

## REVIEW ARTICLE

# Oral pyogenic granuloma: Various concepts of etiopathogenesis

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**ABSTRACT**

Pyogenic granuloma or granuloma pyogenicum is a well-known oral lesion. The name pyogenic granuloma is a misnomer since the condition is not associated with pus and does not represent a granuloma histologically. Pyogenic granuloma of the oral cavity is known to involve the gingiva commonly. Extralingually, it can occur on the lips, tongue, buccal mucosa, palate, and the like. A history of trauma is common in such sites. The etiology of the lesion is not known, though it was originally believed to be a botryomycotic infection. It is theorized that pyogenic granuloma possibly originates as a response of tissues to minor trauma and/or chronic irritation, thus opening a pathway for invasion of nonspecific microorganisms, although microorganisms are seldom demonstrated within the lesion. Pathogenesis of pyogenic granuloma is still debatable. Medline and PubMed databases were searched under the following key terms: Pathogenesis of oral pyogenic granuloma, pyogenic granuloma, and oral pyogenic granuloma. This search was limited to articles on human/animal studies which were published in English language. After reviewing the searched articles, the relevant articles were selected for the present review. Through this article, we have tried to summarize and present all the concepts of pathogenesis related to this most common and most mysterious oral lesion.

**Key words:** Etiopathogenesis, oral, pyogenic granuloma

## INTRODUCTION

Soft tissue enlargements of the oral cavity often present a diagnostic challenge because a diverse group of pathologic processes can produce such lesions. An enlargement may represent a variation of normal anatomic structures, inflammation, cysts, developmental anomalies, and neoplasm. Within these lesions is a group of reactive hyperplasias, which develop in response to a chronic, recurring tissue injury that stimulates an exuberant or excessive tissue repair response. Pyogenic granuloma is of the most common entities responsible for causing soft tissue enlargements.

Occurrence of pyogenic granuloma in man was first described in 1897 by Poncet and Dor. At that time, it was called botryomycosis hominis. Pyogenic granuloma has been referred

to by a variety of other names such as granuloma pediculatum benignum, benign vascular tumor, pregnancy tumor, vascular epulis, Crocker and Hartzell's disease. It was given its present name by Crocker in 1903.<sup>[1]</sup> However, some researchers believe that Hartzell in 1904 introduced the term "pyogenic granuloma" that is widely used in the literature, although, it does not express accurately the clinical or histopathologic features.<sup>[2]</sup>

Angelopoulos AP proposed the term "hemangiomas granuloma" that accurately expresses the histopathologic picture (hemangioma like) and the inflammatory nature (granuloma) of oral pyogenic granuloma.<sup>[2]</sup> Cawson *et al.* suggested that since the blood vessels are so numerous in oral pyogenic granuloma, alternative term for pyogenic granuloma is granuloma telangiectacticum.<sup>[3]</sup>

Pyogenic granuloma is well known in dermatology as skin is a common site for this lesion. The term lobular capillary hemangioma is increasingly gaining favor in the dermatologic literature.<sup>[3]</sup>

## INCIDENCE AND PREVALENCE

Bhaskar *et al.* in their study observed that oral pyogenic granuloma comprised about 1.85% of all oral pathoses,

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other than caries and gingivitis treated at US Army Institute of Dental Research.<sup>[1]</sup> Daley *et al.* found that pregnancy epulides accounted for only 42 of the 757 epulides of all types.<sup>[4]</sup> According to Cawson *et al.* oral pyogenic granuloma is relatively common. It represents 0.5% of all skin nodules in children. The pregnancy tumor variant of pyogenic granuloma occurs in up to 5% of pregnancies.<sup>[3]</sup> Esmeili *et al.* in their review stated that hyperplastic reactive lesions represent as a group the most common oral lesions, excluding caries, periodontal, and periapical inflammatory disease. In this group, the second most common group is represented by hyperplastic reactive gingival/alveolar lesions, including inflammatory gingival hyperplasia, oral pyogenic granuloma, peripheral giant-cell lesion and peripheral cemento-ossifying fibroma.<sup>[5]</sup> Peralles *et al.* in their clinicopathologic study conducted on gingival and alveolar hyperplastic reactive lesions observed that inflammatory gingival hyperplasia and oral pyogenic granuloma were the most common diagnosis.<sup>[6]</sup> In an analysis of 244 cases of gingival lesions in south Indian population, Shamim *et al.* found that nonneoplastic lesions accounted for 75.5% of cases with oral pyogenic granuloma being most frequent lesion, accounting for 52.71% cases.<sup>[7]</sup>

## ETIOPATHOGENESIS

Some authors regard pyogenic granuloma as an “infectious” entity. Kerr has reported staphylococci and botryomycosis, foreign bodies, and localization of infection in walls of blood vessel as contributing factors in the development of the lesion.<sup>[8]</sup> Bhaskar *et al.* observed that bacterial stains have demonstrated the presence of gram positive and gram negative bacilli in oral pyogenic granuloma. But they also suggested that as these organisms were more common in ulcerated than in non ulcerated lesions and more common near surface than in deeper aspects that suggest that these organisms may have been contaminants from oral flora.<sup>[1]</sup> According to Shafer *et al.*, oral pyogenic granuloma arises as a result of infection by either staphylococci or streptococci, partially because it was shown that these microorganisms could produce colonies with fungus-like characteristics. They also stated that it is now generally agreed that oral pyogenic granuloma arises as a result of some minor trauma to the tissues that provide a pathway for invasion of nonspecific types of microorganisms. The tissues respond in a characteristic manner to these organisms of low virulence by the overzealous proliferation of a vascular type of connective tissue. They explain the mechanism by suggesting that tissue response reiterates the well-known biologic principle that any irritant applied to living tissue may act either as a stimulus or as a destructive agent or both. If many cells are present in a small volume of tissue and there is a relative reduction of blood flow through the area as in inflammation, the concentration of the stimulating substance will be high and growth will be stimulated. As differentiation and maturation are attained, the cells become widely separated and the concentration of the substance falls and little growth occurs. In this type of inflammation that results in the formation of

oral pyogenic granuloma, destruction of fixed tissue cells is slight but stimulus to proliferation of vascular endothelium persists and exerts its influence over a long period of time.<sup>[9]</sup> Reichart *et al.* stated that granulation tissue in oral pyogenic granuloma may become contaminated by flora of oral cavity and its surface may often become covered by fibrin which may mimic pus. However, still suppuration is not a characteristic of oral pyogenic granuloma to support infectious origin.<sup>[10]</sup>

Some investigators consider pyogenic granuloma as a “reactive” or “reparative” tumor process. Regezi *et al.* suggest that pyogenic granuloma represents an exuberant connective tissue proliferation to a known stimulus or injury like calculus or foreign material within the gingival crevice.<sup>[11]</sup> Several “etiologic factors” such as trauma, injury to a primary tooth, chronic irritation, hormones, drugs, gingival inflammation, preexisting vascular lesions, chronic irritation due to exfoliation of primary teeth, eruption of permanent teeth, defective fillings in the region of tumor, food impaction, total periodontitis, toothbrush trauma, etc. have been suggested as etiological factors where patients presented with these findings.<sup>[12]</sup>

Murata *et al.* 1997 in their study observed that after any trauma, the key to wound healing is the formation of granulation tissue and this includes the migration of inflammatory cells, migration and proliferation of vascular endothelial cells and fibroblasts and synthesis of extracellular matrix. Such processes of wound healing seem to be controlled by various kinds of cytokines. Out of these cytokines – role of growth factors, particularly bFGF – a heparin binding angiogenic protein, has been found to be highly mitogenic for capillary endothelial cells and to induce angiogenesis. They studied bFGF immunolocalisation in gingiva and oral pyogenic granuloma at its various stages of progression. They suggested that maximum amounts of bFGF are synthesized and released from some macrophages and mast cells into extracellular matrix during neovascularisation of the granulation tissue.<sup>[13]</sup>

Trauma has also been implicated in etiopathogenesis of multiple and satellite oral pyogenic granuloma, although, exact etiopathogenesis that whether it occurs following treatment or de novo, is not clearly understood. But various theories have been proposed. Ainamo suggested that trauma can cause release of various endogenous substances including angiogenic factors from the tumor cells and it may also cause disturbances in the vascular system of the affected area. As there is a site predilection for labial gingiva in the anterior region of the oral vestibule, some authors have postulated that habitual tooth brushing may also be considered as a significant cause of microtrauma and irritation to the gingiva.<sup>[14]</sup>

Yung, Richardson, and Krotochvil suggested hormonal influence on the basis of the observation that pregnancy tumor that occurs in the pregnant women also arises from

the gingiva and has the same microscopic appearance.<sup>[15]</sup> Hosseini *et al.* stated that there are clinical observations that gingiva may be enlarged during pregnancy and may atrophy during menopause. On basis of these observations, gingiva can be regarded as another “target organ” for direct action of estrogen and progesterone.<sup>[16]</sup> In Whitaker *et al.*, study, it was suggested that the quantity of estrogen or progesterone receptors in oral pyogenic granuloma is not the determining factor in its pathogenesis of. Rather, such a role could be attributed to the levels of circulating hormones. The levels of estrogen and progesterone are markedly elevated in pregnancy and could therefore exert a greater effect on the endothelium of oral pyogenic granuloma.<sup>[17]</sup> Ojanotak-Harri *et al.* (1991) stated that it has been shown that pregnancy inhibits the migration of inflammatory cells and fibroblasts. Hence, it seems that pregnancy regulates both the metabolism of progesterone and also influences migration of inflammatory cells in tissue. The level of progesterone available in the active form and “dysfunction” of the inflammatory cells may have a role in development of pregnancy gingivitis and granuloma formation. They suggested co-existence of the two factors prevent acute type of tissue reaction (which keep tissues clinically healthy) to plaque, but allows an increased chronic reaction resulting clinically in an exaggerated appearance of inflammation.<sup>[18]</sup> But, Bhaskar and Jacoway observed that pyogenic granuloma occurs almost as often in males as females; for this reason, a hormonal basis is doubtful.<sup>[1]</sup>

Regezi *et al.* (2003) stated that oral pyogenic granuloma shows obvious histopathological findings of prominent capillary growth in hyperplastic granulation tissue suggesting a strong activity of angiogenesis.<sup>[10]</sup> Kuo, Ying, and Ming stated the role of two angiogenesis enhancers, that is, VEGF and bFGF, and two angiogenesis inhibitors, that is, TSP-1 and angiostatin in mechanism for angiogenesis. Vascular morphogenesis factors Tie-2, angiopoietin-1, angiopoietin-2, ephrinB2, and ephrinB4 were found upregulated in pyogenic granuloma compared to healthy gingiva.<sup>[19]</sup> The importance of decorin, vascular endothelial growth factor, basic fibroblast growth factor, or connective tissue growth factor particularly in angiogenesis associated with a profound inflammation has been proved by some investigators.<sup>[12]</sup>

Kelley and Bernard regard pyogenic granuloma as a “Benign, Acquired, Vascular, Neoplasm”.<sup>[20]</sup> According to Cawson *et al.*, pyogenic granuloma represents vascular proliferations and do not represent a stage in the development of fibrous nodules or merely inflamed fibrous nodules. Regarding the pregnancy pyogenic granuloma, they state that like pyogenic granulomas in a nonpregnant women, pregnancy tumor may show minimal or no inflammation, but vascular proliferation is occasionally very active so as to suggest a neoplasm. Nevertheless, the behavior is benign.<sup>[21]</sup> Davies *et al.*, found inclusion bodies in the fibroblasts suggestive of disordered protein metabolism.<sup>[22]</sup>

## CLINICAL FEATURES

Oral pyogenic granuloma occurs over a wide age range of 4.5 to 93 years with highest incidence in second and fifth decades and females are slightly more affected than males. Gingiva was the predominant site followed by lips, tongue, buccal mucosa, and hard plate. Other sites were the cheek, lips, tongue, palate, mucobuccal fold, and frenum. Intraorally, it can present with a wide array of clinical appearances, ranging from a sessile lesion to an elevated mass. Pyogenic granulomas generally are soft, painless, and deep red to reddish-purple in color.<sup>[1]</sup>

## RADIOGRAPHIC FEATURES

Radiographic findings are absent in pyogenic granuloma. However, Angelopoulos AP in his review observed that localized alveolar bone resorption in rare instances of large and long standing gingival tumors can be seen.<sup>[2]</sup>

## MICROSCOPIC FEATURES

Pyogenic granuloma is partly or completely covered by parakeratotic or non-keratinized stratified squamous epithelium. Major bulk of the lesion is formed by a lobulated or a non lobulated mass of angiomatous tissue. Usually, lobulated lesions are composed of solid endothelial proliferation or proliferation of capillary sized blood vessels. The amount of collagen in the connective tissue of pyogenic granuloma is usually sparse. Surface can be ulcerated and in such ulcerated lesions, edema was a prominent feature and the lesion is infiltrated by plasma cells, lymphocytes and neutrophils.<sup>[1]</sup>

## IMMUNOHISTOCHEMICAL INVESTIGATIONS

Sanguenza and Requena stated that pyogenic granuloma lesions express factor VIII – related antigen positivity in the endothelial cells lining large vessels, but are negative in the cellular areas, whereas Ulex europaeus I lectin binds to endothelial cells in both large vessels and cellular aggregates. Enhanced expression of the bFGF, Tie-2, anti-CD34 and anti alpha SMA antibodies, and vascular morphogenesis factors such as angiopoietin-1, angiopoietin-2, ephrinB2, and ephrinB4. There is also expression of inducible nitric oxide synthase, increased expression of vascular endothelial growth factor, low apoptotic rate expression of Bax/Bcl-2 proteins and strong expression of phosphorylated mitogen activated protein kinase. Polymerase chain reaction investigations for human papilloma virus and human herpes virus type have yielded negative results.<sup>[23]</sup>

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis of pyogenic granuloma includes peripheral giant cell granuloma, peripheral ossifying fibroma, fibroma, peripheral odontogenic fibroma, hemangioma, conventional granulation tissue, hyperplastic gingival inflammation, Kaposi’s sarcoma, bacillary angiomatosis, angiosarcoma, and nonHodgkin’s lymphoma.<sup>[10,24]</sup>

## TREATMENT

Surgical excision is the treatment of choice.<sup>[10]</sup> After surgical excision of gingival lesions, curettage of underlying tissue is recommended.<sup>[25]</sup> Excision with 2 mm margins at its clinical periphery and to a depth to the periosteum or to the causative agent. Any foreign body, calculus, or defective restoration should be removed as part of the excision.<sup>[26]</sup>

## RECURRENCE

Bhaskar and Jacoway has reported recurrence rate of 15.8% after conservative excision.<sup>[1]</sup> Vilmann *et al.* observed that gingival cases show a much higher recurrence rate than lesions from other oral mucosal sites. Pyogenic granuloma lacks infiltrative or malignant potential.<sup>[27]</sup> Sapp *et al.* stated that oral pyogenic granulomas have a relatively high rate of recurrence after simple excision. If patient is pregnant, recurrence is common. Recurrence after surgery in extragingival sites is uncommon.<sup>[28]</sup> Lawoyin *et al.* observed no recurrence in cases treated by surgical excision.<sup>[29]</sup> Al-Khateeb *et al.* (2003) observed a recurrence rate of 5.8% in his study.<sup>[30]</sup>

## CONCLUSION

Pyogenic granuloma or granuloma pyogenicum is a well-known oral lesion. However, etiopathogenesis of oral pyogenic granuloma is still debatable. This article thus attempted to review the main theories of etiopathogenesis and the basis for such observations.

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