

Peripheral ossifying fibroma: a clinical and immunohistochemical study of four cases

José A. García de Marcos¹), María J. García de Marcos²),
Susana Arroyo Rodríguez¹), Jaime Chiarri Rodrigo³) and Enrique Poblet⁴)

¹)Department of Oral and Maxillofacial Surgery, Albacete University Hospital Complex, Albacete, Spain

²)Stomatologist, Private practice, Madrid, Spain

³)Department of Pathology, Albacete University Hospital Complex, Albacete, Spain

⁴)Department of Pathology, Albacete University Hospital and Medical School of Albacete, Albacete, Spain

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Abstract: Peripheral ossifying fibroma (POF) is a lesion of the gingival tissues that predominantly affects women and is usually located in the maxilla anterior to the molars. The definitive diagnosis is established by histological examination, which reveals the presence of cellular connective tissue with focal calcifications. Surgery is the treatment of choice, though the recurrence rate can reach 20%. We present a clinical and histological review – including a detailed immunohistochemical analysis – of four cases of POF diagnosed and treated at our hospital. All four patients were women, and two were pregnant. The immunohistochemical study revealed that the proliferating cells showed myofibroblastic characteristics and did not express estrogen or progesterone receptors. The lesions showed clinically benign behavior. Our results indicate that POF should be considered as a myofibroblastic proliferation, and although the clinical characteristics suggest hormonal influence, we were unable to demonstrate the expression of hormone receptors in the proliferating cellular component. (*J Oral Sci* 52, 95-99, 2010)

Keywords: peripheral ossifying fibroma; oral cavity; epulis; gingival; peripheral cementifying fibroma.

Correspondence to Dr. José A. García de Marcos, Antonio Acuña 10-5A izq, 28009 – Madrid, Spain
Tel: +34-605456183
Fax: +34-967243952
E-mail: pepio2@hotmail.com

Introduction

Peripheral ossifying fibroma (POF) is a lesion of the gingival tissues (1-5) representing up to 2% of all oral lesions that are biopsied (1). Other terms used in reference to POF are peripheral cementifying fibroma, peripheral fibroma with cementogenesis, peripheral fibroma with osteogenesis, peripheral fibroma with calcification, calcified or ossified fibrous epulis, and calcified fibroblastic granuloma (3,6,7).

POF mainly affects women in the second decade of life (1,2,5,6) (50% of all patients being between 5-25 years of age). The lesions are most often found in the gingiva, located anterior to the molars (1,2) and in the maxilla (8). Clinically, POF usually manifests as a well-defined and slow-growing gingival mass measuring under 2 cm in size and located in the interdental papilla region (1,2,5-7,9). The base may be sessile or pedunculated, the color is identical to that of the gingiva or slightly reddish, and the surface may appear ulcerated (1,2,5-7).

The definitive diagnosis is based on histological examination (6,7), with the identification of cellular connective tissue and the focal presence of bone or other calcifications (1,6,8). However, it has not been established whether POF is a tumor or represents proliferation of a reactive nature.

Surgery is the treatment of choice, though the recurrence rate can reach 20%. POF shows a clinically benign behavior (1,2,6,7).

We present a clinical, histological and immunohistochemical review of four cases of POF diagnosed and

treated at our hospital. The study focuses on aspects that have not been previously evaluated and which may help to clarify the nature of these lesions.

Materials and Methods

Specimens from four cases of peripheral ossifying fibroma were retrieved from the Department of Pathology of the Albacete University General Hospital (Albacete, Spain). All the specimens had been fixed in 10% buffered formalin and embedded in paraffin. Slides of paraffin blocks were prepared for immunohistochemical analysis using a standard avidin-streptavidin staining method and a DakoCytomation Autostainer (Dako, Glostrup, Denmark). Briefly, the paraffin sections were deparaffinized and steamed for 40 min in citrate buffer, pH 7, at 95°C. The incubation time with the primary antibodies was 30 min. As secondary antibodies, we used those included in the REAL detection System kit (Dako), with an incubation time of 15 min. The diaminobenzidine reaction was used for visualization, followed by hematoxylin counterstaining. Appropriate positive and negative controls were used.

Primary anti-human antibodies used in this study were as follows: anti alpha-inhibin (monoclonal, clone R1, Dako), anti-vimentin (monoclonal, clone V9, Dako), alpha smooth muscle actin (monoclonal, clone 1A4, Dako), anti-CD117 c-kit (polyclonal, Dako), anti-CD34 class II (monoclonal, clone QBEnd-10, Dako), anti-CD10 (monoclonal, clone 56C6, Novocastra Laboratories, Newcastle, UK), anti-p21 (monoclonal, clone 1F8, Dako), anti S-100 (polyclonal, Dako), anti-vimentin (monoclonal, clone 56C6, Novocastra Laboratories), anti-estrogen (monoclonal, clone 6F11, Novocastra Laboratories), anti-

progesterone receptor (polyclonal, Dako), anti-specific muscle actin (monoclonal, clone HHF35, Dako), and anti-CD68 (monoclonal, clone KP1, Dako).

Results were semiquantitatively evaluated as follows: (-) no staining; (+) weak and focal staining of less than 20% of all spindle cells; (++) intense staining of more than 20% and less than 60% of all cells; and (+++) intense staining of more than 60% of all cells. Only spindle cells were evaluated.

Results

Table 1 shows the clinical characteristics of the four patients included in the study.

All were women, with a mean age of 42 years (range 32-65 years). Two cases (50%) appeared during pregnancy, and the mean time from appearance of the lesion to first consultation was 18.8 months. Fifty percent of the POFs appeared in the maxilla, while the other 50% were located in the mandible. Three cases were located in the molar region, and one in the incisal area. The lesion size ranged from 0.3-1 cm, with a mean size of 0.5 cm. Clinically, two of the cases manifested as a sessile granulomatous lesion, while the other two were pedunculated.

None of the lesions relapsed after resection, with a mean follow-up of 3.9 years (Fig. 1). The lesion in case number 3 had been resected several times in the past at other centers as a consequence of multiple relapses. However, no relapse was observed 1 year after treatment in our hospital.

All the lesions presented a cellular component in the form of fusiform cells, without significant atypias. This proliferation was accompanied by an inflammatory

Table 1 Demographic and clinical characteristics of the patients with peripheral ossifying fibroma

	Sex	Age	Time from appearance to first consultation	Predisposing factors	Location	Size	Clinical manifestations	Postoperative course
Case 1	Female	32	8 months	Pregnancy	Maxilla, incisal region, palatine gingiva	0.5 cm	Sessile, granulomatous lesion	No relapse after 3 years and 10 months
Case 2	Female	65	1 ½ months	–	Mandible, molar region, edentulous crest	0.3cm	Pedunculate lesion	No relapse after 6 years and 6 months
Case 3	Female	35	5 years	Pregnancy	Maxilla, molar region, vestibular gingiva	0.3cm	Sessile, granulomatous lesion	No relapse after 1 year
Case 4	Female	36	6 months	–	Mandible, molar region, lingual gingiva	1 cm	Pedunculate lesion	No relapse after 4 years and 3 months

component of lymphocytes, plasma cells, CD68-positive histiocytes, and multinucleated giant cells. Bone trabecular structures and focal calcification were also observed (Figs. 2 and 3A).

An immunohistochemical study was made to determine the nature of the proliferating fusiform cells. The results are summarized in Table 2 (Fig. 3B-D). The study showed the cells to be of a myofibroblastic nature (vimentin +, actin HHF35 +). The proliferating component did not express estrogen or progesterone receptors.

Discussion

The term “epulis” includes a series of reactive gingival lesions often produced by irritating agents. The diagnosis is usually established on the basis of the clinical findings,

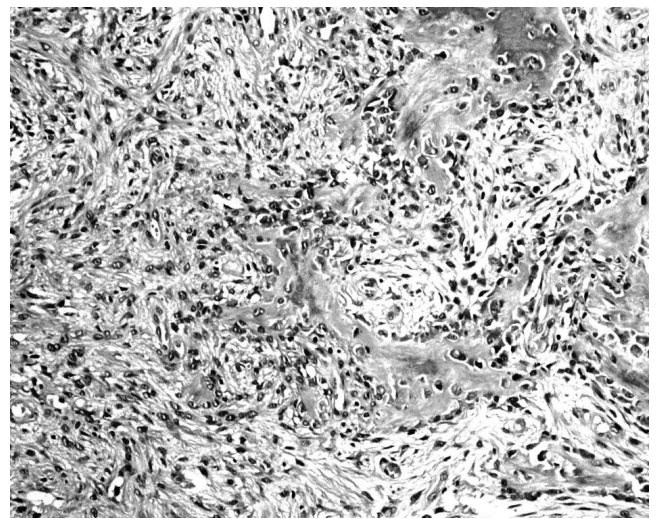


Fig. 2 Fascicles of spindle cells with areas of calcification are observed. An inflammatory lymphohistiocytic infiltration is also noted (H-E staining).

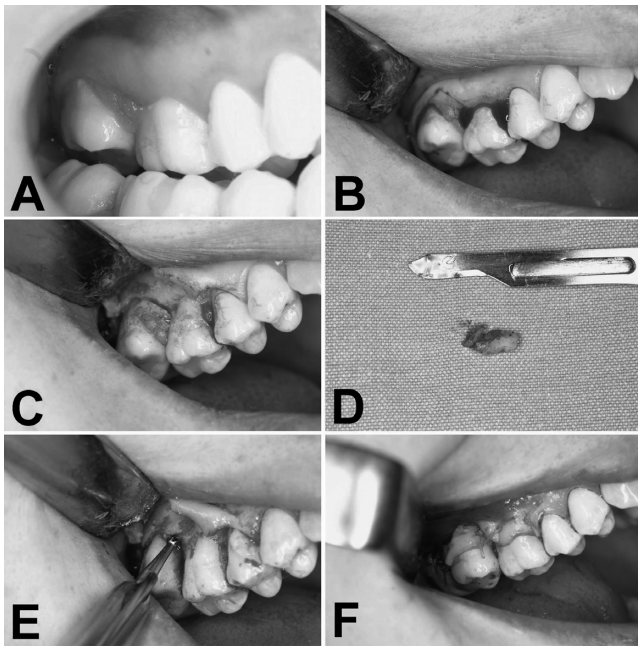


Fig. 1 Case 3. A: Sessile granulomatous lesion located in the interdental papilla between the upper right first and second molars; B: Resection with surgical margins; C: Raising of the mucoperiosteal flap; D: Surgical piece; E: Drilling of the underlying bone; F: Repositioning of the mucoperiosteal flap.

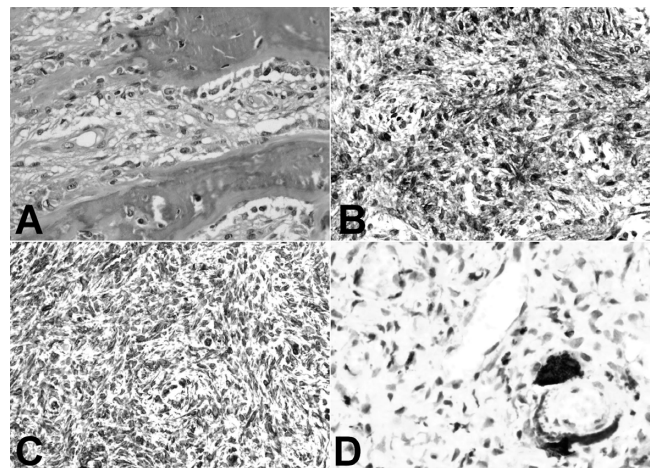


Fig. 3 A: Lesions showed prominent spindle cell proliferation and bone trabecula with osteoblastic rimming (H-E staining); B: Alpha smooth muscle actin immuno staining shows intense cytoplasmic positivity of most cells; C: Immunohistochemically, vimentin showed intense and diffuse cytoplasmic positivity; D: Anti-CD68 revealed that multinuclear giant cells, but not spindle cells, were immunostained.

Table 2 Results of the immunohistochemical study. Results shown are only of the proliferated spindle cells

	c-Kit	REN	Prog	ASM	p21	Vimentin	Actin	CD10	CD34	α-inhb	CD68	Mac 386	S-100
Case 1	-	-	-	-	-	++	++	-	-	-	-	-	-
Case 2	-	-	-	-	-	+++	++	-	-	-	-	-	-
Case 3	-	-	-	-	-	+++	++	-	-	-	-	-	-
Case 4	-	-	-	+	-	+++	+++	-	-	-	-	-	-

with few clinical differences noted among the different disorders included under this term; these disorders include POF, peripheral fibroma, peripheral giant cell granuloma, and pyogenic granuloma (8). The latter condition could represent an early, immature form of POF (2,7,8). Zahang et al. (8), in a study of 2,439 cases of epulis, recorded the following prevalence values: peripheral fibromas, 61.05%, pyogenic granulomas, 19.76%, POF, 17.67%, and peripheral giant cell granulomas, 1.52% (8). POF is firmer and less friable than the rest of the lesions, and typically shows a longer course. This explains the calcification and/or ossification secondary to fibroblast maturation to collagen tissue (2,8).

The etiology and pathogenesis of POF are not known (5-7). It has been suggested that these lesions originate in the cells of the periodontal ligament for the following reasons: POF exclusively appears in the gingival tissue, close to the periodontal ligament; oxytalan fibers are found within the mineralized matrix of some lesions; the age distribution of the lesions is inversely proportional to the number of permanent teeth lost; and the fibrocellular response of POF is similar to that of other reactive gingival lesions originating in the periodontal ligament (3,6). The results that we now report represent further evidence of the fibroblastic-myofibroblastic nature of the lesion, and are consistent with a possible origin in the periodontal ligament.

Since POF has an obvious predilection for females and occurs frequently in specific periods of life such as puberty and pregnancy, the existence of hormonal factors in the development of POF has been suggested in the literature (10). Although all patients in our series were women, and two of the cases appeared during pregnancy, our immunohistochemical study did not show estrogen or progesterone receptor positivity in any case. Failure to demonstrate estrogen or progesterone receptors immunohistochemically may indicate low increases in their levels, or a possible endocrine influence through mechanisms that do not imply an increase in receptor expression. Other factors that have been implicated in the etiopathogenesis of POF are trauma and local irritants such as tartar, microorganisms, and chewing forces (6,7).

It has been suggested that POF would be a consequence of periodontal ligament hyperplasia that may be accompanied by rests of Malassez, which could be incorporated into the lesions, thereby accounting for the POF variant that contains odontogenic epithelium (known as peripheral odontogenic fibroma) (2). Another variant is cemento-ossifying peripheral fibroma, characterized by the presence of cementum within a POF-compatible lesion (5).

The mean age of the patients was 42 years; all subjects

were older than the average age reported in the literature (second decade of life), and the oldest was 65 years old.

Radiologically, and depending on the size of the ossification foci, radiopaque stains can be seen on the periapical or panoramic X-rays (2,6,7,9).

Histologically, POF is composed of cellular fibrous tissue with areas of fibrovascular tissue that often contain an inflammatory component with abundant plasma cells (2). The lesion is not encapsulated (2,7). When the lesions mature, the stromal cellularity decreases, and bony tissue increases (1,6). Ossification is usually seen in the cellular zone, and shows considerable variation both quantitatively and qualitatively. From small rounded calcified deposits to large trabecular bone areas surrounded by osteoblasts may be observed (2). Multinucleated giant cells can be present, though they do not represent an essential component (1,2). Ten percent of all cases of POF may contain odontogenic epithelial nests as vestigial representation of the dental lamina (1). Our patients showed all these differential features. The immunohistochemical study made illustrates a panel of markers that may be used to establish a differential diagnosis with respect to lesions such as pyogenic granuloma or peripheral giant cell granuloma. In addition, the observed immunohistochemical profile indicates that the proliferating cells are of a myofibroblastic nature (i.e., cells sharing morphological characteristics with fibroblasts and muscle cells). Myofibroblastic proliferation has been described as a reaction to inflammation, in pseudosarcomatous proliferations (e.g., nodular fasciitis), or in myofibroblast tumors. The studied cases moreover indicated a CD68-positive histiocytic component intermingling with lymphocytes and plasma cells, suggesting the existence of a reactive phenomenon or a response to inflammation.

The treatment of choice for POF is local resection with peripheral and deep margins including both the periodontal ligament and the affected periosteal component (1,2,6,9). In addition, elimination of local etiological factors such as bacterial plaque and tartar is required (6). The teeth associated with POF are generally not mobile, though there have been reports of dental migration secondary to bone loss. Extraction of the neighboring teeth is usually not considered necessary (2,6).

The exposed bone should be covered with adjacent gingival flaps (9). Chen et al. (9) reported a case in which the gingival defect was satisfactorily covered using an artificial dermal graft. Recurrence is probably a result of incomplete resection of the lesion, failure in sectioning the periodontal ligament, or the development of new lesions (1,2).

Our cases of peripheral ossifying fibroma reflect the

typical features of this disorder, as reported in the literature, and confirm their benign nature. Our results indicate that POF should be considered as a myofibroblastic proliferation, and although the clinical characteristics suggest a hormonal influence, we were unable to demonstrate the expression of hormone receptors in the proliferating cellular component.

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