Modern Pathology (2014) 27, 701–710



# Cellular neurothekeoma: analysis of 37 cases emphasizing atypical histologic features

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**Cellular neurothekeoma is a frequent source of diagnostic difficulty. In order to gain more insight into the range of histologic features of cellular neurothekeoma, we examined all cases from our institution, with a focus on describing atypical histologic features. Cases with sufficient histologic material for evaluation were retrieved. Cases were analyzed for demographics, growth pattern, myxoid stroma, cytologic atypia, mitotic rate, perineural invasion, and other histologic features. The 37 patients (16 M; 21 F) had a mean age of 31.0 years (range: 4–89). Tumors involved the head and neck ($n=16$), arms ($n=11$), trunk and shoulders ($n=8$), and foot ($n=2$). All cases had at least focal nesting of epithelioid to spindled tumors cells characteristic of cellular neurothekeoma. In many, alternate growth patterns were present and represented the dominant pattern in some. These patterns included fascicular ($n=9$), sheet-like ($n=6$), and corded ($n=4$). Myxoid stroma was present in 14 and was prominent in 5. Cytologic atypia was present in 19 patients, with 3 having severe atypia. Mean mitotic rate was 2.0/mm$^2$ (range 0–10 per mm$^2$). Neurotropism was seen in four cases. Other unusual features included collagen trapping, giant cells, hemorrhage, lymphocytic cuffing, chondroid stroma, and cellular vacuolization. Cellular neurothekeoma has a wider range of features than is commonly recognized. The presence of nests of epithelioid tumor cells with characteristic cytologic features, no matter how focal, is a clue to the diagnosis.**
*Modern Pathology* (2014) **27,** 701–710; doi:10.1038/modpathol.2013.190; published online 1 November 2013

**Keywords:** atypical cellular neurothekeoma; cellular neurothekeoma; immunohistochemistry

Cellular neurothekeoma, formerly considered a nerve sheath tumor, is a dermal neoplasm of presumed fibrohistiocytic lineage.[1–3] They typically occur on the head, neck, and upper body of young adults, with a slight female predominance.[2–4] The classic histology of cellular neurothekeoma is of a dermal-based lesion with a lobular growth pattern that forms nests with a swirling to slightly fascicular growth pattern. The tumor cells are epithelioid to spindled with abundant pale eosinophilic cytoplasm, oval nuclei with pinpoint nucleoli. Although most cellular neurothekeomas display these characteristic histologic features, atypical features have been described, including prominent myxoid stroma, cytologic atypia, infiltrative growth, vascular invasion, perineural invasion, fascicular and plexiform growth patterns, and dense hyalinized stroma.[3–9] When atypical features are present, the diagnosis of cellular neurothekeoma can be challenging. For this reason, cellular neurothekeoma with atypical features is a relatively frequent source of referral to our consultation practice. In order to gain more insight into the range of histologic features of cellular neurothekeoma, we examined a large series from our practice with a focus on describing unusual features.

## Materials and methods

We retrieved all cases of cellular neurothekeoma from 1980 to 2012 with sufficient histologic material. We recorded the demographic features and reviewed all slides including H&E-stained sections and immunohistochemical stains. Cases were analyzed for a variety of histologic features such as growth pattern, presence of myxoid stroma, cytologic atypia, mitotic rate, perineural invasion, and vascular invasion. The degree of myxoid stoma was classified as absent, mild (10–25%), or prominent (>25%) The cytologic atypia and pleomorphism were classified as mild, moderate, or severe. Mitotic rate was calculated using the hot spot method per square millimeter similar to the technique employed in the evaluation

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Received 22 July 2013; revised 30 August 2013; accepted 1 September 2013; published online 1 November 2013

of melanomas. Any other atypical features were noted. Results of the immunohistochemical stains were abstracted from reports and, when available, re-reviewed. Reviewed immunohistochemical stains were scored as negative (<5% positivity), weakly positive (5–25% positivity), or positive (>25% positivity).

## Results

After cases with insufficient material were excluded, 37 cases met selection criteria. The tumors were more common in young adults with a mean age of 31 years (range 4–89 years). Similar with previous studies, there was a slight female predominance with a M/F ratio of 1:1.3. The tumors involved the head and neck ($n=16$), arms ($n=9$), trunk and shoulders ($n=9$), foot ($n=2$), and hand ($n=1$). The clinical parameters are summarized in Table 1.

Histologically, all of the cases examined had at least focal areas of classic cellular neurothekeoma morphology with nests or bundles of epithelioid to spindled cells with oval nuclei and pinpoint nucleoli (Figures 1a and b). Although some cases had somewhat infiltrative edges, all were relatively well circumscribed. None had an extensively infiltrative or plexiform growth pattern. Twenty-three of the cases had areas with alternate growth patterns. In nine of the cases, the tumor had areas forming longer fascicles of spindled cells giving the tumor areas resembling cellular benign fibrous histiocytoma (Figure 1c). Further reminiscent of benign fibrous histiocytoma, nine cases had prominent collagen trapping (Figure 1d). Six of the cases demonstrated areas of little intervening collagen giving the tumor a sheet like growth pattern (Figure 2a). Four of the cases had at least some areas consistent with a desmoplastic cellular neurothekeoma with dense hyalinized collagen (Figure 2b). In the desmoplastic cellular neurothekeomas, some had a nested to cord-like arrangement of the tumor cells and myxohyaline stroma reminiscent of a myoepithelial tumor (Figure 2c). Two cases had small nests imparting a nevoid appearance at low power (Figure 2d).

Myxoid stroma was present in 14 cases. Of these cases, 11 had mildly increased myxoid stroma and 5 had prominent myxoid stroma. In most of the cases with myxoid stroma, the tumor cells still maintained a vaguely nested pattern reminiscent of cellular neurothekeoma (Figure 2e). In two cases with marked myxoid stroma, the tumor cells predominantly had a random arrangement to the individual tumor cells (Figure 2f). Focal nests of more conventional cellular neurothekeoma were, however, invariably present even in the most myxoid cases.

Perineural invasion/neurotropism was present in four cases (Figure 3a). The cases with perineural invasion were predominantly nested with two cases having focal fascicular growth. Two of the cases had a markedly myxoid stroma and one had mildly myxoid stroma. No case with perineural invasion had more than mild cytologic atypia, and they had low mitotic rates. None of the cases displayed vascular invasion.

Multinucleated cells and osteoclastic giant cells were present in two cases. In both of these cases, there was evidence of hemorrhage or hemosiderin deposition (Figure 3b).

In four cases, there were areas where the tumor cells had vacuolated cytoplasm imparting a xanthomatous appearance to the tumor cells (Figure 3c). In one case, the tumor cells had a pseudo-granulomatous appearance somewhat reminiscent of sarcoidosis (Figure 3d). A cuff of lymphocytes was variably present around tumor nests in two cases (Figure 3e).

Cytologic atypia was mild in 19 cases with moderate and severe cytologic atypia being present in 15 and 3 cases, respectively, with tumor cells that had enlarged hyperchromatic nuclei. The atypical cells were admixed within a background of more conventional appearing tumor cells (Figure 3f).

**Table 1** Clinical features

| *Case* | *Age, years* | *Sex* | *Location* |
|---|---|---|---|
| 1 | 9 | F | Face |
| 2 | 17 | M | Arm |
| 3 | 15 | M | Shoulder |
| 4 | 89 | F | Face |
| 5 | 9 | M | Foot |
| 6 | 23 | F | Face |
| 7 | 10 | M | Arm |
| 8 | 13 | M | Scapula |
| 9 | 29 | F | Face |
| 10 | 47 | F | Upper back |
| 11 | 72 | F | Hand |
| 12 | 37 | F | Arm |
| 13 | 15 | M | Face |
| 14 | 53 | F | Face |
| 15 | 39 | M | Face |
| 16 | 9 | F | Scalp |
| 17 | 48 | F | Axilla |
| 18 | 47 | F | Arm |
| 19 | 20 | M | Upper back |
| 20 | 47 | F | Arm |
| 21 | 14 | F | Shoulder |
| 22 | 12 | F | Middle back |
| 23 | 32 | M | Scalp |
| 24 | 52 | F | Face |
| 25 | 43 | M | Ear |
| 26 | 9 | F | Chest |
| 27 | 17 | F | Arm |
| 28 | 11 | M | Face |
| 29 | 43 | M | Face |
| 30 | 23 | F | Arm |
| 31 | 81 | M | Arm |
| 32 | 19 | M | Face |
| 33 | 53 | M | Face |
| 34 | 25 | M | Shoulder |
| 35 | 4 | F | Scalp |
| 36 | 31 | F | Foot |
| 37 | 30 | F | Arm |

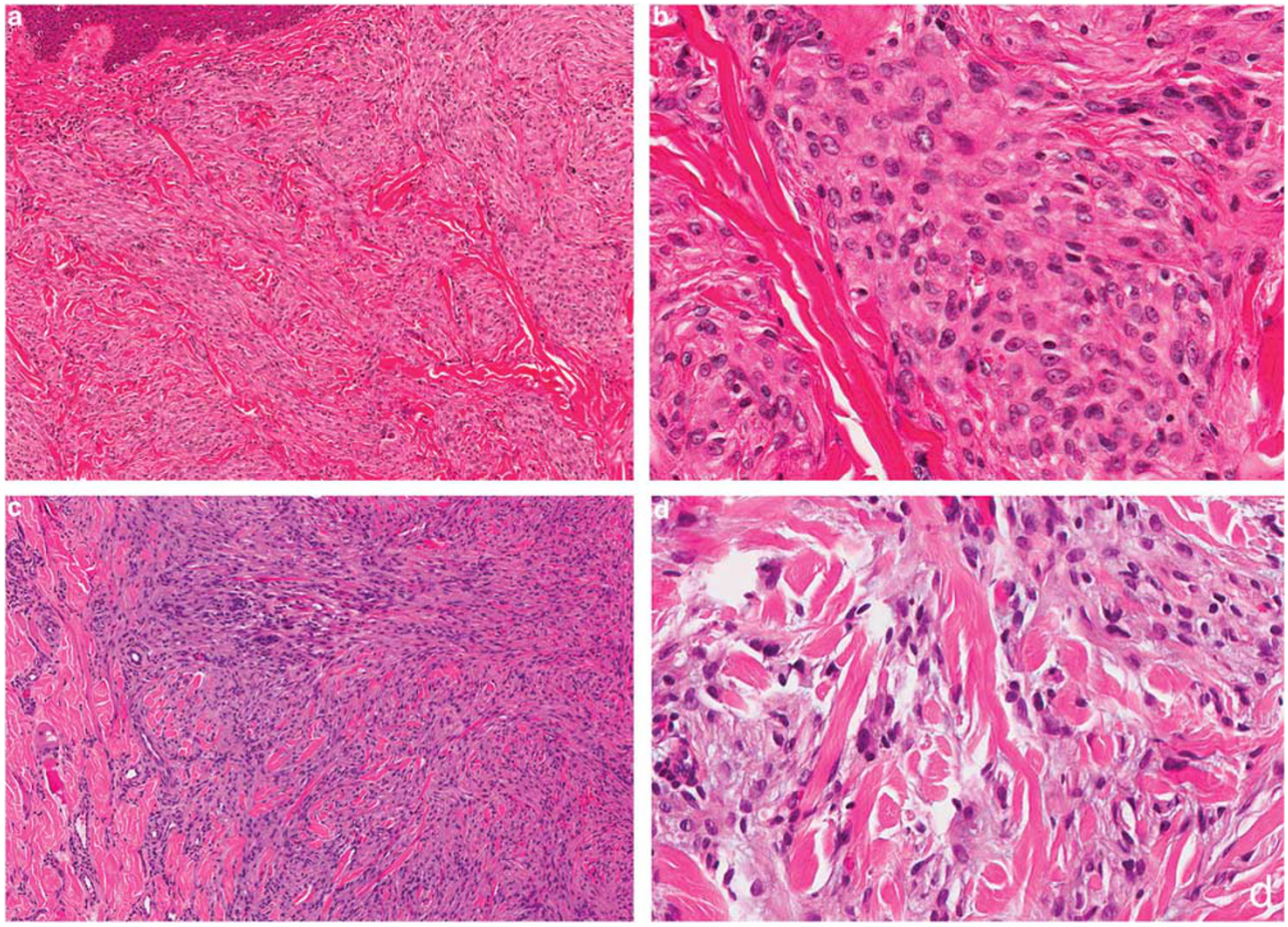

**Figure 1** (**a**) This cellular neurothekeoma had the classic nested growth pattern. (**b**) The tumor cells had an epithelioid appearance with relatively abundant cytoplasm with an open nuclear chromatin pattern and pinpoint nucleoli. (**c**) Fourteen cases had a prominent fascicular growth pattern. In this case, the tumor was reminiscent of a cellular benign fibrous histiocytoma. (**d**) In many cases, the tumor cells interdigitated around pre-existing collagen bundles of the reticular dermis (collagen trapping) similar to dermatofibromas.

The mitotic rate ranged from 0 to 10 mitotic figures per $mm^2$ with a mean mitotic rate of $2/mm^2$. In general, the cases clustered into two groups those that had little to no mitotic figures and those with significant numbers of mitotic figures ($\geq 5$ mitotic figures/$mm^2$; Figure 4a). Atypical mitotic figures were also identified in one case (Figure 4b). The case with atypical mitotic figures had moderate to focally severe cytologic atypia but also areas more resembling a conventual cellular neurothekeoma. Cases with atypia tended to have a higher mitotic rate than cases with only mild atypia, although there was overlap.

Several cases had a combination of the above histologic features (Table 2). All of the tumors invariably had at least focal areas of the more typical nested pattern of cellular neurothekeoma.

All of the cases in which NKIC3 immunohistochemical stains were performed ($n=34$) were positive (Figure 4c), with only one case demonstrating weak immunoreactivity. CD10 was strongly positive in a 29 of 30 cases in which it was performed (Figure 4d). The one CD10-negative case had areas of classic morphologic features of cellular neurothekeoma. Positive immunoreactivity for MiTF was seen in 2/3 (67%) cases. Immunoreactivity for CD68 was seen in 6/13 (46%). Staining for smooth muscle actin was performed on 14 cases and was negative in all but 1 case. Immunohistochemical stains for S100 protein were negative in all 34 cases in which it was performed.

## Discussion

Neurothekeomas were first described by Harkin and Reed in 1969 under the name nerve sheath myxoma.[10] They were then reclassified under the name neurothekeoma by Gallager and Helwig in 1980.[11] It was noted that lesions classified under this name had a varied histologic appearance, leading some to separate the lesions info myxoid, mixed, and cellular lesions.[12] This was understandable given the morphologic overlap. Fetsch *et al* posited in 2005 that these were in fact two separate entities: dermal nerve sheath myxoma, a true nerve sheath tumor,

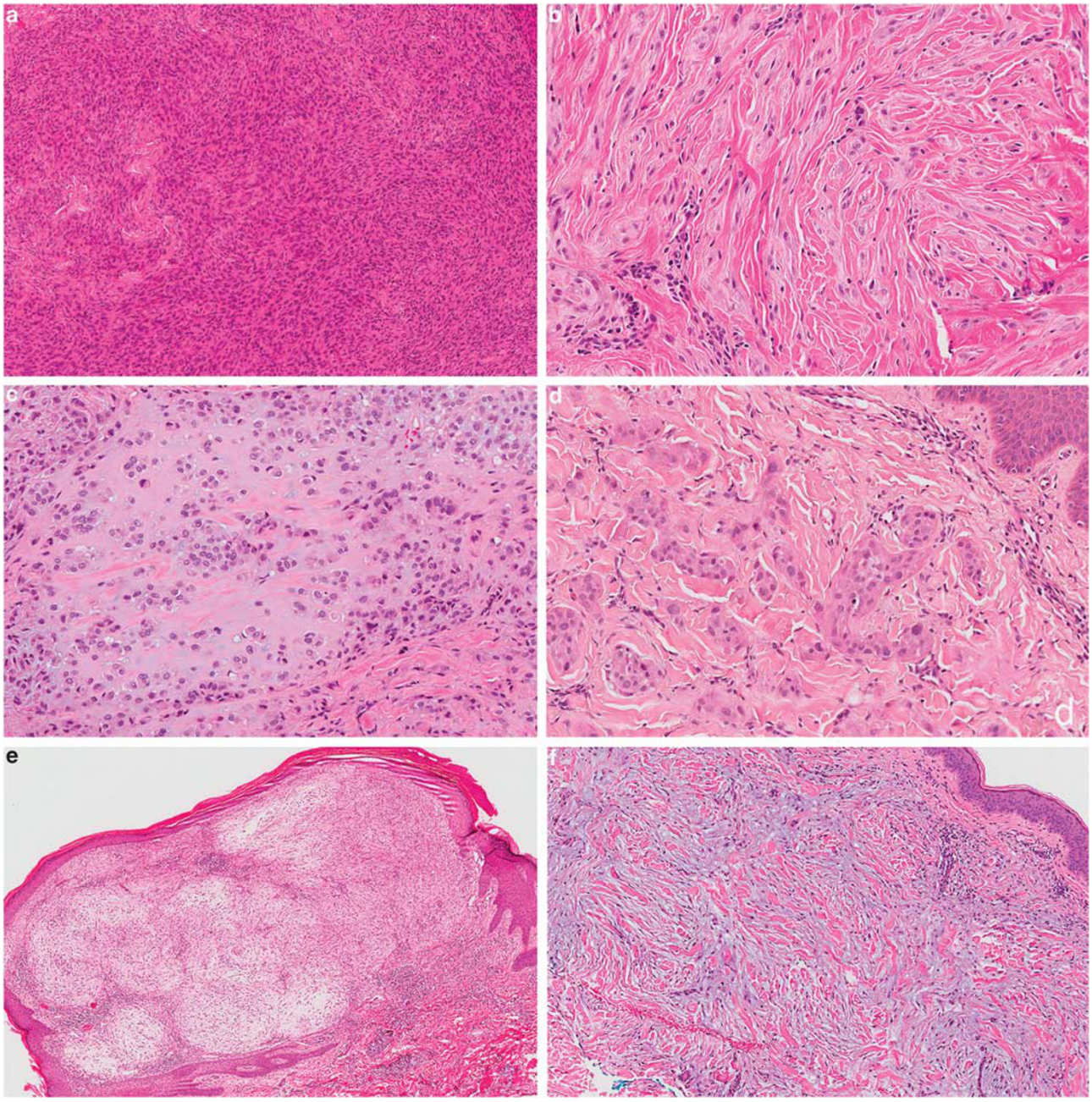


**Figure 2** (**a**) In six cases, there were areas with a confluent sheet-like growth pattern. (**b**) Four cases had features of desmoplastic cellular neurothekeoma with elongated nests and short fascicles embedded in a hyalinized collagenous stroma. (**c**) In this tumor, the tumor cells were arranged in cords and small nests with a myxohyaline chondroid stroma resembling a myoepithelial tumor. (**d**) Two cases had small nevus-like nests of tumor cells. (**e**) Myxoid stroma was present in many cases. In this case with abundant myxoid stroma, a swirling vaguely nested pattern is still evident. (**f**) In this case with abundant myxoid stroma, the tumor largely consisted of randomly arranged bland spindled cells.

and cellular neurothekeoma, a likely fibrohistocytic neoplasm.[13] The myxoid variants differed from cellular neurothekeoma by their distinct septated growth pattern, prominent myxoid stroma and expression of S100 protein and GFAP. This distinction has been supported by other immunohistochemical and ultrastructural evidence.[14] Cellular neurothekeoma consistently lacks expression of nerve sheath markers such as S100 protein[2,12] and ultrastructural examination has not demonstrated evidence of nerve sheath differentiation by electron microscopy.[1,15] Some authors have suggested that cellular neurothekeoma has nerve sheath differentiation by virtue of expression of PGP9.5,[16] but this is completely nonspecific, as a wide range of tumors express this ubiquitin-related hydratase.[17] The evidence that cellular neurothekeoma is most likely not a true nerve sheath tumor underlines the

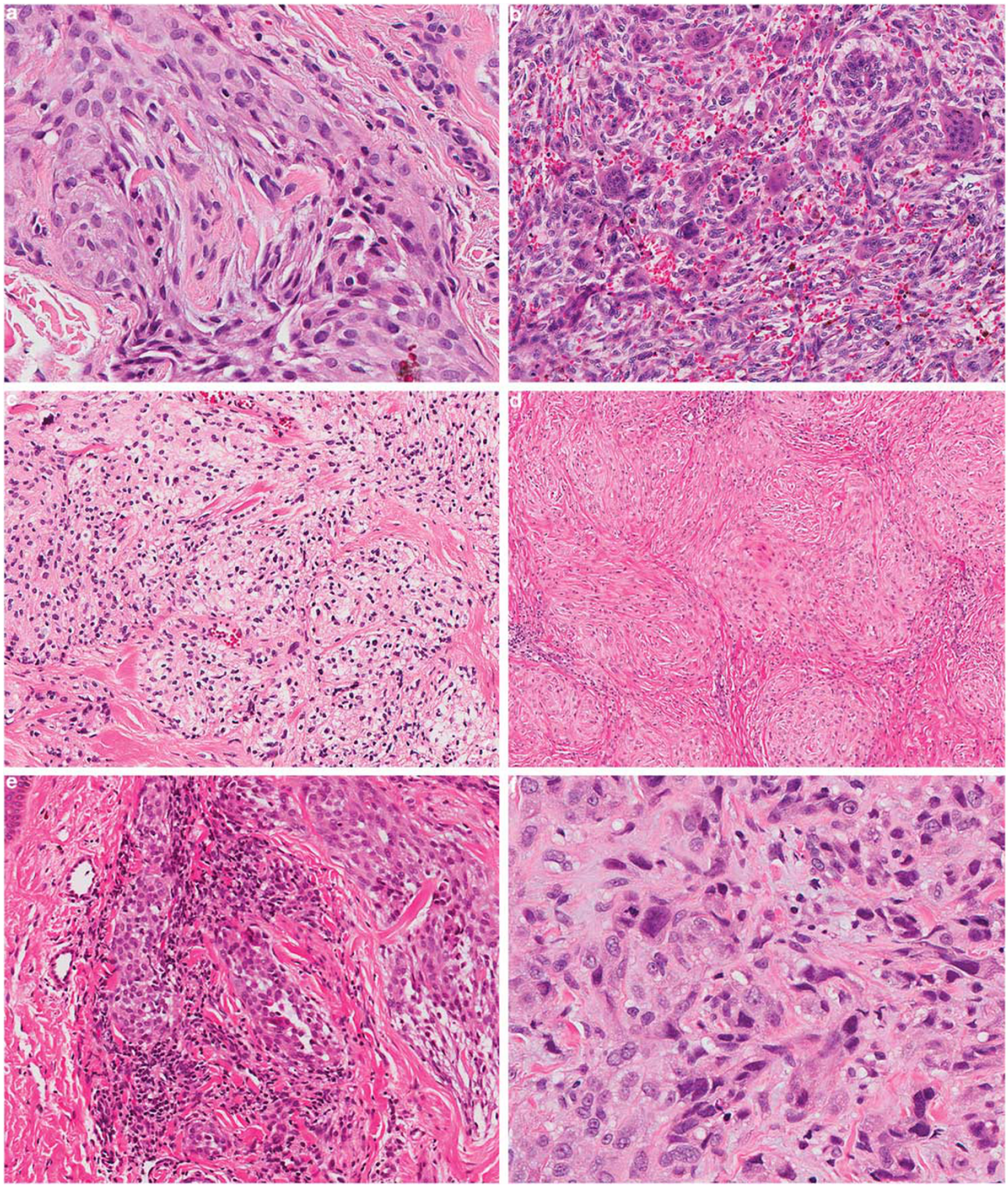

**Figure 3** (**a**) Perineural invasion was present in four cases. (**b**) Hemorrhage and osteoclast-like giant cells were present in two cases reminiscent of plexiform fibrohistiocytic tumor. Neither case had fibromatosis-like fascicles or a plexiform growth pattern. (**c**) In four cases, the tumor had vacuolated cytoplasm imparting a xanthomatous appearance to the tumor nests. (**d**) In one case, the tumor nests consisted of aggregates of eosinophilic cells with a scant lymphocytic cuff resembling sarcoidosis. (**e**) In another case, many of the tumor nests were surrounded by a relatively prominent lymphocytic cuff. (**f**) Moderate-to-severe cytologic atypia was present in 18 cases. In this case, pleomorphic and hyperchromatic atypical cells are admixed with more typical tumor cells of cellular neurothekeoma.

principle that morphologic overlap does not always equate with true relationship. In terms of nomenclature, we have come full circle. In the current WHO classification, dermal nerve sheath myxoma is now the preferred term to avoid confusion with cellular neurothekeoma.[18]

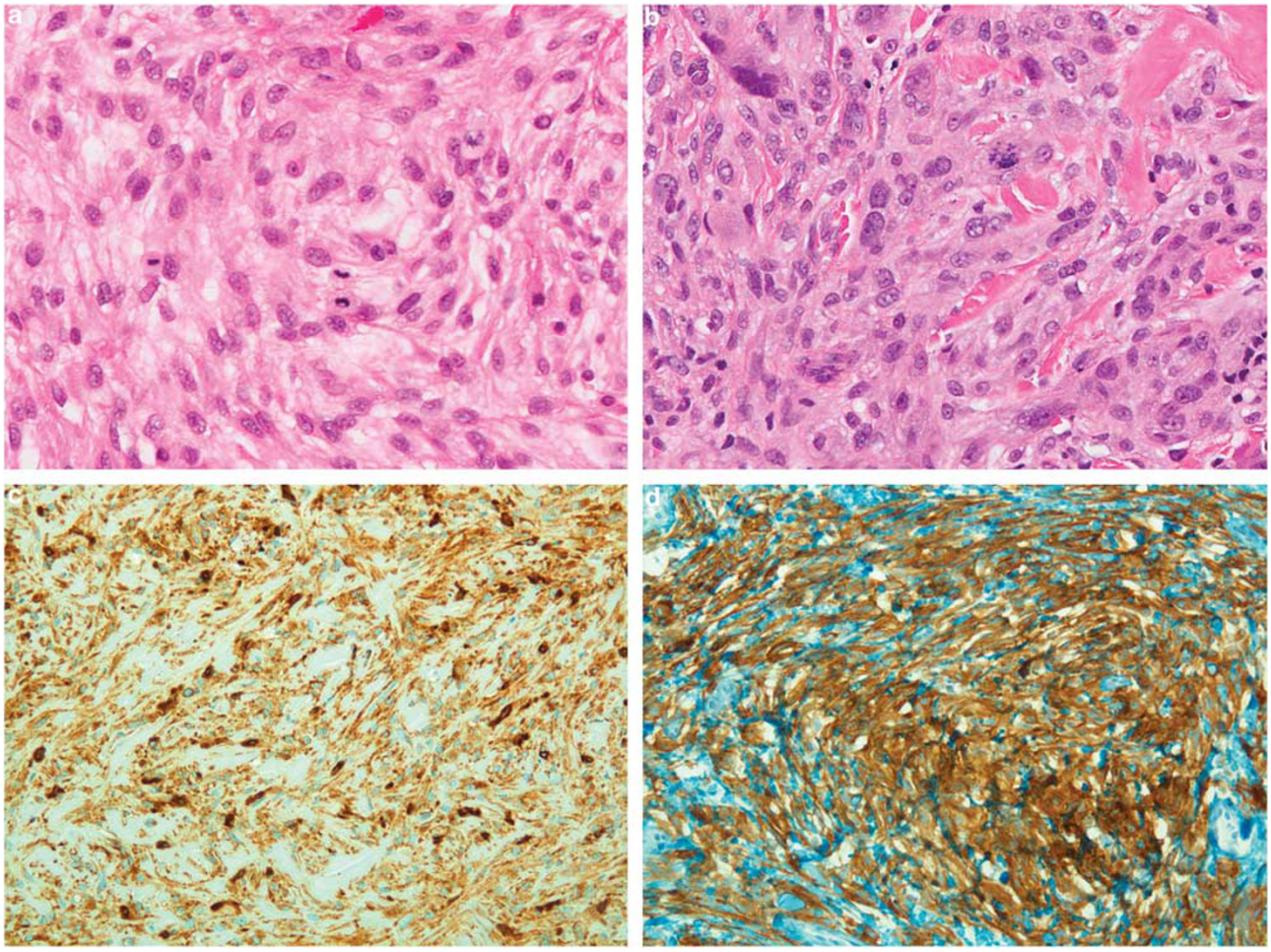

**Figure 4** (**a**) Mitotic figures were identified in most cases. This image is from a typical cellular neurothekeoma. (**b**) One of the cases with prominent cytologic atypia had a rare atypical mitotic figure. (**c**) All of the cases were immunoreactive for NKI-C3. (**d**) With the exception of one case, all were positive for CD10.

The true nature of cellular neurothekeoma remains elusive. There have been many theories regarding the histogenesis of these lesions with authors regarding them as variants of dermatofibromas, leiomyomas, or nerve sheath tumors.[19–22] It has been noted that cellular neurothekeoma can resemble a melanocytic tumor by virtue of its growth pattern, but lack of expression of S100 protein was against a melanocytic origin.[12,22] It is reasonable to classify cellular neurothekeoma as fibrohistiocytic tumors, as suggested by Fetsch *et al*,[3] although this category is itself somewhat of a wastebasket term.

Regardless of the nosological debate, cellular neurothekeoma remains an entity fraught with diagnostic difficulty. Underscoring this difficulty is that in the majority of cases in this series, cellular neurothekeoma was not considered by the referring dermatopathologists/pathologists. This is not a reflection of diagnostic acumen but that cellular neurothekeoma has a greater degree of histologic plasticity than is widely appreciated.

Classically, cellular neurothekeoma is a usually relatively circumscribed, lobular tumor centered in the dermis. In some cases, the periphery of the tumor may have an infiltrative border. In lesions on the face this may result in the tumor infiltrating into underlying skeletal muscle. It is typically composed of nests of epithelioid to slightly spindled tumor cells that often have a subtle whorling pattern. The tumor cells have relatively abundant eosinophilic cytoplasm and round to oval nuclei with small pinpoint nucleoli.

By immunohistochemistry, cellular neurothekeoma is positive for the combination of NKI-C3 and CD10 in almost all cases.[2,3,5,23,24] In our series, all of the cases tested were at least focally positive for NKI-C3 and 29/30 (97%) were positive for CD10. This parallels what has been previously reported in the literature. Immunoreactivity for these antibodies may be positive in a number of other lesions, so they must be interpreted in the correct histologic context.[24] In our opinion, it is the combination of immunoreactivity for both of these markers is most helpful. Immunoreactivity for S100A6 has also been reported to have the same degree of sensitivity in cellular neurothekeoma.[25–28] Other antibodies are

**Table 2** Summary of histologic features

| Case | MFS/ mm$^2$ | Atypia | Myxoid stroma | Unusual features | NKI-C3 | CD10 | Other stains |
|---|---|---|---|---|---|---|---|
| 1 | 0 | Mild | 1+ | Lymphocytic cuffing | NP | NP | S100 − |
| 2 | 8 | Mild | 2+ | Xanthoma-like areas | NP | NP | S100 − |
| 3 | 2 | Moderate | 0 | None | NP | NP | S100 − , SMA − |
| 4 | 0 | Mild | 0 | Xanthoma-like areas | + | NP | S100 − |
| 5 | 1 | Mild | 1+ | Pseudonevoid pattern | + | NP | S100 − , SMA + |
| 6 | 2 | Mild | 1+ | Perineural invasion | + | NP | S100 − |
| 7 | 8 | Mild | 0 | Sheet-like pattern, xanthoma-like areas | + | + | NP |
| 8 | 1 | Moderate | 0 | None | + | + | S100 − |
| 9 | 2 | Mild | 0 | Sheet-like, giant cells and hemorrhage | + | + | S100 − |
| 10 | 0 | Mild | 0 | None | + | NP | S100 − , SMA − |
| 11 | 0 | Moderate | 1+ | Sheet-like, fascicles | + | − | S100 − , CD68 − |
| 12 | 6 | Severe | 1+ | Giant cells and hemorrhage | + | + | S100 − , SMA − |
| 13 | 8 | Moderate | 0 | Sheet-like, corded | + | + | S100 − , SMA − |
| 14 | 1 | Moderate | 0 | Fascicular, xanthoma-like areas | + | + | S100 − , CD68 + |
| 15 | 0 | Mild | 0 | Sarcoid like, lymphocytic cuffing | + | + | S100 − |
| 16 | 1 | Moderate | 0 | Corded, chondroid stroma | + | + | S100 − |
| 17 | 3 | Moderate | 2+ | Sheet-like, fascicles, collagen trapping | + | + | S100 − |
| 18 | 1 | Mild | 1+ | Fascicles, collagen trapping | + | + | S100 − , SMA − |
| 19 | 1 | Mild | 0 | Fascicles, collagen trapping | + | + | S100 − , SMA − , CD68 − |
| 20 | 0 | Moderate | 1+ | Collagen trapping | + | + | CD68 − |
| 21 | 0 | Mild | 2+ | Fascicles, perineural invasion | + | + | S100 − , CD68 − |
| 22 | 3 | Mild | 0 | Fascicles, collagen trapping | + | + | S100 − , SMA − , CD68 − , MiTF − |
| 23 | 1 | Moderate | 0 | Fascicles, collagen trapping | + | + | SMA − |
| 24 | 1 | Severe | 1+ | None | + | + | S100 − |
| 25 | 0 | Mild | 1+ | Fascicles | + | + | S100 − , SMA − , CD68 − |
| 26 | 0 | Mild | 2+ | Fascicles, perineural invasion | + | + | S100 − , SMA − |
| 27 | 2 | Moderate | 0 | Fascicles, collagen trapping | + | + | S100 − , CD68 + |
| 28 | 10 | Moderate | 0 | Fascicles, collagen trapping | + | + | S100 − |
| 29 | 0 | Mild | 0 | Corded | + | + | S100 − , CD68 − |
| 30 | 5 | Moderate | 0 | Corded | + | + | S100 − , SMA − , MiTF + |
| 31 | 0 | Mild | 0 | Sheet like | + | + | S100 − |
| 32 | 1 | Moderate | 0 | Fascicles, collagen trapping | + | + | S100 − , CD68 + |
| 33 | 0 | Mild | 0 | Pseudonevoid | + | + | S100 − , CD68 + , MiTF + |
| 34 | 0 | Moderate | 0 | Fascicles, melanophages | + | + | S100 − , SMA − |
| 35 | 0 | Mild | 2+ | Fascicles | + | + | S100 − , CD68 + |
| 36 | 2 | Moderate | 0 | Hemorrhage | + | + | S100 − |
| 37 | 3 | Severe | 0 | Perineural invasion | + | + | S100 − , CD68 + |

Abbreviation: NP, not performed.

variably helpful. Immunoreactivity for MiTF has been seen in 81–100% of cellular neurothekeoma.[23,29] In this series, two of three cases tested were positive for MiTF. Immunostains for CD68 are insufficiently sensitive, as just under half of the cases tested were positive (6/13). Immunoreactivity for smooth muscle actin has been reported in up to 57% cases,[2] but in our experience this is less common, being present in 1/14 cases in our series. PGP9.5 was once touted as a sensitive marker but lacks sufficient specificity to be useful.[16,17]

Prominent myxoid stroma is a finding that is uncommon in cellular neurothekeoma, generally present in <10% of cases.[2] This feature was somewhat more common in this series, present in five (14%) of our cases. In two of our cases, the myxoid stroma was so prominent that the nested growth pattern of cellular neurothekeoma was almost completely obscured, requiring very thorough examination in order not to miss the focus of more conventional appearing cellular neurothekeoma. The prominent myxoid stroma can cause confusion with dermal nerve sheath myxoma. Our cases with myxoid stroma lacked the fibrous septations and immunoreactivity for S100 protein characteristic of that entity.[13,18] Superficial angiomyxoma could also be considered, but this tumor lacks the nests of tumor cells seen in cellular neurothekeoma.[30] In cases with myxoid stroma and atypia, a myxofibrosarcoma could be considered in the differential diagnosis, but this tumor is centered in the subcutis rather than dermis and has a very infiltrative growth pattern.[18]

The cases of cellular neurothekeoma with a fascicular growth pattern and peripheral collagen trapping were reminiscent of the cellular benign fibrous histiocytoma variant of dermatofibroma. This histologic variant of cellular neurothekeoma has been previously described.[31] Similar to cellular neurothekeoma, cellular benign fibrous histiocytoma affects young adults, but with a slight male predominance.[32,33] In our opinion, the optimal method of distinguishing cellular neurothekeoma from cellular benign fibrous histiocytoma is to look for areas of classic cellular neurothekeoma. Although cellular neurothekeoma can occasionally exhibit

fascicular growth, high mitotic rate, and collagen trapping, similar to cellular benign fibrous histiocytoma, the reverse is not true; cellular benign fibrous histiocytoma does not display areas of nested growth typical of cellular neurothekeoma. Although there are histologic differences, the two entities show molecular overlap with upregulation of the same genes involved in extracellular matrix growth and remodeling, including dermatopontin (*DPT*), a disintegrin and metalloproteinase domain 12 (*ADAM12*), matrix metalloproteinase 1 (*MMP1*), and periston osteoblast-specific factor (*POSTN*).[34] This underscores the classification of cellular neurothekeoma as a so-called fibrohistiocytic tumor.

The cases that had tumor nodules with osteoclast-like giant cells and hemorrhage raise the differential diagnosis of plexiform fibrohistiocytic tumor. Indeed, these entities have significant histologic overlap, leading some authors to suggest that they may be the same entity.[35] Although it is tempting to lump these tumors together based on morphologic similarity, we consider this equivalent to the erroneous classification of cellular neurothekeoma and dermal nerve sheath myxoma as the same entity based on histologic overlap. None of our cases had a plexiform growth pattern that is a defining characteristic of plexiform fibrohistiocytic tumor. The biologic behavior of the two entities is distinctly different. In stark contrast to cellular neurothekeoma, which almost never recurs and essentially never metastasizes (even cases with atypical features), plexiform fibrohistiocytic tumor has a relatively high rate of local recurrence and at least a low risk of metastasis.[36–38] There are some immunophenotypic differences as well. Cellular neurothekeoma is also usually immunoreactive for MiTF and podoplanin, unlike plexiform fibrohistiocytic tumor.[29,39]

Perineural invasion is a feature present in four of our cases. This has been previously highlighted as a histologic feature that is occasionally encountered in this entity.[2,40] This underscores the fact that perineural invasion may be seen in benign entities. The biologic significance of this finding is entirely dependent on the context of the neoplasm displaying this feature.

As expected mitotic activity was generally low in our series. However, 6/37 (16%) were mitotically active with $\geq 5$ mitotic figures per $mm^2$ ($\geq 10$ mitotic figures/10 HPFs). Similar high mitotic rates have been reported in 5–14% of cases[2,3] One case had atypical mitotic figures, but atypical mitotic figures have been noted in up to 9% of cases.[3] Therefore, increased mitotic rates and atypical mitotic figures do not exclude cellular neurothekeoma from diagnostic consideration. Admittedly, a high mitotic rate or atypical mitotic figures should prompt careful scrutiny for typical features of cellular neurothekeoma before rendering the diagnosis.

Although cytologic atypia is not generally ascribed to cellular neurothekeoma, it is relatively common.[2,41–43] Significant cytologic atypia was seen in 9/37 (24%) cases with 1 case showing marked atypia and pleomorphism. This is in line with what has been previously reported, but cytologic atypia is still not widely recognized as a relatively common feature of cellular neurothekeoma.[2]

The presence of cytologic atypia or involvement of the distal extremities could prompt consideration of true sarcomas in the differential diagnosis. Epithelioid sarcoma has a nested growth pattern that can be similar to cellular neurothekeoma and, like cellular neurothekeoma, frequently presents in relatively young patients.[18,44–46] The distribution is different, as epithelioid sarcoma is distinctly more common in the distal extremities, although three of our cases presented on the distal extremities. The tumor nodules of epithelioid sarcoma often have necrosis, features not seen in our cases or other series of cellular neurothekeoma. Epithelioid sarcoma expresses cytokeratins, unlike cellular neurothekeoma, which readily allows for distinction.

In cases with marked pleomorphism, the diagnosis of atypical fibroxanthoma or a pleomorphic dermal sarcoma could be considered. These are less likely considerations as they are tumors that present on sun-damaged skin of the head and neck of elderly patients.[47] Immunostains have little role in the distinction from cellular neurothekeoma, as atypical fibroxanthoma can be positive for NKI-C3 and CD10.[48,49]

Finally, because of the nested growth pattern of cellular neurothekeoma, melanocytic tumors such as an intradermal Spitz nevus or metastatic melanoma could be considered in the differential diagnosis. It should be remembered that stains for NKI-C3 are positive in melanocytic tumors.[50] Unlike true melanocytic tumors, cellular neurothekeoma is negative for S100 protein and more melanocyte-specific markers such as Melan-A and HMB-45.

In conclusion, we have summarized our experience with cellular neurothekeoma. Although most cases of cellular neurothekeoma are relatively straightforward to diagnose, we have encountered a number of cases, primarily in consultation, with unusual features. Cellular neurothekeoma is a tumor with a broader spectrum of histologic features than is appreciated. Recognition of at least focal areas of more conventional cellular neurothekeoma, especially the nested growth pattern, allows for accurate diagnosis of cellular neurothekeoma with atypical features. Immunohistochemical stains for NKI-C3 and CD10 are useful ancillary tests for the diagnosis of cellular neurothekeoma but they need to be interpreted in a strict histologic context. As previously discussed, cellular neurothekeoma, even tumors with atypical features, are benign. The presence of atypical features does not appear to impact behavior. Therefore, recognition of this entity is important to avoid the pitfall of mislabeling a cellular neurothekeomas as something more sinister.

## Disclosure/conflict of interest

The authors declare no conflict of interest.

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