

Pseudoepitheliomatous Hyperplasia: Relevance in Oral Pathology

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Abstract:

Pseudoepitheliomatous hyperplasia (PEH), a neglected entity by oral pathologist possesses utmost importance in the field of research. Of all the investigative challenges, PEH, a reactive epithelial proliferation is seen secondary to lesions with infectious, inflammatory, reactive, and degenerative origin. Small sized samples, incomplete excision, improper orientation, and dense inflammatory changes render diagnostic confront to the oral pathologist in exclusion of frankly invasive malignant lesions like squamous cell carcinoma from lesions exhibiting PEH. The diagnosis can occasionally be difficult as they mimic other lesions also, on clinic-pathological assessment. Thus, this article gives an insight regarding the various concepts of etiopathogenesis, histopathology, differential diagnosis, and malignant potential of PEH. A combined effort of a clinician and pathologist benefits every patient to rule out malignancy and render appropriate treatment as the only local conservative approach is essential to remove PEH associated lesions.

Key Words: Keratoacanthoma, malignant melanoma, pseudoepitheliomatous hyperplasia, squamous cell carcinoma, verrucous carcinoma

Introduction

Pseudoepitheliomatous hyperplasia (PEH) is considered to be a "benign proliferation of the epidermis into irregular squamous strands extending down into the dermis, respectively,¹ with no cytological atypia and mitotic figures."² Dr. Unna (1896) brought to light the first case of PEH as "Epidermal

proliferation overlying a lesion of Lupus Vulgaris." This lesion is also referred as pseudocarcinomatous hyperplasia³ (as they mimic squamous cell carcinoma [SCC])⁴ and invasive epidermal hyperplasia, invasive acanthosis, verrucous epidermal hyperplasia, and carcinomatous hyperplasia.⁵

Clinically, these wounds appear as skin ulcers/wounds, verrucous/multinodular growth, cauliflower growths, and dome-shaped swelling with smooth/warty surfaces.⁵ This reactive proliferation of the epithelium occurs secondary to persistent inflammation resulting from the chronic traumatic wound, ulcer, bacterial/fungal infection, degenerative changes, retained foreign material, dermatitis, traumatic implantation of epithelium, and malignancy.^{2,5} Lesions exhibiting PEH are differentiated by the gold standard of biopsy from invasive malignant lesions. PEH is a benign lesion requiring only local conservative excision while malignant lesion needs radical surgery. As this entity is neglected among pathologist, this article is written in view to enlighten the target readers to set apart his condition from all malignant lesions.

Pathogenesis

PEH is a histopathological pattern rather than disease entity sui generis.⁶ Pathologically, PEH arises due to the release of various cytokines produced by the tumor cells or inflammatory cells subsequently resulting in the proliferation of the overlying epithelium. Normally, any physical/chemical injury outcome is inflammation followed by the removal of devitalized tissue in the first few hours. Later, as a part of body's host immune response, the proliferation of connective tissue by fibroblast and vascular tissue growth occur. Finally, re-epithelization followed by fibrous maturation presents.⁷ Any interruption in this process outcome is a disorderly arrangement of normal epithelial architecture exhibiting PEH. Pathogenesis of individual lesions exhibiting PEH is illustrated with underlying mechanism in Table 1.⁸ Stages of differentiation in PEH include (a) Acanthosis of the overlying epithelium (b) Acanthosis and dyskeratosis, and (c) PEH.⁹

Mechanism of PEH

PEH is a reactive process of epithelial proliferation of mucous and cutaneous surface epithelium. Although literature underlying the basic mechanism of this PEH suggests various reasons, the three most commonly observed factors are (1) Pseudopods of acanthotic epithelium observed in tangential sections wherein the epithelium appear to have

invaded in isolated nests mimic malignancy (2) Regeneration of epithelium over the surface of viable tissue and ulcers – downward growth of epithelium into the underlying dermis (c) Traumatic implantation of epidermis.¹⁰ Broadly, this particular lesion depending on the type of cellular origin could be classified as basal cell origin or squamous cell origin mimicking basal cell carcinoma or SCC, respectively.⁵

Histopathology

Histopathologically, PEH appears with one or more of the following features: A close look at these features is definitely mandatory to differentiate prickle cell proliferation of the normal epithelium from SCC.⁵

Superficial epithelium features:

- Benign appearing squamous epithelium with broadened rete pegs with dermal extension
- Acanthotic epithelium – loss of normal structure
- Few mitotic figures and keratin pearls and rare dyskeratosis
- Absence of cellular/nuclear atypia

- Constituent keratinocytes show enlarged nuclei, small nuclei, and abundant eosinophilic cytoplasm.

Connective tissue:

- Presence of mast cells
- Absence of vascular, lymphatic, and perineural invasion
- Adnexal structures - Squamous metaplasia – epithelium of adnexal structures
- Glandular involvement - Hair follicles, sweat gland and sebaceous gland, mucous gland.

Histological grading – PEH

White and Weidman (1926) described histological grades of PEH into three types.¹¹

Grade I: Hyperplasia, acanthosis, elongation of rete ridges to sweat glands, intact basement membrane.

Grade II: Noticeable proliferation of the rete ridges and extension deeper, irregular inter papillary projections, indefinite basement membrane, cells epithelial down growth assumes embryonic character.

Grade III: Mixture of irregular extensions of the epithelial down growth with the granulomatous formation, embryonic cell character. Appearance similar to well differentiated SCC.

Lesions Exhibiting PEH

This PEH can be encountered in a number of clinically diverse diseases.⁶ The given chart (Table 2)^{5,12-15} exhibits various lesions showing the evidence of PEH, some of which mimicking malignant lesions. In these lesions, a deep biopsy with culture study should be recommended to the clinician as superficial biopsy with insufficient connective tissue portion is difficult to rule out SCC. On observing the histopathological picture with laboratory findings and clinical features, a definitive diagnosis is formulated.

Table 1: Various pathological lesions exhibiting pseudoepitheliomatous hyperplasia. ⁸
• Bacterial infections – Granuloma inguinale, Rhinosporidiosis, Rupial syphilis, Mycobacterial - <i>M. Marinum</i> , <i>M. tuberculosis</i>
• Fungal infections – Blastomycosis, Paracoccidioidomycosis, Coccidioidomycosis, Chromoblastomycosis, Sporotrichoid
• Skin lesions – Prurigo nodularis, Verrucous sarcoïd, Lichen simplex chronicus, Verrucous stage of incontinentia pigmenti, Pemphigus vegetans, Hypertrophic lupus erythematosus, Pyoderma/Pyostomatitis vegetans, Verruciform xanthoma, Granuloma gluteale infantum, Strawberry gum (Wegener’s granulomatosis), Hypertrophic chronic lichen planus, Median rhomboid glossitis, Pyoderma gangrenosum, Lupus vulgaris, Keratoacanthomas
• Chronic inflamed dermatoses – mercury, halogenoderma
• Granulomatous responses – tattoo, bee stinger, and spider bite
• Neoplastic disorders – Inflammatory linear epidermal nevus, granular cell tumor, intramucosal nevi, spitz nevus, verrucous melanoma
• Dermatofibromas
• Elephantiasis verrucosa nostrum (chronic lymphadenoma)
• Deep freezing nitrogen
• Mohs micrographic surgery
<i>M. marinum: Mycobacterium marinum</i>

Table 2: Etiopathogenesis of individual lesions in specific exhibiting PEH. ^{5,12-14}	
Etiology	Changes resulting in PEH
Chronic mechanical irritation	Irregular growth of epithelial and fibroblastic changes by use of mechanical devices (E.g.: Pipe friction/eye glasses) – sustained inflammation
Chronic burns/Margolin’s ulcer	Altered connective tissue changes (hyalinization, fibrinoid changes, and increased fibronectin)
Presence of foreign material	Chronic inflammation of dermis. Cytokines – 1, 10, and 14
Drug-induced gingival hyperplasia	Release of cytokines by usage of anticonvulsants, calcium channel blockers, and immunosuppressants
Bacterial/fungal/mycobacterial infections	<ul style="list-style-type: none"> • Infectious agents cause pseudoepitheliomatous hyperplasia to lift the foreign material from dermal dermis to the exterior via the stratum corneum (transepidermal elimination process) • Presence of acute and chronic inflammatory cells, connective tissue peptides, and dermal changes
Salivary gland	<ul style="list-style-type: none"> • Ischemia of the vasculature supplying salivary gland (trauma, LA, alcohol, smoking, radiation, and surgery procedure) • Reactive necrotizing inflammatory process – minor salivary glands of hard palate • Repair and metaplasia
Granular cell tumors	Release of factors TGF-alpha from tumor cells
Neoplasms	Regulation of EGF and EGFR, TGF, FGF, and PDGF, NGF, IL-1, IL-6, IL-7, IL-8, IL-10, IL-12 ¹⁵

PEH: Pseudoepitheliomatous hyperplasia, TGF: Transforming growth factor, EGF: Epidermal growth factor, EGFR: Epidermal growth factor receptor, FGF: Fibroblast growth factor, PDGF: Platelet-derived growth factor, IL: Interleukin

Table 3: Differential diagnosis of PEH.

Features	PEH ²⁶	Keratoacanthoma ¹³	Squamous cell carcinoma ^{6,17,25,26}	Granular cell tumor ^{12,14,23,27,28}	Necrotizing sialometaplasia ²²	Malignant melanoma ^{24,29,30}	Verrucous carcinoma ²⁶
Histo pathology	<ul style="list-style-type: none"> • Pseudo-invasion • Absence of atypical mitotic figures/cytologic atypia • Rare dyskeratosis • Absence of vascular, lymphatic or perineural invasion 	<ul style="list-style-type: none"> • Central horn filled crater with invaginated epidermis • Irregular projections of epidermis upward into crater and down into dermis 	<ul style="list-style-type: none"> • Sheets of squamous cells with numerous keratin pearls • Enlarged, atypical hyperchromatic nuclei/pleomorphism • Infiltration of strands with non-distinct borders into dermis • Numerous atypical mitotic figures • Vascular, lymphatic, and perineural invasion • Necrosis and hemorrhage 	<ul style="list-style-type: none"> • Sheets of large polyhedral cells with acidophilic granular cytoplasm and pyknotic ovoid/round nuclei (30-60 um) • Stratified squamous epithelium with horn pearl formation 	<p>Abrams <i>et al.</i>:</p> <ul style="list-style-type: none"> • Coagulative necrosis - acini • Squamous metaplasia - ductal epithelium • PEH of epithelium lining gland • Ulceration • Mucous pooling - granulomatous inflammatory process • Intact lobular architecture with benign nuclear morphology • Fibrosis • Preserve lobular architecture • Ordinary appearance of squamous islands or nests with no cytologic atypia 	<ul style="list-style-type: none"> • Epidermal hyperplasia and adnexal structures with irregular cords of epithelial cells into dermis and infiltrating tumor cells • 69% - Acanthosis, hyperkeratosis, papillomatosis, and irregular infiltrating epithelial cords with squamous eddies • 31% PEH with basaloid acanthosis laminated orthokeratosis and horn cysts • Infiltrating epidermal cords with squamous eddies, atypical melanocytes at the epidermal-dermal interface • Pagetoid spread 	<ul style="list-style-type: none"> • Absence of cytologic atypia • Parakeratin plugging • Church spire keratosis • Lack of inflammatory infiltrate • Presence of broad pushing border into dermis
IHC	<ul style="list-style-type: none"> • Less intense staining of p53 (basal cell staining) • E-cadherin is preserved • Linear staining with antibodies to Type IV collagen and laminin • Intense linear continuous staining of basement membrane • Absence of collagenase activity 	Staining seen in <50% cells	<ul style="list-style-type: none"> • Intense staining - p53, MMP-1, Ki67 • Loss of E-Cadherin, collagen IV • Weak or absent staining of basement membrane • >50% cells stained • Collagenase activity positive 	Granular cells - S-100, Neuron-specific enolase positive	Calponin positive, smooth muscle actin, weak cytokeratin-7	S100, HMB 45 and Melan 1 positive	Loss of beta 2 microglobulin
Morphological feature	-	-	<ul style="list-style-type: none"> • High mitotic index, cellular, and nuclear polymorphism • Mean surface area, mean perimeter, and mean diameter raised 	-	-	-	-

PEH: Pseudoepitheliomatous hyperplasia, IHC: Immunohistochemistry, MMP-1: Matrix metalloproteinase-1

Variants of PEH

Atypical PEH

Atypical PEH is lesion similar to PEH exhibiting an epidermal proliferation deep into the underlying soft and hard tissue. Particularly, these lesions lack cytologic atypia (nuclear atypia/ abnormal mitosis/vascular invasion) as SCC.²

Intraosseous PEH

Intraosseous PEH is a rare complication of fistulated chronic osteomyelitis of long bones. They arise as the epithelial structure of gum/periodontium (osteomyelitis). These lesions may sometimes be known with additional terminology as "atypical" due to its bone involvement. As there exists a difference in treatment modalities, PEH has to be sufficiently differentiated from SCC.

Histologically, intraosseous PEH shows proliferating squamous epithelium into medullary spaces without stromal intervention. The basal cell layer is particular oriented opposite to the bony trabeculae surrounding a fibrovascular core. Occasionally, spongiotic non-keratinizing epithelium with an inflammatory cell infiltrate also may be seen. Lesions also reveal a lack of cytological and nuclear atypia. In contrast to intraosseous PEH, SCC exhibits abundant tumor islands in the centro- medullary area surrounded by stroma. Sometimes, SCC may invade into the underlying bone.^{16,17}

Primary gingival PEH

The first case of primary gingival PEH was observed by Elzay and O'Keefe, 1979. Histopathologically, hyperplastic stratified squamous epithelium with acanthosis is seen with surrounding chronic inflammatory cells. Absence of granular cells/mycotic organisms and other conditions associated with gingival growth. Absence of epithelial dysplasia rules out malignancy.^{18,19}

Does a pseudoepitheliomatous lesion turn malignant?

Although various theories have been formulated, the exact pathogenesis of PEH is completely still unclear, but this occurrence should be based in mind not to over-diagnose the proliferating epithelium as SCC due to small and superficial biopsies. The malignant potential of PEH lesions is controversial. Literature has shown that few of such lesions turn malignant when they follow one or more of the following theories of potential malignancy.⁴ It is mandatory to differentiate lesions with PEH from SCC as a treatment for a malignancy involves radical surgery/amputation³ whereas wait and watch policy throughout life is necessary to observe the behavior of PEH lesions.

- Activated keratinocyte theory - Mitotically active keratinocytes proliferate rapidly on stimulation by inflammation from chronic wound dermis
- Changes in the dermis - Abundant hyalinized, fibrinoid collagen and increased fibronectin production - abnormal metabolic activity in keratinocytes

- Altered immune system - Abnormal mitotic events (continued mitotic activity by re-epithelializing cells) undetected by the immune system.

Recent studies have shown that at the genetic level, formalin and paraffin fixed tissue exhibit C15 or F48 and KRT 9 distinctly elevated in SCC than PEH.²⁰ The research also has persuaded the scientist to bring out the multiplex TaqMan polymerase chain reaction (PCR) assay, an ancillary molecular diagnostic tool to distinguish PEH from SCC. This TaqMan PCR assay provides a scientific kit to differentiate SCC from PEH and identification of prognostic markers and molecular pathways as targets for the treatment of cutaneous SCC.²¹

Differential Diagnosis

Few infective to largely invasive malignant neoplasms appear as a differential diagnosis of PEH. The given Table 3^{6,12-14,17,22-30} gives a brief idea regarding various test utilized in their differentiation. Lesions (PEH) mimicking SCC and other related lesions.

Conclusion

PEH is a benign epithelial proliferation identified microscopically in association with various heterogeneous lesions. The pathogenesis of PEH is still unclear; however, a systematic knowledge of PEH is essential to rule out neoplasms. Clinicopathologic correlation remains a gold standard to reach the exact diagnosis. Small sized tissues, improper orientation, and dense inflammations in various lesions exhibiting PEH is challenging for pathologists to differentiate them from frank most aggressive lesions like SCC. Adequate excision and sampling depth render in exclusion of frankly malignant lesions and aid in appropriate treatment to the patient. Collaboration between clinician and pathologist is absolutely essential to deliver suitable treatment to the patient and avoid undesirable consequences.

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