

ORIGINAL ARTICLE

Cutaneous Granular Cell Tumor: A Clinical and Pathologic Analysis of 34 Cases

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Abstract. *Background.* Granular cell tumor (GCT), also known as Abrikossoff tumor, is an uncommon benign neoplasm, probably of neural origin derived from Schwann cells. It presents clinically as a solitary asymptomatic nodule and its pathogenesis has been the subject of much debate in the literature.

Objectives. We aimed to analyze the clinical, histologic, and immunohistochemical characteristics associated with this tumor and to determine whether these findings correspond to those reported to date in the literature.

Methods. In this retrospective study of 34 patients with histologic diagnosis of GCT, we analyzed clinical characteristics (site, age, sex, duration, and suspected diagnosis), histological findings (border, cell atypia and mitoses, involvement of adnexal structures, pseudoepitheliomatous hyperplasia, and presence of the recently described pustulo-ovoid bodies), and immunohistochemical findings (S-100 staining in 16 randomly selected cases).

Results. In total, 58.82 % were men and 41.18 % were women, and the mean age was 31.74 years. The most common site was the oral cavity (61.76 %). The most frequently suspected clinical diagnosis was fibroma (17.65 %). The lesion was poorly defined and diffuse in 85.29 %. Pseudoepitheliomatous hyperplasia was present in 58.82 %. Nuclear atypia was found in 29.41 % and mitoses in 20.59 %. One case was considered malignant (2.94 %) and 2 atypical (5.88 %). Pustulo-ovoid bodies were present in 47.06 % of the cases and S-100 staining was positive in all cases analyzed.

Conclusions. Our series confirms the characteristics described previously for GCT, except for certain peculiarities, and supports the presence of pustulo-ovoid bodies as an additional histologic finding for diagnosis of this tumor.

Key words: granular cell tumor, Abrikossoff tumor, pustulo-ovoid bodies of Milian.

TUMOR DE CÉLULAS GRANULARES CUTÁNEO: ANÁLISIS CLÍNICO-PATOLÓGICO DE TREINTA Y CUATRO CASOS

Resumen. *Introducción.* El tumor de células granulares cutáneo (TCG) o de Abrikossoff es una neoplasia benigna e infrecuente, probablemente de origen neural a partir de las células de Schwann. Clínicamente se manifiesta como un nódulo solitario y asintomático, y su etiopatogenia ha estado ampliamente debatida en la literatura.

Objetivos. Analizar las características clínicas, histológicas e inmunohistoquímicas asociadas a este tumor y determinar si estos hallazgos se corresponden con lo descrito hasta el momento en la literatura.

Métodos. Se realiza un estudio retrospectivo de treinta y cuatro casos con diagnóstico histológico de TCG donde se analizan las características clínicas (localización, edad, sexo, tiempo de evolución y sospecha diagnóstica), histológicas (delimitación, atipia, mitosis, afectación de anejos cutáneos, hiperplasia pseudoepiteliomatosa y presencia de los recientemente descritos cuerpos pustulo-ovoides [CPO]) e inmunohistoquímicas (tinción S-100 en 16 casos seleccionados aleatoriamente).

Resultados. El 58,82 % fueron hombres y el 41,18 % mujeres. La edad media fue de 31,74 años. La localización más frecuente fue la cavidad oral (61,76 %). El diagnóstico clínico más comúnmente sospechado fue el de fibroma (17,65 %). En un 85,29 % se presentaba como una lesión mal delimitada y difusa. La hiperplasia pseudoepiteliomatosa estuvo presente en el 58,82 %. Se encontraron atipias nucleares en el 29,41 % y mitosis en un 20,59 %. Hubo un caso maligno (2,94 %) y dos se consideraron atípicos (5,88 %). Los CPO estuvieron presentes en el 47,06 %. La tinción con S-100 fue positiva en el 100 % de los casos analizados.

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Conclusiones. Nuestra serie confirmaría las características descritas hasta el momento para el TCG salvo con algunas peculiaridades y apoyaría la existencia de los CPO como un nuevo hallazgo histológico adicional para el diagnóstico de este tumor.

Palabras clave: tumor de células granulares, tumor de Abrikossoff, cuerpos pústulo-ovoides de Milian.

Introduction

Granular cell tumor (GCT), also known as Abrikossoff tumor, is an uncommon benign neoplasm thought to be neural in origin and derived from Schwann cells.¹ It typically presents as a slow-growing, solitary, and painless nodular lesion located at the cutaneous and subcutaneous level (43%), on the tongue (23%), or any other part of the body (Figure 1).² It can affect people of any age, race, or sex, although it is more common in those aged between 20 and 40 years, in women, and in black patients.²

Because the lesion is generally nonspecific and does not raise clinical suspicion, diagnosis is by biopsy. Between 1% and 2% of cases are malignant and, in these cases, outcome is usually fatal.³ There have been no reports in children.

Between 5% and 25% of patients have multiple lesions, although this presentation is also uncommon in children.⁴⁻⁶ Familial cases of multiple lesions have been reported, thus raising the possibility that some patients may have a genetic disposition towards this condition. There have also been reports of cases of congenital GCT⁷ and of an association in children between multiple skin tumors and systemic musculoskeletal, cardiovascular, and neurologic abnormalities.^{8,9}

GCT was first described by Abrikossoff in 1926.¹ It has a characteristic histologic appearance that is easily recognized under an optical microscope. However, the pathogenesis of this tumor has long been the subject of research and debate, and its origin has still to be clearly established. Abrikossoff initially described GCT as a “granular cell myoblastoma,” because he thought that its

histologic appearance was similar to that of striated muscle cells.¹ Later studies supported a neural differentiation, the hypothesis first put forward by Feyrter in 1935.¹ In 1962, Fisher and Wechsler used an electron microscope to posit that the condition could represent differentiation from Schwann cells. This is the currently accepted hypothesis for GCT.¹

Under an optical microscope, the cells that make up GCT are large, polygonal, or round, with a central vesicular nucleus, and an eosinophilic and granular cytoplasm. On the overlying epithelium, GCT is associated with variable pseudoepitheliomatous hyperplasia. The individual tumor cells are often separated by fine bands of connective tissue (Figure 2). The prominent granules observed inside the cells are lysosomes or a component of the Golgi apparatus. Routine histopathology shows the granules to be positive for periodic acid-Schiff (PAS) and luxol fast blue, and resistant to diastase, indicating the presence of myelin inside the tumor. Most GCTs are positive for S-100 and CD57. They are also strongly positive for neuron-specific enolase and vimentin, and the presence of myelin-associated glucoprotein has been demonstrated. Pustulo-ovoid bodies of Milian have recently been described as a regular histological finding. These are observed under the optical microscope as large (4-5 μm), round, eosinophilic granules surrounded by a clear halo (Figure 3), although their significance and frequency in this tumor are not clear.¹⁰

Granular cells may also be present in several types of tumor, such as basal cell carcinoma, fibroxanthoma, atypical

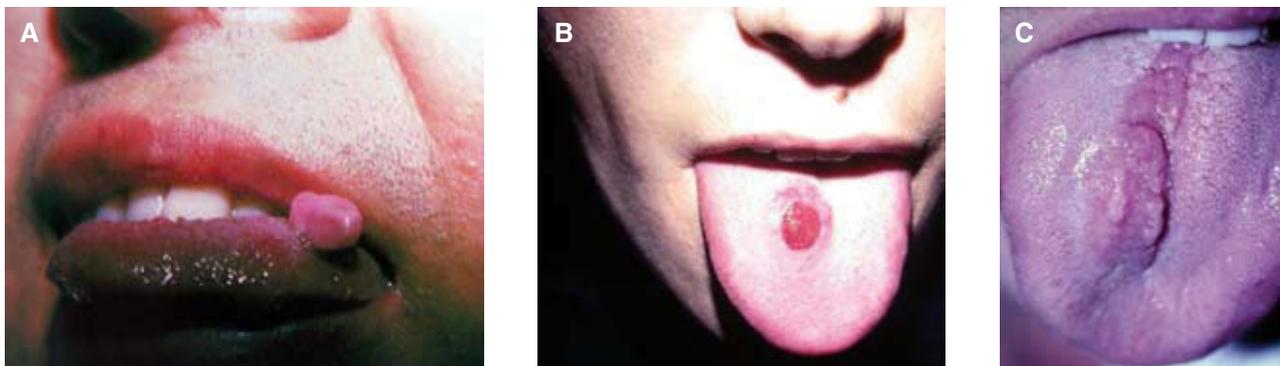


Figure 1. Clinical appearance of a granular cell tumor. A, Polypoid nodule with the appearance of a fibroma on the dorsum of the tongue. B, well delimited violaceous nodule on the dorsum of the tongue. C, Well-delimited flesh-colored nodule.

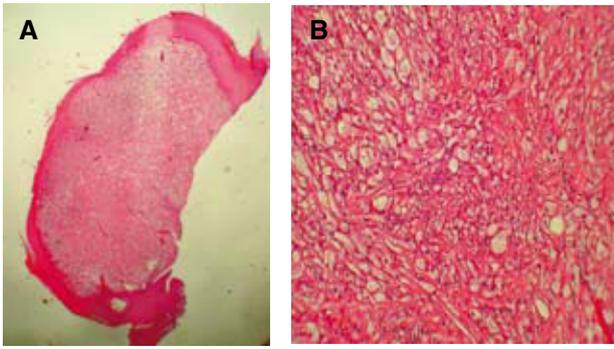


Figure 2. A, Low-magnification view of a granular cell tumor occupying the entire dermis (hematoxylin-eosin, $\times 10$). B, Granular cell tumor composed of large, polygonal, spindle cells with an eosinophilic and granular cytoplasm (hematoxylin-eosin, $\times 100$).

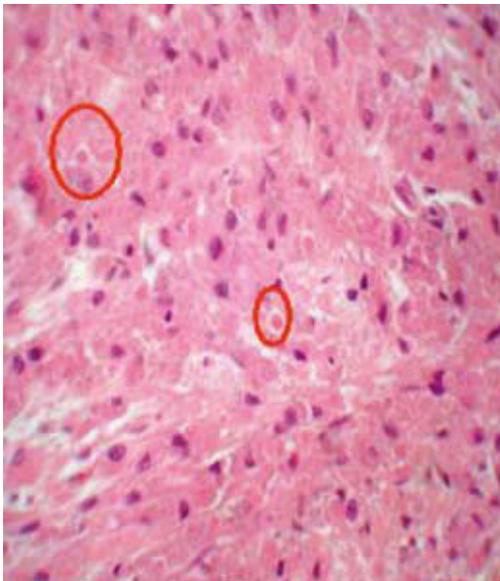


Figure 3. Pustulo-ovoid bodies of Milian (hematoxylin-eosin, $\times 200$).

fibroxanthoma,^{11,12} dermatofibroma,¹³ dermatomyofibroma, dermatofibrosarcoma protuberans, melanocytic nevi,¹⁴ rhabdomyoma, cutaneous angiosarcoma, and cutaneous leiomyosarcoma. This finding is common and nonspecific, and affects part of the lesion. The true GCT can thus be correctly differentiated using morphologic and immunohistochemical criteria. Occasionally, reactive changes associated with surgical wounds can also mimic a GCT.⁶

Recently, there have been reports of GCT with involvement of the dermal-epidermal junction that mimics melanocytic neoplasm,¹⁴ and this could further complicate the differential diagnosis with melanoma. Therefore, immunohistochemical staining could play a very important role (in GCTs, stains would be negative for HMB-45 and

Melan-A, and positive for calretinin and inhibin).

One variety of non-neural GCT, also known as primitive polypoid GCT, is not clearly differentiated. This category seems to possess atypical histologic characteristics that would enable it to be classed as a new entity, thus distinguishing it from neural GCT.^{15,16}

Objectives

The present work aims to analyze the clinical, epidemiologic, histologic, and immunohistochemical characteristics associated with this tumor, and to determine whether these findings correspond to current reports in the literature.

Material and Methods

We performed a retrospective review of 34 cases with histopathologic findings of GCT of the skin and mucosa reported in the dermatology service of the Consorcio Hospital General Universitario de Valencia, Spain, between 1980 and 2007. Clinical characteristics were analyzed in terms of tumor site, age at onset, sex, time from onset to diagnosis, and suspected clinical diagnosis. Histologic characteristics were also analyzed in terms of architecture, cellular and nuclear atypia, number of mitoses, degree of involvement of skin adnexa, presence of pseudoepitheliomatous hyperplasia, and presence of pustulo-ovoid bodies of Milian. Immunohistochemical studies with S-100 were carried out in 16 randomly selected cases.

All cases were fixed in buffered formol, 10% (WWR International), embedded in paraffin, and processed following standard procedures. Sections were prepared with hematoxylin-eosin and, in all cases, PAS staining highlighted the cytoplasmic granules.

Results

Clinical Findings

Of a total of 34 patients (all Caucasian), 20 (58.82%) were male and 14 (41.18%) were female.

Age (not available in 12 cases) ranged from 3 months to 60 years, with a median of 37 years and a mean of 31.74 years (Table 1). In most cases, GCT presented as a single nodule that was generally asymptomatic and involved mainly the oral cavity in 21 cases (61.76%) (Figures 1 and 2), the extremities in 5 cases (17.65%), the cheek in 2 cases (5.88%), the back in 3 cases (8.82%), the trunk in 2 cases (5.88%), and the pubic region in 1 case (2.94%) (Table 1).

The size of the lesion could only be determined in some cases, and ranged from a few millimeters to several centimeters. Information was also scarce for time since onset, which for some patients varied from months to years.

In all cases, surgical resection was the treatment of choice, and no relapses or metastases have been detected in any of the cases to date (time since diagnosis, 4-27 years).

The initial clinical diagnosis of suspected GCT was only made in 5 cases (14.71%), all of which were in the oral cavity (4 on the tongue, and 1 on the gums). The most commonly suspected clinical diagnosis was fibroma in 6 cases (17.65%) (Figure 1), followed by GCT in 5 cases (14.71%), and squamous cell carcinoma in 4 cases (11.76%). Less frequent were dermatofibroma (3 cases, 8.82%), a friction burn (2 cases, 5.88%), and xanthogranuloma (2 cases, 5.88%). Finally, the more anecdotic cases included mucocele, nodules, dermatofibrosarcoma protuberans, leukokeratosis, verruca, cysts, calcified epithelioma of Malherbe, and keratoacanthoma as the initial suspected diagnosis in 1 (2.94%) case.

Histology Findings

In terms of its architecture, GCT appeared as a poorly delimited lesion distributed diffusely in the dermis in 29 cases (85.29%). When it affected the mouth and the oral cavity, it reached the striated muscle, and when it affected the skin and subcutaneous tissue, it reached the panniculus adiposus.

Pseudoepitheliomatous hyperplasia affected 20 cases (58.82%) moderately, and the histologic diagnosis was sometimes mistaken for squamous cell carcinoma when it was very intense and the only specimen available was from a superficial biopsy (Figure 4). The tumor cells were large, polygonal, round, or spindle-like, containing a large volume of eosinophilic cytoplasm and abundant fine granules (Figure 2). The nucleus was generally small to medium and located centrally. It was vesicular or hyperchromatic in appearance, and contained one or several small nucleoli and eosinophils. Nuclear pleomorphism was essentially focal and very slight, although we observed atypical nuclei in 10 cases (29.41%). Mitosis was observed in 7 cases (20.59%), with a range of activity of between 1 and 10 (mean, 2.57; median, 1), which generally varied from 1 to 2 mitoses per microscopic field at 10 \times , except in malignant GCT (1 case, 2.94%), due to its large clinical and histologic extension, the presence of atypical nuclei, mitoses at more than 2 per microscopic field at 10 \times , and nuclear pleomorphism. Two cases (31 and 18; 5.88%) were considered atypical, as they did not fulfill all 3 histologic characteristics. Only the adnexa were involved in 1 case

Table 1. Patient Characteristics

	No. of Patients (%)
Patients evaluated	34 (100)
Tumors evaluated	34 (100)
Sex	
Male	20 (58.82)
Female	14 (41.18)
Location	
Oral cavity	21 (61.76)
Cheek	2 (5.88)
Extremities	5 (14.71)
Back	3 (8.82)
Trunk	2 (5.88)
Pubic bone	1 (2.94)
Age, y	
< 18	6 (17.65)
19-40	8 (23.53)
41-60	8 (23.53)
Unknown	12 (35.29)

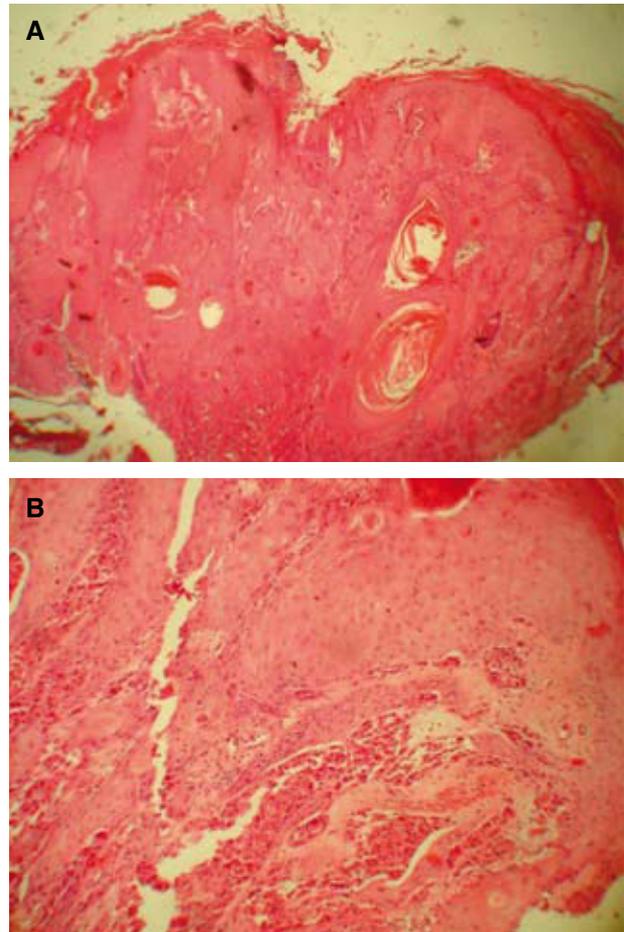


Figure 4. A, pseudoepitheliomatous hyperplasia mimicking squamous cell carcinoma (hematoxylin-eosin, $\times 10$). B, Detail of pseudoepitheliomatous hyperplasia with granular cells in the papillary dermis (hematoxylin-eosin, $\times 200$).

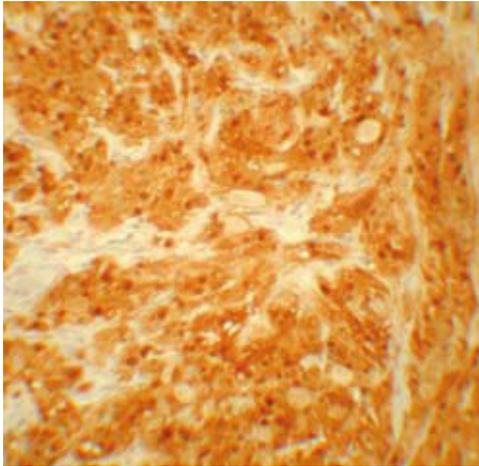


Figure 5. Stain positive for S-100, (×200).

(2.94%), namely, involvement of the eccrine glands. No lymphovascular involvement, necrosis, or perineural involvement was detected in any case.

Pustulo-ovoid bodies of Milian were observed in 16 cases (47.06%). One case (6.25%) had more than 50 of these cells per microscopic field at 10×. Six cases (37.50%) had between 10 and 30 cells per microscopic field at 10× and 9 (56.25%) had fewer than 10 cells per microscopic field at 10× (Figure 3, Tables 1 and 2).

Immunohistochemistry Results

Stains were made with S-100 in 16 randomly selected cases, and they were all positive (Figure 5, Tables 1 and 2).

Discussion

In our series, GCT affected patients of any age or sex. It was more frequent in men and in individuals aged 10 to 40 years. These results contrast with those reported in the literature, where the tumor has always been reported to be more frequent in women, and in patients aged 20 to 40 years. Nevertheless, it is worth noting the far from negligible number of cases in children and adolescents (17.65%), and the fact that there were no cases in black individuals.² In our series, the tumor was more commonly found on the mucosa of the oral cavity than on the skin and subcutaneous tissue.

There were no multiple tumors, familial cases, or congenital lesions, and we did not observe any of the other systemic abnormalities associated with GCT in children reported in the literature.^{8,9}

Staining with S-100 was not possible in all cases, although those in which it was were markedly positive for

S-100. This supports the neural origin of GCT and rules out its inclusion in the variety described by Le Boit et al and subsequently supported by Chaudhry and Calonje,¹⁵ of non-neural dermal GCT, traditionally known as primitive polypoid GCT, which is mainly negative for S-100 and whose histologic characteristics allow it to be differentiated from neural GCT. Those characteristics are as follows: polypoid architecture, epidermal collar, location in the papillary dermis, good delimitation, minimal or no epidermal hyperplasia, cytologic atypia (from mild to moderate compared with focal to diffuse), and increased mitotic activity. Nevertheless, the biological behavior of these tumors is benign and they have a good prognosis.^{15,16}

Only 1 case was considered malignant, and the patient's outcome remains unknown. The diagnosis of malignant GCT was based on the criteria proposed by Enzinger and Weiss. These include a vesicular nucleus with a prominent nucleolus, increased mitotic activity (more than 2 mitoses per 10 high-power fields), a high nucleus-to-cytoplasm ratio, and pleomorphism.³ The term atypical is used when fewer than 3 of these characteristics are present.

Pseudoepitheliomatous hyperplasia was quite a common finding in our series—as many as 58.82% of cases—and in other published series. This seems to be important when making the differential diagnosis with squamous cell carcinoma, with which it is often confused (Figure 4).¹⁷

We can conclude by saying that GCT is an uncommon tumor that only raises clinical suspicion when it is found on the tongue. It seems to be neural in origin (derived from Schwann cells), although a non-neural variety—no cases in our series—does exist. Familial cases, congenital cases, and multiple lesions are uncommon, and it is worth stressing that this tumor has a good prognosis—we detected no recurrences in our series after complete surgical resection. The recently described presence of pustulo-ovoid bodies of Milian could be an additional histologic finding in the diagnosis of this tumor, given its high prevalence in the samples analyzed. It seems that the number of pustulo-ovoid bodies of Milian increases with the age of the tumor. These cells are generated by the gradual accumulation of granules in the interior of the lysosomes, which, because of their maturity, have lost mitochondria and the endoplasmic reticulum; therefore, the cells tend more toward focal secretion of their cytoplasmic material.¹⁰

Our series confirms the characteristics described to date for GCT, except for some peculiar ones such as the high prevalence in children and young adults. It also confirms the presence of pustulo-ovoid bodies of Milian on microscopy. We feel that it is interesting to continue investigating the origins of GCT, since, although our series shows that positivity for S-100 supports a neural origin, this is not confirmed by some published series.^{15,16}

Table 2. Granular Cell Tumor: Summary of Clinical, Histologic, and Immunohistologic Data

Case	Sex	Age, y	Location	Clinical Manifestation	Delimitation	Level of Involvement	POBM	Pseudoepitheliomatous Hyperplasia	Cytology	Mitosis	Involvement of Adnexal Structures	S100
1	M	42	Foot	Fibroma	No	Adipose tissue	No	No	No atypia	No	Eccrine glands	+
2	M	U	Tongue	Mucocele	Yes	Muscle	>50 × 10 (HPF)	No	Atypia	No	No	ND
3	M	33	Tongue	Friction burn	No	Muscle	No	Yes	No atypia	No	No	ND
4	M	30	Tongue	GCT	No	Muscle	No	Yes	No atypia	No	No	ND
5	M	54	Lower back	U	Yes	Reticular dermis	No	No	No atypia	No	No	ND
6	M	U	Lower back	Dermatofibroma	Yes	Muscle	No	No	No atypia	No	No	ND
7	M	U	Groin	Nodule	No	Dermis	20 × 10 (HPF)	Yes	Atypical nuclei	1 × 10 (HPF)	No	ND
8	M	25	Back	DFSP	No	Dermis	3 × 10 (HPF)	No	No atypia	1 × 10 (HPF)	No	+
9	M	U	Tongue	GCT	Yes	Muscle	No	Yes	No atypia	No	No	ND
10	F	U	Tongue	Friction burn	No	Muscle	1 × 10 (HPF)	Atypia	1 × 10 (HPF)	No	ND	NR
11	F	U	Tongue	GCT	No	Muscle	1 × 10 (HPF)	Yes	Atypia	No	No	+
12	M	U	Tongue	U	No	Muscle	20 × 10 (HPF)	Yes	Atypical nuclei	No	No	ND
13	M	U	Forearm	Fibroma	No	Muscle	No	No	No atypia	No	No	+
14	M	46	Jugal mucosa	Squamous cell	No	Muscle	No	Yes	Atypical nuclei	No	No	+
15	M	52	Thorax	Squamous cell	No	Muscle	No	No	No atypia	No	No	ND
16	M	U	Thorax	U	No	Adipose tissue	No	Yes + ulceration	No atypia	No	No	ND
17	M	43	Oral mucosa	Fibroma	No	Muscle	10 × 10 (HPF)	Yes	No atypia	No	No	+
18	M	30	Tongue	U	No	Muscle	1 × 10 (HPF)	Yes	Atypia	2 × 10 (HPF)	No	ND
19	M	U	Gums	Fibroma	No	Dermis	No	No	No atypia	No	No	ND
20	M	39	Lip	Leukokeratosis	No	Muscle	No	No	No atypia	No	No	ND
21	F	3 mo	Gums	Epulis	No	Dermis	No	No	No atypia	No	No	ND
22	F	U	Tongue	Fibroma	No	Muscle	No	Yes	No atypia	No	No	ND
23	F	U	Gums	Fibroma	No	Mucosa	No	No	No atypia	No	No	ND
24	F	37	Soft palate	Verruca	No	Muscle	6 × 10 (HPF)	Yes	Atypia	1 × 10 (HPF)	No	+
25	F	7	Lip	Cyst	No	Muscle	10 × 10 (HPF)	Yes	No atypia	No	No	+
26	F	10	Lip	Dermatofibroma	No	Muscle	10 × 10 (HPF)	No	No atypia	No	No	ND
27	F	18	Tongue	GCT	No	Muscle	5 × 10 (HPF)	Yes	No atypia	No	No	+
28	F	43	Cheek	Calcified epithelioma of Malherbe	No	Cartilage	No	No	No atypia	No	No	+
29	F	42	Palate pillar	Yellow plaque	No	Adipose tissue	5 × 10 (HPF)	Yes	No atypia	No	No	+
30	M	37	Tongue	Squamous cell	No	Muscle	10 × 10 (HPF)	Yes	No atypia	No	No	+
31	F	5	Pubis	JXG/DF	No	Adipose tissue	5 × 10 (HPF)	Yes	Atypia	2 × 10 (HPF)	No	+
32	M	60	Cheek	Keratoacanthoma	No	Dermis	No	Yes	Atypia	10 × 10 (HPF)	No	+
33	F	8	Heel	U	U	U	U	U	U	U	U	ND
34	F	37	LE	Cutaneous horn	No	Dermis	5 × 10 (HPF)	Yes	No atypia	No	No	+

Abbreviations: DFSP, dermatofibrosarcoma protuberans; F, female; GCT, giant cell tumor; HPF, high-power field; JXG/DF, juvenile xanthogranuloma/dermatofibroma; LE, lower extremities; M, male; ND, not determined; POBM, pustulo-ovoid bodies of Milian; U, unknown.

In our opinion, every patient with a GCT should undergo a complete physical examination to rule out the presence of multiple associated tumors and possible visceral involvement. In children, the physical examination takes on even more importance due to the possible, yet uncommon, association with life-threatening systemic musculoskeletal, cardiovascular, and neurologic abnormalities.^{8,9}

Conflicts of Interest

The authors declare no conflicts of interest.

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