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MINIREVIEWS

Multifocal epithelial hyperplasia: Clinical features, diagnosis and management challenges

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Abstract

Multifocal epithelial hyperplasia (MEH), also known as Heck's disease, is a rare and benign condition of the oral mucosa that is strongly associated with low-risk human papillomavirus (HPV) genotypes 13 and 32. This narrative review synthesizes recent findings regarding the epidemiology, viral mechanisms, clinical and histopathological features, diagnostic strategies-including molecular and immunohistochemical methods-and therapeutic approaches to MEH. This disease predominantly affects children and adolescents from Indigenous American countries, although cases have been increasingly reported in nonendemic regions. MEH manifests clinically as multiple, asymptomatic papules or nodules, typically exhibiting a characteristic cobblestone-like appearance. Histologically, it presents with epithelial hyperplasia, koilocytosis, and altered cytokeratin expression. Molecular techniques such as polymerase chain reaction and *in situ* hybridization are pivotal for accurate viral genotyping, while immunohistochemical markers such as CK4/13, Ki-67, and the absence of p16 can be useful adjuncts in differential diagnosis. Despite its self-limiting nature in most cases, treatment may be

warranted in symptomatic or immunocompromised patients. This review highlights the need to improve diagnostic access, develop targeted vaccines, and implement public health strategies in vulnerable communities. It also highlights existing gaps in knowledge, particularly regarding host-virus interactions and the absence of standardized treatment protocols.

Key Words: Multifocal epithelial hyperplasia; Human papillomavirus; Oral lesions; Molecular diagnosis; Indigenous populations; Heck's disease; Epidemiology; Health equity

Core Tip: Multifocal epithelial hyperplasia (MEH), or Heck's disease, is a rare, benign oral mucosal condition linked primarily to low-risk human papillomavirus genotypes 13 and 32. It disproportionately affects marginalized Indigenous American people, especially children and adolescents, driven by factors such as overcrowding and malnutrition. Clinically, MEH manifests as asymptomatic, multiple oral papules or nodules with a distinctive "cobblestone-like" appearance. Diagnosis is enhanced by molecular tools. Although generally self-limiting, improved diagnostic access, targeted vaccines, and tailored public health interventions are crucial for vulnerable communities.

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INTRODUCTION

Multifocal epithelial hyperplasia (MEH), also known as Heck's disease, is a benign proliferation of the oral mucosa primarily associated with human papillomavirus (HPV) genotypes 13 and 32. Although rare, MEH is of particular interest because of its distinctive geographical distribution-showing a high prevalence among indigenous populations of the Americas-and its potential utility as a model for studying virus-host interactions. Epidemiologically, it predominantly affects children and adolescents. Factors such as overcrowding, malnutrition, the HLA-DR4 allele, and immunosuppression favor its development. “Transmission occurs through direct contact, saliva, or fomites, with intrafamilial transmission being notable”[1-4].

MEH is characterized by the appearance of multiple asymptomatic papules or nodules on the oral mucosa, with a classic "cobblestone" appearance (Figures 1 and 2). The diagnosis of MEH is based primarily on clinical features and is confirmed by histopathological analysis. Molecular techniques, such as polymerase chain reaction (PCR) for HPV-13/32, complemented by immunohistochemistry (negativity for p16 and altered cytokeratin patterns), can be employed as useful ancillary tools to supplement and confirm the diagnosis. Histopathologically, it presents with epithelial hyperplasia, acanthosis, and koilocyte. PV-13 and HPV-32 genotypes, which are associated with low oncogenic risk, are the main causative agents, although exceptional cases with HPV-16 have been documented[1,3].

The objective of this review was to synthesize recent knowledge on MEH through an exclusive analysis of literature reviews published between 2020 and 2025, integrating epidemiology, viral mechanisms, diagnosis (clinical, molecular, and immunohistochemical), and treatment, with an emphasis on practical applications for vulnerable populations and the identification of knowledge gaps. This review is particularly essential for oral health professionals in the social context and areas of high vulnerability where early diagnosis can prevent unnecessary or erroneous treatment.

This narrative review employed a focused search strategy targeting high-quality literature (systematic reviews, narrative reviews, and meta-analyses) published between January 2020 and June 2025 in the PubMed and ClinicalKey databases. Using specific search terms, such as "Multifocal Epithelial Hyperplasia", "Heck's disease", and related HPV genotypes, we identified 13 potentially relevant publications, six of which met our strict inclusion criteria. The exclusion criteria included primary research designs, non-English publications, and off-topic content. The selected reviews underwent rigorous qualitative analysis to extract data on the global epidemiology[5-14], characteristic clinicopathological features, modern diagnostic approaches (PCR, *in situ* hybridization), and immunohistochemical marker profiles (cytokeratin, p16, and Ki-67) of MEH (Table 1).

The information presented in Table 2[14-67] and Table 3 reveal that, on the basis of the studies included in this review, MEH exhibits a particular distribution pattern worldwide. Endemic populations with high prevalence stand out, primarily in Indigenous communities of the Americas, such as the Maya, Emberá, and various Amazonian groups. The largest recorded outbreak corresponds to 1465 cases in schoolchildren in Peru, suggesting a strong association between the disease and social determinants such as overcrowding and malnutrition.

In addition to endemic foci, sporadic cases have been documented in more than thirty countries, mostly in migrants from endemic areas or individuals with unrecognized indigenous ancestry. According to reported findings, the highest disease burden is observed in children aged 5-14 years, who represent 69% of the cases. Intrafamilial transmission has

Table 1 Results chronological table of the studies on multifocal epithelial hyperplasia included (2025→2021)

Ref.	Year	Prevalence	Molecular diagnostic methods	Immunohistochemical markers	Number of patients
Bravo *et al*[6]	2024	Increased prevalence in small populations of Native American descent	PCR for HPV13/32; Genomic sequencing (phylogenetic analysis of AlphaPVs); *In situ* hybridization	p16 INK4a (not always overexpressed); Ki-67; Keratins (differentiation)	Not specified (narrative review)
Conde-Ferráez *et al*[3]	2024	38.1% (Peru); 13% (Colombia); 22% *vs* 2%	PCR (HPV13/32); Sequencing (GenBank). Serology	Not specified	3877 children (Peru); 138 schoolchildren
Di Spirito *et al*[2]	2023	51.37%	*In situ* hybridization; PCR; Biopsy + molecular techniques	Not specified	75/146 oral lesions (in 153 children)
Dommisch *et al*[10]	2023	Endemic in Inuit and South American natives; women: 5:1 ratio	PCR for HPV-13 and 32	Not specified	Not specified
Wang *et al*[1]	2023	Rare in Asia (0.02%-35% depending on region); Underdiagnosed in China	PCR (GP5+/6+, MY09/11); Sanger sequencing; RDB genotyping	Not specified	1 clinical case
Sethi *et al*[4]	2021	32.3% (Nahuatl, Mexico); 7.4%-13% (indigenous); 0.11% (Sweden)	PCR (HPV13/32 primers); DNA sequencing; *In situ* hybridization; Microscopy	Cytokeratin 4/13; sensitivity 80%, specificity 70%	95 cases: 54 women, 41 men

PCR: Polymerase chain reaction; HPV: Human papillomavirus.

Table 2 Geographical distribution of multifocal epithelial hyperplasia in the studies included

Country	Ref.	Study	Total patients	Sex distribution	Ethnic origin	Place of study
North America						
Canada	Jarvis and Gorlin[14]	Focal epithelial hyperplasia in an Eskimo population	1591 surveyed; prevalence 86%-12.7% (approx. 137-202 cases)	Not provided	Eastern Arctic Eskimos	University of Minnesota, Minneapolis, United States
Canada	Landells and Prendiville[15]	Oral mucosal lesions in a Somali boy	1 + 1 uncle (Somalia)	Male (patient)	Somali	Vancouver, Canada
Mexico	Tan *et al*[16]	Focal epithelial hyperplasia in a Mexican Indian	1	Male (12 years)	Mexican Indian	Illinois, United States (patient origin Mexico)
Mexico	Sandi *et al*[17]	Comparative treatment of multifocal epithelial hyperplasia	20	11 male, 9 female	Not specified	Hospital Infantil de Mexico, Mexico City
Mexico	Lopez-Villanueva *et al*[18]	HPV-13 in a Mexican Mayan community with MEH	53	75% female, 25% male	Mayan (Yucatán)	Yaxchachén, Yucatán
Mexico	González-Losa *et al*[19]	MEH in a Mayan community	57 (44 fully studied)	61.3% female, 38.6% male	Mayan (Chemax)	Chemax, Yucatán
Mexico	Lama-Gonzalez *et al*[20]	HPV-13 detection in MEH patients and relatives	16	9 female, 7 male	Likely Mayan or Mestizo	Mérida, Yucatán and Quintana Roo
Mexico	Gonzalez-Ló pez[21]	FEH in two communities of Estado de México	61 children + 25 relatives	Mestizo: 18 female/13 male; Mazahua: 17 female/13 male	Mestizo and Mazahua	Estado de México
Mexico	Jiménez Aguilar *et al*[22]	HPV diversity in MEH outbreak	21	10 female, 11 male	Not specified (indigenous predisposition noted)	Navolato, Sinaloa and Mexico City
United States	Waldman and Shelton[23]	FEH in an adult Caucasian	1	Female (56 years)	Caucasian	Fort Bragg, NC, United States
United States	Archard *et al*[24]	FEH in Indian children	19	13 female, 6 male	Navajo, Eskimo (Alaska), Xavante (Brazil)	Gallup, New Mexico

Central and South America						
Bolivia	Decker and De Guzmán[25]	FEH in Mestizos from Cochabamba	4	All male	Mestizo	University San Simón, Cochabamba
Brazil	Witkop and Niswander[26]	FEH in Indians and Ladinos	7	6 female, 1 male	Xavante Indians	Brazil
Brazil	Borborema-Santos *et al*[27]	Oral FEH: 5 cases	5	2 female, 3 male	Indigenous (Central Amazonia)	Manaus, Brazil
Brazil	Rosa *et al*[28]	FEH clinical case	1 + sister	1 male, sister also affected	Caucasian	Porto Alegre, Brazil
Colombia	Gomez *et al*[29]	FEH in Colombian family	7	5 female, 2 male	Mestizo (Black admixture)	Medellín, Colombia
Colombia	Estrada[30]	Caramanta Indians oral findings	3	Not specified	Caramanta Indians	Colombia
Colombia	Estrada[31]	Katíos Indians oral findings	3	Not specified	Katíos Indians	Chocó, Colombia
El Salvador	Witkop and Niswander[26]	FEH in Ladinos	2	1 male, 1 female	Ladino	Santa Ana, El Salvador
Guatemala	Carlos and Sedano[32]	MPVEH study	110	76 female, 34 male	Not specified	Guatemala City and rural areas
Guatemala	Witkop and Niswander[26]	FEH in Quiché-Maya	5	3 male, 2 female	Quiché-Maya	Santa María Cauqué
Paraguay	Fischman[33]	FEH case report (Paraguay and Peru)	1	Male (30 years)	Not specified	Yaguaron, Paraguay
Peru	Fischman[33]	FEH reports (Paraguay and Peru)	≥ 3	Not specified	Amazon Indians (Iquitos), 1 Lima resident	Peru (Iquitos and Lima)
Peru	Guevara *et al* [34]	Prevalence in Mórrope school-children	1465 of 3877	685 female, 780 male	Rural schoolchildren (Indigenous/mestizo)	Mórrope, Lambayeque
Surinam	Starink and Woerdeman [35]	FEH cases in Surinamese patients	2 + 1	1 female/1 male + 1 male	Black Surinamese	Amsterdam, Netherlands (patients born in Surinam)
Venezuela	Navarro *et al* [36]	Prevalence in Sanema and Yekuana	79 of 862	37 female, 42 male	Sanema, Yekuana	Bolívar State, Venezuela
Venezuela	Soneira and Fonseca[37]	Study in Indigenous girls	54 of 160	All female	Indigenous	Venezuela
Europe						
Germany	Binder *et al*[38]	FEH in Black child	1	Male	Black African	Cologne/Graz
Germany	Meissner *et al* [39]	FEH in Crohn's disease patient	1	Male	Not specified	Frankfurt am Main
Germany	Kreuter and Silling[40]	FEH in 7y boy	1	Male	Angolan	Witten and Cologne
Greece	Bassioukas *et al* [41]	Oral FEH	1	Female	Caucasian	Greece
Greece	Laskaris *et al* [42]	First Greek case	1	Female (56 years)	White (Caucasian)	University of Athens
Italy	Bon *et al*[43]	FEH (siblings)	2	1 female, 1 male	Italian	Zürich (patients born Switzerland)
Italy	Bombeccari *et al*[44]	FEH PCR case	1	Male	Bolivian	Milan
Italy	Galanakis *et al* [45]	FEH in HIV patient	1	Male	African	Rome
Lithuania	Puriene *et al* [46]	FEH case report	1	Female (15 years)	Not specified	Vilnius
Netherlands	Starink and Woerdeman [35]	FEH cases	2 + 1	1 female/1 male + 1 male	Black (Surinamese origin)	Amsterdam

Poland	Obalek *et al*[47]	Sporadic cases in girls	2	Female	Polish	Warsaw
Poland	Kubiak and Stępień[48]	FEH in adult male	1	Male	Caucasian	Wrocław
Spain	Segura-Saint-Gerons *et al*[49]	FEH cases	2	1 female 1 male	Saharan; Ecuadorian	Córdoba and Barcelona
United Kingdom	Bradnum[50]	FEH case	1	Male (36 years)	Scottish	Newcastle
United Kingdom	Gusterson and Greenspan[51]	Multiple polypoid oral conditions	1	Female (65 years)	Caucasian	London
United Kingdom	Goodfellow and Calvert [52]	FEH case	1	Male	West Indian	Reading
Africa						
Ghana	Nartey *et al*[53]	Six cases from Ghana	6	5 female, 1 male	West African	University of Ghana
Kenya	Chindia *et al* [54]	FEH in Kenyan children	3	All female	Kenyan	Kenya
Nigeria	Sawyer *et al* [55]	Early West African reports	3	Not specified	West African	Nigeria
South Africa	Harris and van Wyk[56]	Longitudinal study	143	Varied (25 female, 19 male in Garies)	Khoi-San descendants	Garies and Kamieskroon
South Africa	Feller *et al*[57]	FEH in HIV+ child	1	Not specified	Not specified	South Africa
Sudan	Ghandour[58]	Case report	1	Female (girl)	Not specified	Sudan
Asia						
China	Wang *et al*[1]	FEH in Chinese man (case + review)	4	1 female, 3 male	Chinese	Zhejiang University, Hangzhou
Middle East						
Afghanistan (patients in Iran)	Ghalayani *et al* [59]	3 Afghan immigrant cases	3	1 female, 2 male	Afghan	Isfahan University, Iran
Iran	Mansouri *et al* [60]	Extensive FEH case report	1	Male	Iranian	Tehran
Israel	Buchner and Mass[61]	Israeli family with FEH	4 (of 11 children)	3 male, 1 female	North African origin	University of Tel Aviv
Turkey	Köse *et al*[62]	FEH treated with interferon α2a	1	Male	Caucasian	Ankara
Turkey	Akyol *et al*[63]	MPVEH treated with CO2 Laser and IFN	5 (1 + 2 sisters + 2 cousins)	1 male, 2 female, 2 unknown	Turkish	Ankara
Turkey	Artac *et al*[64]	FEH in ADA deficiency	1	Female (12 years)	Turkish	Konya
Turkey	Gültekin *et al* [65]	Oral FEH with HPV sequencing	3	2 female, 1 male	Turkish	Ankara
Turkey	Ozden *et al*[66]	Case report with PCR	1	Female (girl)	Caucasian	Samsun and Ankara
Turkey	Akoğlu *et al* [67]	FEH in Turkish family (HLA-linked)	4	2 male, 2 female	Turkish (Anatolia)	Ankara

FEH: Focal epithelial hyperplasia; PCR: Polymerase chain reaction; HPV: Human papillomavirus; ADA: Adenosine deaminase; IFN: Interferon alpha-2b; HIV: Human immunodeficiency virus; MPVEH: Multifocal papillomavirus epithelial hyperplasia; MEH: Multifocal epithelial hyperplasia.

also been documented, as well as a predominance of cases in women in some series, reaching 71%. The presence of autochthonous cases outside the American continent is notable, such as those reported in Germany (17 cases) and Iraq (7 cases) in the Middle East. From a clinical perspective, in endemic areas, MEH should be considered when multiple oral lesions are present in the pediatric population, whereas in nonendemic regions, investigating migratory backgrounds is crucial. Finally, the observed global distribution suggests that undiagnosed cases may exist because of a lack of clinical suspicion, which highlights the importance of increasing disease recognition in different geographical and population contexts.

Table 3 Summary of the studies[1]

Continent	Number of countries	Total patients (approx.)	Year range of reports
North America	3 (Canada, United States, Mexico)	Approximately 1760 (Canada: Survey of 1591 individuals, with 137-202 cases diagnosed with MEH + 169 Mexican and United States cases)	1965-2023
Central and South America	10 (Bolivia, Brazil, Colombia, El Salvador, Guatemala, Paraguay, Peru, Venezuela, Surinam)	Approximately 1757 (includes 1465 in Peru, 110 from Guatemala, 79 from Venezuela	1956-2015
Europe	9 (Germany, Greece, Italy, Lithuania, Netherlands, Poland, Spain, Sweden, United Kingdom)	Approximately 28 (mostly isolated case reports and small series)	1970s-2015
Africa	5 (Ghana, Kenya, Nigeria, South Africa, Sudan)	Approximately 156 (includes 143 in South Africa longitudinal study + small series elsewhere)	1964-2000s
Asia	1 (China)	4 (cases reported in literature review + current case)	2000s-2010s
Middle East	4 (Afghanistan, Iran, Israel, Turkey)	Approximately 22 (Turkey family clusters + Israel family + Iran/Afghan series)	1973-2010s
Arctic (Greenland)	1 (Greenland)	89 (epidemiological study of 460 examined)	1970
Total	31 countries	Approximately 3816 patients	1956-2023

[1]The highest case numbers come from Peru (1465), Canada (approximately 137-202 cases, extrapolated from a survey of 1591 individuals), and South Africa (143). Many countries in Europe and the Middle East have only 1-3 cases. The full-time range extends from Estrada's first report in Colombia (1956) to the outbreak studied in Mexico (Aguilar-Jiménez, 2023).
MEH: Multifocal epithelial hyperplasia.

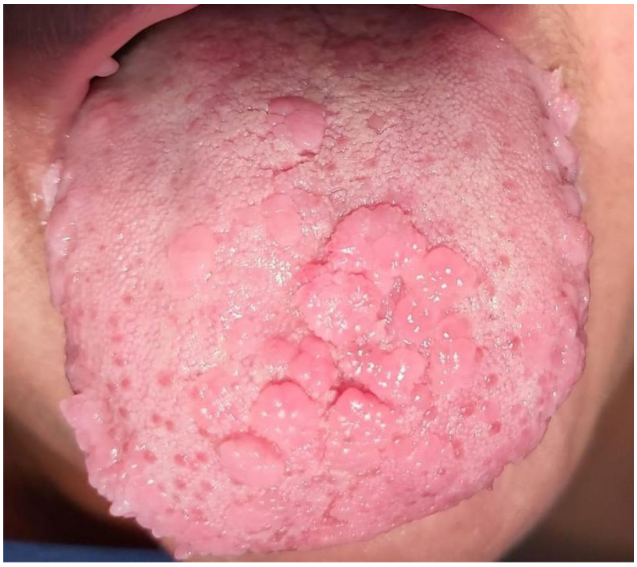

Figure 1 Clinical presentation of multifocal epithelial hyperplasia on the dorsal surface of the tongue, presenting as multiple well-circumscribed, pink papules and nodules.

ETIOLOGY

MEH is caused by HPV infection. The main genotypes associated with MEH are HPV-13 and HPV-32. These are classified as low-risk types because their infections are typically benign and rarely detected in cancerous tissues. HPV-13 is the most frequently identified genotype in MEH cases, especially in Mayan communities in Mexico, where it has been recognized as the sole etiological agent in some outbreaks. HPV-32 is also commonly associated with MEH, particularly in human immunodeficiency virus (HIV) patients[2].

A notable evolutionary paradox exists in the etiology of MEH: HPV-13 and HPV-32 are genetically distinct but cause the same clinical disease. This is paradoxical because such distinct viruses are normally expected to generate different responses. However, other viruses closely related to HPV-13 (such as HPV-44 or HPV-74) or HPV-32 (such as HPV-42) have not been reported to cause MEH. This suggests that the disease phenotype might be more strongly affected by the

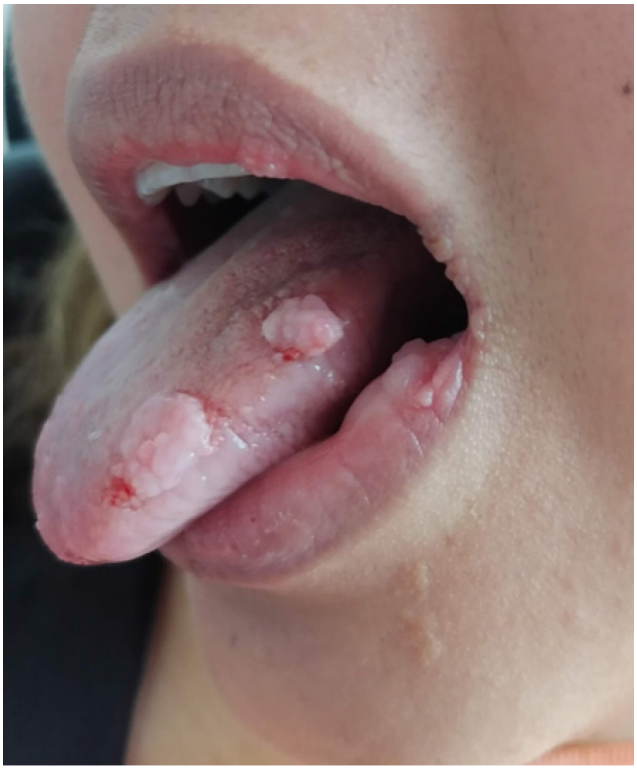

Figure 2 Multifocal epithelial hyperplasia involves the lateral surface of the tongue. The image shows multiple pinkish white, exophytic papules and nodules with a smooth to papillomatous surface.

phenotype of the proliferating epithelial cell than by the specificity of the viral genotype[2].

An apparent evolutionary paradox MEH lies in the ability of HPV-13 and HPV-32 to generate conspicuous proliferative lesions while remaining strictly benign and persisting in human populations. Several mechanisms may contribute to this phenomenon. The oral mucosa provides a tolerogenic environment (interleukin-10, transforming growth factor-beta) that enables viral replication with minimal inflammation, while host immunogenetic factors-such as HLA-DR/DQ haplotypes-may impair efficient antigen presentation, explaining familial and ethnic clustering of cases. In addition, HPV-13 and HPV-32 share phylogenetic proximity but exhibit limited cross-neutralization, which allows their stable co-circulation in the same communities. At the epithelial level, viral proteins appear tuned to promote low-grade proliferation without malignant transformation, ensuring viral spread at low cost for the host. Finally, the influence of salivary factors and the oral microbiome may further dampen innate immune responses and favor persistence. Together, these elements reconcile the paradox by highlighting that MEH reflects a balanced virus-host interaction in which benign, visible lesions enhance household transmission without compromising host survival[3,6].

The HPV genome consists of early genes (E1-E7) that control viral replication and epithelial cell proliferation and late genes (L1 and L2) that encode viral capsid proteins. In low-risk infections, such as those associated with MEH, the viral genome remains as an episome in the cell nucleus, independent of the host DNA, which allows the function of the E2 gene to remain unaltered and, therefore, suppress the transcription of oncogenic E6 and E7 proteins[6].

Detection of HPV-13 and HPV-32 genotypes can be a diagnostic challenge, as most commercial HPV genotyping kits do not include probes for these specific types; this could lead to an underestimation of their prevalence and, consequently, to an underdiagnosis of MEH. Although infrequent, the high-risk genotype of HPV-16 has been detected in some MEH cases, such as in a 65-year-old Indian woman with extensive lesions on the gingiva and other areas of the oral mucosa, along with cutaneous lesions. This underscores the complexity of viral etiology and the need for a deeper understanding of the factors influencing the outcome of HPV infection[7].

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The prevalence of MEH varies considerably depending on the population and geographical region, ranging between 0.02%-35%. This disease is most frequently observed in Indigenous populations of the Americas, with documented outbreaks in communities in Peru (with the largest reported series of 1465 cases), Colombia, Brazil, El Salvador, and Guatemala. In addition to the Americas, MEH cases have been reported in other regions of the world, including Venezuela, Mexico, Ghana, Greece, Iran, and Saudi Arabia. Recently, an increase in the incidence of the disease has been observed in the European region, suggesting a wider distribution than initially thought[4] (Table 2).

MEH is most often diagnosed in children and adolescents, with an average age of lesion onset of 8.46 years in pediatric patients. However, the disease can affect individuals of all ages, with an overall average of 23.1 years and a range of 3-92

years. There is a female predilection in the incidence of MEH, with a male-to-female ratio of 1:1.4 in pediatric cases and 3:4 in the general population. Familial aggregation is a notable feature, with 25.3% of reported cases having a family history of similar oral cavity lesions, and it is common for siblings to be affected[2].

The transmission of MEH occurs primarily through close contact between infected individuals or family members. HPV-13 has been shown to be transmissible through saliva, and the shared use of objects such as kitchen utensils, toothbrushes, and other contaminated fomites can facilitate intrafamilial spread of the disease. Certain socioeconomic and environmental factors, including low annual income, malnutrition, overcrowded living conditions, and poor oral hygiene, are also associated with a high incidence of MEH. Immunocompromised patients, such as those with HIV infection, have an increased risk of developing papillomavirus-related lesions[5].

CLINICOPATHOLOGICAL FEATURES

Clinically, MEH presents as multiple asymptomatic, soft, and well-demarcated papules or nodules (Figures 1 and 2), typically ranging from 1-5 mm in diameter. These lesions can coalesce, forming areas with a characteristic "cobblestone-like" appearance, and their color is similar to that of the surrounding oral mucosa, sometimes with a more whitish coloration. Although it is a rare pathology worldwide, MEH is more common in Indigenous populations of the Americas. However, recent reports suggest a higher incidence in the European region[4].

The most frequent locations for MEH lesions are the lips (upper and lower), buccal mucosa, and tongue. Although less common, they can also affect the hard palate and gingiva; in fact, gingival involvement is considered rare. Two clinical variants have been described: Papulonodular, which predominates in the lining mucosa, and papillomatous, which is found in the masticatory mucosa, such as the attached gingiva and tongue[1].

Clinicians must recognize the rare presentations of MEH to facilitate timely diagnosis and appropriate management, as the condition may be underdiagnosed or mistaken for other diseases because of its clinical variability. MEH is considered a self-limiting disease in many cases and often does not require treatment. Nevertheless, periodic clinical evaluations are advised to detect possible malignant transformations, especially in patients who smoke and/or consume alcohol, although these transformations are extremely rare. Differential diagnoses include a broad spectrum of conditions that may share similar clinical features, such as condyloma acuminatum, verruca vulgaris, squamous papilloma, oral florid papillomatosis, diffuse epithelial hyperplasia, and Cowden syndrome. Less common differential diagnoses include white sponge nevus, multiple endocrine neoplasia type III, neurofibromatosis, tuberous sclerosis, epidermal nevus syndrome, Fordyce granules, and morsicatio buccarum (chronic cheek biting). Accurate clinical recognition, supported by histopathological and molecular evaluation, when necessary, remains key to avoiding misdiagnosis and ensuring appropriate follow-up[1,4].

DIAGNOSIS

The diagnosis of MEH is primarily clinical and is based on its pathognomonic characteristics. However, in some cases, histopathological or virological confirmation may be needed[3]. Histologically, the lesions show squamous epithelial hyperplasia with papillomatosis, acanthosis, hyperkeratosis, and parakeratosis. Elongated and horizontally anastomosing rete ridges are observed, as well as koilocytes, epithelial cells with pyknotic nuclei surrounded by a clear halo, and mitosoid bodies in the upper epithelial layers (Figures 3 and 4). A distinctive pattern known as the "Bronze Age ax-shaped rete ridge pattern" has also been described. For diagnostic confirmation, various tools are employed: Biopsy, PCR analysis for HPV DNA detection, *in situ* hybridization, and immunoperoxidase assays for viral antigens[2].

Molecular findings

Immunohistochemical studies of MEH have evaluated various viral and cellular biomarkers, including cytokeratins, HPV proteins, and proliferation markers.

CYTOKERATIN EXPRESSION AND PROFILE

HPV infection, which is the primary cause of MEH, can alter the expression of cytokeratins in affected tissues. An immunocytochemical study by Ledesma-Montes *et al*[8], which used a polyclonal antibody against high-molecular-weight cytokeratins with the peroxidase-antiperoxidase technique, revealed significant differences in immunostaining between lesional cells and adjacent normal epithelium in MEH patients. A positive reaction to a polyclonal antibody against high-molecular-weight cytokeratins using the peroxidase-antiperoxidase technique revealed strong cytoplasmic positivity in the spinous layer of the lesional epithelium, as well as in the surrounding clinically normal epithelial tissue, suggesting an alteration of the cytokeratin metabolic profile in these epithelial cells due to viral infection. A key finding was that koilocytes and mitosoid bodies, which are histopathological characteristics of MEH, showed negative cytoplasmic reactivity to cytokeratin antibodies. These results suggest that these epithelial cells undergo an irreversible degenerative process related to viral infection and lose the ability to synthesize cytokeratins. Previously, other studies reported that the expression of certain cytokeratins, such as CK14, 15, 16, and 19, is altered in MEH lesions, indicating an anomalous expression pattern[8].

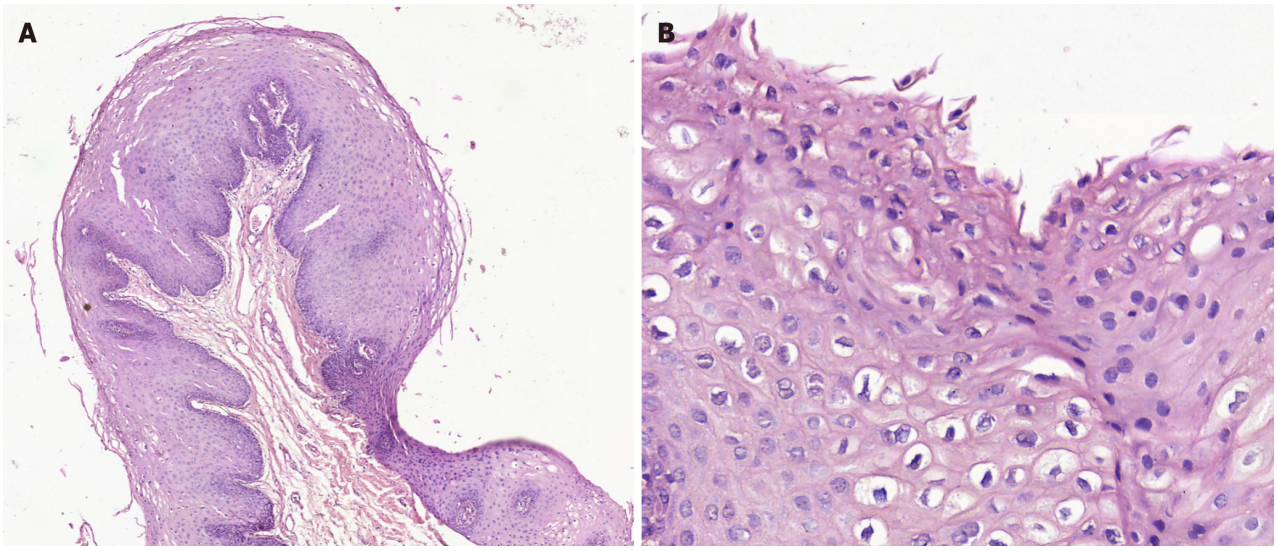

Figure 3 Histopatological image. A: A lesion characterized by the presence of a stratified squamous epithelium parakeratinized with acanthosis and thick and elongated epithelial processes, which give a papillomatous appearance. In some areas, mitosoid and koilocytic figures are observed (50 ×). The connective tissue was well vascularized and free of injury; B: Mitosoid and koilocytic figures (200 ×).

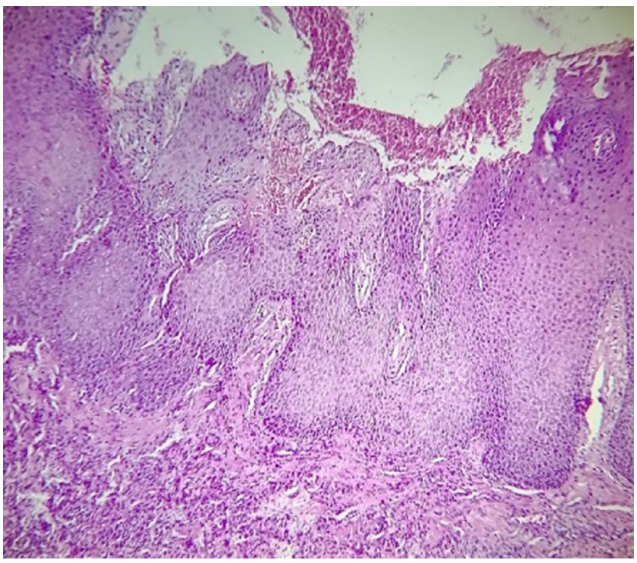

Figure 4 In multifocal epithelial hyperplasia samples, the stratified squamous epithelium presents pronounced hyperorthokeratosis, accompanied by acanthosis and the presence of koilocytes in the intermediate layers. At the base of the epithelium, dense, well-vascularized connective tissue with chronic inflammatory infiltration is present, which is distributed abundantly and diffusely (100 ×).

In contrast, for differential diagnostic purposes, immunohistochemistry for cytokeratins 4 and 13 is a standard test that allows MEH to be differentiated from other lesions. HPV-infected squamous cells in MEH showed strong signals for cytokeratin 4 and 13. This is distinct from what occurs in some cases of white sponge nevus (a genetic disease unrelated to HPV), where a marked decrease or absence of these cytokeratins is observed. This distinction is fundamental for accurate typing, as the clinical and histological presentation of these conditions can overlap[9].

DETECTION OF HPV DNA AND L1

Capsid protein detection of HPV DNA by *in situ* hybridization is crucial for confirming the viral etiology and typing the HPV subtype in MEH. A strong signal for HPV 13 DNA has been demonstrated in squamous cells, particularly toward the apical aspect of the lesion and in cells with perinuclear halos, indicating robust viral replication and the probable presence of infectious virions. Notably, commercial *in situ* hybridization panels for low-risk HPV often do not include the HPV 13 and 32 subtypes, which can lead to false-negative results if specific tests are not performed. Given the high viral load of HPV 13 DNA in MEH lesions, HPV DNA *in situ* hybridization is particularly useful for its typing, despite its

sensitivity generally being lower than that of PCR[9].

The detection of the HPV L1 capsid protein by immunohistochemistry is a marker of productive infection. One study reported a positive result for the HPV L1 capsid protein using a consensus antibody [a consensus antibody is an antibody designed to recognize a conserved or common region among several variants (or genotypes) of an antigen rather than being directed against a specific unique sequence of a single type] (Biocare Medical) in a case of MEH associated with HPV-13, suggesting a productive infection. In the context of HPV, a consensus antibody against the L1 protein, for example, is formulated to detect the L1 capsid protein of multiple HPV types, as it recognizes shared epitopes (similar antigenic sequences) among different genotypes. However, another study that also used a consensus antibody for L1 (Biocare medical) did not detect the L1 capsid protein in patients with Heck's disease, which could be due to insufficient homology of the antibody with the HPV 13 L1 protein. This discrepancy highlights the importance of L1 antibody specificity for infection typing[9].

The detection of HPV in MEH is key for confirming its viral origin and identifying subtypes. *In situ* hybridization effectively identifies HPV DNA, especially subtype 13, but commercial tests may miss relevant genotypes, risking false-negatives without targeted panels. Immunohistochemistry for the HPV L1 capsid protein indicates productive infection; however, the results vary depending on antibody affinity, underscoring the need for subtype-specific antibodies for accurate typing[9].

Immunohistochemistry has also clarified the benign nature of MEH. Studies have shown that the proliferation marker p16, which is typically expressed in high-risk HPV, is absent in all MEH cases as well as in oral condyloma, Heck's disease, and white sponge nevus, indicating the absence of malignant transformation. Unlike that of high-risk HPV, the Ki67 index is not elevated in these benign conditions[8,9].

Similarly, other high-risk HPV biomarkers, such as importin-β, exportin-5, and Mcl1, have not been detected in MEH. This finding reinforces the classification of MEH as a benign condition with no risk of malignant transformation. With respect to Ki67, which is considered the gold standard for evaluating cell proliferation, its expression is limited primarily to the basal cells of the epithelium in MEH patients. This suggests that the marked proliferation of squamous cells is not a distinctive characteristic of MEH, unlike high-risk HPV infections, where the proliferation index is notably higher[2,9].

MANAGEMENT AND TREATMENT

Management and treatment options for MEH are limited and not standardized, ranging from topical to surgical approaches. In many cases, MEH lesions may undergo spontaneous regression, making treatment unnecessary, especially if they do not cause pain, interfere with occlusion, or generate aesthetic or social concerns[2].

Although several therapeutic strategies for MEH have been described-including surgical excision (scalpel, cryotherapy, and CO_2 or Er: YAG laser), as well as topical agents such as imiquimod, trichloroacetic acid, podophyllin, interferon, and vitamin A-the supporting evidence is heterogeneous and largely derived from case reports or small series, with no randomized controlled trials available[2-4]. Recurrence is common across modalities, reflecting the persistence of HPV-infected cells in adjacent clinically normal mucosa. Some reports suggest that CO_2 laser therapy, particularly when combined with adjuvant interferon, may provide lower recurrence rates compared to conventional excision or cryotherapy[62,63]. Nevertheless, access to such technologies is often limited in endemic, resource-constrained settings, where observation or simple excision remain the most feasible approaches[2-4]. Importantly, spontaneous regression has been documented in 60%-80% of pediatric cases within 2-5 years[2,4], supporting expectant management as a rational strategy when lesions are asymptomatic. Taken together, the variable recurrence rates and limited accessibility of advanced therapies highlight the urgent need for standardized, evidence-based protocols that consider both clinical efficacy and equity in resource-limited contexts.

Prevention is based on avoiding contact with infected lesions and reducing susceptibility to infection through immunization. The quadrivalent vaccine (Gardasil), which is directed against low-risk HPV types 6 and 11 and high-risk types 16 and 18, and the bivalent vaccine (Cervarix), which is directed against types 16 and 18, are the main preventive tools available. Although the efficacy of these vaccines for preventing oral HPV infection has not yet been fully evaluated, systemic benefits are anticipated. Notably, poor oral hygiene is associated with the appearance and persistence of MEH. Studies have shown that improved oral hygiene can contribute to lesion regression in some cases[1].

This review summarizes key aspects of MEH, an oral condition associated with HPV, which warrant special consideration. The strong association between MEH and HPV-13/32 infection is well established, with molecular studies demonstrating the detection of HPV-13 in cases from endemic populations[3,4,11]. These genotypes, which are classified as low risk because of their benign clinical behavior and episomal replication pattern, present a fascinating evolutionary paradox: Despite their significant genetic divergence, they produce identical clinical phenotypes, suggesting that host epithelial factors might determine disease manifestation rather than viral genotype specificity[6,8]. Notably, various studies also report the presence of other HPV genotypes, including high-risk types such as HPV-16, in MEH lesions[1,13].

The pediatric predominance of MEH (69.3% of cases occurred between 4 and 19 years of age) likely reflects both immunological factors in primary HPV infection and the greater susceptibility of the developing oral epithelium[3,4]. The notable outbreak of 1465 cases in Peruvian schoolchildren underscores the predilection of the disease for pediatric populations in endemic regions, where socioeconomic factors (overcrowding, malnutrition) and possible genetic susceptibility (the HLA-DR4 allele) create ideal conditions for its spread[3-5].

Although MEH typically follows a self-limiting course (60%-80% spontaneous regression in 2-5 years), clinical surveillance remains essential[2,4]. Our analysis revealed important exceptions, such as: (1) Lesions persisting into adulthood (particularly on the gingiva); (2) A higher risk of recurrence in immunocompromised patients; and (3) The

potential for aesthetic/functional compromise requiring intervention. The observed female predominance (with ratios varying from 1.4:1 to 5:1 according to various studies) raises relevant questions about possible hormonal or immunological modulators of susceptibility, which require further investigation. Similarly, it is possible that this phenomenon is related to a higher frequency of medical and dental consultations among women[4,10].

Although current HPV vaccines do not specifically include the genotypes associated with MEH, as noted by Di Spirito *et al*[2], they could offer relevant indirect benefits[2,6]. These include a reduction in oral coinfections caused by high-risk genotypes, a decrease in viral load in communities where the infection is endemic, and, to a lesser extent, the prevention of malignant transformations, which, although infrequent, represent a clinically significant risk.

From a clinical perspective, MEH management requires an approach tailored to the epidemiological context. In endemic regions, this diagnosis should be systematically included in the differential evaluation of pediatric patients who present with multiple oral papules, particularly those belonging to Indigenous groups or communities with disadvantaged socioeconomic conditions. When resources are available, molecular confirmation by specific PCR for HPV-13/32 is strongly recommended and constitutes the current diagnostic standard[4,8,11]. The therapeutic approach should initially prioritize expectant management, given the frequently self-limiting nature of the disease. Active interventions (surgical or medical) should be reserved for three specific scenarios: (1) The presence of lesions causing functional symptoms; (2) The significant aesthetic impact affecting the patient's quality of life; or (3) Cases in immunocompromised individuals where the risk of persistence or progression is relatively high.

It appears necessary to reevaluate the actual prevalence and potential clinical implications of MEH in Asia, particularly within the Chinese population. Although MEH has traditionally been regarded as an uncommon condition in the region, this perception may be influenced by substantial underreporting and diagnostic challenges[1]. The literature reviewed here suggests that MEH can occasionally be misidentified as other benign oral lesions, and its predominantly asymptomatic nature may contribute to delays in seeking medical care, which in turn may result in a low consultation rate and an underestimation of its true prevalence in clinical records.

While the potential development of vaccines targeting HPV-13 and HPV-32 is conceptually appealing, significant practical and economic challenges must be acknowledged. Current prophylactic HPV vaccines are designed to protect against high-risk oncogenic genotypes (*e.g.*, HPV-16, -18) and common low-risk types associated with anogenital warts (HPV-6, -11), which have far greater global prevalence and disease burden[2,6]. By contrast, MEH is a geographically restricted and relatively rare condition, predominantly affecting Indigenous or socioeconomically marginalized populations[3,4]. This epidemiological profile poses difficulties in justifying the high research and manufacturing costs required to expand vaccine coverage to these uncommon genotypes, particularly given the limited commercial incentive for pharmaceutical companies. Moreover, logistical barriers such as the need for cold-chain infrastructure, vaccine hesitancy, and competing public health priorities in endemic regions further complicate implementation. Consequently, while including HPV-13 and HPV-32 in next-generation vaccines could address an unmet need, it is more realistic in the short term to focus on strengthening early diagnosis, improving access to oral healthcare, and integrating MEH awareness into existing HPV-related public health strategies[2-4,6].

In the research field, three priority areas requiring urgent attention are identified. First, the development of HPV vaccines incorporating MEH-associated genotypes (particularly HPV-13 and HPV-32) represents an unmet public health need, especially for endemic populations. Second, a more in-depth characterization of host genetic factors (such as the HLA-DR4 allele and other polymorphisms) that modulate individual susceptibility and immunological response to these viral genotypes is needed. Finally, the standardization of evidence-based therapeutic protocols for persistent or recurrent cases emerges as a pressing clinical need, considering the current variability in management approaches and the high recurrence rates reported with conventional therapies. These research avenues could not only improve MEH management but also contribute to a broader understanding of HPV infections[3,6,8].

CONCLUSION

MEH represents a clinical entity primarily linked to HPV-13 and HPV-32 genotypes, with a marked prevalence in Indigenous populations due to socioeconomic factors such as overcrowding and malnutrition. Its course is usually self-limiting in children, although intervention is needed in symptomatic patients or in immunocompromised patients. The findings highlight the need for: (1) Vaccines that include these genotypes; (2) Better diagnostic methods accessible for endemic popu-lations; and (3) Comprehensive strategies that combat both the infection and its social determinants. MEH exemplifies how conditions of vulnerability favor infectious diseases, calling for multidisciplinary approaches for their effective prevention and management.

FOOTNOTES

Author contributions: Ramos-Gregorio CO, Bologna-Molina R performed the literature search, interpreted the relevant literature, and drafted the initial manuscript; Bologna-Molina R, Ramos-Gregorio CO, Soto-Najera AC, GómezPalacio-Gastélum M, Isiordia-Espinoza M, Muñoz-Ibarra JJ and Toral-Rizo V and Tremillo-Maldonado O conceived the idea and provided additional input to design the paper; Silveira F, Frenzel Schuch L, Pereira-Prado V and Sicco E prepared the figures and tables and revised the article critically and preformed the final changes.

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