

Multicentric peripheral ossifying fibroma

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Abstract: Peripheral ossifying fibroma (POF) is a common solitary gingival growth thought to arise from the periodontal ligament. Though the etiology of POF remains unknown, some investigators consider it an inflammatory or reactive process, while others suggest it is a neoplastic process. In this report, we present and discuss a unique case of multicentric POF, affecting the maxillary and mandibular gingiva of a 49-year-old Caucasian female with meticulous oral hygiene and routine dental care. Though biopsy samples from multiple sites revealed similar histopathologic features, consistent with POF, the fact that there was a multicentric presentation is a unique phenomenon for this lesion. Multicentric lesions presenting in the oral and maxillofacial region are not typical, but have been observed in conditions associated with known genetic mutations, such as nevoid basal cell carcinoma syndrome (multiple odontogenic keratocysts), multiple endocrine neoplasia type II (multiple neuromas), neurofibromatosis (multiple neurofibromas) and Gardner syndrome (multiple neoplasms). This case is the first one to demonstrate that there may be a multicentric variant of POF that has not been previously

recognized, and given the clinical presentation and multifocal nature of disease, the lesions in this patient are likely the result of genetic mutation(s) that predisposes to gingival soft tissue overgrowths containing mineralized product. (*J. Oral Sci.* 48, 239-243, 2006)

Keywords: peripheral ossifying fibroma (POF); multicentric; multifocal.

Introduction

The peripheral ossifying fibroma (POF) is a common gingival growth usually arising from the interdental papilla. Females are more commonly affected than males, and the anterior maxilla is the most common location of involvement. The lesion occurs in any age group, predominating in the second decade of life (1). POF is typically a solitary, slowly growing nodular mass that is either pedunculated or sessile (2). The surface mucosa is usually smooth or ulcerated and pink to red in color (3,4). Migration of teeth with interdental bone destruction has been reported in some cases (5). POF usually measures <1.5 cm in diameter, but patients with lesions of 6 cm and 9 cm diameter have been reported (5,6). The etiology and pathogenesis of POF remains unknown. Some investigators consider it a neoplastic process, while others argue it is a reactive process; in either case, the lesion is thought to arise from cells in the periodontal ligament. Trauma or local

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irritants, such as dental plaque, calculus, microorganisms, masticatory forces, ill-fitting dentures and poor quality restorations have been implicated in the etiology of POF (2,7).

Clinical findings alone are not sufficient for a diagnosis of POF because there are other conditions that may have similar clinical appearances and clinical courses, such as pyogenic granuloma or peripheral giant cell granuloma. Therefore, biopsy and histopathologic examination is required for definitive diagnosis. The histologic spectrum of POF is wide and has been described in detail by Buchner et al. (3). Basically, the lesion represents varying stages of a fibroma with ossification as the name POF implies; however, ossification or calcification may not be evident in all cases, particularly in earlier stages of lesional growth. POF can produce a mild cupping defect of adjacent alveolar bone. Though radiographic changes are not always seen with POF, occasionally foci of radiopaque material may be seen, particularly in larger lesions or lesions with overt mineralization (8,9). In children, POF has been noted to cause alveolar erosion, displacement of teeth, and a delay in tooth eruption (9). After elimination of local etiological factors like plaque, calculus, ill-fitting dentures and poor quality restorations, local surgical excision of POF is the preferred treatment. Excision should include the periodontal ligament and periosteum at the base of the lesion in order to reduce the chance of recurrence. Recurrence rates of 8% to 20% have been reported (1-4,9).

POF typically occurs as a solitary gingival growth. In this report, we present and discuss a unique case of *multicentric* POF, affecting the maxillary and mandibular gingiva of a 49-year-old Caucasian female. Multicentric lesions presenting in the oral and maxillofacial region are not typical, but have been observed in conditions associated with known genetic mutations, such as nevoid basal cell carcinoma syndrome (multiple odontogenic keratocysts), multiple endocrine neoplasia type II (multiple neuromas), neurofibromatosis (multiple neurofibromas) and Gardner syndrome (multiple neoplasms). This case is the first one to demonstrate that there may be a multicentric variant of POF that has not been previously recognized.

Case Report

A 49-year-old Caucasian female presented to the Oral Health Center at the University of Southern California, School of Dentistry, for routine care and management of multiple, recurring gingival growths. The patient had been managed previously by many physicians and dental specialists for the same complaint, but the lesions were recurrent and persistent. The patient had no children, and no other immediate family members had any similar

problems. The lesions started developing in 1992, initially occurring on one side of the mouth and in the course of the subsequent years it eventually involved both sides. Both maxillary and mandibular gingiva was affected, and the growths appeared as nodular masses with erythematous, ulcerated surfaces (Fig. 1). Pain and bleeding could be induced by palpation of the lesions. The growths were sessile and firm in consistency, measuring from 5 mm in diameter to 3 cm in diameter. The patient maintains good oral hygiene and has been under routine periodontal care since the onset of the lesions in 1992. The patient's main concerns are that the lesions are painful and interfere with masticatory function, and that they are not esthetic and often appear to bulge out from her face, particularly the larger lesions.

Multiple biopsies and numerous conventional surgical procedures, mainly involving simple excision and electrosurgery, had been done over the last 12 years but the lesions recurred within a few months after removal. The patient had also received steroid therapy both intra-lesionally and systemically without much effect. Multiple attempts with antibiotic therapy did not have any effect either, and in 2003 the patient was taking gabapentin, butalbital compound with codeine for pain control, low dose vitamin B-complex and tetracycline with no improvement of her condition. The patient's medical history was significant for measles, mumps, chicken pox and infectious mononucleosis in 1972, anemia in 1999, bladder infections, intermittent headaches and nervousness. She had undergone tonsillectomy in 1968 and removal of a branchial cleft cyst in 1992 without complications (Table 1). The patient gave a history of smoking since she was a teenager, but that she stopped in 1992 shortly before the onset of the lesions. She drank alcohol occasionally and minimally, and denied drug abuse. Routine blood chemistry and complete blood count levels taken yearly were always within normal limits. Laboratory tests performed throughout the course of her condition, which included analysis of most major auto-antibodies, were unremarkable. Comprehensive metabolic work-up along with lipid and thyroid panels were within normal limits. Tests for hepatitis A, B and C were negative and hormonal (LH, FSH) tests were within normal limits. Anaerobic culture and DNA analysis, performed in order to detect periodontal organisms including *Porphyromonas gingivalis* and *Tannerella forsythia* were negative.

Histopathologic examination of biopsy specimens following surgical excision early in the course of disease revealed patterns consistent with the diagnosis of peripheral ossifying fibroma, as interpreted by a dermatopathologist and general pathologist. Biopsy specimens, each obtained from a separate site of involvement in the mandible and

maxilla, demonstrated interweaving fascicles of moderately cellular fibrous connective tissue with scattered inflammatory cells, occasional mitotic figures of normal configuration, minimal collagen under polarized light examination, minimal cytological atypia, no odontogenic epithelium, small islands of acellular, osteoid or cementum-like material near the surgical base of some sections, and no necrosis or evidence of malignancy. Masson-trichrome staining revealed minimal collagen formation but no muscle fibers. Special staining for a neural marker (S-100) and a muscle marker (SMA; smooth muscle actin) were negative.

Recently in 2005, another surgical attempt at excision of the lesions yielded four more biopsy samples, two from the maxilla and two from the mandible, each representing a distinct non-contiguous site of involvement. Microscopic examination of each of these lesions by a board certified oral and maxillofacial pathologist revealed a consistent pattern, similar to the pattern seen in earlier biopsy specimens. All specimens appeared as soft tissue nodules consisting of an oral stratified squamous surface epithelium in association with an underlying proliferation of fibrous and myofibromatous connective tissue arranged in interweaving fascicles (Fig. 2). In some sections, the surface mucosa was ulcerated and exhibited a fibrino-purulent membrane. Osseous-like mineralized tissue of varying sizes could be identified in sections, appearing similar to mature bone with osteocyte-like cells in lacunae. Histopathologic findings were consistent with a uniform diagnosis of multicentric peripheral ossifying fibroma, which correlated with the clinical presentation.

Discussion

Peripheral ossifying fibroma (POF) is a common gingival growth that is thought to be either reactive or neoplastic in nature. Considerable confusion has prevailed in the nomenclature of POF, and this may have contributed to

Table 1 Past medical, dental and treatment history

	Conditions and Treatment
Medical History	Mcasles, mumps, chicken pox and infectious mononucleosis in 1972 Anemia in 1999 Bladder infections Intermittent headaches Nervousness
Surgical History	Tonsillectomy in 1968 Removal of a branchial cleft cyst in 1992 without complications
Dental History	Multiple, recurring gingival growths since 1992 Treatment: i) Multiple biopsies and numerous conventional surgical procedures, mainly involving simple excision and electrosurgery ii) Steroid therapy both intra-lesionally and systemically iii) Antibiotic therapy iv) Gabapentin, Butalbital compound with Codeine for pain control, low dose vitamin B-complex and Tetracycline

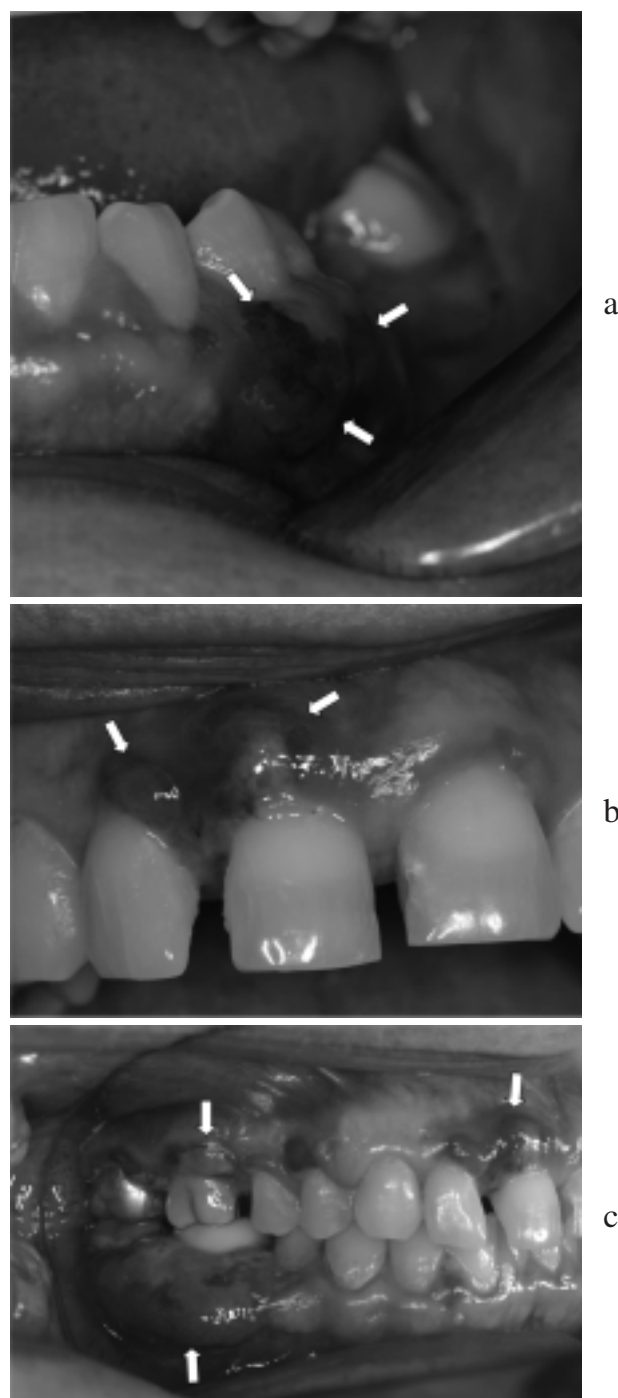
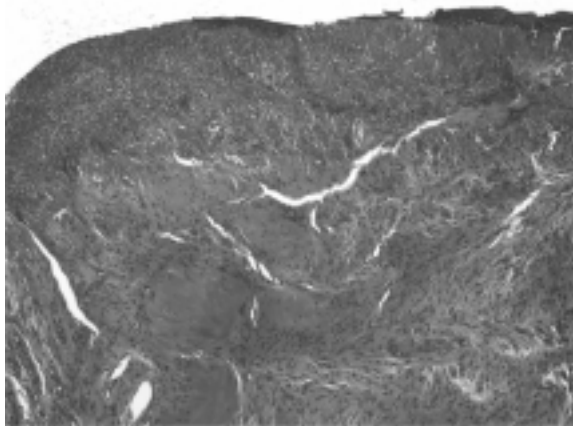
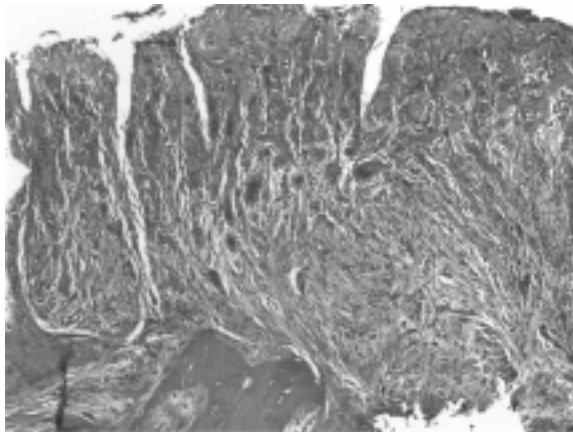


Fig. 1 a. Clinical image of the left mandible showing ulcerated and erythematous nodules (arrows) involving the gingiva in the premolar region.
b. Clinical image of anterior maxilla showing ulcerated and erythematous nodules (arrows) involving the gingiva of the patient's right central and lateral incisors.
c. Clinical image showing a relatively larger ulcerated and erythematous nodular mass (arrows) involving the right posterior mandibular gingiva, and smaller nodules (arrows) affecting the premolar and molar gingiva of the right maxilla in addition to the anterior maxillary lesions shown in Fig. 1b.

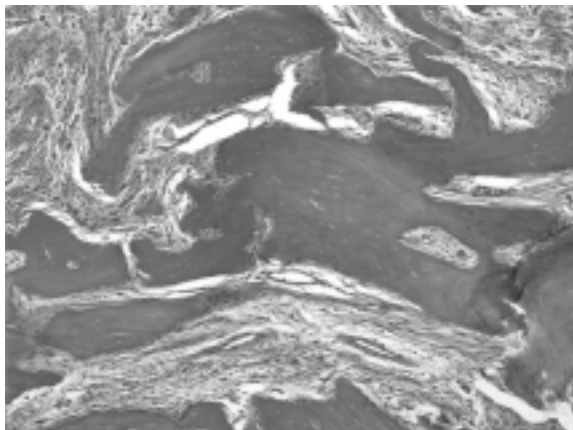
an obscured understanding of these lesions. The commonly used synonyms for POF include peripheral cementifying fibroma, peripheral fibroma with cementogenesis, peripheral fibroma with osteogenesis, peripheral fibroma with calcification, calcifying or ossifying fibrous epulis and calcifying fibroblastic granuloma (3,4). The term 'peripheral odontogenic fibroma' has also been used to describe peripheral ossifying fibroma, but should be avoided since peripheral odontogenic fibroma has been designated by the World Health Organization (WHO) as the rare and extraosseous counterpart of central odontogenic fibroma (7,10,11).



a



b



c

The definitive diagnosis of POF is made by histopathologic evaluation of biopsy specimens. The following features are usually observed during microscopic evaluation: 1) benign fibrous connective tissue with varying content of fibroblasts, myofibroblasts and collagen, 2) sparse to profuse endothelial proliferation, 3) mineralized material which may represent mature, lamellar or woven osteoid, cementum-like material, or dystrophic calcifications. Acute or chronic inflammatory cells can also be identified in lesions. Most of these features were present in our case. Local surgical excision of POF is the preferred treatment, which was performed in this case on multiple occasions over a 12-year period without success since new lesions continued to appear. When POF involves teeth, extraction of teeth is considered unnecessary as a therapeutic modality. In the case presented here, interestingly, the patient had a molar tooth extracted because of a failed root canal, and at the same time a POF adjacent to the tooth was completely excised, but another lesion subsequently appeared at this edentulous site.

Though the etiopathogenesis of POF is uncertain, an origin from cells of the periodontal ligament has been suggested (1,2). The reasons for considering a periodontal ligament origin for POF include: exclusive occurrence of POF in the gingiva (interdental papilla), the proximity of gingiva to the periodontal ligament, the presence of oxytalan fibers within the mineralized matrix of some lesions, the

Fig. 2 a. Surgical biopsy samples from the clinical lesions shown earlier in Fig. 1 revealed a histopathologic pattern similar to the one shown in this photomicrograph, which is consistent with a diagnosis of peripheral ossifying fibroma. Lesions were characterized by a proliferation of fibrous and myofibromatous connective tissue arranged in interweaving fascicles as shown here. (H&E, decalcified specimen, $\times 20$ original magnification)
 b. In most specimens, the surface mucosa was ulcerated as seen in this section. Mineralized (calcified) osseous-like tissue of varying density was also seen in the submucosa, such as the fragment shown at the bottom of this image which appears like a piece of bone. (H&E, decalcified specimen, $\times 20$ original magnification)
 c. Medium-power photomicrograph showing the osseous-like hard tissue identified in the biopsy samples from the patient. This pattern of mineralization in association with a benign proliferation of fibrous connective is highly characteristic for well-developed peripheral ossifying fibromas. (H&E, decalcified specimen, $\times 40$ original magnification)

age distribution which is inversely related to the number of lost permanent teeth, and the fibrocellular response in POF which is similar to other reactive gingival lesions of periodontal ligament origin (2,7). However, the recurrence of POF at an edentulous site in this case may cast doubt on the PDL theory of origin, at least with respect to this particular patient. Classically, local factors such as trauma, or irritants such as dental plaque, calculus, microorganisms, masticatory forces, ill-fitting dentures and poor quality restorations are implicated in POF induction or progression (2,7). In addition, factors such as a high female predilection and a peak occurrence in the second decade of life suggest hormonal influences (4). The etiopathogenesis for the case reported here is uncertain and intriguing because the patient is a female, but the growths continue to recur despite adequate surgical excision, meticulous oral hygiene, elimination of local irritants, and multiple test results indicating normal hormone levels as presented earlier.

POF has always been described as a solitary, slowly growing nodular mass. The case described here is unique because it the first time a multicentric variant of POF has been reported. Multicentric lesions presenting in the oral cavity are not typical, but have been observed in conditions such as nevoid basal cell carcinoma syndrome (multiple odontogenic keratocysts), multiple endocrine neoplasia type II (multiple neuromas), neurofibromatosis (multiple neurofibromas) and Gardner's syndrome (multiple neoplasms) (12). All of these conditions have been associated with inherited genetic mutations, so the potential exists that this case of multicentric POF is the result of a genetic mutation that predisposes to gingival soft tissue overgrowths that contain mineralized product or ossification. Although many consider POF to be reactive in nature as mentioned earlier, this case may represent true neoplasia given the presentation. Unfortunately, little is known with respect to the pathogenesis and molecular or genetic profile of these lesions. Therefore, further analysis of this patient, such as karyotyping, may give insight into any chromosomal or genetic abnormalities that could be present, and whether or not they are constitutional and can be passed to offspring. Tissue specimens acquired from the patient after future excisional biopsies will be used to develop *in vitro* cell cultures in order to serve as an experimental model so that we may begin to characterize the gene expression patterns linked to the pathogenesis of this unique presentation of POF. Further, since the mineralized component of POF is generally poorly understood, it will be interesting to investigate the

mineralization patterns of these lesions and compare them to known hard tissue forming cells, genes and molecular signals that are classically associated with mineralization or ossification.

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