



## Pseudoepitheliomatous Hyperplasia: Harbinger of Underlying Squamous Cell Carcinoma - Lessons Learnt

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### Abstract

Pseudoepitheliomatous hyperplasia (PEH) is a benign condition marked by reactive epithelial proliferation seen in response to various insults like trauma, infection, persistent inflammation and neoplasia. In this report, we discuss a case of a 35-year-old man who presented with a perineal swelling, later turned into a non-healing ulcer, first diagnosed as PEH. Still, after clinical suspicion, a deeper biopsy was conducted, confirming the diagnosis of squamous cell carcinoma and directing treatment appropriately.

Non-healing perineal lesions are not uncommon. Most of the lesions turn out to be Squamous Cell Carcinoma. But, if the histopathological picture suggests Pseudoepitheliomatous Hyperplasia, it is vital to consider the limitations of the biopsy, and a solid clinicopathological correlation is required to look aggressively for underlying Squamous Cell Carcinoma. Due to the benign nature of PEH, most cases are treated via excision biopsy, while grafts or flaps are occasionally required to restore severe tissue defects.

It is therefore crucial to rule out and distinguish this condition from other benign and malignant conditions, as the treatment and prognosis differ widely. It is of utmost importance to sample the base of the lesion, analyze multiple sections, and consider clinical data to ensure an accurate diagnosis.

**Key words** squamous cell carcinoma, pseudoepitheliomatous hyperplasia, perineum, ulcer

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## Introduction

Pseudoepitheliomatous hyperplasia (PEH) is benign hyperplasia of the epidermis occurring mostly in the skin, mimicking squamous cell carcinoma [1]. Clinically differentiating PEH and Squamous cell carcinoma (SCC) is challenging [2, 3]. Examination of multiple sections is needed to obtain adequate information for a prompt diagnosis. Additional sampling to include the base of the lesion is required to rule out squamous cell carcinoma in the deeper sections of the biopsy specimen. PEH is the term used to denote the invasive projections of epithelial cells produced by the hyperplasia of the epidermis at sites of chronic ulcers and irritation. Authors have used other terms to describe PEH: 'pseudocarcinomatous hyperplasia', 'invasive acanthosis', 'verruroid epidermal hyperplasia' and 'carcinomatoid hyperplasia' [4]. It is also seen in mycotic infections, melanocytic lesions, tuberculosis, syphilis and granular cell tumour. PEH consists of elongated epidermal projections with jagged margins and a pointed base. It also features concentric layers of keratinocytes with central keratinization, called the "keratin pearls" [5]. We discuss a case that was first

reported as PEH, but because of clinical suspicion, a repeat deeper excision biopsy was done that confirmed the diagnosis of SCC.

## Case report

A 35-year-old male presented with three months' history of rapidly progressive painful swelling in the perineum. He had high-grade fever and difficulty in voiding and was placed on a suprapubic catheter, as per-urethral catheterization failed. On examination, he was found to have a 4x4 cm tender ulcerative lesion in the perineum. Blood biochemistry showed marked leukocytosis with predominant neutrophilia. Ultrasound of perineum suggested perineal abscess. Emergency incision and drainage was done. Pus culture grew *Klebsiella pneumoniae*. The general condition improved, and was discharged with culture-sensitive antibiotics.

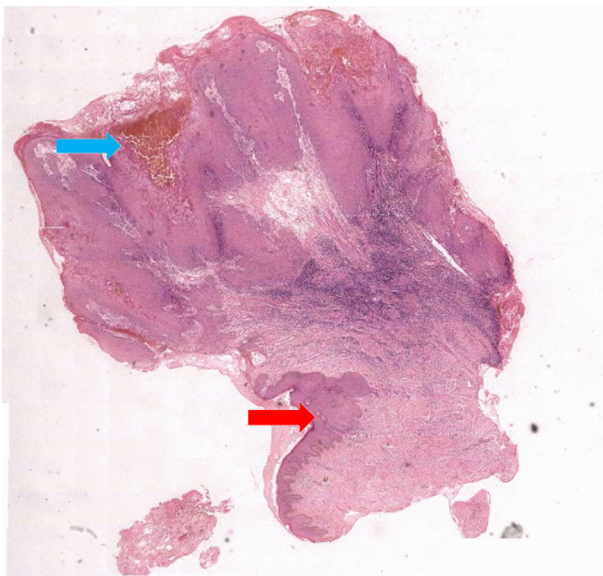
On follow-up after three weeks, the size of the ulcer increased to 5x5 cm with foul-smelling purulent discharge. He was taken up for wound debridement. Edge-wedge biopsy was taken to rule out squamous cell carcinoma. Histopathological examination revealed hyperplastic squamous epithelium with marked hyperkeratosis, parakeratosis, and ulceration with a dense acute inflammatory granulation tissue suggestive of PEH with no evidence of malignancy even in deeper sections (**Figure 1**).

In view of the benign nature of the lesion, he was advised regular wound care at a nearby hospital. After two weeks, he presented with rapidly progressive ulcero-proliferative growth and the repeat edge wedge biopsy was again suggestive of PEH. With a clinical suspicion of Squamous Cell Carcinoma, a wide local excision of the growth was performed. Fasciocutaneous flap reconstruction was done to cover the wide defect (**Figure 2**).

Histopathology suggested squamous cell carcinoma with verrucous background, invading the reticular dermis, with no lymphovascular and perineural invasion (**Figure 3**). Patient received adjuvant radiotherapy.

## Discussion

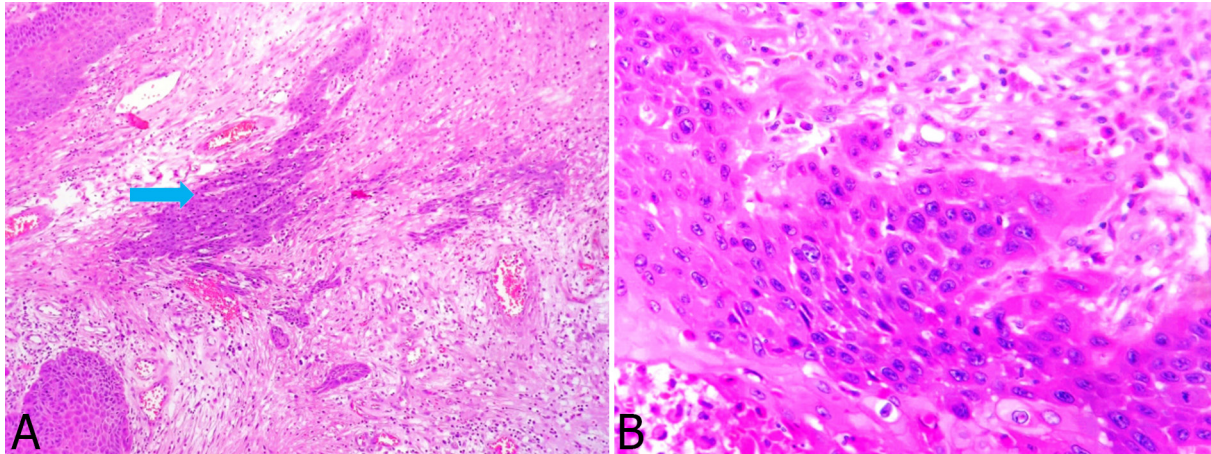
A clear distinction between PEH and SCC may be difficult. PEH can be primary (e.g., primary gingival PEH) or secondary, as in granular cell tumour or chronic irritation. An accurate diagnosis and a strong clinicopathological correlation are warranted before planning a definitive surgery. Our patient presented initially with an infective ulcer, later erupting into a perineal phlegmon with underlying malignancy. He was diagnosed twice with a benign reactive condition, which led to the delay in recognizing the underlying malignant pathology, which in turn delayed the definitive treatment. In most cases, studying multiple histological



**Figure 1.** Low power view microphotograph. Microphotographs showing normal squamous epithelium (red arrow) and marked pseudoepitheliomatous hyperplasia (blue arrow) (H&E X 40).



**Figure 2.** Clinical images of the lesion. Pre operative (Fig. 2a), fascio-cutaneous flaps (Fig. 2b) and post operative (Fig. 2c) images, illustrating the perineal lesion, flaps taken and post-operative healed wound respectively.



**Figure 3. High-power view microphotograph of malignant cells. Islands of malignant squamous cells (H&E X 100) infiltrating into the subepithelium (blue arrow) (Fig. 3a) and Higher power view (H&E X 200) of the malignant cells, with abundant eosinophilic cytoplasm and pleomorphic nuclei (Fig. 3b).**

sections and obtaining detailed clinical information is necessary to make an appropriate diagnosis.

An array of morphological features may help differentiate invasive SCC from PEH on routine haematoxylin-eosin-stained tissue sections. Histologically, PEH has an irregular invasion of the dermis by uneven, jagged, pointed epidermal cell masses and strands with keratin pearl formation [6]. Squamous cell carcinoma usually demonstrates some degree of cytologic atypia, including nuclear pleomorphism, maturational atypia, and mitoses. Furthermore, invasion of epithelial proliferation by leucocytes and disintegration of some of the epidermal cells are classical of PEH, a finding that is absent in SCC. Other features that provide clues for distinguishing these conditions are the width of the strands and the degree of keratinocytic atypia. SCCs have broad strands and a greater degree of atypia compared to PEH. The presence of inflammatory infiltrate does not preclude the diagnosis of SCC.

The role of immunohistochemistry is not well documented. The expression of the p53 protein has been utilised to differentiate

PEH from SCC. However, as it is an indicator of the proliferative capacity of the cells rather than one of malignancy, it has been observed in a variety of skin lesions, including in situ and invasive SCC, Pseudoepitheliomatous hyperplasia, and keratoacanthoma [7]. The number of Langerhans cells in both the conditions was similar. Immunohistochemistry using CD1a for the quantification of Langerhans cells has no added value in differentiating SCC and PEH. However, the density of Langerhans cells was decreased in SCC compared to that of PEH. This finding was correlated with decreased expression of E-Cadherin in squamous cell carcinoma [8]. Matrix metalloproteinase (MMP)-1, or interstitial collagenase, are expressed in low or absent levels in benign mucosal tissue [9, 10]. In SCCs, the epithelial expression of MMP-7, MMP-13, and MMP-12 is raised and provides a diagnostic clue while the expression of MMP-1 along with MMP-3, MMP-8, MMP-9, and MMP-10 is decreased or absent [11]. Loss of MMP-19 and p16 from epithelial cells might be an important indicator of malignancy arising in the setting of chronic wounds that are

**Table 1. Summary of various authors' experiences and previous published literatures on pseudoepitheliomatous hyperplasia (PEH).**

S.No	Authors	Condition
1	Grauwin MY, 1996 [15]	Described PEH as a verrucoid or multinodular lesion, appearing as a cauliflower growth
2	Lynch, Jane, 2004 [16]	Unna in 1896 was the first to describe this entity as an epidermal proliferation overlying a lesion of lupus vulgaris
3	Zayour M, 2011 [17]	Introduced a methodical approach for the diagnosis and management of PEH
4	Sarangarajan R, 2015 [18]	White and Weidman (1926) described histological grades of PEH into three types
5	Johnson DM, 2018 [19]	First to report a case of vaginal PEH associated with squamous cell carcinoma and melanoma
6	Krishnamoorthy et al, 2022 (authors)	First to report PEH of perineum presenting as a perineal phlegmon



exhibiting PEH. Features like keratinocyte necrosis, vascular and perineural invasion are absent in PEH. Zarovnaya et al. in their study on distinguishing Pseudoepitheliomatous Hyperplasia from Squamous Cell Carcinoma in Mucosal Biopsy Specimens from the Head and Neck evaluated the role of p53, E-cadherin, collagen IV and MMP-1 and concluded that properly oriented hematoxylin-eosin-stained sections remain ideal and use of these markers (p53, E-cadherin, MMP-1 and Collagen IV) may have a limited adjunct role due to the small specimen size of the edge wedge biopsy [12]. PEH has also been reported following tattooing in a three-case series and following Mohs micrographic surgery [13, 14]. **Table 1** illustrates the list of various authors who have reported their experiences on PEH.

Management of PEH differs greatly from SCC. As PEH is a benign condition, it can be managed by surgical excision, although grafts or flaps are occasionally needed to reconstruct major tissue defects. However, a flawed diagnosis of malignancy will lead to radical surgery and surgery-related morbidity, but the converse may delay early management [20].

PEH may develop in response to various triggers. Bacterial, viral, fungal infection or underlying malignancy are the major causes. Though PEH resembles SCC histologically, management differs between the two clinically distinct conditions. Hence, to achieve an accurate diagnosis and prompt treatment, it is critical to recognize the pitfalls in diagnosis. Adequate sampling of the base of the lesion, analyzing multiple and deeper sections and proper evaluation of the clinical data are the basic pre-requisites for making an early recognition and appropriate treatment.

### Conclusion

PEH closely resembles SCC. Also, presence of PEH should alert the treating physician to aggressively look for an underlying squamous cell carcinoma. Many a time, an edge-wedge biopsy may be inadequate. Complete excision of the mass might reveal the underlying malignancy in some instances. A high index of clinical suspicion is mandatory for a prompt diagnosis of this rare but invasive pathology.

### Acknowledgements

Nil.

### Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

### Availability of data and materials

All data generated or analysed during this study are included in this publication.

### Author contributions

SK, HS and JSK were involved in performing this surgery; SK was instrumental in writing this manuscript, with microphotographs and histopathological inputs from LDJ.

### Competing interests

The authors declare no conflict of interest.

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