Head and Neck Pathol (2017) 11:404–412
DOI 10.1007/s12105-016-0760-3

CASE REPORT

S-100 Negative Granular Cell Tumor (So-called Primitive Polypoid Non-neural Granular Cell Tumor) of the Oral Cavity

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Received: 16 August 2016 / Accepted: 28 September 2016 / Published online: 5 October 2016

Abstract Four cases of cutaneous S-100 negative granular cell tumor were described in 1991. Until now, only 3 cases of oral involvement have been documented in English literature. Two additional cases of oral S-100 negative granular cell tumor are described. Immunohistochemical markers were applied to exclude other lesions that may show the presence of granular cells. The clinical findings were correlated with the histopathological and immunohistochemical features to arrive at the appropriate diagnosis. S-100 negative granular cell tumors are erythematous polypoid masses commonly mistaken for granulation tissue or a pyogenic granuloma. Any part of the oral cavity may be affected. Histopathologically, the lesions consist of sheets, nests, and fascicles of granular cells that are S-100 negative. The granular cells are non-reactive to SMA, HMB45, Melan A, and CD163. The intracytoplasmic granules are diffusely and strongly positive to NKI/C3. The cell lineage of the S-100 negative granular cell tumor is obscure. Absence of staining with CD163 excludes a histiocytic lineage. Absence of staining with S-100 excludes a neural origin. Absence of staining with S-100 and key melanoma markers HMB45 and Melan A also excludes a melanocytic origin. In this context, positive reactivity with NKI/C3 is indicative of presence of intracytoplasmic lysosomal granules only. Greater awareness of this lesion in the oral cavity will result in better characterization of its biologic potential.

Keywords Granular cell · S-100 · Oral · Mucosal · Non-neural · Polypoid · Primitive · NKI/C3

Introduction

The granular cell tumor (GCT) is a common benign mesenchymal neoplasm. It is defined as, "a neural tumor composed of round and/or spindle cells with pink, granular cytoplasm due to abundant intracytoplasmic lysosomes [1]. Over 50 % of cases arise in the head and neck region and over half of these are diagnosed on the tongue [1]. In a study of 68 cases of oral granular cell tumors, 55 cases (80.8 %) affected the tongue [2]. The GCT arises from peripheral neural elements, particularly the Schwann cell [3, 4]. GCTs are therefore strongly and uniformly positive to S-100 protein [1–5].

In contrast to GCTs, non-neural granular cell tumors are uncommon and only recently described. In 1991, LeBoit et al. [6] described four cutaneous granular cell tumors with a polypoid morphology. Immunohistochemically, the tumors were all S-100 protein negative. They proposed the nomenclature, "Primitive polypoid granular cell tumor" for these lesions. Since this first description, only two series [7, 8] of cutaneous non-neural granular cell tumor have been published in English literature. Three cases of regional lymph node metastasis have been reported [8–10].

At the time of writing this manuscript, there are three case reports in English literature of documented oral involvement by the S-100 negative (non-neural) GCT [11–13]. This paper contributes two more cases of oral mucosal involvement by this unusual lesion. The clinical,

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histopathological and immunohistochemical features of the S-100 negative GCT are discussed. A differential diagnosis based on histopathological features and immunohistochemistry reactivity is presented.

Case 1

A 19-year-old male developed an asymptomatic polypoid mass of the hard palate. The growth had been present for a few weeks. On examination, the mass was erythematous and measured 0.9 cm in its greatest dimension. Three dimensional measurements were not available. A clinical diagnosis of a pyogenic granuloma was given. The growth was removed and submitted for microscopic examination. Histopathological examination showed sheets and nests of oval to polygonal cells with well-defined cytoplasmic membranes and a granular eosinophilic cytoplasm. The nuclei were prominent, vesicular and some cells showed pink nucleoli. Mitotic figures were easily identified and numbered from 3 to 4/10HPF (Fig. 1). No sclerosis or collagen entrapment was seen. Vascularity was prominent. The epithelium was thin with areas of ulceration. The oval to polygonal lesional cells with a granular cytoplasm were negative to S-100 protein (Fig. 2a), CD163 (Fig. 2b), HMB45 and SMA. They were diffusely and strongly positive to NKI/C3 (CD63) (Fig. 3). A diagnosis of an S-100 negative (primitive polypoid non-neural) granular cell tumor was made.

Case 2

A 64-year-old male developed an asymptomatic, polypoid growth of his buccal mucosa. The tumor was present for a few weeks. He said that he frequently bit the mass. There was a history of a biopsy at that location for a lichenoid mucositis. During examination, the lesion was ulcerated and measured 1.0 cm in its greatest dimension. Three dimensional measurements were not available. The clinical diagnosis was granulation tissue. The lesion was excised. Histopathological examination showed an ulcerated, polypoid mass (Fig. 4). Sheets and fascicles of polygonal to oval to plump spindle cells with well-defined cytoplasmic membranes and a granular eosinophilic cytoplasm were seen deep to the fibrin and inflammation associated with the ulceration. The nuclei were prominent, vesicular with prominent pink nucleoli (Fig. 5). The cytoplasmic granules were PAS positive and diastase resistant. Mitotic figures were easily identified and numbered from 2 to 3/10HPF (Fig. 6). Vascularity was prominent. No sclerosis or thick collagen band entrapment was seen. The scant epithelium appeared attenuated and ulcerated. The polygonal to oval to plump spindle cells were negative to S-100 protein (Fig. 7a), CD163 (Fig. 7b), HMB45 and SMA. These cells were diffusely and strongly positive to NKI/C3 (CD63) (Fig. 8). The diagnosis was S-100 negative (primitive polypoid non-neural) granular cell tumor.

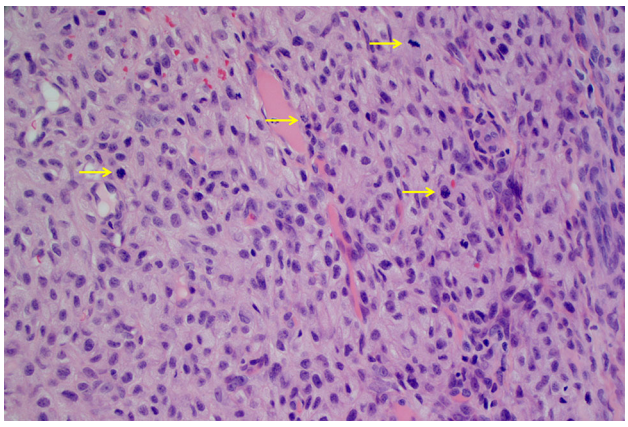

Fig. 1 Sheets of closely packed oval to polygonal cells with an eosinophilic granular cytoplasm. Nuclei are prominent. Mitotic figures are easily found (*arrow*). H & E 20×

Discussion

Since the initial description of the primitive polypoid granular cell tumor by LeBoit et al. [6], two series of 11 and 13 cases each of cutaneous non-neural granular cell tumors have been published [7, 8]. Sporadic case reports including two cases metastatic to regional lymph nodes have been published in English literature [9, 10]. One case from the series of 13 cases by Lazar and Fletcher also showed regional lymph node involvement 25 months after initial presentation [8]. A US National Library of Medicine, PubMed literature search resulted in 3 case reports of lip vermilion and oral involvement by the S-100 negative (non-neural) granular cell tumor. Another case diagnosed as a benign fibrous histiocytoma rich in granular cells [14] is more likely a S-100 negative granular cell tumor of the hard palate as explained later in the discussion.

Clinical Features

Cutaneous lesion Data from the series of 4 cases by LeBoit et al. [6], 11 cases by Chaudhry and Calonje [7] and 13 cases by Lazar and Fletcher [8] were collated (N = 28). An almost equal sex distribution was seen (male = 13 and female = 15). Tumors were seen over an age range from 5 to 83 years with lesions present in most decades. The cutaneous lesions were seen on the back, shoulder, upper and lower extremities, scalp, face, upper lip, neck, hip,

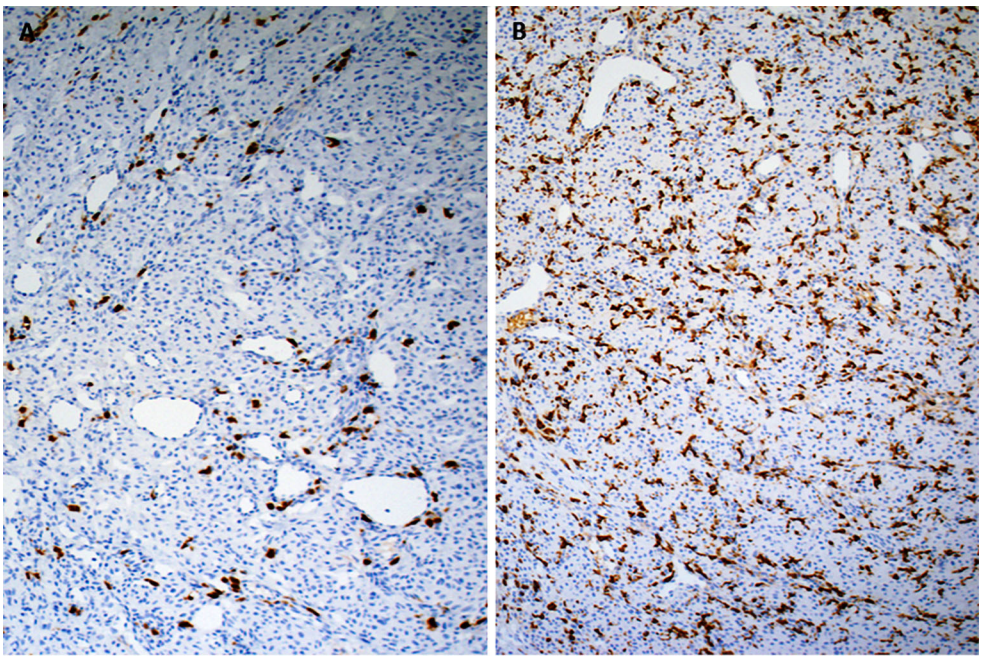

Fig. 2 The granular cells are negative to S-100 protein (**a**) and CD163 (**b**). These antibodies show the presence of dendritic cells and macrophages between the lesional cells

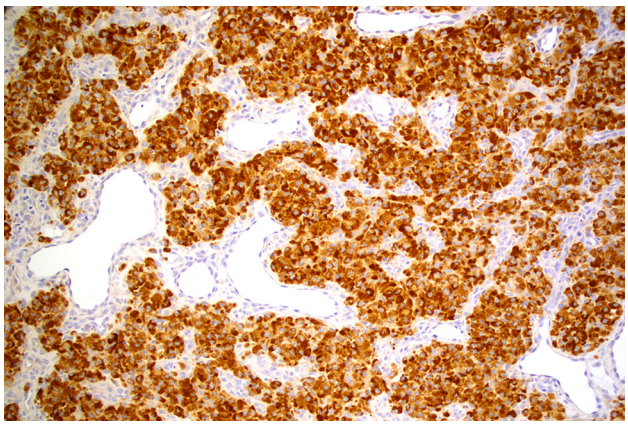

Fig. 3 The granular cells are diffusely and strongly reactive to NKI/C3

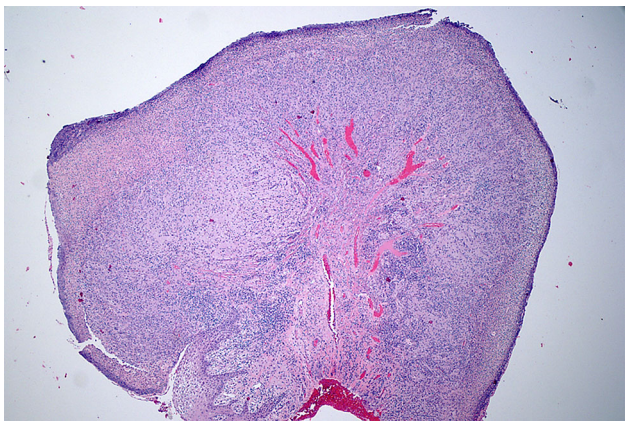

Fig. 4 An ulcerated, polypoid mass of the buccal mucosa (Case 2). H & E 4×

nose and chin. The duration of lesions ranged from 2 months to one year. All the tumors were asymptomatic. Clinically, they were described using terms such as protuberant, dome-shaped, smooth nodules. The tumors ranged in size from 0.2 to 2.8 cm. The tumors were treated with conservative excision with no reported recurrences. Case 11 [8] developed regional lymph node metastasis. The lymph node was excised and no recurrence was noted up to 70 months thereafter. Two other cases of lymph node metastasis have been reported [9, 10]. A 20-year-old female presented with a skin of buttock lesion. The patient was pregnant at the time of initial presentation. The lesion was hemorrhagic and was managed by chemical cautery for 5 months. Postpartum, it was excised. At that time an enlarged regional lymph node showed tumor tissue. Nine months following the lymph node biopsy, the patient was found to be disease free [9]. The second case was of a 13-year-old female with a nodular lesion of the skin over the scapula. The lesion was excised. Four years later, a hypertrophic scar developed at the site of the surgery. The hypertrophic scar and an enlarged axillary lymph node were removed. The lymph node showed metastatic disease. An axillary dissection showed involvement of 5 of 18 lymph nodes. A 3.2 cm extracapsular tumor mass was also removed at that time. An oncologic survey ruled out disseminated disease. No follow-up information is available [10].

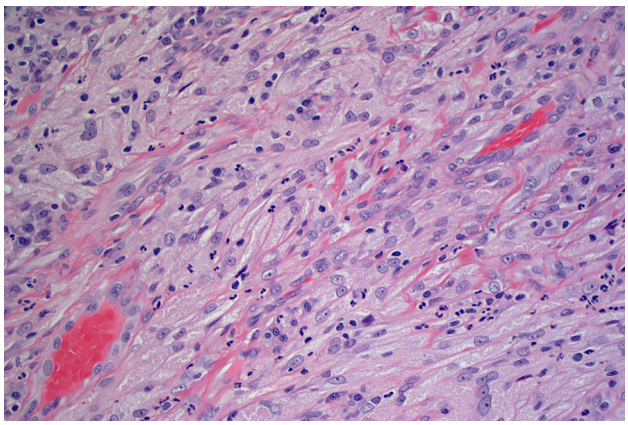

Fig. 5 Fascicles of plump spindle cells with an eosinophilic granular cytoplasm. H & E 20×

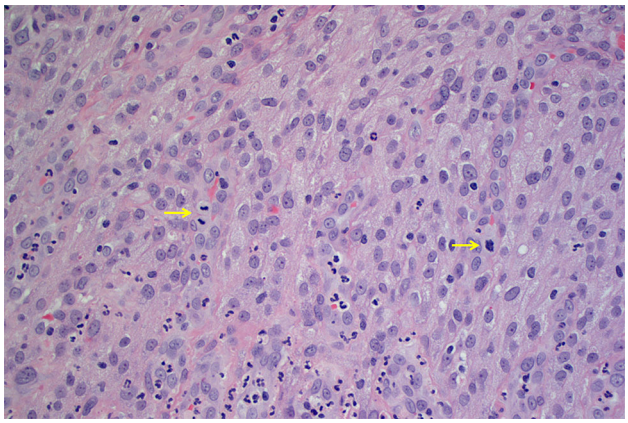

Fig. 6 Mitotic figures are easily identified (*arrow*). H & E 20×

Oral lesions Five cases (including 2 cases from this paper) are reported (Table 1). As with the skin tumors, the oral lesions are also seen across a wide age range from 4 to 64 years. Four lesions were seen in males and 1 in a female. Sites affected by the lesion included the vermilion of lower lip, alveolar ridge over tooth extraction site, tongue, hard palate and buccal mucosa. The lesions were present for a few weeks and each measured approximately 1 cm in size in its greatest dimension. The tumors were asymptomatic and presented as exophytic, red, nodular masses resembling a pyogenic granuloma. The clinical description of the tongue mass was not available [13]. History of trauma at the affected site was present in 2 cases, the case affecting the alveolar ridge reported by Lerman and Freedman [12] and case 2 from this paper. From the histopathological examination (Table 2), it is seen that the removal was incomplete in 3 cases. This information was not available in 2 cases [12, 13]. At the time of writing this manuscript, (24 and 6 months after removal, respectively), there has been no recurrence in our 2 cases.

Histopathological Features

Cutaneous lesions The lesions from the series of 4 cases by LeBoit et al. [6], 11 cases by Chaudhry and Calonje [7] and 13 cases by Lazar and Fletcher [8] showed similar histologic features. The tumors were covered by a thin attenuated epidermis. Some cases showed ulcers. No cases exhibited pseudoepitheliomatous hyperplasia (PEH). The tumors were well-circumscribed and most were bound by an epithelial collaret. The deep margin was poorly demarcated in 3 cases [7]. Tumors consisted of large spindle, ovoid and polygonal cells with an abundant eosinophilic granular cytoplasm. The granules were PAS + and diastase resistant. The cells were arranged in diffuse sheets in one reported series of cases [8]. This information was not available in the other 2 series of cases [6, 7]. The nuclei were prominent, medium to large in size and some nuclei showed prominent pink nucleoli. Varying mild nuclear atypia was noted. Mitotic figures were easily identified. Tumors were well supplied by thin walled vascular channels. Inflammation was sparse. No lymphatic or perineural invasion was seen. There was no necrosis. Also, none of the cases showed any entrapped thick hyalinized collagen.

Oral lesions The 4 lesions (two from previous reports [11, 12] and 2 of our cases) (Table 2) showed ulceration. The tongue lesion [13] was non-ulcerated. In areas, where some epithelium was seen, it was attenuated. PEH was not seen in any of the cases. The removal was incomplete in 3 cases and an epithelial collaret was not seen. This information was not available in 2 cases [12, 13]. One tumor was described as being well-circumscribed although the removal was incomplete [11]. One tumor was described as circumscribed although later it was said to have indistinct borders [13]. Two of the cases in this paper had ill-defined deep margins and case 1 had ill-defined lateral margins also. This information was not available in one case [12]. Like their cutaneous counterparts, the oral tumors consisted of spindle, oval to polygonal cells with abundant eosinophilic granular cytoplasm. The granules were PAS+, diastase resistant in one case. Granules were PAS nonreactive in one case [11]. PAS stain was not used in 3 cases [12, 13 and case 1 in our report] (Table 2). The nuclei were all prominent, vesicular with some prominent pink nucleoli. Two cases had inconspicuous nucleoli [11, 13]. The 2 cases in this report showed prominent mitotic figures (3–4/10HPF, case 1 and 2–3/10HPF, case 2) (Figs. 1 and 6). One previous case showed 1/10HPF mitoses [11] while the other report said that mitotic figures were seen throughout the lesion [12]. The cells were arranged in nests, sheets and fascicles. Vascularity was prominent in 3 cases [12 and 2 cases in our report] (Table 2). This feature was highlighted

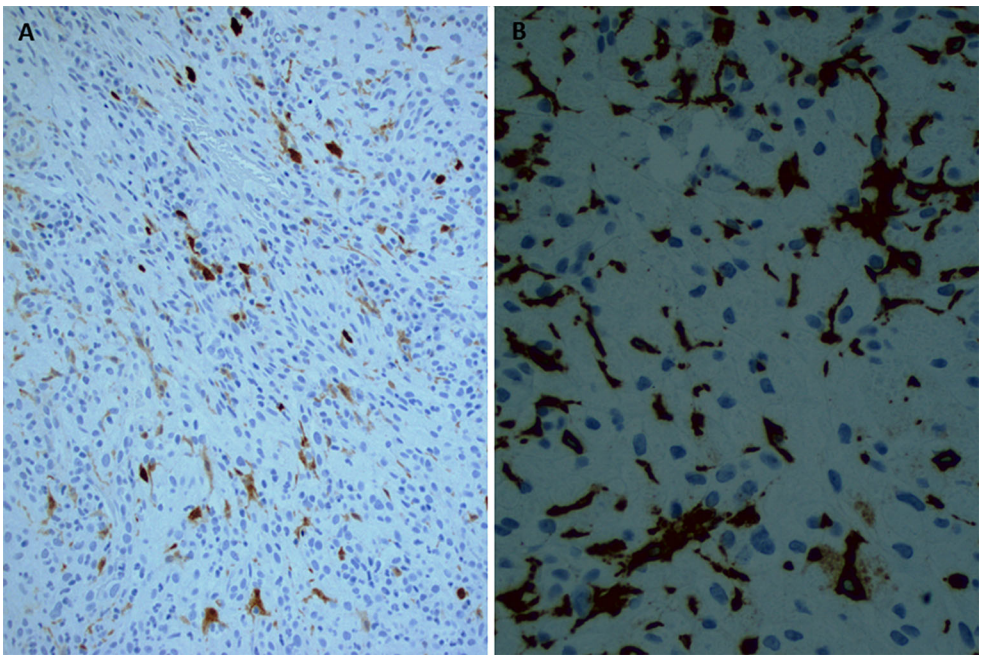

Fig. 7 The granular cells are negative to S-100 protein (**a**) and CD163 (**b**). These antibodies show the presence of dendritic cells and macrophages between the lesional cells. The image B is intentionally kept dark to contrast the non-reactive cytoplasmic outlines of the granular cells

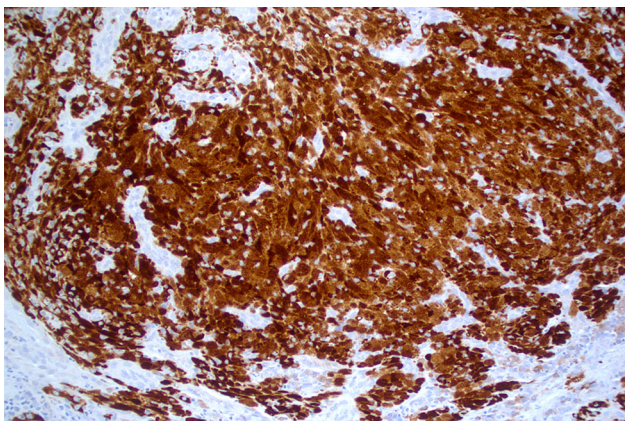

Fig. 8 The granular cells are diffusely and strongly reactive to NKI/C3

very well by the smooth muscle actin stain in the two cases in our report.

Immunohistochemical Features

LeBoit et al. in 1991 [6] reported the first 4 cases of the non-neural granular cell tumor. All 4 tumors were S-100 negative. In the series of 11 cases by Chaudhry and Calonje [7], all 11 cases were non-reactive to S-100 protein. However, all 11 cases were strongly and diffusely positive to NKI/C3 (CD63). This pattern was also seen in the series of 13 cases by Lazar and Fletcher [8]. All cases in these studies were essentially negative to cytokeratin, HMB45, Melan A, SMA, Desmin, EMA and LCA. Reactivity to CD68 was focal in 10 out of 11 [7] and 7 out of 11 [8] cases (Table 3). A similar pattern of staining was noted in the 4 cases of the oral cavity. S-100 protein reactivity was negative while the tumor cells expressed diffuse, strong reactivity to NKI/C3 (CD63). CD68 was focal in one case [12] and diffusely strong in one [13]. In the 2 cases reported in our paper, CD163 was used to detect histiocytic differentiation as it offers a cleaner cell membrane expression in macrophages as compared to the non-specific lysosomal cytoplasmic staining associated with CD68. Tumor cells were negative to CD163. CD163 showed recruited histiocytic cells embedded between lesional cells (Figs. 2b and 7b). Melanoma and muscle markers were negative.

NKI/C3 is an antibody that reacts with a lysosomal membrane protein. It also reacts with melanosomes and is known as melanoma-associated antigen [15]. It has been used as a melanoma marker and therefore has no discriminating value. However, the non-neural granular cell tumor is negative to S-100 protein and other fundamental melanoma markers such as HMB 45 and Melan A.

Strong cytoplasmic reactivity to NKI/C3 and absence of reactivity to CD163 and key melanoma markers only shows increased lysosomal content and does not equate

Table 1 Demographics and clinical features of 5 cases of oral S-100 negative (non-neural) granular cell tumor

Case	Age/sex	Location	Duration	Symptoms	Size	Morphology	History of trauma at site	Clinical diagnosis
Basile and Woo [11]	4/F	Lower lip vermilion	1 month	Asymptomatic	Not mentioned (approximately 1 cm based on Fig. 1)	Nodular, exophytic, firm, sessile	Not available	Red nodule
Lerman and Freedman [12]	43/M	Alveolar ridge, teeth 18 and 19 extraction site	<7 weeks	Asymptomatic	Not mentioned	Irregular, exophytic growth	Extraction of teeth 18 and 19	Red growth
Solomon and Velez [13]	12/M	Tongue	Not available	Not available	1.0 × 0.7 × 0.4 cm (gross description)	Tongue mass	Not available	Not available
This paper case1	19/M	Hard palate	Few weeks	Asymptomatic	0.9 cm	Exophytic growth	Not available	Pyogenic granuloma
This paper case 2	64/M	Buccal mucosa	Few weeks	Asymptomatic	1.0 cm	Exophytic mass	Previous biopsy at site for lichenoid mucositis	Granulation tissue

Table 2 Histopathological features in 5 cases of oral S-100 negative (non-neural) granular cell tumor

Case	Ulceration	Cell morphology and arrangement	Cell cytoplasm	Nucleus	Mitosis	PEH	Vascularity	Margin	Complete excision
Basile and Woo [11]	Yes	Polygonal cells. Sheets and nests	Eosinophilic granules, PAS non-reactive	Vesicular. Inconspicuous nucleoli	1/10 HPF	No. Epithelium flattened	Scattered capillaries	Well circumscribed	No
Lerman and Freedman [12]	Yes	Oval to spindle cells. Fascicles	Eosinophilic granules to clear cytoplasm	Vesicular. Prominent nucleoli	Yes	No	Prominent	N/A	N/A
Solomon and Valez [13]	N/A	Polygonal cells. Syncytial arrangement	Granular amphophilic	Dispersed chromatin. Inconspicuous nucleoli	No	No	N/A	Indistinct borders	N/A
This paper case 1	Yes	Oval to polygonal cells. Sheets and nests	Eosinophilic granules	Vesicular. Some cells with prominent nucleoli	3–4/10 HPF	No. Epithelium stretched	Prominent. Highlighted with SMA	Ill-defined deep and lateral margins	No
This paper case 2	Yes	Polygonal to oval to plump spindle cells. Sheets and fascicles	Eosinophilic granules, PAS positive	Vesicular. Prominent pink nucleoli	2–3/10 HPF	No. Epithelium flattened	Prominent. Highlighted with SMA	Ill-defined deep margin	No

PEH pseudoepitheliomatous hyperplasia, *SMA* smooth muscle actin, *N/A* not available

Table 3 Immunohistochemical reactivity of 5 cases of oral S-100 negative (non-neural) granular cell tumor

Case	S-100	NKI/C3	HMB45	Melan A	CD68	CD163	SMA	Muscle specific actin (HHF 35)	NSE	Vimentin	Cytokeratin
Basile and Woo [11]	–	Strong, Diffuse	NA	NA	–	NA	NA	–	–	Strong, Diffuse	–
Lerman and Freedman [12]	–	Diffuse, Strong	–	–	Focal	NA	Focal	NA	NA	Diffuse, Strong	–
Solomon and Velez [13]	–	NA	NA	NA	Diffuse, strong	–	–	NA	NA	Diffuse, strong	NA
This paper case 1	–	+++Diffuse	–	NA	NA	–	–	NA	NA	NA	NA
This paper case 2	–	+++Diffuse	–	NA	NA	–	–	NA	NA	NA	NA

NA not applied, (−) negative, (+++) positive, strong. Solomon LW, Velez I [13]: Negative to CD56, inhibin, calretinin, CD34, CD1a, Factor XIIIa

with a histiocytic/macrophage or melanocytic lineage. This finding or lack thereof supports the use of the term "primitive" by LeBoit et al. in 1991 [6].

Differential Diagnosis

A variety of tumors of the oral cavity may show the presence of eosinophilic, granular cells. In some tumors, the population of cells with a granular cytoplasm may be limited while in others it may be a predominant feature. The S-100 negative granular cell tumor is therefore a diagnosis of exclusion. The process of exclusion involves correlation of clinical and histopathological features and application of appropriate immunohistochemical markers and interpretation of their reactivity pattern. The S-100 negative granular cell tumor needs to be differentiated from the conventional granular cell tumor, granular cell epulis of newborn, verruciform xanthoma, granular cell leiomyoma, melanoma, atypical fibroxanthoma, cellular neurothekeoma and granular cell variants of the PEComa and benign fibrous histiocytoma.

Over 50 % of cases of the granular cell tumor arise in the head and neck region and over half of these are diagnosed on the tongue [1]. Over 80 % of oral tumors affect the tongue [2]. They form smooth, dome-shaped submucosal swellings usually around 1 cm in size. Histopathologically, they consist of polygonal, round or oval granular cells arranged in sheets, islands and strands that often infiltrate between striated muscle fibers of the tongue. The surface epithelium may frequently exhibit PEH that may incorrectly be interpreted as a well-differentiated squamous cell carcinoma. The tumor cells are diffusely and strongly reactive to NKI/C3 (CD63) and S-100 protein [2]. The granular cell tumor is derived from and is intimately associated with Schwann and perineural cells [3].

The granular cell epulis of the newborn affects the maxillary alveolar ridge of females. It may get large enough to interfere with feeding. It consists of sheets of S-100 negative granular cells [16]. The histogenesis of this lesion is uncertain. According to Damm et al. [16], electron microscopy revealed presence of contractile microfilaments in occasional tumor cells. This lesion is present at birth. It involutes spontaneously or regresses even upon incomplete removal [16].

The verruciform xanthoma is a benign lesion consisting of xanthoma or foam cells in the superficial connective tissue. It is considered to be a reactive process and majority are seen over the masticatory mucosa of the gingiva and hard palate as flat or slightly raised, papillary or warty, yellow–red lesions with a sharply demarcated border. The xanthoma cells are CD68 positive [17]. The xanthoma cells are S-100 negative but NKI/C3 and CD163 positive thereby highlighting their lysosomal content and their histiocytic lineage [18].

Oral leiomyomas are mostly of vascular smooth muscle origin (angioleiomyoma/vascular leiomyoma) and consist of a well-circumscribed submucosal nodule that may often be painful. Histopathologically, vascular channels surrounded by thick coats of SMA positive smooth muscle are seen bundled together into one mass [19]. Conventional leiomyomas and leiomyosarcomas with granular cell change tend to retain the fascicular arrangement of cells with fusiform nuclei. The cells retain reactivity to SMA. They may also be reactive to desmin and caldesmon [20].

Melanomas and benign melanocytic lesions may show granular cell change. They are likely to show a junctional component as well. The lesional cells would be NKI/C3 positive (CD63, melanoma associated antigen). However, the cells would also show strong reactivity to S-100 protein and other key melanoma markers such as HMB45 and Melan A [21].

The atypical fibroxanthoma (AFX) may show granular cell change (Granular cell AFX). This tumor usually affects males in their 70 s. This is a tumor of the sun-damaged skin with a majority of lesions affecting the skin over the scalp and ear. It presents as a rapidly enlarging, ulcerated nodule. Histopathologically, it is hypercellular and shows an epidermal collaret. Tumor cells are pleomorphic, spindle, polygonal and epithelioid and may show a granular eosinophilic cytoplasm. Mitotic activity and multinucleate cells are also seen. Tumor cells are consistently negative to S-100 protein and express reactivity to CD68. Multinucleate cells may be reactive to Melan A. Spindle cells express SMA reactivity and occasional reactivity to EMA [21].

NKI/C3 positive cells that are S-100 negative are also seen in the cellular neurothekeoma. Like the non-neural granular cell tumor, the lineage of differentiation in the cellular neurothekeoma remains obscure [22]. Although a subset of cellular neurothekeomas may show sheets of eosinophilic granular lesional cells, they invariably mingle with areas of the more common micronodular architecture. The nodules of tumor cells are small and of almost uniform size and are separated by dense bundles of hyalinized collagen. Tumor cells often show a whorling pattern within these nodules [23]. Giant cells and myxoid change is frequently seen [22, 23]. Over 50 % of tumors show at least focal reactivity to SMA [22].

PEComas consist of sheets and nests of polygonal to epithelioid cells with an eosinophilic granular cytoplasm. The cells contain a centrally located nucleus. The sheets and nests are interrupted by a delicate vascular stroma [24]. This arrangement bears a superficial resemblance to the non-neural granular cell tumor. Immunohistochemically, the cells of the PEComa are negative to S-100 but reactive to melanoma markers such as HMB 45 and Melan A. They are also reactive to SMA [24].

Granular cell change in benign fibrous histiocytomas has been described [25]. This change is not predominant and overlaps with conventional features including spindle cells and prominent bundles of collagen. A storiform pattern of cell and collagen arrangement may be seen. The epidermis is usually acanthotic. The tumor is S-100 negative and the granular cells are NKI/C3 and CD68 positive. Factor XIIIa and SMA reactivity may be seen in about 50 % of the tumors [25]. Clinically, the lesion is rarely polypoid. A case reported on the hard palate [14] presenting as an exophytic polypoid mass is more likely a S-100 negative non-neural granular cell tumor as it demonstrates no collagen entrapment. Also, the CD68 reactivity is sparse and shows recruited macrophages between the granular cells. Also, as compared to the strong positive internal control of the vascular channel the sparse SMA reactivity of few lesional cells should be considered negative [14].

In conclusion, the oral S-100 negative granular cell tumor is an exophytic, often polypoid neoplasm seen across a wide age range with no gender predilection. Lesions may be present for a few weeks and on presentation are about 1 cm in size and often ulcerated. Any part of the oral cavity may be affected. On physical examination, the tumors appear erythematous and resemble granulation tissue or a pyogenic granuloma. Histopathologically, the epithelium is commonly ulcerated, and where present, attenuated. No PEH is seen. The tumor consists of sheets, nests and fascicles of polygonal, oval or plump spindle cells with copious eosinophilic, granular cytoplasm with prominent vesicular nuclei. Tumor margins may not be circumscribed, especially along the deep margin. Due to this, recurrence may be expected. Mitotic figures are readily seen. There is no collagen or hyaline entrapment among the tumor cells. Vascularity may be prominent and inflammation may be related to ulceration. The tumor cells are S-100 protein and CD163 negative and diffusely and strongly positive to NKI/C3 (CD63). CD68 reactivity is highly variable and its use is discouraged in favor of NKI/C3 (CD63) to demonstrate lysosomal granules. The tumor cells are negative to cytokeratins, SMA, Desmin, HMB45 and Melan A. Cutaneous tumors show an indolent behavior. However, 3 cases of lymph node metastasis have been documented [8–10]. As of now, only 5 cases of oral S-100 negative granular cell tumor have been documented and it is uncertain if the biologic behavior of cutaneous lesions can be extrapolated to oral tumors. Therefore, until substantially more cases of oral involvement are recorded, complete removal and close follow-up for recurrences would be recommended.

Acknowledgments This study was supported in part by the Research and Training Fund of the Department of Oral and Maxillofacial Surgery, University of Washington School of Dentistry.

Compliance with Ethical Standards

Conflict of interest None.

References

1. Barnes L, Eveson JW, Reichart P, Sidransky D, editors. World health organization classification of tumors. Pathology and genetics of head and neck tumors. Lyon: IARC Press; 2005.
2. Vered M, Carpenter WM, Buchner A. Granular cell tumor of the oral cavity: updated immunohistochemical profile. J Oral Pathol Med. 2009;38(1):150–9.
3. Maiorano E, Favia G, Napoli A, Resta L, Ricco R, Viale G, Altini M. Cellular heterogeneity of granular cell tumours: a clue to their nature? J Oral Pathol Med. 2000;29(6):284–90.
4. Miettinen M, Lehtonen E, Lehtola H, Ekblom P, Lehto VP, Virtanen I. Histogenesis of granular cell tumour—an immunohistochemical and ultrastructural study. J Pathol. 1984;142(3):221–9.
5. Chrysomali E, Papanicolaou SI, Dekker NP, Regezi JA. Benign neural tumors of the oral cavity: a comparative

immunohistochemical study. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol. 1997;84(4):381–90.
6. LeBoit PE, Barr RJ, Burall S, Metcalf JS, Yen TS, Wick MR. Primitive polypoid granular-cell tumor and other cutaneous granular-cell neoplasms of apparent nonneural origin. Am J Surg Pathol. 1991;15(1):48–58.
7. Chaudhry IH, Calonje E. Dermal non-neural granular cell tumour (so-called primitive polypoid granular cell tumour): a distinctive entity further delineated in a clinicopathological study of 11 cases. Histopathology. 2005;47(2):179–85.
8. Lazar AJ, Fletcher CD. Primitive nonneural granular cell tumors of skin: clinicopathologic analysis of 13 cases. Am J Surg Pathol. 2005;29(7):927–34.
9. Al Habeeb A, Weinreb I, Ghazarian D. Primitive non-neural granular cell tumour with lymph node metastasis. J Clin Pathol. 2009;62(9):847–9.
10. Newton P, Schenker M, Wadehra V, Husain A. A case of metastatic non-neural granular cell tumor in a 13-year-old girl. J Cutan Pathol. 2014;41(6):536–8.
11. Basile JR, Woo SB. Polypoid S-100-negative granular cell tumor of the oral cavity: a case report and review of literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol. 2003;96(1):70–6.
12. Lerman M, Freedman PD. Nonneural granular cell tumor of the oral cavity: a case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol. 2007;103(3):382–4.
13. Solomon LW, Velez I. S-100 negative granular cell tumor of the oral cavity. Head and Neck Pathol. 2016;10:367–73.
14. Caldeira PC, Ribeiro DC, de Almeida OP, Mesquita RA, do Carmo MA. Tumor of the hard palate. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(6):722–7.
15. Sachdev R, Sundram UN. Frequent positive staining with NKI/C3 in normal and neoplastic tissues limits its usefulness in the diagnosis of cellular neurothekeoma. Am J Clin Pathol. 2006;126(4):554–63.
16. Damm DD, Cibull ML, Geissler RH, Neville BW, Bowden CM, Lehmann JE. Investigation into the histogenesis of congenital epulis of the newborn. Oral Surg Oral Med Oral Pathol. 1993;76(2):205–12.
17. Rawal SY, Kalmar JR, Tatakis DN. Verruciform xanthoma: immunohistochemical characterization of xanthoma cell phenotypes. J Periodontol. 2007;78(3):504–9.
18. de Andrade BA, Agostini M, Pires FR, Rumayor A, Carlos R, de Almeida OP, Romañach MJ. Oral verruciform xanthoma: a clinicopathologic and immunohistochemical study of 20 cases. J Cutan Pathol. 2015;42(7):489–95.
19. Tsuji T, Satoh K, Nakano H, Kogo M. Clinical characteristics of angioleiomyoma of the hard palate: report of a case and an analysis of the reported cases. J Oral Maxillofac Surg. 2014;72(5):920–6.
20. Mentzel T, Wadden C, Fletcher CD. Granular cell change in smooth muscle tumours of skin and soft tissue. Histopathology. 1994;24(3):223–31.
21. Brenn T. Pleomorphic dermal neoplasms: a review. Adv Anat Pathol. 2014;21(2):108–30.
22. Hornick JL, Fletcher CDM. Cellular neurothekeoma: detailed characterization in a series of 133 cases. Am J Surg Pathol. 2007;31:329–40.
23. 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;31:1103–14.
24. Bandhlish A, Leon Barnes E, Rabban JT, McHugh JB. Perivascular epithelioid cell tumors (PEComas) of the head and neck: report of three cases and review of the literature. Head Neck Pathol. 2011;5(3):233–40.
25. Zelger BG, Steiner H, Kutzner H, Rütten A, Zelger B. Granular cell dermatofibroma. Histopathology. 1997;31(3):258–62.