Clinicopathological evaluation of focal reactive lesions of the Gingiva

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ABSTRACT

Introduction
Focal reactive gingival lesions are elicited by chronic irritation primarily due to dental plaque, calculus, over-hanging dental restorations and ill-fitting dental prosthesis. Persistent irritation of the gingiva can lead to tissue injury and trigger inflammation leading to proliferation of endothelial cells, multi-nucleated giant cells, fibroblasts and tissue mineralisation.

Aims
The aim and objectives of the study were to determine the relative frequency and distribution of focal reactive gingival lesions according to sex, age, and anatomical site in patients who presented at the Witwatersrand Oral Health Centre.

Design
Retrospective cross-sectional study

Methods
Convenience sampling of patient records from the years 2011 to 2017 were analysed from the Department of Oral Pathology and the Department of Oral Medicine and Periodontology at the Witwatersrand Oral Health Centre. Sociodemographic variables and clinical features were evaluated.

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Results
Female patients accounted for 70.8% (n = 172) of all focal reactive gingival lesions, with the majority of the lesions having occurred in the maxilla (56.4%; n = 137). The age of patients ranged from 3 months to 88 years.

Conclusion
Contrary to findings in other studies, the peripheral ossifying fibroma was the most common focal reactive gingival lesion, after analysing 243 cases.

Keywords
Focal reactive gingival lesions, pyogenic granuloma, lobular capillary haemangioma. Peripheral ossifying fibroma, focal fibrous hyperplasia and peripheral giant cell granuloma.

Nomenclature
FRGL: Focal reactive gingival lesions
LCH: Lobular capillary haemangioma
FFH: Focal fibrous hyperplasia
POF: Peripheral ossifying fibroma
PGCG: Peripheral giant cell granuloma
Rrb: Rank biserial correlation coefficient
DMF: Decayed, Missing and Filled

INTRODUCTION
Focal reactive gingival lesions (FRGL) are gingival enlargements elicited by chronic irritation primarily due to over-hanging dental restorations, ill-fitting dental prostheses, plaque and calculus¹. The gingiva bears the brunt of this chronic irritation and thus is the most common intra-oral site for these lesions². Persistent irritation of the gingiva can lead to tissue injury and trigger inflammation leading to proliferation of endothelial cells, multi-nucleated giant cells, fibroblasts and tissue mineralisation³. The proliferation can eventually lead to a localised hyperplasia and an exuberant gingival mass⁴. Even though FRGL have similar aetiological factors, the various lesions have characteristic histopathological features, and are considered by most authors as separate distinct lesions⁵. FRGL are generally classified into peripheral ossifying fibroma (POF), lobular capillary haemangioma (LCH), peripheral giant cell granuloma (PGCG) and focal fibrous hyperplasia (FFH)⁶. Some authors have postulated that these pathological entities represent one lesion at various histological developmental stages⁷. They argue that a LCH may develop into a POF or FFH with time through further collagen build up and maturation⁸. However, if this hypothesis is true, a definite age grouping for the different histological entities should be apparent.
The nomenclature of FRGL is vast and complicated, with various terms used interchangeably to describe the various histopathological features of these FRGL. This is best demonstrated where the terms calcifying fibroblastic granuloma, peripheral ossifying fibroma, peripheral cemento-ossifying fibroma, peripheral fibroma with calcification and ossifying fibrous epulis are used to describe the same entity in different studies.

FRGLs are more common in females, which may highlight the influential role hormones may play in the pathogenesis of these lesions. The binding of oestrogen to its receptor may stimulate connective tissue proliferation within the gingiva. A predilection for the anterior regions of the jaws (incisor-canine) compared with posterior areas (premolar-molar) has also been reported for FRGL. The anterior region predilection may be partly explained by the tendency of supragingival calculus to occur predominantly in the anterior mandibular jaw. The pooling of saliva in the anterior mandible provides a rich source of phosphate and calcium supersaturating the dental plaque resulting in calculus formation. The cyclical periods of wetness and dryness in the anterior maxilla associated with mouth breathing has also been implicated in the predilection of FRGL in the anterior regions.

The average diameter for a LCH, FFH and POF is about 20 mm, but the PGCG only averages 10 mm. If not surgically resected early LCH, POF and FFH can enlarge up to 40 mm in diameter causing difficulties with mastication and speech. A predilection for the anterior regions of the jaws (incisor-canine) compared with posterior areas (premolar-molar) has also been reported for FRGL. The anterior region predilection may be partly explained by the tendency of supragingival calculus to occur predominantly in the anterior mandibular jaw. The pooling of saliva in the anterior mandible provides a rich source of phosphate and calcium supersaturating the dental plaque resulting in calculus formation. The cyclical periods of wetness and dryness in the anterior maxilla associated with mouth breathing has also been implicated in the predilection of FRGL in the anterior regions.

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The recurrence of FRGL following the use of conventional excisional techniques is quite common. Incomplete ginglyval excision, persistent gingival irritation resulting from incomplete removal of lesions using a surgical blade have been reported to increase the risk of recurrence. Deep excisions up to the involved periodontal ligaments, removal of chronic gingival irritants and resection by carbon dioxide lasers have been reported to reduce the recurrence rate. Laser surgery is favoured because it promotes hemostasis and carbonisation of soft tissues which results in a precise clean resection.

Other names that have been used to describe the LCH include granuloma pediculatum, pregnancy tumour, benign vascular tumour, vascular epulis and most commonly pyogenic granuloma. The name pyogenic granuloma is misleading because no pus or pyogenic material is associated with the gingival mass. Contamination of the granulation tissue by oral flora in a LCH can result in a fibrin exudate, which to the blind eye looks like pus. Based on over 5200 cases of FRGL in India, USA, Iran and China 25% the LCH comprises approximately 18% to 25% of all FRGL. This is in stark contrast with a study in Nigeria, where the LCH was the most common reactive lesion accounting for 57% of all cases. Studies from USA, England, Brazil and India have reported that LCH has a maxillary jaw predilection. Though a study from Nigeria found no jaw predilection and one from China found a mandibular jaw predilection.

POF generally presents as a pink lesion, with some authors reporting only 36% of the lesions as red. The general histopathologic pattern is primarily of a cellular connective tissue stroma associated with mineralised components. Dystrophic calcifications are more commonly seen in early growths whereas older lesions tend to have cementum or bone elements. It is generally accepted that the POF has a maxillary jaw predilection. Though a study in Nigeria reported that POF is generally a lesion of young females and teenagers with a peak incidence in the second and third decades of life. In contrast, a study from China reported a higher average age of 44 years in patients with POF.

FFH is also referred to as irritation fibroma, traumatic fibroma, fibrous epulis and fibrous nodule. The lesion usually presents as a pink, nodular, non-ulcerated, painless gingival mass. In studies of over 4800 reactive gingival lesions from USA, China and Israel it was reported that FFH was the most common reactive gingival lesion. Though a study in Nigeria found FFH...
to be the third most common reactive gingival lesion. Thus, geographical location and/or ethnicity might play a large part in the relative frequencies of these lesions. Most studies in various countries have reported a female predilection for FFH. In contrast, a study from India reported a male predominance whilst another from Sweden reported no gender predilection. There is no consensus on mean age for patients with FFH as it varies from 3rd to 5th decade of life. FFH generally shows no jaw predilection. However, two studies from Sweden and China reported a mandibular jaw predilection. PGCG has been referred to as giant cell epulis and peripheral giant cell reparative granuloma. PGCG usually presents as a purple to dark red gingival mass. The extensive haemorrhage associated with the lesion will result in accumulation of hemosiderin that will impart the bluish hue. PGCG was the least common reactive gingival lesion in most studies accounting for generally less than 11% of all lesions. However, a study from Iran reported the PGCG as the most prevalent reactive gingival lesion. The lesion is most common in the fourth decade of life and shows a mandibular jaw predilection. On gender distribution, studies of PGCG have reported mixed results. While some studies reported no gender predilection, others reported either a predilection for females or males.

**AIM**

The aim and objectives of the study were to determine the relative frequency and distribution of FRGL according to sex, age, and anatomical site in patients who presented at the Witwatersrand Oral Health Centre.

**Methodology**

**Sampling method**

Utilising convenience sampling of patient records from the Department of Oral Pathology and the Department of Oral Medicine and Periodontology at the Witwatersrand Oral Health Centre, a retrospective cross-sectional study was performed. Past dental records from the years 2011 to 2017 were evaluated to select those with a histopathological diagnosis of FRGL.

**Inclusion and exclusion criteria**

Inclusion criteria were all patients who had dental records that contained at least 70% of the data required for the study. The exclusion criteria for this study were (1) records of patients on anti-convulsant drugs, calcium channel blockers or the immunosuppressant cyclosporin, (2) cases diagnosed as epulis fissuratum, (3) reactive lesions presenting on sites other than the gingiva and (4) neoplastic conditions.

**Data collection and variables**

Histological and clinical history was obtained from the dental records. Sociodemographic variables (age, sex, and occurrence of lesion during pregnancy) and clinical features (pedunculated/sessile lesion, size of lesion, colour, region of jaw affected) were recorded. Gingival lesions were anatomically classified into the following regions anterior (incisor-canine region) and posterior (premolar-molar region) according to the guidelines of Mergoni et al., 2015. If the mass occupied both regions, it was grouped in the location where the bulk of the lesion was found.

**Data analysis**

The relative frequency of histologically confirmed cases of FRGL was analysed by determining what percentage of the total number of histopathology cases analysed in the study was either LCH, POF, FFH or PGCG. For sex, base of attachment and anatomical sites, descriptive statistics, and clinical features (pedunculated/sessile lesion, size of lesion, colour, region of jaw affected) were recorded. Gingival lesions were anatomically classified into the following regions anterior (incisor-canine region) and posterior (premolar-molar region) according to the guidelines of Mergoni et al., 2015. If the mass occupied both regions, it was grouped in the location where the bulk of the lesion was found.

**Table II: Clinical variables**

| Variable                  | LCH (n=80) | POF (n=86) | FFH (n=69) | PGCG (n=8) | Total | P value |
|---------------------------|------------|------------|------------|------------|-------|---------|
| Anatomical distribution   |            |            |            |            |       |         |
| Anterior maxilla          | 37         | 39         | 30         | 2          | 108   | 0.978   |
| Posterior maxilla         | 11         | 8          | 8          | 1          | 28    |         |
| Anterior mandible         | 22         | 29         | 21         | 3          | 75    |         |
| Posterior mandible        | 10         | 10         | 10         | 2          | 32    |         |
| Pregnancy status          |            |            |            |            |       |         |
| Pregnant                  | 15         | 8          | 4          | 0          | 27    | 0.044   |
| Non-pregnant              | 42         | 54         | 44         | 5          | 145   |         |
| Base of attachment        |            |            |            |            |       |         |
| Pedunculated              | 54         | 38         | 29         | 5          | 126   | 0.005   |
| Sessile                   | 26         | 48         | 40         | 3          | 117   |         |
| Colour of lesion          |            |            |            |            |       |         |
| Erythematous              | 67         | 43         | 34         | 2          | 146   | 0.000002|
| Non-erythematous          | 13         | 43         | 35         | 6          | 97    |         |

**Table III: Correlation of size of FRGL and colour**

| Statistical test | Colour of lesion | P value |
|------------------|------------------|---------|
| Diameter          | Rank biserial correlation | 0.175 | 0.006 |

**Table IV: Correlation of size of FRGL and region of jaws**

| Region of jaws (anterior/ posterior) | P value |
|-------------------------------------|---------|
| Diameter                            | 0.126   | 0.05   |

**Table III: Correlation of size of FRGL and colour**

| Colour of lesion | P value |
|------------------|---------|
| Diameter          |         |
| Rank biserial correlation | 0.175 | 0.006 |

**Table IV: Correlation of size of FRGL and region of jaws**

| Region of jaws (anterior/ posterior) | P value |
|-------------------------------------|---------|
| Diameter                            | 0.126   | 0.05   |
assess whether data followed a normal distribution. Cross-tabulation analysis was used to summarise the categorical data. The chi-square test was used to assess statistically significant differences for categorical variables. Spearman rank correlation coefficient was applied to assess the correlation between age and size of FRGL. Rank biserial correlation coefficient (Rb) was used to analyse the correlation between, 1 size of FRGL and sex, and 2 size of FRGL and the jaw affected. The significance level alpha (α) was set at 0.05 for all statistical tests.

Ethical considerations

Ethical clearance was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences at the University of the Witwatersrand (M180672).

RESULTS

A total of 243 cases of FRGL were evaluated and all were included in the study as per selection criteria. Female patients accounted for 70.8% (n = 172) of all FRGL (Table I). The size of FRGL ranged from 4mm to 52mm in greatest diameter and the age of patients in this cohort ranged from 3 months to 88 years. The age did not follow a normal distribution (Shapiro-Wilk test p > 0.05). The recurrence rates of FRGL were 22.2% (n = 54) (Table I); with no statistically significant difference in recurrence rates between males and females.

A total of 56.0% (n = 136) of the lesions occurred on the maxilla. Of the 243 cases, 183 (75.3%) were located anteriorly (incisor-canine region) and 60 (24.7%) cases were located posteriorly (premolar-molar region) Table II. A total of 56.0% (n = 136) of the lesions occurred on the maxilla. Of the 243 cases, 183 (75.3%) were located anteriorly (incisor-canine region), and 60 (24.7%) cases were located posteriorly (premolar-molar region). A total of 11.1% (n = 27) of the lesions were associated with pregnancy, whilst pedunculated lesions accounted for 51.9% (n = 27) of the lesions were associated with pregnancy. Females accounted for 70.8% of all lesions which included in the study as per selection criteria. Female patients accounted for 70.8% (n = 172) of all FRGL (Table I). The size of FRGL ranged from 4mm to 52mm in greatest diameter and the age of patients in this cohort ranged from 3 months to 88 years. The age did not follow a normal distribution (Shapiro-Wilk test p > 0.05). The recurrence rates of FRGL were 22.2% (n = 54) (Table I); with no statistically significant difference in recurrence rates between males and females.

A total of 60.1% (n = 146) of all lesions were erythematous; and the correlation between the colour and the size of FRGL was statistically significant; p value=0.006 (Table III).

The correlation of size of the FRGL and region of jaws affected (incisor-canine/ premolar-molar) yielded statistical significance; p value = 0.05 (Table IV). The correlation between size of FRGL and age of patients was not statistically significant (p = 0.661). The frequency of the various FRGL and decade of life are shown in Figure 1. LCH, POF and PGCG were more frequent in the 3rd decade of life, whilst the FFH was more common in the 4th decade.

DISCUSSION

There is no consensus in the literature on which gingival variant is the most frequent FRGL; with most authors citing either the LCH or FFH. In this study where 243 cases of FRGL, POF (35.4%, n = 86) was the most common, a feature not seen in any recent study utilising similar classification and methodology. The only comparative result found was by Macleod and Soames (1987) in England where POF constituted 40.5% of all gingival epulides. The variation noted in this study may be partly accounted for by the differences in geographic and ethnic factors. Some authors argue that there is bound to be an overlap in histopathological diagnosis since FRGL represent a spectrum of one lesion, thus representing another possible source of the variation. Within a South African setting, this may be linked to challenges in accessing oral health care services, with resultant delayed diagnosis.

Studies in Chile16 and India37 contrary to our findings, found the POF to be the least common FRGL with a frequency of only 2.9% and 9.7% respectively. In most countries the frequency of POF, ranged from 10% to 25%, representing the 2nd or 3rd most common FRGL.16,23,25,31

With a frequency of 32.9% the LCH was the second most common FRGL in this study. This agrees with most global studies that peg the frequency of LCH between 25% and 35% of all FRGL.16,23,31,37 However contrary to our results, a study in Nigeria found the LCH to be the most frequent FRGL with a frequency of 57.0%. The frequency of FFH across the globe is widely dispersed, ranging from 18.9% in Iran1 to 71.1% in Chile16. The frequency of FFH in this study was 28.4% and is comparable to the 31.8% found in Israel31. PGCG was the least common FRGL in this study, a feature also seen in other studies.6,7,16

Numerous scholars have reported that FRGL have a predilection for females.3,23,25,31 This study also found similar findings, with all four variants of FRGL occurring more commonly in females. Females accounted for 70.8% of all lesions which is comparable to 74.2% reported in Brazil1, and marginally more than the 62.7% reported in Nigeria3.

FRGL were significantly associated with pregnancy (p = 0.044), with most cases linked to the LCH (55.6% of all pregnancy cases diagnosed as LCH). This phenomenon was likely due to the vascular effects of female hormones on the gingiva.

There was no statistically significant difference between frequency of FRGL in the maxilla and mandible. The frequency of FRGL in the maxilla was 56.4%, slightly higher than the results seen in Israel (52.2%)31 and Nigeria (50.0%)37. Only the PGCG had a higher frequency in the mandible (62.5%), a trend which has also been seen in Nigeria7, Israel 31 and Sweden32.

Most lesions were located anteriorly incisor-canine region), as was observed in Brazil37. The pooling of saliva in this area favours calculus formation, which may result in gingivitis and most likely FRGL eventually. There was a statistically significant relationship between FRGL and colour (p = 0.000002). LCH was the lesion mostly associated with erythema, with 83.8% of all LCH presenting as erythematous,
In this study 74.9% (n = 182) of all FRGL were greater than 10mm, similar findings were also reported in Pakistan. The FRGL ranged from 4mm to 52mm, mirroring findings in Nigeria. Like the study in Nigeria, the average size of the LCH was found to be the largest of all FRGL. There was a low but statistically significant correlation between the size of FRGL and the colour of the lesions (Rank bivariate correlation = 0.175), with erythematous lesions being generally larger. Low statistically significant relationships were also found between the size of FRGL and location of lesion (anterior/posterior, Rank bivariate correlation = 0.126). Lesions tended to be larger in the posterior region, and this could be partly explained by the fact that patients are more likely to seek treatment earlier for anterior lesions because of a higher aesthetic demand. There was no statistically significant correlation between size of FRGL and age of patients (p = 0.661), with the largest lesion occurring in a 19-year-old female patient.

The youngest patient in the study was 3 months old and was diagnosed with a POF. The baby was healthy and was born with anterior mandibular teeth that later exfoliated. Similar cases have been reported in literature, with the authors assuming the irritation in the periodontal ligament that results from exfoliation may trigger gingival connective tissue metaplasia with resultant dystrophic calcifications. POF, LCH and PGCG occurred more frequently in the 3rd decade of life, with similar results being reported in Nigeria, though a study in Nigeria found lesions more common in the 3rd and 6th decade respectively.

The mean age of patients with POF was 34.7 years, which is comparable to 33.9 years reported in Israel and 31.5 years reported in the USA. Though mean age for POF was noted to be way higher in China at 44.2 years, the mean age for a LCH was 35.3 years, with similar mean ages being reported in the USA and China. The lower mean age for POF compared to LCH does not corroborate the progressive development theory, that postulates that a POF evolves from of LCH via further collagenisation and mineralisation. Thus, this brings into question whether the LCH and POF are the same lesion at various histopathological developmental stages.

There was no statistically significant difference in the recurrence rates of FRGL in this study. The recurrence rate of 22.2% recorded in this study is higher than the 2.9% reported in Nigeria. The POF and FFH had the highest and lowest recurrence rates respectively, a feature also reported in India. There was also no statistically significant difference in recurrence rates between males and females, hence female hormones may not be key to recurrence rates.

**Limitations of study**

The study fell victim to a major hurdle of retrospective studies, that is, all information gathered is solely dependent on the available information in the dental records. Unfortunately, this resulted in insufficient data being gathered on race, plaque index, DMF index, nature of chronic irritation and presence of ulceration. Pregnancy status evaluation was solely based on information gathered on the dental chart, thus some early unknown pregnancies may have gone undetected. Since FRGL in dental charts were mostly classified either as erythematous or non-erythematous rather than specify the true colour of the lesion this might have been a source of error.

**CONCLUSION**

As in most studies the FRGL were more common in females in this study. Contrary to results of similar studies done in other countries, POF was the most common variant of FRGL after analysing 243 cases in this study. Statistical differences for FRGL were noted on pregnancy, base of attachment (sessile and pedunculated) and colour of lesions. An understanding of the clinical picture may aid in the diagnosis of FRGL, but histopathological evaluation is still required for a definitive diagnosis.

Retrospective studies are heavily dependent on data available in patient records. Given the amount of missing data encountered in the study, we recommend detailed and accurate documentation of findings by clinicians in order to facilitate future research. Based on our findings that do not corroborate the progressive development theory of POF from LCH, we recommend more studies on the histopathogenesis of FRGLs.

**Conflict of Interest**

No conflict of Interest. Research was self-funded.

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