



Pseudoepitheliomatous hyperplasia: A review of oral lesions

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ABSTRACT

Pseudoepitheliomatous hyperplasia is a histological reactive pattern of surface epithelium in response to various stimuli from the underlying connective tissue which frequently mimics squamous cell carcinoma. So, differentiation of this entity is of utmost important in the view of treatment planning and approach. This review focuses on those lesions which are encountered in the head and neck region and also the recent concepts related to it.

Keywords: Pseudoepitheliomatous hyperplasia, squamous cell carcinoma, oral lesions.

INTRODUCTION

Pseudoepitheliomatous hyperplasia (PEH) is an abnormal reactive proliferation of the surface epithelium as irregular squamous strands extending down into the underlying connective tissue. It is considered as a histopathological reaction pattern rather than a disease process which should be differentiated from other lesions.^[1] It may involve the epidermis of the skin or the surface epithelium of oral mucosa. These reactive lesions have the histological appearance of exuberant proliferation of epithelium which can frequently be misdiagnosed as squamous cell carcinoma. Although they mimic a neoplastic growth, these set of lesion has to be differentiated from the neoplasms, so that extensive radical treatment can be avoided to treat these lesions.^[2]

Majority of these cases are associated with dermatological diseases; but gingiva, palate and tongue also shows similar lesions.^[3,4] In the palate, necrotizing sialometaplasia and post-resected area of pleomorphic adenoma are associated with pseudoepitheliomatous hyperplasia. Few cases were also reported following tattooing of skin.^[5]

These groups of lesions are categorized as either primary PEH (eg. Primary gingival PEH), or secondary as in case of granular cell tumour or chronic irritation.^[6]

Histopathological appearance:

They exhibit irregular or tongue-like proliferation of the squamous epithelium into the underlying connective tissue. These findings may mimic squamous cell carcinoma, but the hyperplastic cells fail to demonstrate cytologic features of malignancy, even though they may represent reactive atypia. They may have jagged margins, or pointed mass exhibiting keratin pearls.^[7] Histologically, they exhibit extensive acanthosis, for which they are also referred to as invasive acanthosis. The epithelial component may also exhibit few mitotic figures. Other names which were used to refer these lesions are pseudocarcinomatous hyperplasia, verrucoid epidermal hyperplasia, invasive epidermal hyperplasia.^[8] The connective tissue component can show variable extent of inflammatory exudate, but no evidence of vascular or perineural invasion. Some of the glandular structures, if any, may exhibit squamous differentiation.^[7]

Clinical appearance:

There is no distinct clinical picture for PEH. It may present as an elevated nodule, or represent those raised margins of the chronic non-healing wounds. The nodular growth rarely exceed beyond 1 cm, with the exception of granular cell tumour in which the tumour present as several centimeter larger lesion. They may also appear as verrucous growth or smooth/warty dome-shaped lesions. The colour of the lesion also depends on the nature of the underlying condition or inflammation and the depth of the lesion.

Diagnosis of these lesion mainly arrived by biopsy of the lesion, by which it can be confirmed of their reactive nature and not of neoplastic nature, treat them by local conservative approach.^[8]

Mechanism of PEH:

Though the exact pathogenesis of these lesions is unknown, most of them are believed to be due to the effect of the cytokines released from the inflammatory process or from the underlying tumour cell mass. Frequently associated findings which favour or assist these conditions are chronic persistent inflammation in the adjacent areas, chronic non-healing wound, ulcer, infection (mycobacterial, fungal and parasitic), malignancy and retained foreign bodies. They are most commonly observed in case of chronic non-healing wound. Other miscellaneous lesions which can simulate PEH are HIV infected individuals subsequently infected with varicella zoster^[9] and ingestion of halides, presenting as halogenoderma, the histopathological picture of which are very similar to that of deep seated fungal infection.^[10]

Histogenesis of PEH and its related theories mainly revolve around the effects of cytokines released by inflammatory cells or tumour cells. Of the cytokines, most commonly deregulated cytokines are epidermal growth factor (EGF), Transforming Growth Factor- α (TGF- α), Epidermal Growth Factor Receptor (EGFR), Fibroblast Growth Factor (FGF) and Platelet Derived Growth Factor (PDGF).^[11] Among these cytokines, TGF- α , appears to be primarily involved in PEH secondary to tumours.^[12]

In case of PEH, the balance between epithelial and fibroblastic activity are probably altered or lost, thereby leading to chronic exuberant proliferation of epithelial component. Also the extended period of normal inflammatory phase of wound healing is also suggested to be a pathogenic mechanism for PEH. In this case, most common cited factors are cytokines 1, 10, 14.^[13]

Chronic wound with PEH:

Re-epithelization of wound is carried over by the leap frog mechanism of keratinocytes. At the margin of wound, keratinocyte migrate upto 2 or 3 cell length and gets fixed in that position and successive cells migrate over this cell, and this process continues till the entire wound surface is bridged or epithelized. Normally, there will be an increased proliferation of keratinocyte just behind the migrating keratinocyte. Furthermore, basal keratinocyte also secrete MMP-1 which can degrade the matrix formed by the granulation tissue. After complete bridging of wound surface, contact inhibition (with integrins) ceases the production of MMP-1.

In case of persistent irritation of the wound bed, proliferating keratinocyte may still be located at the border of the ulcer, not moving towards the centre of the wound. Along with that, cytokines continue to be produced in the wound, MMP-1 goes uninhibited, all factors favouring the proliferation of keratinocyte in an abnormal fashion.^[14]

Difference between squamous cell carcinoma and PEH:

In contrast to squamous cell carcinoma, these reactive lesions neither exhibit atypical mitotic figures, atypical nuclei, individual dyskeratotic keratinocyte; nor display vascular, lymphatic or perineural invasion.

Other findings, which can help differentiating squamous cell carcinoma from PEH were studied. Langerhans cells in squamous cell carcinoma are found in a very low density compared to that of PEH. This finding was correlated with decreased expression of E-Cadherin in squamous cell carcinoma.^[15] Also expression of p53 is increased in case of squamous cell carcinoma compared to that of PEH^[16] and the expression of p53 is mostly restricted to the basal layer in case of PEH, which is in contrast to the squamous cell carcinoma, where it involves more superficial dysplastic cells.^[11] Studies based on the proliferative potential of both the lesions using PCNA were studied and no significant differences were observed.^[8]

Classification of PEH:

Category	Disease
Bacterial infections ^[10]	Atypical mycobacterial infections (<i>M. marinum</i>) Granuloma inguinale
Fungal/parasitic infections ^[13,17]	Blastomycosis Paracoccidioidomycosis Aspergillosis Cutaneous leishmaniasis
Skin/mucosal lesions ^[18, 11, 19, 10, 29]	Prurigo nodularis Verrucous stage of incontinentia pigmenti Pyoderma/pyostomatitis vegetans Pyoderma gangrenosum Verruciform xanthoma Wegener's granulomatosis Hypertrophic lichen planus Median rhomboid glossitis Keratoacanthoma TUGSE (Traumatic Ulcerative Granuloma with Stromal Eosinophilia)
Neoplastic lesions ^[3, 20, 21, 4, 10]	Granular cell tumour Intramucosal nevi Spitz nevi Melanoma Cutaneous T-cell lymphoma (CD 34+ lymphoproliferative disorders) Pleomorphic adenoma
Chemical induced ^[10]	Halogenoderma
Allergic or foreign body response ^[5]	Tattoo

Pseudoepitheliomatous hyperplasia with intraepithelial microabscesses of neutrophils:^[10]

- i. Pyoderma gangrenosum
- ii. Pemphigus vegetans
- iii. Pyoderma vegetans
- iv. Atypical mycobacterial infection
- v. Deep fungal infection
- vi. Keratoacanthoma
- vii. Halogenoderma

PEH in fungal infection:

Systemic mycosis like paracoccidioidomycosis, have the usual presentation of chronic infection with a granulomatous histological picture. These granulomatous reactions are associated with PEH like features. Since their histological appearance is similar to that of squamous cell carcinoma, studies were done correlating the proliferative nature of PEH associated with fungal infections and squamous cell carcinoma. Proliferative markers Ki-67 and p53 expression were compared and concluded that proliferative index and p53 expression of PEH was comparable to that of the normal tissue and both of which are lesser than that of squamous cell carcinoma.^[13] Some authors also advocate that PEH was one of the mechanisms for elimination of deep seated fungal organism through trans-epithelial route.^[17]

PEH in malignant melanoma:

The association of PEH with malignant melanoma is considered to be very rare, although they are commonly seen in other benign pigmented lesions like Spitz nevi and intramucosal nevi. Regarding the origin of PEH in oral melanoma, it was suggested to be the surface epithelium, whereas the skin lesion are said to have developed from the eccrine glands.^[3] Mott et al analysed the pattern of melanoma cases showing PEH. Among the 13 reviewed cases of melanoma with PEH features, 69% of PEH have acanthosis, hyperkeratosis, papillomatosis and irregular infiltration of epithelium into the underlying connective tissue in the form of squamous eddies. The remaining 31% of cases showed basaloid acanthosis, laminated orthokeratosis and horn cysts.^[22]

Granular cell tumour:

Benign neoplasm which exhibits predominantly polygonal tumour cells with abundance of granules in the cytoplasm and have a small nucleus. These tumour cells usually grow in sheets or nest which are poorly circumscribed in nature. Earlier, these tumours were thought to arise from the muscle; but after several studies, it was suggested that these tumour arise from the nerve and its related structures. So to avoid confusion, the terms which were previously used, granular cell myoblastoma and granular cell neuroblastoma were suspended and the common terminology of granular cell tumour was adapted. Frequently, these tumour exhibit PEH of the surface epithelium, although the mechanism of such features is not clear.^[23] Since most of the PEH are induced by the effect of growth factor on surface epithelium, studies focused on EGFR, EGF and TGF were carried out and compared with normal

epithelium. Among these factors, TGF- α is expressed more in granular cell tumour, implicating its role in epithelial cell proliferation.^[24]

However, there are few studies done with the expression the expression of calretinin in the granular cell tumour. Calretinin positivity was noticed more in the interface between the epithelium and the tumour cells, suggesting that calretinin may be one of the factors which can influence the epithelium to have hyperplastic feature.^[20]

Lichen planus:

Hypertrophic lichen planus are sometimes confused with PEH and in these cases, the differentiation becomes important as there is a slight chance of malignant transformation of lichen planus. Immunohistochemical attempts were made by Lee *et al* using p53 to differentiate PEH in lichen planus and squamous cell carcinoma. The results indicated expression of p53 in all PEH and 75% of squamous cell carcinoma, but the only difference in the intensity of the staining is lower in PEH compared to the squamous cell carcinoma. This result was not significant like other previous studies, which showed preservation of E-cadherin, Langerhans cell, CD1a positivity in PEH, which were significantly decreased in squamous cell carcinoma.^[16, 25]

Necrotizing sialometaplasia:

Benign appearing, self-healing lesion of salivary gland origin, mostly located in the hard palate, although any area of oral cavity having salivary gland tissue are prone to develop this lesion. The exact cause for the lesion is unknown, but it was believed to be due to trauma after local anaesthesia, traumatic injury, previous surgery, ill-fitting dentures, and upper respiratory infections.^[19] Clinically these lesions present as sharply circumscribed ulcer in the hard palate, with raised hyperplastic borders. These hyperplastic borders represent PEH appearance of the lesion, which is noticed in almost all cases of necrotizing sialometaplasia. Along with the borders, squamous metaplasia of ducts and acini, intact lobular architecture (key feature), infarct in lobules with or without mucin spillage and inflammation secondary to mucin spillage are also noticed. These tumours have to be differentiated from squamous cell carcinoma and mucoepidermoid carcinoma. In most of the cases, clinical presentation, along with normally oriented hematoxylin-eosin section, depicting the intact lobular architecture, ductal squamous metaplasia, lack of cellular atypia can lead to the diagnosis.^[26]

Pemphigus vegetans:

Although representing only 1 to 2% of pemphigus, their healing pattern necessitates the separation of this entity. Oral lesions are most commonly seen in gingiva with a purulent surface on a red base. Those denuded areas due to the bullae, attempt to heal by formation of vegetation of hyperplastic granulation tissue. PEH seen only in the advanced lesions, whereas early lesion may exhibit suprabasilar acantholysis.^[10] The features which distinguish pemphigus vegetans with that of pemphigus vulgaris are the presence of extensive infiltration of eosinophils, microabscess formation, and the extent of vesiculation.^[27]

Wegener's granulomatosis:

It is an uncommon disease of unknown cause, characterized by granulomatous lesion involving the respiratory tract, necrotizing glomerulonephritis and systemic vasculitis involving small arteries and veins. Oral lesions are represented by the classical strawberry gingivitis, which most frequently manifest before renal symptoms. Histopathology of oral lesion often shows subepithelial abscesses, along with PEH.^[19]

Miscellaneous lesions:

1. **Median rhomboid glossitis:** An area of depapillated zone in central aspect of dorsum of tongue just anterior to circumvallate papilla. Previously, it was suggested to be developmental defect of persistence of tuberculum impar. Later studies concluded that they are actually caused by candidal infection, which was further proved by resolution of the lesion after administration of antifungals agents. Other fungal lesion which may show features of PEH is chronic hyperplastic candidiasis.^[28]

2. **Epulis fissuratum:** Tumour like growth on the flange region of the ill-fitting denture, characterized by fold of tissue. Although the characteristic histopathological feature is the hyperplasia of fibrous connective tissue, the overlying epithelium exhibits hyperparakeratosis or in some circumstances manifest as PEH.^[19]

3. **TUGSE (Traumatic Ulcerative Granuloma with Stromal Eosinophilia):** A chronic, self-limiting reactive lesion of the oral cavity, most commonly seen in the tongue, although it can be seen in any other oral mucosal regions. It is suggested to be an exaggerated response to trauma, appearing clinically as an area of erythema, surrounding an ulcer covered by fibrinopurulent membrane, with rolled out borders. These lesions can occur at any age, but similar lesions are also observed in infants between one week and one year, referred to as Riga-Fede's disease. Hyperplasia of the surface epithelium is frequently observed in the borders of the lesions. Pathogenesis of the lesion is suggested to be the exaggerated response due to the interaction of mast cells with eosinophils, with the release of inflammatory mediators, resulting in chronic inflammatory response as well as tissue destruction.^[29]

CONCLUSION

Pseudoepitheliomatous hyperplasia are reactive epithelial lesions, in response to various stimuli in the adjacent areas, which can be frequently misdiagnosed as malignancy. To avoid extensive radical surgical procedures, suspecting it to be a malignancy, it is of utmost importance to identify and categorize these lesions which can subside if the underlying pathology is removed or sorted out.

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