Neurothekeoma Versus Melanoma

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Introduction

Although many current textbooks place neurothekeoma under the heading of nerve sheath tumors [1–5], others, such as the most recent WHO Classification of Tumours of Soft Tissue and Bone [6], omit neurothekeoma altogether. This phenomenon likely has roots in the contentious nosological history of neurothekeoma. Introduced into the literature in 1980, the tumor's name reflected its purported nerve sheath origin [7]. Early observers noted some histomorphologic resemblance to dermal nerve sheath myxoma (DNSM), most notably in neurothekeomas with a pronounced myxoid matrix [8]. Consequently, the two lesions were placed on a morphologic continuum, with DNSM often being regarded as a myxoid variant of neurothekeoma[1] (so-called "myxoid neurothekeoma") [9].

However, subsequent studies provided convincing morphologic, ultrastructural, and immunophenotypic evidence that DNSM and "myxoid neurothekeoma" are distinct entities, with demonstrable nerve sheath differentiation in DNSM but not in neurothekeoma [10–13]. Nevertheless, DNSM and "myxoid neurothekeoma" had become intertwined and entrenched in the literature and in textbooks. The term "cellular neurothekeoma"[2] is preferred by some authors [14–17] to emphasize the distinction from the confused and contaminated myxoid end of the spectrum. The ensuing text employs "neurothekeoma" to encompass all morphologic patterns thought to be true neurothekeomas, whether cellular or with myxoid matrix, based on the present understanding of this tumor. Regardless of the adjective placed before it, the appellation "neurothekeoma" has been acknowledged as inappropriate [9, 14] but will likely remain in place until the tumor origin or differentiation is elucidated.

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[1] Other terms that may have been lumped together with "myxoid neurothekeoma" include myxoid tumor of nerve sheath, perineurial myxoma, Pacinian neurofibroma, and bizarre cutaneous neurofibroma [8, 15].

[2] The term "cellular neurothekeoma" was introduced by Barnhill and Mihm [15] as a distinctive subtype of neurothekeoma, but currently, it is best understood as a morphologic pattern on a spectrum of cellular↔myxoid rather than as an actual subtype.

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Features of Neurothekeoma

Clinical Presentation

Neurothekeoma preferentially affects a young patient population, with greater than 85 % of patients being younger than 40 years (Fig. 12.1). Women are affected nearly twice as often as men. The most commonly involved body sites are the head and neck (especially the face) followed by the shoulder region and upper arms [9, 14]. No consistent association with other disease conditions has been established. The lesion is most often solitary, but multifocal cases have been reported [18, 19]. The tumor most often presents as a dome-shaped, pink-tan to red-brown papule or nodule (Fig. 12.2), usually measuring about 1 cm (range 0.3–6 cm). The vast majority are asymptomatic but, rarely, patients report pain or itching. Most are slow-growing, with some patients reporting a 10-year history at presentation. The clinical differential diagnosis usually consists of benign entities such as a cyst, dermatofibroma, or nevus; skin adnexal tumors or basal cell carcinoma may also be considered [9, 14].

Prognosis or Course

No reported case of neurothekeoma has metastasized, and there is only a small risk of recurrence or regrowth associated with incomplete excision (15 % at most) [9, 14]. Therefore, complete excision is the cornerstone of therapy. Location in the head and neck is also correlated with higher recurrence risk, likely reflecting more conservative excisions. There are no established histopathologic features that predict recurrence (see below) [9, 14].

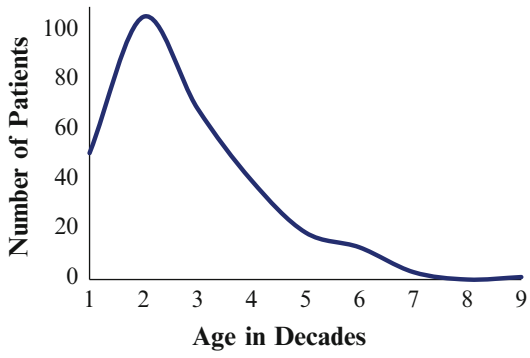

Fig. 12.1 Age distribution for 302 patients with neurothekeoma (compiled from [9, 14])

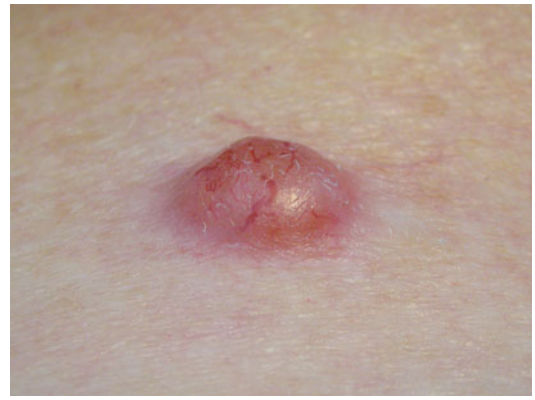

Fig. 12.2 Neurothekeoma, shown here as a well-defined, red-pink nodule. The unusually prominent, arborizing vasculature seen beneath the surface in this case led to a clinical impression of basal cell carcinoma. Original figure from Aydingoz IE, Mansur AT, Dikicioglu-Cetin E. Arborizing vessels under dermoscopy: a case of cellular neurothekeoma instead of basal cell carcinoma. Dermatol Online J. 2013;19(3):5. Retrieved from: http://escholarship.org/uc/item/1nx5r21x. ©2013 Dermatology Online Journal. Reproduced with permission

Etiology/Pathogenesis

Neurothekeoma is a tumor of uncertain origin and unclear differentiation. Based on light microscopy, immunohistochemistry, and ultrastructural examination, various lines of differentiation have been proposed, including (myo)fibroblastic (fibro)histiocytic, and neuroectodermal [9, 20–23]. Microarray data comparing DNSM with neurothekeoma revealed that not only do the two tumors demonstrate divergent expression profiles, but DNSM clustered with schwannoma, while neurothekeoma clustered with cellular fibrous histiocytoma [24]. However, this study utilized a limited number and range of cases, so further investigation is necessary.

Histopathology

Microscopic examination discloses a multinodular, variably circumscribed mass in the dermis and/or subcutis (Fig. 12.3a). The epidermis is not directly involved by tumor but may be atrophic, and a Grenz zone is often seen (Fig. 12.3b) [14, 15, 25]. The mass is composed of whorled nests and bundles of cells (Fig. 12.3c). The whorled, concentric arrangements of cells have been deemed *neuroid* characteristics and likened to *endoneurial-like structures* [15]. The constituent cells range from epithelioid to spindled, with abundant, faintly eosinophilic cytoplasm and indistinct cell borders (Fig. 12.3d). Fetsch et al. [9] noted a somewhat granular quality to the cytoplasm. Nuclei are usually ovoid with fine chromatin and indistinct nucleoli. Dense collagen bands often separate the cellular nests and bundles (Fig. 12.3e). For cases exhibiting florid stromal sclerosis, the term "*desmoplastic cellular neurothekeoma*" has been endorsed by some authors [18, 25, 26]. Myxoid matrix is variably present in neurothekeoma (Fig. 12.3f), accounting for much of its morphologic variability, which is delineated in Table 12.1. Osteoclast-like giant cells are present in 15–39 % of cases, and rarely, Touton giant cells are seen [9, 14]. Mitotic activity varies from none to 41 per 10 high-power fields, with an average of 2–3 per 10 high-power fields [9, 14].

Overall, most neurothekeomas have a banal appearance, but atypical features are well documented [9, 14, 21, 27]. A minority of cases (12–25 %) exhibit focal or scattered atypical cells with enlarged nuclei, coarse chromatin, and prominent nucleoli [9, 14], including tumor giant cells in 5 % of cases [14]. Other atypical features, such as tumor size >2 cm, high mitotic rate, atypical mitotic figures, and infiltration of fat or skeletal muscle, are seemingly insignificant with respect to biologic behavior [9, 14, 25, 27]. Vascular and perineural invasion have been described [21, 27, 28]. Necrosis is exceptional [14]. Other unusual features in neurothekeoma include collagen trapping, hemorrhage, lymphocytic cuffing, chondroid stroma, and cellular vacuolization. In rare cases exhibiting sheet-like growth, there is at least focal nesting of epithelioid and spindled cells characteristic of neurothekeoma [21]. Extensive calcification and even ossification have been reported [29, 30].

Immunophenotype

The immunophenotype of neurothekeoma is nonspecific but fairly consistent (Fig. 12.4) and thus can be supportive of the microscopic impression. S100 protein and GFAP are almost always negative [9, 10, 14], with few reports of focal S100 positivity [16], supporting the argument that it is distinct from DNSM and is not a nerve sheath tumor. Care must be taken to distinguish lesional from non-lesional cells, as S100-positive dendritic cells may be peppered throughout the tumor (Fig. 12.5) [9]. Other markers that are consistently negative in neurothekeoma include Melan-A, tyrosinase, neurofilament, CD34, desmin, and cytokeratins. gp100 (HMB-45) is usually negative, but rare cases demonstrate minimal expression [9].

Notwithstanding the consistent S100 negativity in lesional cells, the frequent expression of MITF, NK1/C3, PGP9.5, and NSE has led several authors to propose a neuroectodermal origin for neurothekeoma [19, 23, 27, 31, 32]. However, this suggestion has been heavily criticized on the basis of the restricted specificities and sensitivities of these markers. For example, MITF expression was observed in over 80 % of neurothekeomas in two large series [9, 14], but a smaller subsequent study reported focal or no expression in most of their cases [33]. MITF also suffers from questionable specificity, with expression reported in many reactive and neoplastic cells of non-neuroectodermal origin [34–36]. Similarly, NK1/C3 expression has been reported in a wide array of neoplasms of many lineages aside from melanocytic, including (fibro)histiocytic tumors [37]. PGP9.5 was originally reported as a marker for neurothekeoma based on a study of 12 cases [32], but its promiscuity was later exposed in a report of strong expression in the vast majority of

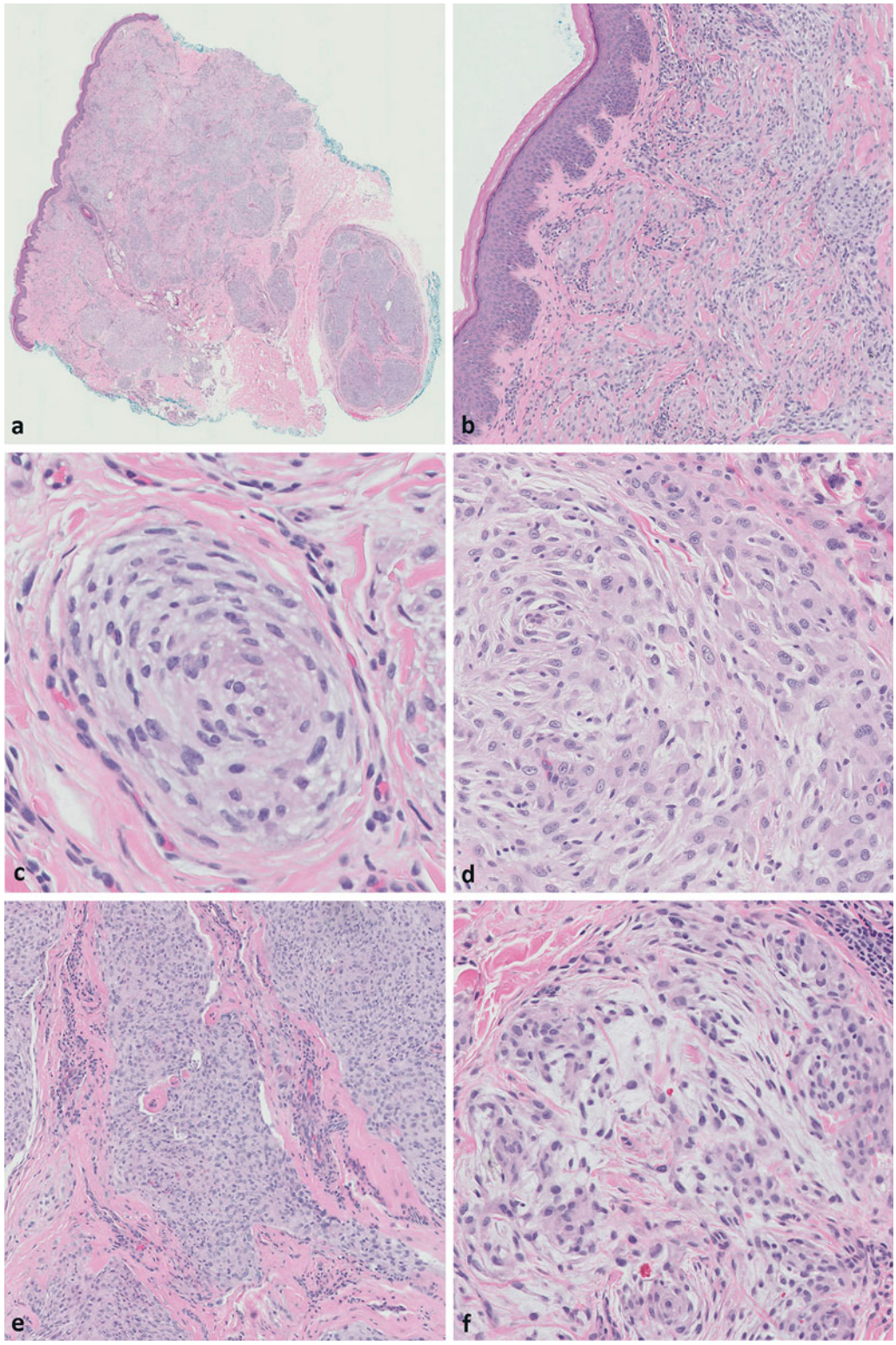

Fig. 12.3 Neurothekeoma. (**a**) Low-power view shows a multinodular, variably circumscribed mass in the dermis and subcutis (H&E, ×1). (**b**) The epidermis is spared (H&E, ×10). (**c**) A whorled nest of cells is depicted (H&E, ×40). (**d**) Cells range from epithelioid to spindled, with abundant, faintly eosinophilic cytoplasm (H&E, ×20). (**e**) Dense collagen bands may separate the nests of cells (H&E, ×10). (**f**) Myxoid matrix is apparent in this view (H&E, ×20)

Table 12.1 Morphologic spectrum of neurothekeoma [9, 14]

	Morphologic patterns[a]			
	Cellular	Mixed	Myxoid	Desmoplastic
Myxoid matrix	≤10 %	>10 % and ≤50 %	>50 %	Focal or absent
Architectural features	Multinodular configuration of whorled nests and bundles, sometimes fascicles Dense collagen among the nests and bundles		Larger nests Cell growth pattern is more random and less whorled/fascicular Dense collagen not as evident	Multinodular, haphazardly arranged fascicles Prominent sclerotic, fibrotic background
Cytologic features	Shape spindled to epithelioid (most have both) Cytoplasm abundant and faintly eosinophilic Cell borders indistinct			
Nuclear features[b]	Shape ovoid Chromatin usually fine Nucleoli usually inconspicuous or pinpoint			
Mitotic figures	Number variable (average 2–3 per 10 HPF, range 0–41 per 10 HPF) Atypical forms rarely seen (2 % of cases)			
Non-lesional cells	Osteoclast-like giant cells in 15–39 % of cases Occasional dendritic cells, mast cells 5 % of cases have Touton or tumor giant cells			
Melanocytic lesions in the differential diagnosis	Spitz nevus (amelanotic intradermal) Melanoma (metastatic or primary intradermal) Nevus (amelanotic intradermal)		Myxoid melanoma	Desmoplastic melanoma or nevi

[a]There is no established clinical significance to subdividing neurothekeomas; rather, the significance lies in illustrating patterns and their corresponding differential diagnoses
[b]Most cases demonstrate minimal nuclear atypia, with a minority (12–25 %) showing focal or scattered atypical cells with enlarged nuclei, coarse chromatin, and prominent nucleoli

non-neuroectodermal and neuroectodermal neoplasms [38]. Two studies endorse S100A6[3] as a more sensitive alternative to PGP9.5 but report a similar poor specificity [16, 31]. Finally, SOX-10, a marker of neuroectodermal differentiation, has been reported as negative in all of 25 neurothekeomas in one series [33]. Therefore, the notion of a neuroectodermal origin for neurothekeoma seems tenuous at best.

Genetic and Molecular Findings

As mentioned previously, microarray analysis revealed disparate expression profiles for neurothekeoma and DNSM, with the former resembling cellular fibrous histiocytoma and the latter resembling dermal schwannoma [24]. No recurring chromosomal abnormalities have been described for neurothekeoma.

Differential Diagnosis: Non-melanocytic Lesions

The most common alternative diagnoses rendered by pathologists for neurothekeoma cases include melanocytic lesions, neural tumors, fibrohistiocytic proliferations, and DNSM (Fig. 12.6) [9, 14], each of which can present as an amelanotic dermal proliferation of epithelioid or spindled cells [15]. The salient discriminatory features for neurothekeoma versus non-melanocytic lesions are reviewed in Table 12.2. Of special note is that neurothekeoma and plexiform fibrohistiocytic tumor are best distinguished on morphologic grounds, as no immunohistochemical marker can

[3] S100A6 must not be confused with S100 protein, with which it is in the same family [16].

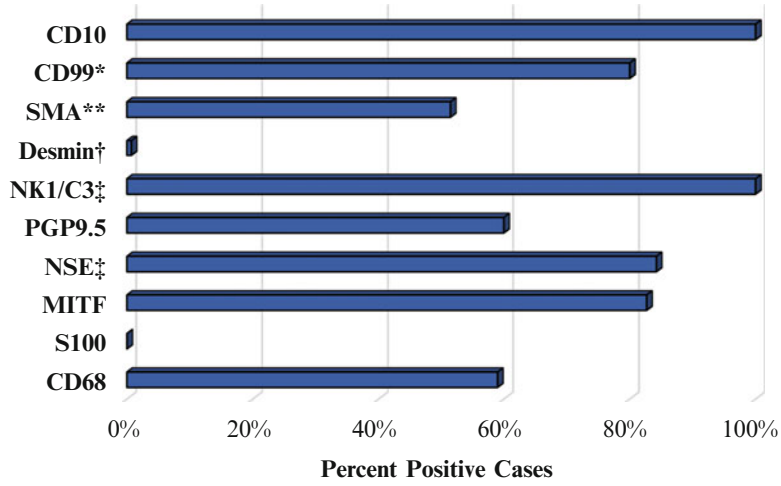

Fig. 12.4 Immunophenotype of neurothekeoma, compiled from the two largest series to date [9, 14]. *Based on only 10 cases. **Focally or diffusely positive. †A single case demonstrated focal desmin positivity. ‡Mostly diffuse positivity

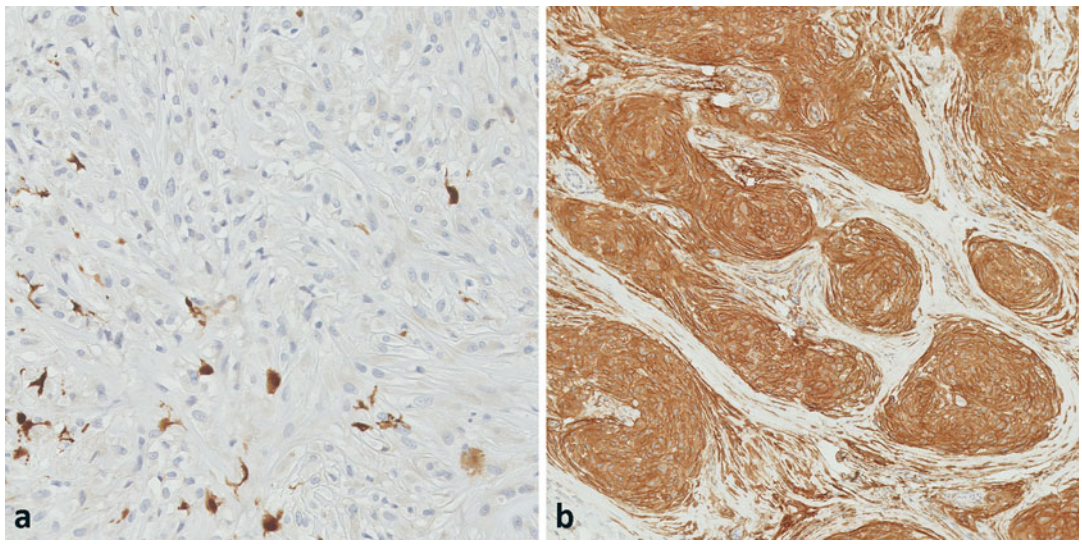

Fig. 12.5 (**a**) The lesional cells are negative for S100, but scattered S100-positive dendritic cells are noted (×20). (**b**) Strong CD10 expression, although not specific, is consistently seen (×10)

distinguish the two with certainty [14, 16, 39]. The distinction is important, as plexiform fibrohistiocytic tumor has some metastatic potential [6]. Other non-melanocytic lesions entering into the differential for neurothekeoma include reticulohistiocytoma and variants of fibrous histiocytoma [9]. Architectural features, such as a lack of whorled growth in reticulohistocytoma or the presence of storiform growth in fibrous histiocytoma, can lead to the correct diagnosis without a need for ancillary studies. Another diagnosis that may be considered is a pilar leiomyoma [40] in cases expressing smooth-muscle actin (SMA). Although neurothekeomas contain spindle cells with eosinophilic cytoplasm, they lack the characteristic cigar-shaped or corkscrew nuclei of

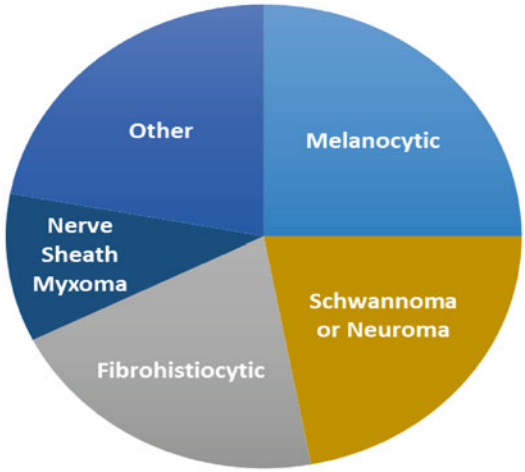

Fig. 12.6 Frequencies of alternative diagnoses for cases of neurothekeoma offered by contributing pathologists in the largest series to date [9]. A malignant diagnosis was considered in 21 % of cases. Diagnoses within the "Other" category include granulomatous processes, skin adnexal tumors, smooth-muscle tumors, granular cell tumors, and various sarcomas

smooth-muscle tumors. Desmin expression can exclude neurothekeoma. Likewise, S100 positivity can exclude neurothekeoma, which resolves the neuronal and Schwannian differentials.

Differential Diagnosis: Melanocytic Lesions

The broad morphologic spectrum of neurothekeoma notoriously overlaps with that of various melanocytic lesions. Although most neurothekeomas have a banal microscopic appearance, a wide range of mitotic activity and cytologic atypia can be seen, permitting consideration of benign and malignant melanocytic lesions alike. As reviewed in Table 12.1, each morphological pattern of neurothekeoma corresponds to its own group of melanocytic entities. Neurothekeomas with the more cellular patterns, owing to their nests or "theques" of spindled to epithelioid cells, overlap with intradermal nevi, Spitz tumors, and melanomas. The so-called *desmoplastic cellular* pattern of neurothekeoma can be confused with desmoplastic melanoma [18, 25, 26]. In cases of neurothekeoma with prominent myxoid matrix, myxoid melanoma may be considered [41–47]. The distinguishing clinicopathologic features of each are discussed below. In any case, the most invaluable distinguishing tool for neurothekeoma versus any melanocytic lesion (aside from careful microscopic scrutiny) is S100 immunohistochemistry. A lack of S100 expression is a hallmark of neurothekeoma, whereas nearly all melanocytic lesions express S100 [41]. Distinguishing neurothekeoma from any malignant melanocytic lesion is of paramount importance, as the clinical ramifications can be drastic.

Neurothekeoma vs. Intradermal Spitz Nevus

In the largest neurothekeoma series to date [9], Spitz nevus was the most commonly considered melanocytic entity in the differential. Neurothekeoma—namely, the cellular pattern—overlaps significantly with amelanotic, intradermal Spitz nevi, both clinically and morphologically. Both affect predominantly young patients (Fig. 12.7) with a female preponderance. The amelanotic Spitz nevus also exhibits a proclivity for the head and neck, where it typically presents as a dome-shaped, red-to-pink papule or nodule [48]. Intradermal Spitz accounts for up to 20 % of Spitz lesions [49]. Histologically, the epidermal changes associated with Spitz nevi tend to be hyperplastic [50–52], which is not a usual feature of neurothekeoma [9, 14, 15]. The overall multinodular shape of neurothekeoma contrasts with the classic wedge shape of Spitz nevi [50]. Although both lesions contain spindled to epithelioid cells in a collagenous stroma, only Spitz nevi show maturation. Additionally, the cellular whorling that is characteristic of neurothekeoma is not a feature of Spitz nevi [15]. Myxoid matrix, if present, steers toward the interpretation of neurothekeoma, as it is very rare in Spitz nevi [53, 54]. Although both lesions can have giant cells, those of neurothekeoma are described as osteoclastic, which are not described in Spitz nevi [49, 51, 52]. The lesions are compared in Table 12.3 and Fig. 12.8.

Table 12.2 The non-melanocytic differential diagnosis of neurothekeoma [6, 9, 10, 14]

	Neurothekeoma	Dermal nerve sheath myxoma (DNSM)	Plexiform fibrohistiocytic tumor	Superficial angiomyxoma (cutaneous myxoma)
Clinical features	Young women > men	Young to middle-aged adults	Children and young adults	Sporadic or associated with Carney's
	Head and neck, especially the face	Distal extremities	Upper extremities, especially the forearm	Trunk, legs, head and neck (eyelids in Carney's)
	Benign; low recurrence rate (<15 %) when incompletely excised	Benign; high local recurrence rate (up to 50 %) when incompletely excised	Metastatic potential; 13–38 % local recurrence rate	Benign, but local recurrence is common (up to 40 %)
Cellular architecture	Poorly marginated, multinodular mass of whorled nests and bundles, sometimes fascicles	Multilobulated mass of sharply demarcated lobules with highly myxoid matrix Prominent peripheral fibrous border	Multinodular mass composed of nodules of histiocyte-like cells and fascicles of spindle cells in varying proportions (fascicles usually longer and better defined compared to neurothekeoma)	Multinodular, myxoid, paucicellular mass with variable dermarcation Cleft-like spaces at the interface of the nodule and surrounding tissue
	Variable myxoid matrix (architecture is more random with more myxoid matrix) Dense collagen among the nests and bundles		Myxoid stromal change can be seen but is not prominent	Wispy collagen fibers throughout the stroma Delicate vasculature
Cellular morphology	Shape is spindled to epithelioid	Shape is spindled, stellate, ring-shaped (resembling adipocytes), or epithelioid (often forming cords and syncytial aggregates)	The spindled cells are (myo) fibroblastic in appearance	Shape is spindled or stellate
	Cytoplasm is abundant and faintly eosinophilic		The histiocyte-like cells may appear epithelioid	Mononuclear or multinucleated
			Less nuclear variability than that seen in neurothekeoma	Nuclear chromatin often "smudgy"
	Cell borders are indistinct			Cytoplasmic-nuclear invaginations common
Osteoclast-like giant cells	Frequent	None	Frequent	None
Immunohistochemical differences	:S100 –, GFAP –, CD34 –	S100 +, GFAP +	No clear distinguishing markers	S100 –, CD34 –

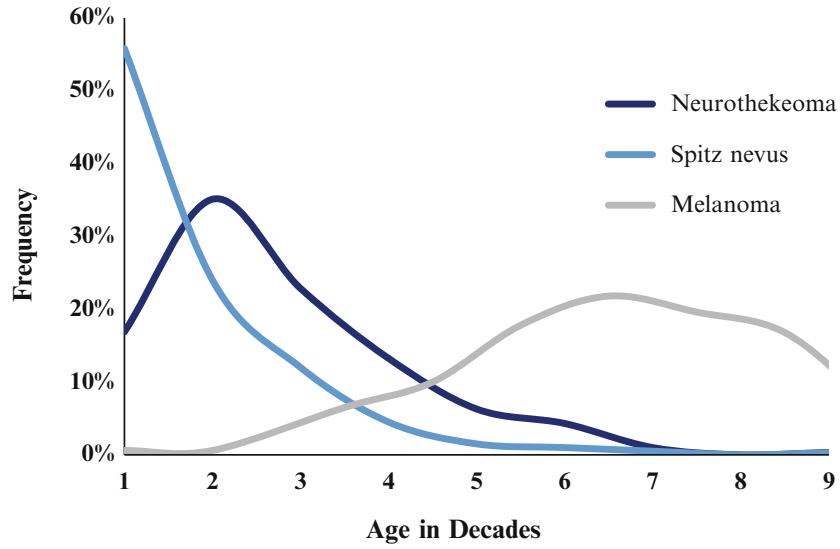

Fig. 12.7 Frequency distribution of age for neurothekeoma [9, 14] versus Spitz nevus [65] and melanoma [66]. Note: melanoma curve approximately reflects the following percentages for age groups: <20 (0.6 %), 20–34 (6.5 %), 35–44 (10 %), 45–54 (17.8 %), 55–64 (21.8 %), 65–74 (19.6 %), 75–84 (16.8 %), and >84 (7 %)

Table 12.3 Neurothekeoma versus intradermal Spitz nevus [9, 14, 15, 50–52]

	Neurothekeoma (cellular pattern)	Intradermal Spitz nevus
Epidermal changes	Effacement of rete pattern, usually with a Grenz zone ± Epidermal atrophy	Epidermis tends to show hyperplastic changes
Shape & location	Multinodular dermal or subcutaneous mass	Often symmetrical, wedge-shaped dermal mass
Architecture	Whorled nests and bundles Margins often infiltrative Dense collagen bands	Small nests, fascicles, and single cells ± Clefting/retraction around nests Collagenous stroma
Cytology	Cells are spindled to epithelioid Cytoplasm is palely eosinophilic, maybe granular No maturation	Cells are spindled to epithelioid Cytoplasm is eosinophilic, amphophilic, or even basophilic, sometimes glassy Maturation
Atypical features	Rarely, marked pleomorphism is present but focal Mitotic activity is variable and not worrisome if present	Limited mitotic activity and nuclear pleomorphism (worrisome if present)
Other features	± Osteoclastic giant cells ± Myxoid matrix ± Ectatic vessels, patchy perivascular lymphoid infiltrates	± Multinucleated cells (not osteoclastic) No myxoid matrix (with rare exceptions) ± Ectatic vessels, patchy perivascular lymphoid infiltrates
Immunohistochemistry	S100 –, Melan-A –	S100 +, Melan-A +

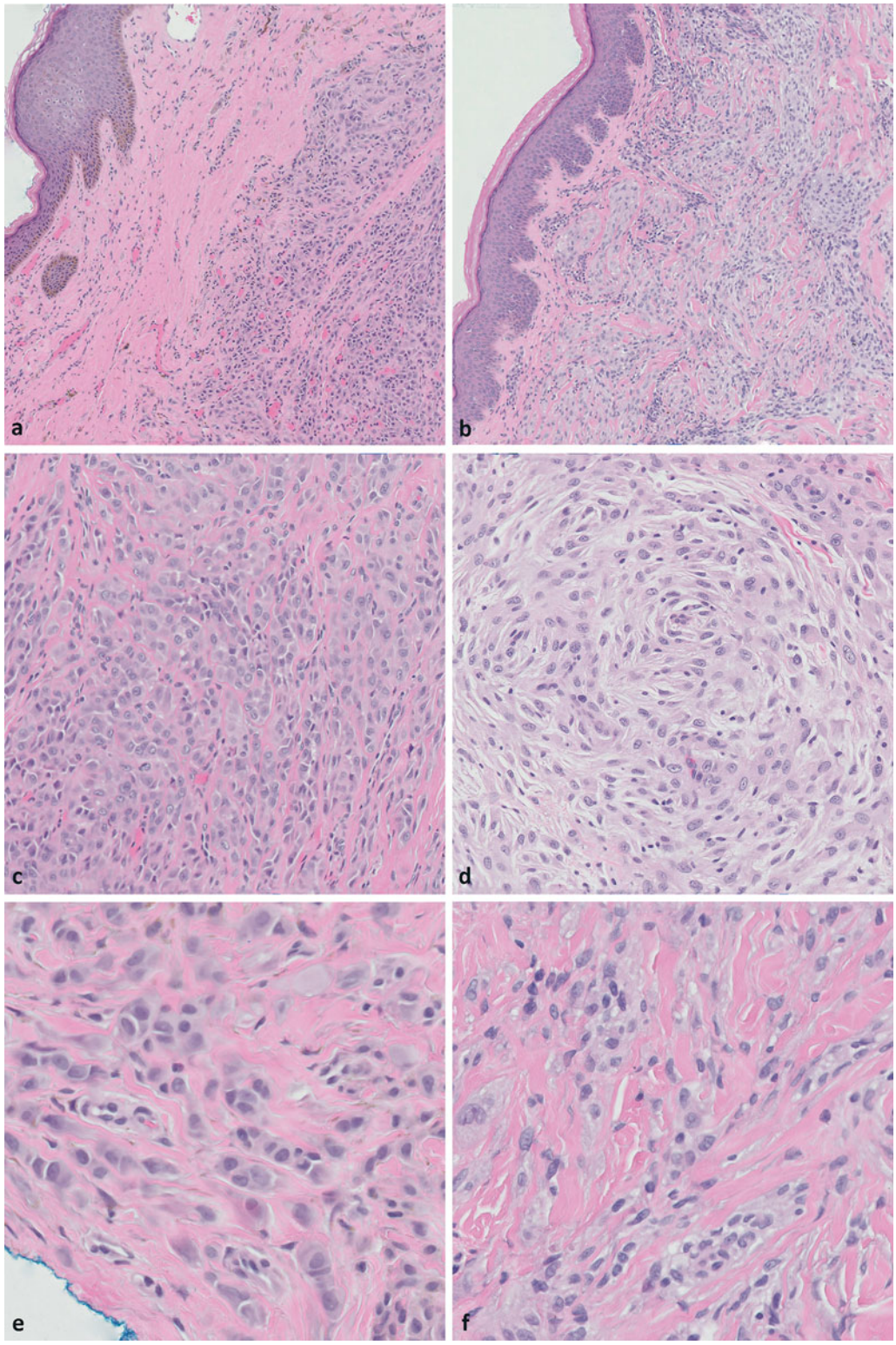

Fig. 12.8 Intradermal Spitz nevus versus neurothekeoma. The panel illustrates Spitz nevus on the left and neurothekeoma on the right. (**a**, **b**) Note that the epidermis is hyperplastic in the Spitz nevus but not in the neurothekeoma (H&E, ×10). (**c**, **d**) Both lesions exhibit spindled and epithelioid cells, but the nests in the Spitz nevus tend to be small and do not form whorls (H&E, ×20). (**e**, **f**) The Spitz nevus exhibits maturation at its base. The cells of neurothekeoma may also disperse and appear smaller at the periphery. However, the cytoplasm is glassy and the cell borders are better defined in the Spitz nevus compared to the neurothekeoma (H&E, ×40)

A very rare variant of Spitz nevus that can masquerade as neurothekeoma is the so-called *plexiform Spitz nevus* [53]. Two cases have been described as symmetrical, plexiform arrangements of fascicles and whorled bundles, circumscribed by a rim of fibrous tissue. Both cases had myxoid stroma and scattered multinucleated giant cells. The cells were eosinophilic, without evidence of maturation or melanin pigment. The lesions were strongly positive for S100 protein, which allowed for definitive separation from neurothekeoma.

Neurothekeoma vs. Intradermal Melanoma

Neurothekeoma can masquerade as metastatic melanoma, and vice versa. The usual patient with metastatic melanoma is older (Fig. 12.7) and has a history of melanoma, but clinical history is not always clear in practice. Moreover, the clinical appearance of both lesions can overlap, with metastatic melanoma often presenting as a variably pigmented nodule. Microscopic examination discloses a nodular proliferation in the dermis or subcutis. Metastatic melanoma does not display the whorled nests of cells typical for neurothekeoma. In addition, dense collagen coursing among cellular nests is not a feature of metastatic melanoma [55]. While the cells of neurothekeoma range from spindled to epithelioid, the cells of metastatic melanoma are often monomorphic and atypical [55]. Most neurothekeomas have a bland appearance; if marked pleomorphism is present, it is focal. Necrosis is exceptional in neurothekeoma but not uncommon in the center of a metastatic melanoma nodule [55]. Osteoclastic giant cells and myxoid matrix favor neurothekeoma, although both have been reported in melanoma [41]. Table 12.4 and Fig. 12.9 compare neurothekeoma to metastatic melanoma.

Table 12.4 Neurothekeoma versus metastatic melanoma [9, 14, 41, 55]

	Neurothekeoma	Metastatic melanoma
Epidermis	Not involved by tumor	Usually no epidermal component ± Epidermal collarette in superficial nodules
Shape & location	Multinodular dermal or subcutaneous mass	Single or multiple dermal or subcutaneous nodules
Architecture	Whorled nests and bundles	Clusters and strands in early metastases; sheet-like growth in developed metastases
	Dense collagen bands	Little or no fibrosis
Cytology	Cells are spindled to epithelioid	Cells are spindled, epithelioid, or small nevoid
Atypical features	Atypia is minimal; marked atypia is focal Average mitotic count: 2–3 per 10 HPF, range 0–41 per 10 HPF	Cells are atypical and variably pleomorphic Mitotic activity usually > 6/mm^2 Intranuclear cytoplasmic pseudoinclusions are common
Other features	± Osteoclastic giant cells Necrosis is almost never seen ± Myxoid matrix ± Ectatic vessels, patchy perivascular lymphoid infiltrates	Frequent vascular invasion Necrosis is not uncommon Inflammation is sparse or absent ± Pigment Any variant of melanoma can have myxoid change
Immunohistochemistry	S100 –, Melan-A –, HMB-45 – (almost always)	S100 +, Melan-A + HMB-45 +

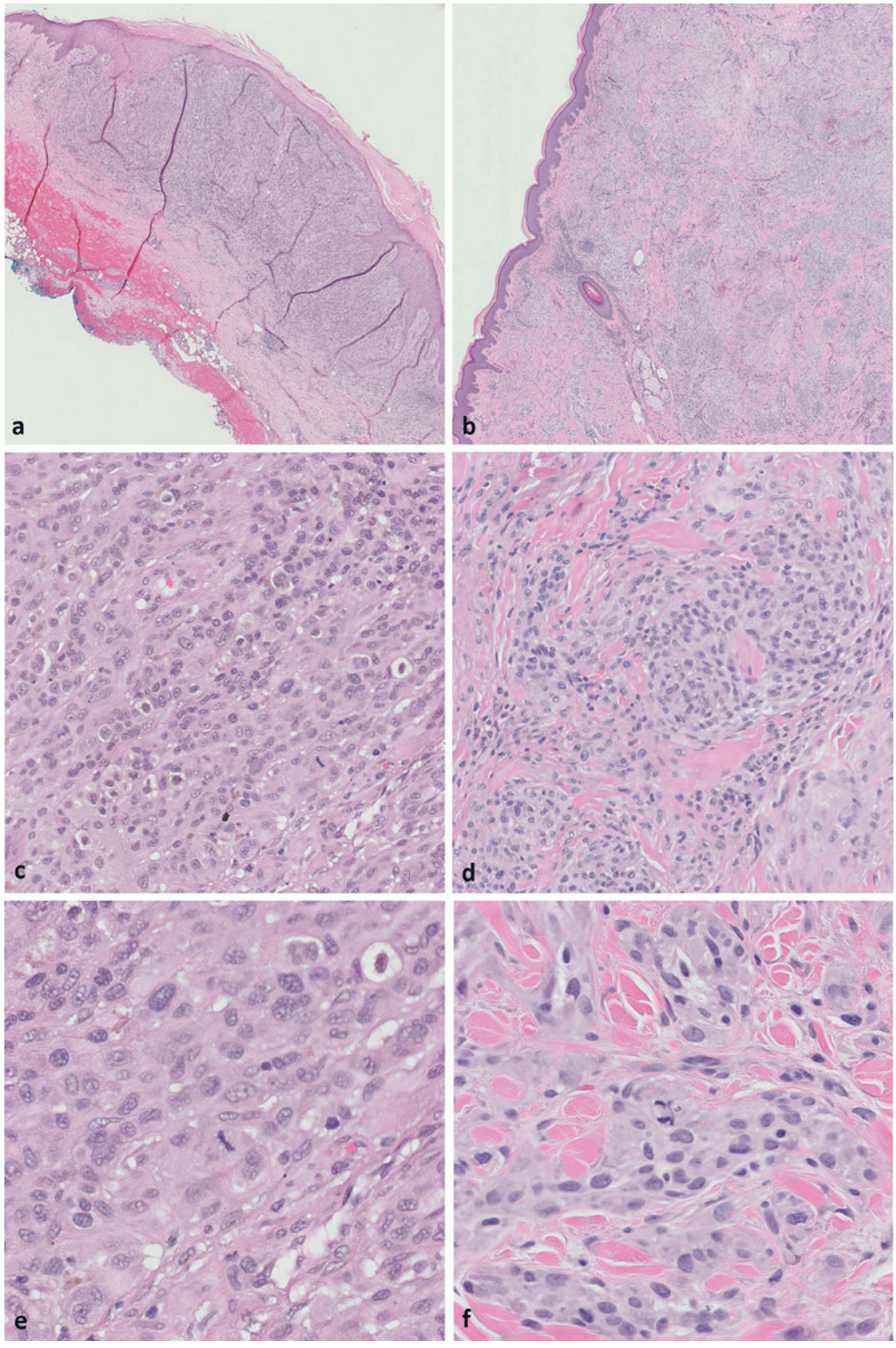

Fig. 12.9 Metastatic melanoma versus neurothekeoma. The panel illustrates melanoma on the left and neurothekeoma on the right. (**a**, **b**) Note that the epidermis forms a collarette around the metastatic melanoma, but no such collarette is present in neurothekeoma (H&E, ×2). (**c**, **d**) The growth pattern in the metastatic melanoma is more diffuse here, not nested or whorled (H&E, ×20). (**e**, **f**) The cells of metastatic melanoma are significantly more atypical than those of neurothekeoma. Both lesions demonstrate mitotic figures in the centers of the images (H&E, ×40)

An entity deemed *primary dermal melanoma* has been proposed as a distinct variant of melanoma that simulates a metastasis but lacks evidence of a primary lesion and has a better prognosis than metastatic melanoma [56]. Clinically, these cases commonly involve the head and neck as well as extremities, where they present as a subcutaneous nodule. Microscopically, they are deep dermal or subcutaneous proliferations of epithelioid or spindled cells (sometimes rhabdoid) with malignant cytologic features and frequent mitotic figures. Some cases demonstrate necrosis and hemorrhage. These tumors express melanocytic markers.

Neurothekeoma vs. Desmoplastic Melanoma

Neurothekeomas with floridly sclerotic stroma, referred to by some as *desmoplastic cellular neurothekeoma*, may evoke a differential that includes desmoplastic melanoma [18, 25, 26]. Like neurothekeoma, desmoplastic melanoma most commonly involves the head and neck, but the typical patient is much older (average 71) [57]. Some desmoplastic melanomas present as a small papule or nodule, and most lack pigmentation [41], which overlaps with neurothekeoma. Both lesions are characterized by a haphazard arrangement of spindle cells, occasionally in bundles, set within a densely collagenous matrix. Neurotropism and Meissner-like corpuscles in desmoplastic melanoma [41] can resemble the *neuroid* features of neurothekeoma. The cytologic features of desmoplastic melanoma can be deceptively bland or clearly malignant. Mitotic activity is variable but usually low [57], like neurothekeoma. Osteoclastic giant cells are more likely in neurothekeoma. The presence of solar elastosis and a lymphoplasmacytic infiltrate within and around the lesion [57] may favor desmoplastic melanoma, although these findings are not specific. As with the other melanocytic tumors, S100 can distinguish the lesions, but with the caveat of very focal expression in some cases [58], warranting careful scrutiny at high power. Additionally, desmoplastic melanoma usually does not express HMB-45 or Melan-A [58, 59]. Notably, SMA can be positive in both[4] [58]. Table 12.5 compares desmoplastic neurothekeoma and melanoma.

Neurothekeoma vs. Myxoid Melanoma

Myxoid change in primary cutaneous and metastatic melanoma has been known to generate confusion with many tumor types [41–47], neurothekeoma among them. Clinically, these melanomas usually present on the limbs and are otherwise similar to primary and metastatic melanomas in general [42]. Microscopic inspection at scanning magnification often reveals a lobulated lesion with fibrovascular septa demarcating the lobules, which resembles the myxoid pattern of neurothekeoma. The myxoid component may be focal or diffuse [41, 43]. Certain features of myxoid melanoma overlap with DNSM more so than neurothekeoma (e.g., the arrangement of cells in cords or strands within mucin pools, scattered pseudolipoblast cells) [41]. Cells within mucin pools may appear smaller than those elsewhere in the lesion [43]. In the non-myxoid regions, cell shape ranges from stellate to spindled to epithelioid. There may be cellular condensations around vessels or around the septa [41, 43]. Mitotic rate is variable [41, 43]. Some cases show confluent necrosis [43, 44], a feature that favors melanoma. Another feature favoring melanoma is any in-situ component. Osteoclastic giant cells favor neurothekeoma. Although melanin pigment is often sparse in myxoid melanomas [41], the tumor's identity is ultimately revealed by S100 immunohistochemistry [41, 42, 47]. Notably, HMB-45 can be focal or negative, especially within myxoid zones [42, 60]. Overall, myxoid melanoma is only rarely encountered, but it carries great potential for diagnostic blunder.

[4] SMA-positive cells in desmoplastic melanoma are likely non-lesional cells (reactive stromal myofibroblasts) [58].

Table 12.5 Desmoplastic cellular neurothekeoma versus desmoplastic melanoma [41, 57, 58, 60]

	Desmoplastic cellular neurothekeoma	Desmoplastic melanoma
Epidermis	No epidermal component Underlying Grenz zone	Overlying epidermis is atrophic or acanthotic ± Atypical intraepidermal melanocytes
Architecture	Multinodular, haphazardly arranged fascicles Prominent sclerotic, fibrotic background	Haphazard and scattered cells but sometimes bundled or storiform Can have markedly elongated fascicles of cells Variable cellularity Mild to marked stromal fibrosis
Cytology	Cells are spindled to epithelioid with pale, eosinophilic cytoplasm	Cells are spindled and may resemble fibroblasts
Atypical features	Usually bland; focal, marked pleomorphism and high mitotic activity in a minority of cases	Variable pleomorphism and mitotic activity Usually some elongated, hyperchromatic nuclei
Other features	± Osteoclastic giant cells ± Myxoid matrix ± Ectatic vessels, patchy perivascular lymphoid infiltrates	± Lymphoplasmacytic infiltrates at tumor front, ± solar elastosis Myxoid matrix is rarely seen
Immunohistochemistry	S100 –, HMB-45 – (almost always)	S100 + (sometimes focal) HMB-45 – (rare, focal expression) Melan-A – (usually)
Pitfalls	Both tumors can have neuroid features SMA expression can be seen in both tumors S100 expression can be focal in desmoplastic melanoma	

Neurothekeoma vs. Intradermal Nevus

Neurothekeoma can exhibit overlapping clinical and histopathologic features with a variety of benign intradermal nevi. For instance, hypopigmented cellular blue nevus occurs in a young population and can involve any body site [61]. Microscopic examination demonstrates a multinodular dermal tumor composed of bundles of spindle cells. Myxoid change can even be seen [62]. Ultimately, its usual dumbbell shape, dendritic or epithelioid melanocytes, and S100 expression reveal its true identity [61]. Deep penetrating nevus may be considered for reasons similar to cellular blue nevus, but pigmentation is a constant feature of this lesion [63]. Desmoplastic (sclerotic) nevus [64] can overlap with the desmoplastic pattern of neurothekeoma. If ever there is uncertainty, S100 expression readily unearths the melanocytic lesions.

Key Points

- Neurothekeoma is a misnamed tumor of uncertain origin and differentiation that has been previously confused with DNSM (a tumor with nerve sheath differentiation).
- It is a benign neoplasm with a proclivity for the head and neck of young women.
- Its histomorphologic plasticity—i.e., its cellular, myxoid, mixed, and desmoplastic patterns—results in overlap with various benign and malignant melanocytic neoplasms.
- Even in the face of marked cellular atypia, there is no evidence of any malignant potential.
- Neurothekeoma lacks a specific immunoprofile:
  - The literature does not suggest a particular panel for supporting the diagnosis, so the choice is ad hoc.
  - Its lack of S100 expression distinguishes it from numerous entities in the differential.

- Consider neurothekeoma when confronted with any unusual dermal tumor that recapitulates, to a variable degree, features of melanocytic, (fibro)histiocytic, and/or neural proliferations, but that does not express S100.

References

1. Weedon D. Weedon's Skin Pathology. 3rd ed. London: Churchill Livingstone Elsevier; 2010.
2. Gnepp D, editor. Diagnostic Surgical Pathology of the Head and Neck, 2nd ed. Philadelphia: Saunders Co. (Elsevier); 2009.
3. Fisher C, Montgomery E, Thway K. In: Epstein J, editor. Biopsy Interpretation of Soft Tissue Tumors. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2011.
4. Busam K. Dermatopathology. Volume in the series: Foundations in Diagnostic Pathology. Elsevier Health Sciences; 2010 [cited 2014 Feb 15]. Available from: Expert Consult
5. Weiss SW, Goldblum JR. Benign tumors of peripheral nerves. Enzinger and Weiss's Soft Tissue Tumors. 5th ed. St. Louis: Mosby; 2007.
6. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone. Lyon: IARC Press; 2013.
7. Gallager RL, Helwig EB. Neurothekeoma—a benign cutaneous tumor of neural origin. Am J Clin Pathol. 1980;74(6):759–64.
8. Pulitzer DR, Reed RJ. Nerve-sheath myxoma (perineurial myxoma). Am J Dermatopathol. 1985;7(5): 409–21.
9. Fetsch JF, Laskin WB, Hallman JR, Lupton GP, Miettinen M. Neurothekeoma: an analysis of 178 tumors with detailed immunohistochemical data and long-term patient follow-up information. Am J Surg Pathol. 2007;31(7):1103–14.
10. Fetsch JF, Laskin WB, Miettinen M. Nerve sheath myxoma: a clinicopathologic and immunohistochemical analysis of 57 morphologically distinctive, S-100 protein- and GFAP-positive, myxoid peripheral nerve sheath tumors with a predilection for the extremities and a high local recurrence rate. Am J Surg Pathol. 2005;29(12):1615–24.
11. Zelger BG, Zelger B. Cellular "neurothekeoma": an epithelioid variant of dermatofibroma? Verh Dtsch Ges Pathol. 1998;82:239–45.
12. Laskin WB, Fetsch JF, Miettinen M. The "neurothekeoma": immunohistochemical analysis distinguishes the true nerve sheath myxoma from its mimics. Hum Pathol. 2000;31(10):1230–41.
13. Argenyi ZB, LeBoit PE, Santa Cruz D, Swanson PE, Kutzner H. Nerve sheath myxoma (neurothekeoma) of the skin: light microscopic and immunohistochemical reappraisal of the cellular variant. J Cutan Pathol. 1993;20(4):294–303.
14. Hornick JL, Fletcher CD. Cellular neurothekeoma: detailed characterization in a series of 133 cases. Am J Surg Pathol. 2007;31(3):329–40.
15. Barnhill RL, Mihm MC. Cellular neurothekeoma. A distinctive variant of neurothekeoma mimicking nevomelanocytic tumors. Am J Surg Pathol. 1990; 14(2):113–20.
16. Plaza JA, Torres-Cabala C, Evans H, Diwan AH, Prieto VG. Immunohistochemical expression of S100A6 in cellular neurothekeoma: clinicopathologic and immunohistochemical analysis of 31 cases. Am J Dermatopathol. 2009;31(5):419–22.
17. de Giorgi V, Alfaioli B, Franchi A, Gori A, Sestini S, Papi F, et al. Cellular neurothekeoma in a girl: could oestrogens favour the development and growth of this rare tumour? J Eur Acad Dermatol Venereol. 2008;22(9):1149–50.
18. García-Gutiérrez M, Toussaint-Caire S, González-Sánchez P, Ortiz-Hidalgo C. Multiple desmoplastic cellular neurothekeomas localized to the face of a 16-year-old boy. Am J Dermatopathol. 2010;32(8): 841–5.
19. Mahalingam M, Alter JN, Bhawan J. Multiple cellular neurothekeomas—a case report and review on the role of immunohistochemistry as a histologic adjunct. J Cutan Pathol. 2006;33(1):51–6.
20. Misago N, Satoh T, Narisawa Y. Cellular neurothekeoma with histiocytic differentiation. J Cutan Pathol. 2004;31(8):568–72.
21. Stratton J, Billings SD. Cellular neurothekeoma: analysis of 37 cases emphasizing atypical histologic features. Mod Pathol. 2014;27(5):701–10.
22. Chang SE, Lee TJ, Ro JY, Choi JH, Sung KJ, Moon KC, et al. Cellular neurothekeoma with possible neuroendocrine differentiation. J Dermatol. 1999;26(6): 363–7.
23. Page RN, King R, Mihm MC, Googe PB. Microphthalmia transcription factor and NKI/C3 expression in cellular neurothekeoma. Mod Pathol. 2004;17(2):230–4.
24. Sheth S, Li X, Binder S, Dry SM. Differential gene expression profiles of neurothekeomas and nerve sheath myxomas by microarray analysis. Mod Pathol. 2011;24(3):343–54.
25. Zedek DC, White WL, McCalmont TH. Desmoplastic cellular neurothekeoma: clinicopathological analysis of twelve cases. J Cutan Pathol. 2009;36(11):1185–90.
26. D'Antonio A, Cuomo R, Angrisani B, Memoli D, Angrisani P. Desmoplastic cellular neurothekeoma mimicking a desmoplastic melanocytic tumor. J Am Acad Dermatol. 2011;65(2):e57–8.
27. Busam KJ, Mentzel T, Colpaert C, Barnhill RL, Fletcher CD. Atypical or worrisome features in cellular neurothekeoma: a study of 10 cases. Am J Surg Pathol. 1998;22(9):1067–72.
28. Cardoso J, Calonje E. Cellular neurothekeoma with perineural extension: a potential diagnostic pitfall. J Cutan Pathol. 2012;39(6):662–4.
29. Goette DK. Calcifying neurothekeoma. J Dermatol Surg Oncol. 1986;12(9):958–60.

30. Rooney MT, Nascimento AG, Tung RL. Ossifying plexiform tumor. Report of a cutaneous ossifying lesion with histologic features of neurothekeoma. Am J Dermatopathol. 1994;16(2):189–92.
31. Fullen DR, Lowe L, Su LD. Antibody to S100a6 protein is a sensitive immunohistochemical marker for neurothekeoma. J Cutan Pathol. 2003;30(2):118–22.
32. Wang AR, May D, Bourne P, Scott G. PGP9.5: a marker for cellular neurothekeoma. Am J Surg Pathol. 1999;23(11):1401–7.
33. Fried I, Sitthinamsuwan P, Muangsomboon S, Kaddu S, Cerroni L, McCalmont TH. SOX-10 and MiTF expression in cellular and 'mixed' neurothekeoma. J Cutan Pathol. 2014.
34. Busam KJ, Iversen K, Coplan KC, Jungbluth AA. Analysis of microphthalmia transcription factor expression in normal tissues and tumors, and comparison of its expression with S-100 protein, gp100, and tyrosinase in desmoplastic malignant melanoma. Am J Surg Pathol. 2001;25(2):197–204.
35. Granter SR, Weilbaecher KN, Quigley C, Fletcher CD, Fisher DE. Microphthalmia transcription factor: not a sensitive or specific marker for the diagnosis of desmoplastic melanoma and spindle cell (non-desmoplastic) melanoma. Am J Dermatopathol. 2001; 23(3):185–9.
36. Folpe AL, Cooper K. Best practices in diagnostic immunohistochemistry: pleomorphic cutaneous spindle cell tumors. Arch Pathol Lab Med. 2007;131(10): 1517–24.
37. Sachdev R, Sundram UN. Frequent positive staining with NKI/C3 in normal and neoplastic tissues limits its usefulness in the diagnosis of cellular neurothekeoma. Am J Clin Pathol. 2006;126(4):554–63.
38. Campbell LK, Thomas JR, Lamps LW, Smoller BR, Folpe AL. Protein gene product 9.5 (PGP 9.5) is not a specific marker of neural and nerve sheath tumors: an immunohistochemical study of 95 mesenchymal neoplasms. Mod Pathol. 2003;16(10):963–9.
39. Wartchow EP, Goin L, Schreiber J, Mierau GW, Terella A, Allen GC. Plexiform fibrohistiocytic tumor: ultrastructural studies may aid in discrimination from cellular neurothekeoma. Ultrastruct Pathol. 2009;33(6):286–92.
40. Calonje E, Wilson-Jones E, Smith NP, Fletcher CD. Cellular 'neurothekeoma': an epithelioid variant of pilar leiomyoma? Morphological and immunohistochemical analysis of a series. Histopathology. 1992;20(5):397–404.
41. Banerjee SS, Harris M. Morphological and immunophenotypic variations in malignant melanoma. Histopathology. 2000;36(5):387–402.
42. Patel P, Levin K, Waltz K, Helm KF. Myxoid melanoma: immunohistochemical studies and a review of the literature. J Am Acad Dermatol. 2002;46(2): 264–70.
43. Hitchcock MG, McCalmont TH, White WL. Cutaneous melanoma with myxoid features: twelve cases with differential diagnosis. Am J Surg Pathol. 1999;23(12):1506–13.
44. Hitchcock MG, White WL. Malicious masquerade: myxoid melanoma. Semin Diagn Pathol. 1998;15(3): 195–202.
45. Ulamec M, Soldo-Belić A, Vucić M, Buljan M, Kruslin B, Tomas D. Melanoma with second myxoid stromal changes after personally applied prolonged phototherapy. Am J Dermatopathol. 2008;30(2): 185–7.
46. Zelger BG, Steiner H, Wambacher B, Zelger B. Malignant melanomas simulating various types of soft tissue tumors. Dermatol Surg. 1997;23(11): 1047–54.
47. Collina G, Losi L, Taccagni GL, Maiorana A. Myxoid metastases of melanoma: report of three cases and review of the literature. Am J Dermatopathol. 1997; 19(1):52–7.
48. Dal Pozzo V, Benelli C, Restano L, Gianotti R, Cesana BM. Clinical review of 247 case records of Spitz nevus (epithelioid cell and/or spindle cell nevus). Dermatology. 1997;194(1):20–5.
49. Weedon D. The Spitz Naevus. Clin Oncol. 1984; 3(3):493–507.
50. Piepkorn M. On the nature of histologic observations: the case of the Spitz nevus. J Am Acad Dermatol. 1995;32(2 Pt 1):248–54.
51. Mérot Y, Frenk E. Spitz nevus (large spindle cell and/or epithelioid cell nevus). Age-related involvement of the suprabasal epidermis. Virchows Arch A Pathol Anat Histopathol. 1989;415(2):97–101.
52. Binder SW, Asnong C, Paul E, Cochran AJ. The histology and differential diagnosis of Spitz nevus. Semin Diagn Pathol. 1993;10(1):36–46.
53. Spatz A, Peterse S, Fletcher CD, Barnhill RL. Plexiform spitz nevus: an intradermal spitz nevus with plexiform growth pattern. Am J Dermatopathol. 1999;21(6):542–6.
54. Hoang MP. Myxoid Spitz nevus. J Cutan Pathol. 2003;30(9):566–8.
55. Heenan P, Maize J, Cook M, LeBoit P. Persistent melanoma and local metastasis of melanoma. In: LeBoit P, Burg G, Weedon D, Sarasin A, editors. Pathology and genetics of skin tumours. IARC WHO Classification of Tumours. Lyon: IARC Press; 2005. p. 90–2.
56. Cassarino DS, Cabral ES, Kartha RV, Swetter SM. Primary dermal melanoma: distinct immunohistochemical findings and clinical outcome compared with nodular and metastatic melanoma. Arch Dermatol. 2008;144(1):49–56.
57. de Almeida LS, Requena L, Rütten A, Kutzner H, Garbe C, Pestana D, et al. Desmoplastic malignant melanoma: a clinicopathologic analysis of 113 cases. Am J Dermatopathol. 2008;30(3):207–15.
58. Longacre TA, Egbert BM, Rouse RV. Desmoplastic and spindle-cell malignant melanoma. An immunohistochemical study. Am J Surg Pathol. 1996; 20(12):1489–500.

59. Prieto VG, Shea CR. Immunohistochemistry of melanocytic proliferations. Arch Pathol Lab Med. 2011;135(7):853–9.
60. Prieto VG, Kanik A, Salob S, McNutt NS. Primary cutaneous myxoid melanoma: immunohistologic clues to a difficult diagnosis. J Am Acad Dermatol. 1994;30(2 Pt 2):335–9.
61. Calonje E, Blessing K, Glusac E, Strutton G. Blue naevi. In: LeBoit P, Burg G, Weedon D, Sarasin A, editors. Pathology and genetics of skin tumours. IARC WHO classification of tumours. Lyon: IARC Press; 2005. p. 95–9.
62. Rongioletti F, Innocenzi D. Sclerosing 'mucinous' blue naevus. Br J Dermatol. 2003;148(6):1250–2.
63. Luzar B, Calonje E. Deep penetrating nevus: a review. Arch Pathol Lab Med. 2011;135(3):321–6.
64. Harris GR, Shea CR, Horenstein MG, Reed JA, Burchette JL, Prieto VG. Desmoplastic (sclerotic) nevus: an underrecognized entity that resembles dermatofibroma and desmoplastic melanoma. Am J Surg Pathol. 1999;23(7):786–94.
65. Vollmer RT. Use of Bayes rule and MIB-1 proliferation index to discriminate Spitz nevus from malignant melanoma. Am J Clin Pathol. 2004;122(4):499–505.
66. National Cancer Institute. SEER stat fact sheets: melanoma of the skin [Internet] [cited 2014 Feb 12]. Available from: http://seer.cancer.gov/statfacts/html/melan.html.