

Frog: A Comprehensive Review.

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Running title: Peripheral gingival lesions

Clinical significance: Peripheral gingival lesions have a large number of confusing names and data attributed to it.

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ABSTRACT

Focal reactive overgrowths (FROG) are the most common oral mucosal lesions with the gingiva being the most predominantly affected site. They arise in response to a trigger by chronic irritants or in relation to some trauma.

Aims and objectives: The aim of this review was to state the clinical, histological and etiological factors for the lesions included under the term “Focal Reactive Overgrowths of Gingiva” or gingival lesions following trauma.

Materials and methods: Data from articles referring to gingival overgrowths from the past 10 years were selected from the database of Medline, Scopus, and Google search engines and only those that fulfilled the criteria of 'gingival overgrowths due to trauma', were selected. Data pertaining to all reactive hyperplasias namely focal fibrous hyperplasia (FFH), pyogenic granuloma (PG), peripheral ossifying fibroma (POF) and peripheral giant cell granuloma (PGCG) were reviewed and analyzed for its clinical, etiological and histological features.

Results: Gingival overgrowths are commonly seen in a large percentage of patients who visit the dental operatory. Focal reactive overgrowths of gingival, though having similar clinical features, are easily distinguishable from each other histopathologically.

Conclusion: Knowledge of the frequency and presentation of the most common oral lesions predominantly affecting the gingiva, and more so the FROG is mandatory, so that the confusion regarding the terminologies used to describe these common gingival lesions can be eliminated.

Keywords: focal reactive gingival lesions; peripheral ossifying fibroma; pyogenic granuloma; peripheral giant cell granuloma; focal fibrous hyperplasia..

INTRODUCTION

The gingiva responds to chronic trauma or irritation such as plaque or calculus, with localized reactive hyperplastic lesions (LRHL) or focal reactive overgrowth of gingiva (FROG) which can be classified into four groups namely:

- Focal Fibrous Hyperplasia,
- Pyogenic Granuloma ,
- Peripheral Ossifying Fibroma, and
- Peripheral Giant cell granuloma.^{1and 2}

Chronic trauma induces inflammation which results in formation of a granulation tissue comprising of collagen fibers, fibroblasts, blood vessels and chronic inflammatory cells like lymphocytes, plasma cells, etc; later, the fibroblasts proliferate and present as an overgrowth called as a 'Reactive hyperplasia'. These growths are not neoplastic, but indicate a slow repair process because of chronic irritation, resulting in granulation tissue and scar formation.

The Periodontologists, Oral, and Maxillofacial Surgeons address these lesions as 'epulis'. Though clinical features help in distinguishing these reactive lesions, it is the histopathological findings,

which are the key to the diagnosis for these lesions. Most data available regarding these lesions is insufficient and confusing.³

DISCUSSION:

FROG: or focal reactive overgrowth of the gingiva is among the most common swellings of the oral cavity and among the most predominant lesions affecting the gingiva.

Focal fibrous hyperplasia (FFH)/Irritation fibroma/Oral focal fibroma

Though the term 'Focal fibrous hyperplasia' describes these lesions clinically, and describes its pathogenesis best, it is not commonly used. Most of the irritation fibromas represent reactive focal fibrous hyperplasia, which occurs following trauma or local irritation.

The lesion occurs at any oral site, but is most commonly seen on the buccal mucosa. FFH of the gingiva occurs in the same age group, site and has a predominant female predilection similar to that of the Pyogenic Granuloma. Hence, it would mean that the inflammatory or reactive hyperplasias of the gingiva might be the fibrous maturation of PG especially in those lesions existing for a long duration of time.³

Oral focal fibroma is a sessile or pedunculated dome shaped swelling which normally exhibits the same color as the surrounding normal mucosa or it may be pale pink in color; if there is bleeding it may appear darker in color. Either the surface may show ulceration due to trauma, or it may sometimes become rough and scaly. Oral fibromas may progressively increase in size to develop over weeks or months to reach its maximum size, which is usually about 1cm in diameter, or may sometimes become larger.

Orthopantomogram, occlusal radiographs and intraoral periapical radiographs show no bone resorption.

Histology may show the typical dense fibrous tissue with few inflammatory cells. The overlying epithelium may be thin, or thick, acanthotic and sometimes ulcerated.⁴

Pyogenic granuloma

Pyogenic granulomas are common lesions occurring on the gingiva, and it spans over a wide age range, with the maximum occurrence being in the 2nd decade of life. Females are more commonly affected than the males. The maxillary gingiva, especially the buccal aspect, is more predominantly affected than the mandibular gingiva, and the anterior segment is more affected than the posterior.³ It causes no bone loss although there is a buccal to lingual extension along the interdental papillae. It has a high recurrence rate. Orthopantomogram, occlusal radiographs and intraoral periapical radiographs show no bone resorption.

Histologically, it is an ulcerated, vascular lesion, with proliferating fibroblasts, budding endothelial cells, dilated vascular spaces and chronic inflammatory cells. Inflammation is invariably present and the absence of it indicates a vascular malformation like a hemangioma.⁵

The main etiology for this condition is poor oral hygiene and it may be a precipitating factor in many pyogenic granulomas. The vascular nature and the rapid growth of PG may be due to the effect of factors

like inducible nitric oxide synthetase (iNOS), vascular endothelial growth factor (VEGF), fibroblast growth factor (bFGF) and connective tissue growth factor (ctGF). Another pathological angiogenesis marker related to PG includes FLT4, a tyrosine kinase receptor. The cause for the increased vessels is due to the factors such as the VEGF and angiostatin. Morphology of blood vessels is determined by the markers such as Tie or tyrosine kinase which have also been detected in the PG. The above mentioned markers indicate a reactive neoangiogenic process. In certain cases the virus, HSV-I, is also said to play an indirect role in the formation of PG, through a VEGF-dependent pathway.⁶ Overexpression of transcription factors STAT3 and P-ATF2 and endothelial markers such as CD105/endoglin and CD 34 are found positive in the PG; and together with the inflammatory markers such as COX-2 and IL-10 are said to play a role in the etiology of oral pyogenic granulomas.⁷

Of the total pyogenic granulomas, 18.5% comprises the **pregnancy granuloma** of the gingiva that develops in about 5% of pregnancies. The progesterone and estrogen hormones make the gingival tissue more susceptible to the chronic irritants. The estrogen enhances the VEGF production in the macrophages and this effect is opposed by androgens, which may cause the occurrence of PG during pregnancy. The lesion in all aspects is similar to the normal pyogenic granuloma except that there is a resolution of the lesion following parturition; thus indicating that probably the hormones play a role in the etiology of pregnancy epulis.

Simultaneously the male sex hormones in males, especially in the age groups 11 to 20 years, could also affect the gingival tissues and produce the pyogenic granulomas. This could also be due to the poor maintenance of oral hygiene in this age group.

Peripheral giant cell granuloma/Giant cell epulis (PGCG)

This is a proliferative gingival lesion seen mainly in the gingiva. It is clinically similar to pyogenic granuloma but differs from it histologically, as it shows the presence of the multinucleated giant cells. There may be no infectious source. It commonly occurs in females with a 2:1 preponderance and shows a wide age distribution with its peak between 41 and 50 years of age. PGCG affects the mandible more than the maxilla, especially in lower premolar region. Orthopantomogram, occlusal radiographs and intraoral periapical radiographs show no bone resorption

Histology: The peripheral giant cell granuloma is unencapsulated, with a rather primitive but uniform mesenchymal cells with oval, pale nuclei and a moderate amount of eosinophilic cytoplasm. Mitotic activity is not usual and may even be more pronounced in lesions developing in children and adolescents. Mitotic activity within the giant cells is mostly not seen, and if present, should be considered as a sign of a sarcomatous change.

Stromal cells either may be spindle in a collagenous fibrous stroma, or may be rounded with a less fibrotic background. Chronic inflammatory cells within the mesenchymal cells or the fibrovascular stroma may be seen. The overlying epithelium may be separated from the lesion by a band of fibrovascular

tissue. Just beneath the ulcerated epithelium, there is the fibrinoid necrotic tissue debris over the granulation tissue.

Together with the above-mentioned histological features, the stroma is filled up with multiple osteoclast-like multinucleated giant cells that contain varying number of pale vesicular or open -faced nuclei similar to those within the surrounding stromal cells. These giant cells also have an eosinophilic cytoplasm, which ultrastructurally, is shown to contain a large number of mitochondrias. Immunohistochemistry depicts the giant cells to be only marginally different from the true osteoclasts. The etiopathogenesis of this lesion and the origin of the multinucleated cells are still unknown, but they are thought to arise from syncytial fusion of mononuclear precursors of osteoclasts and are said to be of the bone marrow origin.

The other common feature is the increased vascularity; with the blood vessels within the lesional stroma showing plump endothelial cell nuclei and scattered extravasated content of the erythrocytes. The lower third of the stroma may also show the metaplastic or osteoid areas. Dystrophic calcifications may also be seen.⁸

Peripheral ossifying fibromas/ peripheral fibroma with ossification/ Ossifying fibrous epulis (OFE)/ peripheral fibroma

Shepherd first reported this entity and called it as an 'alveolar exostosis' in 1844.⁸ Peripheral ossifying fibroma is a commonly observed growth on the gingiva of the teenagers and young adults. It is found to arise from the periodontal ligament⁴ whose pleuripotent cells have the ability to transform into osteoblasts, fibroblasts or cementoblasts.⁸

It is considered a reactive hyperplasia rather than a neoplasia. Though the name may appear similar to the **central ossifying fibroma**, it is not an extraosseous counterpart of that tumor. There was confusion in the terminology of the lesion and it had to be distinguished from the **peripheral odontogenic fibroma**, which has been clarified by the latest WHO classification. It is also different from the **peripheral cemento-ossifying tumor**.³

Ossifying fibrous epulis (OFE)/ peripheral fibroma with calcification were seen more frequently in age group ranging from first to third decades of life, as per the studies conducted. The incidence of the tumor is less in children as well as after the age of 30 years.

Peripheral ossifying fibroma is a common lesion, representing 1-3% of all oral biopsies in most series. It has a female predominance, thus suggesting a hormonal influence in its development. Trauma or irritation caused by dental restorations or prostheses, plaque or calculus is also believed to play a role. It is an exophytic, slow growing, lesion that can be either a red or pink in color, sessile or pedunculated with a smooth or pebbled, irregular surface that may show ulceration and it may vary in size from small to large.⁴

Histology

A large collection of submucosal primitive oval and bipolar mesenchymal cells can be seen in the stroma that may be either fibrotic or highly cellular with the presence of islands and trabaculae of woven or lamellar bone that exhibits osteoblastic rimming. Metaplastic bone may also be seen. The calcified tissues may sometimes exhibit dark-staining globules of acellular cementum and then the term peripheral cementifying fibroma is used. In many cases both bone and cementum may be seen in which case the term peripheral ossifying/cementifying fibroma may be used, and in some early cases only small ovoid areas of dystrophic calcification may be seen. The stroma is found similar to the peripheral giant cell granuloma, excepting that the erythrocyte extravasation is not a feature and the osteoclast-like giant cells are quite rare.⁸

CONCLUSION

The reactive gingival lesions may vary depending on various factors such as the hormonal effects of estrogen and progesterone, intensity of the irritation and the duration of the lesion. Differences in age, sex as well as the distribution of these lesions may occur, therefore are called by varied names. Hence, it can be concluded that the reactive lesions of the gingiva are clinically similar lesions, diagnosed in different stages of maturity.

ABBREVIATIONS

- FROG-----Focal reactive overgrowths
- FFH-----Focal Fibrous Hyperplasia
- PG -----Pyogenic granuloma
- POF-----Peripheral ossifying fibroma
- PGCG-----Peripheral giant cell granuloma
- LRHL-----Localized reactive hyperplastic lesions
- iNOS-----Inducible nitric oxide synthetase
- VEGF-----Vascular endothelial growth factor
- bFGF-----Fibroblast growth factor
- ctGF-----Connective tissue growth factor
- HSV-I-----Herpes Simplex Virus-1
- STAT3-----Signal transducer and activator of transcription 3

- P-ATF2-----Phospho-activating transcription factor 2
- endothelial markers such as CD105/endoglin----Cluster Differentiation 105
- CD 34-----Cluster Differentiation34
- COX-2-----Cyclooxygenase2
- IL-10-----Interleukin 10
- OFE----- Ossifying fibrous epulis

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