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Case Report

Polypoid non-neural granular cell tumor of the oral cavity: case report and literature review

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Aim: To report a case of non-neural granular cell tumor (NN-GCT), an uncommon neoplasm, with only six studies worldwide describing cases involving the oral cavity. **Methods:** A 26-year-old male patient with an erythematous, firm, polypoid nodule in the floor of the mouth that exhibited areas of ulceration and mild bleeding to the touch. A biopsy was performed to aid in the diagnosis. **Results:** Based on the histopathological and immunohistochemical results (vimentin +, CD68 +, S100 -), the diagnosis was compatible with S100-negative (primitive polypoid non-neural) granular cell tumor. No recurrence was observed over two years of follow-up. **Conclusion:** The diagnosis of NN-GCT is extremely challenging because this tumor shares histological and immunophenotypic features with many benign and malignant tumors. Although oral NN-GCT may exhibit unusual and atypical histological features, it has an indolent behavior. Thus, until more cases of oral involvement are reported, complete resection and close follow-up are recommended.

Keywords: Granular cell tumor. S100 proteins. Immunohistochemistry. Mouth neoplasms.

Introduction

Granular cell tumor (GCT) was described for the first time by Abrikossof in 1926. It is defined as a neural tumor composed of round and/or spindle-shaped cells with pink granular cytoplasm as a result of the abundant presence of intracytoplasmic lysosomes. GCT is a common benign mesenchymal neoplasm that is mostly found in the head and neck region, especially the tongue[1]. The strong reactivity of GCT to S100 protein suggests a relationship of the histogenesis of these tumors with perineural cells, particularly Schwann cells[2].

In contrast to typical or conventional GCT, non-neural granular cell tumor (NN-GCT) is an uncommon neoplasm[3]. Clinically, this tumor manifests as an asymptomatic swelling with a nodular, exophytic, and erythematous appearance, similar to pyogenic granuloma[4]. Non-neural GCT was described in 1991 by LeBoit et al.[5] as a 'primitive polypoid granular cell tumor' characterized by well-delimited borders, expansive growth, a polypoid configuration, and the presence of a larger number of mitoses and nuclear pleomorphism when compared to conventional GCT. In addition, NN-GCT does not exhibit immunoreactivity to S100 protein[3-5].

We found 15 articles in the English language literature that document cases or case series of NN-GCT (3–17) and only six describe cases involving the oral cavity[3,4,6-9]. This study reports a case of oral NN-GCT with atypical histopathological characteristics. Its clinical, histopathological and immunohistochemical features, as well as possible differential diagnoses, are discussed.

Clinical case

a 26-year-old African American man without comorbidities, a non-smoker and social drinker, was seen with a 5-cm asymptomatic, pedunculated polypoid nodule in the lingual gingiva that extended to the floor of the mouth and had been present for approximately 3 months. The lesion was located between teeth 35 and 44, had a firm consistency, was erythematous, and exhibited areas of ulceration, with mild bleeding to the touch (Figure 1A). The involved teeth showed slight mobility when manipulated. Radiographic examination revealed an intact lamina dura and the absence of signs suggestive of bone and dental erosion (Figure 1B). The clinical diagnosis was pyogenic granuloma. Surgery was performed under local anesthesia. The lesion was completely excised at its base while preserving the involved teeth. The material was sent for anatomopathological analysis. The surgical wound was closed by first intention without complications. The stitches were removed on postoperative day 7. There were no signs of infection or dehiscence. Macroscopic analysis showed a polypoid appearance, smooth surface, and firm consistency (Figure 1C). Histopathological examination revealed fragments of a mesenchymal benign neoplasm characterized by the proliferation of sheets of large oval or polygonal cells with abundant eosinophilic granular cytoplasm (Figure 2A), associated with the proliferation of spindle-shaped cells, sometimes arranged in a storiform pattern (Figure 2B). The cytoplasmic granules were PAS positive (Figure 2C). Some tumor cells contained a vesicular nucleus and promi-

nent nucleoli, as well as typical and atypical mitotic figures (Figure 2D). Moderate pleomorphism and areas with hyperchromatic cells were also observed (Figure 2E). There were small foci of necrosis in the center (Figure 2F) and on the top of the tumor. Lymphovascular, perineural, and muscular invasion were absent. The lesion was lined with epithelium without atypia and showed an extensive area of ulceration (Figure 2G). The stroma was intensely vascularized and exhibited areas of an intense mixed inflammatory infiltrate associated with ulceration. Although the lesion was well circumscribed, it lacked a capsule.

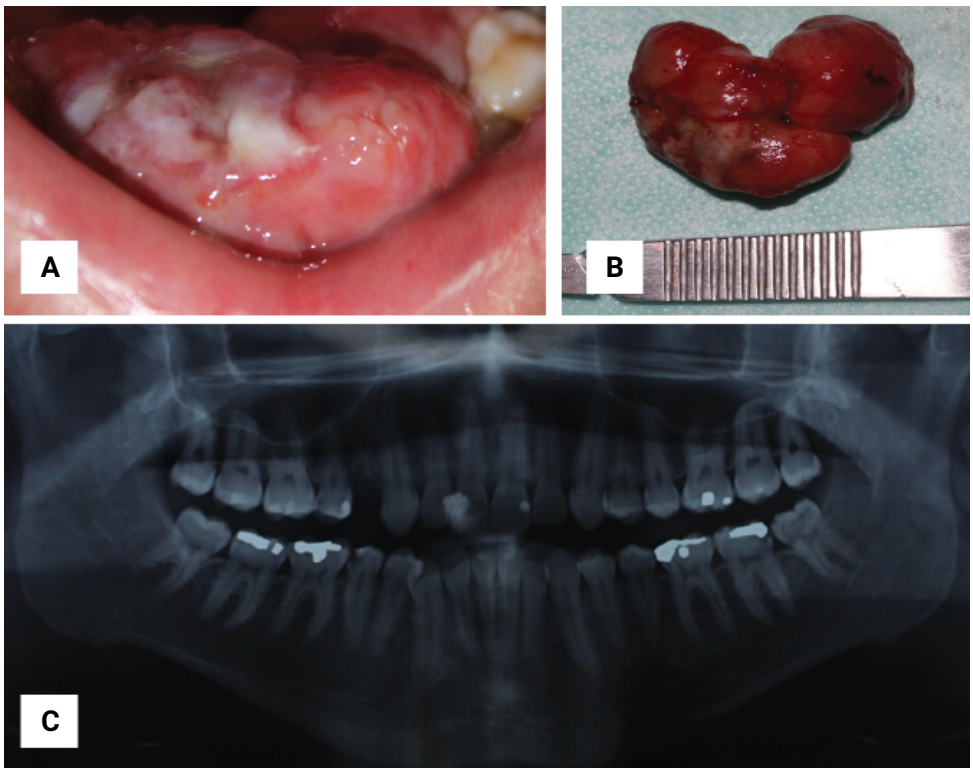

Figure 1. Clinical presentation of non-neural granular cell tumor (A-C). A – Erythematous, polypoid, nodular lesion with foci of superficial ulceration located in the lower alveolar ridge and floor of the mouth. B – Preoperative panoramic radiograph showing no signs of bone or dental involvement. C – Macroscopic view of the lesion showing a polypoid appearance and smooth surface.

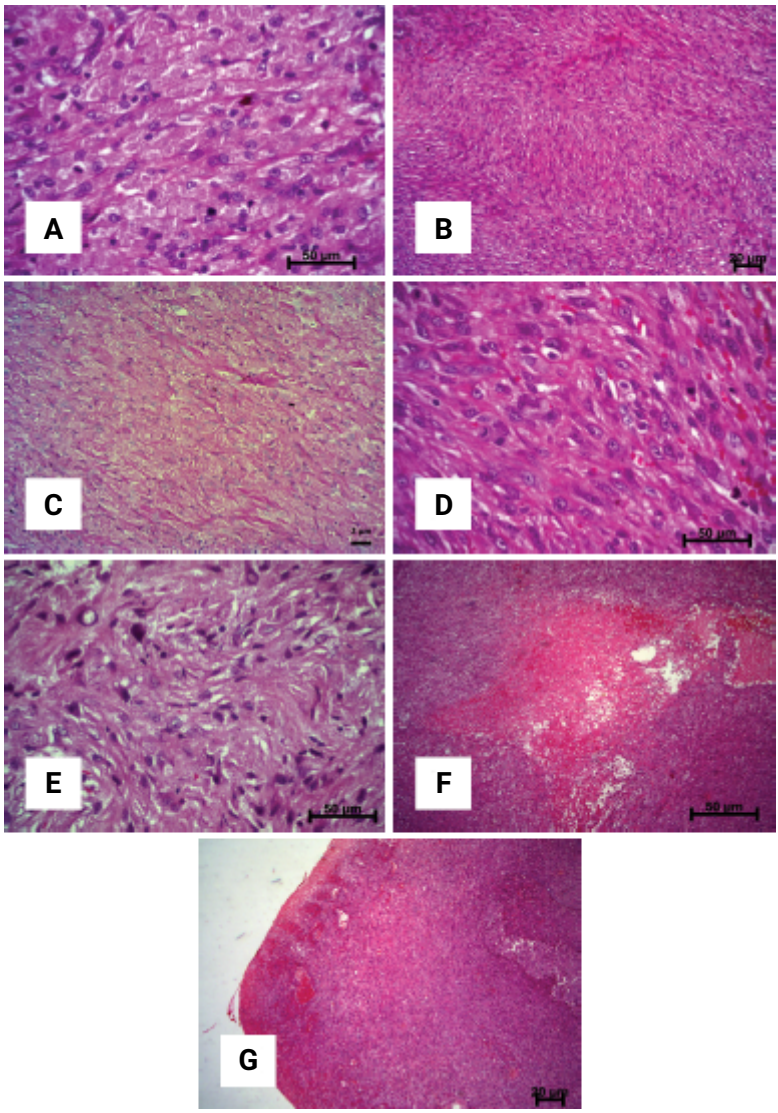

Figure 2. Histopathological features of non-neural granular cell tumor (A-G). A – Proliferation of large oval and polygonal cells with abundant eosinophilic granular cytoplasm. B – Proliferation of spindle-shaped cells. C – Cytoplasmic granules of PAS-positive granular cells. D – Tumor cells with a vesicular nucleus, prominent nucleoli, and mitotic figures. E – Hyperchromatic and pleomorphic tumor cells. F – Necrotic foci in the center of the tumor. G – Extensive area of ulceration on the tumor surface.

Regarding immunohistochemical features, tumor cells were positive for vimentin (100%) (Figure 3A) and CD68 (>80%) (Figure 3B). Positive staining for smooth muscle actin (SMA) was detected in less than 30% of the tumor cells and was present especially in the spindle cell component (Figure 3C). The tumor cells were negative for S100 (Figure 3D), HHF35, CD34, AE1/AE3, HMB45, CD56, and Melan A. Staining for Bcl-2 was rare and positive expression of p53 and Ki-67 was observed in less than 5% of tumor cells (Figure 3E).

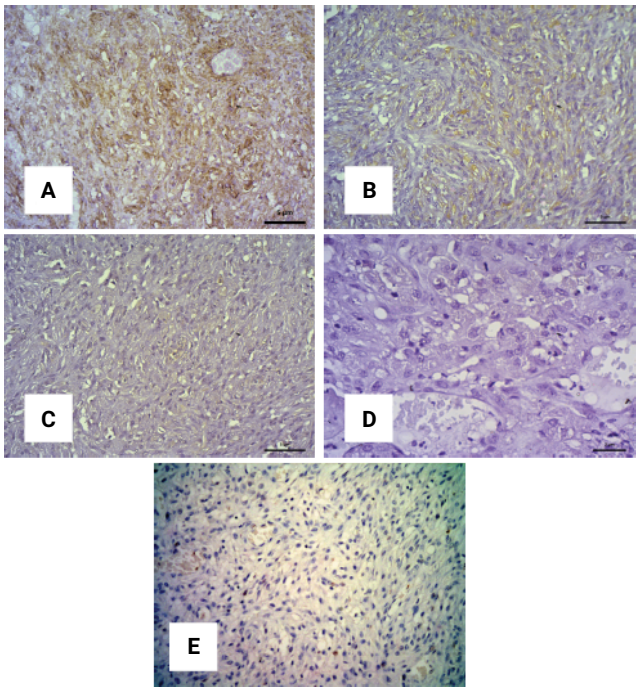

Figure 3. Immunohistochemical features of non-neural granular cell tumor (A-E). A – Tumor cells showing 100% positivity for vimentin B – Tumor cells showing > 80% positivity for CD68. C – Tumor cells showing < 30% positivity for smooth muscle actin. D – Absence of S100 immunoreactivity. E – Positive Ki-67 staining in 5% of tumor cells.

The diagnosis was S100-negative (primitive polypoid non-neural) GCT. The patient has been followed up for 2 years and shows no signs or symptoms of recurrence of the tumor. The teeth are preserved (Figure 4A and 4B).

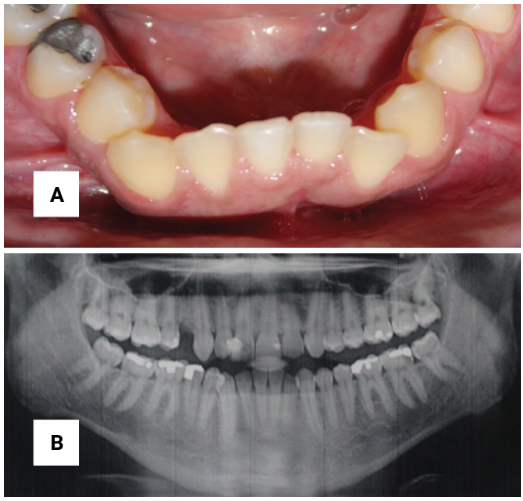

Figure 4. Postoperative follow-up (A-B). A – Clinical presentation after 1 year of follow-up. Note the normal colored mucosa and the absence of tooth mobility in the lower arch and signs of recurrence. B – Postoperative panoramic radiograph (1 year) showing preserved bone and dental contours and no signs of recurrence.

Discussion

Since its first description, a diverse and unusual histopathology of NN-GCT has been reported. Synonyms such as primitive GCT, dermal GCT or S100-negative GCT represent attempts of classifying this tumor, particularly after LeBoit et al.[5] demonstrated negative staining for proteins of different lineages, especially S100 protein. This fact differentiates NN-GCT from conventional GCT. The latter is of neural origin, more specifically Schwann cells, as indicated by the reactivity to S100 protein, i.e., its histogenesis is better established[3,6].

Only eight cases of NN-GCT of the oral cavity have been reported in the literature (Table 1). The mean age of these cases varied widely and there was a higher frequency in males (5 cases) than females (3 cases). The most common clinical presentation was a painless nodule that was similar in color to the adjacent mucosa or erythematous. An ulcerated surface was sometimes observed. Tumor size ranged from 0.3 to 3.8 cm. The lip was the most affected site, followed by the cheek mucosa, palate, tongue, and alveolar ridge. In the present case, the tumor was located in the attached gingiva, extending to the floor of the mouth, and was larger than the cases reported in the literature. It appeared as a painless, erythematous polypoid nodule with foci of ulceration, similar to pyogenic granuloma, in agreement with the published studies.

Table 1. Demographic data and clinical characteristics of nine case of non-neural granular cell tumor (S100 negative) of the oral cavity.

Author	Age (years)	Sex	Size (cm)	Site	Clinical appearance	Recurrence/ metastasis
Present case	26	M	3.8	Gingiva/floor of the mouth	Painless, pedunculated, ulcerated, erythematous, firm polypoid nodule	No
Basile and Woo, 2003	4	F	-	Lower lip	Sessile, erythematous, firm nodule	No
Chaudhry and Calonje, 2005	55	F	1.1	Upper lip	Painless nodule	No
Chaudhry and Calonje, 2005	43	F	0.3	Upper lip	Painless nodule	No
Lerman and Freedman, 2007	43	M	-	Alveolar ridge	Ulcerated, erythematous nodule with irregular borders	No
Solomon and Velez, 2015	12	M	1	Tongue	Polypoid mucosa-colored nodule on the ventral surface of the tongue	No
Rawal and Dodson, 2017	19	M	0.9	Hard palate	Painless, erythematous polypoid nodule	No
Rawal and Dodson, 2017	64	M	1	Oral mucosa	Painless, ulcerated polypoid nodule with a history of trauma	No
Mejía et al., 2019	47	M	1.3	Lower lip	Ulcerated, mucosa-colored exophytic nodule in the mucosa and semimucosa of the lower lip	No

M: male; F: female.

Primitive polypoid GCT of the skin described by LeBoit et al.[5] or dermal NN-GCT[3] exhibits unique histological features such as exophytic and polypoid nodular growth lined with stratified pavement epithelium without atypia. Neoplastic cell proliferation is well delimited and consists of round, polygonal or spindle-shaped cells with abundant granular cytoplasm that stains intensely with PAS. The nucleus of the tumor cells is vesicular or hyperchromatic and significantly larger and more variable when compared to conventional GCT. Prominent nucleoli are also found. The presence of variably shaped typical mitotic figures and lymphatic invasion have also been reported. A mild inflammatory infiltrate can be present but necrotic foci have not been detected[3,5]. The characteristics of the present case were similar to tumors of the skin. However, some features not previously described by LeBoit et al.[5] or Chaudhry and Calonje[3] were observed in the present case, such as proliferation of spindle-shaped cells in a storiform pattern, atypical mitotic figures, and areas of necrosis. We believe that the areas of necrosis detected in the present case are related to a reduction in blood circulation to the cells due to the large size of the tumor.

The first case of NN-GCT of the oral cavity dates back to 2003 and was reported by Basile and Woo[7]. The histology of the tumor present in the lower lip of a 4-year-old girl was consistent with the description of LeBoit et al.[5] (Table 2) and the authors added the presence of spindle cell proliferation in a storiform pattern and myxoid areas. Similarly, most of these morphological features were observed in the present case, including the storiform pattern of proliferating spindle-shaped cells. Two years later, Chaudhry and Calonje[3] published a series of 11 cases of NN-GCT, with only two involving the oral cavity (upper lip). In both cases, a painless nodule was observed in women with mean age of 50 years, which exhibited the same unusual histology (Table 2). Lerman and Freedman[6] reported the case of a 43-year-old man who had a tumor with an ulcerated, erythematous surface and irregular borders. The authors described the same histological findings as Chaudhry and Calonje[3]. Thus, the present case shows additional characteristics, including a biphasic proliferation pattern and the presence of atypical mitotic figures and necrotic foci.

Table 2. Histopathological features of nine cases of non-neural granular cell tumor (S100 negative) of the oral cavity.

Author	Polypoid	Ulceration	Pleomorphism	Cell shape	Typical mitosis	Atypical mitosis	Tissue invasion	Necrosis
Present case	Yes	Yes	Moderate	S, O, P	Yes	Yes	No	Yes
Basile and Woo, 2003	Yes	No	Focal	Varied	Low	No	No	No
Chaudhry and Calonje, 2005	Yes	No	Focal	S and O	Low	No	No	No
Chaudhry and Calonje, 2005	No	No	Moderate	S and O	Low	No	No	No
Lerman and Freedman, 2007	No	Yes	Yes	S and O	Yes	No	No	No
Solomon and Velez, 2015	Yes	No	No	-	No	No	No	No

Continue

Continuation

Rawal and Dodson, 2017	Yes	Yes	No	S, O, P	High	No	No	No
Rawal and Dodson, 2017	Yes	Yes	No	S, O, P	High	No	No	No
Mejía et al., 2019	Yes	Yes	No	-	Low	No	Muscle	No

S: spindle shaped; O: oval; P: polygonal.

Eight years later, Solomon and Velez[9] reported the case of a 12-year-old boy with a mucosa-colored nodule on the ventral surface of the tongue. Microscopically, patterns similar to those seen in conventional GCT were found, i.e., the nodule did not exhibit unusual histological patterns or mitotic figures (Table 2) as observed in previous studies[3,6,7] and in the present case. However, the immunohistochemical pattern was positive for vimentin and CD68 and negative for S100, CD56, CD34, SMA, CD1a and CD163, among other markers. Within this context, Solomon and Velez[9] suggested that S100-negative GCT is a benign process similar to conventional GCT and that conventional GCT is associated with a wide range of clinical and histological features. Thus, the need to distinguish NN-GCT (S100-negative GCT) as a new entity must be evaluated.

Rawal and Dodson[4] added two cases with an erythematous, painless polypoid nodule. One nodule measuring 0.9 cm occurred in the palate of a 19-year-old male patient and the other measuring 1 cm occurred in the oral mucosa of a 64-year-old man. The histological findings included the proliferation of well-circumscribed oval, polygonal or spindle-shaped cells arranged in nests, sheets, and fascicles. These cells exhibited abundant PAS-positive eosinophilic granular cytoplasm and a vesicular nucleus with prominent nucleoli, as well as typical mitotic figures and prominent vascularization, in agreement with the present case. However, the three features identified in our case and mentioned above (atypical mitotic figures, a second pattern of cell growth, and necrosis) were also absent in the NN-GCT described by Rawal and Dodson[4] (Table 2).

The most recent case of NN-GCT (S100 negative) of the oral cavity was that reported by Mejía et al.[8] in a 47-year-old man who exhibited an exophytic, ulcerated lesion in the mucosa and semimucosa of the lower lip. The maximum diameter was 1.3 cm. Microscopic analysis revealed the presence of an ulcerated polypoid lesion characterized by the proliferation of cells with granular cytoplasm and homogeneous nuclei, with a low percentage of mitoses and without cellular atypia, very similar to the case described by Solomon and Velez[9] but different from the present case (Table 2).

Despite the rarity of NN-GCT, it is now possible to characterize and to define criteria for its diagnosis based on the clinical and histopathological data that have been published over the years. Exophytic polypoid growth, an erythematous color or color similar to the adjacent mucosa, and an ulcerated surface are clinical features that resemble pyogenic granuloma and that characterize NN-GCT (Table 1). Regarding histopathological features, the proliferation of PAS-positive oval, polygonal or spindle-shaped

cells that exhibit nuclear pleomorphism, prominent nucleoli, and an increased number of mitotic figures are common findings (Table 2). Over the years, the histological description of this pathology may become more robust and characteristics seen less frequently in oral lesions may be added.

With respect to the immunophenotypic characterization of NN-GCT, some immunohistochemical markers have been recommended to aid in its diagnosis. The absence of S100 immunoreactivity has been observed since the first description of NN-GCT until the most recent publication. However, strong and diffuse positivity for NKI/C3 (CD63) and CD68 has been reported in six of the nine cases of the oral cavity, as well as positive vimentin immunoreactivity in five cases. Negative staining for proteins of cell lines with distinct differentiation such as HMB45, Melan A, SMA, cytokeratin (AE1/AE3), CD56, HHF35, and neuron-specific enolase (NSE) is also observed. Table 3 shows an immunohistochemical panel of markers used by several authors, including this case report, for the characterization and diagnosis of NN-GCT of the oral cavity.

Table 3. Immunoreactivity in nine cases of non-neural granular cell tumor (S100 negative) of the oral cavity.

Author	PAS	Vimentin	CD68	CD63	S100	NSE	HHF35	AE1/AE3	HMB45	CD56	Melan A	SMA
Present case	+	+	+	NT	-	NT	-	-	-	-	-	+
Basile and Woo, 2003	-	+	-	+	-	-	NT	-	NT	NT	-	NT
Chaudhry and Calonje, 2005	NT	NT	+	+	-	NT	NT	-	-	NT	-	-
Chaudhry and Calonje, 2005	NT	NT	+	+	-	NT	NT	-	-	NT	-	-
Lerman and Freedman, 2007	NT	+	+	+	-	NT	NT	-	-	NT	-	+
Solomon and Velez, 2015	NT	+	+	NT	-	NT	NT	NT	NT	-	NT	-
Rawal and Dodson, 2017	+	NT	NT	+	-	NT	NT	NT	-	NT	NT	-
Rawal and Dodson, 2017	+	NT	NT	+	-	NT	NT	NT	-	NT	NT	-
Mejía et al., 2019	NT	+	+	NT	-	-	NT	NT	NT	+	NT	NT

NT: not tested; +: positive; -: negative.

Analysis of the immunohistochemical panel reveals a mesenchymal origin of the granular tumor cells involved in the histogenesis of NN-GCT, as demonstrated by positive staining for vimentin and negative staining for cytokeratins AE1/AE3. The immunopositivity for S100 protein in conventional GCT supports the neural histogenesis of this tumor; however, the cases initially described by LeBoit et al.[5] were negative for S100, as were the nine cases reported in the studies included in the present review[3,4,6-9]. In addition to negative S100 immunoreactivity, Basile and Woo[7] reported negative immunostaining for NSE, a fact that rules out a neural origin and explains the nomenclature of NN-GCT. The present study supports the

non-neural origin by showing negative immunostaining for CD56 (a neuronal cell adhesion molecule expressed on the surface of neurons and glial cells), a known marker of neural tumors[10].

In the present case, 80% of granular cells were positive for CD68. The same was reported for five of the nine cases shown in Table 2[3,6,8,9]. CD68 is a marker related to histiocytic differentiation and is also associated with the presence of lysosomes. However, the expression of CD68 associated with the absence of CD163 (a more specific protein for histiocytic differentiation) proved that it should not be considered a histiocytic/macrophage lineage[4]. Another marker that has shown significant positive expression in the literature is NKI/C3 (CD63). This marker is related to cells of melanosomal origin and has been associated with a higher lysosomal content. However, despite positivity in NN-GCT, the same studies reported negative immunoreactivity for other melanoma-related proteins such as HMB45 and Melan A[3,4,6,7,11], as also observed in the present case. These data reinforce a high content of lysosomes in granular cells and do not indicate histiocytic or melanocytic differentiation.

Electron microscopy analysis of the neoplastic granular cells present in NN-GCT and conventional GCT reveals different complex lysosomal structures[11,12] that explain the high expression of lysosomal membrane-associated markers such as CD68 and NKI/C3 (CD63). These two markers have been cited in some studies on NN-GCT of the skin and oral cavity[3,6,11,12]. According to Basile and Woo[7], overexpression of lysosomes in mesenchymal neoplasms can occur in four situations: 1) degenerative/reactive phenomena in mesenchymal tumors with a well-defined origin; 2) primary nerve sheath tumors such as conventional GCT; 3) hamartomas and/or degenerative phenomena without a defined origin such as congenital epulis; 4) S100-negative polypoid tumor of the skin and mucosa with a nonspecific nature of degenerative granular cells, like the case reported here.

Focal staining of SMA was observed in 30% of the tumor cells, especially in the spindle-cell component. This feature has also been described by Lerman and Freedman[6] and can be explained by the proliferation of spindle-shaped cells arranged in a typical storiform pattern with entrapment of collagen, as reported in the first case involving the oral cavity[7]. Smooth muscle tumors can also exhibit alterations in granular cells; however, although positive for SMA, the tumor cells were negative for HHF35, a specific muscle actin marker[13].

Taken together, the available data indicate that the histogenesis of the present case, as well as of the oral NN-GCT cases reported in the literature, is not well defined due to the lack of expression of specific proteins in the two growth patterns, i.e., granular and spindle-shaped cells. There seems to be consensus among the authors of the studies included in this review regarding the positive expression of NKI/C3 and CD68, markers that only indicate a high lysosomal content in granular cells. Within this context, the diagnosis of NN-GCT becomes extremely challenging because this tumor shares histological characteristics with different tumors and because of the possible presence of atypia. Furthermore, since there is no expression of specific proteins that are important for the identification of other pathologies, the diagnosis is made by exclusion.

For the differential diagnosis, the exclusion process involves the correlation between clinical, histopathological, and immunohistochemical features since a range of benign and malignant oral lesions contain eosinophilic granular cells. Considering histopathological and immunohistochemical features, the following pathologies must be included: conventional GCT (similar morphology but S100 positive); congenital epulis of the newborn (also S100 negative but the lesion is congenital and has specific clinical characteristics); verruciform xanthoma (CD68 positive and S100 negative but NKI/C3 and CD163 positive); granular cell leiomyoma (positive for SMA and other muscle proteins); melanoma (positive for NKI/C3, S-100, HMB45, and Melan A); atypical fibroxanthoma (S100 negative and CD68 and SMA positive); cellular neurothekeoma (positive for NKI/C3, negative for S100, can also be positive for SMA); granular cell variants of PEComa (negative for S100 and positive for SMA, HMB45, and Melan A), and benign fibrous histiocytoma (granular cells positive for NKI/C3 and CD68 and negative for S100 and SMA)[4,14,15].

In view of the unusual histological findings of benign neoplasms such as necrosis and atypical mitotic figures, it was important to include atypical and malignant GCT in the possible differential diagnoses. Fanburg-Smith et al.[12] considered six criteria to be important for the diagnosis of conventional malignant GCT: presence of necrosis, population of spindle-shaped tumor cells, vesicular nucleus with prominent nucleoli, high mitotic activity, increased nuclear cytoplasmic ratio, and pleomorphism. The authors suggested classifying conventional GCTs as benign (meeting none of the criteria and focal pleomorphism), atypical (one or two criteria), and malignant (three or more criteria). In the following years, other authors proposed classifications in an attempt to simplify the decision regarding the nature of conventional GCT. Nasser et al.[16] suggested the classification of CGT as a benign tumor; however, in the presence of necrosis and/or mitosis, the tumor will be classified as uncertain malignant potential. Machado et al.[15] modified the classification of Fanburg-Smith et al.[12] and recommended the denomination of GCT without metastatic potential for benign and atypical tumors and GCT with increased risk of metastasis for tumors with histological patterns indicative of malignancy.

When these criteria are applied to the classical NN-GCT described by LeBoit et al.[5], the tumor would be classified as malignant since it possesses three malignancy-related criteria according to Fanburg-Smith et al.[12], as uncertain malignant potential by Nasser et al.[16], and as increased risk of malignancy by Machado et al.[15]. However, only three of the 45 reported cases of skin NN-GCT had regional lymph node metastasis. Nevertheless, the authors reiterate that NN-GCT is an uncommon neoplasm with a benign behavior and regional metastases are extremely rare[17-19]. Thus, we believe that the classification proposed by Fanburg-Smith et al.[12] for conventional GCT would not be adequate for NN-GCT.

Considering the possible differential diagnosis with malignant GCT, we also performed immunohistochemical analysis of Bcl-2, p53, and Ki-67. The observation of high indices (> 10%), especially for Ki-67 and p53, has been associated with a higher risk of malignancy in conventional GCT[12]. In the present study, the expression of these markers was low (< 5% of tumor cells). This finding may be related to the benign nature of the pathologies, showing low cell proliferation indices.

In view of the above considerations, the best denomination for the present case would be atypical NN-GCT. We believe that the use of the term atypical is appropriate in this case because of the identification of distinct and unusual microscopic features when compared to those reported for NN-GCT, including the presence of atypical mitotic figures and necrotic areas. These characteristics reinforce the need for a more rigorous follow-up of the patient.

We hope that this study contributes to a better understanding and characterization of oral NN-GCT. Despite some atypical histological features and the lack of an established histogenesis, this tumor has a completely indolent behavior. Only eight cases of oral NN-GCT have been documented so far and it remains uncertain whether the biological behavior of skin NN-GCT can be extrapolated to oral tumors. Therefore, until a substantially larger number of cases of oral involvement have been reported, complete resection and rigorous follow-up are recommended.

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Data availability

Datasets related to this article will be available upon request to the corresponding author.

Author contribution

Larissa Abbehusen Couto: analysis and interpretation of data for the work; drafting the work. **Daiana Cristina Pereira Santana:** acquisition, of data for the work; drafting the work. **Ianna Josefa Valeska de Aniz Castro:** analysis of data for the work. **Roberto Almeida de Azevedo:** acquisition, of data for the work; revising it critically for important intellectual content. **Flávia Caló de Aquino Xavier:** analysis and interpretation of data for the work; revising it critically for important intellectual contente. **Jean Nunes dos Santos:** analysis and interpretation of data for the work; revising it critically for important intellectual content. **Águida Cristina Gomes Henriques Leitão:** Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; revising it critically for important intellectual content; Final approval of the version to be published. **All authors agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.** All authors actively participated in the manuscript findings and have revised and approved the final version of the manuscript.

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