Head and Neck Pathol (2018) 12:75–81
DOI 10.1007/s12105-017-0828-8

ORIGINAL PAPER

Multiple Desmoplastic Cellular Neurothekeomas in Child: Report of the First Oral Case and Review of the Literature

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Received: 24 February 2017 / Accepted: 27 May 2017 / Published online: 8 June 2017

Abstract Cellular neurothekeomas (CNs) are distinctive benign tumors of uncertain histogenesis, with predilection for the skin of the head and neck region. We describe the first case of multiple desmoplastic CNs (DCNs) affecting the oral cavity in a 9-year-old girl. Histopathologic evaluation showed a proliferation of spindle and epithelioid cells, forming nests and bundles, supported by exuberant fibrous stroma, as well as scattered multinucleated floret-like giant cells. The tumor cells were immunopositive for vimentin, CD63, CD56, whereas AE1/AE3, S100, CD34, α-SMA, GFAP, EMA, CD57 and NSE were negative. Ki-67 was <2%. Multiple DCNs should be considered in the differential diagnosis of oral nodular lesions.

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Keywords Oral cavity · Cellular neurothekeoma · Desmoplastic cellular neurothekeoma · Immunohistochemistry · Child

Introduction

Cellular neurothekeoma (CN) is an uncommon benign tumor of uncertain histogenesis, being more frequently observed in subcutaneous tissue of the upper limbs, head, neck and trunk. Clinically, CN presents as a solitary non-ulcerated nodule or papule, measuring <2.0 cm in diameter, usually affecting young adults with a slight female predominance [1]. Histologically, this neoplasm is poorly circumscribed occupying the thickness of the dermis, but sometimes it can extend to the subcutis. At higher magnifications, it is noticed the presence of nests and cords of epithelioid to spindle cells with slightly granular eosinophilic cytoplasm surrounding by dense fibrotic stroma. Uncommonly, areas exhibiting plexiform growth pattern or focal cellular atypia can also be visualized [1, 2]. CN behaves in a benign fashion and rarely recur (remarkably, in some incompletely excised facial lesions). Large tumor size (>2 cm) and histologic features such as mitotic figures, cellular pleomorphism and infiltration of fat or skeletal muscle, seem to have no clinical significance [1].

Oral CN is extremely rare [3]. To the best or our knowledge, only 15 oral cases diagnosed as CN and/or nerve sheath myxoma (NSM) have been reported in the English-language literature (Table 1). In this concern, according to relevant studies, the main differential diagnosis for CN is NSM. Unlike NSM, CN rarely occurs on the hands and fingers. Microscopically, CNs show irregular, infiltrative margins, while NSM exhibits lobules well demarcated. NSM is consistently positive for S100 and negative for NKI-C3,

Table 1 Cases of cellular neurothekeoma affecting the oral mucosa in children and adults

Author	Age (years)/ Gender	Site	Size (cm)	Duration before excision	Clinical diagnosis	Original diagnosis	Diagnosis after reclassification[a]	Growth rate/Follow-up
Breuer et al. [24]	12/F	Tongue	2	Birth/12 years	NI	NTK	Probable CN[c]	Rapid in the interval between two operations
Penarrocha et al. [25]	Newborn/F	Tongue	3×2.5	At birth	NI	NSM (NTK)	Probable CN[c]	NI
Barret and Suhr [16]	29/M	Buccal vestibular sulcus	1	NI	Scar tissue	CN	CN	NI
Kim et al. [26]	15/F	Tongue	2.1	7 months	NI	NTK	Probable CN[c]	Slow
Nishioka et al. [17]	53/M	Buccal mucosa	4.0×2.0	NI	Benign tumor	NSM (NTK)	NSM[b]	NI
	2/F	Buccal region	0.7×0.8	9 months	Fibro-epithelial polyp	NSM (NTK)	NSM	NI
	52/F	Lower lip	0.7×0.7	3 years	Benign tumor	NSM (NTK)	NSM	NI
Plaza et al. [27]	64/F	Mouth	NI	NI	NI	CN	CN	NI
	36/F	Cheek	NI	NI		CN	CN	NI
Safadi et al. [28]	32/F	Gingiva	0.8×0.6	NI	NI	NSM (NTK)	Probable CN[c]	NI
Vered et al. [3]	12/M	Buccal gingiva	1	1 year	Fibroma, giant cell lesion	Classic NTK	NSM	NI
	25/M	Buccal gingiva	0.3	>1 year	Fibroma	CN	CN	NI
	31/F	Maxillary vestibule	0.7	4 months	Mucocele	Classic NTK	NSM	NI
	35/F	Palatal gingiva	0.6	20 years	Fibroma	Classic NTK	NSM	NI
Pan et al. [29]	6 months/ M	Upper lip	1	NI	Epidermoid cyst	CN	Probable CN[c]	NI
Emami et al. [30]	15/F	Floor of the mouth	0.8	NI	NI	CN	CN	No recurrence after 8 months
Ishikawa et al. [31]	35/F	Upper Lip	0.35	4 years	NI	CN	Probable CN[c]	NI
Present case	9/F	Buccal mucosa/ upper lip (internal mucosa)	1.5×1.5	3 months	Neurofibroma Schwannoma Myofibroma	CN	CN	No recurrence after 3 years

CN cellular neurothekeoma, *F* female, *M* male, *NTK* neurothekeoma, *NSM* nerve sheath myxoma, *NI* not informed

[a]Diagnosis according to Fetsch et al. [2], Fetsch et al. [4] and Hornick & Fletcher [1] studies

[b]This case showed histopathological features mimicking spindle cell lipoma

[c]Probable CN: incomplete immunohistochemical panel

whereas CN shows an opposite immunostaining pattern [1, 2, 4].

Clinically, oral CN manifests itself as a nodular lesion, firm consistency, covered by normal-appearing oral mucosa, asymptomatic or mildly painful [3]. The clinical differential diagnosis includes benign mesenchymal tumors like neurofibroma, schwannoma, leiomyoma, myofibroma and, eventually, fibrous hyperplasia [1, 3].

Interestingly, several CN cases containing marked stromal hyalinization have been reported, being referred as desmoplastic CN (DCN) [1, 5–8]. Moreover, multiple CNs in the head and neck region affecting a 30-year-old male [9], and multiple DCNs localized to the face of a 16-year-old boy [10], have been reported. To the best of our knowledge, to date, there is no published case showing oral cavity involvement by DCN (Table 2).

We present herein the first case of a 9-year-old girl with multiple DCNs affecting the buccal mucosa and upper lip which appeared over a period of 3 months.

Table 2 Cases of desmoplastic cellular neurothekeoma (DCN) collected in Medline database

Author	Age (years)/ gender	Site	Size (cm)	Duration	Clinical diagnosis	Follow-up without recurrence (months)
D' Antonio et al. [7]	44/M	Thigh	NI	NI	NI	3
Garcia- Gutierrez et al. [10]	16/M	Face	2–3	2 years	Angiofibromas, adnexal neoplasms, xanthogranulomas	NI
Weng et al. [8][a]	29/F	Nose	0.5	2 months	Basal cell carcinoma, epidermoid cyst, follicular neoplasm, adnexal tumor, dermal melanocytic nevus	NI
Zedek et al. [5]	26/F	Ulnar wrist	0.8	NI	Papule	22
	11/M	Posterior scalp	NI	NI	Painful nodule	42
	43/F	Postauricular region	NI	NI	Gray nodule	42
	41/F	Eyebrow	NI	NI	Calcified cyst, pilomatrixoma	31
	3/F	Sternum	NI	NI	NI	NI
	16/F	Buttock	NI	NI	NI	Lost to follow-up
	44/M	Second finger	0.5	3 months	Papule	11
	55/F	Breast	NI	NI	Fibrous histiocytoma	24
	14/M	Thigh	NI	NI	Plaque with central papule	22
	7/F	Arm	1.25	NI	Nodule, pilomatrixoma	13
	52/F	Arm	NI	NI	Keloyd	18
	48/F	Thigh	NI	NI	Cyst	14
Present case	9/F	Buccal mucosa/ upper lip (internal mucosa)	1.5	3 months	Neurofibroma Schwannoma Myofibroma	36

All DCNs were classified according to the diagnostic criteria of the Fetsch et al. [2], Fetsch et al. [4] and Hornick & Fletcher [1] studies

DCN desmoplastic cellular neurothekeoma, *F* female, *M* male, *NI* not informed

[a]Probable DCN: case with incomplete immunohistochemical panel

Case Report

A 9-year-old girl presented to a Stomatology Service (UFVJM), Diamantina, Brazil, accompanied by his father, with multiple, slightly symptomatic, oral nodules affecting the buccal mucosa, which arose over the course of 3 months. During anamnesis, the child reported exacerbation of symptoms during palpation. Moreover, she does not report trauma or previous surgery in the lesional area.

The clinical examination revealed the presence of two submucosal nodular lesions, mobile, painful on palpation, measuring approximately 1.5 × 1.5 cm in diameter, as well as other small, ill-defined lesions, located on the left side of buccal mucosa and upper lip (Fig. 1). The clinical differential diagnoses were neurofibroma, schwannoma or myofibroma. After incisional biopsy of the lesion, the microscopical analysis revealed a diffuse proliferation of spindle cells supported by exuberant connective tissue stroma, permeating bundles of skeletal muscle and adipose tissue in the deeper part. Moreover, a vague micronodular architecture was evidenced. In high-power view, the lesion was composed of epithelioid to spindled cells with palely granular eosinophilic cytoplasm forming nests and bundles, separated by desmoplastic stroma. Moreover, scattered multinucleated floret-like giant cells were visualized (Fig. 2a–c). The cytoarchitectural organization and desmoplastic stroma were highlighted by Masson's Trichrome (Fig. 2d). By immunohistochemical analysis, the tumor

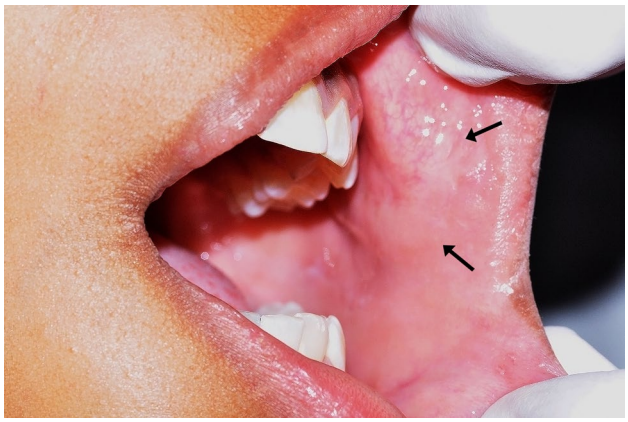

Fig. 1 Clinical features of the desmoplastic cellular neurothekeoma affecting the buccal mucosa and upper lip of the left side in a child patient

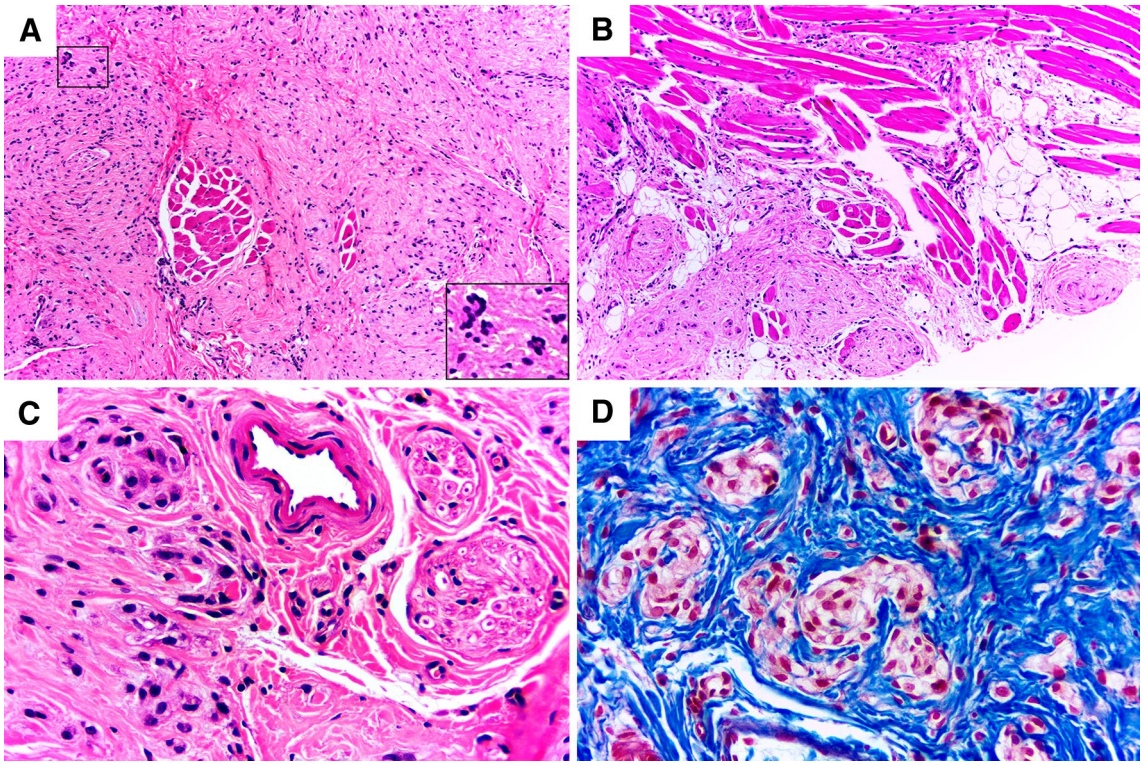

Fig. 2 **a** Diffuse proliferation of spindle cells supported by exuberant connective tissue stroma (H&E, ×10). Notice sparse multinucleated floret-like giant cells (*inset*, ×40). **b** The tumor cells permeate bundles of skeletal muscle and adipose tissue (H&E ×10). **c** In high-power view, visualize epithelioid cells with granular eosinophilic cytoplasm forming nests adjacent to neurovascular bundle (H&E, ×40). **d** The cytoarchitectural organization and desmoplastic stroma are highlighted by Masson's Trichrome (×40)

cells were positive for vimentin, CD63 (NKI-C3), focally for CD56, whereas AE1/AE3, S100, CD34, α-SMA, GFAP, EMA, CD57 and NSE were negative. Ki-67 labelling index was <2% (Fig. 3).

Given the morphological and immunohistochemical findings, was established the diagnosis of oral DCN. Since the patient has other lesional areas, surgical removal of them all, was performed. The material was sent for histopathological analysis that newly confirmed the diagnosis of DCN. After 3 years of follow-up, the patient is well, without recurrence or alteration.

Discussion

The term neurothekeoma was introduced for the first time by Gallager and Helwig in 1980 [11] to describe a superficial skin neoplasm, of probably nerve sheath derivation, predominantly observed in children and adolescents, whereas the term CN was firstly used by Rosati et al. in 1986 [12].

Initially, through a histomorphological analysis, neurothekeoma was classified as cellular, mixed or myxoid, depending on the amount of myxoid matrix [4, 13]. Thus, because of myxoid stroma, some authors initially suggested that neurothekeoma and NSM represented lesions within a morphologic spectrum [13], whereas others questioned this relationship [14, 15]. Actually, there is consensus that NSM is a true nerve sheath tumor regarding their immunohistochemical profile and ultrastructural findings, which is consistent with Schwannian differentiation [2], whereas the nosologic status of neurothekeoma continues to be debated. Thus, on the basis of the results of a large series of NSMs [2] and neurothekeomas [1, 4], it seems that these tumors are unrelated and that the so-called mixed or myxoid neurothekeoma can in fact represent CN with myxoid stroma [1, 2, 4].

A review of the literature was conducted on the information collected from the Medline database (http://www.ncbi.nim.nih.gov) up to December 2016, with cross-referencing using the terms "cellular neurothekeoma and oral mucosa"; "nerve sheath myxoma and oral mucosa". The search resulted in a total of 11 articles [3, 16–24], which reported a total de 17 cases diagnosed as neurothekeoma, CN, NSM/Neurothekeoma and classic neurothekeoma of the oral cavity [3, 16, 17, 24–31] (Table 1). However, after careful examination by using strict criteria [1, 2, 4], only five CNs were identified; of them, a single case in a pediatric patient

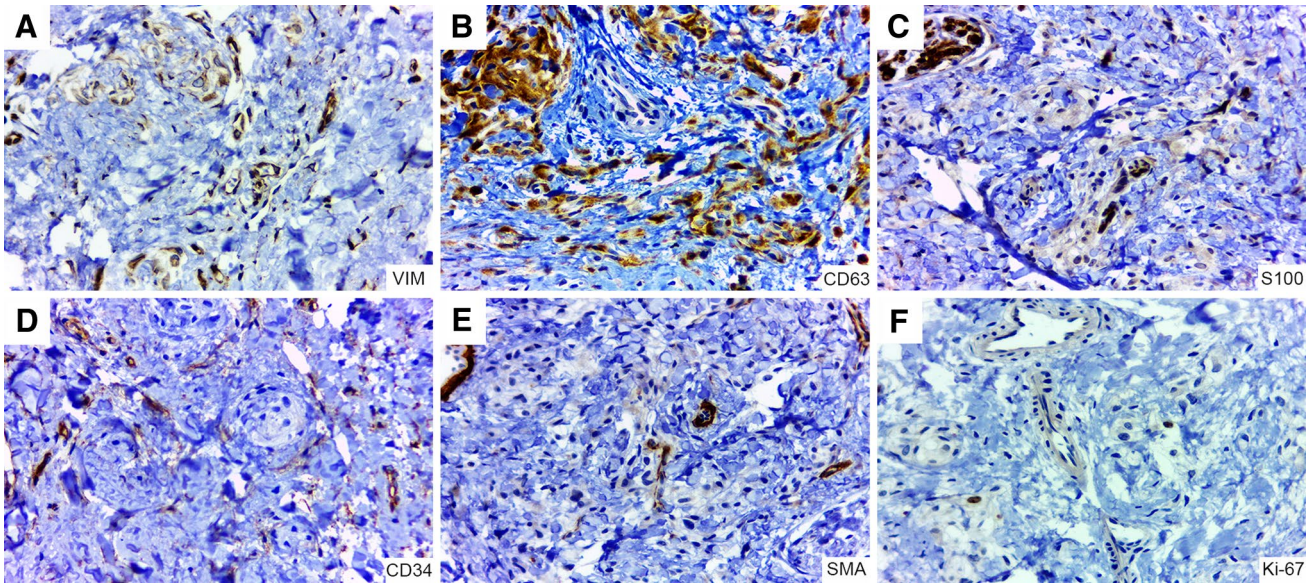

Fig. 3 Immunohistochemical analysis of desmoplastic cellular neurothekeoma. **a** The tumor cells were positive for vimentin and, **b** CD63 (NKI-C3). **c** S100 (nerves serve as a positive internal control), **d** CD34 (endothelial cells serve as a positive internal control) and **e** α-SMA (smooth muscle cells serve as a positive internal control), were negative. **f** The Ki-67 labelling index was <2% (IHQ, ×40). Notice the cytoarchitectural organization of the tumor cells (*nests* and *bundles*) highlighted in all photomicrographs

[30]. Thus, the current case appears to be the second pediatric case of CN affecting the oral mucosa.

Moreover, a review of the DCN cases was also performed. The information was collected from the Medline database (http://www.ncbi.nim.nih.gov) up to December 2016, with cross-referencing using the terms "desmoplastic neurothekeoma", "desmoplastic cellular neurothekeoma" and "desmoplastic nerve sheath myxoma". The search results in a total of 15 cases of DCN in cutaneous localization [5, 7, 8, 10], of which six cases affected pediatric patients, being found a single case with involvement of the face [10]. Thus, the current case appears to be the first report of DCN with involvement of the oral cavity. Furthermore, as we detected clinically two nodular masses admixed with other small, ill-defined lesions on the left buccal mucosa and upper lip, which by histopathological and immunohistochemical analysis proved to be DCN, the final diagnosis was multiple DCNs of the oral cavity. In fact, similar to clinicopathological features of the current case, multiple CNs in the head and neck region affecting a 30-year-old male [9] and multiple DCNs localized to the face of a 16-year-old boy [10] have been reported.

As previously mentioned, the main differential diagnosis for NSM is CN. NSM is a peripheral nerve sheath tumor, with a peak incidence in the fourth decade of life, without gender preference. Notably, NSM have a strong predilection for the extremities, particularly the fingers. Approximately 15% of NSMs show involvement of the trunk or head and neck regions. Microscopically, NSMs exhibit delimited myxoid, multinodular masses, containing spindled and epithelioid Schwann cells, which are S-100, GFAP, NSE and CD57 positive. When treated by simple local excision, NSM shows a relatively high local recurrence rate. Thus, complete local excision with a margin of normal tissue is recommended [2].

The histopathologic differential diagnosis of CN includes plexiform fibrohistiocytic tumor, neurofibroma, schwannoma, Spitz nevus, leiomyoma, benign fibrohistiocytoma and, eventually, melanoma. The DCN should be differentiated from desmoplastic fibroblastoma, desmoplastic nevi and sclerosing perineurioma, including desmoplastic melanoma and desmoplastic squamous cell carcinoma. All these lesions were excluded through of a detailed clinical, histopathological and immunohistochemical evaluation [10, 32].

Interestingly, giant cells (osteoclastic, Touton and/or tumor) were seen in 20 (15%) CN cases [1]. However, differently, in the current case we have observed scattered multinucleated floret-like giant cells (Fig. 1, inset). To the best of our knowledge, this is the first report showing this giant cell type in CN/DCN, which is similar to those observed in giant cell fibroblastoma, pleomorphic lipoma, multinucleate cell angiohistiocytoma, giant cell collagenoma, pleomorphic fibroma, and remarkably, neurofibroma. Moreover, multinucleated floret-like giant cells have been documented in normal tissues such as lower female genital tract, testis, urinary bladder, anus, breast and skin. The histogenesis of multinucleated floret-like giant cells is

unknown; however, some studies indicate that native dermal or interstitial CD34+ fibroblasts/dendritic cells can acquire a reactive multinucleated and floret-like appearance in response to unknown stimuli and/or due to interactions with mast cells [33, 34].

Although DCN is a benign tumor, and knowing that it can present microscopically irregular and infiltrative margins, is recommended the complete surgical excision of the lesion, especially in facial lesions, since it occasionally recurs, many times within a short period following removal [17, 24]. In this way, the current patient is being kept under observation as recommended, and after 3 years of follow-up is well without showing recurrence or alteration.

The current case appears to be the first report showing oral cavity involvement by DCN, which affected a pediatric patient. Microscopically, DCN shows irregular and infiltrative margins and can be misinterpreted as an aggressive lesion, which may result in inadequate treatment. Complete surgical excision of the DCN lesions is recommended, since it can recur, many times within a short period following removal of the lesion. Multiple DCNs, such as shown in the current case, should be considered in the differential diagnosis of oral nodular lesions in pediatric patients.

Acknowledgements The authors would like to thank the parents and child who agreed to participate in this study.

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