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(Giant Cell Fibroma Of Oral Mucosa)

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Certification of the Supervisor

I certify that this project entitled **" Giant Cell Fibroma Of Oral Mucosa: A Literature Review"** was prepared by fifth year student **Aya Kais Mohammed** under my supervision at the College of Dentistry / University of Baghdad in partial fulfillment of the graduation requirements for the bachelor degree in dentistry.

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Dedication

I dedicate this project to Allah, who has been my strength and ultimate guide. To my dear parents , sisters and brother for their endless love, support and encouragement throughout my pursuit for education .To anyone who has shown me friendship and kindness during my field travels.

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Primarily I would like to thank the supreme power the Almighty God for everything in my life, for being able to complete this project with success.

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Abbreviation	Phrase
GCF	giant cell fibroma
PG	pyogenic granuloma
POF	peripheral ossifying fibroma
HMB-45	Human melanoma black antibody-45
CD 68	Cluster of differentiation 68
ACT	Alpha-1 anti-chymotrypsin
HLA-DR	Human leukocyte antigen
CD31	Cluster of differentiation 31
LCA	leukocyte common antigen
PCNA	Proliferating cell nuclear antigen
PGCG	Peripheral giant cell granuloma
Ki67	Protein encoded by MKI67 gene
HHF-35	Clone name for Muscle actin antibody
Bcl-2	B-cell lymphoma 2

Introduction

The giant cell fibroma is a relatively rare benign oral soft tissue lesion which has discriminative clinicopathological features that is enough to distinguish it from the traumatic fibroma as it not appear to be associated with chronic irritation. **(Neville et al., 2015).**

Clinically The giant cell fibroma is an asymptomatic fibrous nodule that is usually less than 1 cm in size, the base may be broad or pedunculated, and the surface may be smooth or lobulated. surface papules can be so numerous that the lesion takes on the clinical appearance of a papilloma. Almost two thirds of the cases occur before age 30 years, and there appears to be a slight female predilection. The most common site of occurrence is the gingiva, representing approximately half of all cases, the mandibular gingiva being affected twice as often as the maxillary. The tongue and palate are also common sites of occurrence **(Gnepp, 2009)**

Histologically, giant cell fibroma shows peculiar characteristics, usually consisting of loosely arranged fibrous connective tissue in the absence or minimum inflammation, and lined with hyperplastic, stratified squamous epithelium. The presence of mono-, bi- or multinucleate, spindle-shaped or stellate giant cells, predominantly located in the papillary lamina propria, is the main histopathological characteristic These mono-, bi- or multinucleate giant cells are not exclusive to giant cell fibroma but are also detected in other fibrous lesions such as ungual fibroma, acral angiofibroma, cutaneous giant cell fibroblastoma and cutaneous collagenoma, The nature of this cell population has been extensively discussed by different researchers but still remains elusive **(Souza et al., 2004)**

Chapter One

Review of Literature

Review of Literature

1.1 Oral fibrous overgrowth

Most of these pathological overgrowth are reactive hyperplastic lesions seen in response to chronic inflammation caused by chronic irritation **(Binita et al., 2016)** Focal fibrous hyperplasia or Irritational fibroma or Traumatic fibroma is one of the most common epithelial benign tumours of the oral cavity **(martin et al., 2014,Ayekinam et al., 2017)** . These localized progressive, proliferation of the oral mucosa are seen in response to injury or local irritation from dental plaque, calculus, sharp edge of grossly decayed teeth, fractured teeth, trapped food particles, ill-fitting dental/oral appliances, food impaction and iatrogenic factors (extended flanges of the denture and over extended dental restorations) **(Binita et al., 2016 , Ayekinam et al., 2017**). These non-neoplastic lesions seen on the buccal mucosa along the line of occlusion (subjected to masticatory trauma) causes esthetic and functional problems **(martin et al., 2014, Astekar et al., 2011 ,pardeshi et al., 2016)**. Focal fibrous hyperplasia affect people of all ages, but females are twice more likely to develop focal fibrous hyperplasia **(martin et al., 2014, Ayekinam et al.,2017).** This is because the female hormones may cause an increased production and accumulation of collagen by fibroblast in the presence of chronic injury **(martin et al., 2014).** Similar lesions like Pyogenic Granuloma (PG), Peripheral Giant-Cell Granuloma (PGCG) and Peripheral Ossifying Fibroma (POF) may also arise in the oral cavity as a result of irritation due to plaque microorganism and other local irritations which are ruled out from focal fibrous hyperplasia by histologic **analysis (martin et al., 2014 ,kolte et al., 2010)** . Focal fibrous hyperplasia presents usually as a yellowish–white or mucosal colored, sessile, smooth-surfaced, asymptomatic, soft

nodule. The surface may be hyperkeratotic or ulcerated, owing to repeated trauma. The most common intraoral site is along the occlusal line of the buccal mucosa – an area subject to masticatory trauma – but it also affects the lower lip, tongue, hard palate and edentulous alveolar ridge **(de Santana Santos et al., 2014).**

1.2 Giant cell fibroma

The giant cell fibroma is an oral soft tissue lesion with distinctive clinicopathological features. Unlike the traumatic fibroma, it does not appear to be associated with chronic irritation.

The giant cell fibroma represents approximately 2% to 5% of all oral soft tissue proliferations submitted for biopsy **(Neville et al., 2015)**

While a histologically similar tumor of skin is the Giant cell fibroblastoma, which is an uncommon fibrohistiocytic tumor first described by Shmookler (1982), It appears as a painless, slowly enlarging, subcutaneous mass and is characterized by the mixed proliferation of fibroblastic cells and multinucleated giant cells within a myxoid or collagenous stroma, including pseudovascular tissue spaces**(Shmookler et al., 1989)** Since the initial description, less than 100 cases of giant cell fibroblastoma have been reported. It is believed that examples of this tumor were diagnosed as a low-grade sarcoma in the past, however, giant cell fibroblastoma and dermatofibrosarcoma protuberans are considered fibrohistiocytic tumors of intermediate grade of malignancy with high incidence of recurrence and with similar biological behavior, Furthermore composite tumors with both components have been reported **(Kholová et al., 2001)**

1.3 Clinical features of giant cell fibroma

There is no gender predilection for GCF **(H Bakos, 1992, Lukes et al., 2005),** many studies have shown a slight female preponderance for the occurrence of GCF **(Weathers and Callihan, 1974, Houston 1982, Wang and Levy 1995**), however, slight male predilection is reported in review of twenty-one GCF cases in clinicopathological study of Sivaramakrishnan et al. (2012).

Though GCF can occur at any age, but it is a lesion of the young, found most commonly in the first three decades of life **(Savage, 1985**), the mean age reported was approximately twenty-nine years in previous studies, however, different mean age of occurrence which is thirty-nine years also was reported this discrepancy may be attributed to the asymptomatic nature of the lesion, genetic and racial differences **(Kuo et al., 2009, Sivaramakrishnan et al., 2012)**It presents clinically as an asymptomatic raised lesion, one centimeter or smaller in diameter, mostly with a bosselated or pebbly surface which can result in a clinical misdiagnosis of papilloma **(figure 1.1.A**), it may be pedunculated or sessile and is found most commonly on the gingiva, with the mandibular gingiva being affected more than the maxillary **(Neville et al., 2015),** It may also be found in extra gingival sites, Including the tongue, palate, and buccal mucosa **(figure 1.1.B),** It is typically of normal mucosal color unless traumatized during mastication or oral hygiene procedures **(Lukes et al., 2005**

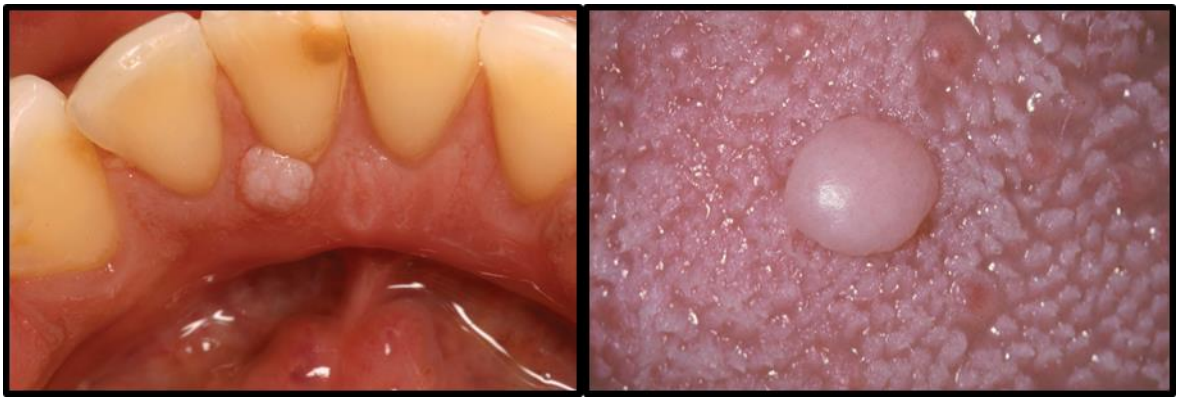

Figure 1.1A papillary growth on the lingual mandibular gingiva. Because of the rough surface, this would be easily mistaken for a papilloma, **Figure1.1.B lesion** Giant Cell Fibroma. Exophytic nodule on the dorsum of the tongue. **(Neville et al., 2015)**

1.4 Histopathological features of giant cell fibroma

Microscopically, the GCF is a sessile or pedunculated mass covered with a thin layer of parakeratinized or orthokeratinized stratified squamous epithelium **(Kuo et al., 2009),** the surface may be lined with hyperplastic, stratified squamous epithelium The tumor is composed mainly of loose or dense fibrous connective tissue with well-formed capillaries and venules. Inflammation is seen only rarely **(Souza et al., 2004)**The phenotypic characterization of the collagen fibers of GCF connective tissue stroma compared to oral fibrous hyperplasia(fibroma) was described by using Picrosirius red polarizing microscopy technique which is a selective histochemical procedure for collagen detection using Picrosirius red stain which is an elongated birefringent molecule that binds to a variety of tissue molecules in addition to collagen and orients parallel to the collagen fibrils, thereby greatly enhancing their natural birefringence which is a measure of the difference in refractive index between the two refracted rays **(Junqueira et al.,**

1979)this study revealed different collagen fiber colors which is predominantly yellow in GCF but green in fibroma, in addition, the collagen fibers of GCF was appeared as more densely packed and the histological pattern of this fibers is perpendicular, while Toida et al., (2001) demonstrate two different histological pattern of fibers in fibroma, one made up of perpendicular fibers (radiating type) and other parallel fibers (reticular type), this suggest that stroma of GCF consisted of more mature collagen fibers **(Mohan, 2014).** The consistent and diagnostic feature is the presence of large stellate giant cells, usually with one or two nuclei. Multinucleated giant cells are seen occasionally. These giant cells are most numerous in the connective tissue just beneath the epithelium. The cytoplasm of these giant cells is well demarcated, and occasional dendritic processes are observed **(figure 1.2),** An artifactual space or separation of the collagen fibers from the cell boundaries is sometimes present **(Kuo et al., 2009).** The description of these cells was demonstrated by **Reibel, (1982)** who found that 5% of one thousand oral fibrous hyperplasia containing stellate and multinucleated giant cells and these stellate cells most often contained only one nucleus while the multinucleated cells were most often angular and both types of cells contained a distinct basophilic cytoplasm. The nuclei peripherally displaced. The cells were often surrounded by an "empty space", in which small dendritic processes were seen contacting the surrounding collagen. The cells were occasionally were occasionally lying in a "cloud" of basophilic ground substance **(Reibel, 1982**). The presence of melanin pigmentation (granules) in the stromal cells firstly described by **Houston, (1982**), after that, few case reports of melanotic macules in conjunction with a giant cell fibroma case was published, which describe the intraoral lesion as a dark, pigmented, hyperplastic area and microscopic examination revealed that the epithelium contained significant increase in the amount of melanin pigment in the basal cell layer, Furthermore, numerous

melanin- engorged macrophages were noted within the superficial lamina propria and a few large cells which were granular, occasionally binucleated, melanin-laden cells scattered across the stroma and the lesion is considered as pigment rich giant cell fibroma **(Seitz et al., 2017),** in order to explain this unique findings and to prove if the pigmentation was due to melanin, Staining with Perls' Prussian blue was done but was negative, then a Masson Fontana reaction was done which give positive results that confirmed the presence of melanin granules, However, Negative staining for HMB-45 ruled out the possibility of melanocytic origin, while staining with CD68 revealed focal positivity in the areas of inflammation suggesting the presence of macrophages which ingested the melanin granules, while, cells that are negatively stained with CD68 maybe giant fibroblasts that had engulfed the melanin granules **(Kulkarni et al., 2017)**

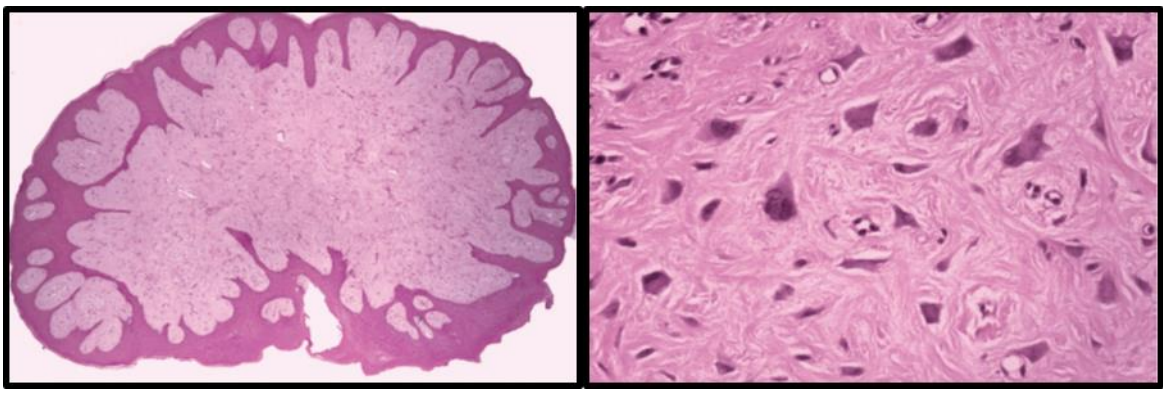

Figure 1.2: Giant Cell Fibroma. A, Low-power view showing a nodular mass of fibrous connective tissue covered by stratified squamous epithelium. Note the elongation of the rete ridges. B, High-power view showing multiple large stellate-shaped and multinucleated fibroblasts **(Neville et al., 2015)**

1.5 Etiopathogenesis of giant cell fibroma

The etiology of giant cell fibroma is not associated with chronic irritation and the source is still unclear **(Kolte et al., 2010, Sekar et al.,2011, Madi et al., 2014, Ambika et al., 2018)** It

is hypothesized that the giant cell fibroma is initiated by a virus, and that the cells of origin might be fibroblasts or vascular smooth muscle cells from normal oral mucosa or from a pre-existing pyogenic granuloma. An ultrastructural study performed by **Weathers and Campbell, (1974)** supported that these cells were large, unusual fibroblasts, the characteristic cells differed from normal fibroblasts with respect to the content of numerous intracellular microfibrils.

Interestingly, there is also a virus-induced tumor of the deer called the fibroblastoma that is histologically similar to the giant cell fibroma, however, the ultrastructural study by Weathers and Campbell did not demonstrate any viral particles in the giant cell fibroma **(Swan, 1988).** A variety of cutaneous lesions containing similar stellate mono- and multinuclear giant cells have been described in humans, such as the fibrous papule of the nose, ungual fibroma, acrai fibrokeratoma, and aerai angiofibroma. **(Zackheim and Pinkus, 1960, Reed and Elmer, 1971,),** The main similarity between this group of cutaneous lesions and the giant cell fibroma is their histological appearance. The differences are that the skin lesions have not been associated with oral lesions, and they do not show the same frequency of occurrence and age distribution **(Weathers &Callihan, 1974),** Three other human mucous membrane lesions have been reported with histopathological similarity to giant cell fibroma: the pearly penile papule of the glans penis **(Winer and Winer, 1955, Ackerman and Kornberg, 1973),** the retrocuspid papilla **(Regezi et al., 1975**) and symmetrical gingival fibromatosis **(Gould and Escobar, 1981)**

Regezi et al, (1975) described a high frequency of similar cells in the so-called retrocuspid papilla and reported that approximately 1 % of irritation fibromas submitted to their department had a histologic pattern in which stellate cells predominated over fusiform fibroblasts. They compared the cells to similar

cells in the fibrous papule of the nose and developed the concept that stellate and multinucleated cells are part of a nonspecific focal fibrous hyperplasia of the lamina properia of the mucous membrane or papillary' dermis to various stimuli. **(Reibel, 1982).**

On the other side, Fibrous hyperplasias are considered reactive proliferations of fibroblastic tissue rather than neoplastic proliferations**(Sapp et al., 2004),** most are the result of chronic injury or irritation, and it is considered to be characteristic of a functional change in the fibroblastic cells **(M.S. et al., 2010),** GCF was believed to arise as a result of a stimulus, the source of which cannot always be determined **(Lukes et al., 2005)** In the same manner, **Sonalika et al., (2014)** reported that a possible viral origin of the tumor has also been postulated but the reason as to why these giant cells are formed still remains uncertain **(Seitz et al., 2017).** Hence, the etiology of GCF is unknown, Irritation and trauma are noted in some cases; however, GCF does not appear to be associated with chronic irritation **(Gnepp**, **2009),** The nature of this cell population has been extensively discussed by different researchers but still remains to be completely established. **(Souza et al., 2004),** and the origin of multinucleated giant cells is a matter of discussion **(Yasuda et al, 1991).**

1.6 Differential diagnosis of giant cell fibroma

The most common provisional diagnosis of GCF is stated by **Huston, (1982)** in his clinicopathological study on four hundred sixty-four GCF cases, who find that (44.6%) were diagnosed as fibroma, (28.9 %) as papilloma, (1.1%) as verruca vulgaris, (1.1%) as peripheral odontogenic fibroma, (0.9%) as pyogenic granuloma, and (0.6%) as peripheral giant cell granuloma and (18.3%) the diagnosis was not specified **(Houston, 1982).**

1.6.1 The retrocuspid papillae

The lesion is considered by some authorities as merely another form of GCF, **(Regezi, 2003, Neville et al., 2015)** but the retrocuspid papilla has a very characteristic location on the mandibular lingual attached gingiva, inferior to the canine, It appears as a small, pink papule measuring up to 5mm and is frequently bilateral. The retrocuspid papilla is considered by other to be developmental**(Sapp et al., 2004),** and due to its clinical appearance and characteristic location, does not warrant biopsy, whereas irritation fibroma and GCF both require biopsy for definitive diagnosis **(Lukes et al., 2005)**

1.6.2 Irritation fibromas

The most frequent clinical diagnosis was fibroma or traumatic fibroma. As stated by **Sivaramakrishnan et al., (2012)** none of the 21 GCF lesions involved in their study were diagnosed correctly as GCF at the time of initial clinical presentation.

Irritation fibroma is of normal mucosal color, unless traumatized, in which the lesion could appear reddened, or whitish due to hyper keratinization, the result of continued irritation after development of the lesion **(Lukes et al., 2005)**

1.6.3 Ossifying fibroma

Is a logical inclusion in the differential diagnosis of this lesion, as it can look much like the GCF clinically**(Haring, 2004),** ossifying fibromas are typically normal mucosal color like GCFs, but they have islands of osteogenic cells dispersed throughout the lesion **(Regezi et al., 1975)** unlike GCF, peripheral ossifying fibroma is found only in the gingiva, occurs more in females, and is thought to arise from the periodontal ligament, while like GCF, it is found more in young adults **(Sapp et al., 2004, Neville et al., 2015)**, the gritty or grainy feel noted

during the biopsy may have also reinforced the surgeon's original impression concerning the type of lesion being excised **(Lukes et al., 2005).**

1.6.4 Papilloma

Which is a common misdiagnosis of GCF. Most have a bosselated or papillary surface, but this was merely a smooth, round, sessile enlargement of the attached gingiva **(Lukes et al., 2005).**

1.6.5 Pyogenic granuloma,

Is commonly found on the gingiva (like GCF), but tends to be red. and bleeds easily if manipulated, unlike most GCFs. which is commonly found on the gingiva of pregnant women and, if a mature lesion, can be pink instead of red **(Sapp et al., 2004, Lukes et al., 2005, Neville et al., 2015).**

1.7 Immunohistochemistry

The origin of Giant cell fibroma has been a subject of much debate **(Pandita et al., 2014)** due to the nature of these stellate shaped mononuclear or multinuclear cells which is not clear and still confusing (**Marx and Stern, 2003**), In his case report and review of literature **Butchi Babu et al., (2010)** stated that "very few cases were seen of this tumor with continuous controversial issues of its origin"

As a result of this debate, several immunohistochemical studies were performed to evaluate the origin of giant cell fibroma, first of all, the study that conducted by **Regezi et al., (1987)** who examined series of fibro-histiocytic lesions to determine the immune profile of these benign and malignant fibrohistiocytic tumors including 8 cases of GCF with their clinical data being retrieved from the Departments of Oral Pathology, University of Michigan and Indiana University, immunohistochemical staining with alpha-1 antichymotrypsin (ACT), muramidase,

HLA-DR, leukocyte common antigen (LCA), S-1OO protein, vimentin, desmin, and keratin were evaluated, the result revealed that the stellate cells of the "giant cell" fibromas were usually ACT and vimentin positive, and muramidase negative, Stellate cells in the lamina propria were occasionally positive for HLA-DR and S-100 protein. Rare LCA-positive dendritic cells were found in the lamina propria, these cells were believed to be indeterminate cells of Langerhans cells and which were ACT positive and frequently HLA-DR positive, this immune profile suggest that GCF likely derived from a primitive mesenchymal cell (which has capabilities of macrophage and fibroblast differentiation).

After that, The Phenotypic characterization of stellate and giant cells in giant cell fibroma were delineated by immunocytochemical study done by **Odell et al., (1994)** in which Sixteen giant cell fibromas were stained for keratin (MNF 116), vimentin, S-100 protein, neurofilaments, glial fibrillary acidic protein, α-smooth muscle actin, desmin, CD31, CD68, Factor Xllla and prolyl 4-hydroxylase, 5B5. Stromal, stellate and multinucleate cells reacted reproducibly only with antibodies to vimentin and prolyl 4-hydroxylase, Sparse mucosa dendrocytes were identified in all cases by Factor Xllla but their numbers were very low except in two cases, including the two possible retrocuspid papillae, dendrocytes were located superficially in the dermal papillae and their highly dendritic morphology was distinctive and readily differentiated from the stellate appearance of the giant cells. In these fourteen cases no giant cells stained with Factor Xllla, two cases contained numerous Factor Xllla-positive cells scattered throughout the connective tissue In one case these cells comprised just less than 50% of the non-endothelial stromal cells present and in the other approximately 25%, In the former, occasional multinucleate cells which were stellate rather than dendritic were positively stained. In both cases an additional population of Factor Xllla negative fibroblasts

and of giant cells positive for vimentin and prolyl 4-hydroxylase was present. The only differences between these cases and the remainder was that they were the most inflamed, and that the lesion with the highest number of dendrocytes was the largest lesion and the only one to have had recurrent trauma noted by the clinician.

This finding of vimentin and prolyl 4-hydroxylase protein immune positivity demonstrates that most of the stromal and stellate multinucleate cells in all giant cell fibromas are fibroblasts. Antibody 5B5 reacts with the active site of prolyl hydroxylase (EC 1.14.11, 2) and immune positivity is fibroblast-associated **(Konttinen et al., 1989, Janin and Chothia, 1990)**because the 4-hydroxylation of proline is a reaction peculiar to collagen synthesis, reactivity for α-smooth muscle actin was limited to vascular smooth muscle cells, in the same context, a review of 103 cases of GCF with immunohistochemical evaluation was done by **Magnusson and Rasmusson, (1995)** from The files of the Department of Oral Pathology, Faculty of Odontology, University of Goteborg between 1978 and 1993, In this period 4629 lesions (18.1%) were coded as fibroepithelial or fibrous hyperplasias. Of these, 103 (2.2%) could be classified as giant cell fibromas on the basis of their histologic appearance in sections stained with hematoxylin and eosin. Immunohistochemical staining was done and demonstrate that Immunoreactivity in the stellate cells was consistently positive for vimentin, and all the 103 cases examined were negative for S- 100 protein, cytokeratin, LCA, and neurofilaments and so they stated that Negative staining for neurofilament and for S-100 protein suggests that the cells are not of peripheral nerve origin, it was also shown that the cells were negative for factor VIII and lectin (indicates no relation to endothelial cells), lysozyme (suggests no relation to giant cells of granulation tissue), and cytokeratin (indicates no relation to squamous epithelial cells). The vimentin positive staining indicates that the stellate cells are of fibroblastic origin, however,

LCA negativity does not exclude the hypothesis of Regezi et al due to the fact that this reagent only reacts with histiocytes and macrophages to a variable extent.

In order to determine the histogenesis of GCF, PCNA and Ki-67 immunoreactivity in multinucleated cells of giant cell fibroma and peripheral giant cell granuloma was done by **Mighell et al., (1996),** PCNA and Ki-67 are both essential to cell cycling but have diverse temporal expression, Comparison of the patterns of nuclear PCNA and Ki-67 immunoreactivity in different cell populations may give insight into the behavior of the cells studied, PCNA immunoreactivity was observed in nearly all nuclei of all GCF multinucleated cells and in many of the surrounding stellate and spindle-shaped mononuclear cells, By contrast, in PGCG, PCNA positive nuclei were observed in many mononuclear cells but not within the centers of multinucleated cells, while no Ki-67 immunoreactivity was observed in the nuclei of multinucleated cells of either GCF or PGCG, This indicates heterogeneity in nuclear PCNA metabolism of GCF multinucleated cells, and it is possible that the most intensely stained nuclei have passed through the cell cycle more recently compared to less immunoreactive nuclei. However, the absence of Ki-67 immunoreactivity in GCF multinucleated cells, and the reported absence of mitoses in a series of 108 GCF **(Weathers and Callihan, 1974)** may indicate that cell cycling in the absence of cytokinesis is not involved in GCF multinucleated cell formation. Alternatively, GCF multinucleated giant cells possibly form by sequential fusion of mononuclear cells, although this cannot be stated with absolute certainty and the histogenesis of GCF multinucleated giant cells remains poorly understood. In contrast, absence of either PCNA or Ki-67 in multinucleated cells of PGCG is consistent with an osteoclast lineage, and formation from differentiated mononuclear cells (**Bonetti et al., 1990, Mighell et al., 1996)** After that, Immunocytochemical Study of 9 cases of giant cell fibroma was published by

Campos et al., (1999), they investigate the immunoreactivity of these cells for leukocyte common antigen, vimentin, tryptase, HLA-DR, alpha-smooth muscle actin, CD68, and S-100, Immunoreactivity in the stellate and multinucleate cells was consistently positive only for vimentin, all specimens were negative for CD68, HLA-DR, tryptase, leukocyte common antigen (LCA), and S-100 protein, and this result suggesting that the stellate and multinucleate cells of GCF have a fibroblast phenotype.

In coordination with Campos and Gomez study, Immunohistochemical evaluation of 30 cases of giant cell fibroma, fibrous hyperplasia and fibroepithelial polyp of the oral mucosa were examined to determine the origin of mono-, bi- and multinucleate stellate giant cells in these lesion by **Souza et al., (2004)** using anti-vimentin, HHF-35, CD68 and factor XIIIa antibodies. Immunoreactivity of the cells was determined in the papillary and reticular lamina propria of these lesions, in the 10 GCF cases, an intense immunoreactivity for vimentin was observed in mono-, bi- or multinucleate stellate giant cells of the papillary (90%) and reticular (70%) lamina propria, For the HHF-35 and factor XIIIa antibodies, labelling in the papillary lamina propria was negative in the majority of the cases, thus they suggest that the mono-, bi- or multinucleate stellate giant cells observed in the lesions studied derived from the fibroblastic lineage.

Different suggestion about the origin of GCF was revealed by **Okamura et al**., **(2009),** they reported a case of GCF of tongue and perform immunohistochemical staining by a series of markers, all stellate giant cells showed strong positivity for vimentin and prolyl-4-hyroxylase, most giant cells showed no positivity for S-100, although some showed moderate S-100 positivity, interestingly, the cytoplasm of HLA_DR/S-100 positive dendritic cells were in close apposition within the stellate giant cells were not positive for both markers, this close spatial relationship were

almost exclusively observed in the lamina propria mucosa, negativity for HHf-3, CD68, α-SMA was observed in all cases, the stellate giant cells were frequently positive for PCNA, occasionally positive for Bax, while Ki-67 and Bcl-2 showed no positivity, they stated that the S-100 positivity might support the hypothesis of Regezi et al., and the origin could be fibroblastic in most cases but there could be other origin including mucosal, dermal, monocyte-macrophages and myofibroblast, the heterogeneity might induced in the presence of certain factors such as inflammation, so reexamination of a large series of GCF using immunohistochemical techniques with suitable panels of markers and other up to date techniques should clarify more precisely the role of stellate giant cells in the pathogenesis of GCF.

Immunohistochemical expression of mast cell tryptase in Thirty cases of GCF with thirty cases of inflammatory fibrous hyperplasia and ten normal mucosae was performed by **De Andrade Santos et al., (2011**), the study revealed that, in epithelial tissue, mast cells were detected in 12 (40%) cases of GCF, 16 (53.3%) cases of inflammatory fibrous hyperplasia , and 2 (20%) normal mucosa specimens. while in connective tissue, mast cells were detected in all cases of GCF, inflammatory fibrous hyperplasia and normal mucosa but with minimum number in GCF and higher number in inflammatory fibrous hyperplasia, this result suggested the involvement of mast cells in epithelial hyperplasia observed in these lesions, probably through induction of heparin-binding epithelial growth factor in keratinocytes, while In this study, GCFs, which are benign neoplasms, presented a smaller mean number of mast cells in the epithelial and connective tissue components than IFHs and normal mucosa specimens. One possible explanation for this smaller number of mast cells in GCF is the scarce to moderate vascularization observed in these tumors.

In a favor of fibroblastic origin **JimSon and JimSon, (2013)** reported a case of gingival GCF and support their diagnosis by immunohistochemical markers including vimentin desmin and PCNA which showed positivity for vimentin that suggest fibroblastic origin, and negativity for desmin which eliminating the possibility of myofibroblastic origin, PCNA showed intense staining which indicate proliferation.

A published Histological Case Report of GCF from D. J. College of Dental Sciences and Research by **Pandita et al., (2014**) to determine the nature of multinucleated fibroblast by special stain Masson Trichrome and Periodic Acid Schiff (PAS) that showed negative staining of vacuolated cells in epithelium and clear spaces surrounding the fibroblast while epithelial cells cytoplasm shows melanin pigments with Masson Trichrome. Immunohistochemical staining showed that the cells were negative for Alpha Smooth Muscle Actin ruling out muscular origin while positive for Vimentin suggesting fibroblastic origin .

The study of Dr.Fatimah ,my supervisor showing that Positive expression of vimentin and CD163 was detected in all cases with a mean of 73.81% and 56.27% respectively, while cytoplasmic reactivity of NGFR (p75NTR) was seen in all cases which were regarded as negative according to the antibody data sheet. The immunohistochemical positivity for vimentin and CD163 suggested that giant cell fibroma has a mixed differentiation mostly fibrohistiocytic that derived from primitive mesenchymal lineage, however, an examination of larger series of GCF cases with the use of a different panel of immunohistochemical markers are suggested for further evaluation of this controversial lesion. The cytoplasmic expression of NGFR(p75NTR) which is positive in all cases requires further validation to be considered as a tumor marker for this lesion **(Fatimah, 2019).**

1.8 Treatment and prognosis

Though there are distinct histopathologic features for GCF, its prognosis is similar to the conventional fibroma/fibroepithelial polyp. A high index of suspicion and appropriate investigative work up is necessary for separate lesions in order to arrive at a suitable diagnosis and offer appropriate therapy**. (Sivaramakrishnan et al., 2012)** The choice of treatment for GCF is surgical excision in adults whereas in children electrosurgery or laser excision is preferred **(Butchi Babu et al., 2010).**Electrosurgery's main advantage is the direct tissue haemostasis without need for sutures **(Anderman, 1982, Minatel Braga et al., 2006),** in addition, there can be access to areas difficult to reach and reduction of chair time **(Anderman, 1982).** Laser therapy has been suggested as an alternative approach **(Genovese and Olivi, 2008, Boj et al., 2011)**, Concerning the excision of soft tissue lesions, CO2 and Nd:YAG laser have been suggested for the excision of fibromas with various advantages such as direct haemostasis and disinfection of the surgical field, minimal postoperative pain and inflammation, elimination of sutures and acceleration of the healing process. However, they lead to vaporization of the lesion and do not allow histopathological analysis of the tissue **(Boj et al., 2011).** Diode and erbium lasers are also optional in the treatment of soft tissues indicated for the excision of lesions while permitting histopathological analysis **(Kotlow, 2004)**

Recurrences are considered rare, and it was noted in two of 464 cases reported by Houston. One lesion recurred once and the other twice **(Houston ,1982),** The recurrence of these cases are reported in few incidences and found to be due to incomplete removal of the lesion **(Madi et al., 2014)**

While in the other clinicopathological studies done by **Kuo et al., (2009)** and **Sivaramakrishnan et al., (2012),** all GCFs were excised surgically and no recurrence was reported so far.

Chapter two

conclusion

Conclusions

Reactive fibrous hyperplastic lesions are common in the oral cavity and have some similarities in the clinical and histopathology features. Nonetheless, the giant cell fibroma is a fibrous tumor with distinctive clinicopathologic features. The etiology is not clear. Its prognosis is similar to that of irritation fibroma. The giant cell fibroma is treated by conservative surgical excision, and its recurrence is rare.

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