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Clinicopathological Characteristics of Oral Pyogenic Granuloma: A Comparative Study

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Abstract: *This paper aimed to compare the histological types of oral pyogenic granuloma (OPG) to determine whether they have different behaviors in relation to demographic, clinical and histological features. This cross-sectional and multicentric study retrieved records from 78 cases of OPG between 2002 and 2009 in two major referral centers of Bahia, Brazil. The slides were reviewed and information on the demographic data (skin color, age and sex), clinical parameters (color of lesion, clinical diagnosis, implantation, aspect, recurrence, size, anatomical site and duration) and histological findings (histological type and fibrous maturation) was gathered. The histological types distinguished the sex (p=0.003), the anatomical site (p=0.005) and the duration of the lesion (p=0.045). Furthermore, the non-LCH (Lobular Capillary Hemangioma) OPG presented a sessile base four times more frequent than LCH OPG, as well as a larger mean size, and all recurrences were in this histological type. These results suggest that LCH and non-LCH OPG showed different demographic features and clinical behaviors, what enforces the hypothesis that there are distinct histological types.*

Keywords : *pyogenic granuloma, lobular capillary hemangioma, oral cavity.*

I. Introduction

Oral pyogenic granuloma (OPG) is a benign lesion relatively common that occurs in skin and mucous membranes [1-5]. In oral cavity, it represents up to 7% of the diagnosed lesions [4. It origins as an enlarged volume of soft tissue, with sessile or pedunculated base sited mainly in the gingiva [3,4,6-8]. The lesion exhibits smooth or lobulated surface with color ranging from pink, red or purple [3,6], and, given the intense vascularization, bleeding occurs frequently [3,5,6].

The OPG was initially described as a fungal infection originated in horses and transmitted to humans as "human botryomycosis" [9]. Then, Hartzel in 1904 introduced the term “pyogenic granuloma” [10], which was subsequently changed to “lobular capillary hemangioma” (LCH) [1,3,11]. The OPG is classified as a benign neoplasm originated from blood vessels [12], and presents two histological types: i) lobular capillary hemangioma (LCH), showing proliferation of blood vessels with lobular aggregates; and ii) non-lobular capillary hemangioma (non-LCH), presenting high vascular proliferation which resembles the granulation tissue [1,11].

Although the OPG is a common lesion [4], there are few researches about OPG, especially in development countries [13,14], and rarely have these histological types of OPG been analyzed in relation to their biological behavior [15]. Therefore, this study aims to compare the histological types of OPG in relation to demographic, clinical and histological features.

II. Materials and Method

This research was previously approved by the Research Ethics Committee (CAAE no 0050.0.059.000-09). Data on OPG lesions that underwent biopsy during the period of 2002 to 2009 were gathered in the Oral Pathology Laboratory of the State University of Feira de Santana and the Laboratory of Oral Surgical Pathology of the Federal University of Bahia (UFBA), which are considered as the major referral centers of the region. Information regarding demographic data (skin color, age and sex), clinical parameters (color of lesion, clinical diagnosis, implantation, aspect, recurrence, size, anatomical site and duration), and histological findings (histological type and fibrous maturation) was obtained.

Slides stained with hematoxylin-eosin (HE) were reviewed by an experienced oral pathologist, in accordance with the Armed Forces Institute of Pathology (AFIP) [12]. For the classification of the lesions as LCH or non-LCH, the identification of lobular proliferation of microvascular elements was considered. Cases that presented morphologic criteria different from OPG were excluded from the study.

The statistical analysis was developed with SPSS 20.0 for Windows (IBM). For nominal variables, either the Chi-square test or Fisher's exact test was performed. For continuous variables, either the Student's t-test or Mann-Whitney U-test was used according to the sample distribution. The confidence interval (CI) was 95% and a p value<0.05 was considered statistically significant. For each variable, the valid cases were described in the table.

III. Results

Out of 121 slides reviewed, 78 filled the morphological criteria that define the histopathological diagnosis of OPG. This series presented 51 females (67.1%) and 25 (32.9%) males, with a male-to-female ratio of 2.04:1. There was predominance of the female sex in second and ninth decade of life. Non-white patients were most commonly affected (n=58; 93.5%). The age of patients ranged from 1 to 96 years (mean age of 36.8±18.6 years), with a high degree of occurrence in the third and fifth decade of life (Fig. 1). Including all cases of the sample, the majority of the lesions was characterized as pedunculated (n=42; 82.4%), nodular (n=23; 79.3%), red (n=44; 78.6%), and situated mainly in the gingiva (n=31; 41.3%). The duration ranged from days to 36 months (mean of 7.4±10.5 months), with size between 0.2 to 5.5 cm (mean of 1.54±0.92 cm). There was a clinical diagnosis of OPG in 78.4% (n=58) of the samples, and the recurrence occurs in 3.8% (n=3) of the lesions. The excisional surgery was the treatment employed for all cases.

Histologically, 20 cases (25.6%) were LCH OPG, and 58 cases (74.4%) were non-LCH OPG. Statistically significant differences between groups were found in relation to sex (p=0.003), anatomical site (p=0.005) and duration (p=0.045) (Table 1).

In microscopic examination, the non-LCH cases generally appeared as nodular or polypoid lesions covered by para-keratinized stratified squamous epithelium showing hyperplasia and ulceration, and sometimes coated with fibrinoid necrosis and scabs. The lamina propria revealed a diffuse chronic inflammatory infiltrate or acute, amid ectatic and congested blood vessels of variable diameters with granulation tissue present in most specimens. In some cases, these cellular elements found were separated or replaced by large collagenous bands, indicating more mature lesions. LCH lesions were generally shown as polypoid or not, coated in the same manner as the non-lobular lesions. The lamina propria presented solid lobes interspersed with fibrous bundles composed by endothelial cells and small blood vessels. Chronic and acute inflammatory infiltrates were present, and many of these cases exhibit epithelial cell colarettes separating the lobes. Mitosis was sometimes seen (Fig. 2).

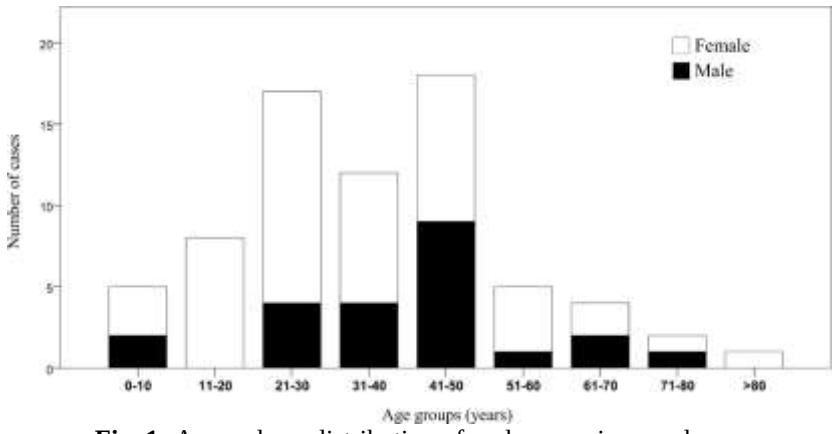

Fig. 1: Age and sex distribution of oral pyogenic granuloma**.**

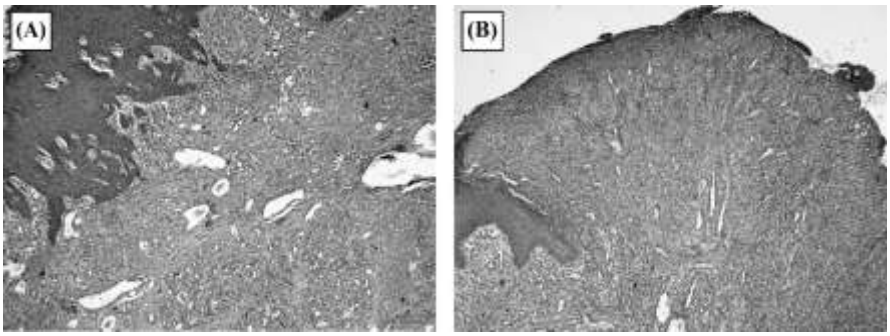

Fig. 2: (A) LCH OPG showing chronic inflammatory infiltrate in lobes separated by large collagenous bands (H/E 5X); (B) non-LCH OPG exhibiting diffuse chronic inflammatory infiltrate and superficial ulceration (H/E 5X).

Table 1: Comparison of histological types of OPG concerning demographic, clinical, and microscopic features.

Characteristics	Valid cases	Histological type stratification		p value
		non-LCH OPG (n=58)	LCH OPG (n=20)	
	[n]	n (%)	n (%)	
Demographic				
Age (years)[a]	[72]	37.1±19.3	36.1±17.2	0.841[¥]
Sex	[76]			
Female		43 (76.8%)	8 (40.0%)	***0.003****
Male		13 (23.2%)	12 (60.0%)	
Skin color	[62]			1.000**
White		3 (6.7%)	1 (5.9%)	
Non-white		42 (93.3%)	16 (94.1%)	
Clinical				
Anatomical site	[75]			***0.005****
Gingiva		28 (50.9%)	3 (15.0%)	
Others		27 (49.1%)	17 (85.0%)	
Aspect	[29]			0.633**
Nodular		15 (75.0%)	8 (88.9%)	
Others		5 (25.0%)	1 (11.1%)	
Clinical diagnosis	[74]			0.538**
Pyogenic granuloma		44 (80.0%)	14 (73.7%)	
Others		11 (20.0%)	5 (26.3%)	
Color	[56]			0.418*
Red		33 (80.5%)	14 (93.3%)	
Others		8 (19.5%)	1 (6.7%)	
Duration (months)[a]	[34]	10.1±12.6	3.0±2.6	***0.045***[‡]
Implantation	[51]			0.241**
Sessile		8 (23.5%)	1 (5.9%)	
Pedunculated		26 (76.5%)	16 (94.1%)	
Recurrence	[78]			#
Yes		3 (5.2%)	0 (0.0%)	
No		55 (94.8%)	20 (100.0%)	
Size (cm)[a]	[75]	1.63±0.98	1.28±0.65	0.153[‡]
Microscopic				
Fibrous maturation	[78]			1.000**
Present		11 (19.0%)	4 (20.0%)	
Absence		47 (81.0%)	16 (80.0%)	

[a] Mean±Standard deviation.
* Chi-square test.
** Fisher's exact test.
[¥] Student's t-test.
[‡] Mann-Whitney U-test.
Variable without conditions for analysis.

IV. Discussion

The pyogenic granuloma represents a benign vascular growth [12] that has histological types with distinct biological behavior of interest for clinical practice [15]. The OPG arises in response to various stimuli such as low-grade local irritation, traumatic injury, sex hormones or certain kinds of drugs [3]. The influence of etiological agents has been related to the formation of different histological types. In non-LCH, OPG is attributed to local irritating factors such as restorations, dental extraction, biting, calculus, etc. However, in LCH OPG the etiology remains unknown [1].

The OPG occurs in all ages [1,4-6,16], with predominance in white patients [13]. In this series, the mean age of 36.8 years was similar to that found by other researches [7,16], but distinguished from studies with mean age of 46.3 and 52.7 years, respectively [1,11]. Non-white patients were more often in the majority of the cases, possibly given the characteristics of the population analyzed, which has a prevalence of blacks and mulattos.

The OPG has a highlighted predilection for females [1,4,6,11,13]. The female steroid hormones act in two ways in the development of OPG: i) increasing the amount of vascular endothelial growth factor (VEGF) produced by activated monocytes and macrophages; and ii) protecting these cells from apoptosis, prolonging the angiogenic effect [17]. In this study, there was a predominance in females, mainly in the second decade of life (Fig. 1) and in non-LCH OPG (p=0.003). Researches also pointed a predilection in females in non-LCH OPG

[1,15]. This result suggests a possible influence of the effects of hormones in the development of non-LCH OPG, differentiating it demographically from LCH OPG.

The pyogenic granuloma has well-defined clinical features in literature [3,4,6,13], and the general results of this paper are similar to other studies [3,13]. However, there are controversies about the clinical aspects of the OPG histological types [1,18]. On one hand, it is recognized that etiological factors cause the formation of a lesion similar to reparative granulation tissue, with appearance often pedunculated (non-LCH OPG); or it origins a lesion histologically analogous to a benign vascular neoplasm with aspect frequently sessile (LCH OPG) [1]. On the other hand, it is suggested that LCH and non-LCH histological types represent different stages in the evolution of a single lesion with varying degrees of proliferative, angiogenic and inflammatory activity [18].

This study showed resemblance between histological types concerning the lesion color ($p=0.418$) and nodular aspect ($p=0.633$). There were no differences in clinical diagnosis ($p=0.538$). The sessile base was 4 times more often in the non-LCH type than in the LCH. However, pedunculated lesions were the majority in both groups, and despite the disagreements [1], this result was similar to those found by other researches [11,15,18].

The gingiva is the most commonly affected site in 44.4-83% of OPG cases, mainly in the maxillary anterior region [6,13]. That is explained by factors such as: i) anatomic features; ii) predominance of local irritation factors, such as biofilm, calculus and foreign material within the gingival crevice [3,4,6,19]; and iii) enhanced susceptibility to hormonal changes, which modify the gingival reparative response to injury [19] possibly influenced by VEGF, basic fibroblast growth factor, or connective tissue growth factor [3]. Gingiva also was the most affected site in this investigation, being 3.4 times more often in the non-LCH type than in the LCH ($p=0.005$). Despite the controversies [18], studies also pointed a higher frequency of lesions in gingiva in non-LCH OPG [1,15], what enforces the hypothesis that there is a distinct predilection in the anatomical site between these histological types.

The duration of the OPG lesions ranges from 1 to 84 months [13], and the size usually varies from a few millimeters to several centimeters, rarely exceeding 2.5 cm [3]. In contrast, this paper presented lesions surpassing 2.5 cm in 13.3% of cases, with sizes up to 5.5 cm in diameter. The non-LCH OPG exhibited a larger mean size than did the LCH OPG (1.63 ± 0.98 vs. 1.28 ± 0.65) with no statistically significant differences ($p=0.153$), like in other investigations [1,18]. Furthermore, the non-LCH type presented a mean duration of lesion 3.4 times higher (or a mean of 7 months more) than the one in the LCH type ($p=0.045$). Considering the relation between the lesion size and the duration, these results contribute to the hypothesis that LCH OPG has a rapid growth, probably due to different features in the proliferative activity [15] and a low apoptotic rate [20], which resembles more the behavior of a hemangioma than a reactive lesion [15].

The treatment of choice for OPG lesions is the surgical excision with removal of irritant agents and screening for histopathological confirmation [3,6]. The recurrence varies from 0 to 14.9% [4,6,11,13,16], as evidenced in this research. In all cases, the excisional biopsy was employed, and the recurrence affected only non-LCH OPG patients. In contrast, this finding differs from literature in the following ways: i) recurrences were found in both histological types with no statistically significant differences observed [18]; and ii) the LCH type was considered a more aggressive lesion than non-LCH, given the higher proliferative activity [15]. It is noteworthy that a possible explanation for higher recurrence in non-LCH OPG may be due to gingiva to present a more susceptibility to recurrences than do other sites [8], and in this series, it was more common in non-LCH OPG ($p=0.005$).

Histologically, the OPG cases of this series filled the morphologic criteria that define these lesions [1,6,11-13]. The specimens were polypoid and ulcerated, with cellular elements in lamina propria representing lobular and non-lobular lesions. The majority of cases exhibited chronic inflammation, with mitosis predominantly in the LCH type probably due to larger proliferative activity [15]. This investigation identified fibrous maturation in both histological types, indicating that lesions were older or in healing phases of the granulation tissue. It contrasts with a hypothesis of a distinct way of development of these lesions related to fibrous maturation [1]. However, another research demonstrates that the values of mean microvessel count (MVC) and inflammatory infiltrate density were significantly lower in the LCH type than in non-LCH [18], what still supports the hypothesis of different histological types.

Study limitations were missing data, absence of information on the etiological factors and no employment of immunohistochemical and histochemical techniques. Researches with larger sample size and with confounding factors controlled and also standardized laboratory techniques are important to highlight the features of the histological types of OPG.

V. Conclusion

The results of this paper agree partially with what has been proposed by other investigations [1,15,18]. It suggests that OPG has two histological types with different demographic features and clinical behavior,

enforcing the hypothesis that OPG presents two distinct histological types. Therefore, this comprehension is very important for better management of such lesions in clinical practice.

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