

Squamous Cell Carcinoma with Pseudo-glandular Features Arising in an Epidermal Cyst: A Diagnostic Pitfall

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Abstract

Introduction: Epidermal cysts are benign lesions that develop at various sites on the body. They are usually present on face, trunk, scalp, and back regions. Transformation of a benign epidermal cyst to malignant cyst is rare. The likelihood of an epidermal cyst transforming into squamous cell carcinoma is between 0.011% and 0.045%.

Case Report: A 55-year-old female presented with swelling in the intergluteal cleft region that persisted for four years, with a sudden increase in size and a discharging sinus for the last two months. A clinical diagnosis of infected dermoid cyst was made and surgical excision was done. The specimen was subjected to histopathological analysis. Grossly noted, a partially skin-covered, globular, grey-white cystic structure measuring 12x7 cm. On microscopy, a diagnosis of Squamous Cell Carcinoma with a Pseudo-Glandular Pattern originating from an epidermal cyst was established. Immunohistochemical analysis ruled out glandular differentiation by showing negativity for markers CEA and CK7.

Discussion: Epidermal cysts represent the most prevalent non-neoplastic cystic lesions encountered on the body. However, the occurrence of malignant transformation in these cysts is exceedingly rare, with only a limited number of cases documented in the literature. Clinicians should consider the possibility of malignant change in instances of longstanding cysts or when there are notable alterations in size, the presence of pain, ulceration, or discharge.

Keywords: Intergluteal region; epidermal cyst; discharging sinus; Squamous cell carcinoma.

Introduction

Epidermal cysts comprise 85-90% of all excised skin cysts; they are usually small, slow-growing, asymptomatic, and benign [1, 2]. The most common sites for developing epidermal cysts are the face, neck, trunk, and scalp [2]. It is reported that various malignancies have developed from epidermal cysts. The development of true squamous cell carcinoma (SCC) from an existing epidermal cyst is rare, with an occurrence rate ranging from 0.011% to 0.045% [1]. Here, we discuss a case of squamous cell carcinoma that originated from an epidermal cyst located in the intergluteal cleft region.

Case Report

A woman in her mid-50s came to the hospital with swelling over the intergluteal region for four years, slow-growing and gradual in onset, also accompanied by the development of a draining sinus over the last two months. There is no significant history related to trauma or iatrogenic injury.

The swelling was 10x10 cm, non-tender, cystic, and non-translucent, with a draining sinus noted in the center of the swelling. All other patient's parameters were found to be within the normal range.

A clinical diagnosis of an infected dermoid cyst was made, which was excised and sent for histopathological study.

Histopathological examination: On gross, a partially skin-covered globular grey-white cystic structure measuring 12x7 cm, with a skin flap measuring 6x4.5 cm; on cut open, the inner surface was irregular grey-white with rough areas. The thickness of the cyst wall was 0.2 cm to 0.8 cm (Figure 1).



Figure 1: A gross image of the specimen: Partially skin-covered, already cut open globular grey-white cystic structure – 12x7 cm, cut section shows grey-white rough areas.

Microscopic examination demonstrated the presence of a cyst wall characterized by a lining of lamellated keratin and a stratified squamous epithelium with a prominent granular layer. At one focus, the cyst wall lining epithelium showed hyperplasia and dysplastic features with invasion into the underlying tissue (Figure 2). The tumor cells were arranged in lobules and nests with intercellular bridges and keratin pearls, which are characteristic features of squamous cell carcinoma. A few cells showed a glandular pattern with vacuolated cells, causing a dilemma between adenosquamous and squamous cell carcinoma with a pseudoglandular pattern (Figure 3).

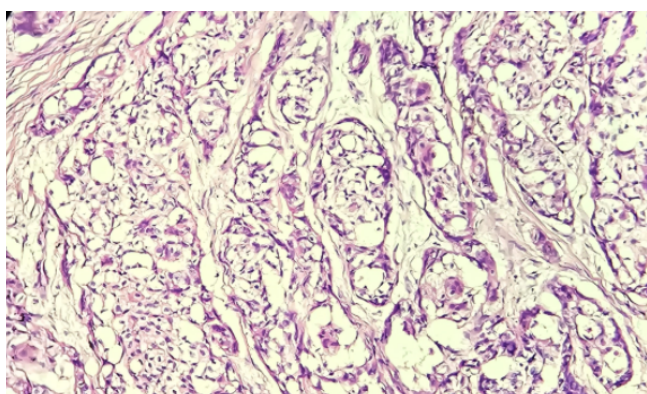


Figure 2: Microscopic image (100x, H&E): Cyst wall lined by normal epithelium (green arrow) and tumor tissue (red arrow).

Immunohistochemical analysis showed strong positivity for squamous epithelium markers cytokeratin (CK) 5/6 (Figure 4) and p40 (Figure 5) and showed negativity for glandular markers carcinoembryonic antigen (CEA) and cytokeratin (CK) 7 (Figure 6), which ruled out glandular differentiation.

A final diagnosis of Squamous cell carcinoma in an epidermal cyst was made. The patient underwent a wide local excision, and the margins were free on histopathological examination.

Discussion

Epidermoid cysts (ECs) represent the most prevalent type of cutaneous cysts and are also known as keratin cysts, epidermal cysts, epidermal inclusion cysts, and infundibular cysts [3].

Cruveilhier initially identified the epidermoid cyst as "tumeurs perlées" in 1835 [4].

These cysts are characteristically lined by stratified squamous epithelium with a prominent granular layer, and the lumen of the cyst produces lamellated keratin [5].

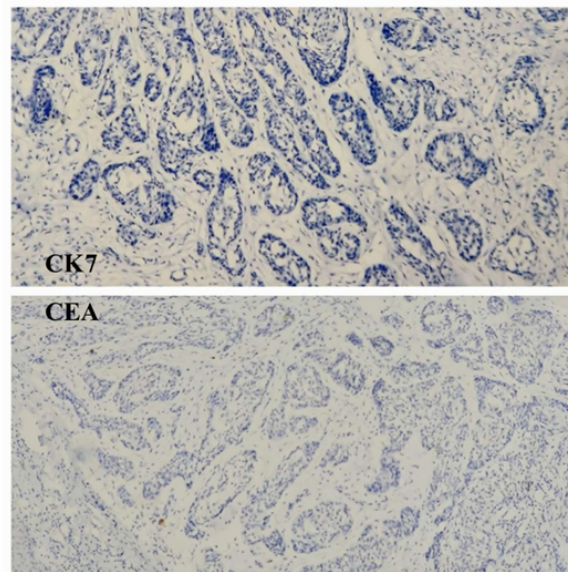


Figure 3: Microscopic image (100x, H&E): Tumor tissue arranged in a pseudo-glandular pattern.

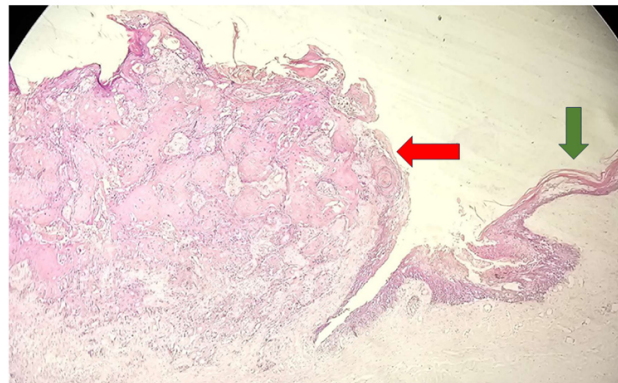


Figure 4: Microscopic image (200x): IHC markers CK5 & CK6 for squamous differentiation showing diffuse intense cytoplasmic positivity.

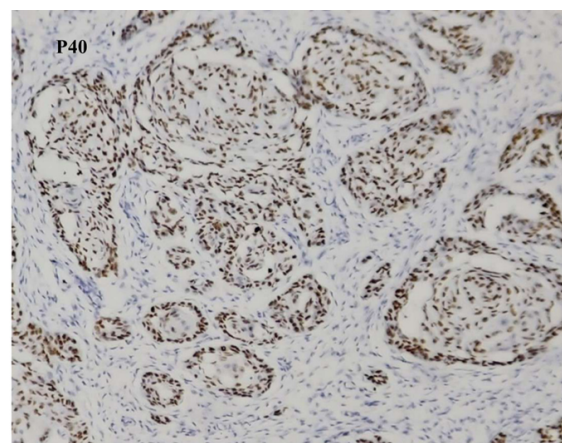


Figure 5: Microscopic image (200x): IHC marker p40 for squamous differentiation showing diffuse intense nuclear positivity.

The scalp, head, neck, face, trunk, and extremities are the most common locations for sebaceous glands and hair-bearing skin, and these areas are typically affected by epidermal cysts [5]. Unusual sites reported in other studies include the sublingual, parotid glands, thymus, breast, spleen, bones, subungual region, palms, soles, elbows, buttocks, scrotum, penis, vulva, perineal areas, and other locations. The cause of epidermal cysts over these unusual sites is primarily due to trauma or iatrogenic injuries [1, 2, 4].

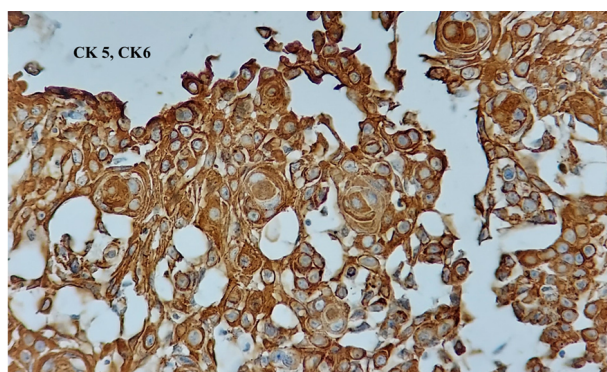


Figure 6: Microscopic image (400x): IHC markers CK7 & CEA for glandular differentiation - negative.

Epidermal cysts can develop at any age and are often tiny, asymptomatic, and slow-growing. They frequently appear as a skin nodule or swelling [2]. On examination, they are firm to hard in consistency. Cystic lesions move in all planes of the dermis when palpated, leading to a wide range of differentials, including neurofibromatosis, neuromas, lipomas, fibromas, sebaceous cysts, dermatomal cysts, trichilemmal cysts, pilonidal sinus, schwannoma, lipomas, steatocystoma, and cutaneous symptoms of Gardner's syndrome [4].

Epidermoid cysts are usually benign and rarely can transform into malignancy. Lopez-Rios et al. were the first to document the malignant conversion of epidermoid cysts. A range of malignancies like squamous cell carcinoma (SCC), basal cell carcinoma, Merkel cell carcinoma, Bowen disease, Paget disease, malignant melanoma, and mycosis fungoides can occur in epidermal cysts. SCC is the most common, with an incidence rate of 0.011%–0.045% [3, 4].

Frank et al. conducted a study involving various cases of squamous cell carcinoma (SCC) originating from epidermal cysts. Their findings were that the head and neck region was the most prevalent site for SCC associated with epidermal cysts, accounting for 54.8% of cases. The average age at diagnosis was 61.8 years, with a range from 28 to 96 years, and a notable male predominance of 69.0%. The mean diameter of the affected epidermal cysts was recorded at five centimetres, with a range of 0.7 to 20 centimetres. Additionally, the mean duration from the appearance of the cyst to diagnosis was approximately 92.6 months, with a range of 0.5 to 480 months. Common presenting symptoms included rapid enlargement of the cyst (48.6%), changes in the overlying skin such as erythema, ulceration, or drainage (38.2%), and pain (24.2%) [6].

Squamous cell carcinoma occurs due to a gradual process of long-lasting intraepidermal dysplasia [7, 8]. The pathogenesis of malignant change in epidermal cysts is unknown. According to previous studies conducted by Frank et al. and Zwald et al., have suggested that there are a few factors that can be responsible for the malignant formation of epidermal cysts, like the use of tobacco, male gender, lesions with prolonged duration, chronic irritation, actinic damage, recurrent infection, repeated trauma, chronic sunlight exposure, advanced age, immunosuppression, and HPV infection. Chronic inflammation can cause damage to cells lining the cyst, leading to dysplastic changes, which, on further irritation, may even lead to malignant changes. Signs that lead to suspicion of malignancy in epidermal cysts include an increase in size, change in consistency from cystic to firm, ulceration, pain, discharge, and bleeding [5, 6, 7].

Epidermoid cyst is usually diagnosed clinically without necessitating any radiological investigation. According to a study by Rajendran R et al., in cases with a clinical dilemma, imaging is performed to delineate epidermal cysts [2].

Ultrasound offers the benefits of being affordable, repeatable, and convenient, with a diagnostic accuracy of 95.4%. The typical ultrasonographical features of benign epidermal cysts are round cystic avascular masses with well-determined edges and an "onion-like" appearance in the dermis and subcutaneous tissue. Also seen are back acoustic amplification and lateral shadow phenomenon. They show solid areas and increased vascularity within the cyst when harboring malignancy [4].

Although not routinely advised in benign cases, CT scans are essential in clinical investigations when malignancy is suspected. The image shows a clearly defined mass with varying density, indicating the presence of keratin and fat, which may undergo calcification. It may show extensions into adjacent structures in cases of malignancy [4].

Simple excision is the choice for treating benign epidermal cysts. Radical excision with a proper margin is the choice for treating malignant cysts. During the excision of the cyst, there should be no spillage of contents into surrounding areas, as it prevents and decreases the intensity of inflammation, which occurs in the postoperative phase, thus allowing an enhanced recovery at the surgical site [2]. Tumor depth and metastasis are important factors that determine the recurrence. Squamous cell carcinomas can recur at a rate of 2.2-11%, with 80-90% of the tumors recurring in the first two to five years of surgery. Wide surgical excision with free margins would lower the risk of recurrence [9].

Histopathology is the key to confirming malignancy in epidermal cysts, as it aids in picking up the features that are suggestive of malignancy, such as atypia, perineural invasion, and an infiltrative growth pattern in prolonged or symptomatic lesions [3].

The microscopy of a benign epidermal cyst shows features like keratinized stratified squamous epithelium lining, a prominent granular layer, and the lumen consists of lamellated keratin and sebaceous material. In a study by Hoang VT et al., the cyst showed cholesterol crystals, forming foreign-body granuloma and chronic inflammation [4].

In a study done by Cancelo P et al., the microscopic features of a cyst undergoing malignant transformation showed a lumen filled with laminated keratin, and dispersed islands of severely atypical neoplastic squamous epithelium arranged in small nests or sheets with an infiltrative growth pattern, absence of intracellular bridges, pleomorphism, marked nuclear irregularity, nuclear hyperchromasia, and increased mitotic figures [1].

Spindle cell SCC, basaloid SCC, verrucous SCC, adenoid SCC, papillary SCC, lymphoepithelial carcinoma, pseudovascular SCC, and adenosquamous carcinoma are different histological variants of SCC. The adenoid/pseudoglandular SCC is characterized by a glandular pattern and mimics adenocarcinoma. Diagnosing such an entity can be difficult if not supported by IHC. If the glandular markers like CK7 and CEA are positive in such cases, then further evaluation for primary or metastatic adenocarcinoma is warranted. Some authors have reported a more aggressive behavior of pseudoglandular SCC than conventional SCC [10].

Immunohistochemistry (IHC) is an essential tool in resolving challenging cases where differentiating between similar conditions becomes essential. In the current study, as well as in the study by Al-Zawi et al., immunohistochemistry demonstrated CK5/6, a cytokeratin marker that, when combined with p40 positivity, helps to confirm squamous origin and to differentiate it from tumors of other origin [1].

Metastasis of the SCC that develops within a cyst to distant sites is rare. It usually metastasizes to regional lymph nodes and lungs, which are cured by surgical excision.

The genetic elements involved in the pathogenesis of squamous cell carcinoma encompass the epidermal growth factor receptor (EGFR) and fibroblast growth factor receptors (FGFRs), both of which are tyrosine kinase receptors, as well as the RAS/MAPK and PI3K signaling pathways, and cell cycle regulatory genes, specifically CDKN2A/RB1 and TP53 [11].

Conclusion

Epidermal cysts are typically classified as benign lesions; however, there exists a rare possibility for transformation into malignancy, predominantly into squamous cell carcinoma (SCC). This risk underscores the importance of a thorough pathological evaluation, particularly in cases presenting with recent changes in size or appearance, atypical locations, or recurrent infections that fail to respond to treatment.

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