

# Oral Pyogenic Granuloma: An Insight into its Etiopathogenesis and Treatment Modalities

Bijo Alexander<sup>1</sup>, Deepa Joseph<sup>2</sup>

<sup>1</sup>Noorul Islam College Of Dental Sciences, Trivandrum, Kerala, India

<sup>2</sup>VPS Lakeshore Hospital and Research Centre, Kochi, Kerala, India.

**Abstract:** *Exophytic gingival lesions are frequently seen in the oral cavity. Pyogenic granuloma, an inflammatory hyperplasia of the oral cavity is commonly seen in the gingiva though other areas like lips, tongue, buccal mucosa and palate are also affected. The term pyogenic granuloma is a misnomer since the condition is not associated with pus and shows no histologic evidence of granuloma. Current concepts point to low grade local irritation, trauma and hormonal influences as possible etiologies. Pyogenic granuloma usually occur in young females predominantly in second decade due to effect of female hormones on the vasculature. The lesion is usually pink to red to purple in color. It is a smooth or lobulated exophytic lesion on a sessile or pedunculated base which is occasionally hemorrhagic. Excision was the treatment of choice though currently lasers, cryosurgery and sodium tetradecyl sclerotherapy are used. Due to high frequency of this lesion in oral cavity during pregnancy, a review of the current etiopathogenesis and treatment protocols are discussed.*

**Keywords:** Exophytic, inflammatory hyperplasia, Pyogenic granuloma, Pregnancy

## 1. Introduction

Soft tissue enlargements of oral cavity may represent variation of normal anatomical structures, cysts, developmental anomalies, inflammation and neoplasms. Reactive hyperplasias can develop in response to chronic recurrent tissue injury that stimulates an exuberant tissue response.

Pyogenic granuloma is one of the most common soft tissue enlargements seen intraorally. The first description of pyogenic granuloma was made by Hullihen in 1844 [1]. The term pyogenic granuloma or granuloma pyogenicum was introduced by Hartzell in 1904 [2]. It develops in up to 5% pregnancies and hence the term pregnancy tumor and granuloma gravidum are commonly used [3].

The early lesions are usually painless but established lesions exhibit reddish to pinkish hue due to hypervascularity and during healing stages a whitish to pinkish hue is seen. Histologically two types of pyogenic granuloma are seen; the lobular capillary hemangioma (LCH type) and the non lobular capillary hemangioma type (non LCH type) [4].

Since pyogenic granuloma has a higher incidence in the oral cavity in pregnant women this review aims to address the etiology, clinical, histological features and treatment protocols for this condition.

### Pyogenic granuloma-etio-pathogenesis

Various etiologies have been proposed for pyogenic granuloma including infections, reactive tumor like lesion to various stimuli, hormones, drugs and trauma. Initially pyogenic granuloma was considered an infectious lesion. Kerr [5] in 1951 reported that botryomycosis and staphylococci, foreign bodies and localization of infection in vessel walls as contributing to development of the lesion.

Bhaskar and Jacoway [6] in their detailed study of four pyogenic granuloma patients in 1966 reported presence of both gram positive and negative bacilli in pyogenic granuloma. They were however unsure if these bacteria were oral flora contaminants or specific causative agents of pyogenic granuloma. The present concept strongly disagrees that pyogenic granuloma is an infectious lesion. Since there is no pus formation and granuloma formation the term pyogenic granuloma is a misnomer. There was no evidence confirming the presence of infectious organisms in larger group of pyogenic granulomas [7].

Trauma has been implicated in etiopathogenesis of pyogenic granuloma. In extragingival pyogenic granulomas, trauma is said to play an important role. Poor oral hygiene, injury to primary teeth [8], aberrant tooth development [9] and even habitual tooth brushing [10] has been shown to cause trauma and irritation leading to pyogenic granuloma formation.

The role of angiogenesis in development of pyogenic granuloma has been well documented. Two angiogenic enhancers VEGF and bFGF and two angiogenesis inhibitors TSP-1 and Angiostatin play a key role in angiogenesis. Compared to healthy gingiva, vascular morphogenesis factors angiopoietin-1, angiopoietin-2, ephrin B2, ephrin B4 and Tie-2 are enhanced in pyogenic granuloma [11].

Davies [12] (1980) in his study in pyogenic granuloma showed evidence of increased fibroblastic synthetic activity with presence of inclusion bodies in the endothelial cells suggestive of faulty protein metabolism. They suggested that pyogenic granuloma constitutes a lesion produced by primitive tissue organizer resulting from gene depression in the papillary fibroblasts as a result of c-type virus infection. Nakumara [13] suggested that low apoptotic rate in pyogenic granuloma is closely related to its characteristic rapid growth and is regulated by Bcl-2 family proteins.

Cyclosporine an immunosuppressant drug has a proven role in pyogenic granuloma formation. Bachmeyer et al [14] reports about a voluminous pyogenic granuloma on the tongue of a 5 year old girl treated with allogeneic bone marrow transplantation for aplastic anemia. Kanda et al [15] reports about a patient developing pyogenic granuloma on the tongue after allogeneic bone marrow transplantation done for multiple myeloma. Fowler et al [16] reports about a pyogenic granuloma associated with a routine GTR using a non resorbable membrane and allograft.

### **Epidemiology**

Even though pyogenic granuloma can occur at any age it is most prevalent in children adolescents and pregnant women. In the pediatric age group the mean age of onset is 6.7 years with 42% of cases occurring before 5 years. In the adult population peak occurrence is in the third decade of life. Oral mucosal pyogenic granulomas have a female to male ratio of 2:1 [17]. Pyogenic granuloma of gingiva is seen in 2 to 5% of pregnancies in the second or third trimester when it is referred to as pregnancy tumor, granuloma gravidum or epulis gravidum [18].

### **Clinical features**

The gingiva is the most commonly affected followed by buccal mucosa, tongue and lips. Majority of pyogenic granuloma are found in the marginal gingiva with only 15% occurring in alveolar part [19]. Lesions are more common in maxillary gingiva than in the mandibular gingiva. Anterior areas are more common than posterior areas and the facial aspect more than lingual aspect [20].

Pyogenic granuloma of the oral cavity appears as elevated, smooth or exophytic, sessile or pedunculated growth covered with red hemorrhagic and compressible erythematous papules that appear lobulated and warty showing ulcerations and covered by yellow fibrinous membrane. Color may vary from pink to red to purple depending on vascularity of lesion. Size varies from a few millimetres to centimetres and is usually slow growing, asymptomatic painless growth but at times it grows rapidly [21]. Bone loss is seen in some rare cases [22].

### **Histopathology**

Two histologic variants of pyogenic granuloma are seen. The first type is lobular capillary hemangioma (LCH type) and the other is non LCH type. The first type has proliferating blood vessels in lobular aggregates with no specific edematous changes. Non-LCH type contains a greater number of blood vessels with small luminal diameter than does central area of LCH type. In central areas of non-LCH pyogenic granuloma a greater number of vessels with perivascular mesenchymal cells not reactive to alpha smooth muscle actin (SMA) is detected compared with lobular areas of LCH type.

Most of the oral pyogenic granulomas are of LCH type. Sato investigated the relationship of human endothelial receptor tyrosine kinase Tie-2 and its expression in the lobular capillary hemorrhage LCH type pyogenic granuloma. They noted the expression of Tie-2 in ovoid cells with presence of alpha SMA antibodies played an important role in development and progression of LCH type pyogenic

granuloma. Yuan et al suggested the etiology of pyogenic granuloma to be due to an imbalance between the angiogenesis enhancers, vascular endothelial growth factors (VEGF), basic fibroblastic growth factor (bFGF) and angiotensin inhibitors angiotensin and thrombospondin 1.

Polymorphs as well as chronic inflammatory cells are consistently present throughout edematous stroma with microabscess formation. Fibroblasts are plump with high mitotic activity.

The natural history of the lesion follows three distinct phases. In the cellular phase the lobules are compact and cellular with little lumen formation. In the capillary phase the lobules become frankly vascular with abundant intraluminal blood vessels. In the involuntary phase, there is tendency for intra and perilobular fibrosis with increased vascular differentiation.

**Pregnancy associated pyogenic granuloma** 5% of pregnancies can develop pyogenic granulomas. The hormonal imbalance coupled with poor oral hygiene, gingival inflammation and bacterial plaque heightens the tendency of gingiva to develop pyogenic granuloma. Pregnancy gingivitis can show a tendency towards localized hyperplasia called pregnancy granuloma which is seen in the first trimester. Plaque can induce catarrhal inflammation in the early stages of pregnancy which leads to hyperplastic gingivitis during last months leading to pyogenic granuloma. Lesions treated during pregnancy often reappear due to incomplete excision or poor oral hygiene [25].

Several molecular mechanisms have been proposed for development of pyogenic granuloma during pregnancy. Profound upheaval of hormones like estrogen and progesterone during pregnancy is associated with changes in function and structure of blood and lymph microvasculature of skin and mucosa. Estrogen accelerates wound healing by stimulating Nerve Growth Factor (NGF). Granulation tissue formation is caused by basic fibroblast growth factor (bFGF), Transforming growth factor beta 1 (TGF-β1) in fibroblast [26]. Progesterone functions as an immunosuppressant in gingival tissues of pregnant women preventing rapid acute inflammatory reaction against plaque but allowing increased chronic tissue reaction resulting clinically in an exaggerated inflammatory appearance [27]. Yuan et al proposed that pyogenic granuloma expressed significantly more VEGF and bFGF than healthy gingiva and periodontium [11].

The regression of pyogenic granuloma after parturition is because in the absence of VEGF, Angiopoietin-2 (Ang-2) causes blood vessels to regress. The protein level of Ang-2 was highest in granulomas in pregnancy followed by those after parturition and child birth. VEGF is also high in pregnancy granuloma and absent after parturition. After parturition there are more apoptotic cells and less Ang-2 than in pregnancy. Hence VEGF alone or in combination with Ang-2 could protect microvessels from apoptosis while Ang-2 alone has no effect [28].

### Differential diagnosis

Proper diagnosis of an oral cavity mass is integral to the management protocols. Biopsy is a very important tool in this regard. Differential diagnosis of pyogenic granuloma includes metastatic cancer, hemangioma, pregnancy tumor, peripheral ossifying fibroma and peripheral giant cell granuloma, conventional granulation tissue, hyperplastic gingival inflammation, angiosarcoma, Kaposi's sarcoma, bacillary angiomatosis and Non-Hodgkin's lymphoma.

Metastatic oral tumor though uncommon is mostly seen in the attached gingiva followed by the tongue. Distant metastasis is the most common etiology and the histopathology should resemble the original tumor. Study by Hirshberg in 157 cases showed that 54% of cases diagnosed were in the 5<sup>th</sup> to 7<sup>th</sup> decade which is uncommon for pyogenic granuloma [29].

Hemangioma, a developmental disorder may often be clinically indistinguishable from pyogenic granuloma. Most hemangiomas are multinodular and bluish red and are commonly seen in the tongue. Compared to pyogenic granuloma, hemangioma has more plump, histiocytoid epithelial cell proliferation without an acute inflammatory cell infiltrate. Immunohistochemical evaluation of VEGF-C1 showed no statistically significant difference in angiogenesis index between pyogenic granuloma and hemangioma [30].

Pregnancy tumor is another differential diagnosis of pyogenic granuloma. Increased prevalence of epulis during pregnancy and tendency to shrink post partum shows that female hormones have a definitive etiology. Pyogenic granuloma is usually confined to the interdental papilla. Daley et al. [31] indicates that pregnancy tumor diagnosis is clinically valid in describing a pyogenic granuloma in pregnancy because it describes a distinct lesion not on a histological basis but on etiology, biologic behavior and treatment protocol.

Peripheral giant cell granuloma is an exophytic lesion seen almost exclusively on the gingiva. It has a bluish purple hue compared to bright red of pyogenic granuloma. Peripheral giant cell granuloma exhibits multinucleated giant cells histologically which is absent in pyogenic granuloma [32].

Even though pyogenic granuloma and conventional granulation tissue exhibit close relationship, pyogenic granuloma exhibits rapid growth, multiple occurrence and frequent recurrence which is absent in granulation tissue [33].

### 2. Treatment

Surgical excisional biopsy is the most commonly used treatment modality even though incision biopsy is done in larger lesions. If lesion is small, painless and devoid of bleeding, clinical observation and followup is useful [34]. The excision should extend deep to the periosteum and teeth should be thoroughly scaled [19].

Laser therapy using continuous and pulsed CO<sub>2</sub> and Nd:YAG systems have the advantage of being less invasive and produce only minimal post operative pain. Rapid healing

can be observed within a few days and as blood vessels are sealed, there is minimal necessity for post surgical dressing. Haemostasis and coagulation improves. It also depolarizes nerves thus reducing postoperative pain. Postoperative discomfort, edema, scarring and shrinkage are minimized with its use [35]. Meffert et al. [36] used flash pump pulse dye laser on a mass of granulation tissue and concluded that previously resolute granulation tissue responded well to the series of treatments with pulsed dye laser.

Cryosurgery is believed to be a good alternative to surgery because of the humidity and smoothness of the oral mucosa and shows good esthetic results [37].

Injection of absolute alcohol in patients with recurrence post cryotherapy was attempted by Ichimiya et al. [38] and concluded that this therapy was less invasive than surgical excision. Use of sodium tetradecyl sulfate (STS) sclerotherapy showed good results because of its simplicity and lack of scarring though multiple sessions were required. STS causes endothelial cell damage and obliterates vessel lumen. [39] Intralesional corticosteroid therapy was useful for highly recurrent lesions [40].

Maintenance of good oral hygiene and regular followup are important in pregnancy. Surgical and periodontal treatment should be performed during the second trimester. Since recurrence of pregnancy tumor is very common it is ideal to wait till parturition before completing treatment. Recurrence in pyogenic granuloma can be due to incomplete excision, injury to area or failure to remove underlying causes. Tavia (1992) demonstrated 16% recurrences in pyogenic granuloma with the gingiva most affected.

### 3. Conclusion

Even though pyogenic granuloma is a non-neoplastic lesion its association with pregnancy makes it important to diagnose, prevent, manage and treat the lesion at the earliest.

### 4. Source of support: None

### 5. Conflict of interest: Nil

### References

- [1] Hullihen SP. Case of aneurism by anastomosis of the superior maxillae. Am. J. Den. Sc. 4, 160-162, 1844
- [2] Hartzell MB. Granuloma pyogenicum. J. Cutan Dis Syph, 520-55, 1904.
- [3] Mubeen K, Vijayalakshmi KR, Abhishek RP. Oral pyogenic granuloma with mandible involvement: An unusual presentation. J. Dent Oral Hyg 3:6-9, 2011.
- [4] Epivatianos A, Antoniadou D, Zaraboukas T et al. Pyogenic Granuloma of the oral cavity. Comparative study of its clinicopathological and immunohistochemical features. Pathol Int 55, 391-397, 2005.
- [5] Ken DA. Granuloma pyogenicum. Oral Surg Oral Med Oral Pathol 4(2):158-176, Feb 1951.
- [6] Bhaskar SN and Jacoway JA. Pyogenic granuloma - clinical features, incidence, histology and result of

- treatment: report of 242 cases. *J Oral Surgery*. Vol 24(5):391-398, 1966.
- [7] Janier M. Infections and angiomatous cutaneous lesions. *J. Mal Vasc* 24, 135-138, 1999.
  - [8] Aguiló LPyogenic granuloma subsequent to injury of a primary tooth. A case report. *Int J Pediatr Dent* 122, 438-441, 2002.
  - [9] Milano M, Flitz CM, Bennett J. Pyogenic granuloma associated with aberrant tooth development. *Tex Dent J*, 118, 166-172, 2001.
  - [10] Ainamo J. The effect of habitual tooth cleaning on the occurrence of periodontal disease and caries. *Suom Hammaslaak Toim*; 67(1); 63-70, 1971.
  - [11] Yuan K, Jin YT, Lin MT. Expression of Tie-2, angiopoietin-1, angiopoietin-2, ephrin B2, ephrin B4 in pyogenic granuloma of human gingiva implicates their role in inflammatory angiogenesis. *J. Periodontal Res* 35: 165-17, 2000.
  - [12] Davies MG, Barton SP, Atai F, Marks R. *J American Academy of Dermatology* 2(2); 132-142, 1980
  - [13] Nakumara T. Apoptosis and expression of Bax/Bcl-2 proteins in pyogenic granuloma: a comparative study with granulation tissue and capillary hemangioma. *J Cutaneous pathology*, Vol 27(8); 400-405, 2001.
  - [14] Bachmeyer C, Devergie A, Mansouri S, Dubertret L, Arachting S. Pyogenic granuloma of the tongue in chronic graft versus host disease. *Annales de dermatologie et de venerologie*. 123(9), 552-554, 1996.
  - [15] Kanda Y, Arai C, et al. Pyogenic granuloma of the tongue after allogeneic bone marrow transplantation for multiple myeloma. *Leukemia and Lymphoma*. Vol 37(3-4): 445-449, 2000.
  - [16] Fowler EB, Cuenin MF et al. Pyogenic granuloma associated with guided tissue regeneration: a case report. *J. Periodontol* Oct 67(10): 1011-5, 1996.
  - [17] Lin RL, Janniger CK. Pyogenic Granuloma. *Cutis* 74: 229-233, 2004.
  - [18] Scheinfeld NS (2008). Pyogenic granuloma. *Skin med* 7: 89-92, 2004.
  - [19] Jafarzadeh H, Sanatkhan M, Mohtasham N. Oral pyogenic granuloma: a review. *J. Oral Sc* 2006; 48(4): 167-175, 2006.
  - [20] Vilman A, Vilman P, Vilman H. Pyogenic granuloma; Evaluation of oral conditions. *BJOMS Vol* 24(5): 376-82, 1986
  - [21] Shafer, Hine, Levy. Edited by Sivaparthasundaram Pyogenic granuloma, pg 201-203, 8<sup>th</sup> Edn,
  - [22] Goodman-Topper ED, Bimstein E. Pyogenic granuloma as a cause of bone loss in a twelve year old child: Report of a case. *ASDCJ. Dent Child* 61; 65-67, 1994.
  - [23] Mills SE, Cooper PH, Fechner RE. Lobular capillary hemangioma: the underlying lesion of pyogenic granuloma. A study of 73 cases from oral and nasal mucous membrane. *Am J Surg Pathol* 4, 470-79, 1980
  - [24] Sato H, Takeda Y, Satoh M. expression of endothelial receptor tyrosine kinase Tie-2 in lobular capillary hemangioma of the oral mucosa: An immunohistochemical study. *J. Oral Pathol Med*: 2002; 31: 432-438, 2002.
  - [25] Hentry F, Quatresoz P, Valverde-Lopez JC, Pierard GE. Blood vessel changes in pregnancy: a review. *Am J Clin Dermatol* 7, 65-69, 2006.
  - [26] Kara N, Wutanabe S. Regulatory roles of sex hormones in cutaneous biology and immunology. *J. Dermatol Sci* 38, 1-7, 2005.
  - [27] Ojanotko-Harri MP, Harri MP, Hurtia HM, Sewon LA. Altered tissue metabolism of progesterone in pregnancy gingivitis and granuloma. *J Clin Periodontol* 18, 262-266, 1991.
  - [28] Yuan K, Lin MT. The roles of vascular endothelial growth factor and angiopoietin-2 in the regression of pregnancy pyogenic granuloma. *Oral Dis* 10, 179-185, 2004.
  - [29] Hirshberg A, Leibovich P, Buchner A. Metastatic tumors to the oral mucosa-analysis of 157 cases. *J. Oral Pathol Med* 22, 385-390, 2005.
  - [30] Freitas TM, Miguel MC, Silveria EJ, Freitas RA, Galvao HC. Assessment of angiogenic markers in oral hemangiomas and pyogenic granulomas. *Exp Mol Pathol* 79, 79-85, 2005.
  - [31] Daley TD, Nartey NO, Wysocki GP. Pregnancy tumor: an analysis. *Oral Surg Oral Med Oral Pathol* 72, 196-199, 1991.
  - [32] Afsaneh Nekouei, Alireza Eshghi, Parisa Jafarnejadi and Zahra Enshaei A review and report of peripheral giant cell granuloma in a 4 year old child. Case reports in dentistry, Vol 2016, Article ID 7536304, 4 pages.
  - [33] Kapadia SB, Heffner DK. Pitfalls in histopathologic diagnosis of pyogenic granuloma. *Eur Arch Otorhinolaryngol* 249, 195-200, 1992.
  - [34] Sills ES, Zegarelli DJ, Hoschander MM, Strider WE. Clinical diagnosis and management of hormonally responsive oral pregnancy tumor (pyogenic granuloma). *J Reprod Med* 41, 467-470, 1996.
  - [35] Kirshner RE, Low DW. Treatment of pyogenic granuloma by shave excision and laser photocoagulation. *Plast Reconstr Surg* 104: 1346-69, 1999.
  - [36] Meffert JJ, Cagna DR, Meffert DM. Treatment of oral granulation tissue with the flash pump pulsed dye laser. *Dermatol Surg* 24, 845-848, 1998.
  - [37] Ishida CE, Ramos-e-Silva M. Cryosurgery in oral lesions. *Int J. Dermatol* 37, 283-285, 1998
  - [38] Ichimiya M, Yoshihawa Y, Hamamoto Y, Muto M Successful treatment of pyogenic granuloma with injection of absolute ethanol. *J. Dermatol* 31, 342-344, 2004.
  - [39] Moon SE, Hwang EJ, Cho KM. Treatment of pyogenic granuloma by sodium tetradecyl sulfate sclerotherapy. *Arch Dermatol* 144, 644-646, 2005.
  - [40] Parisi E, Glick PH, Glick M. Recurrent intraoral pyogenic granuloma with satellitosis treated with corticosteroids. *Oral Dis* 12, 70-72, 2006.
  - [41] Steelman R, Holmes D. Pregnancy tumor in a 16 year old. Case report and treatment considerations. *J. Clin Pediatr Dent* 16, 217-218, 1992.
  - [42] Taira JW, Hill TL, Everett MA. Lobular capillary hemangioma (pyogenic granuloma) with satellitosis. *J. Am. Acad. Dermatol* 27, 297-300, 1992



## Author Profile



**Dr. Bijo Alexander** received his MDS in Oral Pathology from Government Dental College, Trivandrum. He is presently working as Prof & HOD at Noorul Islam College of Dental sciences, Trivandrum.



**Dr. Deepa Joseph** did her DNB training in Obstetrics & Gynecology from Government Medical College, Trivandrum. She is currently pursuing a fellowship in Gynec Oncology at VPS Lakeshore Hospital, Kochi.