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Pseudoepitheliomatous hyperplasia: The link between sporotrichosis and squamous cell carcinoma

Hiperplasia pseudoepiteliomatosa: A ligação entre esporotricose e carcinoma de células escamosas.

Hiperplasia pseudoepiteliomatosa: El vínculo entre la esporotricosis y el carcinoma de células escamosas

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Miguel Augusto Martins Pereira
ORCID: https://orcid.org/0000-0001-5646-2253
Fundação Carlos Chagas de Amparo à Pesquisa do Estado do Rio de Janeiro, Brazil
Universidade Federal Fluminense, Brazil
E-mail: mappereira@icloud.com
Dhara Lima Martins
ORCID: https://orcid.org/0000-0002-8378-4378
Universidade Federal Fluminense, Brazil
E-mail:dharalima@id.uff.br
Luciana Pantaleão
ORCID: https://orcid.org/0000-0001-7480-2530
Universidade Federal Fluminense, Brazil
E- mail:lupantaleao@yahoo.com.br
Enoï Guedes Vilar
ORCID: https://orcid.org/0000-0001-8069-2104
Universidade Federal Fluminense, Brazil
E-mail: enoivilar@gmail.com

Abstract
The pseudoepitheliomatous hyperplasia (PEH) is a benign condition. It is a reactive histological pattern characterized by hyperplasia of the epidermis and adnexal epithelium. Therefore, it can be found in several clinically heterogeneous diseases: Infections, neoplasms, dermatoses with inflammation/chronic irritation, and miscellaneous processes. Among the infections group, deep mycoses stand out, and squamous cell carcinoma (SCC) for the neoplasm. As these two lesions can be observed in the same body regions and present visually similar features, it is also natural that they can be mistaken, as seen in previous works. Thus, we propose an individually based, cross-sectional retrospective review of patients with confirmed sporotrichosis (from a total of 86 cutaneous sporotrichosis cases) in which squamous cell carcinoma was also suspected as a clinical hypothesis. Considering the small sample, a qualitative analysis of the results was made. This paper presents an explanation with a microscopic basis for this diagnostic error. We also recommend examining several histological sections, detailed clinical information, and the use of special stains to avoid misdiagnosis.
Keywords: Carcinoma; Skin; Diagnosis; Biopsy; Epidemiology; Zoonoses.

Resumo
A hiperplasia pseudoepiteliomatosa (HPE) é uma condição benigna. É um padrão histológico reativo caracterizado por hiperplasia da epiderme e epitélio anexial. Portanto, pode ser encontrada em várias doenças clinicamente heterogêneas: infecções, neoplasias, dermatoses com inflamação / irritação crônica e processos diversos. Dentre o grupo de infecções, destacam-se as micoses profundas e o carcinoma espinocelular (CEC) para a neoplasia. Como essas duas lesões podem ser observadas nas mesmas regiões do corpo e apresentam características visualmente semelhantes, também é natural que possam ser confundidas, como visto em trabalhos anteriores. Assim, propomos uma revisão retrospectiva transversal de base individual de pacientes com esporotricose confirmada (de um total de 86 casos de esporotricose cutânea) em que o carcinoma de células escamosas também foi suspeitado como uma hipótese clínica. Considerando a pequena amostra, foi feita uma análise qualitativa dos resultados. Este artigo apresenta uma explicação com base microscópica para esse erro diagnóstico. Também recomendamos examinar várias seções histológicas, informações clínicas detalhadas e o uso de colorações especiais para evitar diagnósticos incorretos.
Palavras-chave: Carcinoma; Pele; Diagnóstico; Biópsia; Epidemiologia; Zoonoses.

Resumen
La hiperplasia pseudoepiteliomatosa (PEH) es una afección benigna. Es un patrón histológico reactivo caracterizado por hiperplasia de la epidermis y el epitelio anexial. Por tanto, se puede encontrar en varias enfermedades clínicamente heterogéneas: Infecciones, neoplasias, dermatosis con inflamación / irritación crónica y procesos misceláneos. Dentro

del grupo de infecciones destacan las micosis profundas y el carcinoma epidermoide (CEC) para la neoplasia. Como estas dos lesiones se pueden observar en las mismas regiones corporales y presentan características visualmente similares, también es natural que se puedan confundir, como se vio en trabajos anteriores. Por lo tanto, proponemos una revisión retrospectiva transversal de base individual de pacientes con esporotricosis confirmada (de un total de 86 casos de esporotricosis cutánea) en los que también se sospechaba como hipótesis clínica el carcinoma de células escamosas. Considerando la pequeña muestra, se realizó un análisis cualitativo de los resultados. Este artículo presenta una explicación con una base microscópica de este error diagnóstico. También recomendamos examinar varias secciones histológicas, información clínica detallada y el uso de tinciones especiales para evitar diagnósticos erróneos.
Palabras clave: Carcinoma; Piel; Diagnóstico; Biopsia; Epidemiología; Zoonosis.

1. Introduction

The pseudoepitheliomatous hyperplasia (PEH) is a benign condition that is often considered a reactive histological pattern rather than a disease itself (Zayour et al., 2011). It is characterized by hyperplasia of the epidermis and adnexal epithelium, mimicking squamous cell carcinoma SCC (Figure 1). The PEH is found in several clinically heterogeneous diseases, which can be grouped into four major groups: Infections, neoplasms, dermatoses with inflammation/chronic irritation, and miscellaneous processes (e.g., tattoo pigments). (Zayour et al., 2011) (Conejero et al. 2020)

However, the microscopic characteristics of PEH in these entities are still necessarily the same. In the group of infections, several deep mycoses stand out, with PEH being described in blastomycosis, paracoccidioidomycosis, sporotrichosis, chromomycosis (chromoblastomycosis), coccidioidomycosis and aspergillosis. (Zayour et al., 2011) (Chandler et al.,1987) As a curiosity, both sporotrichosis and other deep mycoses – or even halogenoderms – neutrophilic microabscesses can be observed in the hyperplastic epidermis of the PEH. (Zayour et al., 2011) (Chandler et al., 1987)

The PEH is clinically presented as a well-demarcated plaque, papule or nodule, with varying degrees of flaking, crust, and color equal to the rest of the skin or tan-pink ulcerations being present. Exuberant PEH gives the lesion a "vegetative" or verrucous appearance. Thus, PEH can guarantee the injury a very similar aspect to SCC and SCC in situ.

In sporotrichosis, especially the lymph-cutaneous form (the most common, corresponding to 80% of patients), which has polymorphic lesions, may present lymphangitis and/or lymph node enlargement resembles metastatic SCC. (Zayour et al., 2011) (Chandler et al., 1987) (Adams et al., 2014) (Hussein., 2005) (Mora et al., 1981) (Orofino-Costa et al., 2017) (Mahajan., 2014) (Pereira et al., 2020) (Gremião et al., 2021) Also, the often painful or even itchy sporotrichosis lesions, (Pereira et al., 2020) may be similar to SCC symptoms and local neuropathic symptoms, such as numbness, burning, paraesthesia or paralysis associated with cutaneous SCC with perineural invasion. (Adams et al., 2014) (Gremião et al., 2021)

2. Methodology

This is a single-center observational retrospective cross-sectional study that resorted to a histopathological analysis for a qualitative analysis of patients with confirmed sporotrichosis in which squamous cell carcinoma was a clinical suspicion. (Ludke & Andre, 2013)

Eligibility criteria and study group: this work was based on a study of 86 consecutive cases of cutaneous sporotrichosis extracted from the records of the Dermatopathology Service of a University Hospital in Brazil, between 2009 and 2017. However, only the confirmed cases of sporotrichosis in which squamous cell carcinoma was a clinical differential diagnosis were analyzed, represented by a total amount of 5 patients.

Histopathological analysis: three dermatopathologists at the university hospital performed histopathological analysis. The slides were stained at Hematoxylin and eosin (H&E) and evaluated for inflammatory infiltrate and granuloma type. In contrast, the presence of fungus was evaluated by Grocott silver and periodic-Schiff acid (PAS) staining. The final diagnosis of sporotrichosis was confirmed by the culture (gold standard). The collection and visualization of the records were performed after

the approval of the directors of the Dermatopathology Service. The patient's anonymity was maintained in the publication of the data.

3. Results and Discussion

Sporotrichosis is an endemic disease prevalent worldwide in tropical and subtropical areas, caused by Sporothrix sp. (Chakrabarti et al., 2015). Infection in humans was first described by Benjamin Schenck in 1898 in the United States, hence the homage to the specie *S. schenckii sensu stricto* (Barros et al., 2010) (Schenck B, 1898). The most relevant pathogenic species are *Sporothrix schenckii sensu stricto*, *S. brasiliensis*, *S. globosa* and *S. mexicana*. (Marimon et al., 2007)

The state of Rio de Janeiro, where this study took place, has been suffering from a sporotrichosis epidemic associated with feline transmission, since 1998, mainly by *Sporothrix brasiliensis*, according to phenotypic studies (Falcão et al., 2019) (Gremião et al., 2021) (Silva et al. 2020) (Schechtman et al. 2022) (Almeida-Paes et al. 2014)

Although it is associated with low mortality, it causes considerable morbidity. However, this situation changed in the context of HIV patients and in socially disadvantaged groups where there are more hospital stays, unusual forms of disease - such as bone sporotrichosis - and mortality (Falcão et al., 2019) (Ramos et al.,2021). Since sporotrichosis is not a reportable disease, its prevalence is unknown, which indicates a much higher number of cases. Moreover, there is evidence of a change in the disease's epidemiological profile, which started to affect more older adults. (Pereira et al., 2020) Thus, given the scenario presented, studies about this deep mycosis are essential for doctors and health organizations.

The present study started with an initial sample of 86 cases of confirmed sporotrichosis cases. We extract those in which SCC was also suspected as a clinical hypothesis. A total of 5 cases were found, representing 5.81% of patients with sporotrichosis. (Pereira et al., 2020)

We then separated and dissected those cases (3 male and 2 female patients). At first, we noticed that all these cases had PEH and ulcerations; as well as the lesions were presented in regions considered to be sun exposed. These lesions were of variable size (0,3 cm to 15 cm; mean 5,6 cm). Lymphadenomegaly was observed in 2 cases (40%); both were negative for PAS / Grocott. Another case of negative PAS / Grocott showed no lymphadenomegaly (Table 1).

All the 5 cases presented (Table 1) were in regions considered sun-exposed, and SCC generally occurs in areas exposed to the sun of individuals with fair and dark skin, the involvement of regions not exposed to the sun being more common in individuals of dark skin. (Hussein., 2005) (Mora et al., 1981)

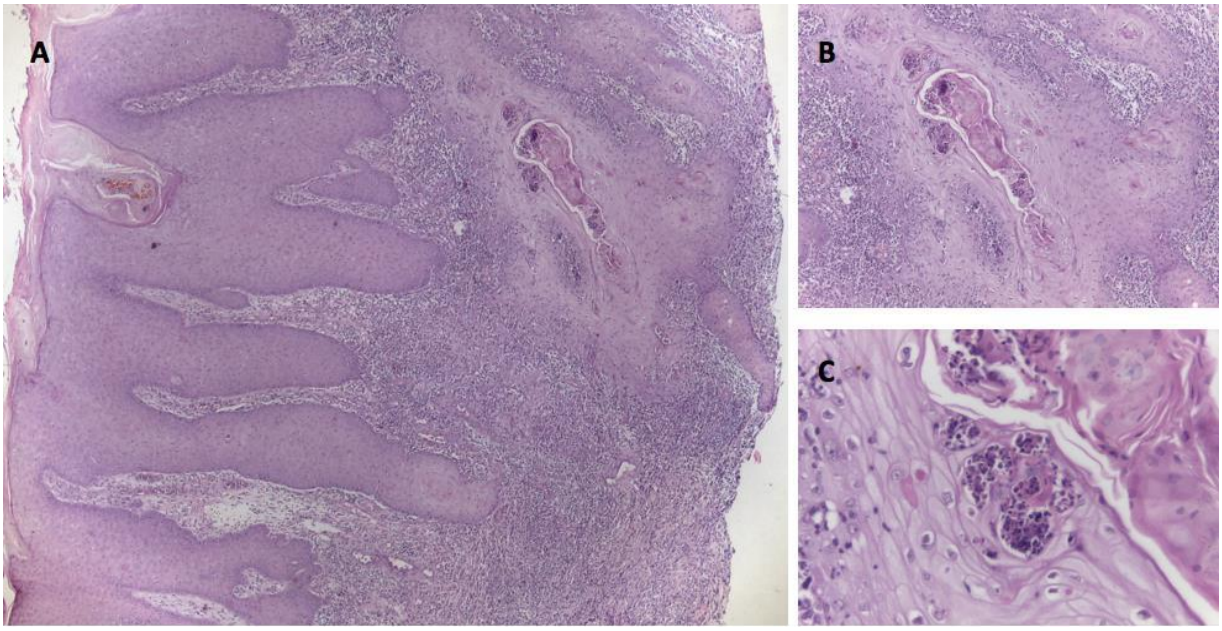
It is also worth mentioning that when there is suppurative and / or granulomatous inflammation, it is crucial use special stains, even if not all our cases presented have been positive for PAS and Grocott (Table 1), as well as cultures for microorganisms to rule out other differential diagnoses (Zayour et al., 2011) (Chandler et al., 1987).

Table 1. Confirmed cases of sporotrichosis in which squamous cell carcinoma was a differential diagnosis. Grocott and PAS stand for Grocott silver and periodic-Schiff acid stainings.

Lesion description	Sex	Skin color	Age	HPE	PAS/ Grocott	Site	Size	Lymphadenomegaly
Nodular and ulcerated with a granular and friable bottom	F	Dark-skinned	79	Present	Positive	Forearm	3,0 cm	Yes
Linear, ulcerated, purulent, erythematous and infiltrated aspect.	M	Brown-skinned	69	Present	Positive	Back	15,0 cm	Yes
Pruritic, ulcerated lesion with erythematous papules	F	White	77	Present	Negative	Hand	5,0 cm	No
Painful, ulcerated lesion with verrucous aspect	M	Brown-skinned	56	Present	Negative	Leg	0,3 cm	Yes
Ulcerated lesion with erythematous papules	M	White	72	Present	Negative	Face (lips)	2,0 cm	No

Subtitle: M = Masculine, F = Feminine. Source: Authors (2021).

Figure 1. Microscopy of an ulcerated and nodular lesion in one of the patients of the study. (A) Extensive area of pseudoepiteliomatous hyperplasia (H&E, 40X), with (B) a focus of necrosis (H&E, 100X) and (C) microabscesses full of neutrophils (H&E, 400X).



Source: Authors (2021).

4. Conclusion

Therefore, it is evident that sporotrichosis, when accompanied by PEH, can be especially difficult to distinguish from the SCC, both from a clinical and histological point of view. Thus, we attribute this curious differential diagnosis to the microscopic phenomenon of PEH. Besides, it is recommended to examine several histological sections, including the base of the lesion, obtaining detailed clinical information and highlighting (in cases of strong suspicion of sporotrichosis or when there is

suppurative and / or granulomatous inflammation) the importance of using special stains and cultures when feasible. As sporotrichosis is a neglected disease and even with areas considered hyperendemic, more studies are always needed in order to eradicate this zoonosis.

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