PERINEURAL INVASION

Perineural invasion in tumors is typically indicative of malignancy. There are exceptions in most organ systems, but interpretation is complicated when the tumor in question also mimics malignancy. An example of this challenge is found in the interpretation of sclerosing epithelial tumors of the skin. The differential diagnosis for this category of tumors includes malignant entities such as infiltrative basal cell carcinoma (BCC), microcystic adnexal carcinoma (MAC), and benign adnexal lesions such as desmoplastic trichoepithelioma (DTE) and syringoma. Until recently, perineural involvement has been considered a feature indicative of malignancy. However, recent reports call this into question.

In a recent series, perineural invasion was identified in sclerosing epithelial tumors with features otherwise characteristic of benign desmoplastic trichoepithelioma. Criteria usually used to distinguish DTE from its neoplastic counterparts include the presence of a symmetric lesion limited to the midreticular dermis, intratumoral CK20 positive Merkel cells (indicating follicular germinative differentiation), positive staining for p75 and CD15, and occurrence on the face of young women. In contrast, infiltrative BCC is characterized by asymmetric deeply invasive tumor islands with increased mitotic activity and stromal epithelial clefts and cytologic atypia. MAC is distinguished by deep invasion, ductal structures, and poor circumscription. Both of the latter entities typically are negative for CK20 and CD15. Because perineural invasion is seen in up to 80% of MAC, and is associated with an increased recurrence rate and poor prognosis, this feature present a challenge when see in benign counterparts.

Perineural invasion can further complicate another challenging diagnosis in cutaneous pathology, cellular neurothekeoma (CN). CN is an unusual tumor of debated histogenesis and variable immunophenotype. The differential diagnosis includes melanocytic and epithelial lesions. Diagnosis is further complicated by the recent observation of perineural involvement in this benign lesion, and reports of atypical histology including increased mitotic rate and cytologic pleomorphism mimicking malignancy. Despite these findings, CN appears to behave in an indolent fashion.

In addition to true perineural invasion mimicking malignancy, there are conditions that mimic PNI and in turn mimic malignancy. One phenomenon recently has been termed “re-excision perineural invasion,” which is thought to
represent proliferation of benign adnexal epithelium around nerves at sites of previous surgery. Other mimics include epithelial sheath neuroma and reparative perineural proliferation. Overdiagnosis of these benign mimics can easily lead to potentially disfiguring overtreatment in cosmetically sensitive areas where this is typically seen, such as the face.

A few other benign skin conditions also occasionally feature perineural involvement. Probably most common is the granular cell tumor, where again the prominent presence of tumor involving nerves may raise concern for malignancy. In one study, up to 80% of otherwise typically granular cell tumors revealed perineural involvement by tumor cells, typically around the periphery of the tumor. Under-appreciation of this phenomenon has led to overaggressive surgery in some cases. The presence of granular cells around nerves may simply represent spread along the nerve sheath, from which these tumors presumably arise.

Skin is not the only organ system in which pathologists must remain aware of the potential for benign perineural involvement by tumors and normal structures. PNI has also been recorded in a spectrum of lesions including sclerosing adenosis of breast, pancreatitis, cholecystitis, endometriosis, and vasitis nodosa.

PSEUDOEPITHELIOMATOUS HYPERPLASIA

Since the times of Arthur Purdy Stout in the early 1900s, the phenomenon of squamous epithelial hyperplasia has been a known mimic of malignancy, as exemplified in cutaneous granular cell tumors. This well-known pitfall is now being seen in newly recognized conditions, and continues to challenge pathologists as a benign mimic of malignancy. There are multiple reports of PEH in tattoos, where the degree of epithelial hyperplasia can be striking, leading to the diagnosis of keratoacanthoma or squamous cell carcinoma. Reaction to red ink is the most common cause, and is now being seen in new clinical settings, such as permanent lipstick tattoos.

It has long been recognized that the degree of epithelial hyperplasia in discoid lupus and hypertrophic lichen planus can lead to a mistaken diagnosis of squamous cell carcinoma, often only revealed to be in error after close clinicopathologic correlation. This trap continues to confound pathologists; in some cases, the use of CD123 immunostaining may help guide the pathologist to the correct diagnosis.

It has also been recently recognized that PEH may mimic a squamous epithelial malignancy in the setting of an underlying malignancy, as in the case of PEH associated with CD30 lymphoproliferative disorders such as cutaneous anaplastic large cell lymphoma.

REACTIVE LYMPHOID INFILTRATES
Overinterpretation of CD30-positive lymphocytes in the skin also deserves mention as a common diagnostic trap. Conditions as banal as arthropod bites, herpes and molluscum infections can be associated with a proliferation of large atypical lymphocytes, and the presence of CD30 staining in this population has led to misdiagnosis of lymphoma on many occasions. Knowledge of the clinical situation, as well as careful study to determine whether the CD30 positive cells account for 70% of the large lymphocyte population (as opposed to 70% of all the lymphocytes) will help the pathologist avoid this particular trap. Another histologic pitfall featuring CD30 expression on lymphocytes, is that of tattoos, which have been reported to fool unsuspecting pathologists as lymphoma in certain cases.

Other common benign traps of lymphoma are caused by inflammatory dermatoses with intraepidermal lymphocytes, often mimicking mycosis fungoides-type cutaneous T cell lymphoma (MF). Reaction to medication is one such culprit, but other entities including lichen slerosus and even benign lichenoid keratosis can be misinterpreted at MF.

PSEUDO-MELANOCYTIC NESTS AND MELANOMA IN SITU

Lichenoid tissue reactions are responsible for another benign mimic of malignancy in skin, beyond the resemblance to MF. There is much attention in the recent dermatopathology literature to the phenomenon of “pseudonests” of melanocytes in benign inflammatory skin conditions. These are especially problematic for the pathologist when the clinical presentation is not available, and when certain special stains are used to identify melanocytes. Most notorious in this pitfall is the use of MelanA staining for junctional melanocytes. This marker can label keratinocytes as well as melanocytes, leading to overdiagnosis of melanocytic proliferations as melanoma in situ. Clinical correlation is often the key to accurate diagnosis, as many of these lichenoid inflammatory lesions represent rashes (lichen planus, lupus erythematosus), rather than solitary pigmented lesions. Even when presenting as a single lesion, benign lichenoid keratoses must be distinguished from regressing melanocytic lesions. To further confound the situation, some in situ melanomas show such profound lichenoid inflammation that they can also be misinterpreted as benign lichenoid keratosis. New immunostains helpful in this distinction include melanocyte nuclear markers MITF and Sox 10.

References:


