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Pyogenic Granuloma: A Review

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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. Extragingivally, 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. Pathogenesis of pyogenic granuloma is still debatable. 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.

Keywords: oral pyogenic granuloma, recurrence, surgical excision.

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.[1] 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.[2]

It is now universally agreed that this lesion is formed as a result of an exaggerated localized connective tissue reaction to a minor injury or any underlying irritation. The irritating factor can be calculus, poor oral hygiene, nonspecific infection, over hanging restorations, cheek biting, etc., Due to this irritation, the underlying fibrovascular connective tissue becomes hyperplastic, and there is a proliferation of granulation tissue which leads to the formation of a PG.[3] Factors such as inducible nitric oxide synthase, vascular endothelial growth factor, or connective tissue growth factor are known to be involved in angiogenesis and rapid growth of PG.[4]

Angelopoulos[5] histologically described it as "hemangiomatous granuloma" due to the presence of numerous blood vessels and the inflammatory nature of the lesion. Cawson et al.,[6] in dermatologic literature, have described it as "granuloma telangiectacticum" due to the presence of numerous blood vessels seen in histological sections.

Because of the high incidence of the oral pyogenic granuloma especially in pregnant women and the critical need for its proper diagnosis and management this review will consider the etiopathogenesis, clinical features, microscopic features, immunohistochemical investigations, differential diagnosis, treatment of this lesion.

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.[7]

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.[8]

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.[9]

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.[10]

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.[1]

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.[11]

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.[12]

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.[13]

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.[14]

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 preventacute 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.[15]

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.[16]

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 (basic fibroblast growth factor) – 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.[17]

Kuo, Ying, and Ming stated the role of two angiogenesis enhancers, that is, VEGF (vascular endothelial growth factor) and bFGF, and two angiogenesis inhibitors, that is, TSP-1(thrombospndin-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.[18]

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.[19]

Davies et al., found inclusion bodies in the fibroblasts suggestive of disordered protein metabolism.[20]

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.[1] The size varies in diameter from a few millimeters to several centimeters.

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.[2]

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.[1]

Immunohistochemical Investigations

Sangueza 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 morphogenesisfactors 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.[21]

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.[10,22]

Treatment

Surgical excision is the treatment of choice.[10] After surgical excision of gingival lesions, curettage of underlying tissue is recommended.[23] 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.[24]

Recurrence

Bhaskar and Jacoway has reported recurrence rate of 15.8% after conservative excision.[1] 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.[25] 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.[26] Lawoyin et al. observed no recurrence in cases treated by surgical excision.[27] Al-Khateeb et al.

(2003) observed a recurrence rate of 5.8% in his study.[28]

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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