

Clinicopathological features of peripheral ossifying fibroma in a series of 41 patients

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Abstract

Peripheral ossifying fibromas are benign mesenchymal lesions that usually arise in the anterior maxilla of young female patients. Histologically they consist of spindle cell proliferation with focal mineralisation. We reviewed 48 specimens from 41 patients and recorded the clinical data, sex, and age of the patients, site and size of the lesions, treatment, and postoperative outcome. Histologically the presence of mature, woven bone, cementum, and calcifications were evaluated and evaluated immunohistochemically. Lesions were more frequent in female patients in the third and fourth decade, and were usually in the lower maxilla and smaller than 2 cm. All lesions were conservatively excised, and they relapsed in eight patients. Histopathologically, the lesions were poorly circumscribed, moderately cellular proliferations, with no discernible architectural pattern. All tumours showed some degree of mineralisation, the presence of immature bone being the most common. Immunohistochemical examination showed staining of tumoural cells for smooth muscle actin and CD68. Lesions tended to occur more commonly in female patients, but one decade later than usually reported. We found a higher recurrence rate in lesions that contained cementum-like material but without bone formation, suggesting a lack of maturation in this group. Immunohistochemical results were consistent with myofibroblastic differentiation but they added no information about the behaviour of the lesions.

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Introduction

Peripheral ossifying fibromas are benign mesenchymal lesions that usually arise in the anterior maxilla. Considerable confusion persists in published reports about its nomenclature, and several synonyms remain in use.^{1,2} It is most commonly regarded as a reactive condition and thought to be

a metaplastic process that involves the superficial periodontal ligament in response to diverse inflammatory conditions, such as calculus, bacterial plaque, orthodontic appliances, ill-adapted crowns, and irregular restorations, which are considered important pathogenic factors.^{1,3–5}

They present as slow-growing, asymptomatic, gingival nodules, most commonly in female patients during their second decade of life. Although the incidence has been estimated at 3% of all oral tumours,^{4–6} they are rarely included in clinical differential diagnoses. Microscopically they are poorly circumscribed, fibrous proliferations of spindle cells that lack atypical features, and their distinctive feature is the synthesis of bone (mature or immature), cementum or calcifications, in

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variable proportions.^{5,7} We know of few immunohistochemical studies, but they support the myofibroblastic nature of the lesion.⁸

Resection, including the periodontal ligament and periosteum, is the treatment of choice. As recurrence rates are estimated at between 8% and 20%,^{2,9} postoperative follow up is essential.

Patients and methods

We retrieved 48 specimens from 41 patients with peripheral ossifying fibromas from the files of the Departments of Pathology of the Clinical and University Hospital of Santiago de Compostela and POVISA Medical Center (Spain). All cases were available for review, including paraffin blocks from 26 cases for immunohistochemical investigation. Clinical files were reviewed and the following data were collected: sex, age, site, size, and postoperative course of the lesions.

The presence of bone, mature (lamellar bone type, organised, and stress-orientated) or immature (woven and osteoid type, random and non-stress-oriented), cementum (mineralised bodies taking the form of basophilic acellular globules), and calcifications (microscopic granular foci of calcifications lacking any kind of organisation), were recorded and evaluated semiquantitatively into four grades: absent, mild, moderate, or intense. The degree of mineralisation was considered mild when it was <10% of the lesion, and intense when it was more than 50%. Cases in between were graded as moderate.

Immunohistochemistry

Tissue sections 3 µm thick were taken, applied to special immunohistochemically-coated slides (DAKO) and stained for SMA (smooth muscle actin), PG-M1 (CD68), ALK, p53, CD34, and factor XIIIa (FLEX Ready to use, Dako), using automated equipment (Dakostain link48, Dako).

Statistical analysis

The significance of differences between values was assessed using SPSS (SPSS 24.0 for Windows, IBM Corp).

Results

Clinical data

The clinical data of the 41 patients are summarised in Table 1. Detailed information of the location of the lesions was provided in 26 cases, in which the involved teeth were specified. The interdental papilla of incisors was the most common site.

Clinically, the lesions were generally described as nodular, ulcerated, painless masses (Fig. 1). Growth was usually

Table 1

Clinical characteristics of 41 patients and 48 specimens.

Variable	No. or mean (range)
Sex:	
Male	18
Female	23
Age (years):	
Mean (range)	38 (10–80)
0–19	8
20–39	16
40–59	11
60 and over	6
Race:	
European	40
Afroamerican	1
Site:	
Upper maxilla	11
Lower maxilla	25
Unknown	5
Teeth affected:	
Incisors	10
Canines	3
Premolars	7
Molars	6
Unknown	15
Size (cm):	
Mean (range)	1.2 (0.5–5)
0–0.9	10
1–1.9	31
2 or more	7
Recurrence (years)*:	
<2	3
2 or more	3
Unknown	2
None	33

* One patient developed three recurrences within 3–4 years of the first operation.



Fig. 1. Lesions were firm, pink, gingival nodules, most commonly located in the anterior part of the mouth in relation with the incisors. They were more common in the upper than in the lower maxilla.

slow, being present for months in many cases; however, the precise timing of evolution of lesions was not recorded. Poor oral hygiene was recorded as an additional finding in many records.

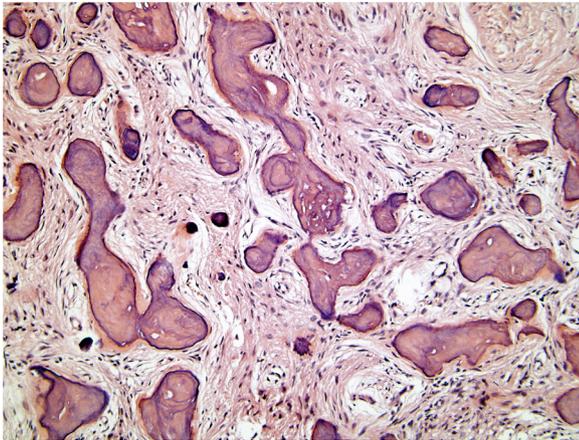


Fig. 2. Histopathologically they were composed of a patternless proliferation of bland spindle cells with variable amounts of mineralisation, mainly in the form of woven bone (haematoxylin and eosin, original magnification $\times 200$).

Table 2
Type and grade of mineralisation in 48 specimens.

Type	Grade			
	–	+	++	+++
Mature bone	22	13	7	6
Immature bone	13	20	11	4
Calcifications	33	11	4	0
Cementum	35	6	6	1

All lesions were treated by conservative excision, and they relapsed in eight patients. Two patients were initially operated on at another centre, so we could study only the relapse, and the time to recurrence after excision was not known.

Histology

Each lesion had a poorly-circumscribed fibrous proliferation with frequent epithelial ulceration and a variable submucosal inflammatory response. Lesions were slightly to moderately cellular and showed no particular architectural pattern. Cells were plump or spindle-shaped, with small nuclei and poorly-defined cytoplasm. There were no signs of pleomorphism or anaplastic features, and mitotic activity was scant or absent. Most cases had some degree of mineralisation showing different combinations of immature (woven) bone, mature (lamellar) bone, cementum, or calcifications (Fig. 2). Only two cases showed no degree of mineralisation: one corresponded to the third recurrence in a patient, and the other corresponding to the first specimen from another patient that showed immature bone in a later recurrence.

The types and degrees of mineralisation are shown in Table 2. Immature bone was the most common, followed by mature bone, calcification, and cementum-like material. Most specimens showed only a low-to-moderate grade of mineralisation. Those cases with large amounts of mature bone were usually less cellular, and the inverse was also true, in that

Table 3
Immunohistochemical data in 26 cases.

Markers	Immunoreactivity			
	–	+	++	+++
Smooth muscle actin	7	14	4	1
CD 34	26	0	0	0
CD 68	12	13	1	0
P53	24	1	0	1
ALK	26	0	0	0

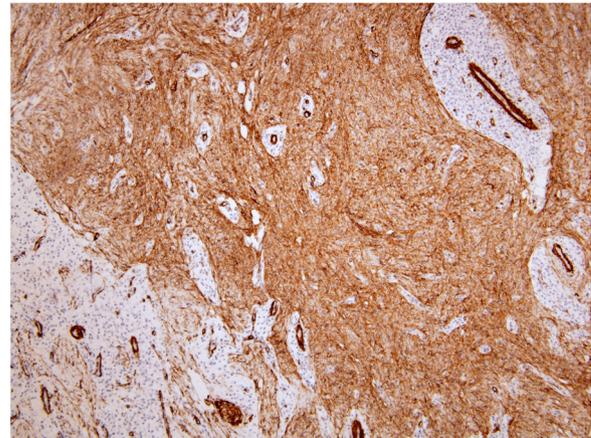


Fig. 3. Immunohistochemistry showed strong staining for SMA in spindle in most cases (immunohistochemical staining for smooth muscle actin, original magnification $\times 100$).

more cellular lesions tended to be harbingers of scarce calcified material of any type. Multinucleated giant cells were found in 23 specimens and showed considerable variation both in amount and distribution among cases. None of the histopathological variables evaluated showed any significant statistical correlation with age, sex, size, or site of the lesions. Nevertheless, cases in which cementum had formed showed a higher rate of recurrence ($p = 0.025$).

Immunohistochemistry

Immunohistochemical results are summarised in Table 3. Staining with SMA was usually diffuse and of moderate to strong intensity in spindle cells (Fig. 3). CD68 was restricted to multinucleated giant cells. None of the cases showed staining for CD 34 or ALK. Nuclear staining for p53 was noted in only two cases (weakly in one and strongly and diffusely in the other). Factor XIIIa was also found in only two cases (those showing only calcifications as the mineralisation component).

Discussion

Intraoral ossifying fibromas have been reported since the late 1940s under many different designations that reflect the controversy surrounding the classification of these lesions.^{1,2}

They are gingival nodules composed of cellular myofibroblastic proliferations that are characterised by randomly dispersed foci of mineralisation in the form of either bone, cementum-like tissue, dystrophic calcifications, or combinations of these.^{5,7} They are rather common, and account for 3% of all oral tumours and 9.6% of all gingival lesions.⁴⁻⁶ However, these figures can be as high as 20% in children.¹ We report a series of 48 tumours in 41 patients from two general hospitals, where they made up 1% of the specimens from oral surgery.

The aetiology and pathogenesis of intraoral ossifying fibromas remains unknown. Whether reactive or neoplastic in nature, they seem to originate from cells in the periodontal ligament, probably related to trauma or local irritants.^{1,3-5} Although the retrospective character of our study precludes the collection of acute data, clinical files reported poor oral hygiene in many cases, suggesting a tenable relation between hygiene and the development of the tumours.

We found the lesion to be more common in female patients (1.3:1), in the lower limits of the ranges reported in previously published series in which numbers ranged from 1.2 - 4-3/1.^{1,2,10} Most of our cases presented during the third and fourth decades of life, contrasting with the more commonly reported occurrence during the first two decades, though six of our cases presented in patients in the seventh decade, indicating that it may present in a wider range of ages than is classically reported.^{2,5,10}

Clinically, the tumours are painless, solitary, exophytic lesions, sessile or pedunculated, and usually found in the interdental papilla of the incisors. We found that the precise location of the lesions was not recorded in 15 cases, and of the 26 remaining cases, 10 were located in relation to the incisors, the most common dental site. However, in contrast to the published reports,^{2,5,10} our cases were more likely to be in the lower than in the superior maxilla (25 compared with 12).

Only five of the 48 lesions (including recurrences) were larger than 2 cm. This agrees with previous reports and, in our opinion, might indicate the limited potential growth of the lesion. Many of the patients delayed seeking assistance for several months, and lesions tended to stabilise without causing migration of teeth or bony destruction. These are unusual findings, and imaging studies are not considered necessary in the evaluation of these fibromas.^{10,11}

Differential diagnosis from other gingival nodules (irritation fibroma, pyogenic granuloma, or peripheral giant cell granuloma) may be difficult or even impossible.^{1,2,5} Although it has been suggested that they could be a more mature variant or an evolution from pyogenic granulomas,^{1,3-5} we have not found any patient with a previous or coexisting lesion of pyogenic granuloma that could support this assessment.

Definitive diagnosis relies on the histopathological evaluation confirming the presence of bone or calcified material

as the key feature.⁷ We found that immature woven bone was the most common type of mineralisation, followed by mature lamellar bone, calcifications, and cementum-like material. Nevertheless these patterns are not isolated, and in most of the cases there was a mixture of these components. Our results do not differ significantly from those of Shetty et al,¹⁰ who also found that woven bone was the predominant type of deposit. Interestingly, we noted an inverse correlation between the degree and type of mineralisation and cellularity of the lesions. Cases with greater deposits of mature lamellar bone tended to be less cellular than those that lacked large deposits of mineralised tissue. This finding could be interpreted as a form of maturation of the lesion. The only significant association we found was that the presence of cementum-like material correlated with a higher rate of recurrence ($p=0.025$). Only two of the eight cases that relapsed contained mature bone in either the primary lesion or in the relapses, and it was abundant only in one of them. These findings might indicate that lesions are unable to synthesise mature bone and that those with material similar to cementum, in particular, tend to relapse more often than bone-forming lesions, which could be interpreted as more mature lesions. No other statistical correlation between histopathological features and clinical data with the outcome of the lesions could be found.

Histopathologically, differential diagnosis from other solitary gingival nodules is not usually difficult. Only those cases that lacked cementum or osteoid formation may pose problems. In this respect, differentiation with the unusual oral, benign, fibrous, histiocytoma with calcifications may be difficult. The lack of storiform arrangement in the lesion and the absence of immunohistochemical staining with Factor XIIIa helps in the differential diagnosis.¹² In this sense, we have two specimens from the same patient (one corresponding to the original case and the other to the second relapse) that presented only calcifications as components of mineralisation, although another specimen from this patient had a little osteoid. The two specimens did not stain for Factor XIIIa, so we have no evidence that cases with fibrous proliferation and only calcifications constitute an entity that is different from peripheral ossifying fibroma.

Its immunohistochemical profile has been poorly documented.⁸ We used a panel of antibodies in 26 specimens, which stained for smooth muscle actin in the spindle cell component in most cases, and confirmed the myofibroblastic nature of the lesion. About half the cases stained for CD68, which is usually restricted to multinucleated giant cells. No cases stained for CD34 and ALK, ruling out any relations with myofibroblastic inflammatory tumours.

There remains debate concerning whether peripheral ossifying fibromas are true neoplasms or exuberant reactive proliferations. They lack the history of previous surgical instrumentation or trauma that usually accompany other

reactive myofibroblastic proliferations. Nevertheless, they contain variable proportions of inflammatory cells, including lymphocytes, histiocytes, or multinucleated giant cells, indicating that an inflammatory process is a constitutive part of the lesion. Surprisingly, we found indisputable nuclear positivity for p53 in two cases. This finding needs further evaluation, but it might indicate that at least some of these lesions are at risk of neoplastic transformation.

Conservative local resection is the preferred treatment, with clear peripheral and deep margins. To reduce the chances of recurrence, excision should include the periodontal ligament and periosteal tissue at the base of the lesion. The elimination of local aetiological factors is also required. The rate of recurrence among our patients was close to the reported upper limits (8%–20%).^{2,9} Some of our patients presented with recurrent lesions even years after primary excision, and one of them had three relapses, the last being 3.4 years after the initial resection. Patients should therefore be followed up for a long time before being discharged from the clinic. Recurrences are probably the result of incomplete resection or failure in sectioning the periodontal ligament. However, the development of new lesions secondary to the persistence of aetiological factors cannot be ruled out completely. In the hospitals where the study took place, surgical margins were not evaluated on this type of specimen, and complete resection was not guaranteed.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Neither was required for a retrospective study.

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