Abstract: Pyogenic granuloma is one of the inflammatory hyperplasias seen in the oral cavity. This term is a misnomer because the lesion is unrelated to infection and in reality arises in response to various stimuli such as low-grade local irritation, traumatic injury or hormonal factors. It predominantly occurs in the second decade of life in young females, possibly because of the vascular effects of female hormones. Clinically, oral pyogenic granuloma is a smooth or lobulated exophytic lesion manifesting as small, red erythematous papules on a pedunculated or sometimes sessile base, which is usually hemorrhagic. The surface ranges from pink to red to purple, depending on the age of the lesion. Although excisional surgery is the treatment of choice for it, some other treatment protocols such as the use of Nd:YAG laser, flash lamp pulsed dye laser, cryosurgery, intralesional injection of ethanol or corticosteroid and sodium tetradecyl sulfate sclerotherapy have been proposed. Because of the high frequency of pyogenic granuloma in the oral cavity, especially during pregnancy, and necessity for proper diagnosis and treatment, a complete review of published information and investigations about this lesion, in addition to knowledge about new approaches for its treatment is presented. (J. Oral Sci. 48, 167-175, 2006)

Keywords: inflammatory hyperplasia; oral cavity; pregnancy; pyogenic granuloma.
injury, hormonal factors (12) or certain kinds of drugs (13). Although it was originally thought to be caused by pyogenic organisms, it is now believed to be unrelated to infection (2,3). So the term “pyogenic granuloma” is a misnomer because the lesion does not contain pus and is not strictly speaking a granuloma (1,3,11,14). It should be emphasized that as infective organisms such as Bartonella henselae (peliosis hepatitis), B. henselae and B. quintana (bacillary angiomatosis), and human herpes virus type 8 (Kaposi’s sarcoma and angiolymphoid hyperplasia) have been identified in other vascular tumors, some authors have postulated that infective agents may play a part in recurrent PG. However, there is no evidence confirming the presence of infectious organisms in larger groups of PGs (15).

Approximately one third of the lesions occur after trauma (16), so the history of trauma before development of this lesion is not unusual, especially for extragingival PGs (3,17). Poor oral hygiene may be a precipitating factor in many of these patients (1,3,11). Agullo (18) reported the formation of PG as a result of an injury to a primary tooth and Milano et al. (19) reported a case of PG associated with aberrant tooth development.

Some factors such as inducible nitric oxide synthase (20), vascular endothelial growth factor (21), basic fibroblast growth factor (22) or connective tissue growth factor (23) are known to be involved in angiogenesis and rapid growth of PG.

Additionally, some drugs such as cyclosporine have an important role in the genesis of PG. Bachmeyer et al. (24) and Lee et al. (25) reported four cases of oral PG in chronic graft-versus-host disease in patients who were under cyclosporine. Also, some iatrogenic stimulations in dental practice may cause PG. Fowler et al. (8) first reported a case in which PG was found associated with guided tissue regeneration. The lesion arose after demineralized freeze dried bone allograft with an expanded polytetrafluoroethylene membrane were utilized to repair osseous defects. Oral complications occur after bone marrow transplantation (BMT) due to regimen-related toxicity of the preparative regimen, and others by infections. Although oral granulomatous lesions are not common after BMT, Kanda et al. (26) presented a patient who developed PG of the tongue early after allogenic BMT done for multiple myeloma.

In 1980, Davies et al. (27) found inclusion bodies in the fibroblasts suggestive of disordered protein metabolism. They suggested that PG constitutes a lesion produced by a primitive tissue organizer resulting from gene derepression in the papillary fibroblasts, perhaps the result of a C-type virus infection. It should be noted that the growth rate of tumors depends not only on the proliferative activity of the tumor cells but also on the rate of cell death. Nakamura (28) suggested that the low apoptotic rate in PG is closely related to its rapid growth and is regulated by Bcl-2 family proteins.

Although PG may occur in all ages (29,30), it is predominant in the second decade of life in young adults, possibly because of the vascular effects of female hormones (1,3,11). Studies done in Jordanian (29) and Singaporean (31) populations were in agreement with this finding. In contrast, a recent study reported that the average patient age was 52 years with a peak incidence of occurrence in the sixth decade of life (9). Some authors believe that patients are mostly males under 18 years of age, females in the age range 18 to 39, and older patients with an equal gender distribution (16). Epivatianos et al. (9) reported predominance in women (1:1.5) and the presence of etiological factors in 16% of cases, whereas, non-LCH PG was associated more frequently (86%) with etiological factors.

Oral PG, which in reality is the most common gingival tumor (32), shows a striking predilection for the gingiva accounting for 75% of all cases, where they are presumably caused by calculus or foreign material within the gingival crevice. The lips, tongue, and buccal mucosa are the next most common sites (1,3,11). Lesions are slightly more common on the maxillary gingiva than the mandibular gingiva; anterior areas are more frequently affected than posterior areas. Also, these lesions are much more common on the facial aspect of the gingiva than the lingual aspect; some extend between the teeth and involve both the facial and lingual gingiva (3). According to Vilmann et al. (4), majority of PGs are found on the marginal gingiva with only 15% of the tumors on the alveolar part.

Clinical Features

Clinically, PG is a smooth or lobulated exophytic lesion manifesting as small, red erythematous papules on a pedunculated or sometimes sessile base, which is usually hemorrhagic and compressible (1,3,11) and may develop as dumb-bell-shaped masses (14). However, Epivatianos et al. (9) reported that the two types of PG were clinically different. They found that LCH PG occurred more frequently (66%) as a sessile lesion, whereas non-LCH PG mostly occurred as pedunculated (77%).

The size varies in diameter from a few millimeters to several centimeters (3,11). Rarely does PG exceed 2.5 cm in size and it usually reaches its full size within weeks or months, remaining indefinitely thereafter (14). Clinical development of the lesion is slow, asymptomatic and painless (3,11) but it may also grow rapidly (33). The surface is characteristically ulcerated and friable (2) which
may be covered by a yellow, fibrinous membrane (11) and its color ranges from pink to red to purple, depending on the age of the lesion. Young PGs are highly vascular in appearance (3) because they are composed predominantly of hyperplastic granulation tissue in which capillaries are prominent. Thus minor trauma to the lesion may cause considerable bleeding, due to its pronounced vascularity (3,11), whereas older lesions tend to become more collagenized and pink (3). Rarely, PG may cause significant bone loss, as reported by Goodman-Topper and Bimstein (34).

**Correlation with Pregnancy**

PG of the gingiva develops in up to 5% of pregnancies (35), hence the terms “pregnancy tumor” and “granuloma gravidarum” are often used (3). The hormonal imbalance coincident with pregnancy heightens the organism’s response to irritation (1), however, bacterial plaque and gingival inflammation are necessary for subclinical hormone alterations leading to gingivitis (36). The development of this particular kind of gingivitis, typical in pregnancy, not different from that appearing in non-pregnant women, suggests the existence of a relationship between the gingival lesion and the hormonal condition observed in pregnancy. Sometimes pregnancy gingivitis can show a tendency towards localized hyperplasia, which is called pregnancy granuloma. Generally it appears in the 2nd - 3rd month of pregnancy, with a tendency to bleed and a possible interference with mastication (37). During the first months of pregnancy, the persistent influence of plaque induces catarrhal inflammation of the gingiva that serves as a base for development of hyperplastic gingivitis during the last months, modulated by the cumulating hormonal stimuli. In uncontrolled cases, PG may arise. This lesion is rarely observed in women with poor oral hygiene in areas with local irritating factors such as improperly fitting restorations or dental calculus. During pregnancy, PG when treated by surgical excision may reappear due to incomplete excision or inadequate oral hygiene (38).

The molecular mechanisms behind the development and regression of PG during pregnancy have been extensively studied. The profound endocrine upheaval of pregnancy is frequently associated with changes in the function and structure of the blood and lymph microvasculature of the skin and mucosa. (39) Recent studies have revealed that sex hormones manifest a variety of biological and immunological effects. Estrogen accelerates wound healing by stimulating Nerve Growth Factor (NGF) production in macrophages, Granulocyte-Macrophage-Colony Stimulating Factor (GM-CSF) production in keratinocytes and basic Fibroblast Growth Factor (bFGF) and Transforming Growth Factor beta1 (TGF-β1) production in fibroblasts, leading to granulation tissue formation. Estrogen enhances Vascular Endothelial Growth Factor (VEGF) production in macrophages, an effect that is antagonized by androgens and which may be related to the development of PG during pregnancy. These regulatory effects of sex steroids may be manipulated as therapeutic or prophylactic measures in PG (40). Ojanotto-Harril et al. (41) suggested that progesterone functions as an immunosuppressant in the gingival tissues of pregnant women, preventing a rapid acute inflammatory reaction against plaque, but allowing an increased chronic tissue reaction, resulting clinically in an exaggerated appearance of inflammation. Yuan et al. (42) proposed that PG expressed significantly more VEGF and bFGF than healthy gingiva and periodontium. Also, angiostatin was expressed significantly less in PG than in healthy gingiva and periodontally involved gingiva.

It should be noted that the molecular mechanism for regression of pregnancy PG after parturition remains unclear. It has been proposed that, in the absence of VEGF, Angiopoietin-2 (Ang-2) causes blood vessels to regress. Yuan and Lin (43) proposed that Tumor Necrosis Factor-α (TNF-α) upregulated the expression of Ang-2 in all endothelial cell types tested. The protein level of Ang-2 was highest in the granulomas in pregnancy, followed by those after parturition and normal gingiva. The amount of VEGF was high in the granulomas in pregnancy and almost undetectable after parturition. After parturition, there are more apoptotic cells and less Ang-2 than in pregnancy, so VEGF alone or in combination with Ang-2 could protect microvessels from apoptosis, while Ang-2 alone had no effect.

Characteristic oral manifestations of hormonal oral contraceptive intake are similar to oral changes associated with pregnancy, such as the pronounced vascularity of the gingiva, hyperplastic gingivitis, and PG. How oral contraceptives influence vascular changes in the periodontium is unclear; prostaglandin E2 may be implicated as a possible mediator of the inflammatory process (44). On the other hand, Nichols et al. (45) indicated that despite the PG relationship to pregnancy and oral contraceptive pills, the periodontium lacks steroid hormone receptors which suggests that estrogen or progesterone are not directly involved in formation of this lesion.

**Histopathology**

Microscopic examination of PG shows a highly vascular proliferation that resembles granulation tissue (3). Numerous small and large channels are formed which are engorged with red blood cells (1,3) and lined by banal flat
or plump endothelial cells that may be mitotically active (16). The blood vessels often show a clustered or medullary pattern separated by less vascular fibrotic septa, leading some authorities to consider PG as a polypoid form of capillary hemangioma or nothing more than an inflamed lobular hemangioma; others prefer to use the term granulation tissue-type hemangioma (14). Some pathologists require these vessels, which are sometimes organized in lobular aggregates, for diagnosis (lobular capillary hemangioma) (3,11,46).

At low magnification, particularly at the lateral edges, a lobular arrangement is noted wherein groups of capillaries proliferate but abruptly stop. Each lobule is surrounded by a thin collagen layer. This arrangement is disrupted at the base, where irregularly shaped larger vascular channels reside and presumably communicate with the proliferation. It is here that some anastomosing channels (resembling angiosarcoma) can occasionally be identified, but they are focal rather than an integral part of the lesion. At higher magnification, another discriminating feature of benign vascular lesion is found: the small capillary endothelial-lined spaces are themselves surrounded by a perithelial or pericytic layer of cells. This double layer of cells, also seen in intramuscular angiomatosis, is not seen in the clonal angiosarcoma (32).

Polymorphs, as well as chronic inflammatory cells, are consistently present throughout the edematous stroma, with micro-abscess formation (2). The fibroblasts are typically plump and mitotic activity may be noted in the stromal cells. Older lesions demonstrate fewer and more mature cells, which are fibrocytes. Occasional lesions demonstrate an extreme predominance of plasma cells, prompting some pathologists to call them plasma cell granuloma, a term that is best avoided because of the potential confusion with mucosal solitary plasmacytoma or multiple myeloma. Rare examples of intravenous PG have been reported (47).

Some scarring may be noted in some of these lesions, suggesting that occasionally there may be maturation of the connective tissue repair process (11). The surface of the lesion may undergo secondary, nonspecific changes that include stromal edema, capillary dilation, inflammation, and granulation tissue reaction (48). The surface is usually ulcerated and replaced by a thick fibrin purulent membrane (3). A mixed inflammatory cell infiltrate of neutrophils is mostly prevalent near the ulcerated surface; chronic inflammatory cells are found deeper in the specimen (3, 11).

In brief, 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 intra-luminal red blood cells. One or more central vessels develop a large lumen with a thick muscular layer resembling a vein. In the involutionary phase, there is a tendency for intra- and perilobular fibrosis with increased venular differentiation (32).

There are two histological types of PG. The first type is characterized by proliferating blood vessels that are organized in lobular aggregates although superficially the lesion frequently undergoes no specific change, including edema, capillary dilation or inflammatory granulation tissue reaction. This histological type of PG was called lobular capillary hemangioma (LCH type) (10), whereas the second type (non-LCH type) consists of highly vascular proliferation that resembles granulation tissue (3, 14). The lobular area of the LCH PG contains a greater number of blood vessels with small luminal diameter than does the central area of non-LCH PG. In the central area of non-LCH PG, a significantly greater number of vessels with perivascular mesenchymal cells non-reactive for α-smooth muscle actin and muscle-specific actin is present than in the lobular area of LCH PG. These differences suggest that two histological types of PG represent distinct entities (9). Toida et al. (49) found that the presence of blood vessels with different luminal diameter in the lobular area of LCH PG and in the central area of non-LCH PG may be because different pathogenic factors influence their development. Epivatianos et al. (9) observed that foci of fibrous maturation were present in 15% of non-LCH PG but were totally absent in LCH PG. Although it is possible that PG can undergo fibrous maturation, they showed that this happened only in non-LCH PG which suggests that the two types of PG have different pathways of evolution.

**Differential Diagnosis**

When a mass is found in the oral cavity, it is important to formulate a differential diagnosis since this would help further evaluation of the condition and management of the patient (48). Biopsy findings have an important role and are definitive in establishing the diagnosis. (11) Differential diagnosis of PG includes peripheral giant cell granuloma, peripheral ossifying fibroma, metastatic cancer (1,11), hemangioma (1,11,16,47,50), pregnancy tumor (37), conventional granulation tissue, hyperplastic gingival inflammation (47,50), Kaposi’s sarcoma, bacillary angiomatosis (16,47,50), angiosarcoma (16), and Non-Hodgkin’s lymphoma (51).

Peripheral giant cell granuloma (PGCG) is an exophytic lesion that is seen exclusively in the gingiva (2) and is clinically similar to PG (11), but PGCG is often more bluish-purple compared to the bright red of a typical PG
(3). Although PGCG is more likely to cause bone resorption than a PG, the differences are otherwise minimal. Generally, this lesion is clinically indistinguishable from a PG but the features that set PGCG apart from other reactive hyperplasias are the appearance of multinucleated giant cells (11) and lack of infectious source (1).

Depending on its duration, PG will vary in texture from soft to firm, and can be suggestive of a fibroma (11) so peripheral odontogenic or ossifying fibroma may be another consideration, although these tend to be much lighter in color (11). Also, it is usually about 1.5 cm in diameter, although some have reached 6 cm in diameter (52). Like PG, it is commonly encountered among pregnant women but unlike PG, this lesion is found exclusively on the gingiva (2), and has a minimal vascular component (11).

Although metastatic tumors to the oral region are uncommon, the attached gingiva is the most common affected soft tissue site followed by the tongue. In nearly 30% of cases, the metastatic lesion in the oral region is the first indication of an undiscovered malignancy at a distant site (53) so the microscopic appearance should resemble the tumor of origin (3). Hirshberg et al. (54) analyzing 157 cases, reported that most cases (64%) were diagnosed in patients in their fifth to seventh decade which is different from PG. The clinical appearance of the metastatic oral lesion in most cases resembled hyperplastic or reactive lesions such as PG.

One important differential diagnosis of PG is hemangioma which is a developmental disorder (1,2), but small lesions may be clinically indistinguishable from PG. Diascopy, the technique of applying pressure to a suspected vascular lesion to visualize the evacuation of coloration, supports the fact that patent blood-filled spaces constitute the lesion. Most oral hemangiomas are located on the tongue, where they are multinodular and bluish red (2). In comparison with PG, hemangioma has more plump, histiocytoid, endothelial cell proliferation without an acute inflammatory cell infiltrate (47,50). Freitas et al. (55) evaluated the immuno-histochemical expression of VEGF-C1 and showed that there was no statistically significant difference in the angio genesis index between PG and hemangioma. There was no statistically significant difference between the lesions in the number of cells highlighted by staining for VEGF-C1. The VEGF-positive cells in PG were macrophages and fibroblasts. These results affirm the role of angiogenic factors in the etiopathogenesis of hemangioma and PG, however, it showed that microvessel quantification is not useful in the differential diagnosis of these lesions.

Another differential diagnosis is pregnancy tumor (pregnancy epulis) (37). There is some disagreement about the validity of the clinical term “pregnancy tumor”. On the basis of its clinical presentation and histologic appearance, some authors believe that it simply represents a PG, whereas others believe that the lesion is unique because of the apparent influence of female sex hormones (56). Increased prevalence of pregnancy epulis toward the end of pregnancy and the tendency for this lesion to shrink after delivery indicate a definitive role for hormones in the etiology of the lesion. (2,57) According to Ojanotko-Harri et al. (41), there is no clinical and histological difference between pregnancy tumor and PG that occurs in non-pregnant patients but some authors believe that unlike PG, pregnancy tumor is usually confined to the interdental papilla (57). Daley et al. (56) indicated that diagnosis of pregnancy tumor is valid clinically in describing a PG occurring in pregnancy, because it describes a distinct lesion not on the basis of histologic features but on etiology, biologic behavior, and treatment protocol.

Conventional granulation tissue is another differential diagnosis that should be considered. Despite the close relationship between PG and conventional granulation tissue, PG shows clinically different behavior, such as rapid growth, multiple occurrence and frequent recurrence, from those in granulation tissue (47,50,58,59).

Hyperplastic gingival inflammation should also be considered. The histopathologic differentiation of PG from hyperplastic gingival inflammation is sometimes impossible, and the pathologist must depend on the surgeon’s description of a distinct clinical mass to diagnose the granuloma (14). Kaposi’s sarcoma of Acquired Immuno-Deficiency Syndrome (AIDS) shows proliferation of dysplastic spindle cells, vascular clefts, extravasated erythrocytes and intracellular hyaline globules, none of which are features of PG (14). The initial diagnosis of Kaposi’s sarcoma requires microscopic evaluation of biopsy material because this disease can mimic a number of intraoral lesions such as PG, bacillary angiomatosis, hemangioma, and lymphoma (60).

Bacillary angiomatosis, also AIDS-related, shows dense, extracellular deposits of pale hematoxyphilic granular material representing masses of bacilli that stain positive with Warthin-Ostarry stain (14).

PG can be distinguishable from angiosarcoma by its lobular growth pattern, well-formed vessels, and cytologically bland endothelial cells (16). Another consideration is Non-Hodgkin’s lymphoma (NHL) of which primary sites in the head and neck are Waldeyer’s ring, paranasal sinuses, salivary glands, the oral cavity, and the larynx. Clinical appearance of gingival NHL varies but is usually found to be an asymptomatic gingival enlargement or mass resembling a PG (51).
**Treatment**

Although many treatment techniques have been described for PG, when it is large or occurs in a surgically difficult area, choosing an appropriate treatment modality can be difficult (35). Excisional biopsy is indicated for treatment of PG, except when the procedure would produce marked deformity; in such a case, incisional biopsy is mandatory (2). So, management of PG depends on the severity of symptoms. If the lesion is small, painless and free of bleeding, clinical observation and follow up are advised (35). Although conservative surgical excision and removal of causative irritants (plaque, calculus, foreign materials, source of trauma) are the usual treatments (1,3,11,61) for gingival lesions, the excision should extend down to the periosteum and the adjacent teeth should be thoroughly scaled to remove the source of continuing irritation (3).

Recently, some other treatment protocols, instead of excisional surgery, have been proposed. Powell et al. (62) reported the use of Nd:YAG laser for excision of this lesion because of the lower risk of bleeding compared to other surgical techniques. They chose the Nd:YAG laser over the CO2 laser, because of its superior coagulation characteristics. White et al. (63) proposed that laser excision is well tolerated by patients with no adverse effects. They also stated that CO2 and Nd:YAG laser irradiation is successful in surgical treatment.

Meffert et al. (64) used the flash lamp pulsed dye laser on a mass of granulation tissue which did not respond to the usual treatment methods and concluded that previously resolute tissue responded well to a series of treatments with the pulsed dye laser. Ishida and Ramos-e-Silva (65) believed that cryosurgery is a very useful technique for treatment of PG. They stated that oral mucosa, because of its humidity and smoothness is an ideal site for this technique. It shows a very good esthetic result and it may be either the first choice or an alternative option to conventional surgery.

Although conservative treatment by techniques such as cryosurgery, laser surgery, and electrodessication are usually adequate, excisional treatment can often result in scars, so Ichimiya et al. (66) attempted a different approach using an injection of absolute “ethanol” in patients with recurrence due to inadequate cryosurgery and concluded that this therapy was less invasive than surgical excision and appeared to be an alternative therapy for PG.

Moon et al. (67) reported that sodium tetradecyl sulfate (STS) sclerotherapy successfully cleared the lesions in most patients, without major complications. They believe that this technique offers a better alternative than excision because of its simplicity and lack of scarring, even though multiple treatment sessions are required. The mechanism of the therapeutic effects of their technique may be mediated by both the specific and the nonspecific actions of STS, which specifically causes endothelial cell damage and obliterates vessel lumina. Moreover, infiltrations of STS into stromal tissues can cause nonspecific necrotic changes. Also, Parisi et al. (33) used a series of intralesionai corticosteroid injections for treatment of PG, particularly for highly recurrent lesions.

Treatment considerations during pregnancy are very important. During this period, careful oral hygiene, removal of dental plaque, and use of soft toothbrushes are important to avoid occurrence of a pregnancy tumor. If uncontrolled bleeding occurs, management should be based on the individual condition and should range from supportive therapy such as desiccation of bleeders; local, firm compression and oral hygiene to blood transfusion, as well as medication to accelerate fetal lung maturity or even termination of pregnancy to save the patient’s life, as with treatment of uncontrollable eclampsia (68). Steelman and Holmes (69) believed that maintenance of oral hygiene and regular follow up appointments should be recommended while pregnant. Surgical and periodontal treatment should be completed, when possible, during the second trimester, with continued surveillance of home care until after delivery (2) but some authors believe that in the gravid patient, recurrence is likely and treatment, to be successful, should await parturition (1). In pregnant women, lesional shrinkage after the birth may make surgery unnecessary (14).

After excision, recurrence occurs in up to 16% of the lesions (70) so in some cases re-excision is necessary (1,3,11). Recurrence is believed to result from incomplete excision, failure to remove etiologic factors, or re-injury of the area (11). Some recurrences manifest as multiple deep satellite nodules that surround the site of the original lesion (Warner-Wilson Jones syndrome) (70). It should be emphasized that gingival cases show a much higher recurrence rate than lesions from other oral mucosal sites (4).

**Conclusion**

Although pyogenic granuloma is a non-neoplastic growth in the oral cavity, proper diagnosis, prevention, management and treatment of the lesion are very important. Pyogenic granuloma arises in response to various stimuli such as low-grade local irritation, traumatic injury, sex hormones or certain kinds of drugs, so removal of causative irritants (plaque, calculus, foreign materials, and source of trauma) is the major line of treatment. Excisional surgery is the treatment of choice for pyogenic granuloma, but some new approaches for treatment such as cryosurgery, excision by Nd:YAG laser, flash lamp pulsed dye laser, injection of ethanol or corticosteroid and sodium tetradecyl sulfate...
sclerotherapy have been reported as alternative therapies. In spite of these treatments, recurrence is not infrequent so in some cases re-excision may be necessary. It should be emphasized that one important point about pyogenic granuloma is the effect of sex hormonal imbalances during pregnancy which is one of the most common causes of pyogenic granuloma. During pregnancy, careful oral hygiene, removal of dental plaque, and use of soft toothbrushes are important to avoid occurrence of pyogenic granuloma.

References
25. Lee L, Miller PA, Maxymiw WG, Messner HA,


