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Multifocal epithelial hyperplasia, a rare oral infection in Asia: Report of twelve cases in Iran

Pegah Mosannen-Mozaffari, Farnaz Falaki, Maryam Amirchaghmaghi, Atessa Pakfetrat, Zohre Dalirsani, Shadi Saghafi-khadem

Assistant professor of Oral Pathology, Mashhad University Of Medical Sciences, Oral Medicine Department, Research Center of Mashhad Dental School, Azadi SQR, Mashhad, Iran

Correspondence:
Oral Medicine Department
Research Center of Mashhad Dental School
No: 91735, Vakil Abad BLV
Azadi SQR, Mashhad, Iran
FalakiF@mums.ac.ir

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Abstract

Objectives: Multifocal epithelial hyperplasia (MEH) is benign, asymptomatic oral disease with viral etiology. The frequency of this disease varies widely from one geographic region to another, and can vary, from 0.002 to 35% depending on the population studied.

Study design: Here we report the clinicopathological features of twelve cases of MEH referred to Oral Medicine Department of Mashhad Dental School for the first time in Iran. Records of patients with the diagnosis of MEH in our department during 7 years were analyzed and data were extracted.

Results: Most of the patients were younger than 20-year-old (66%), and females were predominantly affected (7:12). The mean age of onset was 12.72±10.14 years and the mean duration was 52.54 ± 78.51 months. Patients had multiple, well circumscribed, soft, non tender, flattened papules, with a color similar to the adjacent mucosa, in different areas of the oral cavity but the most affected site was buccal mucosa. Familial history of such lesions was negative in all patients. Only three cases showed spontaneous regression.

Conclusion: In spite of rare nature of this disease in Asia, it seems that it is not the case in Khorasan Province, southeast Iran.

Key words: *Focal epithelial hyperplasia, human papilloma virus, Heck's disease, Iran, case report, oral medicine.*

Introduction

Multifocal epithelial hyperplasia (MEH), previously known as focal epithelial hyperplasia (FEH, Heck's disease) is a relatively rare disease of the oral cavity in most countries (1).

It was first described by Estrada (1) in a Colombian Indian population and several reports from different countries have been published there after (2). The lesions appear as multiple, circumscribed, soft, non tender, flattened or rounded papules, with a color similar to the adjacent mucosa or a whitish color (1). Surface of the lesions is smooth and it varies from 0.1 cm to 1 cm in size, although papules may coalesce and give raise to a cobblestone appearance, several centimeters in diameter (3). In some cases a papillomatous surface has been reported (4). Flaitz has suggested compromised occlusion and sucking behavior as a cofactor in dissemination (4). The most common sites of involvement are the lips, buccal mucosa and the tongue, but in rare occasions soft palate or floor of the mouth may also be involved (4-6). The diagnosis is based on the clinical findings.

Histological findings consist of parakeratosis and acanthosis of epithelium which is the hallmark of focal epithelial hyperplasia. The ridges are widened, often confluent and sometimes club shaped (7). Koilocytic changes, similar to that seen in other HPV infections and nuclear degeneration resembling a mitotic figure (mitosoid cell), are the evidences for viral etiology (1,2).

Viral etiology was first suggested by Estrada and further investigators confirmed this hypothesis (8). Molecular techniques such as polymerase chain reaction (PCR) or in-situ hybridization can be used to examine the presence of human papilloma virus (HPV) in many instances. The most common associated subtypes are 13, 32, although Cross reaction with other subtypes (6,11,16,8,55) has also been reported (1,3,7).

Certain HLA subtypes have been related to this disease (9). Immunohistochemical analysis for cytokeratines has been performed on MEH lesions but the results were nonspecific like every other acanthotic epithelial lesion in oral cavity (2).

No treatment is necessary because of the regressive nature of the disease (1,3,7), unless in the case of interference with function or aesthetic (6). Surgical excision, electrosurgery, cryosurgery, sulfonamides, vitamin A, Co2 laser and alfa-2b interferon are suggested treatments (1,3,10).

Generally MEH is a very rare disease in Asia. We report 12 cases of MEH referred to Oral Medicine Department of Mashhad Dental Faculty. All of our patients were resident of Khorasan Province (Northeast, Iran).

Materials and Methods

In this retrospective study, records of twelve patients with the diagnosis of MEH were extracted from the archive of Oral Medicine Department of Mashhad Dental Faculty from December 2002 to March 2009 and demographic information, clinical features and histopathological characteristics of patients were recorded.

Results

Twelve cases of MEH were recorded that 7 cases were female and 5 were male. The age of our patients were between 8 to 43 years of age; with the mean age of 19.50 ± 13.04 (F: 16.57 ± 8.10, M: 23.60 ± 18.25). All the patients were otherwise healthy and from a middle socioeconomic group.

Clinical features

The predominant clinical feature in our patients consisted of multiple, well circumscribed, soft, flat top papules (Fig. 1 pt no. 3) In three cases, white color appearance was seen in buccal mucosa as a result of frictional keratosis. In others, the color was similar to adjacent mucosa. The most affected site was buccal mucosa, especially across the occlusal plan, (all of our patients), followed by lip mucosa or commissure (8:12 cases). One patient did not remember the exact time of appearance of lesions. Of the 11 reminders, the age of onset was from 7 to 42 years and the mean age at onset was 12.72±10.14 years. The duration of the lesions was from 2 months (a 9 year-old female) to 22 years (a 32 year-old female).

The mean duration time was 52.54 ± 78.51 months, approximately 4.5 years in 11 cases. There were not any other oral lesions in our patients. Only in 2 patients spontaneous regression was observed. Familial history of such lesions was negative in all patients. The clinical characteristics are summarized in (Table 1).

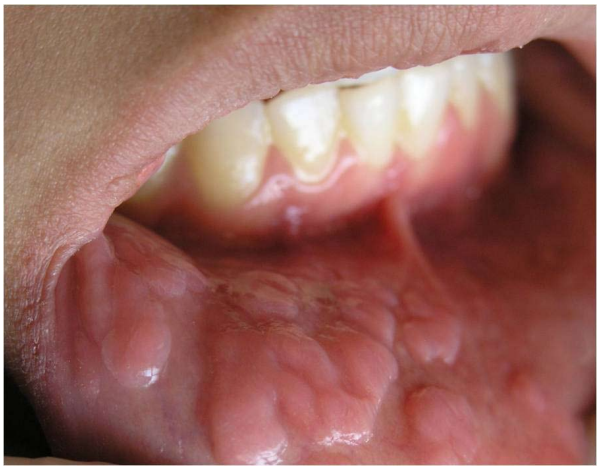

Fig. 1. Multiple, soft, well circumscribed, flat papules on labial mucosa and lip commissure of Pt. No.3.

Table 1. Characteristics of lesions clinically diagnosed as MEH disease.

Case	Age	Sex	Site	Age of onset	Duration	Regression	Association with HPV(type)
1	12	F	Buccal mucosa, Lower lip mucosa and commissure	11	6 months	No	Yes(13)
2	13	F	Buccal mucosa, Lower and upper lip mucosa, Retromolar pad	13	1 month	Yes(complete ,after 2 years)	Yes(32)
3	15	F	Buccal mucosa, Lateral border of the tongue, Attached gingiva	7	8 years	No	Yes(13)
4	12	F	Buccal mucosa, Lip commissure, Retromolar pad	7	5 years	Yes(complete ,after 5 years)	Yes *
5	13	M	Buccal mucosa,, Lip commissure Hard palate, Attached Gingiva	13	3 months	Yes(relatively)	Yes(13)
6	9	F	Buccal mucosa, Lateral border and dorsal of tongue	9	2 months	No	Yes(13)
7	43	M	Buccal mucosa, lateral boder of tongue	42	6 months	No	Yes(13)
8	32	F	Buccal mucosa, lateral boder of tongue	10	22 years	No	N-A
9	44	M	Buccal mucosa	?	Not determined	No	N-A
10	23	F	Buccal mocusa, Lower lip mucosa, Attached gingiva	15	7 years	No	N-A
11	10	M	Buccal mucosa, Lower lip mucosa and commissure	6	4 years	No	N-A
12	8	M	Buccal mucosa, Lower and upper lip mucosa and commissure, Attached Gingiva, Floor of the mouth	7	8 months	No	N-A

*This sample was strongly positive for HPV but none of 13,32,16 and 18 subtypes were positive.

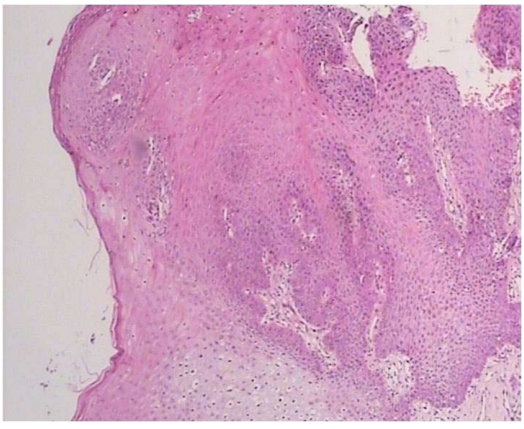

Fig. 2. Acanthosis of the epithelium with broad and elongated rete ridges (×100 Magnification, H&E).

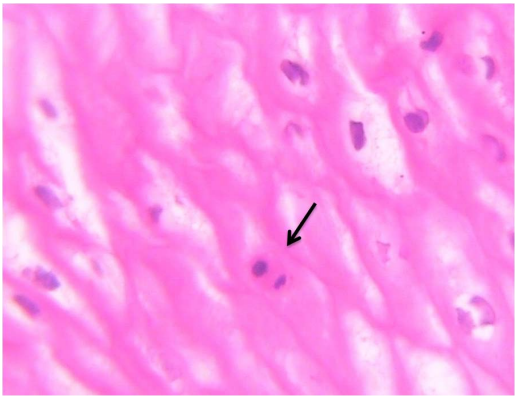

Fig. 3. Mitosoid figure a highly diagnostic feature of MEH (×400 Magnifications, H&E).

Histopathological findings

Acanthosis of the oral epithelium was the constant finding. Reteridges were widened confluent and at the same depth of adjacenct normal reteridges. (Fig. 2 pt no.3).

In three patients orthokeratinization of superficial epithelium was oblivious.

In 7:12 of patients PCR was performed to determine presence of HPV. It was positive in all of patients. Subtype 13 was detected in five patients and 32 in one patient. In one patient with strong reactivity for HPV, none of tested subtypes (13,32,16 and 18) were positive (Fig. 3).

Discussion

Multifocal epithelial hyperplasia (MEH) is a rare entity in Asia, but it seems that in northern east of Iran it is not uncommon. No report of this disease exists in Iran.

This disease appears in the first and second decades of life and frequently affects children but other age groups may also be involved. (3,7) We encountered a wide age range at onset (7 to 42 years).

The mean age of onset in our patients was 12 years that is more than previous reports (it has been 9-11 years) (1,8). Although poverty has been suggested as a relative factor in many studies (1-3, 8), but all of our patients were from a middle socio economic group.

Affirming to most studies, the majority of patients were female (7:12) (1,2,7,8), although some studies have reported a male predilection (2,11,12).

Familial involvement has been reported in most previous studies, but our patients didn't report such finding. Genetic predisposition (e.g. HLA-DR) and living in crowded conditions and use of common devices are possible causes of this concordance (1,2).

Clinically, multiple flat top papules with a color similar to adjacent mucosa were observed in different oral sites (1,2,8). In irritation areas whitish color due to keratosis was seen, as with previous reports (8,10). The most frequent site of involvement in our cases was buccal mucosa and lip commisure which was compatible with most studies (1,2,8), although lower lip mucosa, upper lip, ventral tongue and oropharynx have been reported in some series (8,10). Buccal lesions were distributed along the occlusal plan. In addition, lower lip and lateral tongue were affected more frequently than upper lip and other tongue portions respectively, suggesting trauma as a contributing factor.

Viral etiology was established in 7:12 of patients and HPV13 has been the most associated subtype (5 cases), that was similar to other studies (1,3,7,8,11). HPV32 was also positive in one patient. Although HPV13, 32 has been considered as etiologic factor in MEH, but there are only few reports about presence of HPV32 in the literature. This may be due to heterogenisity of the populations (8,13). Carlos in a study of 110 patients, noticed predilection of HPV13 for keratinized mucosa and subtype 32 for non keratinized mucosa (6).We couldn't assess this correlation because of small sample size. In one patient (Pt No.4) with strong reactivity for HPV, none of tested subtypes (13,2,16 and 18) were positive. She was a healthy 12- year-old girl without any evidence of sexual abuse or activity or genital involvement. This issue in addition to absence of tongue lesions excluded condyloma acuminatum as a possibility.

There is one study that suggests HPV 24 as etiologic factor in long standing types of FEH (previously known as Heck's disease) (14). Malignant transformation has been reported in this case, although accuracy of clinical diagnosis in that case remains doubtful. In our cases no malignant changes was observed even after 22 years duration (Case No.8).

MEH is considered as a regressive lesion, (1,3,7) but in our patients only 3:12 reported regression. Regression can be due to maturation of immune system in adulthood (1).

Duration of the lesions was between 2 months and 22 years. Catherine Flaitz, Ledesma-Montes and others reported duration of few months to 30 years, in their patients (1-4). Recurrence after regression is an occasional finding, although it sometimes depends on treatment modalities. We didn't see any recurrence in our regressed cases.

Differential diagnosis consists of condyloma acuminatum, verruca volgaris, papilloma, irritation fibroma, verusiform xantoma, juvenile papillomatosis and syndromes such as multiple endocrine neoplasia ш, neurofibromatosis, tuberous sclerosis, Cowden and Goltz-Gorlin.

The most confusing ones are condyloma acuminatum (C.A.) and irritation fibroma. In C.A. there are clustered papules with papillary surface in ventral tongue and floor of the mouth as a result of orogenital contact with an infected partner. MEH lesions tend to be flatter and more numerous and location of lesions is very characteristic.

If discrete papules are present, irritation fibroma should be considered in differential diagnosis. Pale appearance, increasing size and an obvious irritation can be helpful to distinguish fibroma from MEH.

Conclusion

Although MEH is considered a rare condition in Asia, in a 7 years period, 12 cases were observed in our area (northeast, Iran).Further epidemiologic studies are required to estimate the exact prevalence of this entity.

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