Oral granular cell tumors: an analysis of 10 new pediatric and adolescent cases and a review of the literature

Robert B. Brannon* / Payal M. Anand**

Clinicopathologic studies on the granular cell tumor, a submucosal benign soft-tissue neoplasm, have not addressed the pediatric and adolescent population. This study of patients from birth to 19 years of age describes clinically and microscopically 10 new cases and combines them with 24 well-documented pediatric cases previously published in the English-language literature. Of the 34, patient ages ranged from 3 to 19 years (mean age 14.5 years) with a female-to-male ratio of 3.3 to 1. The most common location was the tongue (50%) and lips (25%). In neoplasms whose epithelial findings were documented microscopically, a reactive pseudoepitheliomatous (pseudocarcinomatous) hyperplasia of the overlying epithelium occurred in 29%. The recurrence rate was less than 10% following conservative surgical excision. This study reveals that an oral granular cell tumor in the first decade of life is an uncommon event and discusses the importance of differentiating between squamous cell carcinoma and granular cell tumor.

J Clin Pediatr Dent 29(1): 69-74, 2004

INTRODUCTION

Granular cell tumors are uncommon soft-tissue neoplasms that manifest in the oral cavity as firm, white-to-pink-to-yellowish submucosal nodules. These tumors may occur in almost any tissue or organ of the human body, but are most commonly found in the skin, subcutaneous tissue, and oral mucosae.[1,2] In fact, the tongue is the most common site, accounting for one-third to one-half of all reported cases.[3] Although the granular cell tumor is usually solitary, a patient may have multiple separate tumors.[4]

Of major significance is the histological finding of pseudoepitheliomatous (pseudocarcinomatous) hyperplasia of the epithelium overlying the granular cell tumor, which has been reported in 9% to 85% of all cases.[1,3,5] Failure to identify microscopically this benign epithelial proliferation can result in a misdiagnosis of squamous cell carcinoma.

Granular cell tumors have been reported in patients over a very wide age range with a mean age of occurrence between the fourth and sixth decades of life and are generally thought to be rare in children.[2-4] Many series have reported on the granular cell tumor, but they have not focused on the pediatric-adolescent population. Therefore, the purpose of this paper is to investigate the clinicopathologic features of a series of granular cell tumors occurring in children and adolescents from the Louisiana State University School of Dentistry (LSUSD) and to compare these findings with well-documented cases previously reported in the English-language literature.

METHODS

The clinical data of 10 biopsied pediatric-adolescent cases of granular cell tumors of oral mucosae accessioned by the Louisiana State University School of Dentistry (LSUSD) Department of Oral and Maxillofacial Pathology from January 1, 1969, to April 23, 2003, were reviewed. All cases were microscopically reviewed (RBB) and fulfilled the histological criteria for oral granular cell tumors as defined by Neville *et al*.[3] In this study the pediatric-adolescent population was from birth to 19 years of age.

A review of the English-language literature revealed 26 well-documented granular cell tumors in 24 patients whose age range was birth to 19 years.[6-21] Demographic, clinical, and follow-up information on these cases is shown in Table 2. Numerous other published series of

* Robert B. Brannon, DDS, MSD, Associate Professor, Department of Oral and Maxillofacial Pathology, Louisiana State University School of Dentistry, New Orleans, LA.

** Payal M. Anand, BDS, Resident, Department of Periodontics, Louisiana State University School of Dentistry, New Orleans, LA, LSUHSC Institutional Review Board #5747

Send all correspondence to Dr. Robert B. Brannon, Department of Oral and Maxillofacial Pathology-Box 114, Louisiana State University School of Dentistry, 1100 Florida Avenue, New Orleans, LA 70119.

Voice: 504-619-8551
Fax: 504-619-8751
E-mail: rbrann@lsuhsc.edu

granular cell tumors provided only an age range with no correlation of the age of the patient to location of the lesion or other demographic and clinical information. Some of these series did have at least one patient in the first or second decade of life; however, they were not included because of the lack of detail from each case.

RESULTS

There were 61 oral granular cell tumors in the 54,220 accessioned cases in the LSUSD oral pathology files. Of these 61 cases, 10 (16%) were in the pediatric-adolescent age group.

A summary of the demographic, clinical findings, treatment, and follow-up of the well-documented oral granular cell tumors in the literature, in addition to the 10 new cases, is shown in Table 1, for a total of 36 cases in 34 patients. The age of the patients ranged from 3 to 19 years with the average being 14.5 years. Eleven (32%) occurred in patients between 0 and 12 years of age, but only two of those were in the first decade of life. Twenty-six (76%) of the 34 patients were female. The most common location for the 36 tumors was the tongue (50%) followed by the lips (25%). The majority were painless, firm or often indurated submucosal nodules averaging 1.0 cm in diameter (Fig 1). A few were described as sessile or raised. In the current study, 7 (70%) of the cases were clinically interpreted as granular cell tumors or fibromas.

In agreement with the previously published authors, we observed a similar spectrum of histological features. The 10 cases of granular cell tumors in this study lacked encapsulation and were composed of large, oval cells with granular cytoplasm arranged in sheets and cords that encompassed peripheral nerves and skeletal muscle bundles (Figure 2). In 3 of the 9 cases the overlying stratified squamous epithelium exhibited pseudoepitheliomatous hyperplasia, one was florid, and two were mild and focal (Figure 3). In one case there was no epithelium for evaluation. Only one case was completely excised; the remaining 9 had one or more specimen margins positive for tumor.

All of the lesions reported in the literature were treated by conservative surgical excision with the exception of one, which was treated by enucleation. Clinical follow-up was recorded in 12 of the reported cases (Table 1). Follow-up ranged from 5 months to 7 years (mean 5 years). In 2 cases the length of follow-up time was not provided. Only one case recurred.

DISCUSSION

Tumors of the head and neck in children are uncommon and represent less than 5% of all head and neck tumors.[22] These head and neck tumors in children represent a heterogeneous group of conditions that range from congenital malformations to benign and malignant neoplasms.[22,23] Reported series on oral and head and neck tumors in children indicate a very low frequency of occurrence for the granular cell tumor in children. There were no granular cell tumors among the 293 oral tumors (patients: 0 to 14 years of age) reported by Bhaskar[24] or the 172 oral tumors (patients: 0 to 18 years of age) reported by Maaita.[25] Likewise, Rapidis *et al.* found no granular cell tumors in the 1,007 tumors of the head and neck (patients: 0 to 16 years of age).[22] Two patients with granular cell tumors were among the 161 oral tumors (patients: 0 to 15 years of age) reported by Jones.[7] In the study by Stewart *et al.*[26] 9 (19%) of 48 granular cell tumors occurred in patients 0 to 20 years of age, which is similar to the current study in which 10 (16%) of 61 were in patients 0 to 19 years of age. In the former study, the patients were in the first and second decades of life; in the latter, they were in the second only.

Granular cell tumors have been reported in patients ranging in age from the very young[19] to those over 100.[27] Most studies demonstrate a female predilection in the range of 1.8 to 2.4:1.[4,28] Any race may be affected, but several studies have shown a definite predominance in blacks.[2,27,29,30] A summary of the demographic and clinical data from the reported cases of oral granular cell tumors in children and adolescents, in addition to the data from the 10 new cases in this study, is shown in Table 1. This brings the number of well-documented cases of children with oral granular cell tumors to 34. Interestingly, 32 of the patients were in the second decade of life. The ages of the patients in the first decade of life were 3 years and 7 years. The female to male ratio was 3.25:1, which is in keeping with other reported series that included adults.

The tongue (50%) followed by the lips (25%) was the most common location for the 36 granular cell tumors in this study (Table 1). Of the 18 tongue lesions, 13 were on the dorsum, 2 were on the lateral border, and the specific location was not specified in 3 cases. Virtually all mucosal sites were involved in the remaining 9 cases. These findings are very similar to the reported oral sites of involvement in adults.[11,26] Although the granular cell tumor is usually solitary, a patient may have multiple separate tumors.[4] Two of the 34 patients were reported to have a synchronous oral granular cell tumor. In addition, one 15-year-old patient with a granular cell tumor of the tongue subsequently developed a cutaneous lesion.[20] Collins and Jones reported a case and reviewed the literature on multiple granular cell tumors with oral and extraoral involvement and found 17 cases, all in adults.[4] According to the survey, multiple lesions occurred in 7% to 25% of all cases. In the current study and literature review, the incidence of multiple granular cell tumors was 9% in the 0 to 19 years of age group.

Clinically, oral granular cell tumors usually present as painless, slightly raised, firm or often indurated submucosal lesions. Palpation of the lesion reveals no distinct borders even though clinically they appear well circumscribed. These ill-defined, indurated features

Table 1. LSUSD Data on Granular Cell Tumors in 10 Patients.

Case ID	Age (Years)	Gender	Race	Site (No. of lesions)	Treatment	Follow-up (Years)
Hagen et al[6]	19	F	Not Stated	Dorsum tongue	Excision	Not available
Jones[7]	10	F	Not Stated	Dorsum tongue	Not Stated	Not available
Jones[7]	11	F	Not Stated	Dorsum tongue	Not Stated	Not available
Pasqual and Pasqual[8]	16	M	W	Tongue NOS*	Excision	Not available
Whitten[9]	15	M	W	Upper lip	Excision	Not available
Bahuth et al[10]	11	M	B	Dorsum tongue	Excision	1 NR‡
Miller et al[11]	17	F	Not Stated	Dorsum tongue	Not Stated	Not available
Miller et al[11]	10	F	Not Stated	Tonsillar pillar	Not Stated	Not available
Miller et al[11]	10	F	Not Stated	Junction hard & soft palate	Not State	Not available
Miller et al[11]	19	M	Not Stated	Lateral border tongue	Not Stated	Not available
Beemster et al[12]	12	M	W	Dorsum tongue	Excision	1+ NR‡
Worsaae et al[13]	14	F	W	Floor Mouth sublingual papilla	Excision	5 NR‡
Worsaae et al[13]	17	M	W	Dorsum tongue (2)	Excision of both lesions	7 NR‡ both lesions
Worsaae et al[13]	15	F	W	Dorsum tongue	Excision	7 NR‡
Noonan et al[14]	10	F	Not Stated	Gingiva	Excision	“NR”‡
Noonan et al[14]	15	M	Not Stated	Tongue NOS*	Excision	“NR”‡
Matthews and Mason[15]	17	F	Not Stated	Lower lip	Not Stated	Not available
Matthews and Mason[15]	19	F	Not Stated	Soft palate	Not Stated	Not available
Skoglund and Holst[16]	18	F	W	Labial gingiva, anterior maxilla	Excision	2 NR‡
Miettinen et al[17]	11	F	Not Stated	Lower lip	Not Stated	Not available
Uhrenholt et al[18]	18	F	Not Stated	Uvula	Excision	5 months Recurrence
Truhan et al[19]	3	F	Not Stated	Vermilion border lower lip (2)	Excision of both lesions	Not available
Alessi et al[20]	15	F	Not Stated	Tongue NOS* and Hand†	Excision (Tongue)	5 NR‡ (Tongue)
Garlick et al[21]	7	M	Not Stated	Buccal mucosa	Enucleation without mucosa	5 NR‡
LSUSD	12	F	W	Right lower lip	Excision	Not available
LSUSD	16	F	B	Midline dorsum tongue	Excision	Not available
LSUSD	16	F	B	Right lower lip	Excision	Not available
LSUSD	17	F	B	Left oral commissure	Excision	Not available
LSUSD	17	F	W	Left anterior dorsum tongue	Excision	Not available
LSUSD	17	F	W	Right dorsum tongue	Excision	Not available
LSUSD	17	F	B	Left lower lip	Excision	Not available
LSUSD	18	F	W	Right lateral border, posterior 1/3 tongue	Excision	Not available
LSUSD	18	F	W	Midline dorsum tongue	Excision	Not available
LSUSD	19	F	W	Left lower lip	Excision	Not available

* NOS = Not otherwise specified
† Subsequently developed cutaneous granular cell tumor on hand
‡ NR = No recurrence

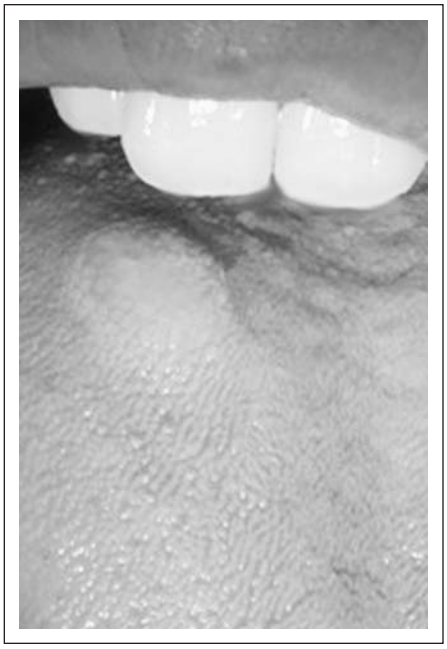

Figure 1. Granular cell tumor on the right dorsum of the tongue is raised and firm.

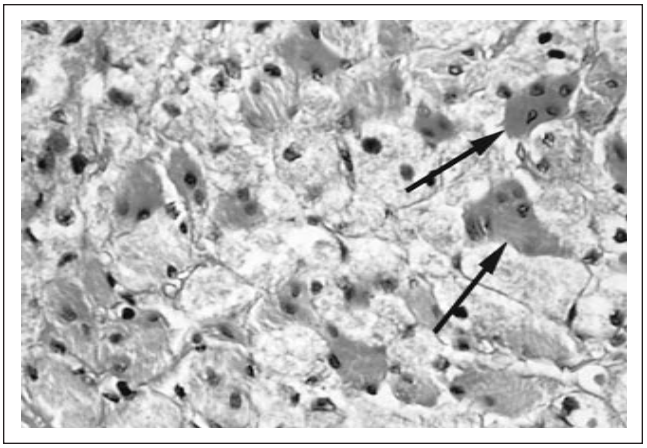

Figure 2. Skeletal muscle fibers (arrows) surrounded by granular cells (hematoxylin and eosin, original magnification x400).

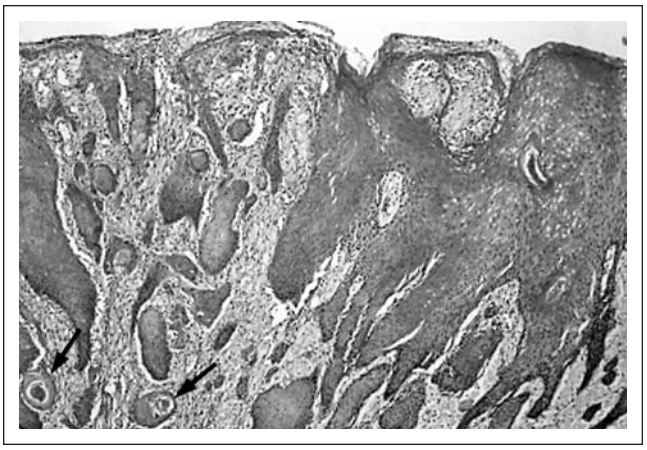

Figure 3. Granular cell tumor with granular cells and overlying stratified squamous epithelium exhibiting pseudoepitheliomatous hyperplasia. Note the downgrowth of islands of squamous cells and keratin pearls (arrows) in lower left corner. (hematoxylin and eosin, original magnification x40).

suggest the possibility of malignancy.[1,29] Some oral granular cell tumors exhibit a normal mucosal color although most are light yellow and/or white.[13,29]

The provisional clinical diagnoses in this study were variable with granular cell tumors and fibrous lesions comprising 7 of the 10 cases. These findings are comparable to those of Beemster *et al*.[12] in which 7 of 8 granular cell tumors were clinically thought to be fibrous lesions. In children and adolescents, lesions that can resemble granular cell tumors are primarily of mesenchymal (connective tissue) origin and include focal fibrous hyperplasias (fibroma, fibrous scar), peripheral nerve tumors (schwannoma, neurofibroma), and lipomas. Salivary gland tumors are also a consideration when granular cell tumors are in the appropriate anatomic locations.

Histologically, granular cell tumors are composed of sheets and nests of large, oval cells with abundant granular cytoplasm and small round nuclei.[3] These tumors lack encapsulation and often extend from the mucosal epithelium to the underlying skeletal muscle and peripheral nerves. The granular cells are often intimately associated with the aforementioned muscle and nerve bundles, appearing to emanate from them. Because of this close association with the granular cells and skeletal muscle, Abrikossoff, who is generally credited with the tumor's description in 1926, coined the term "granular cell myoblastoma."[4] It is also known by other names including Abrikossoff tumor,[28] and, because more recent investigations have discovered the presence of S-100 protein, a marker of Schwann cell differentiation, granular cell schwannoma.[29,31] However, the histogenesis of the granular cell tumor has been controversial, but recent immunohistochemical studies have suggested a neural and/or neuroendocrine origin for the granular cells.[32,33] Nevertheless, because the histogenesis is still subject to interpretation, the more generic term, granular cell tumor, is favored.

Of major significance is the microscopic finding of pseudoepitheliomatous hyperplasia of the overlying epithelium, which has been reported in up to 85% of all cases.[1,3,5] This benign epithelial reaction has been misdiagnosed as squamous cell carcinoma resulting in radical surgical procedures and morbidity.[6,12,19,27,29,34] Therefore, a deep biopsy is mandatory because it reveals the granular cells beneath the malignant-like appearance of the epithelium with pseudoepitheliomatous hyperplasia. The overlying epithelium was specifically addressed in only 14 of the 26 cases reported in the pediatric-adolescent age group.[7,10,13,15,16,18,19,21] Biopsy specimens in 2 of the aforementioned cases had no

epithelium. Pseudoepithe-liomatous hyperplasia was present in 3 (25%) of the 12 cases, which is similar to the finding of 33% in the current study. In addition, albeit rare, malignant granular cell tumors have been reported.[2,3]

Overall, the reported recurrence rate has varied widely from less than 10%,[1] despite incomplete excision in many cases, to as high as 50%.[20] However, the consensus among most investigators for oral granular cell tumors favors a relatively low recurrence rate. In the pediatric-adolescent age group, 12 cases reported a follow-up of 5 months to 7 years (mean, 5 years).[12-14,16,18,20,21] Eleven (11) of the 12 had no recurrences. In the twelfth, follow-up on a granular cell tumor of the uvula that recurred was interpreted to be residual.[18] Adequacy of excision was addressed in only 4 cases.[13] There were no recurrences despite incomplete excision in 3 of the 4 cases.[13] These observations support the benign nature of the granular cell tumor.[1,13]

CONCLUSIONS

This study adds 10 new cases of granular cell tumor to the 24 previously reported well-documented cases. The following may be concluded from the results of this study and literature review regarding granular cell tumors in children and adolescents (ages birth to 19):

The granular cell tumor is an uncommon lesion in children and adolescents. In this population, the peak incidence is in the second decade; the incidence of granular cell tumors in the first decade is very uncommon (less that 10%). Granular cell tumors have a female predilection and are found most often on the tongue, especially the dorsum, but may occur at any oral mucosal site.

In the child-adolescent age group, granular cell tumors have a low recurrence rate (less than 10%). Nevertheless, treatment should be directed towards complete surgical excision. It is important to note that the benign occurrence of pseudoepitheliomatous hyperplasia in granular cell tumors may be misinterpreted microscopically as squamous cell carcinoma, especially in superficial biopsies.

As with any questionable lesion, the clinician must ask the pathologist to review the microscopic findings if a malignant diagnosis is not consistent with the clinical findings. Correlation of the clinical findings with the microscopic features will yield the correct diagnosis and avoid unnecessary treatment for the patient.

ACKNOWLEDGEMENTS

We wish to acknowledge the assistance of Jessica Hawkins, manager of graphic arts and photography, Michael Higgins, editorial consultant, Maureen Raymond, computer services software supporter, and Elizabeth Strother, head dental librarian for their assistance in the preparation of this article. All are with the Louisiana State University School of Dentistry.

REFERENCES

1. Lack EE, Worsham GF, Callihan MD, et al. Granular cell tumor: a clinicopathologic study of 110 patients. J Surg Oncol 13: 301-316, 1980
2. Apisarnthanarax P. Granular cell tumor. An analysis of 16 cases and review of the literature. J Am Acad Dermatol 5: 171-182, 1981.
3. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral & Maxillofacial Pathology. 2nd ed. Philadelphia, Pa, WB Saunders Co, 465-466, 2002.
4. Collins BM, Jones AC. Multiple granular cell tumors of the oral cavity: report of a case and review of the literature. J Oral Maxillofac Surg 53: 707-711, 1995.
5. Bangle R Jr. A morphological and histochemical study of the granular cell myoblastoma. Cancer 5: 950-965, 1952.
6. Hagen JO, Soule EH, Gores RJ. Granular-cell myoblastoma of the oral cavity. Oral Surg Oral Med Oral Pathol 14: 454-466, 1961.
7. Jones JH. Non-odontogenic oral tumours in children. Br Dent J 119: 439-447, 1965.
8. Pasqual HN, Pasqual RJ. Granular-cell myoblastoma of tongue: report of a case. Oral Surg Oral Med Oral Pathol 24: 592-593, 1967.
9. Whitten JB. The fine structure of an intraoral granular-cell myoblastoma. Oral Surg Oral Med Oral Pathol 26: 202-213, 1968.
10. Bahuth JJ, Lee WW, Acquarelli MJ. Granular cell myoblastoma of the tongue. Arch Otolaryngol 91: 161-165, 1970.
11. Miller AS, Leifer C, Chen S-Y, Harwick RD. Oral granular cell tumors; report of twenty-five cases with electron microscopy. Oral Surg Oral Med Oral Pathol 44: 227-237, 1977.
12. Beemster G, van der Kwast W, Schoen J, van der Waal I. Granular cell tumor of the tongue. Int J Oral Surg 8: 128-132, 1979.
13. Worsaae N, Schwartz O, Pindborg JJ. Follow-up study of 14 oral granular cell tumors. Int J Oral Surg 8: 133-139, 1979.
14. Noonan JD, Horton CE, Old WL, Stokes TL. Granular cell myoblastoma of the head and neck: review of the literature and 10 year experience. Am J Surg 138: 611-614, 1979.
15. Matthews JB, Mason GI. Oral granular cell myoblastoma: an immunohistochemical study. J Oral Pathol 11: 343-352, 1982.
16. Skoglund LA, Holst E. Granular cell tumor on the alveolar ridge in an adult patient: report of a case. Int J Oral Surg 12: 60-63, 1983.
17. Miettinen M, Lehtonen E, Lehtola H, Ekblom P, Lehto VP, Virtanen I. Histogenesis of granular cell tumour—an immunohistochemical and ultrastructural study. J Pathol 142: 221-229, 1984.
18. Uhrenholt L, Nielsen M, Christensen L. Granular cell tumor of the uvula. Arch Otorhinolaryngol 243: 293-295, 1986.
19. Truhan AP, Esterly NB. Firm linear plaque on the lip of a child. Granular cell tumor (granular cell myoblastoma, granular cell schwannoma). Arch Dermatol 121: 1199, 1202, 1985
20. Alessi DM, Zimmerman MC. Granular cell tumors of the head and neck. Laryngoscope 98: 810-814, 1988.
21. Garlick JA, Dayan D, Buchner A. A desmoplastic granular cell tumour of the oral cavity: report of a case. Br J Oral Maxillofac Surg 30: 119-121, 1992
22. Rapidis AD, Economidis J, Goumas PD, et al. Tumours of the head and neck in children: a clinico-pathological analysis of 1,007 cases. J Craniomaxillofac Surg 16: 279-286, 1988.
23. Posnick JC. Paediatric craniofacial surgery: historical perspectives, recent advancements and refinements. Br J Oral Maxillofac Surg 33: 343-361, 1995.
24. Bhaskar SN. Oral tumors of infancy and childhood: a survey of 293 cases. J Pediatr 63: 195-210, 1963.
25. Maaita JK. Oral tumors in children: a review. J Clin Pediatr Dent 24: 133-135, 2000.
26. Stewart CM, Watson RE, Eversole LR, Fischlschweiger W, Leider AS. Oral granular cell tumors: a clinicopathologic and immunocytochemical study. Oral Surg Oral Med Oral Pathol 65: 427-435, 1988.
27. Vance SF III, Hudson RP Jr. Granular cell myoblastoma. Clinicopathologic study of forty-two patients. Am J Clin Pathol 52: 208-211, 1969.

28. Becelli R, Perugini M, Gasparini G, Cassoni A, Fabiani F. Abrikossoff's tumor. J Craniofac Surg 12: 78-81, 2001.
29. Dunlap CL, Barker BF. Diagnostic problems in oral pathology. Semin Diagn Pathol 2: 16-30, 1985.
30. Frable MA, Fischer RA. Granular cell myoblastomas. Laryngoscope 86: 36-42, 1976.
31. Fliss DM, Puterman M, Zirkin H, Leiberman A. Granular cell lesions in head and neck: a clinicopathological study. J Surg Oncol 42: 154-160, 1989.
32. Junquera LM, de Vicente JC, Vega JA, Losa JL, Albertos JM, López-Arranz JS. Granular-cell tumours: an immunohistochemical study. Br J Oral Maxillofac Surg 35: 180-184, 1997.
33. Williams HK, Williams DM. Oral granular cell tumours: a histological and immunocytochemical study. J Oral Pathol Med 26: 164-169, 1997.
34. Strong EW, McDivitt RW, Brasfield RD. Granular cell myoblastoma. Cancer 25: 415-422, 1970.