

Pyogenic Granuloma: A Literature Review and A Case Report

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ABSTRACT

Pyogenic granuloma of the oral cavity is a common, non-neoplastic, vascular tumor. The etiology is not clear and it is suggested to be attributed to different factors. It might be caused by a reaction to a stimulus such as trauma, viruses such as HSV-1, hormonal changes, as well as other factors such as tooth eruption or medication. Clinically it appears as a painless tumor that tends to bleed easily, with red color and rarely may be accompanied by a periodontal abscess and bone loss. Biopsy is the most common tool used for the diagnosis. Its treatment is usually surgical excision and lately the use of lasers for its excision has emerged. Special care should be given to pregnant women where the treatment varies. The aim of this review is to present the background of oral pyogenic granuloma and the case report presents the situation, histological image and treatment of an adult woman patient.

Keywords: Lesion, oral pyogenic granuloma, pregnancy, vascular tumor.

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I. INTRODUCTION

Pyogenic granuloma (PG) is a common lesion, a benign, nonneoplastic vascular tumor. In 1897, Poncet and Dor first described this lesion and the term “pyogenic granuloma” or “granuloma pyogenicum” was introduced by Hartzell in 1904 [1], [2]. Although, the scientific community considers that the term: “granuloma” is a misnomer, because it is not associated with pus and has different histological image [2]. It appears in different body locations, such as skin, eyes, known as lobular capillary hemangiomas and the oral type is very common, mainly at gingiva (75%), following by lips, tongue, buccal mucosa and palate, as extralingival sites [3], [4]. In the oral cavity, maxilla is more involved than mandible [3]. The diagnosis is easy nowadays and it is based not only on biopsy, but also on innovative methods. The treatment is a challenging issue, but as medicine progresses, it is something feasible.

II. MATERIAL AND METHODS

PubMed, Cochrane and Scopus databases were searched up to December of 2021. A manual search of recently published journals was also conducted. The keywords used

were the following: pyogenic granuloma, oral pyogenic granuloma, etiology, treatment. The screening included only papers in English language.

III. RESULTS AND DISCUSSION

A. Etiology

Pyogenic granuloma (PG), as it is a vascular tumor, includes angiogenesis as process acquires some growth factors and pro-angiogenic cytokines (VEGF) and is regulated by an equally varied group of inhibitors (angiostatin) of neovascularization [5]. The endothelial cells in PG express Cluster of Differentiation 34 (CD34), Intercellular Adhesion Molecule 1 (ICAM-1), and Vascular Adhesion Molecule 1 (VCAM-1) associated with an increased microvascular density [6].

Studies and clinical experience prove that PG is a reaction to a stimulus, such as local irritation and trauma. A group of different factors like puberty, pregnancy, viruses, calculus, injury to a primary tooth, eruption of permanent teeth, chronic irritation due to exfoliation of primary teeth, imperfect restorations in the region of lesion, gingival inflammation, periodontitis, hormones, medication (cyclosporine, lamivudine, indinavir, isotretinoin, docetaxel, the Epidermal

Growth Factor Receptor (EGFR) inhibitors and anticancer agents such as pyrimidine analogs, taxanes, epidermal growth factor receptor inhibitors, tyrosine kinase inhibitor and B-Rapidly Accelerated Fibrosarcoma (BRAF) inhibitors, and immunosuppressants such as Tumor Necrosis Factor alpha (TNF-alpha) antagonists and mammalian Target Of Rapamycin (mTOR) inhibitors [7], [8], food impaction and trauma, as a result of wrong toothbrushing technique can act as stimuli [1], [3].

One of the most vital predisposing factors is puberty and pregnancy. The common resultant between them is the increase of the sexual hormones. PG during pregnancy affects the 5% of them, with both higher predilection for anterior gingiva of maxilla and new bone formation. In most cases, presents when a woman is pregnant in late first trimester, because of high levels of progesterone and poor oral hygiene and regresses after childbirth [9]. In order to be more specific, PG is the result of overproduction of Vascular Endothelial Growth Factor (VEGF) and b-Fibroblast Growth Factor (bFGF) and decrease of angiostatin, thrombospondin-1 and estrogen receptors. Progesterone and estrogens modify the answer to gingivitis and local irritations [10]. 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 pregnancy tumor [2]. Moreover, pregnancy's levels of progesterone prevent dilation of gingival vessels, the blood circulation blocks and increased susceptibility to mechanical irritation. Another finding is the increased number of periodontal pathogens, such as *Porphyromonas gingivalis* and *Prevotella intermedia*, during pregnancy, can activate gingival fibroblasts and keratinocytes, in order to form a tumor against the plaque [10].

Recent studies demonstrate that HSV-1 is correlated with the development of PG. Generally, other members of the human herpesviridae group, the Epstein-Barr virus and the Kaposi's sarcoma-associated herpesvirus (HHV-8), can play the role of the generative cause at neoangiogenesis and neolymphangiogenesis by directly stimulating various signaling pathways via the VEGF protein family and their receptors. The existence of HSV-1 DNA on the tissue and HSV-IgG complexes may increase VEGF and MMP-9 production as both intervene in the process of formation of new vessels. The nuclear and cytoplasmic HSV-I staining patterns in non-CPE-presenting epithelial cells are in line with a chronic, low-productive type of HSV infection, as observed in other chronic HSV infections [8].

It is a clear assumption that trauma and chronic irritation are the main factors of the creation of PG, but they do not suffice, because the occurrence of the microbial factor or a syndrome is vital. For example, a gingival inflammation, like the periodontal abscess and bone loss, is a fertile ground at local irritants, which permits the ingress into the gingival connective tissue of low virulent oral microflora [11]. In this frame, the result of some studies shows that a group of around 14-15 species of *Actinomyces* and especially *Actinomyces Israeli*, which is detected normally in oral flora, incriminates for increase of probability of PG [12]. Moreover, PG case reported in patient with Sturge-Weber Syndrome (SWS), or Encephalotrigeminal angiomatosis. This syndrome is responsible for gingival enlargement, because of increasing

the vascular component, and the additional local irritation by plaque and calculus act as the "perfect combination" for the PG [13].

A rare case of natal tooth appeared as a cause of PG. Natal tooth is a tooth present at the time of birth. The 1-10% of them is supernumerary and the majority is early eruption of normal dentition. The intraoral existence of natal tooth, combined with breastfeeding and sucking, drives to the appearance of PG, as a local irritation [14].

Nowadays, the development of oral surgery seems to have specific weight in etiology of PG. The application of free revascularized flap (FRF) at the management of oral cancers and the progress of dental implants are guilty. Of course, the main base of all is the combination of poor oral hygiene, calculus and the wrong formation of prosthetics, the healing cups and the abutments of implants. Especially, "metal-like" particles and have postulated that these particles could be the result electrochemical phenomena, corrosion, friction, or a synergistic combination of these events. Once released, these particles may trigger an inflammatory response mediated by cytokines and macrophages [15]. Evidence shows the formation of granulation tissues around implant abutments that are implemented in orally rehabilitated sites by FRF [16]. PG associated with implants is more frequent in men, and associated with the posterior regions of the jaws, mainly the mandible. All of them connected with lower levels of oral hygiene and plaque control [17].

B. Diagnosis

The intraoral appearance of a lesion, which is bleeding, soft, painless, and deep red to reddish-purple in color, leads the patients to dentist at most cases. Radiographic findings do not exist in PG, except of rare cases, which coexist with periodontal abscess and bone loss [1], [11]. In addition, radiography is very useful to determine any bone loss in malignancy or alveolar bone erosion combined with tooth mobility and also it helps identify foreign bodies [3].

The most applied method of diagnosis of PG is the biopsy. Histopathologically, hematoxylin-eosin (H&E) stained section reveals lobular aggregates of capillary-sized vessels, which are lined by plump endothelial cells, with scattered fibroblasts and various amounts of inflammatory infiltrate [7]. The classification of PG's developments consists of (i) cellular phase, (ii) capillary phase or vascular phase, and (iii) involutionary phase [6]. Furthermore, the Immunohistochemistry (IHC), using VEGF marker, presents the endothelial cells positive for vascular markers such as CD31, CD34, ICAM-1, VCAM-1, factor VIII antigen, and WT-1, they were negative for glucose transporter protein isoform-1 (GLUT-1) [6], [7]. Some more specialized techniques are associated with marking components of Renin-Angiotensin System (RAS), such as 3,3'-Diaminobenzidine (DAB) immunohistochemical (IHC) staining, PG-Derived Primary Cell Lines, NanoString mRNA analysis, RT-qPCR and Western blotting (WB) performed on total protein extracts [18].

On the last trends of imaging, powerful diagnostic weapons are the Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasound (US) and Color Doppler Ultrasound (CDUS). These methods are available for the assessment of oral vascular lesions, like PG [19].

The most important axes of diagnosis of PG are the rapid enlargement, the tendency to bleed easily and the CDUS features. Nevertheless the biopsy is the only way of definite diagnosis [19].

The differential diagnosis of pyogenic granuloma includes damages with same clinical features, such as traumatic fibroma, parulis, post-extraction granuloma, peripheral giant cell granuloma, peripheral ossifying fibroma, peripheral odontogenic fibroma, hyperplastic gingival inflammation, Kaposi's sarcoma, amelanotic melanoma, bacillary angiomatosis, angiosarcoma, metastatic cancer, non Hodgkin's lymphoma, and hemangioma (hemangioendothelioma, infantile hemangiomas, and vascular malformations) [3], [6].

C. Treatment

The therapeutic protocol of PG includes the surgical excision mainly. The margins of excision are 2 mm around the lesion and the depth until the periosteum or to the causative agent. Any foreign body, calculus, or defective restoration should be removed as part of the excision [1]. Depending on the size of lesion, if it is small, painless and free of bleeding, oral prophylaxis and removal of causative irritants is advised and if it is large, a thorough oral prophylaxis followed by surgical excision using gingivectomy or flap surgery procedures is done [3]. At most cases, the treatment begins with scaling and curettage. This procedure accompanied with bleeding, which stopped within few minutes by applying pressure with gauze. The patient was advised to perform and maintain thorough oral hygiene by brushing twice a day and to use chlorhexidine mouth rinse of 0.12% twice daily [20].

Special care is given to pregnancy. There is a range of preventive treatment, such as careful oral hygiene, removal of dental plaque, and use of a soft toothbrush. In some cases, shrinkage of the lesion after pregnancy may make surgical treatment unnecessary. However, if necessary treatment can be completed in the second trimester with follow up [3]. Because of the bleeding and secondarily infected masses preoperative oral antibiotics were prescribed (amoxicillin 500 mg and metronidazole 500 mg three times a day for 1 week) together with 0.2% chlorhexidine mouthwash and recommendation of proper oral hygiene [9]. The recall program concerns a 4 week appointment [10].

Innovative measures of treatment include laser therapy, such as diode lasers of wave-length between 808 to 980 nm or solid-state neodymium - yttrium aluminum garnet (Nd: YAG) lasers, erbium-YAG (Er: YAG) and CO₂ lasers [6]. It is a fact that excision up to periosteum followed by scaling and root planning of the adjacent teeth is the usual treatment but involves risk of bone exposure of large area, bleeding, pain, bone loss and might result in unaesthetic appearance in the anterior region. The solution is a papilla preservation flap, while the underside of the flap, as well as the bone surface, was irradiated with diode laser (K-LASER®, wavelength: 970 nanometers, power output: 3.5 joules) in a focused, pulsed, contact mode for three cycles of 30 s each, to remove any possible remnants of PG and prevent its recurrence [21].

A diode laser is a semiconductor device, which uses aluminum, gallium, arsenide, and occasionally indium as the active medium. The radiation is coherent in the visible or

infrared spectrum with wavelengths ranging from 810nm to 980nm. Diode laser is safe to use for the treatment of PG, because these wavelengths are absorbed properly by soft tissues, which contains melanin and hemoglobin, and at the same time are poorly absorbed by calcified tissue such as hydroxyapatite and water present in the enamel and bone [22]. Another significant feature is the activation of proliferation of fibroblasts at low energy. Reports of excision of pediatric PG refer that diode lasers would reduce stress and fear in pediatric patients and would also minimize discomfort both during and after surgery [23].

The type of laser plays important role. From the available types, CO₂ and Er: YAG lasers, due to their high water absorption and less penetration compared to Nd: YAG and diode lasers are suitable means for cutting. The coagulation caused by these two lasers is also less. Also, Nd: YAG and diode lasers are not suitable for bone resection. As the Er: YAG lasers are not so aggressive to cutting, the remaining tissue has more pathological value. Furthermore, if PG occurs around the implant, Er: YAG has the advantage of removing the lesion with minimal damage to the implant. The difficulty and the requirement of technical knowledge of using CO₂ lasers have as a result the minimum application of them. Diode laser has shown excellent results in cutaneous pyogenic granulomas with only minimal pigmentary and textural complications [24].

As a conclusion, the advantages of lasers compared with traditional methods include sterile conditions, reduction of bleeding, good possible estimation of cutting depth, precision of cutting, reduction in the number of instruments, often no need for suturing, pain reduction intra- and post-operatively, no inhibition of, and perhaps even promotion of wound healing, less scars, staff and time [24].

Nowadays, there are more therapeutic methods and measures, such as the flash lamp pulsed dye laser, cryosurgery, sodium tetradecyl sulfate sclerotherapy. Particularly for highly recurrent lesions, intralesional injection of absolute ethanol, corticosteroids were successfully attempted [2].

IV. CASE REPORT

A 47-year-old woman, systematically healthy presented with an asymptomatic gingival lesion between the teeth #11 and #12. The lesion was well defined, covered the interdental space and approximately the one third of the clinical crowns of #11 and #12. It was soft, mobile, lobulated and it was bleeding after stimulus. There were found neither periodontal pockets nor radiographic findings.

The first step of treatment was surgical excision of the lesion. The margins of excision were extending 2mm beyond the lesion. The tissue was placed into solution of 10% formaldehyde and the trauma was sutured. The patient was advised to perform and maintain thorough oral hygiene by brushing twice a day and rinsing with chlorhexidine 0.12% twice daily for 1 week.

Histological examination included staining of histological sections with Hematoxylin and Eosin, showed epithelial erosion and neoplastic capillary vessels with lymphocytes and plasma cell infiltration, without signs of malignancy.

The presumptive diagnosis of pyogenic granuloma was confirmed due mainly to high vascularity of the lesion.



Fig. 1. The gingival lesion between the teeth #11 and #12.



Fig. 2. Surgical excision of the lesion

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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