Original Article

Peritrabecular Clefting in Differentiating Ossifying Fibroma from Fibrous Dysplasia of the Jaws

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Abstract

Context: Fibrous dysplasia (FD) and ossifying fibroma (OF) are the most prevalent fibro-osseous lesions in Nigerians and present with overlapping clinical, radiological, and microscopic features, resulting in diagnostic challenges for the pathologist and surgeon. **Aims:** The objectives of this study were to differentiate between FD and OF using clinical features, radiographic features, growth rate, and microscopic method to evaluate the prevalence of peritrabecular clefting. **Settings and Design:** Random sampling was used to select the sample size of 30 for each lesion from cases diagnosed from 1994 to 2014 in the oral biopsy service of Lagos University Teaching Hospital. **Subjects and Methods:** Hematoxylin and Eosin sections were prepared from retrieved blocks of FD and OF which had been blinded. Each section was divided into four quadrants, largest vertical and horizontal dimensions of cleft surrounding five trabeculae in each quadrant were measured with ocular grid and multiplied to project an estimation of area of each cleft. Data retrieved on clinical and radiographic information were statistically compared to differentiate between the lesions. **Statistical Analysis Used:** Statistical Package for the Social Sciences for Windows (version 16.0, Chicago, IL, USA) was used. **Results:** In the study, 77% of FD had clefts, none was seen in OF. This difference was statistically significant $P = 0.001$. Ill-defined radiographic borders occurred in 60% of FD, well-defined borders occurred in 81% of OF. In lesions with mixed radiolucency and radiopacity, an association was established between border definition and type of lesion. $P = 0.02122$. **Conclusions:** Peritrabecular clefting was observed in 77% of FD, while this feature was not observed in OF and could therefore serve as a reliable parameter to differentiate the lesions.

Keywords: Fibrous dysplasia, ossifying fibroma, peritrabecular clefting

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Introduction

One of the most confusing areas of pathology involves the group of lesions termed benign fibro-osseous lesions (BFOLs).[1,2] This term is descriptive but diagnostically nonspecific. BFOLs encompass a varied group of pathologic conditions that include neoplasms such as ossifying fibroma (OF), developmental conditions such as fibrous dysplasia (FD), and reactive lesions such as osseous dysplasias.[2] Basically, the pathology of BFOLs consists of normal bone being replaced by proliferating fibrous connective tissue that contains variable amounts of mineralized products which may be bone and/or cementum-like calcifications.[1] OF and FD are the most common BFOLs that occur in the maxillofacial region.[1,2]

FD is a genetically based sporadic disease of bone, which occurs in two forms: monostotic (when it affects a single bone) and polyostotic (when it affects multiple bones).[3-5] When FD involves more than one bone in a contiguous fashion in the craniofacial region, it is regarded as craniofacial FD.[4,5]

OF is a true benign fibroosseous neoplasm derived from multipotent mesenchymal blast cells of periodontal ligament origin; hence, the presence of fibrous, osseous, and or cemental differentiation within the tumor connective tissue.[6,7] Various terminologies have therefore been ascribed to OF (cemento-OF, cementifying fibroma, and OF)

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depending on the amount and type of mineralization within the tumor.[6,7]

Juvenile psammomatoid ossifying fibroma (JPOF) and juvenile trabecular ossifying fibroma [JTOF] are both considered aggressive variants of the OF. They have been reported to have a tendency to occur more in children and adolescents, more complex histologic picture and locally aggressive growth.[1,2] The JPOF predominantly affects the extragnathic facial bones, particularly the periorbital, frontal, and ethmoid bones.[1,2,5] The lesion clinically manifests as progressive and sometimes rapid expansion of the affected area. With symptoms including exophthalmos, bulbar displacement, proptosis, impaired vision, facial swelling, nasal obstruction, periorbital pain, headache, and sinusitis.[1,2]

The JTOF commonly develops within the jaw bones, with maxillary lesions occurring more frequently.[1,2] The lesion typically presents as a progressive and sometimes rapid expansion of the affected area similar to the JPOF and symptoms include epistaxis, proptosis, exophthalmos, and diplopia. Pain is only rarely described.[1,2,5]

FD has been reported to have a global prevalence of 2.5% of all bone tumors (benign and malignant) while they constitute 7.5% of benign bone tumors.[8,9] Although few studies reported that OF may constitute 20.3% and 62% of BFOLs,[10,11] its precise global frequency remains unknown due to the dearth of epidemiological studies and different terminologies that have been ascribed to its description.[12]

Previous studies[13-16] have documented the presence of overlapping features in the clinical, radiological, and microscopic features of FD and OF which results in a diagnostic challenge for both the pathologist and surgeon.[13-16] Perhaps, this denotes that these lesions may either be lesions at either end of a single morphological spectrum or two distinct entities. As the evolution and surgical management of the two lesions differ, it is important to distinguish these lesions. FD is treated by a re-contouring procedure without resection, to minimize morbidity as its growth tends to stabilize or on occasions, stop when maturity is attained, while OF is treated by surgical excision.[2,5]

Peritrabecular clefting is a histopathologic event characterized by empty spaces partially or completely encircling lesional trabecular bone.[2,3,17] Its presence may be an important diagnostic feature for FD. The present study aims to evaluate the utility of peritrabecular clefting in distinguishing between OF and FD.

Subjects and Methods

From the biopsy service of the department of oral and maxillofacial pathology/biology, record of oral biopsies and all cases of oral maxillofacial bone tumors accessioned during the period 1994–2014 were retrieved for the analysis. From a total of 209 cases of fibro-osseous lesions (FOLs) diagnosed from 1994 to 2014, 61 cases were histologically diagnosed as FD, and 138 cases as OF. These cases were subjected to the exclusion and inclusion criteria to determine appropriate samples for the study. Cases without available formalin fixed, paraffin embedded blocks, inadequate clinical record, and those diagnosed as peripheral lesions were excluded.

All cases diagnosed as FD, OF, cementifying fibroma, and cemento-OF during the period were retrieved for this study. Hematoxylin and eosin (H and E)-stained slides of all cases that satisfied the inclusion criteria were retrieved. Clinical information on each lesion which consisted of age, sex, duration, site, and size of each lesion as well as radiographic findings was retrieved. Ethical approval was sought and obtained from the Health Research and Ethics Committee of the Lagos University Teaching Hospital.

Assessment for peritrabecular clefting

A total of 49 cases of FD and 123 cases of OF fulfilled the inclusion criteria. Random sampling technique was then used to select the minimum sample size of 30 for each lesion calculated based on a previous study on the prevalence of FD in relation to all benign bone tumors.[9] This selection was done by separating the lesions into two different containers, one contained blocks of FD lesions while the other contained blocks of OF lesions. After each pick, the container was agitated to ensure that those picked were not predetermined. Data retrieved on clinical and radiographic information of the selected samples of OF and FD such as age, gender, duration, site, and radiographic border distribution were statistically compared.

The retrieved paraffin blocks selected for FD and OF were blinded and coded by labeling them from 1 to 60. Using a microtome, 5 μ thick sections was cut for light microscopic analysis of peritrabecular clefting and confirmation of histologic diagnosis. Each H- and E-stained section was assessed for the presence of peritrabecular cleft [Figures 1 and 2]. For this purpose, each section was

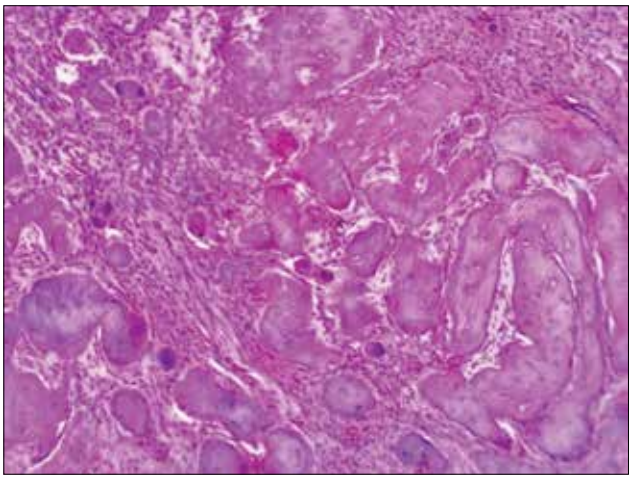

Figure 1: Photomicrograph of ossifying fibroma showing fibrous connective tissue proliferation with cementum-like and osseous differentiation. (H and E, ×400)

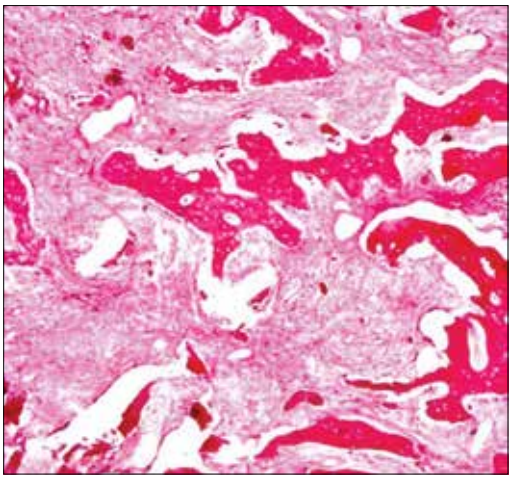

Figure 2: Photomicrograph of fibrous dysplasia showing peritrabecular clefting-characterized by empty spaces partially or completely encircling lesional trabecular bone. (H and E, ×400)

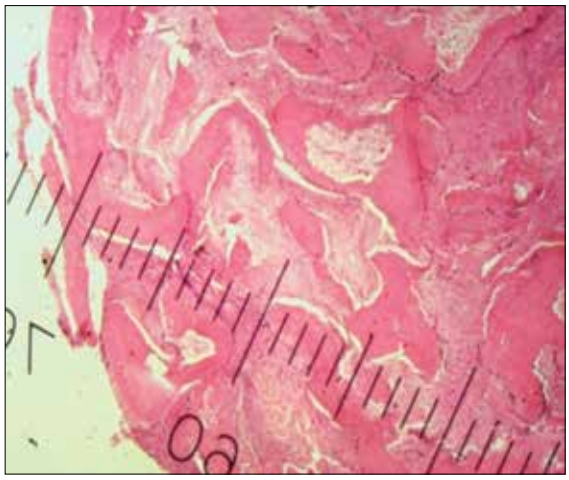

Figure 3: Photomicrograph showing measurements with the ocular grid (H and E, ×400)

divided into four quadrants and the cleft surrounding the five trabeculae (randomly selected) in each of the four quadrants was measured with an ocular grid [Figure 3]. The two largest dimensions of the cleft (vertical and horizontal) were measured, and then multiplied to project an estimation of the area of each cleft. Evaluation was done at ×40 objective/eye piece magnification. The ocular grid was graduated as 20 units per 0.1 mm in the vertical dimension, the interval between 1 and 2, 2 and 3 etc., is 0.1 mm each; however, the grid is graduated as 20 units/0.1 mm; hence, each interval will be 0.1 mm divided by 20 mm which equals 0.005 mm. 0.005 mm = 0.5 μ. Following documentation of data on the occurrence of peritrabecular space, blinded slides were revealed to determine how many of FD and OF had peritrabecular clefts and mean area of peritrabecular clefting was statistically related to the type of FOL, whereas mean area of peritrabecular cleft was determined for each patient.

Using a conventional light microscope, all sections were examined by three oral and maxillofacial pathologists. Reconciled observation was recorded for each parameter investigated. When all evaluations had been completed, the slides were decoded to expose which lesion (FD or OF) had which score or observation.

Estimated tumor growth rate

The estimated tumor growth rate for FD and OF was computed from the largest diameter of the tumor at presentation (tumor growth rate = largest diameter at presentation divided by duration of tumor [in months] at presentation). Estimated mean growth rate for FD was subsequently computed and compared statistically with the estimated mean growth rate for OF. Number of peritrabecular spaces was related to the age and site of occurrence of the lesion. Student's *t*-test was used to compare the mean area of peritrabecular clefting scores in FD and OF.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences, version 16.0 (IBM SPSS Statistics). Variables such as age, sex, site, and radiographic border definition were presented by frequency tables, bar charts, and cross tabulation. The number of FD and OF with peritrabecular clefting was expressed as percentages/proportion. The Chi-square test was used to compare the proportion of radiographic and histologic features. Statistical significance was set as $P < 0.05$.

Results

Fibro-osseous lesion, fibrous dysplasia, and ossifying fibroma as proportion of oral biopsies and maxillofacial bone tumors

During this period, FOLs accounted for 7% of all oral biopsies, 27.6% of benign maxillofacial bone tumors, and 19.4% of maxillofacial bone tumors (benign and malignant). There were 61 cases of FD, representing 29% of FOLs, 2.0% of oral biopsies, 8.1% of maxillofacial benign bone tumor, and 5.7% of maxillofacial bone tumors (benign and malignant). In this study, 138 cases of OF observed represented 66.0% of FOL, 4.6% of oral biopsies, 18.2% of maxillofacial benign bone tumors, and 12.8% of all maxillofacial bone tumors (benign and malignant).

Age group, gender, and site distributions of fibrous dysplasia and ossifying fibroma

FD was most commonly observed in the age group of 10–19 years, where 23 cases of FD (37.7%) were observed. OF was most commonly observed in the age group of 20–29 years where 45 cases (32.6%) were observed [Figure 4]. FD was observed at a mean age of 20.63 ± 9.42 years, age range of 4 –55 years while OF was observed at a mean age of 29.52 ± 13.26 years [Table 1], age range of 11–68 years. The difference in the mean age of occurrence between FD and OF was statistically significant ($t = 4.729$, df = 197 $P = 0.001$).

FD was observed more frequently in females, 36 cases (59.02%) than males, 25 cases (40.98%) [Table 1] at a female-to-male ratio of 1.44:1. OF was also observed more frequently in

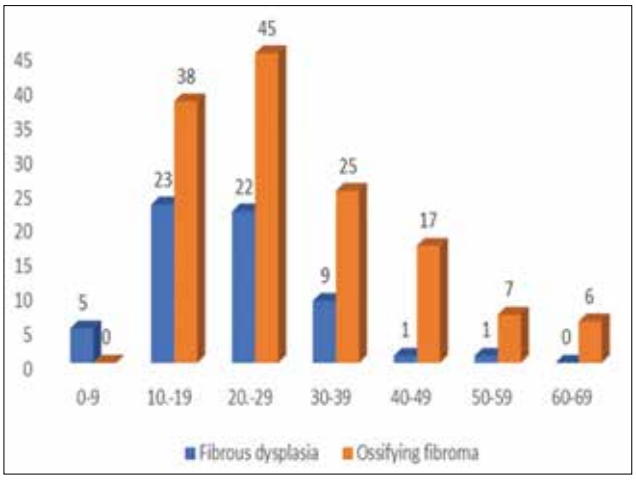

Figure 4: Age distribution of fibrous dysplasia and ossifying fibroma

Table 1: Distribution of FD and OF by clinical and radiographic features

Features	FD	OF
Mean Age(years)	20.63	29.52
Gender		
Male	25	53
Female	36	85
Anatomic Site		
Maxilla	52	51
Mandible	9	87
Radiographic Border		
Ill defined	17	5
Well defined	8	43
Mean duration(years)	5.8	3.5
EMTGR*	0.12459	0.22483
Peritrabecular clefting(%)	77	0

*Estimated mean tumour growth rate. Difference in mean age of occurrence between FD and OF was statistically significant (t = 4.729, P<0.05) Maxillary lesions that were FD was significantly higher than maxillary lesions that were OF (P<0.05) In lesions with mixed radiolucency and radiopacity, an association was established between border definition and the type of lesion. X^2 = 5.4324, df = 1, P = 0.02122

females, 85 cases (61.59%) than males 53 cases (38.41%) at a female-to-male ratio of 1.6:1. The difference in female-to-male ratio in FD and OF was not statistically significant (χ^2 = 0.118, df = 1, P = 0.731).

FD was observed more commonly in the maxilla 52 cases (85.25%) than mandible 9 cases (14.75%). OF, on the other hand, was observed more commonly in the mandible, 87 cases (63.04%) than maxilla 51 cases (37.0%) [Figure 5]. The proportion of maxillary lesions that were FD (82.25%) was significantly higher than the proportion of maxillary lesions that were OF (37.0%) (P < 0.05). In addition, the proportion of mandibular lesions that were OF (63.04%) was significantly higher than the proportion of mandibular lesions that were FD (14.75%) (P < 0.05).

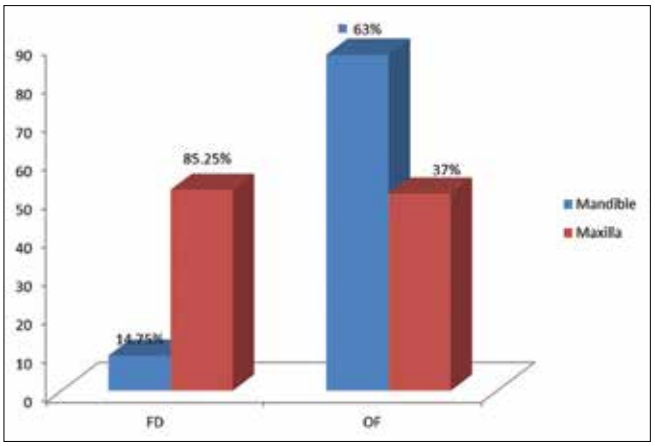

Figure 5: Site distribution of fibrous dysplasia and ossifying fibroma

Radiographic border definition of fibrous dysplasia and ossifying fibroma

In general, ill-defined radiographic borders were seen in 60% of FD (26 from 43 cases) and well-defined radiographic border occurred in 81% of OF (90 from 101 cases). In lesions with mixed radiolucency and radiopacity, an association was established between the border definition and the type of lesion. χ^2 = 5.4324, df = 1, P = 0.02122 [Table 1]. However, no statistically significant association was observed between border definition and type of lesion with respect to radiolucent and radiopaque radiographic patterns. FD presented with a significantly higher proportion of cases with ill-defined border (17 cases, 77%) than OF (5 cases, 23%). Furthermore, OF presented with a significantly higher proportion of cases with well-defined border (43 cases, 84%) than FD (8 cases, 16%).

Duration and estimated tumor growth rate of fibrous dysplasia and ossifying fibroma

The mean duration of FD lesions at presentation was 5.8 years (standard deviation [SD] ± 6.19994), whereas the mean duration for OF lesions at presentation was 3.5 years (SD ± 3.49886). Record of size, based on estimated largest diameter, was recorded in only 29 cases of FD and compared with that of 29 cases of OF. The rate of growth of FD, based on estimated largest diameter per month, varied from 0.01-0.50 cm (mean 0.12459 ± 0.127554), whereas the rate of growth of OF, based on estimated largest diameter per month, varied from 0.02 to 0.75 cm (mean 0.22483 ± 0.209176) [Table 1].

There was no statistically significant difference in estimated tumor growth rate between FD (mean 0.12459 ± 0.127554 cm/month) and OF (mean 0.22483 ± 0.209176 cm/month) (t = −2.203, P = 0.06, df = 56).

Peritrabecular clefting analysis

In the 60 randomly selected blocks (30 FD, 30 OF), 77% of FD (23 out of 30) had clefts, whereas no cleft was seen in any case of OF (0 out of 30). This difference was statistically significant P = 0.001. The mean area of the clefts was 4.22

Table 2: Comparison of mean area of cleft between age-groups and gender

Variables	Mean area of clefts
Age-group	
0-9	5.8±1.134
10-19	5.3±1.121
20-29	4.9±0.991
30-39	4.6±0.987
40-49	0
50-59	3.8±0.911
Gender	
Male	4.178±1.133
Female	4.121±0.9513

Difference in mean area of clefts between age groups and gender was not statistically significant.

$\mu m^2 \pm 0.572$ (range = 1.5 μm–7 μm). The extent and area of the clefts varied between the FD cases. Female patients had more clefting, 43% (15 out of 35) than males 32% (8 out of 25); however, this difference was not statistically significant. Patients in the first decade of life had the highest mean area of clefting (5.8 μm^2); there was, however, no statistically significant difference in mean area of clefts between the age groups [Table 2].

Discussion

The observation of a higher occurrence of BFOLs in this study than the findings from studies from other countries[18-20] is consistent with earlier observations that BFOLs are more common among Nigerians (reference). Contributing factors such as environmental and hereditary factors have been suggested to explain higher occurrence of BFOLs in Nigeria than in the other parts of Africa.[18] The present study which revealed a peak age of occurrence of the second decade for FD, in which 37.7% of cases was observed, and a peak age of the third decade for OF, in which 32.6% of cases were observed, is in agreement with other studies.[11,12] However, Vegas *et al*. reported a peak age prevalence of the fourth and sixth decades, respectively, for OF and FD.[19]

FD, which was observed at a statistically significant lower mean age of 20.63 ± 9.42 years than OF (mean age of 29.52 ± 13.26 years) is consistent with the findings from other studies.[11,20] A higher prevalence in females than males observed for each of FD and OF, at a female-to-male 1.44:1 (FD) and 1.6:1 (OF) is consistent with the trend that has been reported in the scientific literature.[12,21,22] Early presentation as a result of greater consciousness of esthetics in females may account for the higher frequency of occurrence in females than males, which was observed in this study.

This study further revealed that FD has a predilection for the maxilla (85.25%), whereas OF has predilection for the mandible (63.04%). This finding is in agreement with the reports of predilection of FD for the maxilla and OF for the mandible.[12,23] The reason for FD and OF having predilection for the maxilla and mandible, respectively, is not yet understood. In this study, 60% of FD cases had ill-defined radiographic borders, whereas ill-defined radiographic border occurred in 19% of OF. In lesions with mixed radiolucency and radio-opacity, an association was established between border definition and the type of lesion. However, no association was observed between border definition and type of lesion, with respect to radiopaque and radiolucent radiographic patterns. This is consistent with the study by Lu *et al*.[24] who reported ill-defined borders in 68.5% of FD and well-defined borders in 85.5% of OF.

Observation in this series that 77% of FD cases had peritrabecular clefting while no case of OF had clefting suggests that the presence of peritrabecular clefting may be an important histologic parameter in identifying FD of the jaws and differentiating it from OF. This observation is consistent with report from the study by Ribeiro *et al*.[3] who observed that 86.5% of cases of FD had clefting, while this feature was not seen in any case of OF. It is important to note, however, that the absence of peritrabecular clefting does not rule out a diagnosis of FD.

In this study, clefting was not seen in 23% of FD, an observation that is higher than 13.5% reported by Ribeiro *et al*.[3] The cases without peritrabecular clefting in this series were in the first, second, and third decades in contrast to Ribeiro *et al*.[3] who observed that 3 out of 5 cases without peritrabecular cleft in their study were seen in very young patients. However, they also observed many young patients in their study who had clefting; hence, peritrabecular clefting is not directly associated with age. Even though it was observed in this study that the patients in the first decade of life had the highest mean area of clefting, there was no significant difference in the mean area of clefting among age groups.

The biologic mechanisms responsible for the formation of peritrabecular clefting are unknown. It has been regarded as an artifact that results from tumor retraction occurring during routine tissue processing for the preparation of light-microscopy sections.[25] It has also been associated with abnormality in the expression of basement membrane proteins, collagenases, or other enzymes.[26] If peritumoral clefting is regarded as retraction artifact that occurs during tissue fixation, decalcification, sectioning, or processing, it is a distinctive feature seen in FD and was not observed in any case of OF even though the tissues were fixed, decalcified, sectioned, and processed in exactly the same way.

The prognostic and diagnostic significance of peritumoral clefts, separating tumor cells from adjacent stroma in tumors such as basal cell carcinoma, prostatic adenocarcinoma, breast carcinoma, and squamous cell carcinoma of the esophagus have been documented.[25,27] Peritumoral clefts have also been observed in the frozen sections of breast carcinomas,[28] signifying that they may in fact represent real spaces around the nests of tumor cells, and supporting the theory that clefting is a biological feature of certain tumors and not a retraction artefact.

Conclusions

Peritrabecular clefting was observed in 77% of FD, whereas this feature was not observed in OF and could therefore serve as a reliable parameter to differentiate FD from OF of the jaws, even though its absence does not rule out a diagnosis of FD. Further studies should be done to investigate the cause of peritrabecular clefting and why it is a feature of certain tumors while it is absent in others.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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