

Neurothekeoma: An Analysis of 178 Tumors With Detailed Immunohistochemical Data and Long-term Patient Follow-up Information

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Abstract: This report describes the clinicopathologic findings in 176 patients who presented with 178 tumors currently referred to as neurothekeomas. Our study group included 64 males and 112 females, ranging from 20 months to 85 years old at the time of their first surgical procedure (median age: 17 y). Twenty-four percent of patients were ≤ 10 years of age and only 20% of patients were ≥ 30 years of age at initial diagnosis. The patients typically presented with a solitary, superficial, slow-growing, and relatively asymptomatic mass in the 0.3 to 2.0 cm size range. One patient had multiple tumors. More than 75% of the lesions involved the head (n = 63), upper extremities (n = 44), and shoulder girdle (n = 27) regions. The tumors were evident a few weeks to 4 years (median duration: ≈ 7 mo) before surgical resection was sought. Histologically, the lesions involved the dermis and/or subcutis, and they formed multinodular masses with varying amounts of myxoid matrix and peripheral fibrosis. On the basis of the amount of myxoid matrix, the tumors were subclassified as cellular (n = 63), mixed (n = 67), or myxoid (n = 48). All cases had spindled and epithelioid mononuclear neoplastic cells with relatively abundant cytoplasm and indistinct cell borders. The majority of cases also had occasional multinucleated tumor cells. The lesional cells had a strong tendency for whorled growth, and oftentimes, focal fascicular growth was also present. Nuclear atypia was minimal in 62 cases, mild in 73 cases, at least focally moderate in 41 cases, and focally marked in 2 cases. Mitotic activity ranged from 0 to 124 mitotic figures/25 wide-field high power fields (WHPFs) (median mitotic count: 4 mitotic figures/25WHPFs). Twenty-five lesions had > 10 mitotic figures/25WHPFs. A total of 16 cases (9%) had atypical mitotic figures. Osteoclastlike giant cells were detected in 39% of cases. Immunoreactivity was typically

present for vimentin, NK1/C3, CD10, microphthalmia transcription factor, and PGP9.5, and focal reactivity was sometimes noted for smooth muscle actin and CD68. All tumors tested were negative for S100 protein, glial fibrillary acidic protein, and Melan A. The overwhelming majority of cases had involvement of the tissue margins. A complete follow-up record is available for 71 patients (40.3%) with follow-up intervals ranging from 3 years 2 months to 34 years 9 months (median: 17 y 9 mo). Limited or incomplete follow-up information is also available for an additional 14 patients with follow-up intervals ranging from weeks to approximately 10 years (median: 5 mo). Regrowth of tumor after biopsy or local excision was reported in 13 patients, one of whom had 2 recurrences. However, because of the nature of our consultation practice and a tendency for clinicians to specifically send us cases with a complex clinical course, this is believed an overestimation of the true recurrence rate. Neurothekeomas are morphologically and immunohistochemically distinct from true nerve sheath myxomas. An origin from fibroblastic cells with the ability to differentiate into myofibroblasts and a tendency to recruit histiocytic cells is postulated.

Key Words: cutaneous myxoma, immunohistochemistry, nerve sheath myxoma, neurofibroma, peripheral nerve sheath tumor, plexiform fibrohistiocytic tumor, soft tissue tumor, superficial angiomyxoma

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Neurothekeoma is a term introduced by Gallagher and Helwig²¹ in 1980 to describe a superficial tumor of purported nerve sheath derivation. Traditionally, this tumor has been subclassified as cellular, mixed, or myxoid, depending on the amount of myxoid matrix. Nerve sheath myxoma has often been included in the morphologic spectrum of neurothekeoma.^{1,4-7,16,20,24,40} Specifically, it has frequently been regarded as a myxoid variant of neurothekeoma, even though Gallagher and Helwig and a number of other authors have disputed this assertion.^{21,25,37} Recently, we published a large series of nerve sheath myxomas and demonstrated, without doubt, that they are separate and distinct from neurothekeoma.¹⁹ The current series critically analyzes the morphologic, immunohistochemical, and behavioral characteristics

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of neurothekeoma. It includes previously unreported immunohistochemical findings and has long-term patient follow-up information.

MATERIALS AND METHODS

Archival material, accessioned to the Armed Forces Institute of Pathology (AFIP) between January 1970 and June 1999, was the sole source of cases for this study. Computer printouts were obtained for all tumors coded as a neurothekeoma or nerve sheath myxoma, regardless of anatomic site. All specimens with available histopathologic material were reviewed (n = 345). Within this group, we identified 178 tumors from 176 patients that fulfill strict criteria for a diagnosis of neurothekeoma. Tumors with insufficient histopathologic material to establish a diagnosis with full confidence or that would now be more appropriately classified as another tumor type (eg, nerve sheath myxoma, superficial angiomyxoma, plexiform

fibrohistiocytic tumor, etc) were excluded. Within the exclusion subgroup, there were 58 nerve sheath myxomas.

All hematoxylin and eosin-stained, ancillary histochemical, and immunohistochemical sections were examined. All immunohistochemical studies were performed on formalin-fixed tissue samples using the avidin-biotin complex immunoperoxidase technique with diaminobenzidine as the chromogen. The primary antibodies, dilutions, and pretreatments are listed in Table 1.

The tumors were subclassified as cellular neurothekeomas when they had $\leq 10\%$ myxoid matrix, mixed-type neurothekeomas when they had > 10 and ≤ 50 myxoid matrix, and myxoid neurothekeomas when they had $> 50\%$ myxoid matrix.

Mitotic activity was assessed by reporting the number of mitotic figures identified in 25 wide-field high power ($40\times$) fields (WHPFs) (Olympus BX40 microscope with WH10X-H/22 eyepieces and a UPlan Apo $40\times/0.85$ objective; field area: 0.237 mm^2). To obtain an

TABLE 1. Immunoreagents Used in the Analysis of Neurothekeoma

Polypeptide	Clone	Pretreatment*	Antibody Dilution	Commercial Source
Keratins†	AE1/AE3 and LP 34	Protease 1, 8 min	1:400	CHEMICON, Temecula, CA
CK7	OV-TL	Protease 1, 8 min	1:400	DakoCytomation California Inc. Carpinteria, CA
CK20	K20.8	Protease 1, 8 min	1:200	DakoCytomation
CEA	A0115	Protease 1, 8 min	1:600	DakoCytomation
Epithelial antigen	BER-EP4	Protease 1, 8 min	1:50	DakoCytomation
EMA	Mc5	Protease 1, 8 min	Predilute	Ventana Medical Systems, Tucson, AZ
NFP	2F11	Protease 1, 8 min	1:200	DakoCytomation
NSE	VI-H14	—	Predilute	Ventana Medical Systems
S100 protein	Polyclonal	—	1:600	DakoCytomation
GFAP	Polyclonal	Protease 1, 8 min	1:4000	DakoCytomation
HMAA	NKI/C3	—	1:30	Biogenex, San Ramon, CA
PGP9.5	10A1	EDTA	1:50	Novocastra Laboratories Ltd, Newcastle upon Tyne, UK
MITF	34CA5	EDTA	1:50	Novocastra Laboratories
H. melan.	HMB-45	—	1:50	DakoCytomation
Tyrosinase	NCL-TYROS	CC1	1:20	Novocastra Laboratories
CD1a	O10	EDTA	1:20	Immunotech, Miami, FL
CD10	56C6	CC1	Predilute	Cell Marque Corp, Hot Springs, AR
CD31	JC/70A	Protease 1, 8 min	1:25	DakoCytomation
CD34	QBEnd/10	Protease 2, 4 min	Predilute	Ventana Medical Systems
CD56	123C3	CC1	1:200	Zymed Laboratories Inc, San Francisco, CA
CD57	HNK-1	Steam retrieval, 20 min	1:50	Becton-Dickinson, Mountainview, CA
CD68	KP1	Protease 1, 4 min	1:100	DakoCytomation
CD99	12E7	CC1	1:150	DakoCytomation
CD117	Polyclonal	CC1	1:100	DakoCytomation
CD163	10D6	EDTA	1:200	Novocastra Laboratories
Factor VIIIrAg	Polyclonal	Protease 1, 8 min	1:1600	DakoCytomation
Factor XIIIa	Polyclonal	Protease 1, 8 min	1:1600	CalBioChem Corp, San Diego, CA
Lysozyme	Polyclonal	EDTA	1:1200	DakoCytomation
Synaptophysin	Polyclonal	CC1	Predilute	Ventana Medical Systems
Chromogranin	Polyclonal	—	1:200	DakoCytomation
α -SMA	1A4	—	1:1600	Sigma Chemical St Louis, MO
Desmin	D33	CC1	1:200	DakoCytomation
Desmin	DE-R-11	Protease 1, 8 min	Predilute	Ventana Medical Systems
Calponin	CALP	Protease 1, 8 min	1:400	DakoCytomation
Collagen IV	CIV 22	Protease K, 5 min	1:400	DakoCytomation

*All pretreatment, except steam retrieval, was performed on the BenchMark Auto Stainer (Ventana Medical Systems, Inc, Tucson, AZ).

†A keratin cocktail.

α -SMA indicates α -smooth muscle actin; CC1, cell conditioning solution—a predilute tris-based buffer produced by Ventana Medical Systems, that at elevated temperatures hydrolyzes covalent bonds formed by formalin fixation; CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; H. melan., human melanosome; HMAA, human melanosome-associated protein; MITF, microphthalmia transcription factor; NFP, neurofilament protein; NSE, neuron-specific enolase.

estimate of the mitotic activity one would anticipate in 50 “standard” 40 × HPFs with a 20-mm eyepiece diameter, multiply the number of mitotic figures we obtained by 1.65.

Follow-up information was obtained by reviewing submitted medical records and by telephonic or written communication with the patients or their clinicians.

RESULTS

Clinical Findings

The study group contained 176 patients, ranging from 20 months to 85 years old at first surgical excision (Fig. 1). The mean and median ages for the group were 21 and 17 years, respectively. There were 64 males and 112 females for a M:F ratio of approximately 1:2. There were very few active service military or veteran patients, so this did not significantly impact on the age or sex distributions. Patients with solitary tumors had involvement of the head (n = 62), neck (n = 4), upper limb girdles (n = 27), arms (n = 36), hands (n = 7), thorax (n = 13), pelvic girdle (n = 4), legs (n = 18), feet (n = 2), and an unspecified site (n = 2). One unique 26-year-old male patient, who is suspected of having neurofibromatosis-1, had a history of cutaneous lesions dating back to early childhood; some of these lesions (including 3 tumors that we examined from the chin, right arm, and back) had histologic features of neurothekeomas, whereas others were neurofibromas. For the entire group, the most common sites of involvement on the head were the nose (n = 17) and scalp (n = 15), followed by the orbital region, cheeks, and chin (n = 6, each).

The preoperative tumor duration for 104 patients ranged from a few weeks to 4 years (median: 7 mo). Sixty-six percent of the lesions were present for < 1 year. The patients usually presented with a dome-shaped, papular, or nodular mass of firm consistency with pink-tan to reddish-brown coloration. The lesions were generally stated to be slow-growing and either painless or only mildly symptomatic with pressure.

The preoperative clinical impression was often vague, and commonly, the process was simply described as a nodule or mass. However, more specific clinical

impressions included an epidermal, pilar, or “sebaceous” cyst (n = 33), nevus (n = 16), dermatofibroma/fibrous histiocytoma (n = 12), skin adnexal tumor (the most frequently mentioned type being a pilomatricoma) or basal cell carcinoma (n = 11), insect bite or type of granulomatous reaction (n = 8), keloid or scar (n = 3), hemangioma variant (n = 2), neurofibroma (n = 2), and malignant melanoma (n = 1). Five additional lesions were generically interpreted as a tumor (benign or malignant) or sarcoma, not further specified. Forty-three patients (24.4%) had a biopsy (ie, a shave, punch, or biopsy, not further specified) as the initial procedure. All other patients (n = 133) had surgical enucleation or simple local excision.

Contributing pathologists considered a wide variety of entities in the differential diagnosis, but the most frequently mentioned were neurothekeoma (n = 42), melanocytic tumor variants (especially a Spitz nevus) (n = 34), neurofibroma, schwannoma or a neuroma variant (n = 30), a fibrohistiocytic tumor (n = 28), and nerve sheath myxoma (n = 14). Other entities, considered for 6 or more cases, included a granulomatous process, skin adnexal tumor, fasciitis, myxoid malignant fibrous histiocytoma (myxofibrosarcoma), smooth muscle tumor, skeletal muscle tumor (including rhabdomyosarcoma), and malignant peripheral nerve sheath tumor. Less common, but notable, considerations included a plexiform fibrohistiocytic tumor, superficial angiomyxoma (cutaneous myxoma), epithelioid sarcoma, juvenile xanthogranuloma, ectopic meningioma, granular cell tumor, extraskeletal myxoid chondrosarcoma, and clear cell sarcoma. Many other entities were also entertained in the differential, but these are too numerous to mention. Of interest, a malignant diagnosis was considered for 21% of the cases.

Additional Clinical Observations and Family History

Information on skin tone was available for 60 patients and 55% had a fair complexion, 38% had a medium complexion, and 7% had dark skin. Five of the patients with fair skin reported the presence of many nevi. Eye color was available for 51 patients and 39% had blue eyes, 14% had hazel eyes, 12% had green eyes, and 35% had brown eyes.

Notable medical conditions in the patient cohort included suspected or confirmed fatty tumors (n = 3), disseminated superficial actinic porokeratosis (n = 1), keloid formation (n = 1), malignant melanoma (n = 1), a history of asthma, allergic colitis and a linear epidermal nevus (n = 1), a childhood history of thrombocytopenia followed by the development of Tourette syndrome (n = 1), an arteriovenous malformation (n = 1), hypothyroidism (n = 1), an undescended testis (n = 1), breast cancer and a benign renal tumor (n = 1), and squamous carcinoma of the nose and colon cancer (n = 1).

Notable medical conditions in first degree family members included malignant melanoma (n = 3), a “pre-cancerous” melanocytic lesion (n = 1), basal cell or

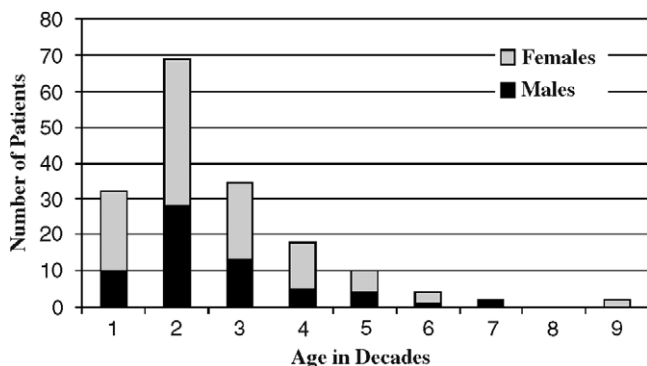


FIGURE 1. Age and sex distribution for 172 patients with a neurothekeoma.

squamous carcinoma (n = 2), lipomas (n = 2), a keloid (n = 1), a brain tumor (n = 4; reported to be a grade 3 astrocytoma for one individual), a phyllodes tumor of the breast (n = 1), breast cancer (n = 1), colon cancer (n = 1), and a thyroid adenoma (n = 1).

Gross and Microscopic Findings

Given the small size of most lesions, the pathologists' gross descriptions were usually very brief and often consisted only of the overall dimensions of the specimen with a notation that the sample contained skin. Because the material was typically bisected or step sectioned, in most instances, it was not possible to obtain precise tumor dimensions. In general, however, approximately 30% of cases had a tumor < 0.5 cm, 50% had a tumor 0.5 to 1.0 cm, and 20% had a tumor > 1.0 cm. Only 17 cases (9.6%) had overall dimensions of ≥ 2 cm, and of these, we were able to confirm an actual tumor size of ≥ 2 cm in only 2 instances, with the largest tumor measuring 3.0 cm in histologic sections.

Microscopic examination was performed on 196 specimens, including 37 initial biopsies, 5 secondary biopsies, 129 initial local excisions, 21 secondary local excisions, and 1 secondary partial excision. In addition, 1

patient had 3 separate neurothekeomas removed by local excision from the chin, right arm, and back; as noted previously, this patient is suspected of having neurofibromatosis-1 and has had other neurothekeomas and also neurofibromas removed from other sites, in the past.

The tumors were nonencapsulated, and at low magnification, they typically formed multiple, closely situated, small to medium-sized nodules, separated by varying amounts of collagen. Of the 178 tumors examined, 159 involved the dermis, 18 had no recognizable dermal tissue for evaluation, and 1 did not involve the dermis. Subcutaneous involvement was documented in 120 tumors and was absent in 18 examples. Forty lesions had insufficient tissue to assess for subcutaneous involvement. Five tumors, all from the facial region, involved superficial skeletal muscle. The tumors had variable amounts of myxoid matrix, and based on criteria in the Materials and Methods section, 63 tumors were subclassified as cellular neurothekeomas, 67 were designated mixed-type neurothekeomas, and 48 were myxoid neurothekeomas (Figs. 2–4). The amount of myxoid matrix influenced the overall size of individual tumor nodules, so that the largest nodules tended to be present in myxoid neurothekeomas. The amount of myxoid

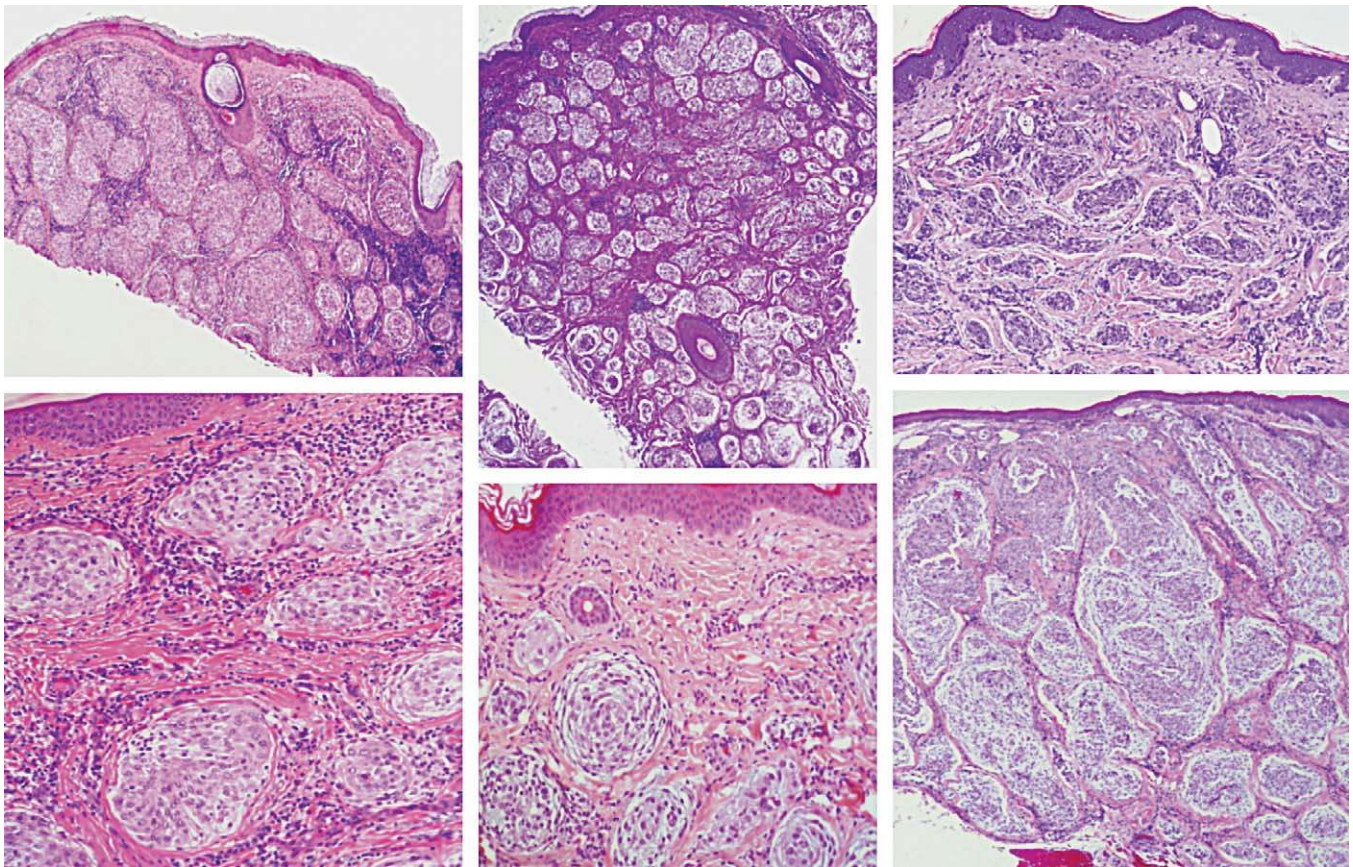


FIGURE 2. Low-power views of several different neurothekeomas, illustrating a tendency for the process to form multiple discrete nodules within the dermis and superficial subcutis. These nodules can have varying amounts of myxoid matrix and often exhibit a whorled growth pattern.

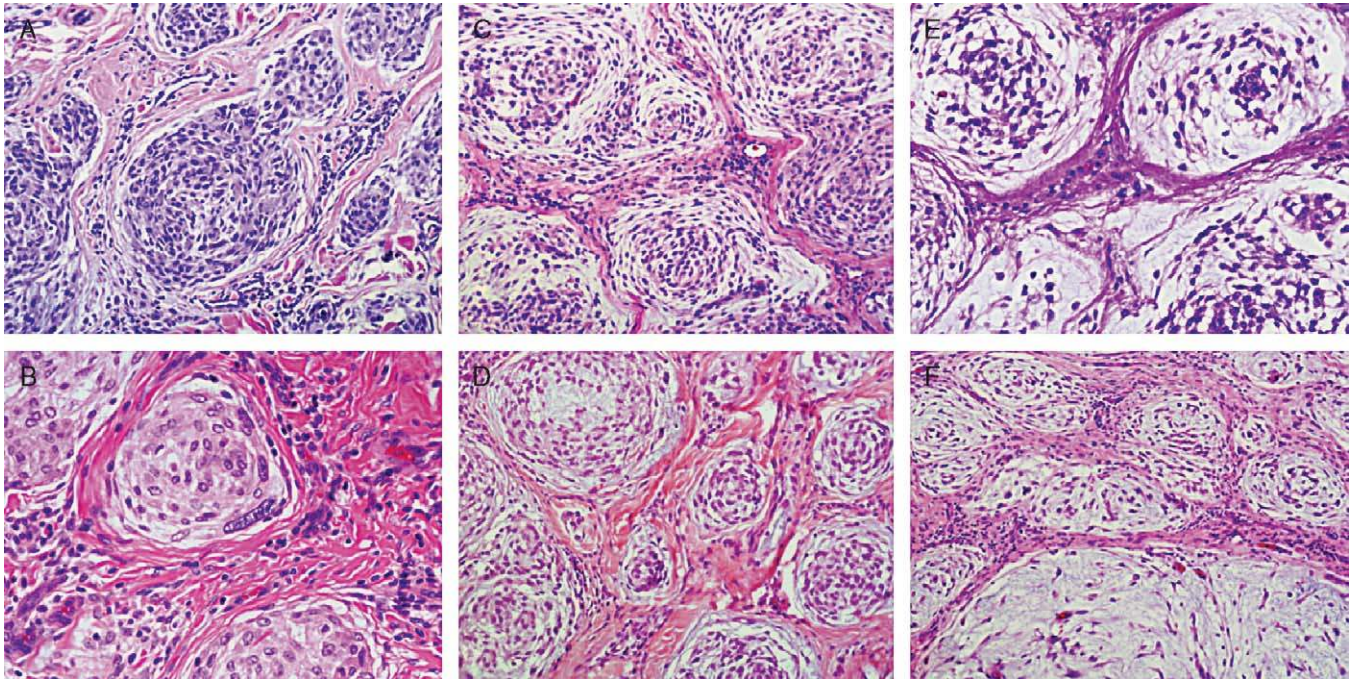


FIGURE 3. A to F, Intermediate-power views of neurothekeomas with varying amounts of myxoid matrix. Note a paucity of myxoid matrix in illustrations (A) and (B) and an abundance of myxoid matrix in illustrations (E) and (F). Also note the coexistence of bland and moderately atypical tumor cells within one tumor nodule in illustration (B).

matrix also influenced the growth pattern of the tumor cells. As a result, myxoid neurothekeomas sometimes had large areas where tumor cells exhibited a “random” growth pattern. These tumors often had only small foci

where tumor cells had a well-defined whorled growth pattern, and 41 of the 48 cases (85%) lacked fascicular growth. In contrast, whorled growth was a characteristic, and often well-defined, feature of both the cellular and

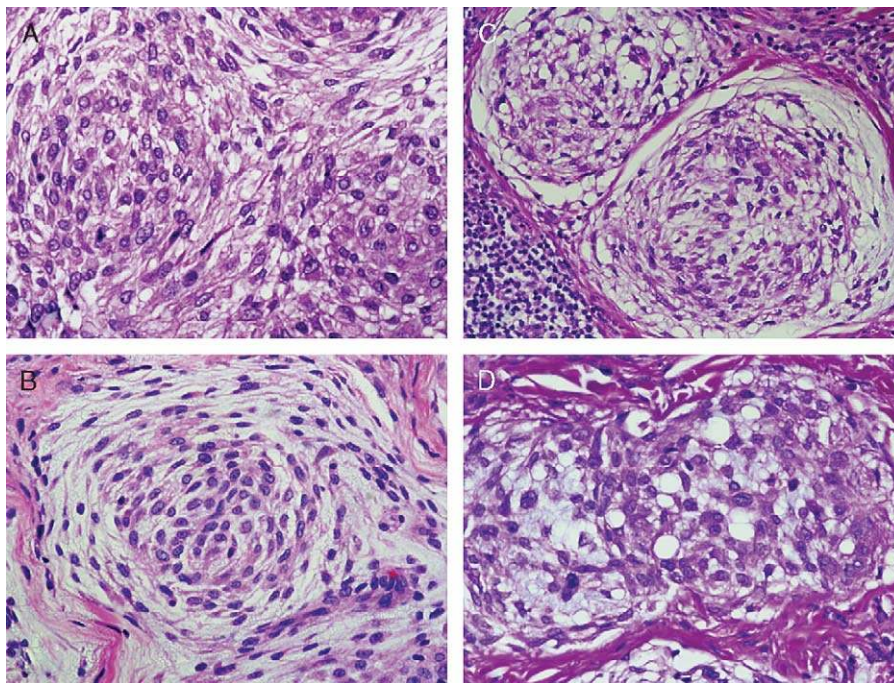


FIGURE 4. A to D, High-power views of 4 neurothekeomas. Note varying amounts of myxoid matrix, whorled growth, and eosinophilic, somewhat granular, cytoplasm.

mixed-type neurothekeomas, and these tumor subtypes had at least a minor element with fascicular growth in 63% and 52% of cases, respectively. Although almost all tumors were associated with some sclerotic collagen, this was most pronounced in cellular neurothekeomas and least evident in the myxoid examples. Moderate or marked collagen deposition around individual tumor nodules was noted in 40% of cellular, 13% of mixed-type, and 2% of myxoid neurothekeomas.

All examples contained spindled and epithelioid tumor cells with relatively abundant, somewhat granular-appearing, eosinophilic cytoplasm. In most cases, spindled cells predominated, and in a few cases, epithelioid cells were notably infrequent. When the tumor cells were closely apposed, cell borders were typically indistinct. There was no tendency for the lesional cells to form discrete corded or closely packed syncytial-like aggregates, as seen in true nerve sheath myxomas, and tumor cells with ringlike morphology were exceptionally uncommon, and for practical purposes, only encountered very infrequently in highly myxoid examples. The neoplastic cells had minimal atypia in 62 cases, mild atypia in 73 cases, focally moderate atypia in 22 cases, more generalized moderate atypia in 19 cases, and focally marked atypia in 2 cases (Fig. 5).

The tumors had variable mitotic activity. Twenty-seven cases (15.2%) had no apparent mitotic activity within 25 wide-field high power fields (WHPFs). Ninety-five tumors (53.4%) had 1-5 mitotic figures and 31 tumors (17.4%) had 6-10 mitotic figures per 25WHPFs. Twenty-five cases (14.0%) had > 10 mitotic figures/25 WHPFs, and of these, 5 had more than 20 mitotic figures in 25

WHPFs. The maximum number of mitotic figures identified in 25WHPFs was 124. Sixteen tumors contained one or more atypical mitotic figures. Thirteen of these tumors had at least focal moderate nuclear atypia, and one example had focal marked atypia. The median mitotic count of this subgroup was 6.5 mitotic figures/25 WHPFs.

Thirty-nine percent of cases contained osteoclastlike giant cells (Fig. 6). These cells were generally sparse and did not appear to be neoplastic. They were identified in 33% of cellular, 35% of mixed-type, and 50% of myxoid neurothekeomas. Inflammatory cells were often associated with the neurothekeomas, but in most instances, they were not a prominent feature. The most common inflammatory cells were lymphocytes. Less often, plasma cells, eosinophils, and rarely, polymorphonuclear leukocytes were also noted. Histiocytes and dendritic (antigen-presenting) cells were also present, often in considerable numbers as demonstrated by immunohistochemistry, but they were less discernable in the hematoxylin and eosin-stained sections.

Immunohistochemical studies were available for 126 of the 178 tumors (71%) (Fig. 7). In order of frequency, the neoplastic cells were immunoreactive for vimentin (100% of 39 cases), NKI/C3 (100% of 47 cases), CD10 (100% of 41 cases), microphthalmia transcription factor (MITF) (83% of 52 cases), CD99 (80% of 10 cases), collagen IV (80% of 10 cases), neuron-specific enolase (66% of 35 cases), PGP9.5 (60% of 50 cases), CD68 (59% of 71 cases), muscle-specific actin (42% of 12 cases), and α -smooth muscle actin (38% of 56 cases). The lesional cells were consistently nonreactive for S100 protein

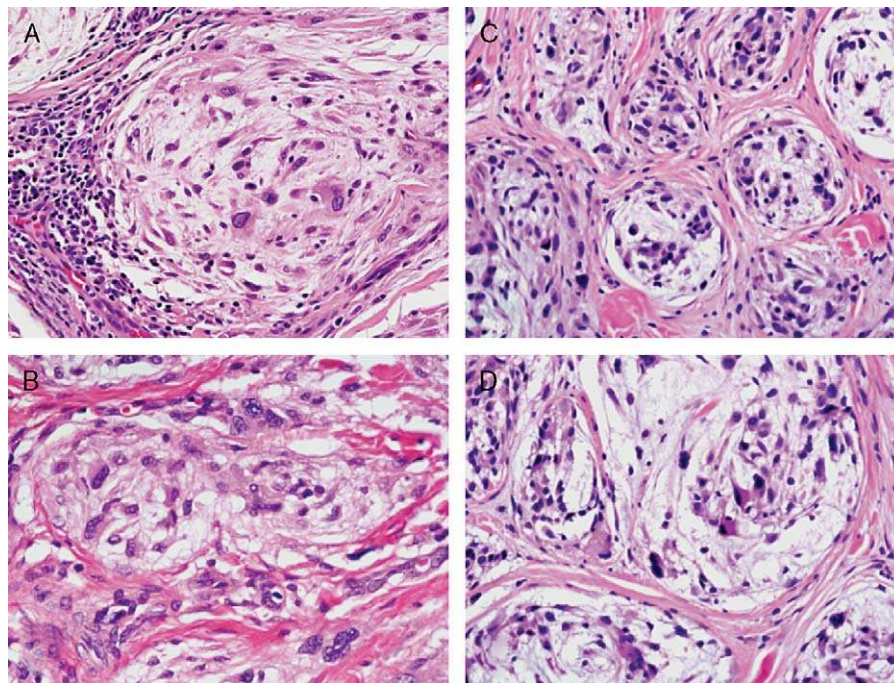


FIGURE 5. A to D, Intermediate-power and high-power views of neurothekeomas forming small nodules with varying amounts of myxoid matrix. Note focal nuclear atypia and pleomorphism.

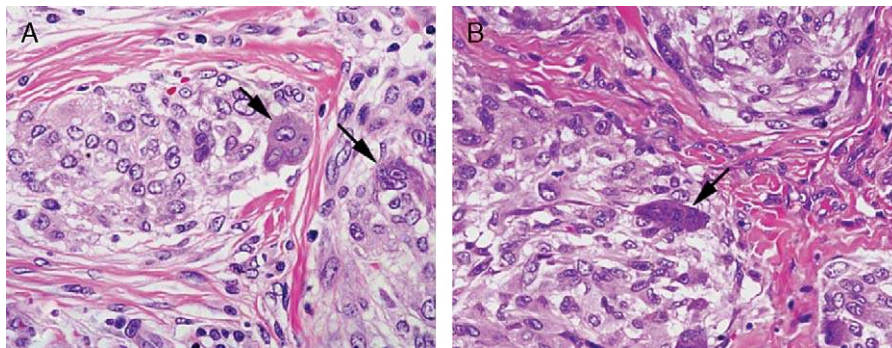


FIGURE 6. A and B, High-power views of 2 neurothekeomas with osteoclastlike giant cells (see arrows).

(n = 119), glial fibrillary acidic protein (GFAP) (n = 12), Melan A (n = 11), tyrosinase (n = 4), neurofilament protein (n = 27), CD34 (n = 29), D33 desmin (n = 31), CD163 (n = 25), CD117 (n = 11), MAC387 (n = 10), lysozyme (n = 5), polyclonal CEA (n = 6), and factor VIIIrAg (n = 5). Although studied to a very limited

extent, 3 tumors were negative for CD31 and BER-EP4; 2 tumors were negative for chromogranin, CD1a, and CK20; and 1 case each was negative for calponin, DER-11 desmin, CK7, and CD45RB. Three of 59 cases had a small amount of reactivity for HMB-45; the significance of this finding is unclear given the fact that all were S100

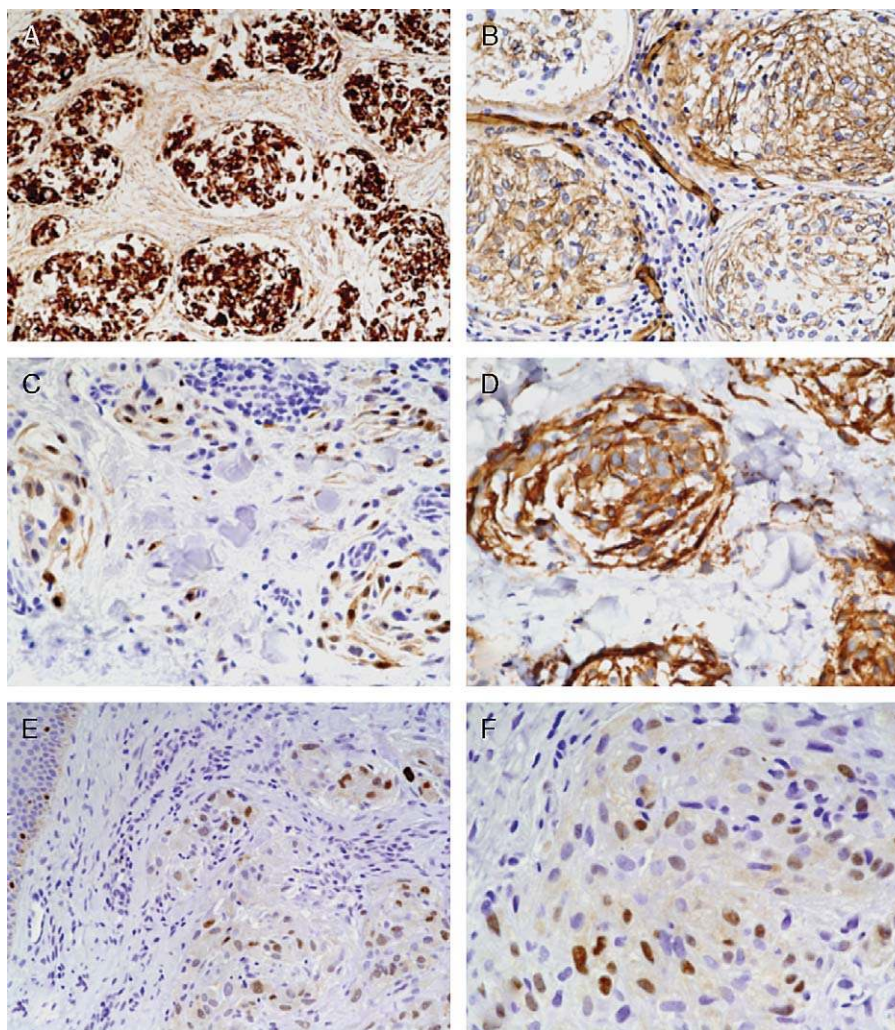


FIGURE 7. A to F, Immunohistochemical results for neurothekeomas. Note immunoreactivity for NK1/C3 (A), collagen IV (B), PGP9.5 (C), CD10 (D), and MITF (E, F).

protein negative. Six of 45 cases (13%) had trace to focal reactivity for CD57, and 3 of 18 cases (17%) had focal weak reactivity for CD56. One of 42 cases had a small amount of reactivity for our keratin cocktail, and a different case among 42 examined had very limited reactivity for epithelial membrane antigen. Finally, 1 of 2 cases tested for synaptophysin had focal weak reactivity of uncertain significance.

Nonlesional (recruited) dendritic cells, present as part of the host response, were reactive for S100 protein, factor XIIIa, CD163, and CD68. They were sometimes abundant but tended to be fairly evenly distributed in a "salt and pepper"-type pattern amongst the tumor cells. CD117-positive mast cells were also occasionally noted.

Of all 196 examined specimens, only 27 (including 1 initial biopsy, 18 initial local excisions, and 8 secondary local excisions) had negative resection margins. For 11 specimens (1 initial biopsy, 9 initial local excisions, and 1 secondary local excision), margins could not be accurately assessed. All of the remaining specimens (n = 158, including 35 initial biopsies, 102 initial local excisions, 18 secondary procedures, and the 3 separate locally excised lesions from the patient with multiple lesions) were interpreted as having a positive resection margin.

Follow-up Information

Complete follow-up information, ranging from 3 years 2 months to 34 years 9 months (median: 17 y 9 mo), is available for 71 patients (40.3%). Two additional patients, both of whom presented with disease in their 80s, are known to be dead of an unrelated cause, 4 years 11 months and approximately 10 years after excision of their neurothekeoma. There are also 12 patients, currently lost to follow-up, for whom we have limited follow-up information (range: < 1 mo to 1 y 4 mo; median: 5 mo). This information was either provided to us by the contributing pathologists at the time of our initial consultation (n = 11) or was obtained by reviewing a tumor recurrence; all 12 patients had more than 1 surgical procedure.

Among the 71 patients that we have complete follow-up, 47 (66.2%) had only 1 surgical procedure and are alive and well with no evidence of disease. Eight patients (11.3%) had regrowth of tumor that led to a second procedure. Four of these were initially managed by a shave biopsy, one by tumor enucleation, and 3 by local excision. The tumors were reexcised 4 months to 2 years after the first procedure (2 by a repeat shave biopsy, 1 by a large punch biopsy, and 5 by local excision), and all individuals are alive and well with no evidence of disease. Additionally, 15 of the 71 patients had reexcision of the initial tumor site in an attempt to assure complete removal. Among this group, the reexcision specimens were found to be positive for residual tumor in 6 cases (all initial specimens were biopsies), negative for tumor in 3 cases (all initial specimens were local excisions), or were unavailable for review (6 cases). Finally, 1 exceptional patient with complete follow-up, who is now 35 years old, has had innumerable cutaneous tumors over his lifetime,

with initial onset during his toddler years. This patient probably has neurofibromatosis-1. Some of the patient's cutaneous tumors, including the 3 we personally examined, are neurothekeomas, whereas others were neurofibromas. None of the neurothekeomas are known to have recurred after local excision.

Only scant information is available for the 2 patients dead of unrelated causes. For 1 patient, there is no information as to whether or not a recurrence developed. For the other, the patient's son did not recall any recurrence, and the cause of death was a cerebral vascular accident.

Among the 12 patients with partial clinical follow-up information, 5 had regrowth of tumor. These patients had a biopsy/partial excision (n = 2) or local excision (n = 3) as initial management and had secondary procedures consisting of a punch biopsy (n = 1), partial excision (n = 1), or local excision (n = 3), 2 months to 1 year later. One of these individuals developed a second recurrence also managed by local excision, 1 year 1 month after the first recurrence. Four of the 5 patients had experienced regrowth of tumor before the case was sent to us in consultation. Only the last patient, with 2 recurrences, was examined by us at the outset of disease. The remainder of the patients (n = 7), who were initially managed by biopsy (n = 4) or local excision (n = 3), had reexcision of the tumor bed to insure complete removal. Six of the follow-up specimens contained residual tumor, and 1 (initially managed by local excision) was negative for tumor. All 7 of these cases were submitted for our review after the second procedure.

DISCUSSION

Since the initial description of neurothekeoma in 1980,²¹ there has been considerable controversy over how it relates to nerve sheath myxoma.^{25,37,40,41} Pulitzer and Reed fostered the belief that neurothekeoma and nerve sheath myxoma were the same clinicopathologic entity,^{22,33} and this opinion has been supported by others.^{1,4,16,20,24} However, evidence has mounted over the years that these are, in fact, distinct and unrelated processes,^{3,8,25,37,40,42} and corroboration of this view has recently been presented in a large series of true nerve sheath myxomas.¹⁹

The current study of 178 neurothekeomas from 176 patients is a detailed analysis of the tumor's clinical characteristics, morphologic spectrum, and immunoprofile. Cases selected for inclusion were carefully screened, in light of current knowledge, to prevent contamination by potential mimics that undoubtedly have found their way into other series in the past. However, even with refinement of the diagnostic criteria, our results still correlate surprisingly well with the original findings of Gallager and Helwig.²¹ We documented a wide age range (ie, 20 mo to 85 y) but one strongly skewed towards the second decade of life (median age: 17 y). Fifty-nine percent of patients were < 20 years of age at initial diagnosis, and 80% were < 30 years of age. Female

patients outnumbered males by a margin of almost 2:1. The tumors had a strong predilection for the head (especially the nose, scalp, orbital regions, cheeks, and chin), arms, and upper limb girdles, with more than 3/4 of cases involving these 3 sites. The trunk, pelvic girdle, legs, hands, and feet were less commonly affected.

Neurothekeomas typically present as asymptomatic, solitary, slow-growing, dome-shaped masses that involve the skin and superficial subcutis. Deep involvement of the subcutis is uncommon, and skeletal muscle involvement is rare and largely restricted to the facial region. Histologically, the tumors can be segregated into 3 subgroups, based primarily on the amount of myxoid matrix. By our criteria, examples with $\leq 10\%$ myxoid matrix were classified as cellular neurothekeomas (35.4% of cases), and tumors with $> 10\%$ but $\leq 50\%$ myxoid matrix were designated mixed-type neurothekeomas (37.6% of cases). Myxoid neurothekeomas (27% of cases) had $> 50\%$ myxoid matrix. Despite the differences in matrix, all tumors shared certain features, including: (1) the presence of epithelioid and spindle cells with relatively abundant, somewhat granular-appearing, eosinophilic cytoplasm, (2) a tendency for tumor cells to form multiple small nodules with whorled and sometimes focal fascicular growth, (3) an association with variable amounts of sclerotic collagen, (4) the occasional presence of osteoclastlike giant cells, and (5) a similar immunoprofile. The majority of these tumors have relatively "innocent" histology. They tend to be small, often 1 cm or less in size, and just over three-quarters of the lesions in our study had no more than mild cytologic atypia, with another 12% of cases having only focal moderate atypia. Additionally, more than 2/3 of cases had no more than 5 mitotic figures/25 WHPFs. However, as other authors have noted,^{9,21,33} neurothekeomas can occasionally have atypical features, including increased nuclear atypia, an elevated mitotic count, and even atypical mitotic figures. We found generalized moderate or focally marked atypia in 12% of cases, a mitotic count of > 10 mitotic figures/25 WHPFs in 14% of cases, and atypical mitotic figures in 9% of cases.

Partial or complete follow-up information was available for 85 (48.3%) of the 176 patients included in this study. Clinical regrowth of tumor was documented in 13 individuals. Assuming neither of the 2 patients who are dead of an unrelated cause had regrowth of tumor, this would be a "recurrence" rate of 15.3%. However, this figure, in all probability, is an overestimation of the true recurrence rate, for several reasons. First, 11 of the 13 cases with regrowth of tumor were set to us in consultation after the fact, and these cases undoubtedly skew data in favor of recurrence. Second, 46% of these cases were managed by a shave biopsy, or in one instance, a "partial" excision, so one would assume they inherently have greater potential for regrowth than similar lesions managed by an excisional procedure. For patients that we were involved in management from the outset, the recurrence rate was only 3.3%.

When the patient subgroup with clinical regrowth of tumor (herein referred to as group C; $n = 13$) was compared with the entire study group of neurothekeomas (group A; $n = 178$) and to the group of patients for whom we had complete follow-up with no recurrence after a single surgical procedure (group B; $n = 47$), several interesting findings were noted. The patient group with clinical regrowth of tumor (group C) had a higher percent of myxoid neurothekeomas (38.5% vs. 27% and 23.4% for groups A and B, respectively), a greater number of cases with no subcutaneous tissue in the specimen for examination (38.5% vs. 22.4% and 29.8%), a greater percentage of biopsy specimens (46.2% vs. 21.7% and 29.8%), an elevated F:M ratio of $> 3:1$ (vs. $\approx 2:1$ and $< 3:2$), and a higher number of cases involving the face (46.2% vs. 33% and 23.4%). Patients with regrowth of tumor also had a lower median age than the other 2 groups (15 vs. 17 and 19). In addition, the histologic specimens from these patients had involvement of the tissue edge in all cases we were able to evaluate this parameter, whereas this was true for 88.1% and 86.7% of groups A and B, respectively. The tumors in group C did not have greater nuclear atypia or mitotic activity or a different immunoprofile from the other 2 groups. Although it is difficult to draw definite conclusions from these data, given the small number of patients with regrowth of tumor, many of these findings seem quite logical. First, we suspect there may be a tendency for highly myxoid tumors, in general, to have enhanced recurrent potential (eg, cutaneous myxoma and nerve sheath myxoma both have recurrence rates of greater than 30%). Second, because a high percentage of these lesions were on the face of young females, this may have predisposed clinicians toward a more conservative initial procedure, that is, a biopsy that failed to include subcutaneous tissue. Because the overwhelming majority of neurothekeomas involve the superficial subcutis (87% of all cases in which this parameter could be assessed), this may have left behind sufficient tumor burden to incite regrowth/recurrence.

Analysis of the 12 cases in which residual tumor was found in a secondary procedure performed to insure complete removal (herein referred to as group D) revealed a very high percentage of initial specimens to be biopsy procedures (83.3% vs. 21.7% and 29.8% for groups A and B, respectively). This subgroup also had a slightly higher percentage of cases with no subcutaneous tissue in the specimen (33.3% vs. 22.4% and 29.8%), and with tumor extending to the initial resection margin (91% vs. 88.1% and 86.7%). However, the subgroup with residual disease did not have an unusually high number of myxoid neurothekeomas, tumors involving the face, or tumors with atypical morphologic features. Although it is possible some of these patients might eventually have developed a clinical recurrence if they had not had their second procedure, others (especially those with a low tumor burden) may not have, given the previously stated findings that a full 86.7% of patients in group B (those with complete follow-up who did not develop a

recurrence after only one surgical procedure) had tumor extending to the tissue edge and 29.8% of their specimens were biopsies.

The present data and past studies are insufficient, in our opinion, to make a definite statement regarding the clinical significance of the atypical features noted in this report (ie, increased nuclear atypia, an elevated mitotic count, and atypical mitotic figures). We are not aware of a neurothekeoma with atypical features having behaved in a low-grade malignant fashion, but we cannot definitely rule out such a possibility. It is clear from the very low metastatic rates of some “borderline” soft tissue tumors that large numbers of cases with long-term follow-up are needed to identify the infrequent example with an adverse outcome. This is especially true when the majority of examples are small at presentation and when they have a predilection for the skin. There are additional complicating factors, as well. First, we found that when patients had an atypical neurothekeoma, this was usually documented in the pathology report and accompanied by a recommendation for reexcision, indicating a bias toward more aggressive intervention in these cases to reduce the risk (real vs. perceived) of an adverse outcome. Second, we have a strong suspicion that some pathologists (both dermatopathology and soft tissue experts) dispense with the neurothekeoma designation, in favor of a diagnosis of superficial malignant fibrous histiocytoma or myxofibrosarcoma, when atypia and/or mitotic activity reach their “critical” threshold. Although we remain neutral on this last point, clearly, it has the effect of not only reducing the overall pool of potential cases, but also eliminates some of the most likely candidates for an adverse event, and therefore, impacts on the determination of “safety” thresholds (if needed) for the atypical subgroup.

What is the derivation of neurothekeoma and is the current appellation appropriate? Our histologic and immunohistochemical findings do not conclusively point to a specific cell of origin for this tumor. Although others may argue that a number of findings in this study are consistent with a neural or melanocytic derivation, it is prudent to point out that none of the immunohistochemical markers commonly positive in neurothekeoma are neural-specific or melanocyte-specific. Also, the consistent lack of immunoreactivity for S100 protein (119 cases tested) militates strongly against a biologically benign peripheral nerve sheath or melanocytic neoplasm. Other points against a peripheral nerve sheath origin include a lack of reactivity for GFAP and the consistent expression of CD10 in neurothekeomas, as noted in this study and one previous case report.³¹ Although the latter antigen is widely distributed,^{27,28} preliminary observations (J.F.F., M.M.) indicate it is typically absent in Schwann cell proliferations (including nerve sheath myxoma). We suspect, based on: (1) the morphology of the tumor cells, (2) the population of nonlesional (recruited) cells (including osteoclastlike giant cells), (3) the occasional presence of neoplastic cells with actin expression, (4) the CD99 and CD10 expression, and (5) an occasional resemblance to plexiform fibrohistiocytic tumor, that this neoplasm is

most likely derived from fibroblastlike cells that have the capacity to produce myxoid matrix and differentiate into myofibroblasts, that may have some inherent phagocytic properties, and that have the ability to recruit a variety of “inflammatory” cell types. As a result, we do not believe the appellation “neurothekeoma” is accurate. Perhaps, a more appropriate designation would be “superficial micronodular (myxo/myo)fibroblastoma.”

The differential diagnosis of neurothekeoma includes the true nerve sheath myxoma, superficial angio-myxoma (cutaneous myxoma), melanocytic neoplasms, reticulohistiocytoma, a fibrous histiocytoma variant, and the plexiform fibrohistiocytic tumor. True nerve sheath myxomas have a peak incidence in the fourth decade of life, occur with approximately equal frequency in males and females, have a strong predilection for the extremities (especially the hands), and have a high local recurrence rate when incompletely excised.¹⁹ They only rarely involve the head and neck region. Nerve sheath myxomas characteristically form superficial, highly myxoid, multinodular/multilobular masses with a prominent peripheral fibrous border. They contain spindled, stellate-shaped, ring-shaped, and epithelioid Schwann cells, and the last are often organized into cords and closely packed syncytial-like aggregates. The tumor cells are strongly immunoreactive for S100 protein and GFAP, and epithelial membrane antigen is sometimes detectable in residual perineurial cells at the tumor periphery.^{19,25} Nerve sheath myxomas are rarer than neurothekeomas by a factor of at least 3. In the past, they were often erroneously included within the myxoid subgroup of neurothekeoma, but it is now clear, on the basis of the clinical demographics, histomorphology, and immunohistochemical findings noted above, that they are a separate and distinct clinicopathologic entity (Fig. 8). Rarity, coupled with previously scant and sometimes

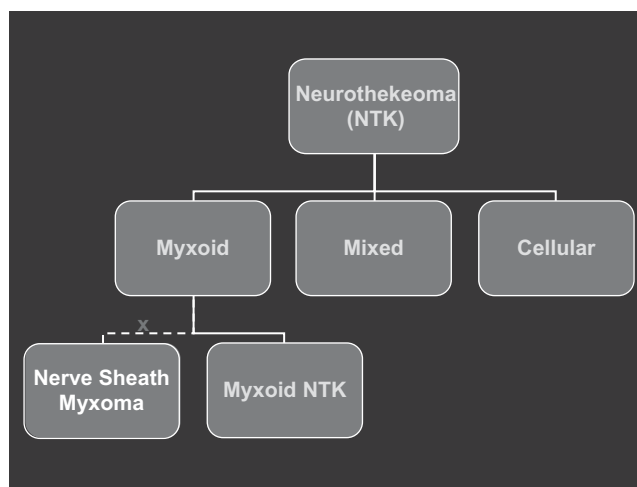


FIGURE 8. Neurothekeomas can be subclassified into 3 categories on the basis of the amount of myxoid matrix. Nerve sheath myxomas have often been included in the myxoid subgroup, but there is now compelling evidence that they are a separate and distinct entity.

conflicting immunohistochemical reports, and the fact that legitimate neurothekeomas can have abundant myxoid matrix, undoubtedly fostered some of the confusion. The distinction is clinically relevant, because nerve sheath myxomas have a substantially higher local recurrence rate than neurothekeomas.

Superficial angiomyxoma (cutaneous myxoma) forms highly myxoid multilobular/multinodular masses within the dermis and subcutis.^{1,2,12,15,18} This entity contains mildly pleomorphic, mononucleated and multinucleated, stellate-shaped and spindled, tumor cells. The lesional cells often have “smudgy” nuclear chromatin, and cytoplasmic-nuclear invaginations are common. Scattered acute and chronic inflammatory cells are sprinkled throughout the myxoid matrix. From an immunohistochemical standpoint, this tumor often has reactivity for CD34, it can have some reactivity for actin, and it is generally either negative or only weakly reactive for S100 protein.¹⁸ As noted previously, all examples of neurothekeoma examined in the current series were negative for CD34 expression. Superficial angiomyxomas are weakly linked to Carney’s complex,¹⁴ and they have a recurrence rate in the 30% to 40% range, significantly higher than is seen with neurothekeomas.^{1,2,12,18}

Melanocytic tumors are frequently included in the differential diagnosis of neurothekeoma. In our series, the most common melanocytic entity to be considered by contributors was a Spitz nevus. However, a diagnosis of malignant melanoma was also proposed for 7 tumors. Melanocytic tumors, in general, enter into the differential diagnosis because neurothekeomas present as superficial neoplasms that features plump epithelioid and spindle cells with nested growth and focal whorling. A Spitz nevus, in particular, is a consideration, because its age range and anatomic distribution overlap with neurothekeoma. Complicating matters is the presence of some immunohistochemical overlap between melanocytic tumors and neurothekeomas, namely the presence of MITF,³² PGP9.5,^{20,26,39} and NKI/C3.^{9,10,26,32,42} However, as already noted, neurothekeomas are uniformly negative for S100 protein, and they are typically negative for other key “melanocytic” markers such as HMB-45, Melan A, and tyrosinase. It is notable that we found a small amount of reactivity for HMB-45 in 3 of 59 tested cases, but we do not interpret this as compelling evidence for melanocytic differentiation. Rather, we regard this as an aberration, possibly a false-positive reaction (as we have occasionally encountered in other tumor types, including “fibrohistiocytic” processes), or alternatively, the result of phagocytized melanocytic debris (eg, melanosomes). Although PGP9.5 and NKI/C3 have some limited utility in the diagnosis of neurothekeoma, they are clearly not specific for melanocytic or neural differentiation.^{13,35} The MITF antibody used in our study is purported to have specificity for the M isoform, and therefore, is often viewed as specific for cells undergoing melanogenesis. However, we suspect this antibody cross-reacts with other MITF isoforms, because we commonly find nuclear reactivity in histiocytic cells, and a positive

reaction has been noted by others in tenosynovial giant cell tumors, giant cell tumors of bone, and a variety of other entities.^{30,32,38}

Reticulohistiocytoma (solitary epithelioid histiocytoma) has a wide age range and anatomic distribution.²⁹ It can bear some resemblance to neurothekeoma, because it presents as a superficial nodular mass and features plump epithelioid cells. However, the lesional cells have little tendency for packetted or whorled growth, and oftentimes, some of the cells will demonstrate peripheral cytoplasmic retraction with filopodialike extensions, a helpful clue to the diagnosis of histiocytic lesions, in general. Reticulohistiocytoma is a true histiocytic disorder with strong immunoreactivity for CD163 and CD68.

There are many recognized variants of fibrous histiocytoma,¹¹ but there are none with the characteristic growth pattern and histology detailed above for neurothekeoma. Most superficial fibrous histiocytomas form solid masses that are stromal mucin-poor. These lesions characteristically feature random storiform growth, and they often have a distinctly stellate-shaped interface with normal adjacent soft tissue.

Plexiform fibrohistiocytic tumor primarily affects children and young adults.^{17,23,34} It has a female predominance and occurs with greatest frequency in the upper and lower extremities. This entity does have some morphologic overlap with neurothekeoma, and it is only fair to point out that we have encountered rare tumors where we were unable to make a confident distinction between these 2 processes. It is notable that both tumor types feature spindled and epithelioid cells, both have a multinodular growth pattern, and both can have osteoclastlike giant cells. Unfortunately, there is only limited immunohistochemical data on plexiform fibrohistiocytic tumor, and it is unclear if its immunohistochemical “fingerprint” is clearly distinct from neurothekeoma. Therefore, the distinction between these tumors currently rests on morphology. As a general rule, plexiform fibrohistiocytic tumors tend to spare the upper dermis and they usually have greater subcutaneous involvement than neurothekeomas. They contain better defined, more elongate, tumor cell fascicles that feature spindled cells with more of a myofibroblastic flavor. Myxoid matrix is not a prominent component of plexiform fibrohistiocytic tumors, and these lesions generally lack the nuclear variability and occasional pleomorphism encountered in neurothekeomas. The distinction is clinically relevant, because plexiform fibrohistiocytic tumors are widely regarded as borderline neoplasms that, on rare occasion, have been documented to metastasize.^{17,34,36}

In summary, we have presented the clinical, histopathologic, and immunohistochemical findings for 178 neurothekeomas from 176 patients. Our data support previous conclusions that this entity is separate and distinct from true nerve sheath myxomas. The derivation of this tumor is unclear, but in our opinion, an origin from fibroblastlike cells seems most likely. Neurothekeomas have a peak incidence in the second decade of life; a

female predominance; a strong predilection for the head, upper extremities and shoulder girdles; and a low local recurrence rate. Atypical examples of neurothekeoma are underrepresented in the literature, and their clinical significance remains unclear. These latter tumors require further study; however, complete excision with follow-up should prove adequate in most, if not all, instances.

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