Amlodipine induced plasma cell granuloma of the gingiva: A novel case report

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Abstract

Drug-induced gingival overgrowth (DIGO) can be a serious concern for both patients and clinicians. DIGO is a well-documented side-effect of some pharmacologic agents, including, but not limited to, calcium channel blockers, phenytoin, and cyclosporine. Plasma cell granulomas (pseudotumors) are exceedingly rare, non-neoplastic, reactive tumor-like proliferation, primarily composed of plasma cells that manifest primarily in the lungs, but may occur in various anatomic locations. Intraoral plasma cell granulomas

involving the lip, oral mucosa, tongue, and gingiva have been reported in the past. This is the first case report of amlodipine induced plasma cell granuloma of the gingiva in the medical literature presenting a 54 year-old female patient with hypertension, who received amlodipine (10 mg/day, single dose orally) for 2 years, sought medical attention because of developing maxillary anterior massive gingival overgrowth causing functional and esthetic problem, which was treated by excisional biopsy. Histologically, these lesions were composed of mature plasma cells, showing polyclonality for both lambda and kappa light chains and fibrovascular connective tissue stroma confirming a diagnosis of plasma cell granuloma. This case also highlights the need to biopsy for unusual lesions to rule out potential neoplasms.

Key words: Amlodipine, chronic periodontitis, immunohistochemistry, polyclonal plasma cell granuloma, reactive lesion

INTRODUCTION

Drug-induced gingival overgrowth (DIGO) remains a significant problem for the dental clinicians. An increasing number of medications are associated with the gingival overgrowth. Currently, more than 20 prescription medications are associated with the gingival enlargement.[1] Amlodipine is a third-generation dihydropyridine calcium channel blockers (CCB) that is used in the management of both hypertension and angina. Ellis *et al.*, first reported gingival sequestration of amlodipine and amlodipine-induced gingival overgrowth (AIGO).[2] Since then, very few isolated cases of AIGO have appeared in the dental literature although there are numerous reports of nifedipine induced gingival overgrowth until date. The incidence of gingival hypertrophy with nifedipine therapy has been reported to be as high as 20%. The prevalence of AIGO has been shown to be between 1.7% and 3.3%.[3]

Plasma cell granuloma is a rarely described tumor of unknown etiology and pathogenesis. Other synonyms have been used to describe similar lesions, such as inflammatory pseudotumor, histiocytoma, xanthomatous granuloma, inflammatory myofibroblastic tumor, and spindle cell pseudotumor.[4] It occurs primarily in the lungs, but has occurred in other extra-pulmonary sites. This lesion is not a neoplastic process, nor is it associated with a monoclonal expansion of a single plasma cell instead; this is a reactive, inflammatory lesion[5] which usually involves the mobile tissues of the oro-nasopharyngeal region, such as paranasal sinuses, buccal mucosa, tongue,[6] and lip.[7] They are even rarer on the gingiva and very few case reports have been documented.[8] It is often unusual and is associated with some chronic antigenic exposure. This could be due to periodontitis, periradicular inflammation or foreign bodies.[9]

There are no reports of amlodipine-related plasma cell granuloma of gingiva existing in the extant literature. The present case report describes an unusual case of amlodipine induced massive plasma cell granuloma on the gingiva.

CASE REPORT

A 54-year-old female patient reported to the multispecialty private dental clinic (Latur, India) with the chief complaint of diffuse swelling in the right maxillary anterior region. Patient was not aware of such growth until 8 months back when she noticed a small slowly growing bead-like nodular enlargement of the gums that gradually progressed to the present size covering almost the entire front teeth. Her past medical history revealed that the patient was hypertensive for last 2 years and was under medication (amlodipine 10 mg, once daily).

The lesion was asymptomatic, but the patient complained it to be severely interfering with mastication, speech, and oral hygiene practice resulting in functional and aesthetic problem. On intraoral examination, the lesion was a well-circumscribed exophytic sessile spherical mass of 1.5 inches diameter with color same as that of the surrounding oral mucosa with the scattered erythema [Figure 1]. The lesion was extended from distal surface of upper right canine to distal surface of upper left central incisor crossing the midline. It was non-tender and firm on palpation. All teeth involved in lesion were mobile and pathologically migrated. AIGO was also present in dentate area of lower arch. Poor oral hygiene status of the patient was assessed from the presence of local irritating factors contributing to the mild inflammatory component of the gingival enlargement.

Complete hemogram showed all blood counts to be within the normal limits. Urine examination was normal. Intraoral periapical radiograph and orthopantomogram in the region of AIGO showed generalized advanced horizontal bone loss around all teeth resulting in pathologic migration

The lesion was biopsied under local anesthesia. Maxillary teeth involved in lesion were extracted. The area was sutured and the specimen submitted for histopathological examination. As the extraction of all the remaining teeth with poor prognosis was planned substitution of amlodipine was not considered. Planned extraction of remaining mandibular teeth was carried out in subsequent

appointment. Following healing period of 2 months complete denture prosthesis was given to the patient.

Histopathological examination using hematoxylin and eosin stain, revealed proliferative parakeratinized stratified squamous epithelium, connective tissue with sheets of plasma cells intermixed with scattered small lymphocytes. The plasma cells were fairly uniform in appearance with scattered nucleoli present. Occasional dutcher bodies were seen overlying the plasma cell nuclei. The inflammatory infiltrate also contained varying numbers of neutrophils, lymphocytes and macrophages. Nuclear atypia was not seen [Figure 2].

Immunohistochemical study of the biopsy material revealed the polyclonal plasma cell infiltrate uniformly positive for CD138, a marker for plasmacytoid cells [Figure 3] and kappa light chain [Figure 4] and weak expression was noted for the lambda light chain. Absence of findings from common tetrad of multiple myeloma (CRAB: C = Calcium (elevated), R = Renal failure, A = Anemia, B = Bone lesions) ruled out its possibility.

On the basis of clinicohistopathologic examination and immunohistochemistry, a confirmative diagnosis of plasma cell granuloma was made. Healing was uneventful and the patient is presently under follow-up since 5 months. There has been no evidence of recurrence [Figure 5].

DISCUSSION

Amlodipine is commonly prescribed in family practice for hypertension. Gingival overgrowth is an often overlooked, but potentially harmful side-effect of treatment with amlodipine and other CCB. The reason for this adverse event is not absolutely known, but two main inflammatory and non-inflammatory pathways have already been suggested. The proposed non-inflammatory mechanisms include defective collagenase activity due to decreased uptake of folic acid, blockage of aldosterone synthesis in the adrenal cortex and consequent feedback increase in Adrenocorticotropic hormone level, and up-regulation of keratinocyte growth factor. Alternatively, inflammation may develop as a result of direct toxic effects of concentrated drug in gingival crevicular fluid and/or bacterial plaques. This inflammation could lead to the up-regulation of several cytokine factors such as Transforming growth factor beta.[10] In a series of 150 cardiac patients, it was found that amlodipine at a dose of 5 mg/day cannot induce gingival hyperplasia even if taken more than 6 months.[11]

Plasma cells are terminally differentiated B lymphocytes, which are typically found in the red pulp of the spleen, medulla of the lymph nodes, tonsils, lamina propria of the entire gastrointestinal tract, mucosa of the nose and upper airway, and sites of inflammation. A plasma cell's main function is to produce immunoglobulins or antibodies.[5] Periodontal lesions with a predominance of plasma cells were reported initially by during late 1960s[12] and only very few case reports have been documented since then.[13-16] These cases reported a similar reactive gingival growth with similar histological and clinical appearance, which was

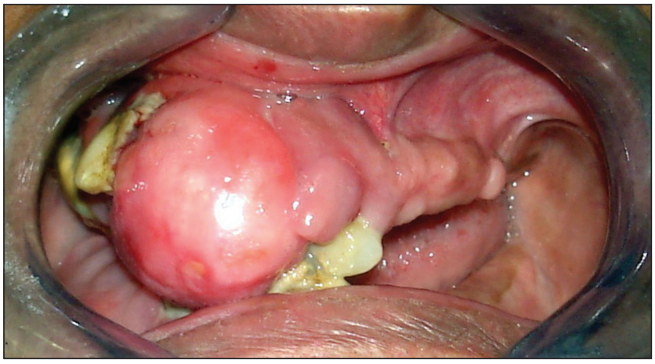

Figure 1: Pre-operative clinical presentation of amlodipine induced plasma cell granuloma of gingiva

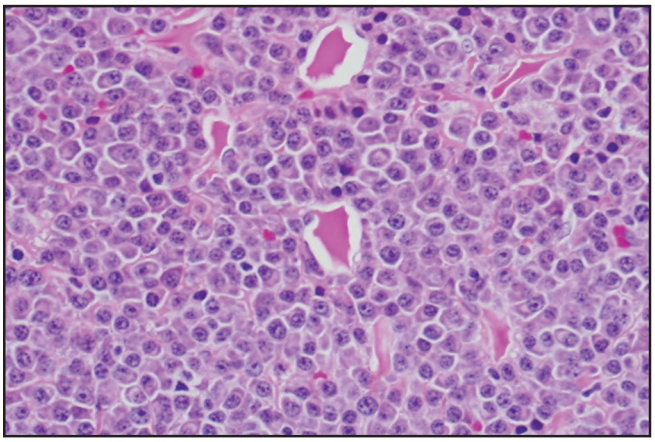

Figure 2: High power microscopy: H and E staining shows sheets of plasma cells intermixed with scattered small lymphocytes

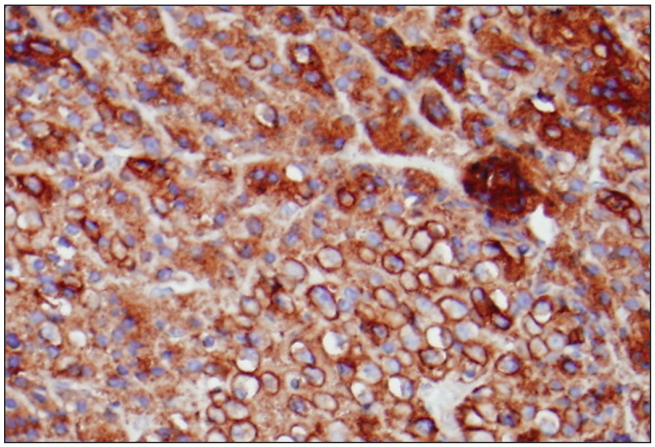

Figure 3: Positive staining for D138

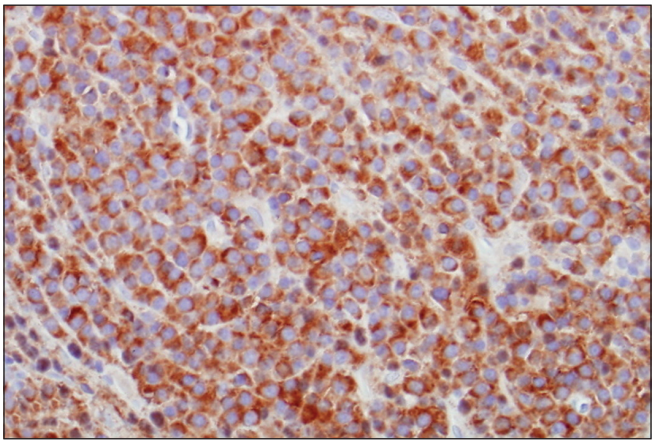

Figure 4: Positive staining for kappa light chain

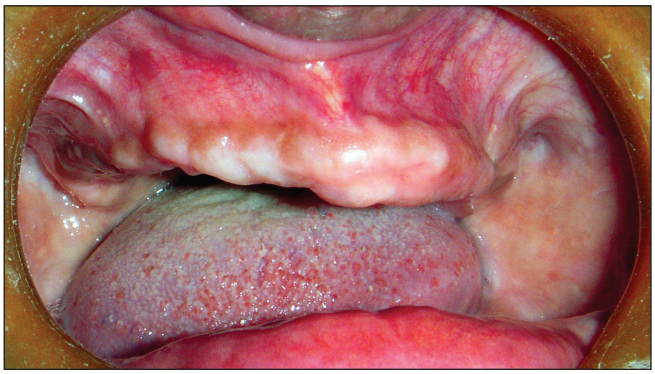

Figure 5: Post-operative clinical presentation

treated by excisional biopsy, as in the present case.

Gingival plasma cell granulomas have been reported in patients with cyclosporine-induced gingival overgrowth. It was suggested that interleukin-6 and phospholipase C-γ1 may induce heavy plasma cell infiltration in cyclosporine-induced gingival overgrowth.[17]

It is important to differentiate plasma cell granulomas from tumors of bone such as multiple myeloma, solitary myeloma, and soft-tissue myeloma (extramedullary plasmacytoma) considering the poor prognosis of these neoplasms. Plasmacytoma and plasma cell granuloma are soft-tissue tumors. Differentiating the type of soft-tissue tumor is mandatory, as plasma cell granuloma may be benign, extramedullary plasmacytoma may be malignant or a precursor to malignancy.[13,18]

Histologically, extramedullary plasmacytoma consists of mixture of typical and atypical plasma cells while plasma cell granuloma consists of normal plasma cells and small lymphocytes that are surrounded by connective tissue septa.[16] The immunohistochemical analysis have shown that in the case of malignancy ratio of the kappa to lambda light chain may be greater than 10:1 or 1:10, whereas in a reactive lesion the ratio is 2:1.[19]

Plasma cell lesions with the predominance of plasma cells may represent an autoimmune reaction or an alteration of blood-flow imposing congestive vasodilatation or lesions occurring due to parasitic infiltration.[6,20] Recent studies have reported that a gingival plasma cell granuloma shows variable gene expression for cell-mediated immunity and stromal tissue degeneration, undergoing sclerotic fibrosis with a persistent inflammatory reaction.[21]

In conclusion, amlodipine induced plasma cell granuloma of gingiva is a distinct pathological entity characterized by the presence of mature polyclonal plasma cell sheets and fibrovascular connective tissue stroma. While the mechanism of amlodipine-induced gingival plasma cell granuloma of gingiva is considered to be multi-factorial, the drug/cellular interaction may play an important role in the pathogenesis of this entity. This case highlights the need to biopsy unusual lesions to rule out potential neoplasms and also emphasizes the need to submit the excised tissue for histopathological examination regardless of clinical notion and/or perceived surgical success.

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