Peripheral Giant Cell Granuloma: Recurrence, A Persisting Problem

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Abstract
Peripheral Giant Cell Granuloma is a non-neoplastic, tumor-like, reactive lesion occurring exclusively on gingiva/ alveolar crest. It is thought to arise from the periodontal ligament or periosteum. Clinically, it bears resemblance to pyogenic granuloma, peripheral ossifying fibroma and many other peripheral soft tissue lesions seen in the oral cavity, thereby making histopathology mandatory for the diagnosis of this lesion. The lesion although being relatively common still carries a lot of ambiguity. The ambiguity is in terms of its etiology, growth potential, biological behavior (recurrence), histogenesis of its cells as well as its treatment. The entity further holds significance because of its notorious behavior and its high tendency to recur. The present paper describes a case report on recurrent peripheral giant cell granuloma with a comprehensive insight of the literature on its clinical and histological aspects. Special attention has been given on the histogenesis of its cells and treatment of this lesion.

Keywords
Peripheral Giant Cell Granuloma; Giant Cell Lesion; Multinucleated Giant Cells; Mononuclear Stromal Cells; Myeloid Tumor; Osteoclasts

Abbreviations
Peripheral Giant Cell Granuloma (PGCG), Central Giant Cell Granuloma (CGCG), Peripheral Ossifying Fibroma (POF),

Introduction
The giant cell granuloma of the jaws is a non-neoplastic lesion characterized by the presence of few to many multinucleated giant cells in a cellular background composed of mononucleated stromal cells with ovoid to spindle-shaped nuclei (Kramer, 1991). Giant cell granuloma may occur within the bone (central giant cell granuloma [CGCG]) or on the gingiva or edentulous alveolar processes (peripheral giant cell granuloma [PGCG]). CGCG accounts for approximately 7% of benign lesions of the jaws, is locally destructive and occasionally shows an aggressive biologic behavior, especially in younger patients (Sidhu M.S., Parkash H., and Sidhu S.S., 1995; Kruse-Losler, Diallo, Gaertner, Mischke, Joos and Kleinheinz, 2006). In contrast, PGCG is a common peripheral soft tissue lesion that arises mostly as a response to the presence of local irritants. The site of occurrence is usually the periodontium including the gingival and the periosteum overlying the alveolar ridges (Katsikinis, Kakarantza-Angelopoulou and Angelopoulo, 1988).

In 1962, Gottsegen led to the finding that most of the periodontal surgeries often led to the development of peripheral giant cell granulomas as a consequence (Gottsegen, 1962). Some researchers however have also proposed that factors imposing local insults to the mucosa including invasive minor surgical procedures are important etiological factors responsible for the development of this entity (Jaffe, 1953; Bernier and Cahn, 1954). Therefore, patients belonging to low socio-economic strata usually are more prone to develop peripheral giant cell granuloma as a result of persistently compromised oral hygiene and accumulation of local factors which act as important etiological factors for the development of this lesion (Eronat, Aktug, Glinbay and Unal, 2000). Choi et al have also reported the development of peripheral giant cell granuloma in a case of hyperparathyroidism secondary to renal failure (Choi, Terzian, Schneider and Trochesset, 2008). PGCG develops exclusively on gingival and edentulous alveolar ridges. The lesion characteristically presents as a deep red or purplish exuberant mass (Neville, 2004). Mandible is more
commonly affected than the maxilla and most of the lesions are usually seen in the premolar-molar region (Shafer, 1983; Bhat, Jayakrishnan, Rao and Kudva, 1999). Malignant transformation of these lesions has never been reported however the lesions usually recur due to incomplete excisions with a recurrence rate of around 10% (Katsikeris, Kakarantza-Angelopoulou and Angelopoulou, 1988). Histology of the lesion is characteristic consisting of a non-encapsulated highly cellular mass with abundance of multinucleated giant cells dispersed throughout which actually are the hallmark of these lesions (Regezi, 2000). Hence, diagnosis of this lesion is crucial and should be included in the list of differentials of the common peripheral soft tissue lesions of the jaws because of its high potential for recurrence and its occurrence associated with certain systemic conditions. Histopathology should be considered as the gold standard in its diagnosis due to its non-specific clinical and radiological features (Shafer, 1983).

1 Case Report

A 36 year old male patient visited a private dental practitioner with a chief complaint of swelling in relation to lower right back tooth region which interfered during mastication since 5 months. Patient noticed a small swelling in relation to interdental papilla in 45,46 region around 5 months back. The swelling was insidious in onset and gradually increased to present size over a period of last 5 months. The swelling was initially painless but developed intermittent inflammation and pain when traumatized. The swelling was recurrent in nature. A similar lesion had earlier appeared around 8 months back and was treated with Laser. The lesion showed recurrence after 2 weeks and was then treated using electrocautery. In the present situation, extra-oral examination didn’t reveal any obvious abnormality. There was no associated lymphadenopathy. Intra-oral examination revealed a 1.5 x 1.5 cm, sessile, roughly ovoid, reddish pink, nodular gingival overgrowth on the lingual aspect of attached gingiva in relation to 44,45,46 region. The growth extended from the distal aspect of 44 to the mesial aspect of 46 (Figure 1). Routine blood investigations were found normal. Serum parathormone, alkaline phosphatase and calcium and phosphorus levels were within normal limits. Radiological examination did not reveal any evidence of bone loss in the area presenting with the lesion. Considering the past history and previous histopathological report that was supportive for Peripheral Giant Cell Granuloma (PGCG) and present clinical and radiographic findings, a provisional diagnosis of Peripheral Giant Cell Granuloma was given with Pyogenic Granuloma and Peripheral Ossifying Fibroma as important differential diagnoses.

Knowing the previous history of recurrences, a complete treatment was planned to get the best possible results. Treatment started with non-surgical periodontal therapy including a thorough scaling and root planing and patient was put on maintenance phase. This was done to remove all possible local factors which could have been responsible for the initiation and if not initiation, then, a rapid proliferation of the lesion and also to avoid the recurrence of the lesion knowing that the lesion was not a fresh lesion per se but a recurrence of the previously treated lesion. Patient was recalled after 15 days after a prophylactic antibiotic coverage that was advised to be started 5 days prior to the appointment. Under local anaesthesia, localized periodontal flap surgery was performed with elevation of buccal and lingual flap after incision and thorough debridement with complete removal of subgingival calculus and debris was accomplished. Complete excision of the lesion was done and care was taken to remove the entire base of the lesion along with 1mm of healthy margin around the tissue (Figure 2). The lesion was stored in 10% formalin and sent for histopathological examination. The surgical site was sutured with simple interrupted sutures for better approximation.
and periodontal pack was given. Histopathology showed the lesional tissue covered with a proliferating parakeratinized stratified squamous epithelium. Underlying connective tissue stroma revealed the presence of plump proliferating fibroblasts with numerous multinucleated giant cells with haphazard nuclear arrangements and few to numerous nuclei (Figure 3a). Both types of giant cells described in literature as Type I and Type II (Bernier and Cahn, 1954; Kruse-Losler, Diallo, Gaertner, Mischke, Joos and Kleinheinz, 2006) i.e. those that are large and with vesicular nuclei and those that are smaller in size with compact nuclei (close faced nuclei) were evident (Figure 3b). Numerous vascular spaces, indicative of high vascularity of the lesion, with giant cells in the lumen of the blood vessels, indicative of the vascular etiology of the lesion, were also evident throughout the sections (Figure 3c). Certain giant cells showed pseudopodia-like extensions of their cytoplasm and appeared to engulf mesenchymal cells. Phagocytic vacuoles were evident in the giant cells (Figure 3d). The lesion also appeared to have a pseudo-capsule like structure known otherwise as “Grenz zone”. Chronic inflammatory cell infiltration chiefly consisting of lymphocytes was also present (Figure 3e-low power; Figure 3f-high power). Connective tissue was interspersed with abundant giant cells with vesicular nuclei and prominent nucleoli signifying the high activity of cells (Figure 3g). After 7 days, periodontal pack and suture removal was carried-out and the surgical site was examined which revealed good healing. Follow-up appointments were performed at 1 month, 6 months and 12 months intervals. Healing was uneventful (Figure 4), and no recurrence was observed even after 12 months. During this period, the patient did not report any complaints and no other treatment was needed.
Figure 3d Few giant cells showing pseudopodia-like extensions of cytoplasm

Figure 3e Pseudo-capsule like structure, “Grenz zone”, with chronic inflammatory cell infiltration in the lesion in low power (4x view)

Figure 3f Similar view in high power (10x view)

Figure 3g Connective tissue interspersed with abundant giant cells with vesicular nuclei and prominent nucleoli signifying high activity of cells

Figure 4 Uneventful healing of the tissue post-excision

2 Discussion

PGCG is not a true neoplasm but rather a benign, hyperplastic, reactive lesion caused by local irritation or chronic trauma (Medi, Eshghyar, Jafari, Lassemi, Navi and Abbas, 2007). Although the exact etiology is still not clear, many authors consider the lesion as an abnormal proliferative response (Gunhan M., Gunhan O., Celasun, Mutlu, and Bostanci, 1998). Certain hormones (estrogen and progesterone) that are supposed to have an immunosuppressive action may contribute to the growth of this lesion while hyperparathyroidism has been suggested as one of the rare etiologies of the occurrence of this lesion (Parbatani, Tinsley and Danford, 1998). The latter is usually suspected when multiple lesions are identified and the patient suffers recurrences despite adequate treatment (Katsikeris, Kakarantza-Angelopoulou and Angelopoulo, 1988).

Peripheral giant cell granuloma has no specific age predilection however most of the cases occur between 40 years to 60 years with approximately 20-30% occurring in the 1st two decades of life (Giansanti and Waldron, 1969). Pindborg et al. suggested that the most common location for the development of PGCG is the region from 1st premolar to 2nd molar (Pindborg, 1994), however Shafer (1983) and Giansanti and Waldron. (1969) were of the opinion that the lesion is generally present in the incisor-canine region. PGCG affects females more than males (Shafer, 1983).

PGCGs are rather unique lesions of oral cavity occurring on gingival or alveolar mucosa, but never found on tissues that are not supported by periosteum, which supports evidence for its origin. The size of the lesion varies between 0.5 to 1.5 cm. Bodner et al reviewed 15 cases of large (more than 2 cm) lesions
sustaining its innate growth potential and showed that patients with poor oral hygiene or with xerostomia are at a higher risk to have larger lesions (Bodner Lipa, Peist Mauricio, Gatot Albert, and Fliss Dan, 1997). The consistency of the lesion is dependent on the age of the lesion because as the time passes, maturation of the lesion (increase in collagen fibers) occurs and consistency shifts from being soft to firm (Muratakgül, Güngürmü and Harorli, 2004). Ulceration and bleeding can also be seen secondary to trauma (Eversole and Rovin, 1972).

Radiographic features usually are not very pronounced. However, sometimes they reveal superficial destruction of the alveolar margin or crest of the inter-dental bone when the lesion is seen associated with the teeth. In cases, where the granuloma is associated with the edentulous ridge, it characteristically exhibits superficial erosion of the bone with peripheral “cuffing” of the underlying bone (Shafer, 1983).

The differential diagnosis of peripheral giant cell granuloma includes pyogenic granuloma, fibrous epulis, peripheral ossifying fibroma, inflammatory fibrous hyperplasia, peripheral odontogenic fibroma and papilloma, all of which present with similar clinical and radiographic findings. Thus, in such cases a definitive diagnosis can only be established through histopathological examination (Regezi, 2000).

The histopathology of PGCG reveals a large number of multinucleated giant cells in a well-vascularized fibro-cellular stroma. In some cases, the giant cell may be found within the lumen of the capillaries. The exact origin of giant cells is still uncertain. Many opinions have been offered in the literature as osteoblasts, phagocytes, endothelial cells and spindle cells being the progenitors for the giant cell proliferations (Reichart and Philipsen, 2000). Hemorrhage, hemosiderin pigment, inflammatory cells and newly formed bone or mature calcified material may be present throughout the cellular stroma (Dayan, Buchner and Spirer, 1990). A zone of dense connective tissue representing a pseudo-capsule known as ‘Grenz zone’ usually separates the giant cell proliferations from the superficial epithelial layers (Osman A Etoz, Ahmet Emin Demirbas, and Mehmet Bulbul Ebru Akay, 2010). Apart from fibroblasts which are the basic element of the lesion, chronic inflammatory cells are usually seen in abundance with neutrophils mainly encountered in the ulcerated bases of the lesions.

Treatment consists of local surgical excision down to the underlying bone (Neville, 2004). A thorough debridement of local factors or irritants is also required (Regezi, 2000). If resection is only superficial, the growth may recur. Exposure of all bony walls following a thorough surgical resection responds satisfactorily most of the time (Medi, Eshghyar, Jafari, Lassehi, Navi and Abbas, 2007).

A recurrence rate of 5.0-70.6% has been reported in various epidemiologic studies (Reichart and Philipsen, 2000). A recurrence rate of 5% has been reported by the studies conducted by Giansanti and Waldron (1969), while a study by Eversole et al showed a recurrence of 11% (Eversole and Rovin, 1972).

Recurrences are believed to be related to lack of inclusion of the periosteum or periodontal ligament in the excised specimen (Regezi, 2000). A wide base re-excision of the lesion is often found to be satisfactory in treating these cases (Neville, 2004). In our case, recurrence was thought to be due to an inadequate therapy and incomplete removal of the base of the lesion by laser and electrocautery procedures. The treatment rendered in this case was surgical excision down to the level of underlying bone and curettage followed by oral prophylaxis. The 12 month follow-up of the patient showed no recurrence indicating that the given treatment along with maintenance of a good oral hygiene was sufficient for the complete cure of the lesion.

3 Conclusion
In conclusion, an early and precise diagnosis of PGCG is important to avoid unnecessary aggressive therapy. Complete removal of the lesion with proper periodontal therapy should be the treatment protocol to avoid recurrence. Identification of etiological factors is also important to avoid recurrence of such lesion. A definitive diagnosis of PGCG on the basis of clinical, radiological and histopathological examination thus leads to a proper treatment of the lesion lessening trauma to the subjacent vital structures.
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