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Atypical cellular neurothekeoma: a case report with a novel *NF1* mutation

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Abstract

Atypical cellular neurothekeoma is a rare benign soft-tissue tumour that usually arises in the head and neck region, shoulder girdles, and proximal extremities, predominantly in young women. This dermal neoplasm is under-reported in the literature and is not uncommonly misdiagnosed as a malignant tumour due to its worrisome histologic characteristics. Currently, the diagnosis of cellular neurothekeoma relies on a panel of non-specific immunohistochemical markers and its etiopathogenesis is unknown.

Herein, we present the case of an atypical cellular neurothekeoma in the arm of a 49-year-old woman, describing its microscopic features and immunohistochemical profile. Additionally, we present a novel heterozygous predicted inactivating *NF1* mutation, not previously reported, which was identified using high-throughput molecular techniques. Such finding might provide insights into the pathogenesis of neurothekeoma, potentially contributing to future refinements in diagnosis, which would enable more precise identification of this neoplasm.

Keywords Atypical cellular neurothekeoma, Whole exome sequencing, NF1

Background

Neurothekeoma is a rare benign soft-tissue tumour that generally presents as a solitary, slow-growing, non-painful or mildly symptomatic dermal-based nodule. It preferentially arises in the head and neck region, shoulder girdles and proximal upper extremities. It mainly affects children and young adults with a median age at presentation in the second decade of life. A female predilection is noted, with a F: M ratio ranging from 1.8 to 4.3:1 in larger series [1–3].

From a pathologic standpoint, neurothekeomas are classified into myxoid, mixed and cellular variants, depending on the percentage of mucopolysaccharide extracellular matrix present within the tumour [1].

Since Gallanger and Helwing introduced the term neurothekeoma in 1980 [2], there was considerable debate in the past surrounding the relationship between the so-called myxoid variant of neurothekeoma and dermal nerve sheath myxoma [1, 4]. However, it is now clear-based on clinical, morphologic, immunohistochemistry, ultrastructural, and gene expression profiles- that they are different clinicopathological entities [1, 3–5]. However, the line of differentiation of neurothekeoma is a subject of debate and its etiopathogenesis is still unknown [1, 3, 4, 6–8].

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Rosati et al. [9] were the first to use the term "cellular neurothekeoma" (CNT). This variant of neurothekeoma is troublesome to diagnose because of its resemblance to other dermal tumours and absence of specific immunohistochemical or molecular diagnostic markers. Besides, a subset of CNT can exhibit atypical features, such as large tumour size, high mitotic rate, atypical mitotic figures, marked pleomorphism, infiltration of fat and skeletal muscle, and vascular invasion [1, 3, 10–22]. These worrisome features have not been shown to adversely impact the benign behaviour of CNT. Nonetheless, due to their rarity, the knowledge about prognosis and relevance of such atypical features might not be fully mature. Atypical cellular neurothekeomas (ACN) are not extensively represented in literature, which might lead to under-recognition. Their histologic appearance is worrying and sometimes mistaken for a *bona fide* malignant neoplasm, an incertitude that might carry potential therapeutic and prognosis implications for the patient.

Herein we present the clinical, histopathologic, immunohistochemical and molecular features of an ACN harbouring a novel heterozygous *NF1* mutation. We review the available literature, focusing on the clinical significance of atypical features. We search for previously reported associations with neurofibromatosis and, additionally, we discuss pertinent differential diagnoses.

Case presentation

Patient's information and clinical features

A 49-year-old female without relevant personal clinical, surgical, medication, or family history, presented with a three-year history of a slow-growing, non-painful nodule in the lateral aspect of her left arm, first noted in 2020. The patient referred that the mass originated at a previous vaccination site of an unknown covid-19 vaccine.

Based on the information contained in the medical referral form, the physical examination revealed a 2.5 cm, non-painful mass with intact overlying skin. The ultrasound showed a 1.5 cm, solid, round and well-circumscribed superficially located mass in the upper third of the left arm.

In October 2023, the patient underwent an excisional biopsy. Following an original diagnosis of high-grade sarcoma, the patient was referred to oncologic surgery in December 2023 and a review of the original histopathological diagnosis by a soft tissue pathologist was requested.

Results

Histopathology and immunohistochemistry

According to the original Pathology report, the tissue obtained by the excisional biopsy revealed a 2.5 cm soft, glistening, homogeneously white dermal nodule with intact overlying skin and scant subcutaneous tissue.

Histologically, the dermal neoplasm was circumscribed, non-encapsulated, and was separated from the non-involved epidermis by a Grenz zone. The subcutis was also spared (Fig. 1a).

The neoplasm exhibited a multinodular growth pattern, consisting of tightly disposed, small to medium-sized nodules, divided by collagen (Fig. 1b). Focally, the margins of the tumour infiltrated dermal collagen (Fig. 1c).

Most nodules were solid and hypercellular, composed of plump spindle and epithelioid cells with fairly large amounts of eosinophilic cytoplasm. The neoplastic cells were arranged primarily in a random or nested pattern with strands of hyaline collagen wrapped around either nests or individual cells (Fig. 1d). Focally, there was an intersecting or parallel fascicular growth pattern in which the cells were associated with a varied amount of sclerotic collagenous extracellular matrix (Fig. 1e-f). A minority of the nodules (<10%) had copious myxoid extracellular matrix and exhibited less cellularity, characterized by non-cohesive cells in a whorled pattern, displaying similar cytomorphology (Fig. 2a).

There was widespread nuclear atypia, characterized by nuclear enlargement, vesicular chromatin, and prominent nucleoli. Focal anisokaryosis was observed. The mitotic count was 9/10 HPF (1HPF=0.2 mm) and atypical mitotic figures were present (Fig. 2b-c). Tumour necrosis was absent. Occasional osteoclast-like giant cells were present and there were tumour infiltrating lymphocytes either individually or in interstitial aggregates (Fig. 2d).

The main differential diagnoses considered were a cellular neurothekeoma with atypical features and a melanocytic neoplasm. The neoplastic cells were strongly and diffusely positive for CD63/NKI-C3, NSE, CD10, and showed patchy positivity for MITF. The immunohistochemical profile, albeit unspecific, supported the morphologic diagnosis of atypical cellular neurothekeoma. The cells were also strongly and diffusely positive for TFE3, showed widespread positivity for ERG with varied intensity, and were focally and weakly positive for Cathepsin K. The cells were negative for CKAE1/AE3, S100, HMB45, MART1, SMA, desmin, CD34, GFAP, MUC4 and ALK. Nuclear staining for INI1 was retained. The results of immunohistochemistry are shown in Fig. 3; Table 1.

RNA-based targeted massive parallel sequencing

By RNA-based targeted massive parallel sequencing (MPS), no clinically significant variants were detected in the analysed genes. The tumour mutational burden (TMB) study reported 3.9 mutations/Mb (low TMB) and stable MSI (4.7% unstable sites).

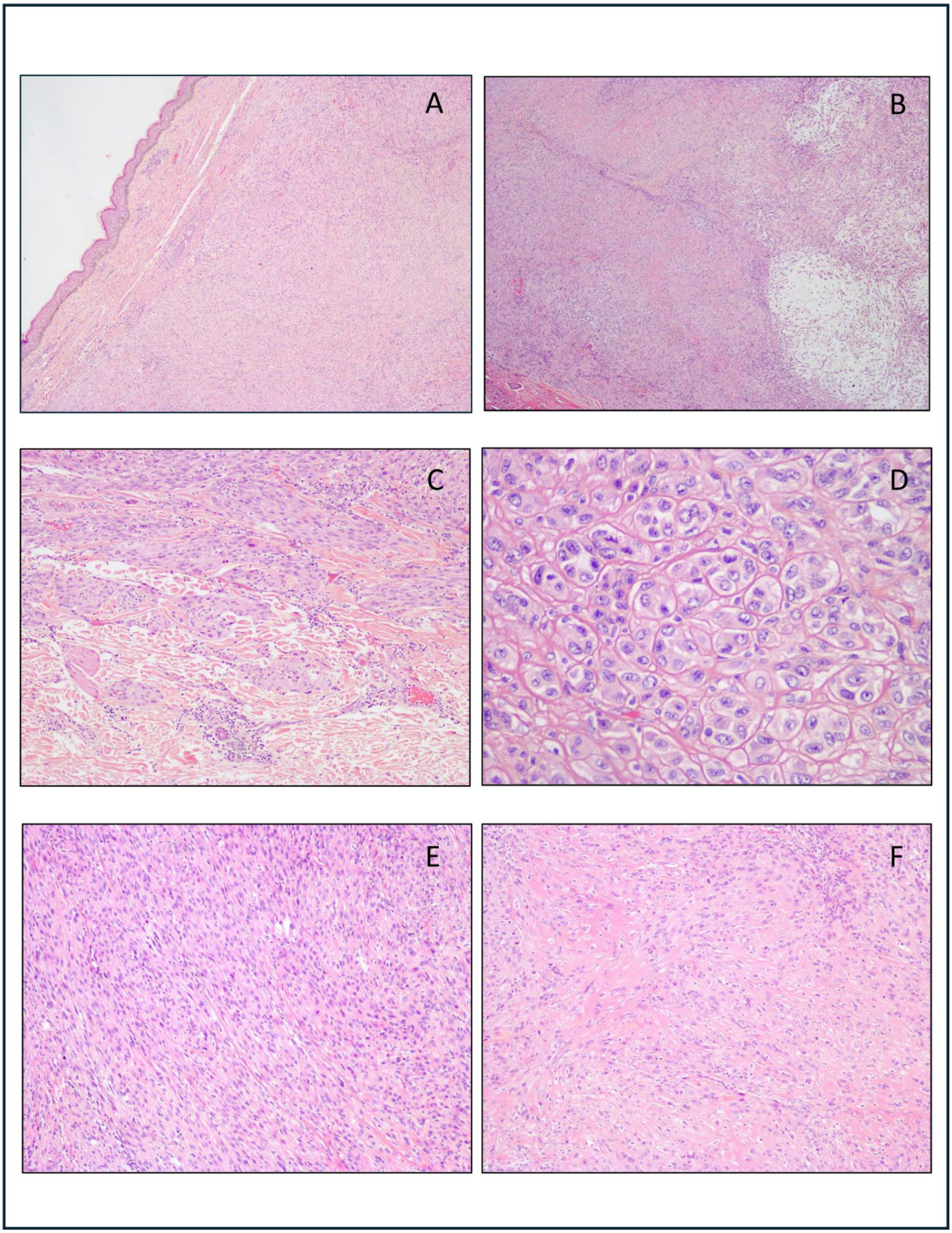

Fig. 1 Microscopic appearance of atypical cellular neurothekeoma. (**A**) Dermal tumour sparing overlaying skin by a "Grenz zone" (H&E; x40 magnification). (**B**) Multinodular growth pattern and biphasic appearance (H&E; x40 magnification). (**C**) Focally infiltrative margins dissecting dermal collagen (H&E; x100 magnification). (**D**) Bright collagen strands separating nests and single tumour cells (H&E; x400 magnification). **E**-**F**) Hypercellular nodules showing fascicular growth pattern of spindled and epithelioid cells in a variably collagenous background (H&E; x100 magnification)

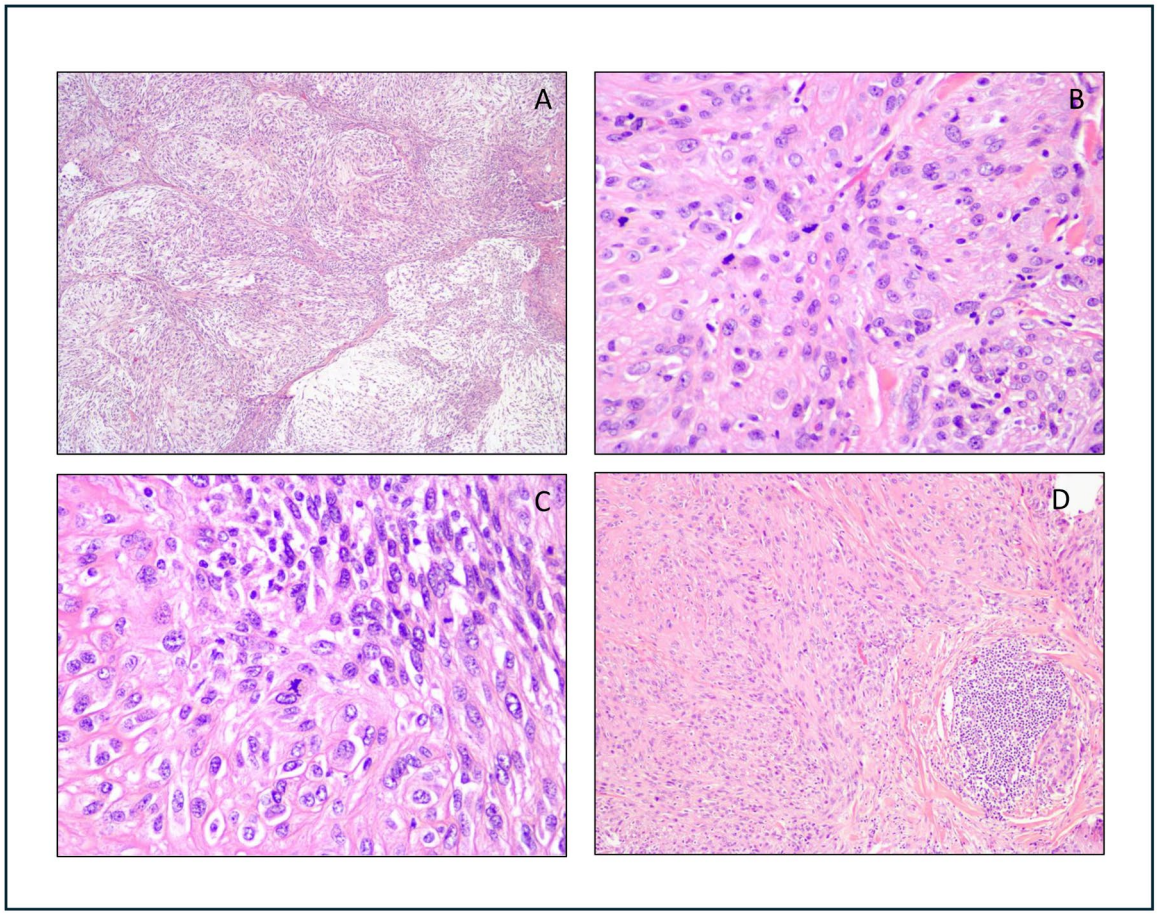

Fig. 2 Microscopic appearance of atypical cellular neurothekeoma. (**A**) Myxoid nodules of the tumour (H&E, x40 magnification). (**B**) Moderate cytologic atypia, nuclear pleomorphism and increased numbers of mitotic figures (H&E, x400 magnification). (**C**) Atypical mitotic figures were sporadically present (H&E, x400 magnification). (**D**) Interstitial aggregates of lymphocytes (H&E; x100 magnification)

Whole exome sequencing

To further characterize this lesion, whole exome sequencing (WES) of tumour tissue was performed. Clinical WES analysis identified that the tumour was heterozygous for the duplication variant, c.4333-2dup, which lies in the essential splice acceptor site, in intron 32 of *NF1* (data available at the NCBI-SRA accession number SRR31203095).

Follow up and outcomes

The patient was alive and disease-free at last follow-up, twelve months after the excision.

Discussion and conclusions

Cellular neurothekeomas (CNT) are benign tumours that can rarely recur locally in a non-destructive fashion after incomplete excision. No events of metastases have been documented in literature. In Hornick et al.'s series on CNT [3], 10 out of 69 tumours (14.5%) with available follow-up information (mean follow-up: 44 months) recurred once after a mean interval of 18 months. All the tumours that recurred had been marginally excised or had intralesional excisions. In Fetsch et al.'s series [1], eight out of 71 tumours (11.3%) with complete follow-up information (median follow-up: 207 months) recurred between four and 48 months from primary surgery. A variety of atypical histologic features are known to occur in cellular neurothekeomas [1, 3, 10–22]. In neither series did atypical features correlate with recurrence. However, research focused on the implications of atypical histologic features in ACN is limited, thus the clinical relevance of such characteristics may not be asserted. Despite there being no known instances of neurothekeoma with atypical features behaving in a low-grade malignant manner, the possibility cannot be entirely ruled out due to the rarity of adverse outcomes in similar soft tissue tumours with low metastatic rates [1]. Importantly, the definitions of the parameters that characterise a neurothekeoma as having "atypical features"- such atypia, pleomorphism,

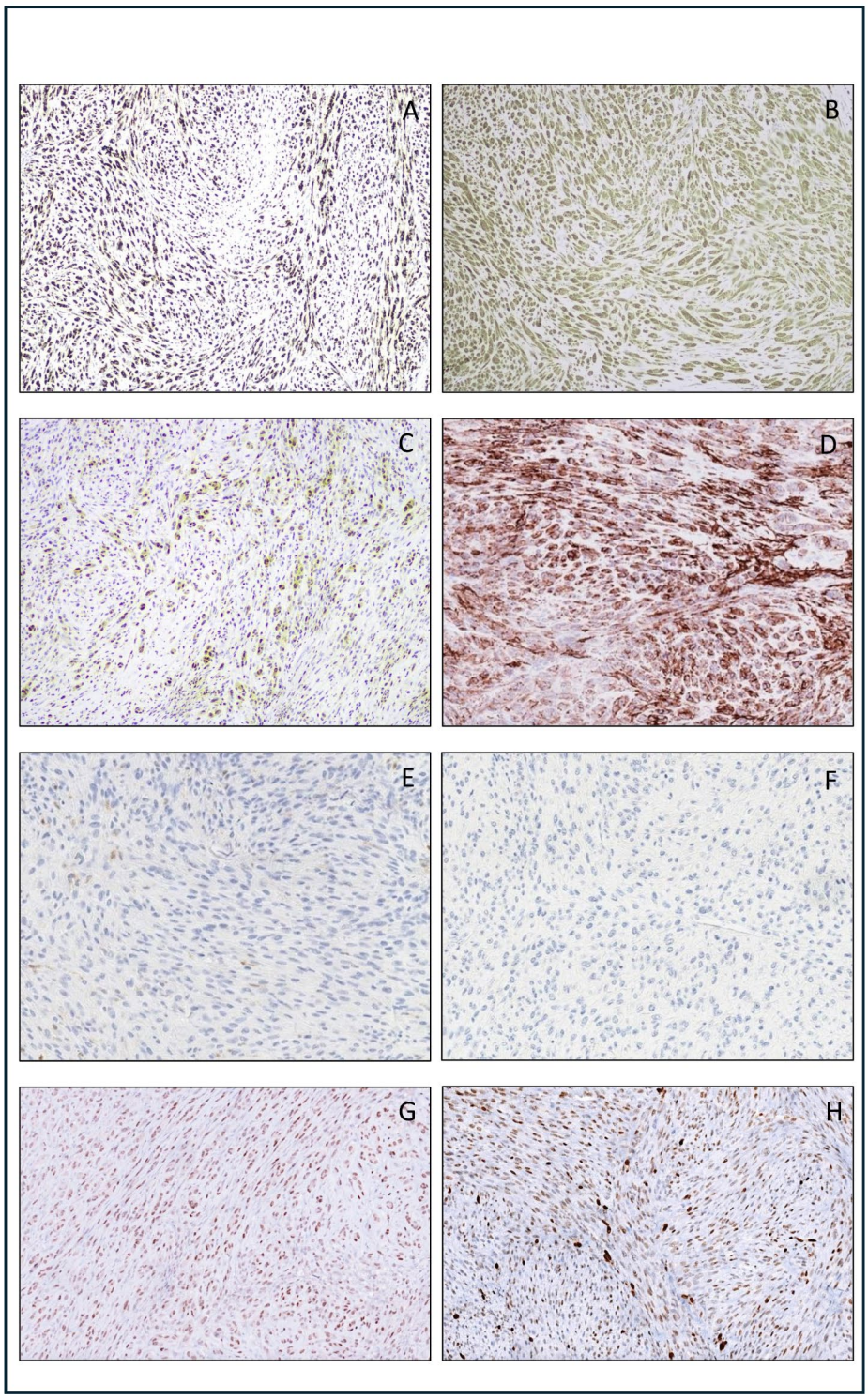

Fig. 3 Immunohistochemical features of the tumour. The tumor cells showed strong positivity for (**A**) CD63/NKI-C3 (x100 magnification), (**B**) NSE (x100 magnification), (**C**) MITF (x100 magnification) and (**D**) CD10 (x100 magnification). They were negative for (**E**) S100 (x200 magnification and **F**) MART1 (x200 magnification). Tumor cells were also positive for **G**) TFE3 (x100 magnification) and **H**) ERG (x100 magnification)

Table 1 Methods and results of immunohistochemistry

Antibody	Source	Dilution/pH/antigen retrieval	Detection method	Result
CD63/NKI-C3	Ventana/Roche	RTU/High pH/97°C/20 min	Polymer-based	+
MUC4	Vitro Master Diagnóstica	RTU/High pH/97°C/20 min	Polymer-based	-
GFAP	Ventana/Roche	RTU/High pH/100°C/20 min	Polymer-based	-
MITF	Dako/Agilent	1:15/High pH/97°C/20 min	Polymer-based	+
CD34	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	-
NSE	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	+
INI-1	Ventana/Roche	RTU/High pH/100°C/20 min	Polymer-based	Retained
SMA	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	-
TFE3	Ventana/Roche	RTU/High pH/100°C/20 min	Polymer-based	+
CD10	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	+
ERG	Ventana/Roche	RTU/High pH/100°C/20 min	SA/Bi	+
CK AE1/AE3	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	-
HMB45	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	-
Melan A (A103)	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	-
Desmina	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	-
S100	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	-
Cathepsin K (CK4)	Novocastra	RTU/Low pH/ Heat-induced/ 30 min	Polymer-based	+/-
ALK (CD246)	Dako/Agilent	RTU/High pH/97°C/20 min	Polymer-based	-

Ventana Medical Systems, Tucson, United States of America; Vitro S.A., Granada, Spain; Agilent Pathology Solutions, California, United States of America; Novocastra, Newcastle, United Kingdom; RTU: ready-to-use/prediluted; SA/Bi: streptavidin/biotin method

Table 2 Definition of atypical features in neurothekeomas

Author	Atypical features and definitions			Outcome*
	Pleomorphism/atypia	High mitotic rate	Large tumour size	
Busam et al. 1998 (*N* = 10)	Marked cytologic pleomorphism (descriptive)	Not specified	> 1.0 cm	7/7 NED (Mean FU: 27 months)
Fetsch et al. 2007 (*N* = 178)	Generalized moderate or focally marked atypia (descriptive)	> 10 / 25 WHPF (field area: 0.237 mm2)	NC	63/71 NED 8/71 NED ASLR (Median FU: 207 months)
Hornick et al. 2007 (*N* = 73)	Pleomorphism (descriptive)	≥ 5 / 10 HPF (field area: 0.25 mm2)	≥ 2.0 cm	59/69 NED 10/ 69 NED ASLR (Mean FU: 44 months)

N: Number of cases; NC: not considered; HPF: high power field; WHPF: wide high–power field; NED: No evidence of disease; NED ASLR: No evidence of disease after single local recurrence; FU: follow–up. * Denominators refer to number of patients with available follow–up

size and mitotic count- are heterogeneous and subjective across the literature (Table 2).

Other worrisome findings seldom described in neurothekeomas are intravascular invasion [3, 10], neurotropism [3, 18, 22], atypical mitosis [1, 3, 20–22], and necrosis [11, 15]. Additionally, although infiltration to subcutis is considered an atypical feature, its relatively common appearance ranging from 25 to 67% in the larger series [1, 3, 10] might even suggest that subcutaneous involvement may be typical for neurothekeoma.

Beyond the considerations above, the widespread atypia, the high mitotic count (9/10 HPF) including atypical ones and the relatively large size (2.5 cm) of the case presented here, renders this neurothekeoma "atypical" based on the definitions proposed.

Clinically, the patient was older than the mean age of presentation of this neoplasm, although a wide age range has been described in the largest series of neurothekeoma [1, 3, 22]. The case presented here arose at a previous vaccination site for an unspecified COVID-19 vaccine after an unknown interval of time. To the best of our knowledge, there are no reports of benign soft tissue tumours arising after COVID-19 vaccination in literature. However, there is one case of an undifferentiated pleomorphic sarcoma originating at the vaccination site of a second dose of Moderna COVID-19 vaccine [23], and two cases of Kaposi sarcoma following second and third doses of Modena and AstraZeneca vaccines [24, 25]. The latter were reactivations of pre-existing Kaposi sarcoma at sites distant from the COVID-19 vaccine administration. The mechanisms involved are unknown [26]. These cases are very rare, and more research is needed to confidently stablish a potential connection of those reports with COVID-19 vaccines.

Our finding of a novel heterozygous *NF1* c.4333-2dup adds to the sparse literature addressing genetic alterations in neurothekeomas. Previously, Yin Cheng et al. reported aberrant immunohistochemical expression

of TFE3 in four neurothekeoma cases that lacked *TFE3* gene translocations or amplifications by fluorescent in situ hybridization [27]. Similarly, our case showed strong and diffuse immunohistochemical nuclear expression of TFE3 despite the absence of single nucleotide variants (SNV) or gene rearrangements.

By MPS of a neurothekeoma in a 53-year-old man, Ortega et al. [28]. identified point mutations in the oncogenes PI3K w552, ALK P1469S, SMO G461S and ERBB3 L77M. These mutations were absent in the current case, as determined by RNA targeted MPS and whole exome sequencing.

Using in silico splice prediction tools (ASSP and NNSPLICE), it is suggested that *NF1* c.4333-2dup variant might affect splicing by causing the loss of a constitutive splice site and the introduction of a new splice site. This alteration could lead to a frameshift and consequent premature termination of the protein, resulting in loss-of-function. This variant has not been previously reported in the literature in individuals affected with neurofibromatosis type 1 and it is not present in the population database (gnomAD). The patient presented here did not have personal or family history of neurofibromatosis type 1, nor did she exhibit the clinical characteristics outlined by The National Institutes of Health diagnostic criteria for this syndrome [29]. Neurothekeomas are not in the spectrum of benign tumours associated with neurofibromatosis type 1 and acquired somatic mutations in *NF1* are reported in many human neoplasms [29]. Interestingly, though, in the series of 178 cases of neurothekeomas by Fetsch et al., one patient was suspected to have neurofibromatosis type 1 due to a history of multiple cutaneous lesions since early childhood. Upon review, three of these lesions had histologic features of neurothekeomas, whereas others were neurofibromas [1].

The NF1 gene encodes neurofibromin, which is ubiquitously expressed with the highest levels found in cells of the central nervous system. Neurofibromin is a multidomain molecule with tumour suppressor functions. This is achieved mainly through the GAP-related domain (GRD), which stimulates the conversion of metabolically active Ras-GTP to the inactive guanosine diphosphate-bound form with the consequent suppression of the activation of downstream effectors of the RAF/MAPK and PI3K/AKT signalling pathways, involved in growth control, cellular proliferation and survival. Neurofibromin's tumour suppressor activity is postulated to be exerted through several other less-understood intracellular processes [30, 31].

Loss-of-function variants in NF1 are known to be pathogenic [32, 33], but the role of this finding in neurothekeoma could not be ascertained without further research in the relatively unexplored area of neurothekeoma pathogenesis.

The immunohistochemical profile of CNT is nonspecific, but a panel of antibodies is useful to rule out entities in the differential diagnosis, primarily melanocytic neoplasms (melanoma, Spitz naevus), dermal nerve sheath myxoma (DNSM), plexiform fibrohistiocytic tumour and cutaneous myoepithelial tumour.

Although dermal-based and lacking an epidermal or junctional component, melanocytic neoplasms enter the differential diagnosis of CNT. However, the lack of immunoreactivity for S100, HMB45, and MART1, despite unspecific immunoreactivity for MITF, NSE, and CD63/NKI-C3, rules out diagnostic possibilities within the melanocytic line of differentiation. To be noted, PRAME has been shown to be variably expressed in a recent series of cases of neurothekeomas [34].

In contrast to CNT, DNSM typically arises in the distal extremities. Although both tumours share a multinodular growth pattern and exhibit myxoid extracellular stroma, the absence of immunoreactivity for S100 and GFAP confidently excludes DNSM.

Plexiform fibrohistiocytic tumour (PFT) is located deeper in the dermis compared to CNT, typically at the dermal-subcutaneous junction. Unlike the well-circumscribed borders of CNT, PFT is widely infiltrative. It is biphasic, with histiocytoid cells, osteoclast-like giant cells, and myofibroblastic spindle cells expressing SMA.

Cutaneous myoepithelial tumours may share the circumscription, lobulated architecture, and myxoid stroma of CNT. While in general, they are cytologically bland, some cases exhibit severe atypia and brisk mitotic activity (Myoepithelial carcinoma) [35]. These tumours are positive for cytokeratin and/or EMA, with most also expressing S100, GFAP, p63, and myogenic markers. Additionally, a subset carries FET protein family gene rearrangements (*EWSR1/FUS*) with various fusion partners, aiding diagnosis.

Approximately a fifth of CNT are mistakenly diagnosed as malignant neoplasms [1]. When the clinical information is limited or the diagnosis is based solely on incomplete histologic characteristics, certain features in ACN may prompt the pathologists to rule out sarcomas such as sclerosing epithelioid fibrosarcoma, epithelioid sarcoma, epithelioid haemangioendothelioma, atypical fibroxanthoma or pleomorphic dermal sarcoma.

CNT may show extracellular hyaline collagen, with bright collagen strands wrapping around epithelioid cells, feature that might resemble sclerosing epithelioid fibrosarcoma (SEF). SEF occurs in older individuals and is deep-seated. When clinical and imaging data are incomplete, MUC4 negativity confidently rules out SEF.

The epithelioid cytomorphology of CNT might warrant differentiation from a superficially located classic epithelioid sarcoma (ES), which typically affects acral extremities and exhibits granulomatous nodules of epithelioid

and spindled cells. ES shows INI1 loss, and immunoreactivity with epithelial markers and CD34 which are absent in CNT.

Without complete clinical and gross information, epithelioid cytomorphology, myxoid stroma, diffuse nuclear TFE3 immunoreactivity, and ERG positivity as shown by our case, may suggest epithelioid haemangioendothelioma (EHE). TFE3 overexpression is characteristic of YAP1-TFE3 EHE, which lacks myxoid stroma, but can also occur in EHE with WWTR1-CAMTA1 fusions [36, 37]. Positivity for MITF, NSE, and CD63/NKI-C3, along with the absence of cytoplasmic vacuolation and immunoreactivity for epithelial markers, help differentiate CNT from EHE.

In cases with marked pleomorphism, atypical fibroxanthoma or pleomorphic dermal sarcoma might be considered, but these usually affect sun-damaged skin in elderly patients. Immunohistochemistry is of limited use for differentiation, as atypical fibroxanthoma can also be positive for NKI-C3.

Importantly, the widespread and marked nuclear atypia and high mitotic rate in the presented neoplasm, coupled with epithelioid cytomorphology and focal myxoid stroma makes it extremely challenging to differentiate ACN from a myxoid sarcoma with epithelioid features. Although these features mimic those seen in the epithelioid subtype of myxofibrosarcoma, making this distinction particularly difficult, the latter is distinctly infiltrative, and it contains the hallmark curvilinear vessels with perivascular condensation which are absent in ACN.

The case presented does not exhibit histological features characteristic of a malignant peripheral nerve sheath tumour (MPNST), yet this may remain a diagnostic possibility due to the inactivating NF1 mutation found. Nevertheless, as determined by RNA targeted MPS and whole exome sequencing, this tumour did not harbour inactivating mutations in SUZ12 or CDKN2A/B, which are frequently and concurrently found with neurofibromin inactivating mutations in NF1-associated MPNST [38, 39].

In summary, the identification of a novel heterozygous *NF1* c.4333-2dup variant might contribute to our understanding of genetic alterations in neurothekeomas, which is currently limited. Despite its potential implications, research is needed to validate this finding and potentially understand its functional impact and role in neurothekeoma pathogenesis. Such research could ultimately help refine the diagnosis of ACN, which currently relies on a panel of non-specific immunohistochemical markers, improve recognition and avoid misdiagnosis with malignant tumours.

Abbreviations

F	M ratio: female: male ratio
CNT	cellular neurothekeoma
ACN	atypical cellular neurothekeoma
MPS	massive parallel sequencing
TMB	tumour mutational burden
MSI	microsatellite instability
WES	whole exome sequencing
HPF	high power field
WHPF	wide high-power field
SNV	single nucleotide variants
GRD	GAP-related domain
GTP	guanosine-5′- triphosphate
DNSM	dermal nerve sheath myxoma
PFT	Plexiform fibrohistiocytic tumour
SEF	sclerosing epithelioid fibrosarcoma
ES	epithelioid sarcoma
EHE	epithelioid haemangioendothelioma
MPNST	malignant peripheral nerve sheath tumour

Author contributions

V.G: drafted the manuscript, was involved in clinical data acquisition and prepared the figures and tables; M.P: carried out the histopathological diagnosis, initiated the molecular investigations and co-wrote the manuscript; A.I.P: was involved in the histopathologic diagnosis of the patient, adquisition of data and review of the manuscript; S.G.T.D: carried out the RNA targeted NGS, its analysis and interpretation and reviewed the manuscript; E.C.P: carried out the analysis and interpretation of whole genome sequencing and co-wrote the manuscript. All authors read and approved the final manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Bioethics statement

This study obtained the approval of the ethics committee of the Metropolitan Hospital of the Social Security Fund of Panama. Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no competing interests.

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References

1. 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.
2. Gallager RL, Helwig EB. Neurothekeoma-a benign cutaneous tumor of neural origin. Am J Clin Pathol. 1980;74(6):759–64.
3. Hornick JL, Fletcher CD. Cellular neurothekeoma: detailed characterization in a series of 133 cases. Am J Surg Pathol. 2007;31(3):329–40.
4. 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.
5. Argenyi ZB, Kutzner H, Seaba MM. Ultrastructural spectrum of cutaneous nerve sheath myxoma/cellular neurothekeoma. J Cutan Pathol. 1995;22(2):137–45.
6. 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.
7. 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.

8. 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.
9. Rosati LA, Fratamico FC, Eusebi V. Cellular neurothekeoma. Appl Pathol. 1986;4(3):186–91.
10. 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.
11. Bhatia S, Chu P, Weinberg JM. Atypical cellular neurothekeoma. Dermatol Surg. 2003;29(11):1154–7.
12. Benbenisty KM, Andea A, Metcalf J, Cook J. Atypical cellular neurothekeoma treated with Mohs micrographic surgery. Dermatol Surg. 2006;32(4):582–7.
13. Campanati A, Brandozzi G, Sisti S, Bernardini ML, Offidani AM. Atypical neurothekeoma: a new case and review of the literature. J Cutan Pathol. 2007;34(5):435–7.
14. Wilson AD, Rigby H, Orlando A. Atypical cellular neurothekeoma-a diagnosis to be aware of. J Plast Reconstr Aesthet Surg. 2008;61(2):186–8.
15. Mertz KD, Mentzel T, Grob M, Pfaltz M, Kempf W. A rare case of atypical cellular neurothekeoma in a 68-year-old woman. J Cutan Pathol. 2009;36(11):1210–4.
16. Gullett AE, Jimenez-Quintero LP, Prieto VG, Ivan D. Atypical cellular neurothekeoma in a pregnant woman. Arch Dermatol. 2011;147(11):1342–3.
17. Han TY, Han B, Lee YC, Lee JH, Son SJ. A rare case of atypical Myxoid Cellular Neurothekeoma in a 6-Year-old girl. Pediatr Dermatol. 2016;33(2):e123–4.
18. Tran P, McLemore M. Atypical cellular neurothekeoma: a potential diagnostic pitfall for benign and malignant spindle cell lesions in skin. J Cutan Pathol. 2018;45(8):619–22.
19. D'Alessandris N, Picchetto A, Pignataro MG, Cerbelli B, Manzo D, Rocca CD, d'Amati G, Pernazza A. Atypical cellular neurothekeoma (ACN) of the elderly: case report and brief review of the literature. Pathologica. 2020;112(4):210–3.
20. Pedroni G, Paganelli A, Bassoli S, Kutzner H, Cesinaro AM, Magnoni C. Atypical cellular neurothekeoma: report of a case. Dermatol Rep. 2021;14(2):9327.
21. Sperling LC, Hardy CL, Love TV. Atypical cellular neurothekeoma: a lamb in wolf's clothing. JAAD Case Rep. 2022;30:111–3.
22. Stratton J, Billings SD. Cellular neurothekeoma: analysis of 37 cases emphasizing atypical histologic features. Mod Pathol. 2014;27(5):701–10.
23. Bae E, Bae S, Vaysblat M, Abdelwahed M, Sarkar K, Bae S. Development of high-Grade Sarcoma after Second Dose of Moderna Vaccine. Cureus. 2023;15(4):e37612.
24. Martínez-Ortega JI, Ramirez Cibrian AG, Martinez-Jaramillo E, García Silva MDC. Sporadic Kaposi Sarcoma following a COVID-19 vaccine: Mere coincidence or something more? Cureus. 2024;16(2):e53925.
25. Hitzenbichler F, Weber M, Salzberger B. Infection image: reoccurrence of Kaposi`s sarcoma after SARS-CoV-2 mRNA vaccination in an HIV-infected patient. Infection. 2024;52(1):283–4.
26. Chen J, Dai L, Barrett L, James J, Plaisance-Bonstaff K, Post SR, Qin Z. SARS-CoV-2 proteins and anti-COVID-19 drugs induce lytic reactivation of an oncogenic virus. Commun Biol. 2021;4(1):682.
27. Cheng Y, Zhang N, Deng Z, Guan X, Xu J, Qu L, He L. Expression of TFE3 in Cellular and Myxoid Type of Neurothekeoma: four cases in Young Children and adolescents. Fetal Pediatr Pathol. 2023;42(4):679–84.
28. Ortega M, Sparks J, Nava VE, Smith SDB. Neurothekeoma with PI3K w552*, ALK P1469S, SMO G461S, and ERBB3 L77M genetic alterations. Am J Dermatopathol. 2022;44(12):958–60.
29. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988;45(5):575-8.
30. Philpott C, Tovell H, Frayling IM, Cooper DN, Upadhyaya M. The NF1 somatic mutational landscape in sporadic human cancers. Hum Genomics. 2017;11(1):13.
31. Yap YS, McPherson JR, Ong CK, Rozen SG, Teh BT, Lee AS, Callen DF. The NF1 gene revisited - from bench to bedside. Oncotarget. 2014;5(15):5873–92.
32. Fahsold R, Hoffmeyer S, Mischung C, Gille C, Ehlers C, Kücükceylan N, Abdel-Nour M, Gewies A, Peters H, Kaufmann D, Buske A, Tinschert S, Nürnberg P. Minor lesion mutational spectrum of the entire NF1 gene does not explain its high mutability but points to a functional domain upstream of the GAP-related domain. Am J Hum Genet. 2000;66(3):790–818.
33. Sabbagh A, Pasmant E, Imbard A, Luscan A, Soares M, Blanché H, Laurendeau I, Ferkal S, Vidaud M, Pinson S, Bellanné-Chantelot C, Vidaud D, Parfait B, Wolkenstein P. NF1 molecular characterization and neurofibromatosis type I genotype-phenotype correlation: the French experience. Hum Mutat. 2013;34(11):1510–8.
34. Cesinaro AM, Piana S, Paganelli A, Pedroni G, Santandrea G, Maiorana A. PRAME expression in cellular neurothekeoma: a study of 11 cases. J Cutan Pathol. 2022;49(4):338–42.
35. Hornick JL, Fletcher CD. Cutaneous myoepithelioma: a clinicopathologic and immunohistochemical study of 14 cases. Hum Pathol. 2004;35(1):14–24.
36. Flucke U, Vogels RJ, de Saint Aubain Somerhausen N, Creytens DH, Riedl RG, van Gorp JM, Milne AN, Huysentruyt CJ, Verdijk MA, van Asseldonk MM, Suurmeijer AJ, Bras J, Palmedo G, Groenen PJ, Mentzel T. Epithelioid Hemangioendothelioma: clinicopathologic, immunhistochemical, and molecular genetic analysis of 39 cases. Diagn Pathol. 2014;9:131.
37. Doyle LA, Fletcher CD, Hornick JL. Nuclear expression of CAMTA1 distinguishes Epithelioid Hemangioendothelioma from histologic mimics. Am J Surg Pathol. 2016;40(1):94–102.
38. Lee W, Teckie S, Wiesner T, Ran L, Prieto Granada CN, Lin M, Zhu S, Cao Z, Liang Y, Sboner A, Tap WD, Fletcher JA, Huberman KH, Qin LX, Viale A, Singer S, Zheng D, Berger MF, Chen Y, Antonescu CR, Chi P. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. Nat Genet. 2014;46(11):1227–32.
39. Pemov A, Hansen NF, Sindiri S, Patidar R, Higham CS, Dombi E, Miettinen MM, Fetsch P, Brems H, Chandrasekharappa SC, Jones K, Zhu B, Wei JS, National Intramural Sequencing Center (NISC) Comparative Sequencing Program; National Cancer Institute (NCI) Division of Cancer Epidemiology and Genetics (DCEG) Cancer Genomics Research Laboratory, Mullikin JC, Wallace MR, Khan J, Legius E, Widemann BC, Stewart DR. Low mutation burden and frequent loss of CDKN2A/B and SMARCA2, but not PRC2, define premalignant neurofibromatosis type 1-associated atypical neurofibromas. Neuro Oncol. 2019;21(8):981–92.

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