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DOI
10.3889/oamjms.2017.079

Publication date
2017

Document Version
Final published version

Published in
Open Access Macedonian Journal of Medical Sciences

ID Design 2012/DOOEL Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2017 Jul 25; 5(4):439-444.
Special Issue: Global Dermatology
https://doi.org/10.3889/oamjms.2017.079
eISSN: 1857-9655
Case Report

Fibroepithelioma of Pinkus (FeP) Located in the Left Lower Quadrant of the Abdomen - Case Report and Review of the Literature

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Citation: Mihai MM, Voicu C, Lupu L, Koleva N, Patterson JW, Lotti T, Lotti J, França K, Batashki A, Bakardzhiev I, Wollina U, Tchernev G. Fibroepithelioma of Pinkus (FeP) Located in the Left Lower Quadrant of the Abdomen - Case Report and Review of the Literature. Open Access Maced J Med Sci. 2017 Jul 25; 5(4):439-444. https://doi.org/10.3889/oamjms.2017.079

Keywords: fibroepithelioma of Pinkus; basal cell carcinoma; trichoblastoma; trichoepithelioma.

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Received: 01-Apr-2017; **Revised:** 22-Apr-2017; **Accepted:** 23-Apr-2017; **Online first:** 19-Jul-2017

Funding: This research did not receive any financial support.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

BACKGROUND: Fibroepithelioma of Pinkus (FeP) is an uncommon and controversial skin lesion, sharing features of both basal cell carcinoma (BCC) and trichoepithelioma. In this article, we present a case of FeP and synthesise current concepts on the etiopathogenesis, diagnosis and treatment of this uncommon tumour.

CASE REPORT: We report the case of an 88-year-old male patient presenting to the dermatology clinic for a sharply demarcated, pink, exophytic cutaneous tumour situated in the left inguinal region. The histopathological examination performed after complete surgical excision of the lesion revealed a diagnosis of FeP. A systematic review of the literature was conducted. The terms `fibroepithelioma` and `Pinkus` have been searched in bibliographical databases, including PubMed and Google Scholar, without time limitation up to February 15th, 2017. Seventy-nine articles that fulfilled all the required conditions were identified. Relevant citations and additional articles identified from references have been assessed. The systematic review included a total number of 452 cases of FeP.

CONCLUSION: Even though FeP is considered a relatively rare tumour, its true incidence rate might be higher than previously believed. The clinical aspects of the lesion described in this paper and its location in the left lower quadrant of the abdomen are classic features of FeP. Histopathologic examination revealed features of both BCC and trichoepithelioma. Further epidemiological studies are required to clarify whether patients with FEP should be screened for the occurrence of other malignancies.

Introduction

Fibroepithelioma of Pinkus (FeP) is an uncommon and controversial skin lesion, sharing features of both basal cell carcinoma (BCC) and trichoepithelioma. While some authors differentiate trichoblastoma from trichoepithelioma, the World Health Organization classifies the terms synonymously [1]. In the present paper, we will use the term trichoepithelioma.

FeP was described for the first time by Hermann Pinkus in 1953, who regarded this skin lesion as a variant of BCC [2], a theory that continued for many years [3, 4]. Recent research has highlighted the fact that BCC and trichoepithelioma have the same origin; that is, the epithelial stem cells of the hair follicle [5, 6]. Such a concept has led to the proposal that FeP might be a trichoblastic tumour intermediate between trichoepithelioma and BCC [7]. The clinical presentation of FeP is that of a flesh-coloured, well-demarcated, sessile, dome-shaped papule or

pedunculated tumour frequently often located in the lumbosacral area. The clinical differential diagnosis includes benign tumours such as intradermal nevus, fibroma, acrochordon, and seborrheic keratosis [8], as well as a variety of cutaneous neoplasms, including basal cell carcinoma and amelanotic melanoma. The pathogenesis of FeP is still a matter of debate. As is the case with conventional BCC, theories include mutations in the tumour suppressor gene P53 and the PATCHED gene, inducing inhibitory signals in the Hedgehog pathway [7]. There are several reports on the dermatoscopic, reflectance confocal microscopic, and histopathologic features of FeP. The treatment of choice is complete surgical excision. Other surgical techniques, such as cryosurgery, electrodesiccation and Mohs micrographic surgery have also been performed successfully [7].

In this article, we present a case of FeP and summarise current concepts on the etiopathogenesis, diagnosis and treatment of this uncommon tumour.

Case Report

An 88-year-old male presented to the dermatology clinic for evaluation, diagnosis and treatment of a skin tumour that had been slowly growing for the preceding five years in the left inguinal region. There were no complaints regarding pain or itching of the skin lesion. The patient's medical history revealed several cardiovascular risk factors: an elevated blood pressure and non-insulin dependent diabetes mellitus type 2 but was otherwise unremarkable. Clinical examination revealed a sharply demarcated, pink, exophytic cutaneous tumour with a lobulated, cerebriform surface, measuring approximately 5 x 3.6 cm situated in the left lower quadrant of the abdomen (Fig. 1a). Paraclinical Diagnostic tests were unremarkable. Abdominal ultrasound, chest x-ray and ultrasound of the axillary and inguinal lymph node groups showed no evidence of disease progression or other abnormal findings. In the light of the history of tumour growth and clinical differential diagnosis, the lesion was surgically excised with wide margins under local anaesthesia, thus creating an elliptical defect (Fig. 1b), followed by the primary closure (Fig. 1c) and by the application of antiseptic dressings. Postoperatively, the patient was well and was discharged with a set of follow-up instructions. Histopathologic examination of the excised cutaneous tumour showed a polypoid tumoral proliferation with superficial ulcerated areas (Fig. 2b). Focal solid cribriform areas (Fig. 2a), tumour islands and long anastomosing strands and columns of basaloid cells with scant cytoplasm, hyperchromatic nuclei and moderate cytologic atypia could be seen projecting downwards from the epidermis into the papillary dermis. Relatively frequent mitoses could be seen along with abundant fibro hyaline tumoral stroma. Based on the clinical and microscopic features, a final diagnosis of fibroepithelioma of Pinkus was made. The pathology report confirmed its complete excision, with tumour-free surgical resection margins.

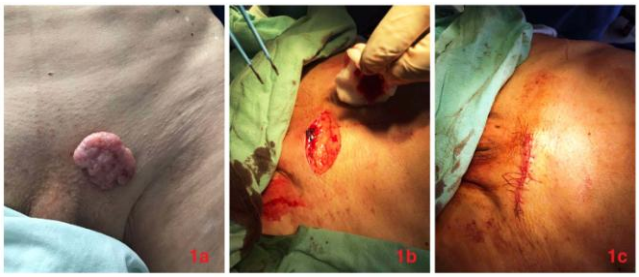

Figure 1: 1a) Cutaneous tumour in the left inguinal region; 1b) Elliptic surgical defect after haemostasis, ready for reconstruction; 1c) Primary closure of the defect with interrupted non-absorbable sutures

Discussion

FeP was first described as a distinct clinicopathologic entity by Hermann Pinkus in 1953 [2]. In a retrospective study that included over 900 epitheliomas, he described four cases with unique clinical and microscopic features, emphasising their importance in enhancing the understanding of epitheliomas in general [2].

While FeP is considered a relatively rare tumour, it is probably underreported. It can be easily confused with other benign skin tumours that may not be treated or biopsied [9]. After a thorough literature review, we identified 79 articles reporting a total number of 452 FeP cases. FeP usually appears in the fourth to fifth decades of life [10], although two cases of FeP in children have been reported [11, 12]. In the largest clinical study, Bowen et al. (2005) observed a slightly higher prevalence rate in women: 54% of 114 patients [13].

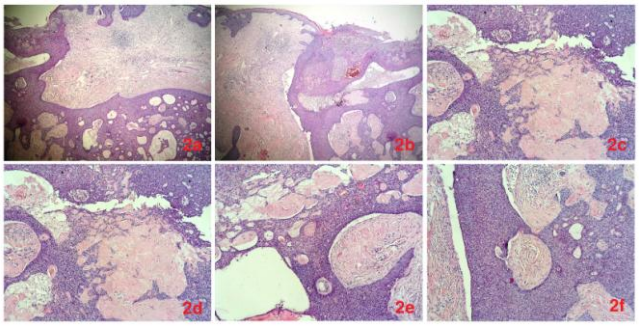

Figure 2: Several histopathologic images from the tumour, showing branching cords of basaloid epithelium, some narrow (2a - lower left, 2c and 2d - centre, and figure 2e - upper left) and some more broad (2b and 2f), within a cellular fibrotic stroma

After almost 65 years since the first description of FeP, its classification and pathogenesis are still matters of debate. The following alternatives were taken into consideration: a premalignant tumour, a fenestrated trichoepithelioma subtype, or an indolent BCC subtype. The first reports described FeP as a BCC subtype. Due to its indolent, long-term course, and histological particularities it was further classified as a premalignant tumour - a precursor of BCC. In 2005, Bowen et al. argued that FeP is a trichoepithelioma rather than a BCC subtype, based upon their histopathological and immunohistochemical studies of 75 FePs [13]. The same year Ackerman et al. provided criteria for the histopathologic differentiation of FeP from trichoblastoma (trichoepithelioma) and classified `the fibroepithelial tumour of Pinkus as a trichoblastic (Basal-cell) carcinoma` [4], reflecting the controversial nature of the problem.

It is well known that BCC can spread directly into the dermis, by perifollicular or perineural extension. However, BCC might also spread via eccrine ducts. In 1994, Stern et al. hypothesised that eccrine ducts might serve as the starting point of FeP development, based on the immunohistochemistry of 9 tumours that stained positively for carcinoembryonic antigen (CEA) [14]. This glycoprotein is usually found in eccrine sweat glands as well as gastrointestinal tumours and fetal tissues. In 2007 Stern and Haupt provided another argument that supports this theory: FeP lesions have been found in glabrous skin areas that lack hair follicles [15]. In 2007, Kurokawa et al. also supported the hypothesis, proposing that FeP may originate from intraepidermal eccrine ducts and afterwards proliferate into the dermis [16]. An important observation is that BCC might replace a FeP or develop independently by the eccrine ductal spread.[14]

Further contributing to the debate regarding the true origin of this tumour, it has been shown that both Merkel cells and androgen receptors are found in FeP.

In a study of 76 adnexal tumours of skin Wollina and Schrepel (2006) reported that trichoepitheliomas had an increased proliferative activity but not an increased number of MC (17). In basal cell carcinomas and trichofolliculomas, however, MC was found near proliferating tumour cells. Androgen receptors are expressed in BCCs, but only exceptionally in trichoepitheliomas [7]. Katona et al. (2007) observed that 10 out of 13 FeP, as well as 8 out of 11 BCCs, stained positively for androgen receptors [7]; only 2 out of 15 trichoepitheliomas expressed androgen receptors [7]. These results support the theory that FeP is an indolent BCC subtype. Merkel cells are a feature of benign follicular tumours, and it is well known that moderate hyperplasia of Merkel cells is present in chronic sun-damaged skin and hypertrophic actinic keratoses [18]. Merkel cells are found in trichoepitheliomas but are absent in BCCs [7]. This supports the theory that FeP may be a fenestrated trichoepithelioma subtype.

To provide more clarity in this debate, Sellheyer et al. (2012) used a stem cell marker, PHLDA1 (TDAG51), which is expressed in the basal cell layer during embryogenesis and is present in trichoepitheliomas, but not BCCs. The results were consistent with a mixed histological pattern, showing an anastomosing network of thin cellular strands positive for PHLDA1 and basaloid nests with negative results for this marker [3]. The authors concluded that FeP is a premalignant lesion with a specific type of epidermal hyperplasia that stains positively for PHLDA-1 and has the capability of developing multifocal BCCs [3].

Previous literature reports have linked FeP with several risk factors:

Genetic factors: Some authors theorise that, like BCC, mutations in p53 and PATCHED-1 genes may also be responsible for the development of FeP [7, 19] and that both tumours originate in the follicular germinative cells. Others suggest that FeP might be a premalignant lesion that progresses to BCC by acquiring additional genetic mutations [20] or that it might develop from seborrheic keratosis, based on some histopathologic similarities [4]. Also, FePs have been identified in continuity with both BCC and seborrheic keratosis [4].

Radiotherapy: There is a frequent occurrence of FeP in patients with a history of radiotherapy. Hartschuch et al. observed hyperplasia of Merkel cells in chronic radiation dermatitis, as well as their presence in FePs and trichoepitheliomas, though they are absent in BCCs. The researchers further suggested that Merkel cells might be responsible for the benign biological behaviour of the tumours that have them [18]. Although previous irradiation might constitute the initial carcinogenic factor in some cases, this is not invariably the case, and the evolution and prognosis of the tumours are the same when compared to those due to other triggering factors [21]. ***Sun-exposure:*** It was observed that unlike BCCs, FeP has a predilection for sun-protected skin, is often located in the dorsal, lumbar and sacral regions. Bowen et al. showed that only 5% of tumours develop in anatomic sites that receive significant amounts of solar elastosis [13].

Association with other neoplasms: Some authors have suggested that FeP might be a reactive process (22) associated with other neoplasms, including breast cancer [23, 24], extramammary Paget's disease [25], gastrointestinal neuroendocrine tumours [26] or BCCs and Gorlin-Goltz syndrome [27]. Longo et al. (2016) investigated whether FeP is an expression of a more complex gastrointestinal syndrome and observed that in 9 of the 49 cases it was associated with gastrointestinal tumours [26]. The expression of CEA in both FeP and gastrointestinal tumours could suggest a common pathogenesis [14].

Further epidemiological studies are required to clarify whether or not these associations are coincidental and whether patients with FEP should be screened for the occurrence of other malignancies [26]

Chronic inflammation: There has been a case report of malignant degeneration in a chronic lower limb ulcer with the histological image of a FeP [28]. Clinically, most FePs appear in individuals between 40 and 60 years old, with a history of BCC [19], of solitary or multiple slow-growing papules or plaques. Typically, the lesions appear as flesh-coloured, pink, red, grey or even brown [29, 30], firm, sessile or pedunculated papules with a broad base. As previously noted, and in contrast to most BCCs, FeP develops mainly in sun-protected areas such as the lower back, inguinal, and crural areas, or the extremities. Atypical clinical forms of FeP may present as multiple lesions with different presentations [30]; these include ulcerated lesions or tumours arising in atypical locations such as the head, axillae, torso, umbilicus [31], plantar region [14, 32], or even on mucocutaneous junctions [33].

FeP is considered to be either a rare tumour or an underdiagnosed one because of its non-specific clinical appearance. Therefore, it can easily be mistaken for a wide variety of skin lesions such as acrochordons, intradermal or compound nevi, sebaceous nevi, seborrheic keratoses, fibromas, lipomas, cysts, and even amelanotic melanomas [10, 30, 34, 35].

Regarding diagnostic methods, the dermoscopy of FeP is not specific, as there are mixed features of BCC and trichoepithelioma, consisting of polymorphous vessels - mainly short arborizing and dotted types, gray-brown and gray-blue areas and dots, and shiny white streaks (also known as crystalline structures) [8, 36], secondary to fibrosis. Some structures similar to BCC or seborrheic keratosis may be present, such as ulceration, large ovoid nests, and milia-like cysts. Recently, Kornreich et al. reported an additional dermoscopic feature of FeP; namely, a white network, which could be more specific for FeP [37]. The white network is the manifestation of elongated hyperplastic, anastomosing epithelial strands [37]. This finding, together with additional BCC-related dermoscopic features, may facilitate the diagnosis of FeP [37].

The main reflectance confocal microscopy findings of FeP include a fenestrated pattern corresponding to the fibrous stroma and the presence of bright cells in pigmented lesions [38].

The histopathological features of FeP are distinctive, characterised by long, anastomosing strands of basaloid cells, embedded in a fibrous stroma, that project downwards from the epidermis and extend into the papillary dermis, giving the tumour a honeycomb or sponge-like appearance [22]. The cells from the edge of the strands are columnar and arranged in a palisade. Sometimes, follicular germ-like structures can be identified within the tumour [4]. FeP usually has a distinct interface with the normal, underlying dermis [13], but sometimes tumour cells may extend into the reticular dermis [4].

FeP is typically treated by complete surgical excision, with generally excellent results [10]. Other possible treatment options include cryosurgery, electrodesiccation, or Mohs micrographic surgery [7]. In contrast to the treatment of some BCCs, topical Imiquimod 5% has been proven to be ineffective in the treatment of FeP [36]. Overall, FeP is a not-aggressive tumour with no metastatic potential and good prognosis after complete surgical excision [39].

In conclusion, the tumour presented in our case report appeared in a male in his eighties, which stands in contrast to epidemiological studies in which the majority of FePs appear to occur in women in the fourth to fifth decades of life. Nevertheless, the clinical features of the lesion and its location in the left lower quadrant of the abdomen are classical presenting features of FeP. The systematic review performed in this paper includes a total number of 452 FePs that have been reported in the medical literature. Even though FeP is considered a relatively rare tumour, its true incidence rate might be higher than suggested in published studies. Outside of dermatology, FeP is a relatively unknown tumour in the medical field, and, as indicated by our review, it can be easily confused with other benign or even malignant tumours.

The histopathologic findings appear to support Ackerman's theory that FeP is a 'trichoblastic (basal-cell) carcinoma' [4], sharing both features of BCC and trichoepithelioma. To further sustain this argument, the history of our patient's tumour evolution raises the hypothesis that a lesion originating as a trichoblastoma may have acquired additional genetic mutations over time, progressing to the premalignant lesion described in our histopathology report.

There is no known history of radiotherapy in our patient, and the abdominal ultrasound, chest x-ray and ultrasound studies of the axillary and inguinal lymph node groups showed no evidence of disease progression or other malignancies. Further epidemiological studies will be required to clarify whether or not these associations are merely hypothetical or fortuitous, or if patients with FeP should be carefully screened for the occurrence of other malignancies.

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