

## Pseudoepitheliomatous Hyperplasia in Oral Lesions: A Review

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### Abstract:

Pseudoepitheliomatous hyperplasia (PEH) is a histopathological reaction pattern to various stimuli, which includes trauma, infection, inflammation, neoplasia. It is seen as tongue like epithelial proliferation invading the connective tissue and should not be mistaken for squamous cell carcinoma (SCC). This review enlists oral lesions which exhibit PEH with a note on how to differentiate SCC from PEH.

**Key Words:** Pseudocarcinomatous hyperplasia, pseudoepitheliomatous hyperplasia, squamous cell carcinoma

### Introduction

Pseudoepitheliomatous hyperplasia (PEH) is a reactive epithelial proliferation seen in response to wide variety of conditions including infections, neoplasia, inflammation and trauma. It is characterized by hyperplasia of epidermis and adnexal epithelium and it closely mimics squamous cell carcinoma (SCC). Some authors use pseudocarcinomatous hyperplasia for the same. Other terms used in the literature to designate PEH are invasive acanthosis, verrucoid epidermal hyperplasia and carcinomatoid hyperplasia.<sup>1</sup> The function of PEH is unclear and is hypothesized to be physiological response to several forms of skin damage. It is thought to act as defensive mechanism for transepithelial elimination of foreign body material.<sup>2</sup>

### Clinical Features

PEH is a reactive process to an external stimuli or underlying disease process. Clinically it does not present with distinctive features. Usually, PEH is seen as a well-demarcated plaque or nodule with variable degrees of scaling and crusting. Ulceration

may be present. Papules or nodules may range from <1 cm as in Granular cell tumor to several centimeters in diameter as seen in deep fungal infections. Color of the lesion may be as that of mucosa or pigmented in case of melanoma.<sup>3</sup>

### Histological Origin of PEH

PEH appears to be proliferating from overlying epithelium although studies have shown it to be arising from interfollicular epithelium, eccrine units and other skin adnexae. Hanly *et al.* from their study observed PEH mostly in mucosal surfaces rich in salivary glands and suggested it to be probably of glandular origin.<sup>4</sup> In a study by Mott *et al.* it was concluded to be from both epidermis and the adnexae.<sup>5</sup> These findings were reproduced by Fu *et al.* in their study.<sup>6</sup>

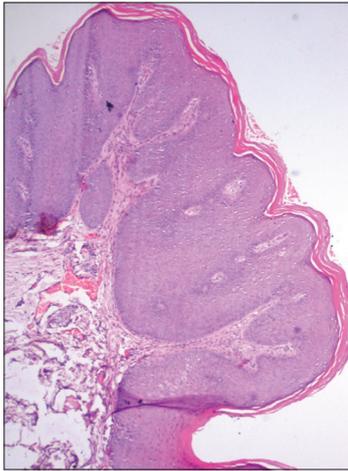
### Histopathology of PEH

PEH involves a degree of epithelial thickening, the epithelial stromal interface in this pattern is less well defined and the proliferating epithelial tongues tend to anastomose entrapping the stromal compartment.<sup>7</sup> At scanning magnification, PEH consists of elongated thick downward projection of the epidermis usually with jagged borders and a sharply pointed base. There is often hypergranulosis and ortho- or parakeratosis. PEH can also feature concentric layers of unusually looking keratinocytes with a focus of central keratinization, which is keratin pearl formation. Mitotic figures may be seen, but they are not numerous or atypical<sup>3</sup> (Figures 1 and 2).

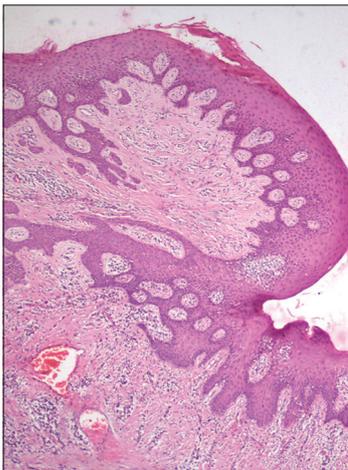
### PEH and SCC

It is often difficult to distinguish PEH from SCC because of histological similarities especially in small oral biopsy specimens. Histopathological features that favor SCC include presence of nuclear atypia, increased mitosis, individual necrotic keratinocytes, and epithelial invasion deep into the connective tissue. In PEH care should be taken to identify underlying disease process. A thorough clinical examination and multiple sections usually help in arriving at the diagnosis, although sometimes additional biopsy may be required. In mucosal membranes, distinguishing SCC from PEH becomes critical because mucosal SCC has poor prognosis with early local infiltration and lymphnode metastasis.<sup>8</sup>

Many immunohistochemical markers are used in various studies in an attempt to differentiate PEH and SCC. Study by Zarovnyaya and Black using p53, E-Cadherin and matrix metalloproteinases-1 (MMP-1) found that SCC showed increased staining for p53 and MMP-1 whereas E-cadherin



**Figure 1:** Hematoxylin and eosin stained section showing tongue like epithelial proliferations in small oral biopsy specimen  $\times 10$ .



**Figure 2:** Hematoxylin and eosin stained section  $\times 10$  pseudoepitheliomatous hyperplasia seen in non-specific chronic inflammatory lesion.

showed less intense staining.<sup>8</sup> Furthermore, there was p53 nuclear staining restricted to basal cell layer in PEH a striking feature useful to differentiate the two entities.<sup>9</sup> Other studies using AgNOR,<sup>10</sup> PCNA,<sup>11</sup> Langerhans cells<sup>12</sup> were of limited value and more studies are required in this field.

Since PEH is a reactive response to underlying disease process, it can be seen in variety of conditions. Lesions which consistently show PEH and has been enlisted in pathology textbook and journal<sup>13-15</sup> are considered as associated with PEH and have been described in this review. The lesions which are documented in literature search as incidental finding/case report fall in the second category in this review.

Oral condition associated with PEH:

- Blastomycosis<sup>17</sup>
- Wegener's granulomatosis<sup>19-21</sup>
- Granular cell tumor (GCT)<sup>22,23</sup>
- Necrotizing sialometaplasia (NS)<sup>24-26</sup>

- Pemphigus vegetans (PV)<sup>27,28</sup>
- Median rhomboid glossitis<sup>29</sup>
- Epulis fissuratum<sup>30</sup>
- Chronic hyperplastic candidiasis<sup>30</sup>

Oral conditions that may show PEH:

- Oral malignant melanoma<sup>31</sup>
- Intramucosal nevus<sup>32</sup>
- Spitz nevus<sup>33</sup>
- Oral squamous acanthoma<sup>34</sup>
- Oral submucous fibrosis<sup>35</sup>
- Actinomycosis<sup>36</sup>

### Lesions that are Associated with PEH

#### **Blastomycosis**

Blastomycosis is a granulomatous disease with systemic manifestations caused by the dimorphic fungus known as *Blastomyces dermatitidis*. The disease is endemic in eastern half of United States. Infection is acquired by inhalation of spores. Most cases are asymptomatic although few may have pulmonary complaints.<sup>16</sup> Histological examination of the lesional tissue shows features of granulomatous inflammation with brisk neutrophilic infiltrate. Within the infiltrate, there are large spherical double contoured 8-15  $\mu\text{m}$  multinucleated yeast. Budding forms have a characteristic broad base. They may be rare, and special stains (periodic acid-Schiff, Grocott's methenamine silver) may help reveal their presence.<sup>1</sup> The inflammatory reaction often causes proliferation of the overlying epithelium resulting in marked PEH which has striking resemblance to SCC. Therefore careful examination of the tissue is required.<sup>16</sup>

#### **Wegener's granulomatosis**

Wegener's granulomatosis is an idiopathic disease characterized by systemic vasculitis of small arteries and veins, necrotizing granulomatous lesions of respiratory tract and necrotizing glomerulonephritis.<sup>18,19</sup> Most clinical characteristics of this disease are non-specific, making clinical diagnosis challenging. Oral lesions are characterized by hyperplastic gingival tissue described as "strawberry gingivitis" where gums resemble over ripe strawberries which is considered nearly pathognomonic feature by Stewart *et al.*<sup>20</sup> Diagnosis of Wegener's granulomatosis in oral lesions is based on clinical presentation, serum positivity for cANCA and histopathologically presence of PEH, micro-abscesses and multinucleate giant cells.<sup>21</sup>

#### **GCT**

Granular cell tumor is a benign neoplasm, first described in 1926 by Abrikossoff. It occurs in the head and neck region, and the tongue is the most common location. A wide variety of cell types has been proposed as the cells of origin, including histiocytes, fibroblasts, myoblasts, neural sheath cells, neuroendocrine cells, and undifferentiated mesenchymal cells. Histogenesis of this lesion is controversial despite many studies. Currently based on the close anatomical

relationship of GCTs to peripheral nerve fibers; ultrastructural demonstration of myelin figures and axon-like structures; immunohistochemical reactivity with S-100 protein, neuron-specific enolase and myelin proteins, a neural origin (schwann cell type), is in favor.<sup>22</sup>

Histopathologically GCT is characterized by the accumulation of plump cells with abundant granular cytoplasm. Surface epithelium may or may not show proliferative changes in the form of PEH which may sometimes be mistaken for SCC in small oral biopsy specimen.<sup>23</sup>

#### **Necrotizing sialometaplasia**

NS is a benign self-limiting inflammatory salivary disorder. Etiology is unknown, but it appears to result from infarction caused by the use of local anesthesia, alcoholic abuse, traumatic injury, surgical procedure, upper respiratory infection, allergies and is seen mostly in smokers.<sup>24</sup> NS primarily affects the minor salivary glands of the palate appearing as a raised ulcer with erythematous border. It is a self-limiting condition, which heals over 5-8 weeks.<sup>25</sup>

Characteristic histological features of NS shows undisturbed lobular architecture of salivary gland tissue, squamous metaplasia of the ducts and acini, PEH of the overlying epithelium and mixed inflammatory cell response. PEH of the overlying squamous mucosa is commonly present when the lesion involves the palate.<sup>26</sup> NS mimics malignancy both clinically and histologically hence careful examination of the tissue is required to arrive at the diagnosis.<sup>37</sup>

#### **Pemphigus Vegetans**

Pemphigus vulgaris is an autoimmune disorder characterized by production of IgG auto antibodies against intercellular adhesion protein desmoglein, leading to acantholysis. Pemphigus vegetans is a rare variant of Pemphigus vulgaris characterized by heaped up, cauliflower-like vegetating plaques in the flexures.<sup>38</sup> Oral involvement is common characterized by cerebriform tongue,<sup>27</sup> cobble stone mucosa.<sup>28</sup> On microscopy Pemphigus vegetans exhibits hyperkeratosis, papillomatosis, acanthosis and suprabasilar clefts with acantholytic cells.<sup>39</sup> Presences of an eosinophilic response, formation of microabscesses, and extent of vesiculation have been proposed as possible histopathological features for distinguishing pemphigus vegetans from pemphigus vulgaris.<sup>40</sup> Direct immunofluorescence of perilesional skin demonstrates intercellular IgG and occasionally C3. Indirect immunofluorescence is positive for circulating IgG in the majority of patients.<sup>41</sup>

#### **Chronic hyperplastic candidiasis**

Chronic candidal infections are capable of producing a hyperplastic tissue response. They are seen inducing PEH in chronic inflammatory conditions such as inflammatory papillary hyperplasia, median rhomboid glossitis, epulis fissuratum.<sup>30</sup>

#### **Median rhomboid glossitis**

This is a depapillated rhomboidal area in the centre line of the dorsum of tongue anterior to the circumvallate papillae, earlier considered to be the persistence of tuberculum impar. Later studies have concluded it to be due to candidal infection. The similar lesion can be seen on the palate in the corresponding site and is known as kissing lesion. Usually, the patient is a smoker. A similar lesion may be seen in HIV disease or precipitated by corticosteroids. A biopsy is not usually needed as the location is typical and tumors are rare at this site. Anti-fungal therapy resolves the lesion distinguishing it from carcinomatous changes. Histology however may show pseudocarcinomatous features.<sup>42</sup>

#### **Epulis fissuratum**

Epulis fissuratum is a tumor-like hyperplasia of fibrous connective tissue that develops in relation to an overextended or ill-fitting denture. It appears as a single or multiple fold or folds of hyperplastic tissue in the alveolar vestibule. The size of the lesion can vary from 1 cm in size to massive lesions that involve most of the length of the vestibule. Histopathology features fibrous connective tissue and hyperplastic epithelium, few cases exhibiting PEH. It is usually treated by relining or rebasing of the ill-fitting denture.<sup>42</sup>

#### **Conclusions**

PEH is a reactive florid epithelial proliferation that may be observed in oral biopsy specimens. They are usually indicators of underlying pathology. Careful evaluation based on the clinical and histopathological features help to arrive at the diagnosis.

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