Problematic Cutaneous Neural Tumors

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As our recent attention in dermatopathology has shifted more to the superficial soft tissue neoplasms, the field of cutaneous neural neoplasms has also been considerably expanded. Much of the new information provided us with better characterization of existing tumors, but also with the diagnostic dilemma of dealing with a group of “newly” described entities. Many of these newly described lesions have no well-established clinical features, reproducible histologic features, or a predictable histologic behavior. While their recognition is important for diagnostic purposes, their significance remains questionable. The purpose of this presentation is to summarize some of the most important observations of selected entities of this field.

The developments in cutaneous neuropathology can be divided into three main categories:

1) Well-established entities with new information
2) Recently established entities with new developments
3) New observations on evolving entities.

Because of the time limitations, only the following selected examples will be discussed from each category.

1. Cellular Neurofibroma with Atypia

While the relationship between neurofibroma—neurofibromatosis—malignant peripheral nerve sheath tumor is well established, the relevance of cytologic atypia in solitary
neurofibromas has not been well defined. A relatively recent study by Lin BT et al(1) tried to address this issue and found there was a subset of neurofibromas in which the cytologic atypia or hypercellularity alone was not indicative of malignancy. These tumors were characterized by the usual growth pattern of neurofibromas, but composed of cells with mild to severe cytologic atypia, hyperchromasia, bizarre giant cells, low mitotic activity (1<10 HPF) and focal degenerative changes. Despite the concerning morphologic changes in the tumors, the patients did well on conservative treatment.

This study suggests that a separated designation for neurofibromas with these features is justifiable and cytologic atypia alone may not be a marker of malignancy in neurofibromas. Consequently, patients with these lesions can be treated conservatively.

2. Cellular Neurothekeoma

Although Rosati et al described this entity in 1986 and the clinicopathologic features have been well established, its histogenesis has remained controversial(2). It has been postulated that cellular neurothekeoma represent the less-differentiated end of the nerve sheath myxoma spectrum, based on the occasional co-existence of myxoid and “cellular” features within the same lesions(3,4). This has been further complicated by the observation of divergent mesenchymal differentitation within the tumor, such as smooth muscle, cartilaginous, osteoid and neuroendocrine(5-8). While earlier immunohistochemical and electron-microscopic studies appeared to support the light microscopic observation of divergent mesenchymal differentiation(9-10), numerous recent studies offered a wide range of speculations for its histogenesis (11-15).

Although the original assumption on biologic behavior of cellular neurothekeoma was benign, it was recently challenged by a study of Busam et al(16), who described a cytologically atypical, mitotically active variant of this lesion. A conservative excision is recommended for partially removed lesions, however Mohs surgery was also advocated (17-18).
3. **Cellular Schwannoma:**

Cellular Schwannoma is usually a tumor of deep soft tissues and the viscera; however, hypercellular variants of schwannomas rarely occur in the superficial dermis representing considerable diagnostic dilemma\(^{(19)}\). The diagnostic difficulty stem from the disagreement between experts regarding the acceptable mitotic rate and the tumor related degenerated features. Extrapolation of the diagnostic criteria of deeply located tumors to a superficially located tumor is questionable and resulted in confusing spectrum of terminology such as, cellular schwannoma, atypical schwannoma, and “borderline-transformed” schwannoma\(^{(20-26)}\).

In the superficial dermis these lesions are particularly difficult, because of the often-epithelioid cytology, nuclear atypia, mitotic figures and the associated lymphoid infiltrate imitating nodular amelanotic melanoma, which may or may not express melanosome-related antigens.

Unfortunately, so far, no comprehensive studies have been performed to address this issue satisfactorily. The pathologist is left to his best judgment to use clinicopathologic correlation to advise on the biologic behavior of the lesion\(^{(27)}\).

4. **Epithelial Sheath Neuroma and Dendritic Cell Neurofibromas with Pseudorosettes**

These cases represent very new observations on developing entities. **Epithelial sheath neuroma** is a bizarre combination of epithelial sheath surrounding nerve bundles. The histogenesis is controversial\(^{(28)}\). The epithelial cells appear to be benign and unlikely represent a perineurial tumor spread. Despite the distinct appearance, the changes most likely represent a reactive or metaplastic process rather than a true de-novo neoplasm.

**Dendritic cell neurofibroma** is a better-defined entity composed of multinodular proliferation of small-lymphocyte-like cells and large cells with vesicular nuclei and dendritic extension\(^{(29)}\). The smaller cells have a rosette-like arrangement around the larger cells in a
neurofibromatous background. The cells express S-100 protein, CD57, and epithelial membrane antigen. Because of the ganglion and rosette-like structures, the differential diagnosis can be extensive. While so far, there has not been a satisfiable explanation for this peculiar combination of changes, the morphologic findings appear to be quite consistently encountered\textsuperscript{(30)}.

As this summary illustrates, several new morphologic subtypes of cutaneous neural tumors have been recognized. It is important to emphasize that despite the striking morphologic features, the clinical characterization of these lesions is still evolving, and the biologic potential of these lesions has not been fully established yet. While reclassification of these lesions may be necessary in the future, familiarity with these new developments remains important for better patient management.
References


