

Fibroepithelioma of Pinkus Revisited

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ABSTRACT

Background: Fibroepithelioma of Pinkus (FeP) is considered a variant of basal cell carcinoma (BCC); however, in the past 20 years, some researchers have argued for its classification as a trichoblastoma. Recently, use of a new immunostaining marker and further dermoscopic characterization of FeP have advanced the debate about its proper classification.

Purpose: A review of the evidence for and against classification of FeP as BCC or trichoblastoma is presented.

Methods: Using PubMed, the term FeP was searched and relevant citations were assessed. Additional relevant articles were identified from references of key papers.

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Results: FeP shares characteristics of both trichoblastoma and BCC.

Conclusion: Derived from the same cell type, BCC and trichoblastoma may be best considered as representing opposite ends of a spectrum of differentiation, with FeP deserving an intermediate classification.

Keywords: Basal; Carcinoma; Cell; Fibroepithelioma; PHLDA1; Pinkus; Trichoblastoma; Trichoepithelioma

INTRODUCTION

Fibroepithelioma of Pinkus (FeP) is an uncommon skin lesion originally thought to be a rare variant of basal cell carcinoma (BCC). In the past couple decades, controversy has developed over whether FeP is a type of BCC or a trichoblastoma. Both trichoblastoma, a benign neoplasm, and BCC, a malignant neoplasm, are thought to be derived from follicular epithelial stem cells in the bulge area of the hair follicle [1–3]. Follicular stem cells in turn give rise to follicular germinative cells, also known as trichoblasts, which can develop into all the components of the folliculo-sebaceous-apocrine

unit [4–7]. Trichoblasts that give rise to trichoblastoma and basal cell carcinoma express common epithelial keratins and are differentiated toward the outer root sheath and the companion layer of the hair follicle [8, 9]. Follicular cells that instead express hair keratins give rise to hair fiber, while those expressing yet another different set of keratins give rise to the inner root sheath [9]. In this paper, FeP is reviewed and the arguments for and against its classification as a trichoblastoma or BCC are presented.

METHODS

Using PubMed, the term FeP was searched and relevant citations were assessed. Additional relevant articles were identified from references of key papers [1–66]. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

HISTORY

FeP was first described in 1953 by Hermann Pinkus as “an unusual variety of basal-cell epithelioma”, which he considered to be premalignant [10]. In a 1965 paper, he elaborated that “the epithelial part of premalignant fibroepithelial tumors resembles that of trichoepitheliomas in its degree of differentiation, while the growth characteristics of the entire tumor is closely related to superficial basal cell epithelioma of the trunk”, in some cases transforming into an ulcerating basal cell epithelioma [11], thereby justifying its categorization as a type of BCC. Following Pinkus’s description, FeP was generally accepted to be a variant of BCC until

Hartschuh et al. in 1997 and Bowen et al. in 2005 suggested that FeP might be more closely related to trichoblastoma than to BCC [12, 13], unleashing a controversy.

NOMENCLATURE

Some authors suggest that the term trichoepithelioma refers to a superficial trichoblastoma [5, 14]. The World Health Organization uses the terms synonymously [15]. The terms are used interchangeably in this paper.

INCIDENCE

FeP is relatively rare, with Dr. Pinkus identifying only 4 cases among 900 epitheliomas [10]. In series of BCCs, the frequency of FeP ranges from 0.2% to 1.4% [16–18]. However, FeP may be underreported, as it can resemble other benign tumors which may not be biopsied [19]. FeP usually presents in adults older than age 50 [20], and women may be affected slightly more often than men (54% female in Bowen et al.’s series of 114 patients) [13]. Rare cases of children with FeP have been reported [21, 22].

CLINICAL PRESENTATION

FeP typically presents as a skin-colored, firm, dome-shaped, sessile, fleshy papule or plaque, which can mimic a pedunculated fibroma, acrochordon, seborrheic keratosis, or dermal nevus (Fig. 1) [11, 23, 24]. It may be pigmented [24–26], and patients can—albeit uncommonly—present with multiple lesions [25]. It most often occurs on the lumbosacral area but may also occur on the abdomen, head, axillae, thigh, groin, and plantar foot [19, 20, 27, 28]. It often develops in patients with a

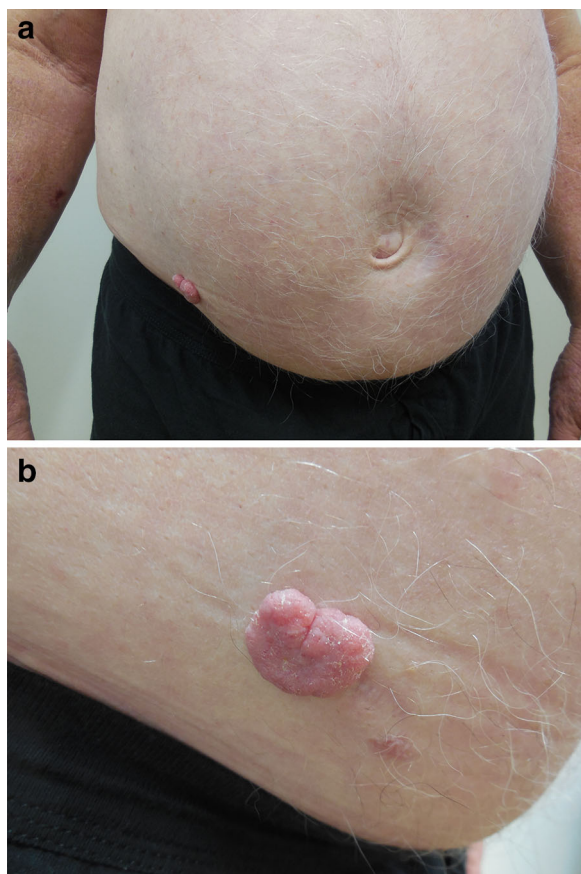


Fig. 1 a, b Fibroepithelioma of Pinkus: clinical presentation. Distant and frontal (a) and closer and lateral (b) views of a fibroepithelioma of Pinkus in a 72-year-old man with a history of several biopsy-confirmed basal cell carcinomas and squamous cell carcinomas and a family history of melanoma. He presented with a 3 × 2-cm pedunculated, flesh-colored to pink nodule on his right trunk which had been present for 10 years. The truncal nodule developed at the site of a robotic prostate surgery incision scar. The differential diagnosis included basal cell carcinoma (fibroepithelioma of Pinkus variant), fibrolipoma, keloid, metastatic prostate cancer, neurofibroma, pedunculated nevus, and squamous cell carcinoma

history of BCC [26] and may have increased prevalence in irradiated skin [12].

DERMOSCOPY

Dermoscopy reveals fine arborizing vessels [19, 29] and white septal lines or streaks [19],

which are thought to be a consequence of significant fibrosis. Some lesions have distributed gray-brown structureless pigmentation and gray-blue dots [19].

PATHOLOGY

The histopathology of FeP is, as Pinkus described it, “peculiar and unmistakable” [10]. Thin anastomosing strands of basaloid or squamous keratinocytes project downward from the epidermis in a fenestrated pattern [30]. The cords of epithelial cells are embedded in abundant fibrous stroma, like window frames separating panes of glass (Figs. 2, 3) [13, 19]. From a three-dimensional perspective, the tumor resembles a honeycomb or sponge composed of thin epithelial septa, with the intervening spaces filled with stroma [11, 19]. Columnar cells at the edge of the fenestrations are arranged in a palisade (Fig. 4) [5]. Nubs of follicular germlike structures sometimes protrude from the fenestrations into the fibrotic stroma [5]. Follicular germ-like structures may be seen [4], in keeping with the tumor’s derivation from follicular germinative cells. The anastomosing network extends into

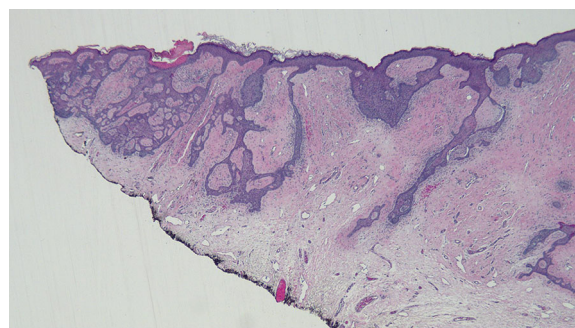


Fig. 2 Fibroepithelioma of Pinkus: pathology. The tumor shows a fenestrated pattern of anastomosing epithelial strands on the *left* and significant dermal fibrosis on the *right*. On the *left*, the fenestrated portion of the lesion has a blunt interface with the underlying dermal stroma. Hematoxylin and eosin: ×2

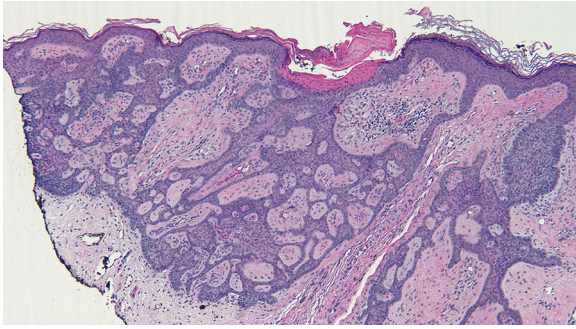


Fig. 3 Higher magnification of the fenestrated portion of the tumor. Strands of basaloid epithelial cells project down from the epidermis and anastomose, dividing fibrous dermal stroma like frames dividing window panes. Hematoxylin and eosin: $\times 4$

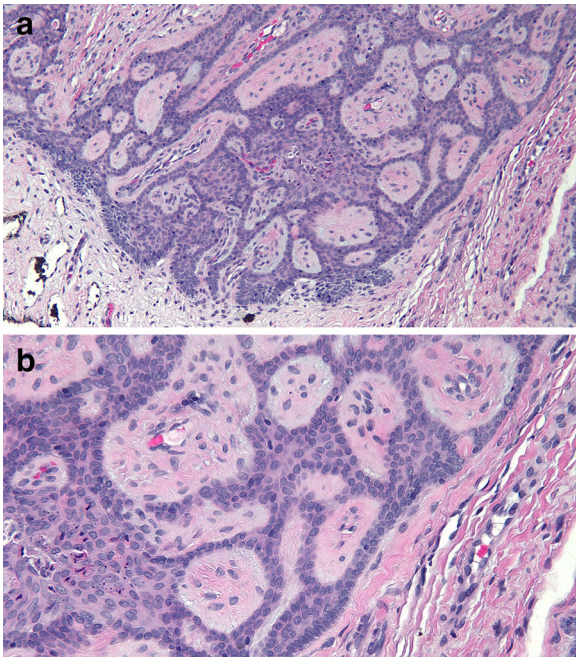


Fig. 4 a, b At medium (a) and high (b) magnification, peripheral palisading of the fenestrations is evident. Hematoxylin and eosin: **a** $\times 20$, **b** $\times 40$

the papillary dermis and expands it, causing it to push up on the epidermis, which results in the lesion's polypoid appearance [31].

Typically, the lesion has a blunt interface with the underlying dermis, with no infiltration of the normal dermis or subcutis (Fig. 2) [13]. Overabundant stroma may help contain the

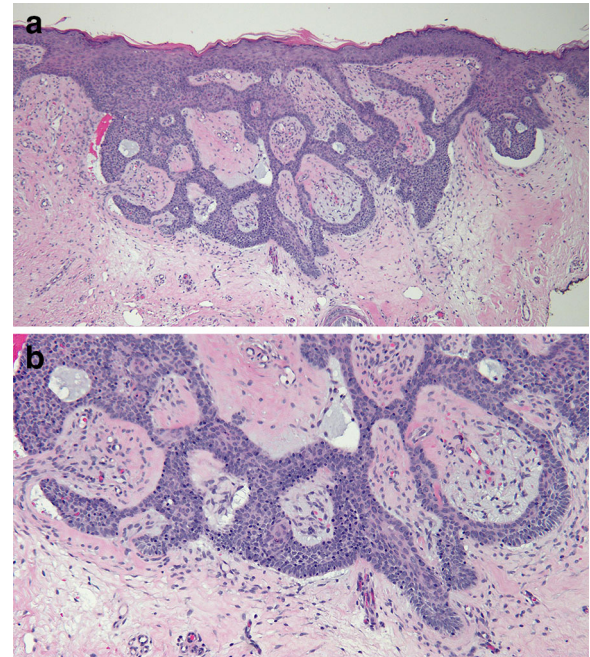


Fig. 5 a, b Multiple clefts of stromal retraction are seen (a). Blue-gray staining mucin is present in the stroma and stromal clefts (b). Hematoxylin and eosin: **a** $\times 10$, **b** $\times 40$

tumor from infiltrating into the reticular dermis, which is one of the reasons Pinkus considered it premalignant [10]. However, tumor cells may extend into the reticular dermis [5]. Clefts between fenestrations and stroma, indicative of stromal retraction, may be present and filled with mucin (Fig. 5) [5, 13, 32].

FeP may be seen in continuity with seborrheic keratosis or other types of BCC [5, 17, 29, 33, 35]. In some cases, nodular BCC appears to have developed from what began as a FeP [5].

DIFFERENTIAL DIAGNOSIS: CLINICAL

The clinical differential diagnosis of FeP is listed in Table 1 [20, 25, 34–36]. FeP may mimic acrochordon [20], amelanotic melanoma [20, 25, 35], compound nevus [20, 36], hemangioma [20, 35], neurofibroma

Table 1 Clinical differential diagnosis of FeP

Acrochordon [20]
Amelanotic melanoma [20, 25, 35]
Compound nevus [20, 36]
Fibroepithelial polyp [35]
Fibrolipoma
Fibroma [34]
Hemangioma [20, 35]
Keloid [34]
Lipofibroma
Lipoma
Neurofibroma [20, 25, 35, 36]
Nevus lipomatosus
Nevus sebaceous [20, 36]
Papillomatous melanocytic nevus [25]
Pedunculated nevus
Pyogenic granuloma [20, 35]
Seborrheic keratosis [20]

FeP fibroepithelioma of Pinkus

[20, 25, 35, 36], nevus sebaceous [20, 36], pyogenic granuloma [20, 35], and seborrheic keratosis [20]. For pedunculated FeP lesions, the differential may also include fibrolipoma, fibroma [34], lipofibroma, lipoma, nevus lipomatosus, pedunculated nevus, and papillomatous melanocytic nevus [25].

DIFFERENTIAL DIAGNOSIS: PATHOLOGY

Histologically, Ackerman et al. describe FeP as “so distinctive that, for practical purposes, no real differential diagnosis exists” [5]. However, reticulated seborrheic keratosis, tumor of follicular infundibulum, and eccrine syringofibroadenoma may be considered in the histopathological differential [5]. Although

reticulated seborrheic keratosis, follicular infundibulum tumor, and eccrine syringofibroadenoma have fenestrations formed by columns of epithelial cells, these are composed only of squamous cells, whereas fenestrations in FeP consist of both squamous and germinative cells [5]. Additionally, eccrine syringofibroadenoma and seborrheic keratosis have no follicular differentiation [5]. FeP’s histology is also similar to that of mammary intracanalicular fibroadenoma, but FeP is distinguished by its connections with the overlying epidermis and its lack of glandular tissue [10].

IMMUNOHISTOCHEMICAL STAINING

Immunostaining is not typically performed because FeP’s distinctive histology obviates the need for additional confirmation. When performed, staining with cytokeratin 20 (CK20) identifies Merkel cells in 85% of FePs [37]. FePs have diffuse expression of the proto-oncogene BCL-2 [38]. Staining for tumor protein p53, proliferation marker Ki-67, and nestin is weak in the fenestrated areas but stronger in the BCC-like nodular areas [13, 29, 31]. Androgen receptors are expressed in 77% of FeP, with more expression in the anastomosing cords than in the basophilic nubs, where they may be completely absent [37].

PATHOGENESIS

The pathogenesis of FeP has not been fully elucidated. Some argue that eccrine ducts provide an initial template down which FeP may spread, similar to how BCC may spread down hair follicles [28]. As the FeP progresses, eccrine ducts may be replaced completely by

solid strands of tumor [28]. Carcinoembryonic antigen (CEA) is a glycoprotein found in sweat glands as well as gastrointestinal tumors and fetal tissues [39]. Stern et al. found that 9 of 12 FePs examined stained positive for CEA, indicating the presence of eccrine ducts [28]. Lending support to the theory that eccrine ducts provide a template for FeP growth is the relatively high incidence of FeP on the glabrous sole of the foot, which has many eccrine sweat glands and few hair follicles [28]. Roth et al. found that 6 of 20 (30%) BCCs on the sole were FePs [40]. However, others have argued that eccrine ducts do not anastomose and that the eccrine duct foci in FePs may represent normal eccrine ducts trapped within the tumor or ductal differentiation [41].

Development of BCC and FeP on the glabrous skin of the sole of the foot, which lacks hair follicles [28, 40] and presumably lacks follicular germinative cells, suggests that not only follicular germinative cells but also eccrine gland stem cells may give rise to BCC and FeP [42].

Fibroepithelioma-like hyperplasia has been associated with Paget disease, especially anogenital Paget disease, which raises the possibility that in some cases it may be a reactive process [43]. Finally, mutations in tumor suppressor genes p53 and patched-1 (ptch1) may predispose to the development of FeP [26], but there is some evidence that the level of p53 in FeP is lower than that in BCC [13].

Ackerman et al. suggest that FeP may develop from seborrheic keratosis, since FePs often have infundibular tunnels filled with corneocytes in lamellate array, which may be the remnants of seborrheic keratosis [4]. Others propose that cases of FeP in continuity with nodular BCC indicate that trichoblastoma can

progress to BCC with the acquisition of additional genetic mutations [17].

TREATMENT

Complete excision is the typical treatment for FeP [20], and prognosis is good. Aggressive biologic behavior with local destruction or metastasis is extremely rare [44]. However, there is at least one report of a metastatic BCC with some FeP histopathology [45].

CLASSIFICATION OF FEP

The controversy about the proper classification of FeP centers around its common locations and histopathologic and immunohistochemical features (Table 2) [4, 5, 10, 11, 13, 15, 17, 19, 28, 29, 31, 33, 34, 37, 38, 45–55, 61, 63, 65, 66].

Location

The argument that FeP should be characterized as a trichoblastoma rather than a BCC has been made most persuasively by Bowen et al. [13]. The authors point out that FePs tend to occur in locations that are relatively uncommon for BCC. While FeP occur most often on the trunk, 80% of BCC occur on the head and neck, with only 15% of BCC occurring on the trunk [13], which receives less sun exposure. Yet, trichoblastoma are also most common on the head and neck [15, 46], so FeP's relatively low prevalence on the head and neck does not clearly support either classification. Some argue that the relatively high incidence of FeP on the sole of the foot suggests that FeP is more closely related to BCC than trichoblastoma, as trichoblastoma rarely occurs on the sole of the foot [47].

Table 2 Comparison of the physical exam findings, histopathology, immunostaining, and behavior of fibroepithelioma of Pinkus, basal cell carcinoma, and trichoblastoma

Characteristic	Fibroepithelioma of Pinkus	Basal cell carcinoma	Trichoblastoma
Physical exam			
Location	T trunk most common [13]; sole of foot relatively common [47]	Head and neck most common [13]	Head and neck most common [15, 46]
Dermoscopy	Fine arborizing vessels [19, 29]	Larger arborizing vessels [19, 48]	Fine arborizing telangiectases, crown vessels [48]
	White striae [19]	White striae [48]	White striae [48]
	Irregular gray-brown pigmentation and small gray-blue dots [19]	Gray-blue globules [19]	Brown globules [48]
Histopathology			
Continuity/contiguity	May be in continuity with BCC [4, 17, 29, 33, 34]	May be in continuity with other types of BCC [4]	May be in contiguity, but not continuity, with BCC [4]
Encapsulation	Blunt interface with underlying dermis [13]	Infiltrates dermis and subcutaneous tissue [13, 37]	Well circumscribed [52]
Fenestrations	Fenestrated [10]	Not fenestrated	Not fenestrated [4]
Follicular differentiation	Intermediate differentiation; follicular germs sometimes associated with rudimentary follicular papillae [5]	Less differentiated [4, 51]	More differentiated; discrete follicular papillae affiliated with discrete follicular germs [4, 51]
Horn cysts	Common [4]	Uncommon [53]	Common [53]
Mitotic figures	Sometimes present [4]	Increased [52, 53]	Absent or rare [4, 52, 53]
Necrosis	BCC-like areas may have necrosis [13]	Necrotic cells [4, 52]	No necrotic cells [4, 52]
Peripheral palisading	Common [11]	Common [51]	Common [51]

Table 2 continued

Characteristic	Fibroepithelioma of Pinkus	Basal cell carcinoma	Trichoblastoma
Solar elastosis	Uncommon [13]	Common [13, 49]	Less common [50]; present only above the lesion, not below [49]
Stroma	Clefts between trichoblast aggregations and adjacent stroma [4] Clefts between BCC-like nests and adjacent stroma may be filled with mucin [13] Fibroblast-rich [13]	Clefts between trichoblast aggregates and adjacent stroma [4] Mucin-rich [52, 54, 55] Fewer fibroblasts [49]	Stromal clefts, but no clefts between trichoblasts and stroma [4] Rarely mucinous [5] Fibroblast-rich [13]
Immunostaining			
Androgen receptor expression	Present in 77%; stronger in fenestrations than basaloid nubs [37]	Present in 73% [37]	Present in 17% of trichoepitheliomas and 0% of trichoblastomas [37]
BCL-2	Diffusely positive [38, 65]	Diffusely positive [38, 52]	Typically peripheral staining only, but variable; not a reliable differentiator [52, 66]
CD34	Usually absent in peri-tumoral stroma [38]	Usually absent in peri-tumoral stroma [38], but variable; not a reliable differentiator [63]	Usually present in peritumoral stroma [38], but variable; not a reliable differentiator [63]
CEA	Variable [28]	Rarely stain positive [28, 66]	Rarely stain positive [28, 66]
CK20 + Merkel cells	Merkel cells present in 85% [37] but fewer in BCC-like areas [13]	Merkel cells rare [31]	Merkel cells typical [31]
Ki-67 (stained by MIB-1 antibody)	Weak in typical FeP areas [13]; stronger in BCC-like areas [13]	Strong [13, 29, 38]	Low [38]

Table 2 continued

Characteristic	Fibroepithelioma of Pinkus	Basal cell carcinoma	Trichoblastoma
Nestin	Nestin present in stroma surrounding BCC-like areas but absent from thin anastomosing strands [31]	Labels stroma of BCC [31]	Expressed in peri-tumoral stroma [61]
p53	Weak in most FeP areas [13, 29]; stronger in BCC-like areas [13]	Moderate to strong [13, 29]	Weak [13]
PHLDA1	Anastomosing strands positive; basaloid nubs negative [31]	Negative [31]	Positive [31]
Behavior			
Clinical behavior	Typically not aggressive [31], but one report of metastasis [45]	More aggressive [31]; locally destructive with rare metastasis [52]	Benign [52]
Treatment response to imiquimod	Unresponsive [19]	Responsive [19]	Not evaluated

BCC basal cell carcinoma, *FeP* fibroepithelioma of Pinkus

Dermoscopy

From the perspective of dermoscopy, FeP shares similarities with both BCC and trichoblastoma. FeP and trichoblastoma have small, fine arborizing vessels [19, 29, 48] that are similar to those seen in other BCC but smaller in caliber and less branched [19, 48]. White striae, thought to result from fibrosis, can be seen in FeP, BCC, and trichoblastoma [19, 48]. The gray-blue dots of FeP are suggestive of the gray-blue globules described in BCC [19], while trichoblastoma has been described as having brown globules [48]. Crown vessels may be present in trichoblastoma [48] but are not typically seen in FeP or BCC. Overall, FeP, trichoblastoma, and BCC possess significant dermoscopic similarities and cannot always be distinguished.

Pathology

With regard to histology, Bowen et al. argue that the histology of FeP differs from BCC in that FeP typically has a blunt interface between the lesion and the underlying dermis; blunt interface was seen in all 75 FeP lesions reviewed by Bowen et al. [13]. In contrast, Ackerman et al. show photographs of FeP extending into the dermis and contained within subcutaneous fat [5]. These lesions are well circumscribed, however—a characteristic usually associated with benign lesions. Additionally, FeP rarely have significant dermal solar elastosis [13], which is common in BCC [13, 49] and less common in trichoblastoma [49, 50].

While trichoblastomas tend to be well differentiated toward follicular papillae [4, 51], and BCC tend to be less differentiated [4, 51], FeP tend to have an intermediate amount of differentiation; in FeP, follicular germs may or may not be associated with rudimentary follicular papillae [4, 5].

Similarly, the amount of mitotic figures [4] and necrosis [13] in FeP is intermediate to that of BCC, in which mitotic figures and necrosis are common [4], and trichoepithelioma, in which they are rare or absent [4, 52, 53]. However, horn cysts, which are common in FeP [4], are often seen in trichoepithelioma but rarely seen in BCC [53].

Bowen et al. argue that FeP's stromal composition is more consistent with trichoblastoma than BCC, because fibroblast-rich stroma is typically seen in benign lesions like trichoblastoma [13]. However, the stromal retraction and mucin deposition seen in FeP [13] is more consistent with BCC [4, 5, 52, 54, 55].

Associated BCC

Multiple cases of FeP in continuity with nodular BCC [4, 17, 29, 33, 34] suggest FeP's close relationship with BCC. From the perspective of one who believes FeP is BCC, Ackerman explains that it is not unusual for more than one type of BCC to be in continuity, so it is not surprising to find FeP in continuity with BCC; in contrast, BCC and trichoblastoma occur only in contiguity, not in continuity [4]. As mentioned above, Misago et al. posit that cases of FeP in continuity with nodular BCC may illustrate how trichoblastoma can transform into BCC as additional genetic mutations are accumulated [17].

Immunohistochemistry Staining

CK20 Staining

Expression of cytokeratins, which are well-established markers of epithelial differentiation, may be used to differentiate neoplasms and identify their cells of origin [8]. Kurzen et al. found that trichoblastomas and

BCCs express similar cytokeratin profiles. Both consistently express CK6hf, CK14, and CK17, while neither expresses hair keratins [8]. Of the 19 cytokeratins studied by Kurzen et al., only CK20, which is found in Merkel cells, was useful for differentiating BCC and trichoblastoma [8]. Merkel cells, the neuroendocrine cells of the skin [12, 56], are commonly found in trichoblastomas but are generally absent from basal cell carcinoma [8, 12, 31].

Hartschuh et al. identified CK20-positive Merkel cells in the fenestrated portion of FePs but not in other types of basal cell carcinoma and therefore suggested that FeP is more closely related to trichoblastoma than BCC [12]. Bowen et al. reported similar findings of CK20-positive Merkel cells in the fenestrated areas of FePs but not in other types of basal cell carcinoma [13]. In the “BCC-like areas” of FePs they found fewer Merkel cells (2 of 5 specimens) or an absence of Merkel cells (3 of 5 specimens) [13], a pattern corroborated by Katona et al. [37]. However, LeBoit et al. point out that this method of differentiation is not absolute: cases of invasive neoplasms containing Merkel cells have been documented [58].

PHLDA1 Staining

In 2006, Ohyama et al. characterized a follicular stem cell marker, PHLDA1 (pleckstrin homology-like domain, family A, member 1), that was found to be more sensitive and specific for differentiating trichoblastoma from BCC than CK20-stained Merkel cells [31, 57, 59]. PHLDA1 is consistently positive in trichoepitheliomas and negative in BCCs [31, 57]. Sellheyer et al. found that all 19 of 19 trichoepitheliomas were immunoreactive for PHLDA1 while all 11 of 11 basal cell carcinomas lacked PHLDA1 expression [57].

In FePs, Sellheyer et al. found that PHLDA1 labels the fenestrations but not the basaloid nubs; all nodular parts of the tumor were negative for

PHLDA1 [31]. Sellheyer et al. found that, as basaloid sprouts develop from the fenestrations, they lose their immunoreactivity for PHLDA1 [31]. This is not dissimilar from Bowen et al.’s findings that the fenestrations stained positive for CK20 but few CK20-positive Merkel cells were found in the basaloid nubs; indeed, Sellheyer et al. found that immunoreactivity for PHLDA1 and presence of Merkel cells are correlated in FePs [31].

However, Sellheyer et al.’s interpretation is completely different from Bowen’s. Sellheyer et al. propose that the fenestrated network that contains Merkel cells and stains positive for PHLDA1 is a tumor-specific form of epidermal hyperplasia that is part of the tumor but not itself malignant [31]. Sellheyer et al. agree with Pinkus’s original description that “the real BCC in FeP are the basaloid nubbins” and view the loss of PHLDA1 immunoreactivity as part of the progression from benign epidermal hyperplasia to malignant BCC [10, 31]. Therefore, they argue that the presence of Merkel cells in the epidermal hyperplasia of FeP does not disqualify FeP from being a BCC [31].

Nestin Staining

Similarly, Sellheyer et al. found nestin immunoreactivity in the BCC-like, PHLDA1-negative portions of the FePs but no nestin in the fenestrated, PHLDA1-positive portion of the FeP [31]. Nestin is a neuroepithelial stem cell protein that labels the stroma of BCC [31, 60]. Since the stroma of BCCs stains positive for nestin, Sellheyer et al. posit that the presence of nestin in the BCC-like areas of FePs indicates that they are true BCCs [31]. However, this argument is somewhat undermined by another paper by Sellheyer et al. that reports that nestin is also expressed trichoblastoma and trichoepithelioma [61].

Ki-67 and p53 staining

The pattern of basaloid nubs staining more similar to BCC and fenestrations staining more similar to trichoblastoma is also seen in staining for the protein product of tumor suppressor gene p53 and the cellular proliferation marker Ki-67. Bowen et al. reported that staining for p53, which is mutated and overexpressed in 56% of BCC, was generally low in FePs. Similarly, staining with MIB-1 antibody, which recognizes Ki-67 antigen in formalin-fixed, paraffin-embedded tissue [62], was also lower than in typical BCCs [13]. However, the “BCC-like areas” of the FeP stained stronger than the rest of the FeP for p53 and Ki-67 [13].

CD34 Staining

The amount of CD34, a hematopoietic progenitor cell antigen, in peritumoral stromal cells has been proposed as a differentiator between trichoepithelioma and basal cell carcinoma [63, 64]. The stroma immediately surrounding trichoepitheliomas typically stains positive for CD34, while stroma immediately adjacent to basal cell carcinomas typically does not [38], but there is some variability [63]. Naeyaert et al. found that CD34 expression in FeP is generally absent in the peritumoral stroma, as it is in BCC [38].

BCL-2 Staining

With regard to the staining for the proto-oncogene BCL-2, Naeyaert et al. and Marusic et al. found that FePs are diffusely positive, similar to BCC [38, 52, 65], whereas in trichoepitheliomas, BCL-2 positivity is typically limited to the periphery [42, 66]. However, BCL-2 may also be diffusely positive in trichoepithelioma and is not considered a reliable differentiator [52, 66].

Carcinoembryonic Antigen (CEA) Staining

Despite the theory that FeP may spread down eccrine ducts and the detection of CEA in some FePs [28], Swanson et al. found that CEA is usually absent in both BCC and trichoepithelioma [66]. Therefore, the presence of absence of CEA staining is not helpful for categorizing FeP as one or the other.

Androgen Receptor Staining

The similarly high prevalence of androgen receptors in FeP and BCC (77% vs. 73%) and the absence or rarity of androgen receptors in trichoepithelioma and trichoblastoma (17% and 0%, respectively; $p = 0.0007$) supports classification of FeP as BCC [37].

Clinical Behavior and Response to Therapy

FeP's non-aggressive clinical behavior seems more similar to trichoblastoma than BCC. Additionally, FeP may respond differently to treatment than BCC; Zalaudek et al. reported a man with a FeP that was resistant to 5% imiquimod treatment, whereas his other BCCs resolved with this therapy [19].

CONCLUSION

Review of the evidence for and against classification of FeP as BCC or trichoblastoma finds that FePs possess characteristics of both. Dermoscopy findings and the amount of mitotic figures, necrosis, and follicular differentiation are intermediate between trichoblastoma and BCC. Its mucin-rich stroma and stromal retraction are more similar to BCC, although its relative lack of solar elastosis and relative prevalence of horn cells are more consistent with trichoblastoma.

Immunohistologically, the fenestrated portion of the tumor more closely resembles trichoblastoma while the solid basaloid nubs more closely resemble BCC, with regard to PHLDA1, p53, and Ki-67 staining, and can become full-fledged BCC. With regard to CD34, BCL-2, and androgen receptor expression, FeP is more similar to BCC. In its behavior, it generally seems more similar to trichoblastoma, despite one case of FeP histopathology in metastatic BCC [45]. Some characteristics of FeP are distinct from both BCC and trichoblastoma, such as its predilection for the trunk and its fenestrated histology.

To some extent, whether the lesion should be considered a trichoblastoma until BCC develops within it, or whether it should be called BCC from the beginning, since it may give rise to BCC, seems a semantic issue. Perhaps Katona et al. make the most reasonable proposal—that FeP may be a trichoblastic tumor intermediate between trichoblastoma and BCC [37]. Considering that trichoblastoma and BCC share a common cell of origin [37] and represent two different points in the differentiation of that progenitor cell [55], with similar cytokeratin profiles and mutations in the tumor suppressor *ptch1* [8, 37, 58], it makes more sense to consider them on a spectrum from benign to malignant rather than to attempt to draw an artificial line between the two. In his 1965 paper, Pinkus said, “Having been able to collect a graded series from the typical premalignant fibroepithelial tumor to the plate-like or almost macular basal cell epithelioma of the very superficial type, I find it impossible to draw a distinct line anywhere in this series” [11]. This review of FeP, and the evidence to classify the tumor as either a BCC or a trichoblastoma, finds the line similarly difficult to draw, and perhaps doing so is unnecessary.

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