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International Journal of Clinical Case Reports and Reviews
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Research Article

Head and Neck Neurothekeoma of Lower Lip with Aggressive Reconstruction using Bengt-Johanson's Step Technique: Case Presentation and Systematic Review of Literature

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Received Date: March 08, 2022 | **Accepted Date:** March 16, 2022 | **Published Date:** March 21, 2022

Citation: Romano A, Committeri U, Troise S, Maglitto F, Dell'Aversana Orabona G, Norino G, Sani L, Arena A, Barone S, Iaconetta G, Califano L. (2022). Head and Neck Neurothekeoma: Systematic Review of Literature and Presentation of a Lower Lip Aggressive Case Reconstructed with Bengt-Johanson's Step Technique. *International Journal of Clinical Case Reports and Reviews*. 11(1); DOI: 10.31579/2690-4861/212

Abstract

Aim: Neurothekeoma is a benign lesion of superficial tissue mainly localized in the head-neck area. The aim of the article is to provide a systematic literature review on the tumor's main characteristics and its correct surgical treatment. We support our theory with the report of an aggressive case of the lower lip region which required a large excision and reconstruction with local flaps.

Materials and Methods: The literature review is based on the scientific materials produced from December 1980 to March 2020 on the head and neck neurothekeomas. In total, 76 papers were included in the study. We presented a classic neurothekeoma S-100 protein positive case that required wide local excision with healthy margins and reconstruction with Bengt-Johanson's step technique.

Results: Most of the papers were case reports (47,4 %) and reviews (19,7 %) with 721 evaluated neurothekeomas. The male to female ratio was 1:1,8 with a mean age of 26,4 years. The most frequent site of lesions was the head (36,1%), and the three subtypes were divided in cellular (65,7%) mixed (17,5%) and classic (16,8%). The classic neurothekeoma resulted more immunoreactive for S-100 Protein while cellular neurothekeomas for NKI/C3. Our case was successful without recurrence at 1 year follow-up.

Conclusion: Our review highlights that neurothekeoma mainly occurs in young women in the superficial planes of the head and neck. The most frequent type is the cellular one, but the most aggressive is the classic type due to a high local recurrence of protein S-100. A local excision is sufficient for the cellular neurothekeoma, while for the classic type a wide local excision with healthy tissue margins is necessary. The treatment of our case demonstrates that by following this guide, relapse can be avoided.

Keywords: facial neurothekeoma; head and neck; lower lip; Bengt-Johanson's step technique, S-100 protein

Introduction

Neurothekeoma is a benign tumor first described by Harkin and Reed in 1969 and classified as "nerve sheath myxoma" [1]. The term neurothekeoma was coined in 1980 by Gallagher and Helwig in their report on 53 dermal tumors with similar features. [2] Argenyi et al [3] further classified neurothekeoma as classic, cellular and mixed type according to cellularity, mucin content, and growth pattern.

The term "classic neurothekeoma" (classic NTK) will be used henceforth when referring to a tumor also known as a nerve sheath myxoma characterized by an abundant myxoid matrix, and scattered collections of epithelioid schwann cells in corded, nested or syncytial- like patterns, and typically S-100 immunoreactive [4].

The "cellular neurothekeoma" (cellular NTK) is a tumor composed of nests and bundles of variably epithelioid-to-spindled cells often separated

by dense collagen septae and classically S-100- negative but NKIC3 positive [5].

The so-called "mixed-type" of neurothekeomas shows overlapping features of both variants [6]. The tumors have been subclassified as cellular neurothekeomas when they have <10% myxoid matrix, mixed-type neurothekeomas when they have >10% and <50% myxoid matrix, and myxoid neurothekeomas when they have >50% myxoid matrix [7].

Generally, the neurothekeoma tumor manifests itself as an asymptomatic, solitary, slow-growing nodule that involves the skin and superficial subcutis of the head and neck region, or of the extremities. It usually requires surgical excision that, based on histopathological and immune histochemical features, can be less or more extended.

In this paper, an extensive review of the literature related to head and neck neurothekeomas has been conducted. Furthermore, a case of lower lip classic neurothekeoma, treated by our team, is presented. The aim of the study is to show the clinical, histopathological and immunohistochemical features of these tumors, and to offer indications for the different surgical procedures according to the characteristics of the neoplasms.

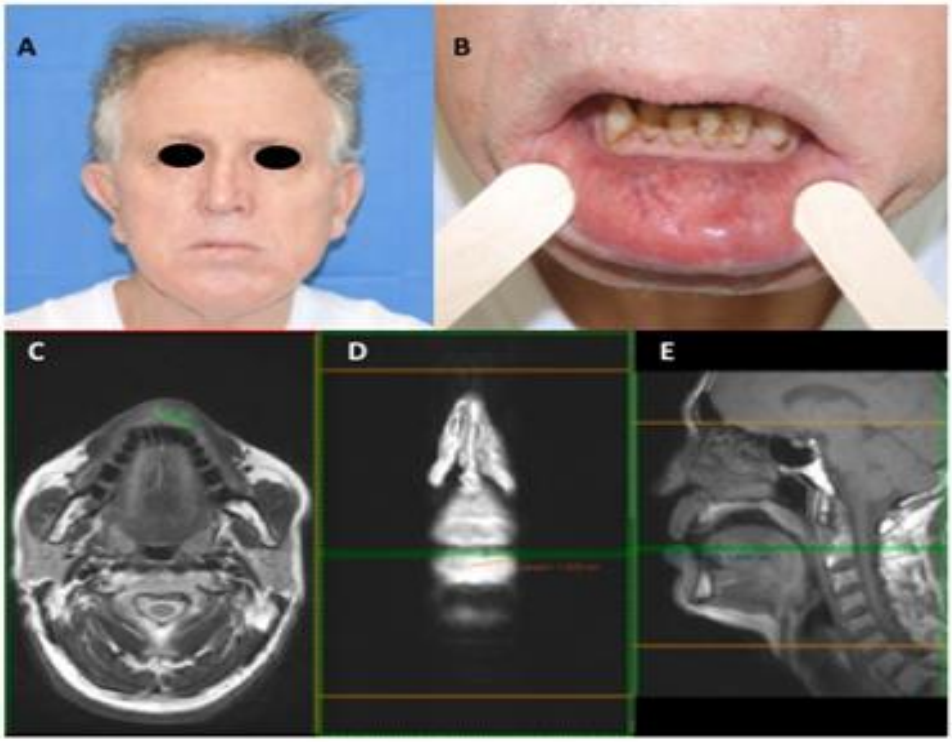
Materials and Methods

We report the case report and the literature review process.

Case Report

On February 2020, a 64 years old patient was admitted at the Maxillo-Facial Surgery Unit of Federico II University of Naples. The patient was affected by a neoplasia of the lower lip. The Magnetic resonance imaging (MRI) with contrast showed a non-homogeneous captive mass of 2 cm in diameter, hypointense in T1 and hyperintense in T2 in the lower lip that was scarcely differentiated between the skin and the deep muscle planes (Figure 1). Further histological examinations based on incisional biopsy showed a neoplasm with appreciable mitotic activity, with prevalent lobulated areas alternating with diffuse areas, composed of fascicles of fusate or epithelioid cells immersed in a myxoid matrix. The neoplasm resulted immunoreactive to S-100 protein but not to CD31, CD34, p63, CK, Mart1, and HMB45.

An elective surgery to remove the tumor and reconstruct the region was performed.



A) Cutaneous Frontal View of the tumor
B) Mucosal view of the tumor
C) Axial
D) Coronal and
E) Sagittal plan of the tumor.

Figure 1: *Pre surgical evaluation*

Surgical Procedure

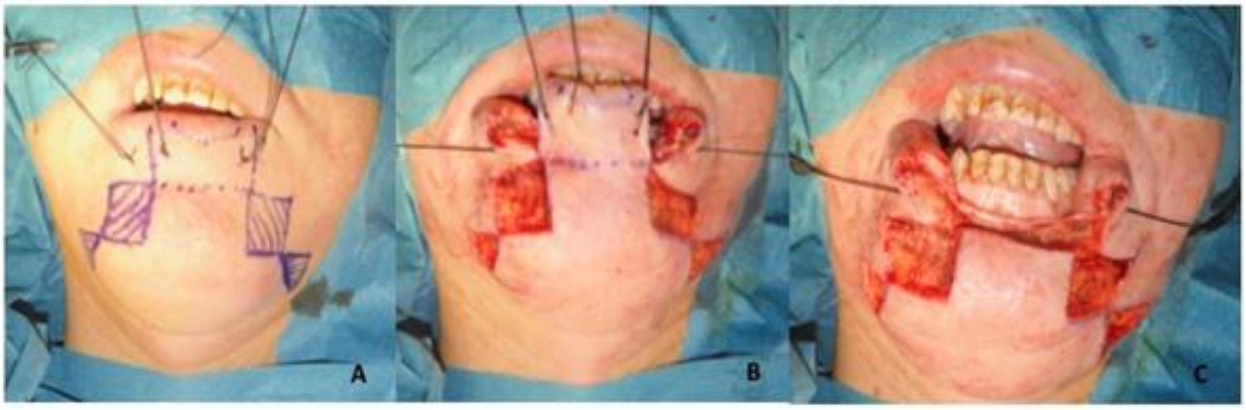
The surgical procedure consisted of 2 steps. Firstly, the tumor removal and after the use of a stairs flap (Bengt-Johanson's Step Flap [8]) to reconstruct the defect. Antisepsis procedures were performed with iodine-povidone solution and administration of 1g of intravenous Ceftriaxone. Local anesthesia was realized by infiltration of a 2% carbocaine solution and adrenaline to obtain hemostasis and flap hydrodissection.

Step 1: Tumor excision

The tumor excision was planned with a margin of 1 cm, the corners of healthy tissue were tensioned by n. 2 silk sutures in order to reduce the traumatism of healthy tissue, and to allow a better removal of the tumor.

The tumor was removed at full thickness, was oriented with nylon threads and sent for histopathological examination.

The residual defect measured about 4 cm, >50% of lower lip (Figure 2).

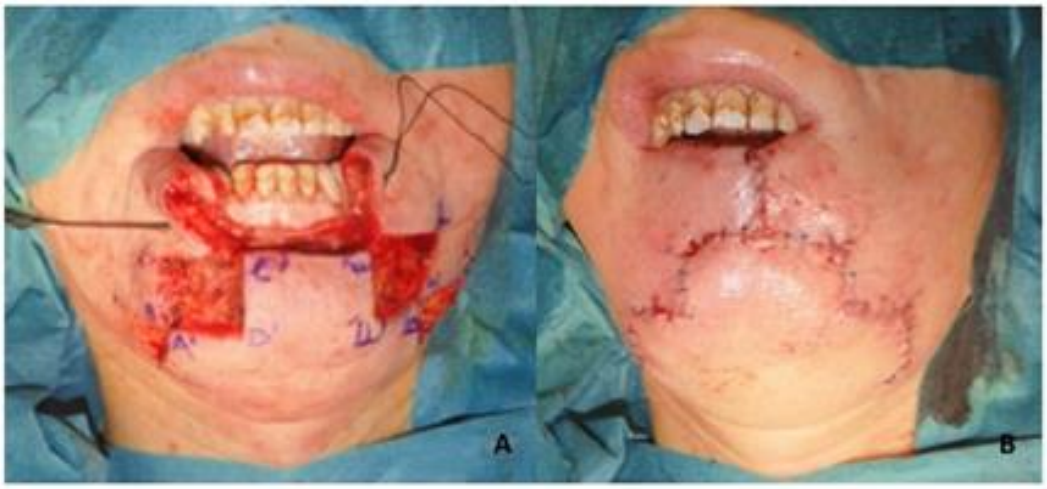


A) Surgical Planning
B) Tumor delimitation
C) Removed tumor with a final defect of 3 cm.

Figure 2: *Tumor Removal*

***Step 2: Bengt-Johanson's Step Flap Reconstruction* [8]**

In our case the defect was paramedian and greater than 2 cm in width. Therefore, 2 asymmetric flaps with bilateral staircase technique were performed (Figure 3). Two incisions were made bilaterally from the lateral sides of the defect, extended horizontally and vertically downward, toward to the chin for 2 cm. The incisions ended with the Burow triangles, with an inferiorly located apex, and a base that approximately corresponds to 2/3 of the last horizontal incision. The dissection was performed above the mimic muscles, by setting up a flap of skin and subcutaneous, with preservation of the orbicularis oris, depressor anguli oris, and depressor labii inferioris. The rectangles below the steps have been removed and the Burow triangles were then excised. In the last stage, the flaps are advanced and approximated using a layered closure. The two extremities of the flap were transposed medially one towards the other to ensure a coverage of the surgical gap without tension. The closure of the orbicularis muscle and of the vestibular fornix mucosa was performed with vicryl 4.0 sutures. The skin was closed with nylon 5.0 mattress sutures. At the end of the case, the gastric nose tube was positioned to reduce the opening of the mouth in the first days of post-surgery.



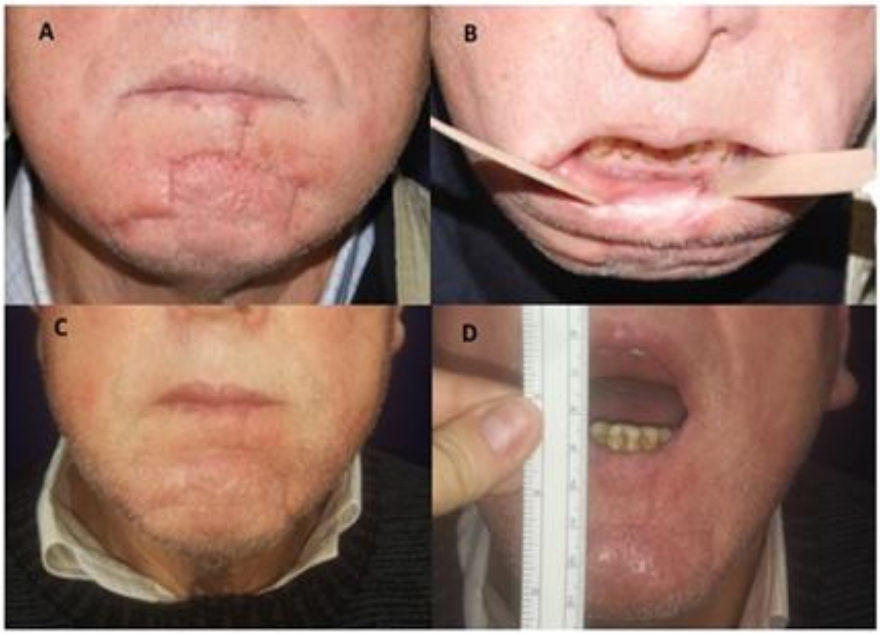
A) Reconstruction surgical planning
B) Final result after cutaneous suture in Nylon.

Figure 3: *Bengt-Johanson's step technique for lower lip reconstruction.*

Post-operative outcome

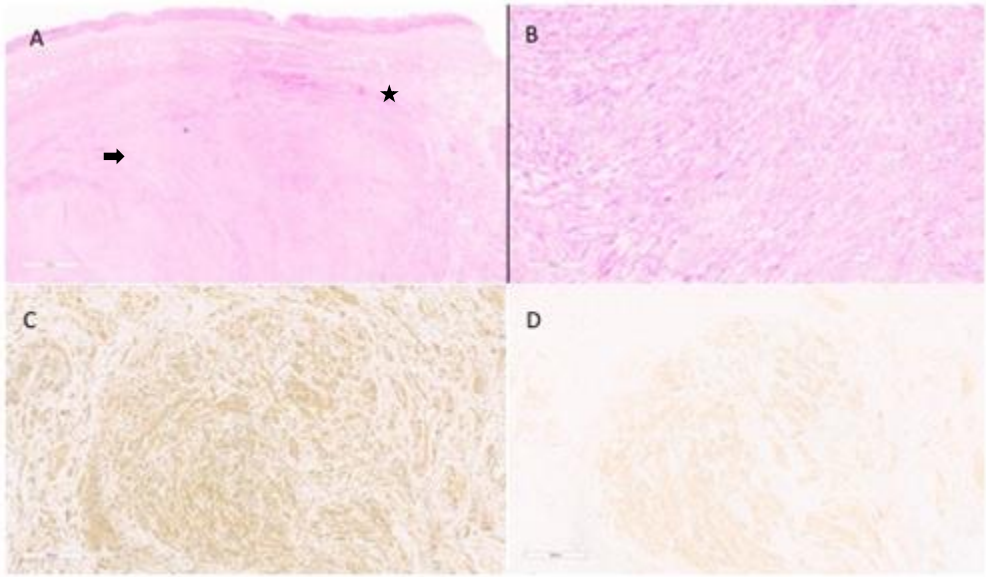
During the postoperative period, the patient continued the antibiotic therapy with ceftriaxone 1 gr x1/die for 7 days and daily local disinfection. Sutures were removed after 15 days. Oral and dental hygiene was required combined with diet through gastric-nose tube for 15 days.

Outpatient follow-up controls were performed at 15 days, one month, two months, and up to one year. The local examination showed a result of lip competence, symmetry and absence of microstomy (Figure 4). Definitive histopathological examination revealed a classic neurothekeoma with fascicles of spindle cells dipped in a myxoid stroma. Tumor cells were positive for vimentin and s-100 protein with high mitosis (ki67 40%) (Figure 5). At one year of follow-up, recurrence was absent.



A) Cutaneous and B) mucosal final result at 1 month.
C) Cutaneous view and D) Final buccal opening at 1 year.

Figure 4: *Post-surgical follow-up*



A) Low power magnification showed a non-capsulated neoplasm, with prevalent lobulated areas (*star*) alternating with diffuse areas (*arrow*), composed of fascicles of fusate or epithelioid cells immersed in a myxoid matrix (haematoxylin and eosin, original magnification, x2);

B) Higher magnification highlighted appreciable mitotic activity (haematoxylin and eosin, original magnification, x10)

C) and D) Positivity for vimentin and S100 (protein s100 and vimentin, original magnification, x4).

Figure 5: *Histology of the case of Classic Neurothekeoma.*

Review Process

Study Design

The literature review on head and neck neurothekeomas was realized adhering to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [9].

Data Research

The data were collected from December 1980 to March 2020, and the primary source was the online database of the U. S. Library of Medicine (PubMed). The Medical Subject Headings (MeSH) used were: Neurothekeoma, Face, Head, Neck, Treatment. For the literature search, keyword Neurothekeoma was paired sequentially with the other 4

keywords, having this final formula: (neurothekeoma AND face OR facial) OR (neurothekeoma AND head) OR (neurothekeoma AND neck) OR (neurothekeoma AND therapy OR treatment OR therapeutics). To avoid the loss of interesting articles, accepted by March 2020, a second research was always carried out on Pubmed using only the keyword neurothekeoma and, later on, the results were crossed.

Eligibility Criteria

The PubMed search results were screened, and duplicate articles were eliminated. Studies conducted on humans and published in English were considered. The titles and abstracts of the records were screened by one author using the inclusion criteria. We found 103 occurrences in the first research and 283 in the second research. Then the PubMed search results were screened by a carefully reading, and 220 papers were excluded for title not inherent or the duplicates; 48 papers were excluded for the absence of abstract. Moreover, among the 118 remaining PubMed studies, 10 papers not in English, 16 not referring to head and neck, and 1 not referred to humans were excluded (elegibility criteria). At the end, among the 91 studies remaining, 10 papers were excluded because of the presence of only abstract and 5 papers were excluded after a complete reading because not interesting for the topic.

The total number of articles included in our review were 76. The selection process was summarized in Figure 6.

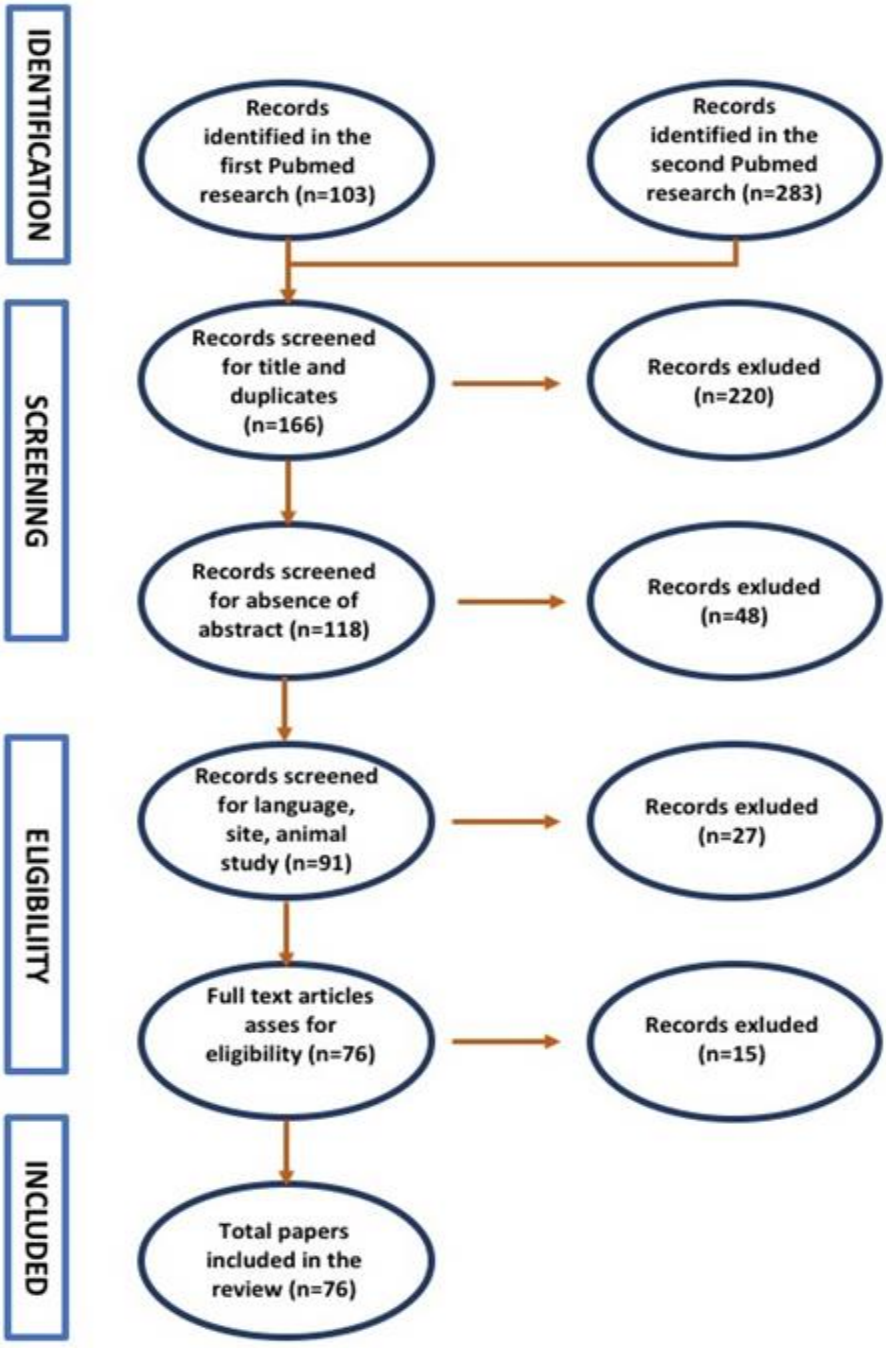


Figure 6: *PRISMA Statement*

Data Extraction

Data extracted from each article included the type of study, total cases, sex and age of cases, sites of lesions, diameter (if reported) of lesions, invaded tissue, histological and cytological features, expressed immunohistochemical markers, type of treatment performed, subtypes of neurothekeoma. For the purposes of this study, the primary outcome was to identify the characteristics of the different neurothekeoma subtypes and to choose the correct surgical treatment according to these features.

Results

All the 76 analyzed papers and their features are shown in Table 1.

The types of study were divided in 36 case reports (47,4 %), 15 reviews (19,7 %), 12 case series (15,8 %), 12 retrospective observational studies (15,8 %) and 1 letter to editor (1,3 %). In total, the evaluated neurothekeomas cases were 721.

Author/ Year	Type of Study	N° Cases	Sex	Side of Lesion	Ø	Local Invasion	Cytological Markers	Hystological Features	Surgical Treatment	Final Diagnosis
Gallager [2] 1980	observational retrospective	53	44 F 9 M	15 up ext, 15 face, 1 oral cavity, 3 neck, 5 shoulder, 3 trunk, 5 lower ext , 2 back	1 cm	37 subcutis, 26 dermis	/	nests of spindle cells between bundles of dermal collagen with eosinophilic cytoplasm. Frequent atypical hyperchromatic nuclei and mitotic figures varying from none to 5/10 high-power fields.	Excision	/
Barnhill [5] 1991	case series	11	8 f 3m	2 scalp, 2 back, 2 nose, 1 chin, 1 shoulder, 1 up extremities, 1 Forehead, 1 ear	/	dermis	S-100, Vimentin and SMA	fascicular pattern (cellular neurotek); prominent myxoid stromal change (classic neurotek)	Excision	8 cellular 3 myxoid
Fetsch [7] 2007	observational retrospective	176	112 F 64 M	17 nose, 15 scalp, 31 face, 4 neck, 70 up ext, 17 trunk, 20 lower ext, 2 not reported	1,1 cm	120 subcutis, 5 muscles plane, 51 dermis	Vimentin, NKI/C3, MiTF, PGP9.5, CD10, NSE, CD68, CD99, alfaSMA, Collagen IV, HMB-45	nests and bundles of epithelioid cells and spindle cells; eosinophilic cytoplasm; dense hyaline collagen. mild cytological atypia; mitotic rate 3/10 high power fields	133 Excision, 33 enucleoresection	63 cellular neurotek, 66 mixed, 47 classic neurotek
Almeida [11] 2018	case report and review	1	f	multiple localized oral cavity	2 cm	submucosal	vimentin, CD63, CD56, whereas AE1/AE3, S100, CD34, α-SMA, GFAP, EMA	spindle and epithelioid cells, forming nests and bundles, supported by fibrous stroma. Rare presence of giant cells.	Enucleoresection	classic neurotek
Misago [13] 2004	case report	1	F	scalp	1,5 cm	subcutis	S-100A6 protein, PGP9.5, CD10, CD68 (KP1), PG-M1, Vimentin	Nests of epithelioid cells with abundant and pale eosinophilic cytoplasm, surrounded by spirally arranged stellate cells associated with a moderate amount of mucin. The mitosis rate was 2-3 / 10 high-power fields, without atypical mitotic figures The stroma was collagen and often associated with dense, sclerotic, or hyalinized collagen	Excision	cellular neurotek
Maktabi [14] 2019	case report and review	1	m	lateral canthus	1,5 cm	dermis	CD68, Vimentin, D2–40, SMA	nests of epitheli-oid/spindle cells separated by fibrous septae within a myxoid background	Excision	Mixed
Safadi [15] 2010	case report and review	1	F	Oral cavity	2 cm		S-100, NSE	fusiform cells with eosinophilic cytoplasm, myxoid stroma	enucleoresection	classic neurotek
Park [16] 2016	case report	1	f	Scalp	6 cm	dermis	vimentin, CD68, CD10	spindled and epithelioid cells arranged in fascicles	Excision	cellular neurotek

								and nodules separated by a collagen-rich stroma		
Benbenisty [17] 2006	case report and review	1	F	nasal wing	4 mm	dermis	NSE, MiTF, NKI / C3, PGP9.5, SMA, CD10 vimentin, CD68	nests of epithelioid cells with abundant vacuolated eosinophilic cytoplasm; nuclei with moderate atypia round or ovoid. frequent mitotic figures (4/10 high power fields) but absence of atypical mitoses.	Large enucleoresection	neurotekeoma cellulare ATIPICO
Campanati [18] 2006	case report and review	1	f	chin	6 cm	skeletal muscle	PGP, Ki-67	diffusely infiltrative borders, vascular invasion, high mitotic	Large Enucleoresection	Atypical neurotek
Wilson [19] 2008	case report	1	F	nasal wing	1 cm		NKI / C3, PGP9.5.	spindle cells, focal atypia, high mitotic activity	Large enucleoresection	Atypical neurotek cellular
Papadopoulos 2004 [20]	case report and review	1	M	neck	1 cm	dermis		Splindle in a myxoid stroma and separated by strands of collagen. Tumor cells nuclei were fused and rare mitoses were present.	Excision	neurotek mixed
Hornick [21] 2007	observational retrospective	133	83 F 45 M	27 up ext, 20 face, 10 nose, 4 lip, 3 scalp, 5 neck, 23lower ext, 16 trunk, 13 shoulder, 12 back	1.1 cm	69 dermis, 63 subcutis, 1 not reported	NKI / C3, SMA, NSE	nests and bundles of epithelioid cells and spindle cells with pale eosinophilic cytoplasm; dense hyaline collagen. mild cytological atypia; mitotic rate 3/10 high power fields	enucleoresection	cellular neurotek
Rodriguez [23] 2015	case report	1	F	orbit	2 cm		CD34, S-100 protein	myxoid nodules with spindle-shaped or stellate cells; abundant myxoid matrix; no atypia were observed	enucleoresection	classic neurotek
Sanchez-Orgaz 2011 [24]	case report	1	M	orbit	1,5 cm		S-100, vimentin, CD68, CD34 e CD10, EMA.	spindle and stellate cells; abundant myxoid matrix. Ki-67 was less than 1%.	enucleoresection	classic neurotek
Jaffer [25] 2009	observational retrospective	43	24 f 19 m	9 upper and 4 lower ext, 7 scalp, 5 face, 5 thorax, 5 shoulder, 1 back 7 not available	/	/	S- 100, Vimentin, CD68, NSE, CD56	plexiform, multinodular, and diffuse, osteoclast-like giant cells, and little or no myxoid stroma,	Excision and Enucleoresection	8 Myxoid, 15 Mixed, 20 Cellular
See [26] 2019	case series and review	2	2 M	orbit	1 cm		aSMA, MITF, CD10, CD68	spindle cells with fusiform to oval nuclei with prominent nucleoli, rare mitotic figures; vascular channels	Excision	cellular neurotek
Murphrey [27] 2020	case series and review	7	4 M 3 F	3 trunk, 3 upper ext 1 nose	/		CD68, NKI/C3	nests of epithelioid cells with abundant eosinophilic pale colored cytoplasm, fascicular growth. The cellular stroma has been described as collagenic and dense or fibrous	Excision	cellular neurotek
Barnhill [29] 1990	case series	5	3 F 2 M	5 head-neck (1 frontal, 2 scalp, 1 neck, 1 chin)	1 cm	dermis	/	fascicles of spindle and epithelioid cells with nuclear atypia, mitotic figures (2/10 per field) and abundant eosinophilic cytoplasm, myxoid stroma and sclerotic collagen with the presence of giant cells	Excision	cellular neurotek

Suh [30] 1992	case report	1	F	scalp	/	dermis	S-100	fusiform and stellate cells; abundant myxoid stroma, eosinophilic cytoplasm, vacuolated nuclei	Excision	neurotek classic
Tiffee [31] 1996	case report and review	1	F	Lower lip	/	dermis	S-100	fusiform and stellate cells; abundant myxoid stroma	enucleoresection	neurotek classico
Tomasini [32] 1996	case series	2	1 F 1 M	1 trunk, 1 frontal	/	dermis	Vimentin, actin, XIIIa Factor	epithelioid or spindle cells organized in plexuses, large vacuolated eosinophilic cytoplasm; myxoid stroma	Excision	neurotek cellular
Breuer [33] 1999	case report	1	F	tongue	2 cm	Muscles plan	vimentin	spindle cells with few mitoses; hyaline collagen	enucleoresection	cellular neurotek
Yee Hang [34] Wong 2001	case report	1	M	Maxillary and ethmoidal sinuses	/	/	S-100	spindle cells in sclerotic stroma	enucleoresection	neurotek classic
Cohen [35] 2004	case report	1	M	Superior Alveolar crest	3,5 cm	Maxillary bone plane	vimentin, NKIC3	irregular cell nests in a densely fibrotic stroma; vesicular, ovoid or irregularly shaped nuclei; abundant mitotic activity, 15 mitoses for 10 high-power fields	Excision	cellular neurotek
Ward [36] 2005	case series	13	9 F 4 M	3 scalp, 2 neck, 1 face, 3 up and 1 lower ext, 2 trunk, 1 not reported	1 cm		Vimentin, actina (1 cases + S-100 like malignant tumor)	fusiform cells with eosinophilic cytoplasm, myxoid stroma	enucleoresection	Classic neurotek
Mahaling am[37] 2006	case report and review	1	M	face	3 cm		vimentin, NKI/C3, PGP 9.5, factor XIIIa CD68	/	Excision	cellular neurotek
lopez capeda[38] 2007	case report	1	F	nose	1,5 cm		vimentin, mucina, neurofilament	spindle cells arranged in nests with mitosis and collagen	Excision	cellular neurotek
Koumanis [39] 2007	case report	1	M	nose	1,5 cm		vimentin	/	enucleoresection	classic neurotek
Mathew[40] 2008	case report	1	M	Lower eyelid	2 cm		S-100	fusiform and stellate cells; myxoid stroma with collagen vortices, Schwann cells and elongated mast cells. very low mitotic activity	enucleoresezion	classic neurotek
Zedek[41] 2009	observational retrospective	12	9 F 3 M	2 face, 1 scalp, 4 up and 2 lower ext, 3 trunk	2 cm		NKI/C3, laminin, CD68, CD10	absence of atypia, 0.67 / 10 mitosis, large vacuolated eosinophilic cytoplasm, stromal sclerosis	Excision	neurotek cellular
Wartchow [42] 2009	case series	1	M	Mandibular gum (reg. 31)	1.7 cm		actina, S-100 / CD1a, CD4 e CD68	16/10 mitosis per field, myofibroblastic characteristics, ki67 <2%	Excision	neurotek cellular
Muller[43] 2009	case report	1	F	Medial canthus (left eye)	1 cm		NKI / C3, SMA, S100 protein	/	Excision	Neurotek mixed
vered [44] 2010	observational retrospective	4	2 F 2 M	Oral cavity	8 mm		cellular (S100A6, NSE, PGP9.5, vimentin, NKI/C3); classic	/	Excision	Cellular neurotek

							(S100A6, NSE, PGP9.5, vimentin, S-100)			
Papalas[45] 2010	case series	3	3 F	2upper eyelid, 1 lower eyelid	6 mm		2 casi NKI.C3 CD34 positivi, 1 caso S-100, GFPA, Vimentin positivo.	/	Excision	2 cellular neurotek, 1 classic neurotek
Sheth[46] 2011	observational retrospective	14	11 F 3 M	face 2, art sup 7, art inf 3, tronco 2	/		classic/myxoid: S100B, aSMA; cellular: NSE, aSMA, F13A, NKIC3, podoplanin D2-40,	/	Enucleoresection	6 cellular neurotek, 8 classico neurotek
Pan[47] 2011	case report	1	M	Upper lip	8 mm		NSE, alfaSMA, cd34	hypercellular epithelioid cells with diffuse and fascicular growth patterns. Casually focal mitosis. No atypia was found.	Excision	cellular neurotek
Yamada[48] 2013	letter to editor	1	F	nose			Vimentin, MiTF, NKI/C3, Glut-1, PGP9.5, CD10, NSE, CD68, CD99.	subcutaneous multi-lobular nodular lesion spindle cells separated by a sclerotic stroma and with eosinophilic cytoplasm, ki67 <1%	Excision	neurotek cellular
Suarez [49] 2013	observational retrospective	18	17 F 1 M	5 nose, 4 upper and 3 lower ext 3 trunk , 2 face, 1 scalp			KBA.62, CD10	epithelioid cells intercalated between bundles of fibrotic collagen, sclerotic large, pale and eosinophilic cytoplasm with mild pleomorphism	Excision	1 neurotek classic; 17 neurotek cellular
Stratton [50] 2013	observational retrospective	37	21 F 16 M	13 face, 3 scalp, 11 upper ext 4 trunk 4 shoulders 2 lower ext			NKI/C3, MiTF, CD68, CD10	epithelioid or spindle cells; large vacuolated eosinophilic cytoplasm; myxoid stroma. 4 cases of perineural invasion. 19 cases of cytological atypia, 2/10 mitosis per field	Excision	33 neurotek cellulari 4 neurotek classici
yun [51] 2014	case report	1	F	Left eyebrow skin			CD68, Vimentin	thin spindle-shaped and stellate cells within an abundant myxoid stroma	Excision	Neurotek mixed
Wang [52] 2016	observational retrospective	7	4 M 3 F	not avaible			NKI / C3, PGP9.5, CD68	/		nerotek cellulare
Tham [53] 2016	case report	1	M	Oral cavity			S-100	fusiform and stellate cells; abundant myxoid stroma	Enucleoresection	neurotek classic
Boukovalas [54] 2016	case report	1	F	Nasal wing	8 mm	subcutis	MiTF	nests and fascicles of spindle and epithelioid cells with pale eosinophilic cytoplasm and vesicular nuclei; background of dense collagen,	Excision	cellular neurotek
Bartake [55] 2017	case report	1	F	hard palate	1,5 cm	submucosal	S100	myxomatous tissue, stellate and spindle-shaped cells and nerve fibers.	Enucleoresection	classic neurotek
Mora-Cantallops [56] 2020	case report	1	M	Medial rectus muscle	1 cm	muscolo retto mediale	S-100, CD34, CD56	myxoid matrix with fusocellular and stellate cells.	enucleoresection	classic neurotek

Massimo [57] 2020	case series and review	2	1 M 1 F	1 wrist, 1 upper lip	8 mm	dermis	CD10, CD68, SMA, and vimentin;	spindle and epithelioid cells with eosinophilic cytoplasm and mild atypia	Excision	2 cellular neurotek
Aronson [58] 1985	case report	1	f	scalp	2,5 cm	dermis	S 100, CEA, DAKO	Polygonal cells; elongated eytoplasmic processes	Excision	classic neurotek
Henmi [59] 1986	case report	1	f	right nostril	1 cm	dermis	S- 100	cell nests consisting of atypical epithelial-like cells	Enucleoresection	classic neurotek
Mason [60] 1986	case report	1	f	lip	1 cm	dermis	/	nests and whorls of spindle-shaped cells with abundant myxoid cytoplasm	Excision	Cellular neurotek
Pepine [61] 1992	case report	1	m	nose	1 cm	dermis	/	epithelioid and stellate cells in a myxoid stroma	Enucleoresection	classic neurotek
Husain [62] 1994	case report and review	14	8 f 6 m	3lower and 3 up extremities, 2 thorax, 2 scalp, 1 shoulder, 1 lip, 1 face, 1 forhead	/	dermis	S- 100,	stellate and spindle-shaped cells; Nuclear pleomorphism	Excision	3 myxoid 11 cellular
Peñarrocha [63] 2000	case report	1	F	tongue	3 cm	muscles plane	S-100, protein, NSE, and vimentin	fusiform cells with wavy cytoplasm, abundant capillary neovascularization; myxoid stroma	Enucleoresection	classic neurotek
Barrett [64] 2001	case report	1	m	buccal vestibular sulcus	1 cm	submucosal	NKI/C3, NSE, SMA PGP, XIIIa, S100	pale epitheliod cells separated by fasciles of spindle cells	Excision	nerotek cellular
Laskin [65] 2000	case series	11	6 f 5m	2 head, 2neck, 4 lower and 3 up extremities	/	dermis	S100, CIV, SMA, XIIIa	multinodular or lobulated architecture of spinde cells	Excision	classic neurotek
Schorting huis 2001 [66]	case report	1	m	tongue	0.8 cm	muscles plane	S- 100, EMA	stellate and spindle-shaped cells with basophilic ovoid vesicular nuclei scattered in a myxoid and avascular stroma	Enucleoresection	classic neurotek
Makino [67] 2002	case report and review	1	m	tongue	1 cm	muscles plane	S100, NSE, VM	spindle- or stellate-shaped cells with a myxoid background.	Enucleoresection	classic neurotek
Levin [68] 2002	case report	1	m	nose	4 cm	dermis	S- 100, desmin, vimentin	spindled and ovoid, cells separated by thick collagen bands.	Enucleoresection	classic neurotek
Page [69] 2004	case series	11	8 f 3m	5 nose, 2 neck, 2 lower and 1 upper extremities, 1 shoulder	/	dermis	Mitf, NKI/C3	spindled and epithelioid cells,	Excision	2 Cellular 9 Mixed
Kim [70] 2006	case report	1	f	tongue	2 cm	muscles plane	CD56, CD68 (clone PG-M1), and desmin	lobules of well-circumscribed oval-to-spindle neoplastic cells in a poor myxoid stroma fibrous connective tissue,	Excision	cellular neurotek
Nishioka [71] 2009	case series	3	2 f 1 m	oral cavity	2 cm	submucosal	S-100 protein, NSE, NGFR	pindle cells admixed with varying amount of myxoid matrix	Excision	cellular neurotek
Plaza [72] 2009	observational retrospective	31	23 f 8 m	10 upper and 5 lower extremities, 4 nose, 4 scalp, 3 thorax, 3 face, 2 shoulder	/	dermis	S100A6, SMA	nests and bundles of epithelioid cells	Excision	cellular neurotek
Garcia - Gutiérrez [73] 2010	case report	1	m	multiple localized to the face	2-3cm	dermis	S100A6, CD63 (NKI/C3), CD10, and PGP 9.5 (Figs. 5A–D), XIIIa and vimentin.	spindled to epithelioid cells embedded in a sclerotic stroma with focal areas of stromal hyalinization	Enucleoresection	classic neurotek

Kah [74] 2011	case report	1	f	palpebral	1,5 cm	dermis	CD63	spindle to polygonal cells within a myxoid stroma; eosinophilic cytoplasm	Enucleoresection	classic neurotek
Fox [75] 2012	case series	14	6 f 8 m	3 neck, 4 upper and 2 lower extremities, 2 back, 1 thorax, 1 scalp, 1 shoulder	/	dermis	PAX2, NKI/C3, CD10,MiTF	nests and fascicles of histiocytoid to spindled cells; of nests by collagen bands	Excision	cellular neurotek
Emami [76] 2013	case report	1	f	oral floor	0,8 cm	submucosal	CD63, NKI-C3, XIIIa	spindle and epitheloid cells	Excision	cellular neurotek
Requena [77] 2013	case series	9	4 f 5 m	lip	/	dermis	S100A6, MiTF, NKI/C3, PGP9.5, EMA, and NSE	plexiform pattern of nests of spindle cells embedded in a slightly myxoid stroma	Excision	cellular neurotek
Rozza De Menezes[78] 2013	case report and review	1	f	right buccal mucosa	1,5 cm	submucosal	anti-S-100, NSE, EMA	spindle and stellate cells with ovoid vesicular nuclei; myxoid stroma with sparse collagen fibers	Enucleoresection	classic neurotek
Bashline [79] 2014	case report and review	1	f	scalp	0,5 cm	dermis	NK1C3	spindled and epithelioid cells; fascicular growth pattern	Excision	cellular neurotek
Fried [80] 2014	observational retrospective	34	20 f 14 m	7 nose, 11 upper and 5 lower extremities, 3 neck, 3 face, 3 shoulder, 2 thorax,	/	dermis	SOX-10, S100, NKI/C3, SMA, MiTF	spindled and/or epithelioid cells arranged in a fascicular and/or nested pattern with sparse (cellular) or abundant (classic) myxoid component	Excision and Enucleoresection	25 Cellular 8 mixed 1 NSM
Navarrete - Dechent [81] 2015	case report	1	m	forehead	4 mm	dermis	CD10	spindle cell tumor, including an eosinophilic cytoplasm with mild cellular pleomorphism and moderately dense fibrous stroma	Enucleoresection	classic neurotek
Bhat [82] 2015	case report	1	f	neck	4 mm	dermis	S100	stellate cells with cytoplasmic processes, round to spindle lacking the nuclear atypia and occasional giant cells	Excision	cellular neurotek
Gray [83] 2016	case report	1	m	eyelid	4mm	dermis	PGP 9.5, CD68, XIII	nests and bundles of epithelioid to spindled cells with abundant eosinophilic cytoplasm, separated by sclerotic collagen	Excision	cellular neurotek
Frydrych [84] 2017	case report	1	f	tongue	6 mm	muscles plane	S100, vimentin,	stellate and spindle-shaped cells. Rare Nuclear pleomorphism and mytotic figures	Enucleoresection	classic neurotek
Cavacchini [85] 2018	Case series	2	1 f 1 m	forehead, thing	7 mm	dermis	EMA, NKI/C3	Spindle cells; abundant eosinophilic cytoplasm with vesicular nuclei and mild atypia	Excision	cellular neurotek
Gallo [86] 2019	case series	2	1 f 1 m	1 wrist, 1 upper lip	7 mm	dermis	CD10, CD68, vimentin, and SMA	plexiform and multinodular pattern of spindle and epithelioid cells; multinucleated cells and scattered mitotic figures	Excision	cellular neurotek

Table 1: *Paper's check list*

Clinical features

In most cases the female sex was involved (462 F – 64,1%) with a male to female ratio of 1:1,8. The average age of 721 cases was 26,4 years, with the youngest case of 6 months old, and the oldest of 88 years old. 52.1% of cases were aged between 6 months and 25 years, 35.6% between 26 and 50 years, 12.3% between 51 and 88 years. Neurothekeomas typically presented as asymptomatic, solitary, slow-growing lesions with a mean diameter of 1,5 cm (the smaller lesion measured 0,4 cm while the larger

6 cm). The sites of lesions were: 260 head (36,1%), 187 upper extremities (25,9%), 85 trunks (11,8%), 84 lower extremities (11,6%), 36 shoulder (5%), 23 neck (3,2%) and 46 not reported (6,4%). The 260 head cases were divided in 116 face (44,6%), 59 nose (22,7%), 49 scalp (18,8%), 11 oral cavity (4,2%), 10 lip (3,9%), 7 forehead (2,7%), 6 tongue (2,3%), 2 others (1 medial rectus muscle and 1 paranasal sinuses – 0,8%).

Histological and Cytological features

Histologically and cytologically Neurothekeomas were divided in three subtypes: cellular (65,7%) mixed (17,5%) and classic – myxoid (16,8%). All the subtypes presented as dome-shaped masses that most frequently involved the subcutaneous/submucosal plane (55,1% of the total cases) and dermas (41,5%). Skeletal muscle involvement was uncommon (2,9%) and largely restricted to the facial region (mimic muscles and rectus medial muscle). Bone plane involvement was rare (0,5%) and limited to maxillary and mandibular bones. The differences among the 3 subtypes of tumors lied in histology and cytology: 1) Cellular neurothekeoma was characterized by nests of spindle or epithelioid cells immersed in a fibrotic stroma with the presence of sclerotic collagen fibers, and non-tumor multinucleated and osteoclastic giant cells. Tumor cells had abundant eosinophilic cytoplasm with vesicular nuclei, mild atypia and low mitotic rates (ranged from 0 to 16 mitotic figures for mm^2 with a mean mitotic rate of 4/mm^2). Perineural invasion was uncommon, while vascular invasion was completely absent. Three cases of cellular neurothekeomas were described as atypical because of diffusely infiltrated borders, vascular invasion, severe cellular atypia, and frequent mitosis (until 15/ mm^2). 2) Classic neurothekeoma was characterized by bundles of stellate cells immersed in a myxoid stroma without collagen fibers. Tumor cells had abundant eosinophilic cytoplasm with vesicular nuclei, mild atypia and low mitotic rates (mean mitotic rate of 3/mm^2). 3) Mixed neurothekeoma was characterized by features of both other subtypes, in particular both myxoid stroma and sclerotic collagen fibers.

Immunohistochemical features

In order of frequency, the neoplastic cells of classic neurothekeomas were immunoreactive for S-100 Protein (86,9% of all cases), vimentin (47,8%), muscle-specific actin, a-smooth muscle actin and EMA (31,8%), neuron-specific enolase (NSE), GFAP, CD10, CD34 and XIIa Factor (18,2%) while NKI/C3 and PGP9.5 in a minor percentage of cases. In order of frequency, the neoplastic cells of cellular neurothekeomas were immunoreactive for NKI/C3 (62,1%), CD68 (55,2%), Vimentin and a-smooth muscle actin (41,4%), CD10 (37,9%), PGP9.5 (34,5%), NSE and microphthalmia transcription factor (MITF) (31,1%), S-100 Protein and XIIa Factor (20,7%) while CD99, collagen IV, HMB45, CD34, NGFR, PAX2, EMA and Podoplanin D2-40 in a minor percentage of cases. In the mixed neurothekeomas, in addition to the markers already mentioned, also CD56 and SOX10 were found.

Surgery and Follow-up

In all cases, the tumors were treated by surgery. In particular, cellular neurothekeomas were treated by a simple excision, while classic and mixed neurothekeomas as well as the atypical cellular forms were treated by enucleoresection with healthy margins and, if necessary, reconstruction.

The reported percentage of recurrence was 7,5% without cases of metastasized tumor.

Main features of the three neurothekeomas types are summarized in Table 2.

Types and rates	Clinical features	Histological features	Cytological features	Immunohistochemical features	Treatment
Cellular NTK (65,7%)	-asymptomatic, solitary, slow-growing lesion -mean diameter of 1,5 cm	-deep planes not involved -<10% of myxoid matrix - nests of spindle with the presence of sclerotic collagen fibers	-eosinophilic cytoplasm - vesicular nuclei - mild atypia - mean mitotic rate of 4/mm^2	In order of frequency: NKI/C3, CD68, Vimentin, a-smooth muscle actin, CD10, PGP9.5, NSE and microphthalmia transcription factor (MITF)	Simply Excision
Classic NTK (16,8%)	-asymptomatic, solitary, slow-growing lesion -mean diameter of 1,5 cm	-deep planes not involved >50% of myxoid matrix - bundles of stellate cells immersed in a myxoid stroma without collagen fibers	-eosinophilic cytoplasm - vesicular nuclei - mild atypia - mean mitotic rate of 4/mm^2	In order of frequency: S-100 Protein, vimentin, muscle-specific actin, a-smooth muscle actin and EMA, neuron-specific enolase (NSE), GFAP, CD10, CD34 and XIIa Factor	Enucleoresection with healthy margin
Mixed NTK (17,5%)	-asymptomatic, solitary, slow-growing lesion -mean diameter of 1,5 cm	-deep planes not involved ->10– <50% of myxoid matrix - features of both other subtypes, in particular both myxoid stroma and sclerotic collagen fibers.	-eosinophilic cytoplasm - vesicular nuclei - mild atypia - mean mitotic rate of 4/mm^2	Both the markers of other subtypes	If S-100 +: Enucleoresection with healthy margin

Table 2: *Summarized features of the three neurothekeomas types*

Discussion

Neurothekeoma is a slow-growing benign tumor that interests mainly superficial tissues and has been studied since the 1980s. The first author who coined this term was Gallager [2] who, in a retrospective observational study on 53 patients, described a benign tumor of the dermis having a neural origin and a relationship to the Schwann sheath cells of peripheral nerves. The interest in the study of this type of lesion has grown over the years, and several authors dedicated to defining the origin, the etiopathogenesis and the clinical, histological, and immunohistochemical characteristics. Thus, the data obtained from our review were compared with the international literature on this topic. [10] First of all, Neurothekeomas tends to occur in younger age, around the second or third decades with a mild female predominance [10]. Our review, according to literature analysed, highlights a male to female ratio of 1:1,8 and a mean age of 26,4 years [11]. The tumors have been classified in three subtypes based on etiopathogenetic, cyto-histological, and immunohistochemical characteristics: cellular neurothekeomas with <10% of myxoid matrix, mixed-type with 10– <50% of myxoid matrix and myxoid neurothekeomas with >50% of myxoid matrix[7]. The term ''cellular neurothekeoma'' was first used by Rosati et al. in 1986 to distinguish it from the myxoid variant which was defined as "classic neurothekeoma" [12].

The cell of origin of NSM is controversial: Fetsch et al [7] postulated that SMA and EMA positivity suggests some similarity to histiocytic cells and fibroblasts, while S100 protein and NSE to Schwann cells or other perineural cells. So cellular NTK can origin by histiocytic cells and fibroblasts, while classical NTK by Schwann cells and other perineural cells. Moreover, Misago et al [13] distinguished a histiocytic origin from a fibroblastic or nervous one, based on the expression of different genes: Cellular neurothekeoma expressed genes involved in macrophage differentiation, Cell migration, cytoskeleton organization, Fibroblast growth, tissue remodeling, ECM mineralization such as ADAM12, DPT, FAP, PDPL, MMP1 and TNFAIP6. Classic neurothekeoma expressed genes involved in neural crest development, myelin and axonal growth and neuronal adhesion such as SOX10, MPZ, NTM, SOX2, PMP2, NCAM1, MBP and SORBS1. KP-1 and PG-M1 expression is associated to histiocytic differentiation [13].

Our review, according with the literature [14,15], highlights that the head and neck are the most affected sites (39,3%) with the face and the nose at the highest occurrences. Cases of the oral cavity are rare and mainly concentrated on the area of the lips (3,9%). The most common intraoral site is the tongue.

Several authors [7,14,15] reported that tumors were non-capsulated, located in dermal tissue with a subcutaneous involvement in 85% of the cases, and typically organized in multiple small nodules. Our research confirms that the involvement of the deep planes is rare (3,4%). Mean diameter was 1,5 cm, 90% of lesions between 0,4 cm and 2 cm, but tumor size of 6 cm was described and defined as atypical [16-18]. Wilson et al [19] affirmed that it is characterized by large size of up to 6 cm, penetration into subcutaneous fat or muscle, diffusely infiltrating borders, vascular invasion, a high mitotic rate, and marked cytological pleomorphism. Based on our data, the most common subtype is Cellular Neurothekeoma (65,7%). All the three subtypes of tumors were associated with some sclerotic collagen that was most present in cellular neurothekeomas and least evident in the myxoid examples. Moderate or marked collagen deposition around individual tumor nodules was noted predominantly in cellular neurothekeomas. Osteoclast giant cells are also present, but they are generally sparse and do not appear to be neoplastic [7]. They are identified predominantly in cellular neurothekeomas. The myxoid stroma is more abundant in the classical subtype [20].

In terms of cytomorphology, in accordance with literature [21] cellular neurothekeomas were composed of spindle cells (28%), of epithelioid cells (14%), and of cells with variably epithelioid to spindled features (58%). Classic neurothekeomas were composed of spindle cells (54%), of stellate shaped cells (49%) and of epithelioid cells (7%). The tumor cells contained pale vacuolized eosinophilic cytoplasm and in 70% showed mild atypia in terms of abundant vesicular, ovoid or irregularly shaped nuclei with prominent nucleoli. Cellular neurothekeomas in 10% of cases showed giant cells. The mean mitotic rate was 4 per 10 high power fields (HPF) (range, 0 to 16) for cellular neurothekeomas and 3 per 10 HPF for classic neurothekeomas. Only 4% of total tumors showed perineural invasion, and 3% showed vascular invasion.[3 - 7]

In terms of immunohistochemical features, our review showed that the neoplastic cells of classic neurothekeomas were mainly immunoreactive for S-100 Protein (86,9% of all cases), vimentin (47,8%), muscle-specific actin, a-smooth muscle actin and EMA (31,8%) and neuron-specific enolase (NSE), GFAP, CD10, CD34 and XIIa Factor (18,2%). The expression of these factors confirms the neuronal or perineuronal origin of the classical neurothekeoma. Moreover, the expression of the S-100 protein is connected with a high local recurrence. [3 - 7] In their observational study, Fetsch et al [22] documented 16 on 34 (47%) recurrent disease on follow-up in classic neurothekeomas S-100 protein positive locally excised. Considering a relatively high local recurrence rate, a complete local excision with a margin of healthy tissue should generally be considered an optimal treatment of the disease. Hence, as the analysis of the literature [15,23,24] revealed, classic neurothekeoma with S-100 protein positivity should be excised with safety margins to prevent local recurrences. This result justifies our aggressive surgical approach with safety margins of 1 cm of healthy tissue.

The neoplastic cells of cellular neurothekeomas were mainly immunoreactive for NKI/C3 (62,1%), CD68 (55,2%), Vimentin and a-smooth muscle actin (41,4%), CD10 (37,9%), PGP9.5 (34,5%), NSE and microphthalmia transcription factor (MITF) (31,1%) confirming the histiocytic and fibroblastic origin. [13,25] The analysis of literature [26,27] showed that in these cases the recurrence rate is low, so the chosen treatment is a local excision with a few millimeters of healthy tissue.

Our case was a classic neurothekeoma with immunoreactivity to the s-100 protein. For this reason, we opted for a surgical treatment of complete excision with margins of 1 cm of healthy tissue. Considering the position and the size of the tumor, this excision required a reconstruction with local flaps. Based on data for the selected case in the literature, the Bengt-Johanson's step flap was considered the best option. [8,28] This technique has proved to be effective both in terms of functionality and aesthetics for our patient. Furthermore, the large excision with safety margins avoided relapses at the one-year follow-up.

Conclusion

Our review highlights that neurothekeoma is a benign tumor that mainly afflicts young women and mainly occurs in the superficial planes of the head and neck. Among the three types, the cellular type is the most frequent, but the most aggressive is the classic one because the expression of the S-100 protein determines a high local recurrence. For this reason, a local excision treatment is sufficient for the cellular neurothekeoma while in the classic type with the presence of this protein, a wide local excision with healthy tissue margins is required. The treatment of our case demonstrates that, by following this guide, relapse can be avoided.

Declarations

Funding: Not applicable

Conflicts of interest: The authors report no conflicts of interest

Availability of data and material: Not applicable

Code availability: Not applicable

Ethics approval: Only the patient's consent was requested.

Consent to participate: Patient's consent was obtained.

Consent for publication: Patient's consent was obtained.

Financial Disclosure Statement: The authors have no financial interest to declare regarding the content of this article.

References

1. Harkin JC, Reed RJ. (1969). Tumors of the peripheral nervous system. Atlas of tumor pathology, 2nd series, fascicle 3. Washington DC: Armed Forces Institute of Pathology. 60-64.
2. Gallager RL, Helwig EB. (1980). Neurothekeomaea benign cutaneous tumor of neural origin. Am J Clin Pathol. 74:759-764.
3. Argenyi ZB, LeBoit PE, Santa Cruz D, Swanson PE, Kutzner H. (1993). Nerve sheath myxoma (neurothekeoma) of the skin: light microscopic and immunohis- tochemical reappraisal of the cellular variant. J Cutan Pathol. 20:294-303.
4. Blumberg AK, Kay S, Adelaar RS. (1989). Nerve sheath myxoma of digital nerve. Cancer; 63:1215-1218.
5. Barnhill RL, Dickersin GR, Nickeleit V, Nickeleit V, Bhan AK, Muhlbauer JE, Phillips ME, Mihm MC Jr. (1991). Studies on the cellular origin of neurothekeoma: clinical, ligh microscopic, immunohistochemical, and ultrastructural observations. J Am Acad Dermatol. 25:80-88.
6. MentzelT. (1999). Cutaneous neural neoplasms-an update. Pathologe. 20:98-109.
7. Fetsch JF, Laskin WB, Hallman JR, Lupton GP, Miettinen M. (2007). Neurothekeoma: An Analysis of 178 Tumors with Detailed Immunohistochemical Data and Long-term Patient Follow-up Information. Am J Surg Pathol. 31:1103–1114.
8. Blomgren I, Blomqvist G, Lauritzen C, Lilja J, Peterson LE, Holmström H. (1988). The Step Technique for the Reconstruction of Lower Lip Defects after Cancer Resection: A Follow-up Study of 165 Cases. Scandinavian Journal of Plastic and Reconstructive Surgery. 22(1):103-111.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 151:264-269.
10. Kao EY, Kernig ML. (2021). Neurothekeoma. In: StatPearls. Treasure Island (FL): StatPearls Publishing.
11. Almeida TFA, Verli FD, Dos Santos CRR, Falci SGM, Almeida LY, Almeida LKY, Mesquita ATM, León JE. (2018). Multiple Desmoplastic Cellular Neurothekeomas in Child: Report of the First Oral Case and Review of the Literature. Head Neck Pathol. 12(1):75-81.
12. Rosati LA, Fratamico FC, Eusebi V. (1986). Cellular neurothekeoma. Appl Pathol. 4:186-191.
13. Misago N, Satoh T, Narisawa Y. (2004). Cellular neurothekeoma with histiocytic differentiation. J Cutan Pathol. 31(8):568-572.
14. Maktabi AMY, Al-Hussain H, Khoja H, Alkatan HM. (2019). Unusual Recurrent Lateral Canthus Mass in a 16-Year-Old Male Patient: Neurothekeoma. Case Rep Oncol. 12(3):693-697.
15. Safadi RA, Hellstein JW, Diab MM, Hammad HM. (2010). Nerve sheath myxoma (neurothekeoma) of the gingiva, a case report and review of the literature. Head Neck Pathol. 4(3):242-245.
16. Park MC, Seung WB. (2016). Cellular Neurothekeoma of the Scalp in the Elderly. Brain Tumor Res Treat. 4(1):17-20.
17. Benbenisty KM, Andea A, Metcalf J, Cook J. (2006). Atypical cellular neurothekeoma treated with Mohs micrographic surgery. Dermatol Surg. 32(4):582-587.
18. Campanati A, Brandozzi G, Sisti S, Bernardini ML, Offidani AM. (2007). Atypical neurothekeoma: a new case and review of the literature. J Cutan Pathol. 34(5):435-437.
19. Wilson AD, Rigby H, Orlando A. (2008). Atypical cellular neurothekeoma-a diagnosis to be aware of. J Plast Reconstr Aesthet Surg. 61(2):186-188.
20. Papadopoulos EJ, Cohen PR, Hebert AA. (2004). Neurothekeoma: report of a case in an infant and review of the literature. J Am Acad Dermatol. 50(1):129-134.
21. Hornick JL, Fletcher CD. (2007). Cellular neurothekeoma: detailed characterization in a series of 133 cases. Am J Surg Pathol. 31(3):329-340.
22. Fetsch JF, Laskin WB, Miettinen M. (2005). Nerve sheath myxoma: a clinicopathologic and immunohistochemical analysis of 57 morphologically distinctive, S-100 protein- and GFAP-positive, myxoid peripheral nerve sheath tumors with a predilection for the extremities and a high local recurrence rate. Am J Surg Pathol. 29(12):1615-1624.
23. Rodríguez-Uña I, Troyano-Rivas JA, González-García C, Chícharo-de-Freitas R, Ortiz-Zapata JJ, Ortega-Medina L, Toledano-Fernández N, García-Feijoo J. (2015). Orbital nerve seath myxoma with extraocular muscle involvement: a rare case. Semin Ophthalmol. 30(4):316-320.
24. Sánchez-Orgaz M, Grabowska A, Arbizu-Duralde A, Romero-Martín R, Patrón M, Diéguez E, García-Cabezas MA. (2011). Orbital nerve sheath myxoma: a case report. Ophthalmic Plast Reconstr Surg. 27(4):106-108.
25. Jaffer S, Ambrosini-Spaltro A, Mancini AM, Eusebi V, Rosai J. (2009). Neurothekeoma and plexiform fibrohistiocytic tumor: mere histologic resemblance or histogenetic relationship? Am J Surg Pathol. 33(6):905-913.
26. See TRO, Stålhammar G, Grossniklaus HE. (2019). Neurothekeoma of the eye, conjunctiva, and periorbital adnexa: A report of two cases and brief review. Surv Ophthalmol. 64(6):852-857.
27. Murphrey M, Huy Nguyen A, White KP, Krol A, Bernert R, Yarbrough K. (2020). Pediatric cellular neurothekeoma: Seven cases and systematic review of the literature. Pediatr Dermatol. 37(2):320-325.
28. Roldán JC, Schulte-Mattler W. (2016). Stein's Double Cross-Lip Flaps Combined with Johanson's Step Technique for Subtotal Lower Lip Reconstruction. Plast Reconstr Surg Glob Open. 4(2):615.
29. Barnhill RL, Mihm MC Jr. (1990). Cellular neurothekeoma. A distinctive variant of neurothekeoma mimicking nevomelanocytic tumors. Am J Surg Pathol. 14(2):113-120.
30. Suh YL, Song KY, Kim JM. (1992). Nerve sheath myxoma (neurothekeoma)--a case report. J Korean Med Sci. 7(1):85-89.
31. Tiffee JC, Pulitzer DR. (1996). Nerve sheath myxoma of the oral cavity: case report and review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 82(4):423-425.
32. Tomasini C, Aloi F, Pippione M. (1996). Cellular neurothekeoma. Dermatology. 192(2):160-163.
33. Breuer T, Koester M, Weidenbecher M, Steininger H. (1999). Neurothekeoma, a rare tumour of the tongue. ORL J Otorhinolaryngol Relat Spec. 61(3):161-164.
34. Wong BY, Hui Y, Lam KY, Wei WI. (2002). Neurothekeoma of the paranasal sinuses in a 3-year-old boy. Int J Pediatr Otorhinolaryngol. 62(1):69-73.

35. Cohen NA, Samadi DS, Pawel BR, Kazahaya K. (2004). Cellular neurothekeoma of the maxilla. Ann Otol Rhinol Laryngol. 113(5):384-387.
36. Ward JL, Prieto VG, Joseph A, Chevray P, Kronowitz S, Sturgis EM. (2005). Neurothekeoma. Otolaryngol Head Neck Surg. 132(1):86-89.
37. Mahalingam M, Alter JN, Bhawan J. (2006). Multiple cellular neurothekeomas-a case report and review on the role of immunohistochemistry as a histologic adjunct. J Cutan Pathol. 33(1):51-56.
38. López-Cepeda LD, Navarrete-Franco G, Novales-Santacoloma J, Enriquez-Merino J. (2007). Scar-like lesion on dorsal nose (cellular neurothekeoma). Head Face Med. 3:39.
39. Koumanis DJ, Glickman LT. (2007). Facial neurothekeoma in a 10-year-old child. Can J Plast Surg. 15(3):175-177.
40. Mathew S, Nandeesh BN, Vasu U, Michael SG. (2008). Neurothekeoma of the eyelid: a case report. Indian J Ophthalmol. 56(4):334-336.
41. Zedek DC, White WL, McCalmont TH. (2009). Desmoplastic cellular neurothekeoma: Clinicopathological analysis of twelve cases. J Cutan Pathol. 36(11):1185-1190.
42. Wartchow EP, Goin L, Schreiber J, Mierau GW, Terella A, Allen GC. (2009). Plexiform fibrohistiocytic tumor: ultrastructural studies may aid in discrimination from cellular neurothekeoma. Ultrastruct Pathol. 33(6):286-292.
43. Müller CS, Tilgen W, Kutzner H, Pföhler C. (2009). Recurring mixed-type neurothekeoma of the face. Dermatoendocrinol. 1(4):220-222.
44. Vered M, Fridman E, Carpenter WM, Buchner A. (2011). Classic neurothekeoma (nerve sheath myxoma) and cellular neurothekeoma of the oral mucosa: immunohistochemical profiles. J Oral Pathol Med. 40(2):174-180.
45. Papalas JA, Proia AD, Hitchcock M, Gandhi P, Cummings TJ. (2010). Neurothekeoma palpebrae: A report of 3 cases. Am J Dermatopathol. 32(4):374-379.
46. Sheth S, Li X, Binder S, Dry SM. (2011). Differential gene expression profiles of neurothekeomas and nerve sheath myxomas by microarray analysis. Mod Pathol. 24(3):343-354.
47. Pan HY, Tseng SH, Weng CC, Chen Y. (2014). Cellular neurothekeoma of the upper lip in an infant. Pediatr Neonatol. 55(1):71-74.
48. Yamada S, Kitada S, Nabeshima A, Noguchi H, Sasaguri Y, Hisaoka M. (2013). Benign cutaneous plexiform hybrid tumor of perineurioma and cellular neurothekeoma arising from the nose. Diagn Pathol. 8:165.
49. Suarez A, High WA. (2014). Immunohistochemical analysis of KBA.62 in 18 neurothekeomas: a potential marker for differentiating neurothekeoma, but a marker that may lead to confusion with melanocytic tumors. J Cutan Pathol. 41(1):36-41.
50. Stratton J, Billings SD. (2014). Cellular neurothekeoma: analysis of 37 cases emphasizing atypical histologic features. Mod Pathol. 27(5):701-710.
51. Yun SJ, Park HS, Lee JB, Kim SJ, Lee SC, Won YH. (2014). Myxoid Cellular Neurothekeoma: A New Entity of S100-Negative, CD68-Positive Myxoid Neurothekeoma. Ann Dermatol. 26(4):510-513.
52. Wang GY, Nazarian RM, Zhao L, Hristov AC, Patel RM, Fullen DR, Chan MP. (2017). Protein gene product 9.5 (PGP9.5) expression in benign cutaneous mesenchymal, histiocytic, and melanocytic lesions: comparison with cellular neurothekeoma. Pathology. 49(1):44-49.
53. Tham AC, Chilagondanahalli NL, Bundele MM, Kanagalingam J. (2016). Oral Neurothekeoma of the Right Buccal Mucosa. Case Rep Otolaryngol. 4709753.
54. Boukovalas S, Rogers H, Boroumand N, Cole EL. (2016). Cellular Neurothekeoma: A Rare Tumor with a Common Clinical Presentation. Plast Reconstr Surg Glob Open. 4(8):1006.
55. Bartake A, Palaskar SJ, Narang B, Kathuriya P. (2019). Nerve sheath myxoma of the oral cavity: a distinct entity. Br J Neurosurg. 33(2):213-214.
56. Mora-Cantallops A, Won-Kim HR, Navarro-Cantero A, Martínez-San-Millán J, Sales-Sanz M. (2021). Nerve Sheath Myxoma Involving the Medial Rectus Muscle: A Case Report. Ophthalmic Plast Reconstr Surg. 37(2):60-62.
57. Massimo JA, Gasibe M, Massimo I, Damilano CP, De Matteo E, Fiorentino J. (2020). Neurothekeoma: Report of two cases in children and review of the literature. Pediatr Dermatol. 37(1):187-189.
58. Aronson PJ, Fretzin DF, Potter BS. (1985). Neurothekeoma of Gallager and Helwig (dermal nerve sheath myxoma variant): report of a case with electron microscopic and immunohistochemical studies. J Cutan Pathol. 12(6):506-519.
59. Henmi A, Sato H, Wataya T, Inaniwa Y, Mori Y. (1986). Neurothekeoma. Report of a case with immunohistochemical and ultrastructural studies. Acta Pathol Jpn. 36(12):1911-1919.
60. Mason MR, Gnepp DR, Herbold DR. (1986). Nerve sheath myxoma (neurothekeoma): a case involving the lip. Oral Surg Oral Med Oral Pathol. 62(2):185-186.
61. Pepine M, Flowers F, Ramos-Caro FA. (1992). Neurothekeoma in a 15-year-old boy: case report. Pediatr Dermatol. 9(3):272-274.
62. Husain S, Silvers DN, Halperin AJ, McNutt NS. (1994). Histologic spectrum of neurothekeoma and the value of immunoperoxidase staining for S-100 protein in distinguishing it from melanoma. Am J Dermatopathol. 16(5):496-503.
63. Peñarrocha M, Bonet J, Minguez JM, Vera F. (2000). Nerve sheath myxoma (neurothekeoma) in the tongue of a newborn. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 90(1):74-77.
64. Barrett AW, Suhr M. (2001). Cellular neurothekeoma of the oral mucosa. Oral Oncol. 37(8):660-664.
65. Laskin WB, Fetsch JF, Miettinen M. (2000). The neurothekeoma: immune-histochemical analysis distinguishes the true nerve sheath myxoma from its mimics. Hum Pathol. 31(10):1230-1241.
66. Schortinghuis J, Hille JJ, Singh S. (2001). Intraoral myxoid nerve sheath tumour. Oral Dis. 7(3):196-199.
67. Makino T, Utsunomiya T, Kamino Y, Kobayashi R, Fukumoto M, Yamamoto H, Nagura H. (2002). Nerve sheath myxoma of the tongue in a child. Int J Oral Maxillofac Surg.; 31(4):451-454.
68. Levin KA, Hayden R, Hanau CA, Galindo LM. (2002). Cytologic findings of myxoid neurothekeoma: case report based on fine-needle aspiration cytology, immunohistochemistry, and correlating histopathology. Diagn Cytopathol. 27(3):173-176.
69. Page RN, King R, Mihm MC Jr, Googe PB. (2004). Microphthalmia transcription factor and NKI/C3 expression in cellular neurothekeoma. Mod Pathol. 17(2):230-234.
70. Kim HJ, Baek CH, Ko YH, Choi JY. (2006). Neurothekeoma of the tongue: CT, MR, and FDG PET imaging findings. AJNR Am J Neuroradiol.; 27(9):1823-1825.
71. Nishioka M, Aguirre RL, Ishikawa A, Nagumo K, Wang LH, Okada N. (2009). Nerve sheath myxoma (neurothekeoma) arising in the oral cavity: histological and immunohistochemical features of 3 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 107(5):28-33.
72. Plaza JA, Torres-Cabala C, Evans H, Diwan AH, Prieto VG. (2009). Immunohistochemical expression of S100A6 in cellular neurothekeoma: clinicopathologic and immunohistochemical analysis of 31 cases. Am J Dermatopathol. 31(5):419-422.
73. García-Gutiérrez M, Toussaint-Caire S, González-Sánchez P, Ortiz-Hidalgo C. (2010). Multiple desmoplastic cellular

neurothekeomas localized to the face of a 16-year-old boy. Am J Dermatopathol. 32(8):841-845.
74. Kah TA, Yong KC, Annuar FH. (2011). Neurothekeoma palpebrae in association with multiple superficial angiomyxomas: Tegumental Angiomyxoma-Neurothekeoma syndrome (TAN syndrome). Clin Pract. 1(3):67.
75. Fox MD, Billings SD, Gleason BC, Moore J, Thomas AB, Shea CR, Victor TA, Cibull TL. (2012). Expression of MiTF may be helpful in differentiating cellular neurothekeoma from plexiform fibrohistiocytic tumor (histiocytoid predominant) in a partial biopsy specimen. Am J Dermatopathol. 34(2):157-160.
76. Emami N, Zawawi F, Ywakim R, Nahal A, Daniel SJ. (2013). Oral cellular neurothekeoma. Case Rep Otolaryngol. 2013:935435.
77. Requena L, Sitthinamsuwan P, Fried I, Kaddu S, Schirren CG, Schärer L, Hantschke M, Cerroni L, McCalmont TH, Kutzner H. (2013). A benign cutaneous plexiform hybrid tumor of perineurioma and cellular neurothekeoma. Am J Surg Pathol. 37(6):845-852.
78. Rozza-de-Menezes RE, Andrade RM, Israel MS, Gonçalves Cunha KS. (2013). Intraoral nerve sheath myxoma: case report and systematic review of the literature. Head Neck. 35(12):397-404.
79. Bashline B, Morrison M, Cha HC, Ramirez J. (2014). A Case of a Cellular Neurothekeoma Presenting with Headaches and Review of the Literature. Dermatopathology (Basel). 1(1):29-34.
80. Fried I, Sitthinamsuwan P, Muangsomboon S, Kaddu S, Cerroni L, McCalmont TH. (2014). SOX-10 and MiTF expression in cellular and 'mixed' neurothekeoma. J Cutan Pathol. 41(8):640-645.
81. Navarrete-Dechent C, Curi-Tuma M, Marín C, González S, Sandoval-Osses M. Cellular neurothekeoma: case report and its (un) relation with nerve sheath myxoma. An Bras Dermatol. 90(3(S1)):156-159.
82. Bhat A, Narasimha A, C V, Vk S. (2015). Nerve sheath myxoma: report of a rare case. J Clin Diagn Res. 9(4):7-9.
83. Gray ME, Palileo CM, Sheridan RM. (2016). Cellular neurothekeoma of the eyelid in a 6-year-old boy. J AAPOS. 20(4):374-376.
84. Frydrych AM, Firth NA. (2017). Oral nerve sheath myxoma: a rare and unusual intraoral neoplasm. Clin Case Rep. 6(2):302-305.
85. Cavicchini S, Guanziroli E, Del Gobbo A, Scaparro M, Gianotti R. (2018). Neurothekeoma, a hard to diagnose neoplasm among red nodules. Australas J Dermatol. 59(4):280-282.
86. Gallo G, Kutzner H, Mentzel T, Cesinaro AM. (2019). Cellular neurothekeoma: Report of two cases with unusual immunohistochemical features. J Cutan Pathol. 46(1):80-83.

DOI: 10.31579/2690-4861/212