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Case Studies

Perineural Invasion in the Absence of Malignancy: Report of Two Cases and Review of the Literature

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Key Words
Reexcision perineural invasion · Perineural invasion · Skin · Epithelial neoplasms

Abstract
Perineural invasion is usually associated with invasion of the perineural space by malignant tumors. In this report, we describe 2 cases of perineural infiltration by benign-appearing epithelial cells in the skin. One case concerns a tumor-free reexcision specimen of a basal cell carcinoma and the other one an ulceration at the outer ear, consistent with acanthoma fissuratum, without a history of a previous excision. This finding was interpreted as a reactive process with dislocation of epithelium from the overlying epidermis into the perineural space.

Introduction

Perineural invasion (PI) is typically seen in association with malignant tumors but can occasionally be seen in benign lesions, for example in benign breast diseases [1, 2] or in chronic pancreatitis [3]. In addition, the presence of benign prostate glands in the perineural space has been observed several times [4–6]. In the skin, the presence of benign-appearing epithelium in the perineural space is mainly reported in reexcision specimens [7–10].

We observed PI by benign-appearing epithelium in 2 patients. One case concerns a tumor-free reexcision specimen of a previously removed basal cell carcinoma and the other one represents a tumor-free excision from the ear with an ulceration, consistent with acanthoma fissuratum. The second patient had no history of a previous excision.

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Case Reports

Case 1

A 73-year-old male patient had a biopsy of a basal cell carcinoma of the outer ear. Three months later, the basal cell carcinoma was incompletely excised. Two weeks later, another reexcision was made. The reexcision specimen showed an infiltration of the perineural space by bland-appearing squamous hyperplastic epithelium, which was immunohistochemically positive for AE1/3 and negative for S100 (fig. 1). Neither sweat glands nor hair follicles were found nearby, and no residual tumor was detected.

Case 2

A 90-year-old female patient had an excision of an ulcerated lesion of the outer ear. Clinically, a chondrodermatitis nodularis helicis or an ulcerated basal cell carcinoma were suspected. Histology revealed an ulceration with regenerative epithelial proliferations and a chronic inflammation, as can be seen in acanthoma fissuratum. In the upper dermis, a peripheral nerve was engulfed by benign-appearing epithelial cells, which were immunohistochemically positive for AE1/3 and negative for S100 (fig. 1). Neither sweat glands nor hair follicles were found nearby.

Discussion

Reexcision perineural invasion (RPI) was first reported by Stern and Haupt in 1990 [7], who described 2 cases of perineural invasion by epithelial cells in reexcision skin specimens removed because of melanocytic lesions in the original biopsy material. A spread from the primary tumor could easily be excluded in these cases, as the tumors in the original biopsy represented nonepithelial lesions. According to Stern and Haupt [7], criteria to diagnose RPI include the absence of PI beyond the previous biopsy site, benign appearance of the perineural epithelial cells, and the absence of residual malignant epithelial tumor in the environment of the involved perineurium. Wu et al. [8] reported a case in which atypical squamous epithelium was found in the perineural space of a reexcision specimen of a posttraumatic scar in the original specimen. As the patient had no history of carcinoma, and neoplastic cells were present neither in the original biopsy nor in the reexcision specimen, they interpreted the finding as RPI with reactive or reparative atypia. In 2003, Chen [9] reported the presence of bland-appearing squamous epithelium in association with nerve fibers in 5 cases. Two cases represented reexcision specimens (1 of a squamous cell carcinoma and 1 of a basal cell carcinoma), whereas the remaining 3 patients had no history of excision or trauma (2 were associated with early prurigo nodularis and 1 with folliculitis). He suggested the term ‘reactive neuroepithelial aggregates of the skin’. In 2006, Beer [10] reported RPI in reexcision specimens of 4 patients after removal of a melanoma. Sites most likely to be affected by RPI are the trunk, head and neck (table 1).

The pathogenesis of RPI is unclear. Stern and Haupt [7], who found sweat gland ducts next to the involved nerves, interpreted RPI as a reactive or reparative process of eccrine glands induced by surgical injury. Beer [10] suggests a mechanical implantation of eccrine glands into the perineural space during surgery. Wu et al. [8] propose that RPI results from displacement of the overlying epidermis or nearby hair follicles, and Cramer [11] suggests that RPI might represent squamous metaplasia of perineural epithelium. We interpret the finding primarily as a result of dislocation of epithelium from the overlying epidermis into the perineural space. Neither sweat glands nor hair follicles were found nearby in our cases.

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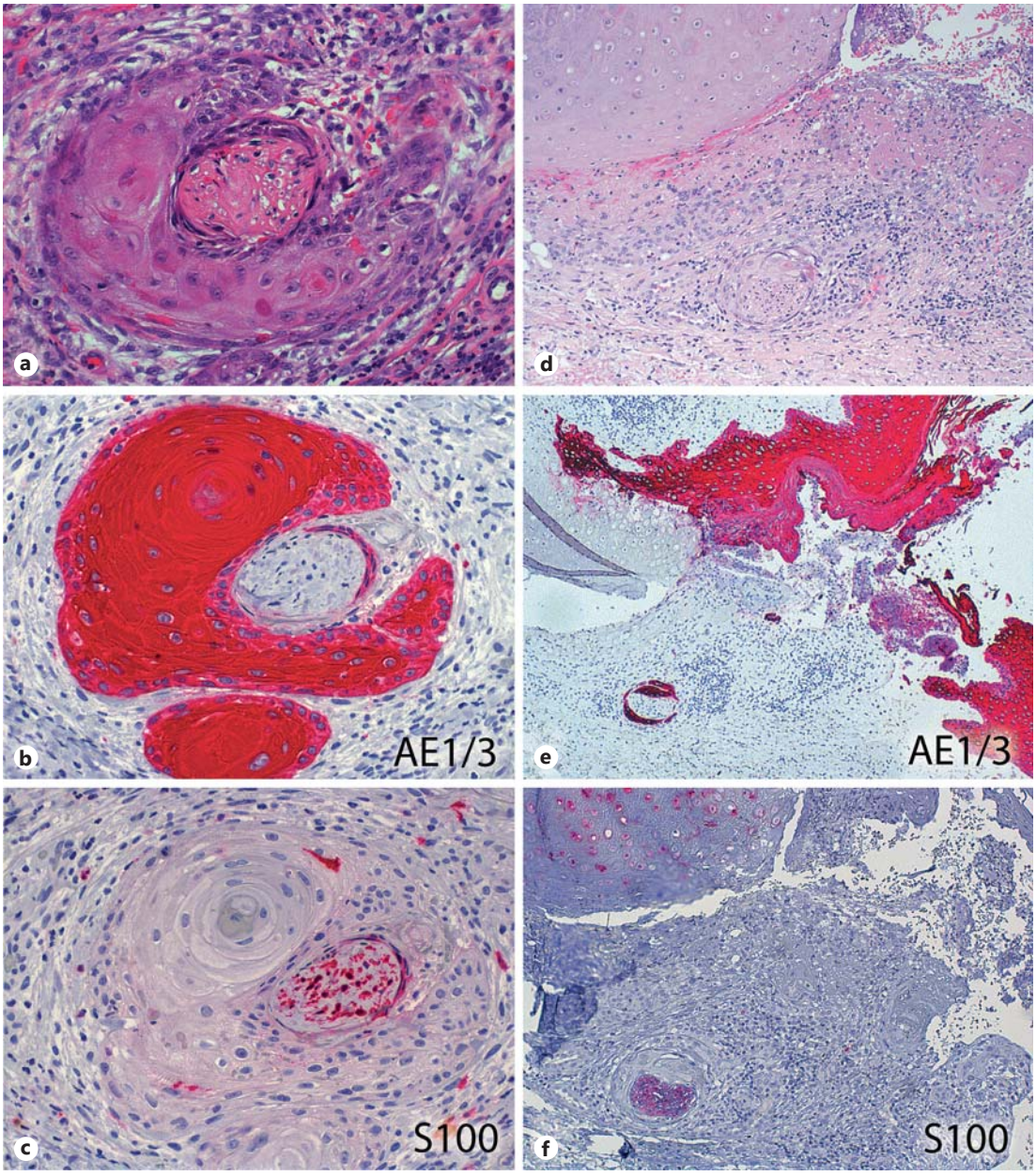

Fig. 1. a–c Reexcision specimen of a basal cell carcinoma showing an infiltration of the perineural space by bland-appearing squamous hyperplastic epithelium, which is immunohistochemically positive for AE1/3 and negative for S100. **d–f** Excision specimen from the outer ear of an ulceration with regenerative epithelial proliferations and chronic inflammation, consistent with acanthoma fissuratum. In the upper dermis, a peripheral nerve is engulfed by benign-appearing epithelial cells, which are immunohistochemically positive for AE1/3 and negative for S100.

PI is an infrequent finding in basal cell carcinomas with a reported incidence of 0.18% [12]. It occurs more frequently in aggressive types of basal cell carcinomas with an incidence of 3% [13]. PI in basal cell carcinomas is associated with larger, more aggressive tumors and a higher recurrence rate [14]. The differentiation between true PI by malignant cells and RPI in reexcision specimens of the skin may be difficult. Bechert and Stern [15] reviewed the

Table 1. Reports of perineural invasion by benign epithelial proliferations in the skin

	Age, years	Gender	Location	Clinicopathological context
Stern and Haupt [7]	26	male	lower back	reexcision of a spindle cell nevus
	81	female	cheek	reexcision of a lentigo maligna
Wu et al. [8]	53	male	forehead	reexcision of a posttraumatic scar
Chen [9]	66	male	neck	reexcision of a squamous cell carcinoma
	68	male	cheek	reexcision of a basal cell carcinoma
	66	male	cheek	folliculitis
	39	female	columella	early prurigo nodularis
	75	male	temple	early prurigo nodularis
Beer [10]	52	male	back	reexcision of a melanoma
	51	female	unknown	reexcision of a melanoma
	60	male	lower back	reexcision of an in situ melanoma
	52	male	abdomen	reexcision of an in situ melanoma
Present cases	73	male	ear	reexcision of a basal cell carcinoma
	90	female	ear	acanthoma fissuratum

literature for PI in basal cell carcinomas. They identified 310 cases of basal cell carcinomas with PI in large retrospective studies and found that in 196 (63%) of these cases, PI occurred in reexcision specimens [15]. Because of the high percentage of PI occurring in reexcision specimens versus primary excisions, they speculate that many cases of reported PI in basal cell carcinomas might actually represent RPI. One of our cases represents a reexcision specimen of a basal cell carcinoma. Therefore, the possibility of perineural invasion by residual tumor has to be taken into consideration. The squamous differentiation of the epithelium, the absence of atypia and the lack of residual tumor favor the diagnosis of a reactive RPI. Furthermore, PI could not be observed in the original biopsy. The second patient has no history of prior surgery, which supports Chen's [9] finding that RPI may occur unassociated with prior surgery.

In summary, RPI is an infrequent finding. However, it is important that pathologists are aware of this uncommon lesion to avoid misdiagnosis of malignancy.

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