybridization (ISH) testing for low-risk HPV subtypes (first test: HPV -6, -11, -40, -43, -44, -54, -69, -70, -71, and -74; second test: HPV -6, -11, -42, -43, and -44) and high-risk HPV subtypes (first test: HPV -16, -18, -26, -31, -33, -35, -39, -45, -51, -52, -53, -56, -58, -59, -66, -68, -73, and -82; second test: HPV -16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and -68) was negative. Given high clinical suspicion for FEH, additional testing was performed. Testing for the HPV L1 capsid protein using a consensus antibody (Biocare Medical) was positive (Fig 3). Additional ISH testing for HPV -6, -7, -11, -13, -16, -18, -30, -31, -32, -33, -35, -42, -43, -44, -45, -51, -52, -57, -68, and -70 yielded a strongly positive signal for HPV-13 (Fig 4).[8] The signal was most pronounced at the epithelial surface, suggesting a productive HPV infection. No signal was evident for the other probes except for weak cross-hybridization. Ultimately, a diagnosis of FEH was made.

The patient elected for treatment with cryotherapy. At subsequent visits, he noted better resolution of lesions previously biopsied than those treated with cryotherapy. He subsequently elected for removal of remaining lesions with excision. These lesions were sharply dissected with a 15 blade, were cauterized, and were left to heal with

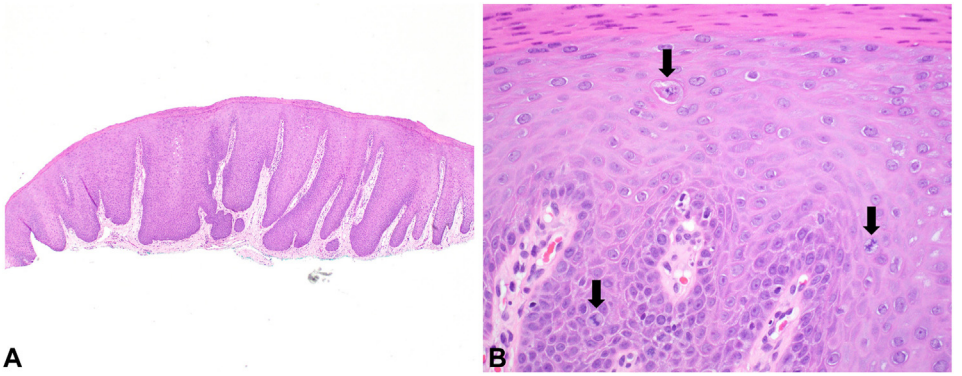

Fig 2. Hematoxylin and eosin (H&E) stained shave biopsy of the midline lower lip mucosa showing parakeratosis, epithelial hyperplasia, and elongated rete ridges (**A**, 40×) and 3 karyorrhectic cells, 2 of which appear "mitosoid" as indicated by the lower *black arrows*, but are located away from the basal layer (**B**, 400×).

secondary intention. Treated lesions healed well without evidence of recurrence. He did not develop an immunosuppressive condition during 1 year of follow-up.

DISCUSSION

This case is unique for several reasons. Most cases of FEH occur in children or in immunocompromised adults[3]; however, our patient is a healthy adult. FEH is endemic in some ethnic groups such as the Inuit community from Greenland and North Canada, the Embera-Chami community in Colombia, the Waimiri-Atroari community in Brazil, and descendants of the Khoi-San population in South Africa.[3] Poverty, malnutrition, overcrowding, and immunosuppression may contribute to transmission.[2] Genetics may contribute to FEH, as a study noted increased prevalence of FEH in individuals with the human lymphocyte antigen DRB1*0404 allele.[3] Only 1 other case has been reported in a person of Haitian descent.[2] In that case, HPV-32 was detected (as opposed to HPV-13 in our case), and the patient was an immunosuppressed child (as opposed to a healthy adult in our case).[2] Five other cases have been reported in individuals of Caribbean descent (Table I).[2,4-7] In those cases, the average age was 21 years old, and there was an even distribution by sex.

Commercially available HPV low-risk ISH testing was negative in our study; however, HPV-13 and HPV-32 are not often included in low-risk panels. Therefore, a negative low-risk ISH result may not rule out FEH. The presence of HPV-13 can result in a false negative for both low and high-risk HPV groups, so further testing may be indicated.[9] It is important to differentiate FEH from other oral verruca that may be acquired due to sexual contact, particularly as some HPV subtypes may lead to cancer.[9] In children, this is especially important to identify sexual abuse.[9]

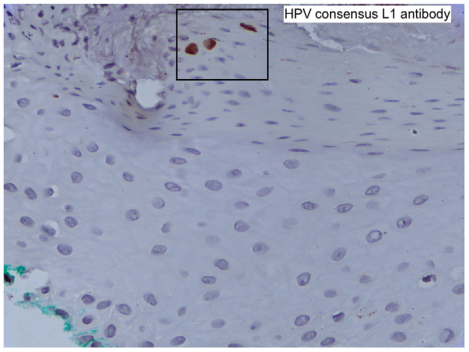

Fig 3. Expression of the HPV L1 capsid protein using a HPV consensus L1 antibody. *HPV*, Human papillomavirus.

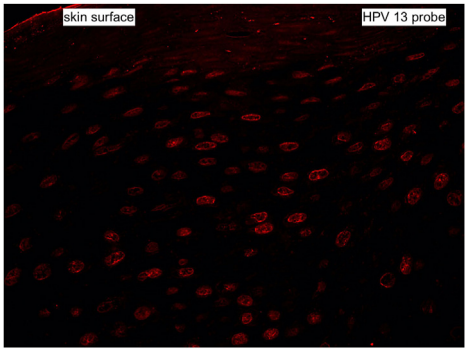

Fig 4. In situ hybridization testing using a *red fluorescent*-based signal for HPV-13. *HPV*, Human papillomavirus.

Treatment of FEH is optional, but some patients may request treatment due to lesion size, location, cosmesis, or physical irritation. Treatment modalities include imiquimod 5% cream, 80% trichloroacetic

Table I. Reported cases of focal epithelial hyperplasia in individuals of Caribbean descent

Report	Ethnic origin	Age, sex	Family history	Immunosuppression history	HPV subtype	Treatment	Outcome
Phillips et al,[4] 1968	Puerto Rico	10F	NR	No	NR	Biopsy and empiric treatment with tetracycline 250 mg QID for 14 d	No recurrence at biopsy sites, lost to f/u at 2 mo
Stiefler et al,[5] 1979	Puerto Rico	31M	Yes, mother	No	NR	Excision	No recurrence in ensuing months
Lazaroza et al,[6] 1988	Cuba	26M	No	No	NR	Leukocyte interferon-alpha cream	Marked flattening and whitening of lesions after 6 wk
Pila Pérez et al,[7] 2013	Cuba	20F	No	No	NR	Cryotherapy	Marked reduction and disappearance of almost all lesions with maintenance therapy
Gemigniani et al,[2] 2015	Haiti	11F	NR	Yes	HPV-32	Topical 5% imiquimod cream, topical retinoid, and quadrivalent HPV vaccine	Complete clinical improvement and no recurrence at 1 y
Current case, 2023	Haiti	30M	No	No	HPV-13	Excision	No recurrence in ensuing months

F, Female; *f/u*, follow-up; *M*, male; *NR*, not reported; *QID*, four times daily.

acid, topical or systemic interferon, cryotherapy, electrocoagulation or electrodesiccation, surgical resection, and laser therapy.[1,3] Some lesions resolve without treatment, and recurrence is possible.[3] As FEH cases with HPV-16 and HPV-18 have been reported, HPV vaccination is recommended.[1] Current HPV vaccines do not target HPV-13 or HPV-32; however, there may be some vaccine cross-protection between subtypes.[1]

In conclusion, we present a case of FEH associated with HPV-13 in a healthy Haitian adult. FEH in Caribbean individuals is rare, with only 5 other cases reported in the literature. Negative low-risk HPV testing does not preclude FEH because HPV-13 and HPV-32 are not typically included in low-risk panels.

Conflicts of interest

None disclosed.

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