Review Article

Heterogeneous conceptualization of etiopathogenesis: Oral pyogenic granuloma

ABSTRACT

Oral pyogenic granuloma or granuloma pyogenicum is a conspicuous lesion. The word pyogenic granuloma is a misterm since the situation is not related with pus and histologically does not exemplify a granuloma. An oral pyogenic granuloma is obvious to involve the gingiva generally. Extragingivally, it can present on the buccal mucosa, lips, tongue, and palate. A report of trauma is prevalent in such sites. The pathogenesis of the lesion is still unclear, although it was initially supposed to be a botryomycosis infection. It is suggested that etiology of pyogenic granuloma was the reaction of tissues to minor injury or chronic irritation, thus open a pathway for the entrance of nonspecific microorganisms, although microorganisms are not often expressed within the lesion. Hence, this review recapitulates all diverse concepts of pathogenesis associated with this most often and most mysterious lesion of the oral cavity.

Keywords: Etiopathogenesis, oral cavity, oral pyogenic granuloma, pathology

INTRODUCTION

Pyogenic granuloma or granuloma pyogenicum is benign, soft, usually solitary, the nonneoplastic vascular proliferation of the skin and oral cavity. Pyogenic granuloma has been pertaining by a diversity of another name such as granuloma pediculatum benignum, pregnancy tumor, vascular epulis, and Crocker and Hartzell's disease. The present name was given by Crocker in 1903. The term "pyogenic granuloma" or "granuloma pyogenicum" stated by Hartzell in 1904.[1]

It is a kind of hyperplasia which commonly present in the mouth; histologically, the proliferation of granulation tissue with inflammatory infiltrate chiefly lymphocytes and significant angiogenic capacity; for this basis, the new formation of a vascular channel of different measurement are ordinarily present, these developments show instantaneous inception and completion inside the tissue.[2] From the histological standpoint, this lesion classified into two groups: capillary lobular hemangioma when the organization of capillary vessels is present into granulomatous tissue lobes enveloped by a thin bands of collagen, such development is called as capillary lobular hemangioma, whereas when the formation of vascular channels is intervolved in the tissue without evident order, called as an lobular capillary hemangioma.[3]

EPIDEMIOLOGY

Some authors observed higher pervasiveness in females (1:1.5) and the existence of local etiologic factors in 16% of complete cases. It is mostly present in the gums (75% of all cases).[4]

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ETIOPATHOGENESIS

Certain authors considered pyogenic granuloma as an "infectious" establishment. Kerr has suggested botryomycosis, staphylococci, foreign particles, and accumulation of infection inlining of the blood vessel as conducive factors in the advancement of the lesion.[5] The bacterial stains have indicated the immediacy of Gram-positive and Gram-negative bacilli in the lesion reported by Bhaskar and Jacoway. However, they also suggested that this microorganism may have been contaminants from oral microflora as they were more common in ulcerated than in nonulcerated lesions and mostly near the surface than in deeper aspects.[6]

As reported by Shafer *et al*., oral pyogenic granuloma appears as a consequence of infection by either bacteria streptococcus or staphylococci, relatively because it was depicted that these microorganisms could develop colonies with the fungus-like diagnostic. They also observed that the lesion could arise as a reaction of some minor trauma to the tissues that impart a pathway for the intrusion of nonspecific varieties of microorganisms. The characteristic tissues response takes place to these organisms of low virulence with the passionate proliferation of a vascular kind of connective tissue. They also explained that any irritant actionable to the living tissue may exploit either as a stimulus or destructive agent or combination of both.[7]

The assiduousness of the stimulating substance will be high, and development will be stimulated if numerous cells are present in a minor volume of tissue and there is a relative depletion of blood flow through the area as in inflammation. As maturation and differentiation are accomplished, the cells become broadly separated, and the concentration of the substance reduces, and compact growth occurs. In this kind of inflammatory reaction, that results in the establishment of oral pyogenic granuloma, destruction of cells of fixed tissue is little, but the impetus to the proliferation of vascular endothelium persists and employs its effect over a long period. Reichart and Philipsen reported that the granulation tissue of oral pyogenic granuloma may become perverted by oral microflora and its surface may frequently become covered by fibrin which may resemble pus. However, quiet suppuration is not attributed feature of oral pyogenic granuloma to assist infectious origin.[8]

Few investigators examined pyogenic granuloma appears as a "reactive" or "reparative" tumor process. Regezi *et al*. stated that pyogenic granuloma an exuberant proliferation of connective tissue to a notable stimulus or injury like foreign particles or calculus within the gingival crevice.[9]

Various "etiologic factors" such as trauma, chronic irritation, drugs, hormones, gingivitis, chronic irritation related with exfoliation of deciduous teeth, eruption of permanent teeth, faulty filling, food impaction, complete periodontitis, and trauma due to a toothbrush have been proposed as etiological factors where patients dispensed with these findings.[2]

Murata *et al*. reviewed in their study that after any kind of trauma, the essential to wound healing is the development of granulation tissue and this incorporates the emigration of inflammatory cells, exodus, and proliferation of vascular endothelial cells and fibroblasts cells and formation of extracellular matrix. The processes of wound healing appear to be controlled by diverse kinds of cytokines. The role of growth factors, extremely basic fibroblast growth factor (bFGF)-a heparin-binding angiogenic protein, has been established to be particularly mitogenic for cells of capillary endothelium and induces angiogenesis. They observed an immunolocalization of bFGF in oral pyogenic granuloma and gingiva at its different stages of progression. They stated that extreme quantity of bFGF is produced and released from some mast cells and defence cells such as macrophages into the extracellular matrix during neovascularization of the granulation tissue.[10] Trauma has also been incriminating in an etiopathogenesis of numerous and planetoid oral pyogenic granuloma, although obvious etiopathogenesis that whether it arises after treatment or *de novo*, is not distinctly apprehend.

There are various theories contemplated, Ainamo reported that the tumor cells release various endogenous substances along with angiogenic factor due to trauma and it often also result in distraction in the vascular system of the ostentatious area. Some authors have suggested that habit of tooth brushing often also be contemplated as a remarkable cause of irritation and microtrauma to the gingival as there is a site preference for labial gingiva in the front region of the oral vestibule.[11] Yung, Richardson, and Kratochvil stated the role of a hormone associated with pregnancy tumor that present in the pregnant women also emerges from the gingiva and has similar microscopic features.[12]

Hosseini *et al*. stated that the gingiva may be accreted during pregnancy and often atrophy during menopause clinically. They also observed that gingiva can be proposed as another "target organ" for the direct action of estrogen and progesterone hormone.[13] Whitaker *et al*. in their study reported that the quantity of progesterone and estrogen receptors is not the regulating factor in its pathogenesis of. Preferably, such a role could be assigned to the elevation of circulating hormones. The quantity of progesterone and

estrogen are remarkably increased in pregnancy and could consequently employ a greater impact on the endothelium of this lesion.[14] Ojanotak-Harri *et al*. stated that it has been shown that pregnancy inhibits the migration of inflammatory cells and fibroblasts.

It has been shown that pregnancy modulates both the metabolism of progesterone and also effect relocation of inflammatory cells within the tissue. The standard level of active form of progesterone and "dysfunction" of the inflammatory cells may have a role in the establishment of pregnancy gingivitis and formation of granuloma. The concurrence of the two factors inhibit an acute type of tissue reaction to plaque but permit an enhanced chronic reaction resulting clinically in an overestimated impression of inflammation.[15] Bhaskar and Jacoway reported that pyogenic granuloma mostly occurs in males than females; for this point of view, the role of the hormone may an etiological factor is doubtful.[6]

Histologically, Regezi *et al*. examined prominent proliferation in hyperplastic granulation tissue suggesting a strong enterprise of angiogenesis.[8] Kuo, Ying, and Ming reported two angiogenesis enhancers, such as vascular endothelial growth factor (VEGF) and bFGF, and two angiogenesis inhibitors, that is, thrombospondin-1 and angiostatin in an implement for angiogenesis. Vascular morphogenesis factors, that are, angiopoietin-1, angiopoietin-2, ephrinB2, and ephrinB4, were upregulated in comparison to healthy gingival.[16] Some investigators have been proved that the significance of bFGF, VEGF, or connective tissue growth factor, especially in angiogenesis related with a profound inflammation.[2]

According to Kelley and Bernard, pyogenic granuloma is a "Benign, Acquired, Vascular, Neoplasm".[17] Cawson *et al*. stated pyogenic granuloma as vascular proliferation and do not exemplify a stage in the establishment of fibrous nodules or entirely inflamed fibrous nodules. They observed that like pyogenic granulomas in nonpregnant women, pregnancy tumor may exhibit lowest or no inflammation, but the proliferation of vascular tissue is sometimes very active so as to recommend a neoplasm. However, nature is benign.[18] Davies *et al*. observed inclusion bodies in the fibroblasts reminiscent of disarranged protein metabolism.[19]

The roles of angiogenic factors in pathogenesis of pyogenic granuloma in pregnancy are regulated by female sex hormones

Histologically, the prominent feature of pyogenic granuloma is angiogenesis within the connective tissue, which has been premeditated a hormone-associated lesion depends on clinical observations. Although inflammatory cytokines and angiogenic factors have been suggested to play roles in the pathogenesis of the lesion, their relationship to steroid hormones of female still remains to be expounded. The process of apoptosis is principal in limiting inflammation; it has been also suggested that steroid hormones could protect granuloma cells from apoptosis and consequently, lead to an overzealous inflammatory response.

In pregnancy, female steroid hormones may have binary effects on the pathogenesis of pyogenic granuloma. In inflamed tissue, the concentration of angiogenic factors increases by hormones with a reduction in apoptosis of granuloma cells to expand angiogenic effect.[20]

CLINICAL FEATURES

Oral pyogenic granuloma generally arises in the range of 4.5–93 years with the preeminent incidence in second and fifth decades and females are commonly affected than males.

Extraorally, the most common site was gingiva followed by lips, tongue, buccal mucosa, and hard plate, mucobuccal fold, and frenum. Intraorally, it appears from a sessile lesion to an elevated mass. Pyogenic granulomas mostly are soft in consistency, painless, and deep red to reddish-purple in color.[1]

RADIOGRAPHIC FEATURES

No significant radiographic features are seen. Although some author observed localized alveolar bone resumption in rare case of enormous long-standing gingival tumors.[4]

MICROSCOPIC FEATURES

The epithelium is parakeratotic or non-keratinized stratified squamous epithelium overlying the connective tissue stroma is seen. The chief bulk is formed by a lobulated or a non-lobulated bundle of angiomatous tissue. The lobulated lesions are imperturbable of solid endothelial proliferation or proliferation of endothelial-lined blood vessels. The quantity of bundle of collagen in the connective tissue of pyogenic granuloma is generally scanty. The surface ulceration can be seen, and in such ulcerated lesions, edema was a principal feature, and the lesion is infiltrated by lymphocytes plasma cells, and neutrophils.[1]

IMMUNOHISTOCHEMICAL INVESTIGATIONS

Sangueza and Requena *et al*. in their study observed that pyogenic granuloma lesions manifest antigen positivity related

with factor VIII in the endothelial cells lining substantial vessels, but demonstrate negativity in the cellular areas, whereas Ulex europaeus I lectin combines to endothelial cells in both cellular cumulativeness and large vessels. Increased proclamation of the vascular morphogenesis factors such as angiopoietin-1, angiopoietin-2, ephrinB2, and ephrinB4 and bFGF, Tie-2, anti-CD34, and anti-alpha smooth muscle actin antibodies. There is also a manifestation of analytical nitric oxide synthase, an enhanced indication of vascular endothelial growth factor, minimal apoptotic rate declaration of Bax/Bcl-2 proteins, and maximum assertion of phosphorylated mitogen-activated protein kinase. Polymerase chain reaction examinations for human herpesvirus and human papillomavirus have provided negative results.[21]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pyogenic granuloma includes fibroma, peripheral odontogenic fibroma, hemangioma, angiomatosis, angiosarcoma, non-Hodgkin's lymphoma conventional granulation tissue, hyperplastic gingival inflammation, peripheral giant cell granuloma, peripheral ossifying fibroma, and Kaposi's sarcoma.[1,8]

TREATMENT

Surgical excision is the therapeutics of choice. The following surgery of gingival lesions, curettage of underlying tissue is advocated.[22] Clinically, surgical excision should be given with 2 mm margins at its periphery and to a distance inward to the periosteum or the etiologic agent. Any calculus, foreign body, or impaired restoration should be removed as embodied of the excision.[23]

RECURRENCE RATE

The recurrence rate is 15.8% after conservative excision reported by Bhaskar and Jacoway.[6] Vilmann *et al*. stated that the cases of gingiva show a much greater recurrence rate than lesions from other mucosal sites of the oral cavity. The lesion lacks infiltrative or potential of malignancy.[24] According to Sapp *et al*. pyogenic granuloma have a considerably high rate of recurrence after normal surgical excision. In case of pregnancy, recurrence is common. In extragenital sites recurrence following surgery is uncommon.[25]

DISCUSSION

In the oral cavity, the pyogenic granuloma is kind of an inflammatory hyperplasia. The histopathological examination should be done properly of all submitted excised lesion to rule out more significant diseases in view of primary or metastatic malignancies may present as pyogenic granulomas. The injection of intralesional corticosteroids for frequently recurrences appears questionable since substantial documentation considering this option is lacking. The laser 15 is very critical, commonly requires no anesthesia, and fabricates excellent cosmetic results. Consequently, laser therapy may provide more assurance in recurrent/multiple lesions but needs further clinical trials. The higher occurrence of pyogenic granuloma in a pregnant woman (Granular gravidarum) permits a thorough examination of the oral cavity.[26]

CONCLUSION

Pyogenic granuloma or granuloma pyogenicum is a well-known benign, nonneoplastic vascular lesion of the oral cavity. The maxillary gingival is the most affected site, and in case of pregnancy proper diagnosis, prevention, management, and treatment of the lesion is predominant. Despite various treatment options, recurrence is frequent, and in few cases, re-excision may be compulsory. The adoption of deterrent methods during pregnancy, such as use of soft tissue brush, maintenance of better oral hygiene will reduce the risk of pregnancy tumor. The patient follow-up is important in preventing the recurrence of pyogenic granuloma.[26]

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