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Research Article

Recurrent pyogenic granuloma: an update

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ABSTRACT

Background: Given the fierce controversy about the nature of pyogenic granulomas, starting with its unfitting name and ending up with its ideal treatment modality, this paper tries to numerically identify some predisposing factors of recurrence.
Methods: The literature was initially reviewed and a total of twenty recurrent cases of pyogenic granuloma were contrasted, on one hand, to their initial appearance. On the other hand, all are contrasted to a similar number of normal mucosa using three histochemical stains: Alcian blue, periodic acid-Schiff and Masson's trichrome.
Results: For all recurrent lesions, all specimens showed myxoid structure histologically even if their initial appearance had possessed a sparse myxoid structure. The age of recurrence has been correlated to the histochemical findings. For the Alcian Blue stain (AB), the value of t-test was 3.808840. The pertaining value of P was 0.000593. The result was significant at $P \leq 0.05$. For the PAS stain, the value of t-test was 3.640327. The value of P was 0.000871. The result was significant at $P \leq 0.05$. In Masson's trichrome staining, the value of t-test was 3.100816. The value of P was 0.002942. The result was significant at $P \leq 0.05$. Accordingly, all stains showed significant difference in fibrous content in the initial and recurrent lesions. Conversely, the count of both endothelial vessels and inflammatory infiltrates in the recurrent lesions were significantly lower than the primary precursors.
Conclusions: Given that collagen fibers are continually degraded and resynthesized while proteolytic degradation occur outside the cells through the activity of enzymes called matrix metalloproteinases (MMPs), it is suggested that MMPs -positively expressed by PAS reactions- account for the spacing of the fibrous stroma, allowing for reshaping the three dimensional structure of the connective tissue. Myxoid structures are certainly promoting recurrence either via excessive secretion of hyaluronic acids or unknown mechanisms. The undisputed fact is the presence of myxoid structures in all our reported recurrent cases. Both inflammatory cascade and endothelial proliferation have no vital role in the recurrence according to our morphometric results. Finally, PAS stain should give more details in examining PGs than the other recruited counterparts.

Keywords: Recurrent pyogenic granuloma, PAS stain, Myxoid structures, Etiopathogensis

INTRODUCTION

Injury of the connective tissue stimulates parenchymal and stromal cells to undergo desmoplastic changes.[1] Exuberant connective tissue injury is known to occasionally induce the so called "pyogenic granuloma".[2] Given the multiple components of the connective tissue, three stains are used to measure such changes at various levels. A desmoplastic response is characterized by larger stromal cells with increased extracellular fibers and immunohistochemically by transformation of fibroblastic-type cells to a myofibroblastic phenotype. Irritation and injury of CT induce a remarkable proliferation of fibroblasts with subsequent secretion of collagen. The newly secreted collagen acts as a scaffold for infiltration of cells to the site of injury. In a similar

vein, extracellular matrix components such as proteoglycans and glycosaminoglycans, which are highly negative in H&E staining, undergo proliferative changes. However, some degradation occurs providing some space for new vasculature to start an angiogenesis.[1] Pyogenic Granulomas (PGs) are typically red and smooth or lobulated with hemorrhagic and compressible features (Cf. Figures 1 & 2). Older lesions become more pink and collagenized. PGs are composed mainly of lobular masses of hyperplastic granulation tissue along with endothelial proliferation as well as a confluence of inflammatory infiltrates (Cf. Figure 3). Classical treatment is the surgical decision; however, other recent treatment modalities are more advocated.[2-7]

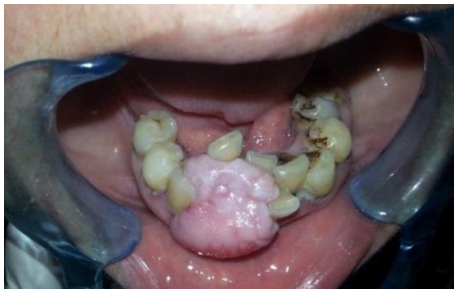

Figure 1: A clinical picture of a recurrent mandibular pyogenic granuloma which intervenes the crowding mandibular incisors.

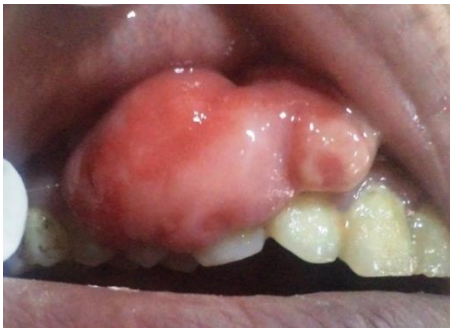

Figure 2: A clinical picture of a recurrent exophytic maxillary pyogenic granuloma which occupies most of the upper right quadrant.

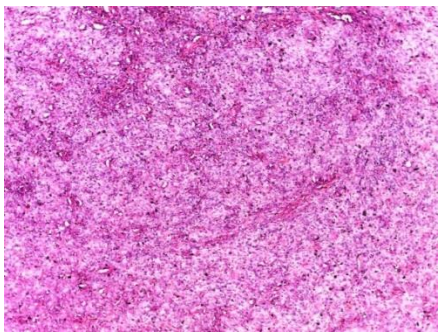

Figure 3: A classical H&E photomicrograph displaying chronic inflammatory cells and numerous endothelial spaces which are dotting a collagenous stroma (Magnification 10x).

METHODS

Besides the systematic review of literature, twenty archival cases of recurrent pyogenic granuloma were histologically contrasted to their de novo appearance. Sections from the paraffin blocks of PG, recurrent PG and normal mucosa were stained with Hematoxylin And Eosin (H&E), alcian blue, Periodic Acid-Schiff (PAS), and Masson's trichrome. H&E was used in confirming the diagnosis and identifying the myxoid areas, if any, in the histological sections.[1]

Four fields were captured at magnification (40x) from the slides by a digital camera mounted on light microscope, Olympus CHT, Optical. Co. Ltd, Japan, to be digitally processed by Image analysis software (Image J 1.42, NIH, USA). Tagged sections were selected. Selections were harmonized for color threshold ahead of converting the image into 8-gray scale type and automated to the optimal threshold.

Surface area and area fractions were calculated for the stromal fibrous content and inflammatory infiltrates were counted in the selected fields. Data were transferred to an MS excel sheet to calculate the mean value of surface area and mean area fraction. Both readings, slides of cases before recurrence and after recurrence, were contrasted using t-test for two dependent means.

All findings were contrasted to twenty archival cases of normal mucosa using the one-way ANOVA with post-hoc Tukey HSD test.

The periodic acid-Schiff reaction stains carbohydrates and carbohydrate-rich macromolecules. Accordingly, it is used to demonstrate glycogen in cells, mucus in various cells and tissues, the basement membrane that underlies epithelia, and reticular fibers in connective tissue. Accordingly, PAS stain was used to stain not only collagenous fibers but also glycosaminoglycans and reticular fibers. Alcian blue was used to stain collagen and mucogingival proliferation. Similarly, Masson's trichrome was recruited. The P value was considered significant when it was lower than 0.05 and highly significant when it was lower than 0.01.

RESULTS

Selection of cases from the complete achieves was random. Further stratification was posed according to the submitted age group. In the histological examination, surface areas and area fractions of the collagenous and inflammatory infiltrates were measured. The presence and absence of myxoid structures were traced. All aimed at fathoming the nature of recurrent PG and accounting for recurrence.

For all recurrent lesions, all specimens showed myxoid structure histologically even if their initial appearance had possessed sparse myxoid structure.

The age of recurrence has been correlated to the histochemical findings. The categorization of the age grouping is shown in Table 1.

Table 1: Age grouping and incidence of occurrence of the twenty cases.

Age group	Incidence
32-38	3
39-45	5
46-52	4
53-59	4
60-66	4

Four captures of the most representative fields were pictures at a magnification power of 40x, from the various stains, where surface area and area fractions were measured for the endothelial vessels and the inflammatory infiltrates were counted in the selected fields (Figure 4-8).

Data were transferred to an MS excel sheet to calculate the mean value of surface area and mean area fraction. Both readings, slides of cases before recurrence and after recurrence, were contrasted using t-test for two dependent means as shown in Table 2-5.

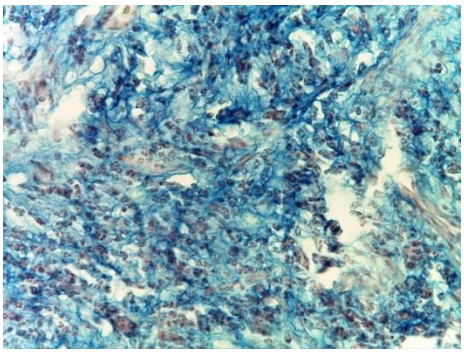

Figure 4: An alcian blue stained photomicrograph displaying chronic inflammatory cells (brown) and a collagenous stroma (blue) (Magnification 40x).

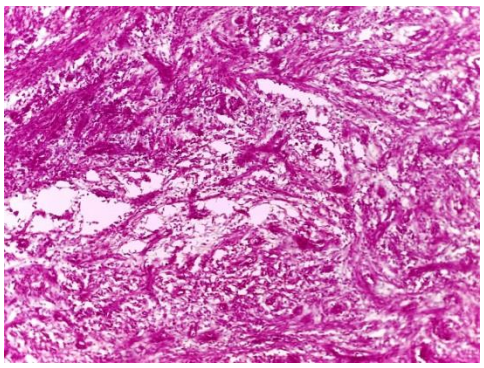

Figure 5: A PAS stained photomicrograph displaying chronic inflammatory infiltrates, collagenous and reticular fibers as well as other structures of ECM (Magnification 10x).

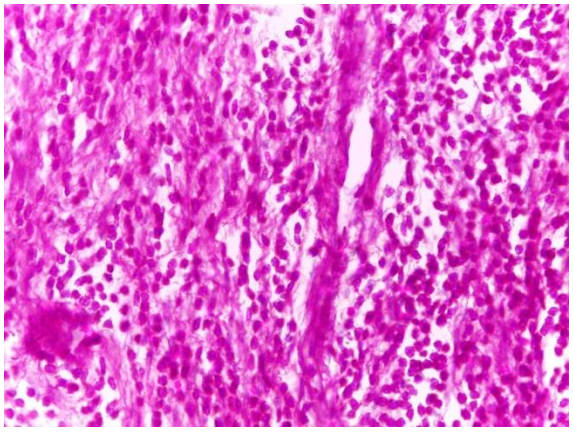

Figure 6: A PAS stained photomicrograph displaying chronic inflammatory cells, numerous endothelial spaces and a fibrous stroma (Magnification 40x).

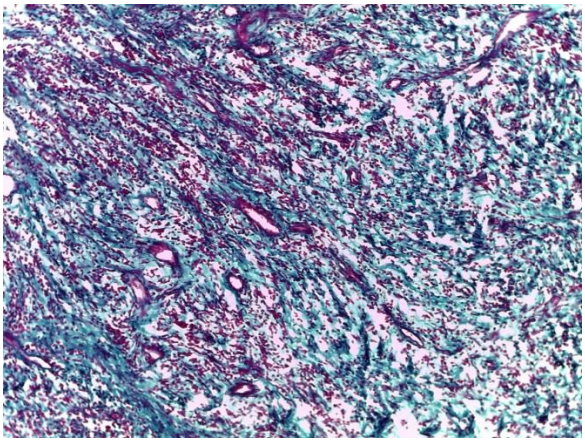

Figure 7: A Masson's trichrome stained photomicrograph displaying chronic inflammatory cells (brown) and numerous endothelial linings (brown) as well as rich collagenous stroma (Magnification 10x).

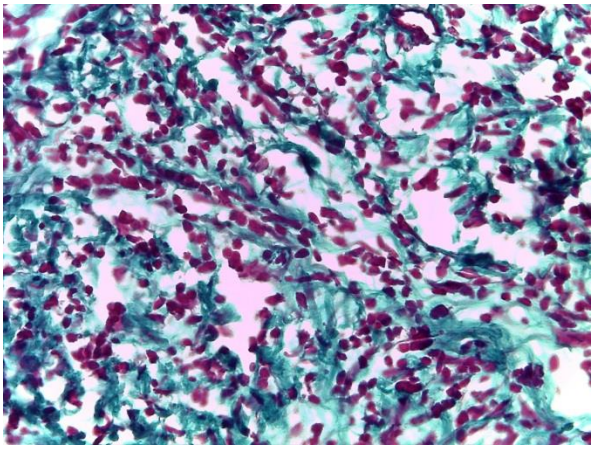

Figure 8: Masson's trichrome stained photomicrograph displaying chronic inflammatory cells and fibrous stroma (Magnification 40x). The area fraction was digitally calculated where inflammatory infiltrates were manually counted.

Table 2: The mean area fraction of fibrous stroma of the three stains (before and after recurrence).

Case	Mean area fraction of fibrous stroma (AB)	Mean area fraction of fibrous stroma (PAS)	Mean area fraction of fibrous stroma (MT)	Mean area fraction of fibrous stroma (AB)	Mean area fraction of fibrous stroma (PAS)	Mean area fraction of fibrous stroma (MT)
	Before recurrence			After recurrence		
1	0.49	0.3	0.31	0.52	0.32	0.32
2	0.52	0.42	0.21	0.62	0.44	0.22
3	0.39	0.27	0.22	0.38	0.31	0.23
4	0.37	0.3	0.19	0.35	0.32	0.21
5	0.55	0.32	0.24	0.61	0.34	0.26
6	0.38	0.39	0.19	0.43	0.41	0.21
7	0.42	0.29	0.24	0.49	0.32	0.28
8	0.51	0.48	0.19	0.59	0.51	0.21
9	0.48	0.28	0.26	0.47	0.32	0.31
10	0.44	0.46	0.17	0.52	0.52	0.21
11	0.35	0.29	0.31	0.39	0.32	0.33
12	0.51	0.42	0.2	0.56	0.44	0.21
13	0.28	0.29	0.2	0.29	0.32	0.21
14	0.41	0.31	0.17	0.41	0.32	0.14
15	0.49	0.25	0.2	0.44	0.26	0.21
16	0.50	0.33	0.3	0.52	0.32	0.31
17	0.38	0.34	0.22	0.41	0.29	0.21
18	0.42	0.25	0.24	0.46	0.32	0.21
19	0.40	0.38	0.45	0.42	0.42	0.51
20	0.72	0.34	0.19	0.81	0.32	0.21

For the Alcian Blue stain (AB), the value of t-test is 3.808840. The pertaining value of P is 0.000593. The result is significant at P ≤0.05. In the PAS stain, the value of t is 3.640327. The value of P is 0.000871.

The result is significant at P ≤0.05. In Masson's trichrome staining, the value of t is 3.100816. The value of P is 0.002942. The result is significant at P ≤0.05.

Accordingly, all stained showed significance difference in the fibrous content in the initial and recurrent lesions.

For the PAS stain, the value of t is -2.197664. The value of p is 0.020286. The result is significant at P ≤0.05. Similarly, the MT stain showed a t-value of -4.292347. The value of P is 0.000197. The result is significant at P ≤0.05.

By comparing the three stains, the p-value corresponding to the F-statistic of one-way ANOVA (40.0793) is lower than 0.05, suggesting that the one or more staining outputs of fibrous stroma are significantly different.

The post-hoc Tukey HSD test follows to identify which of the staining outputs are significantly different from each other.

Table 3: The mean count of inflammatory infiltrates of the three stains (before and after recurrence).

Case	AB	PAS before	MT	AB	PAS after	MT
1	0.042	0.063	0.034	0.038	0.058	0.018
2	0.021	0.031	0.041	0.029	0.021	0.031
3	0.043	0.064	0.036	0.04	0.048	0.03
4	0.061	0.091	0.036	0.056	0.081	0.036
5	0.019	0.025	0.036	0.024	0.045	0.025
6	0.031	0.045	0.044	0.037	0.049	0.04
7	0.041	0.062	0.036	0.039	0.052	0.036
8	0.021	0.0315	0.062	0.024	0.0305	0.062
9	0.045	0.051	0.031	0.045	0.051	0.028
10	0.028	0.042	0.036	0.068	0.042	0.024
11	0.028	0.042	0.036	0.038	0.042	0.033
12	0.028	0.042	0.072	0.034	0.042	0.059
13	0.215	0.322	0.036	0.215	0.322	0.036
14	0.123	0.185	0.234	0.123	0.145	0.234
15	0.21	0.356	0.034	0.21	0.326	0.028
16	0.043	0.061	0.034	0.043	0.061	0.032
17	0.134	0.201	0.034	0.134	0.201	0.034
18	0.041	0.063	0.047	0.041	0.043	0.043
19	0.124	0.163	0.034	0.124	0.163	0.032
20	0.041	0.061	0.065	0.034	0.052	0.061

Table 4: Results of Tukey HSD test in comparing the three stains in measuring the fibrous changes.

	Tukey HSD Q statistic	Tukey HSD P value	Tukey HSD inference
H&E vs. Alcian blue	0.2547	0.8999947	Insignificant
H&E vs. PAS	6.9608	0.0010053	**P <0.01
H&E vs. Masson's	12.9878	0.0010053	**P <0.01

The p-value corresponding to the F-statistic of one-way ANOVA (5.9686) is lower than 0.01 which strongly suggests that the one or more staining outputs of inflammatory infiltrates are significantly different. The post-hoc Tukey HSD test follows to identify which of the staining outputs are significantly different from each other. This means that recurrent PG has a significant decrease in the number of the inflammatory infiltrates.

Table 5: Results of Tukey HSD test in comparing the three stains in measuring the inflammatory infiltrates.

	Tukey HSD Q statistic	Tukey HSD P value	Tukey HSD inference
H&E vs. Alcian blue	3.4397	0.0797522	Insignificant
H&E vs. PAS	5.8665	0.0010053	**P <0.01
H&E vs. Masson's	2.2638	0.3853986	Insignificant

Concerning the correlation between aging and fibrous content of the lesions, the value of R is 0.6374. This is a moderate positive correlation between aging and fibrous content of the lesions. The P value is 0.002503. The result is significant at P <0.05. However, when it comes to aging and inflammatory infiltrates of the lesions the R value is -0.7408. This is a moderate negative correlation between aging and inflammatory infiltrates of the lesions. The P value is 0.000192. The result is significant at P <0.05. It means that inflammatory infiltrates, unexpectedly, decrease in recurrent lesions. This should prompt renewed speculations about the role of the confluence of such infiltrates in aggravating the condition.

DISCUSSION

Most cell types in loose connective tissue are transient wandering cells that migrate from local blood vessels in response to specific stimuli. Loose connective tissue is, therefore, the site of inflammatory and immune reactions where it swells substantially. In areas of the body where foreign substances are continually present, large populations of immune cells are maintained.

Pyogenic Granuloma (PG) is usually defined as an inflammatory hyperplasia in response to underlying irritating factor.[2] The name pyogenic granuloma, though it is popular, is a misnomer since the condition is not associated with pus and does not represent a true granuloma histologically,[3] PG develops in response to various stimuli such as low-grade local irritation, traumatic injury or conspicuous hormonal changes.[4]

Over time, PG has been given several names to reflect its etiopathogenesis. In 1844, Hullihen described the first case of pyogenic granuloma in the English literature Hartzell, in 1904, has coined the term of "pyogenic granuloma" or "granuloma pyogenicum"; eponymically Crocker and Hartzell's disease. However, it is Angelopoulos who described the histological picture of PG; depicting it as "hemangiomatous granuloma" due to the presence of numerous blood vessels and the inflammatory nature of the lesion. In a similar vein, Cawson et al. have designated it "granuloma telangiectacticum" Moreover, they described two forms of PGs, the lobular capillary hemangioma (LCH) and the non-lobular capillary hemangioma (non-LCH). Pyogenic granulomas commonly occur on the skin or the oral cavity but seldom in the gastrointestinal tract. Among other given names, botryomycoma, benign pedunculated granuloma, pseudobotryomycosis, fibroangioma, hemangiomatous granuloma, lobular hemangioma, eruption haemangioma and pregnancy tumor for females come atop.[5]

In the past, etiopathogenesis of pyogenic granulomas were attributed to pyogenic organisms.[6,7] It is, now, proved to be unrelated to infection. Etiologic factors of pyogenic granuloma are multifactor including chronic low grade irritation,[2] physical trauma,[8] hormonal influence[9,10] and some drugs.[11] Bad oral hygiene is considered an irritating participating factor of pyogenic granuloma.[2,8,12] Dental plaque, calculus, overhanging marginal restorations, peri-implantitis,[13] and others can promote developing pyogenic granulomas. Extragingivally, biting on oral mucosa may induce pyogenic granuloma especially in the buccal mucosa.[2,14,15]

Piercing of tongue and lips may be traumatic enough to develop granulomas.[16] Other traumas, which are associated with developing pyogenic granulomas, encompass iatrogenic dental injuries.[17] Microtraumas due to tooth brushing,[18] some orthodontic appliances[19,20] and tooth extractions[21] are, sometimes, causative as well.

Hormonal changes in pregnant females have proved to play a great role in evoking the formation of granulomas due to high hormonal levels of estrogen and progesterone. The high vascularization, proliferation, and vascular permeability have been ushered to develop pyogenic granuloma and pregnancy tumor.[2,8,12] The pregnancy tumor occurs in about 5% of pregnant females. The periods of puberty and menopause have been noticed to start similar growths as well.[22]

Among inducing drugs of the granulomas are cyclosporine,[23-25] erythropoietin,[26,27] anti-CD 20 monoclonal antibody therapy,[28] systemic retinoids,[29] acitretin,[30] topical retinoids,[31] antiretroviral,[32] panitumumab,[33] antineoplastic agents in chemotherapy,[34] capecitabine,[35] mitoxantrone,[36] taxanes docetaxel,[37] paclitaxel[38] and mTOR inhibitors.[39]

Clinically, the PG is a smooth or lobulated mass that is usually pedunculated, although some lesions are sessile.[2] The incidence of lobular capillary hemangioma of PG, which occurs more frequently in sessile form, is approximately 66% whereas non-lobular capillary hemangioma of pyogenic granuloma occurs in pedunculated form 77%.[40]

The pyogenic granuloma develops as firm erythematous, ulcerative, hemorrhagic bright red to purple red lobulated mass[2] or friable polyploidy papule.[41] Color rages from pinkish to reddish. This depends on the duration of the lesion since older lesions tend to become more collagenized and pink whereas younger ones are more vascular.[8,42] This finding is supported by our scan of the twenty recurrent lesions whose color was pinkish and inflammatory infiltrates were much fewer.

The lesion size varies from few millimeters to larger size in several centimeters.[8] The average size of the pyogenic granuloma does not exceed 2.5 centimeters expect in rare cases only[43] and extra-orally.[44] The lesion reaches its full size within weeks to months.[45]

The pyogenic granuloma is asymptomatic and painless but it often easily bleeds due to its highly vascularity.[2] The lesion is slowly growing but it may grow rapidly.[46]

The main site in oral cavity where the pyogenic granuloma develops is the gingiva with frequency 75% of all cases because the high vascularity of the free gingiva, where the lips[47] 3%, tongue 4%,[48] and buccal mucosa are the next more common sites.[2,49] Rarely the pyogenic granuloma may develop in upper labial mucosa, and the hard palate.[50]

Pyogenic granuloma can develop at any age, the commonest affected age is the first decades in children and young adults because of the highly vascularity of the oral tissue, which is richer in young ages than older ages. With regard to gender, females are more predictable for developing PG than males (1.5:1) due to their hormonal changes during puberty, menopause, administration of contraceptive and pregnancy.[2,40]

The Radiographic features of PG are not useful because PG is a soft tissue vascular which rarely cases bony saucerization or significant bone, which may be evident radiographically.[51,52]

Histologically, the microscopic examination of the PG shows a highly vascular proliferation. Numerous small and larger endothelium-lined channels are usually engorged with red blood cells. These vessels may organize in lobular aggregates that is gives it the lobular appearance. The surface is usually ulcerated and replaced by thick fibrinopurulent membrane. A mixed inflammatory cell infiltrate of neutrophils, plasma cells, lymphocytes and mast cells coexist. The neutrophils are most prevalent near the ulcerated surface where the chronic inflammatory cells are found deeper in the specimen. The significant increase in the average mast cell count per microscopic field in pyogenic granuloma in comparison to normal oral mucosa strengthens the possibility of a role of mast cells in the pathogenesis of pyogenic granuloma. Older lesion shows more fibrous histopathological after undergoing fibrous maturation.[53,54] Our study of the twenty recurrent cases of PG supports the mixture of inflammatory infiltrates.

Sometimes pyogenic granulomas show myxoid background which is a loose pale to lightly basophilic mucin-like storma.[55] Myxoid occurs also in other tumors, these tumors categorized in a group called myxoid tumors, this group characterized by their tendency to recur locally[56] as Aggressive Angiomyxoma with recurrence rates range from 25%to 47% after 5 years of surgical removal,[57] Chondromyxoid fibroma with high recurrent rate after 2 years of curettage,[58] pleomorphic adenoma with recurrence rate 33%,[59] myxoid liposarcoma with high recurrence rate 50%,[60] myxoid leiomyoma with recurrence rate 40%,[61] odontogenic myxoma with recurrence rate average 25%,[62] myxoid neurofibroma,[63] myxoid nuerothekeoma,[64] myxoid lipoblastoma,[65] myxofibrosarcomas with high local recurrence rate 61%,[66] Undifferentiated embryonal sarcoma,[67] myxoid plexiform fibrohistiocytic tumor with recurrence rate from 12.5% to 40%,[68] parachordoma with recurrence rate up to 20%,[69] acral myxoinflammatory fibroblastic sarcoma with recurrence rate about 67%,[70] atrial myxoma with recurrence rate 3%,[71] cutaneous myxoma,[72] ossifying fibromyxoid tumour with recurrence rate 22%,[73] juxta-articular myxoma with recurrence rate 34%,[74] myxopapillary ependymoma with recurrence rate 9%,[75] myxoid dermatofibrosarcoma protuberans,[76] myxoid malignant peripheral nerve sheath tumour with recurrence rate from 40-68%,[77-79] extraskeletal myxoid chondrosarcoma,[80] myxoid liposarcoma with recurrence rate 13%.[81]

Imunohistochemically, expression of PG was positive in factor VIII-related antigen in the endothelial cells lining large vessels, but are negative in the cellular areas. Enhanced expression was remarkable in the bFGF, Tie-2, anti-CD3 and anti-alpha SMA antibodies, and vascular morphogenesis factors such as angiopoietin-1, angiopoietin-2, ephrinB2, and ephrinB4.[82]

The treatment of PG is classically done via surgical excision. The excisional biopsy should examine histopathological. For gingival pyogenic granulomas, the excision should extend down to periosteum and the

adjacent teeth should be thoroughly scaled to remove any source of continuing irritation.[2]

The surgical excision can be achieved by many techniques which include the conventional surgical excision by blade, excision by laser, cryosurgery, electro-cautery and electrodessication. Using Nd:YAG laser is very benefit for removing this lesion because of the lower risk of bleeding,[83] its superior coagulation characteristics,[4] it is more tolerated by patients and has no adverse effects.[84]

A flash lamp pulsed dye laser have been used also in removing the lesion.[85]

Cryosurgery is another technique of conservative surgery has been used in removal the pyogenic granuloma.[86] Using electrocautery can offer less bleeding from the operative field. However, pain after surgery is higher in patient with mass excised using electrocautery as lateral thermal damage could not be avoided. While ultrasonic scissors used as well in removing pyogenic granulomas,[87] the ultrasonic scissors offer faster re-epithelialization and greater tensile strength.[88]

On the one hand, surgical excision still seems to be the successful treatment of choice in minimizing the recurrence of lesion especially when exacerbating factors such as hormonal imbalances exist.[20] On the other hand, there are other non-surgical treatment modalities of PG which include injection of ethanol or corticosteroid and sodium tetradecyl sulfate sclerotherapy.[89] Injection of ethanol or corticosteroid is used in cases of recurrent PG. Moreover, both do not leave scars in contrast to surgically excising the lesion.[90,91]

Prognosis of the PG usual is good. In rare instances, multiple recurrences have been noted, with recurrence rate is up to 16%. The recurrence rate is higher for pyogenic granulomas removed during pregnancy. The recurrences occur in gingival lesion higher than other oral mucosal sites lesion. The recurrence occurs maybe because incomplete safely removal of the lesion, incomplete removal of the etiologic factors or re-injury of the site.[2,3,8,92,93]

CONCLUSION

Given that collagen fibers are continually degraded and resynthesized while proteolytic degradation occurs outside the cells through the activity of enzymes called matrix metalloproteinases (MMPs), it is suggested that MMPs, positively expressed by PAS reactions, accounts for the spacing of the fibrous stroma allowing for reshaping the three dimensional structure of the connective tissue. All, along with the remodeling of resynthesized collagen, add up to the swollen nature of the PG to accommodate the stromal changes. This is why PG granuloma stop growing after reaching a certain size, recurs if the MMPs are adequately active after incomplete excision. The size after recurrence is directly proportional to the inherent persistent defective MMPs.

Inflammatory infiltrates and endothelial proliferation have no vital roles in recurrence. However, myxoid structures are certainly promoting recurrence either via excessive secretion of hyaluronic acids or unknown mechanisms. The undisputed fact is the presence of myxoid structures in all our reported of recurrent cases requires a rapt attention to the underlying predisposing factors.

Finally, PAS stain should give more details in examining PGs than the other recruited counterparts.

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