

## Case Report

# Multifocal epithelial hyperplasia in an adult female

## 一名成年女仕的多灶性上皮增生

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Multifocal epithelial hyperplasia is an uncommon benign condition characterised by multiple papular proliferation of oral epithelium. It is associated with human papillomavirus 13 and 32. This report describes a case of multifocal epithelial hyperplasia in a 43-year-old female from Saudi Arabia. The clinical criteria, histopathological features and immunohistochemical profile are discussed.

多灶性上皮增生是一種少見的良性皮膚病變，其特徵為多發的口腔上皮丘疹狀增生，與人類乳突病毒十三和三十二型有關。本報告描述一名四十三歲沙特阿拉伯女仕的多灶性上皮增生的個案，並討論其臨床診斷標準、組織病理學特徵和免疫組化染色概況等。

**Keywords:** Heck's disease, human papillomavirus, multifocal epithelial hyperplasia, p16, Saudi Arabia

**關鍵詞：**赫克氏病，人類乳突病毒，多灶性上皮增生，p16，沙特阿拉伯

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## Introduction

Multifocal epithelial hyperplasia (MEH) or Heck's disease is an uncommon asymptomatic proliferation of oral epithelium that was first reported in Latin American literature in 1956.<sup>1</sup> It usually presents in children and young adults as

multiple asymptomatic papules or nodules on the oral mucosa with female predominance.<sup>2,3</sup> Although this disease has been reported in the North, Central and South American Indians and the Eskimos living under a variety of environmental conditions, cases from other parts of the world are also reported.<sup>4-6</sup> The disorder is due to human papillomavirus (HPV) infection and HPV 13 and 32 DNA has been consistently detected in these lesions.<sup>7,8</sup> The factors that determine disease susceptibility are not fully understood, but immunocompromised status and genetics are thought to play a major role in the vulnerability to HPV 13 or 32 viruses infection.<sup>9,10</sup> We report a case of MEH with discussion of the clinical, histopathological, and immuno-histochemical (IHC) diagnostic features in an adult Saudi female.

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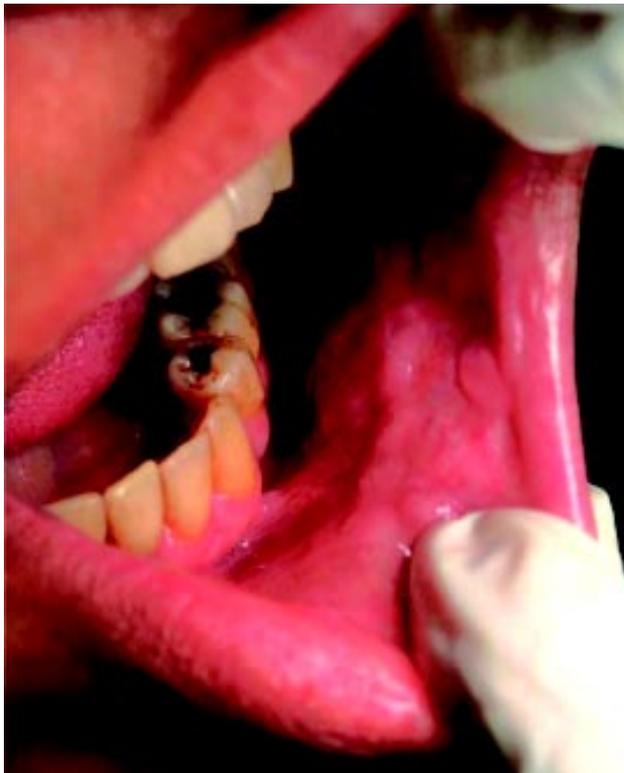
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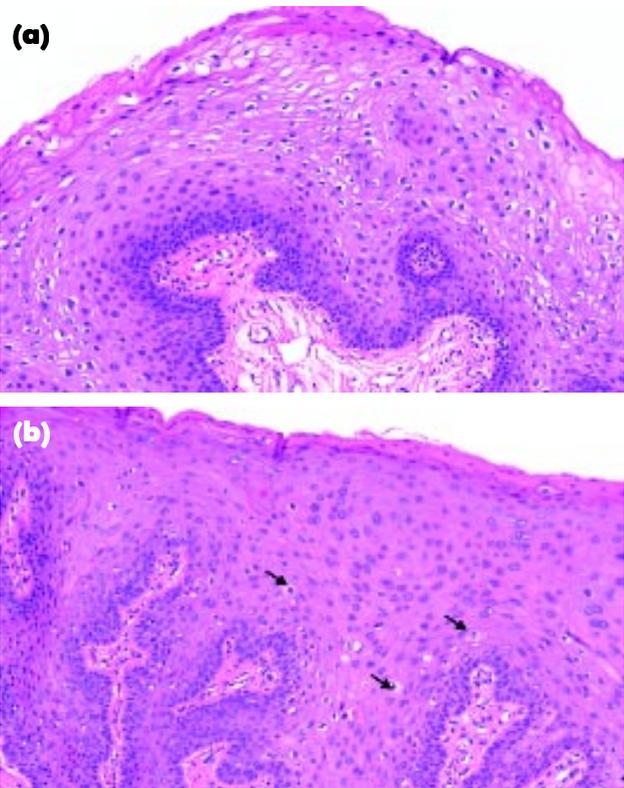
## Case report

A 43-year-old Saudi female was referred to the oral medicine clinic at the College of Dentistry, King Saud University for evaluation of "lip swellings" incidentally discovered during routine dental visit. The medical history revealed vitamin D deficiency and a recent history of alternating episodes of constipation and diarrhoea. Intraoral examination revealed multiple cobblestone-like papules, situated on the upper and lower labial mucosa and right and left buccal mucosa (Figure 1). Though the patient was aware of the lesions for several years, she assumed that they were normal. An incisional biopsy was taken from the buccal lesions under local analgesia (2% lignocaine HCL with 1:80,000 adrenaline) to rule out Crohn's disease. The biopsy specimen received in histopathology laboratory consisted of a (1.3x0.5x0.2 cm) wedge-shaped soft tissue fixed in 10% formaldehyde. Microscopically, the haematoxylin and eosin (H&E)-stained sections

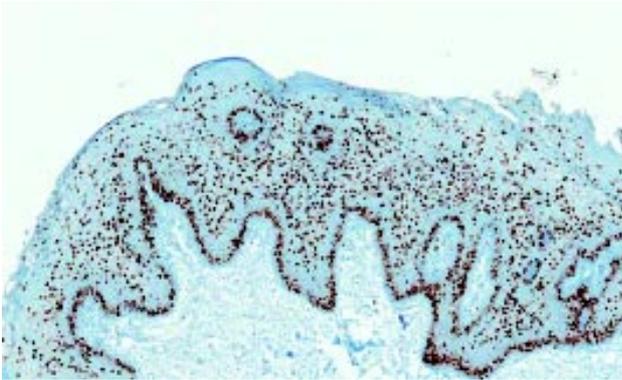


**Figure 1.** Labial and buccal mucosa showing multiple papular lesions.

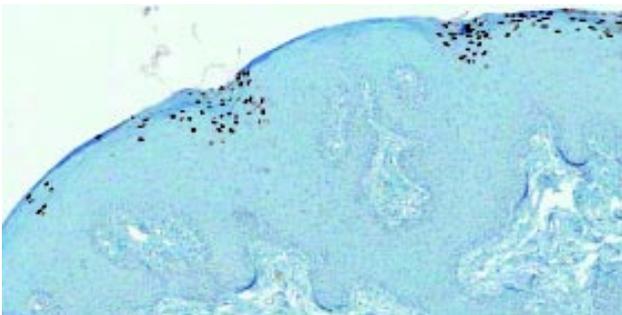
showed fragments of oral mucosa exhibiting parakeratosis and acanthosis. Koilocytic changes and few mitosoid bodies were evident (Figures 2a and 2b). The clinicopathological features were suggestive of multifocal epithelial hyperplasia. Polymerase chain reaction for the detection of HPV was not available in our laboratory, so immunohistochemical detection was performed on the formalin-fixed, paraffin-embedded tissue using the following markers: anti-p16 (CDKN2A/p16INK4a, 1:50, Abcam), anti-Ki-67 (MM1 mouse, 1:100, Novocastra) and anti-HPV (4C4 mouse, 1:5, Novocastra). The immunostaining was strongly positive for Ki-67, HPV and negative for p16 (Figures 3 and 4). The patient has been kept under observation for her oral lesions and referred to an internal medicine specialist to evaluate the gastrointestinal tract symptoms.



**Figure 2.** (a) The overlying epithelium exhibits parakeratosis, koilocytosis and basal cell hyperplasia (H&E, original magnification x 20). (b) Several mitosoid figures in the spinous cell layer (H&E, original magnification x 40).



**Figure 3.** Ki-67 expression in all epithelial layers. (Ki-67- IHC, original magnification x 20).



**Figure 4.** Multifocal reactivity to anti-HPV antibodies within the superficial epithelium. (HPV 4C4, IHC, original magnification x 40).

## Discussion

The diagnosis of MEH is not of significant challenge provided that comprehensive intra- and extra-oral examination is made and patient's medical history is carefully reviewed. However, atypical presentation of the disease, especially in an adult patient with systemic symptoms and signs, may obscure the diagnosis. The differential diagnosis of multiple papular lesions of oral mucosa with a cobblestone appearance includes multiple hamartoma syndrome (Cowden disease), pyostomatitis vegetans, Crohn's disease, multiple endocrine neoplasia syndrome (MEN 2B) and MEH.<sup>11</sup> The clinical appearance of isolated lesions in MEH is uncommon, though it is frequently confused with papilloma, condyloma acuminatum or lesions related to child abuse.<sup>3</sup> Typically, MEH presents as multiple, asymptomatic, well-

demarcated, papular lesions ranging in size from a few millimetres up to 1 cm. They are usually sessile with a smooth or papillary surface. While the papular lesions may be scattered over the oral mucosa, these lesions are typically clustered with a tendency to confluence, presenting sometimes with a cobblestone or fissured appearance. It primarily affects the lips, lateral borders of the tongue and the buccal mucosa bilaterally, sparing the attached oral mucosa, floor of mouth, soft palate and oropharynx.<sup>3,12</sup>

An adequate and representative biopsy of the lesions is recommended to confirm the clinical diagnosis and areas of ulceration should be avoided. Multifocal epithelial hyperplasia shows a spectrum of histopathological changes. The diagnostic features include epithelial hyperplasia and acanthosis. The surface usually exhibits parakeratosis and some superficial epithelial cells show koilocytosis which is considered one of the specific cytopathic effects of HPV.<sup>7,12</sup> Some keratinocytes in the spinous layer show abnormal nuclei with coarse, clumped chromatin similar to a mitotic figure, hence these cells are called mitosoid cells or mitosoid bodies. Mitosoid figures are reported to be seen in more than 90% of the cases.<sup>13</sup>

In most of the cases, the diagnosis is straightforward from the clinical and histopathological features. Polymerase chain reaction (PCR) and DNA sequencing might be indicated in doubtful situations to confirm the diagnosis and identify the HPV subtype.

Ancillary studies of HPV subtyping such as PCR testing and HPV in-situ hybridisation (ISH) analysis were not available in our laboratory; therefore, we followed the protocol adopted by the affiliated hospital in cases of cervical biopsies suspicious for high-risk HPV. Immunohistochemical detection of HPV, p16 and Ki-67 was performed.

Expression of p16INK4a and Ki-67 has been used in conjunction with HPV detection as biomarkers in cervical intraepithelial neoplasia (CIN) and is

correlated with high-risk HPV infection.<sup>14</sup> However, p16 is overexpressed in a subset of oral tumours apparently lacking evidence for the presence of HPV DNA.<sup>15</sup> p16INK4a is one of the most well-known indirect markers of HPV integration. It acts as a tumour suppressor by blocking cdk4- and cdk6-mediated retinoblastoma tumour-suppressor protein (pRb) phosphorylation, resulting in the inhibition of E2F dependent transcription and inhibition of cell cycle progression at the G1 to S checkpoint.<sup>16</sup> The expression of the human Ki-67 protein is strictly associated with cell proliferation. The fact that the Ki-67 protein is present during all active phases of the cell but is absent from resting cells makes it an excellent marker for determining the so-called growth fraction of a given cell population.<sup>17</sup>

The immunohistochemical profile of the current case is in support of low-risk HPV infection in which p16 might be negative with increased proliferative activity of the keratinocytes as shown by the overexpression of Ki-67. It is well documented that the majority of MEH cases are caused by HPV 13 and less commonly HPV 32.<sup>18</sup> Anti-papillomavirus antibody (clone 4C4) used in this report is specific for HPV types 6, 11 and 18 but might cross-react with other HPV types. Therefore, the absence of epithelial dysplastic changes associated with specific clinical presentation precludes high-risk HPV involvement.

Multifocal epithelial hyperplasia is described in most of the reports as a benign condition that tends to heal spontaneously and therefore requires no treatment, except when the lesions lead to functional or aesthetic impairment.<sup>13,19</sup> Several treatment modalities have been reported such as surgery, cryotherapy, CO<sub>2</sub> laser ablation and interferon- $\alpha$ .<sup>20,21</sup> Follow-up of the patients is essential for the evaluation of treatment outcomes since recurrences are not uncommon.

In conclusion, to the best of our knowledge, this is the first report of MEH in an adult Saudi female. While MEH is an uncommon disease, particularly

in adults, it should be included in the differential diagnosis of multiple papular lesions affecting oral mucosa. Critical medical history and comprehensive clinical examination are required to rule out more serious systemic conditions associated with multiple oral papular lesions.

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