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Original Research Article

Comparison of proliferative potential in variants of ossifying fibroma (OF) of craniofacial complex

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ABSTRACT

Aim: Comparison of proliferative potential in JTrOF , PsOF and OF of craniofacial complex using CDK4 and pHH3.

Introduction: Fibro-osseous lesions (FOL) refers to a poorly defined diverse group of lesions affecting the jaws and craniofacial complex. This spectrum of lesions includes fibrous dysplasia, cement-osseous dysplasia and two histological variants of ossifying fibroma - Despite benign neoplasms, both the variants of ossifying fibroma are characterized by rapid growth, potential for local invasiveness and a tendency to recur. According to the literature, the recurrence rate of JTrOF is about 20% where as PsOF is from 30-56%. Diagnosis is based on histopathology and imaging of the lesion. Early diagnosis allows for the resection of a smaller lesion , reducing the chance of damage to nearby structures. Various biomarkers such as oncogenes CDK4, MDM2, p53 and α-SMA have been investigated in bone pathology to predict biological behaviour of these lesions for precise treatment planning.

Materials and Methods: Immunohistochemical expression of CDK4 and pHH3 will be assessed in histopathological diagnosed cases of juvenile trabecular ossifying fibroma, psammamatoid ossifying fibroma and conventional ossifying fibroma.

Results: The immunohistochemical expression of CDK4 was 100% in JTrOF and PsOF and 60% in OF. The expression of pHH3 was weak and focal in JTrOF and PsOF and also weak in OF.

Conclusion: This study reveals the genetic mechanism involved in pathogenesis of aggressive variant of OF. Pre-treatment biopsy and CT scan are necessary for proper diagnosis and treatment planning of the lesion.

1. Introduction

Fibro-osseous lesions (FOL) are a poorly defined and diverse group of lesioncharacterized by the replacement of normal bone architecture with fibroblast and collagen fibers that contain foci of mineralization might vary in appearance and encompasses a spectrum that includes fibrous dysplasia, cemento- osseous dysplasia and two histological variants of ossifying fibroma - Juvenile trabecular ossifying fibroma (JTrOF) and psammamatoid ossifying fibroma (PsOF).[1–4]

Juvenile Trabecular Ossifying Fibroma typically occurs in younger individuals with mean age of 15 years while the Psammomatoid Ossifying Fibroma variant affects a wider age range with mean age 20 years and a propensity for extragnathic locations (sinus, orbital bone).[4,5] Despite benign neoplasms both the variants are characterized by rapid growth, potential of local invasiveness and tendency to recur. Diagnosis is based on histopathology and imaging of the lesion. Early diagnosis allows for resection of a smaller lesion reducing the chance of damage to nearby structures.[6]

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The basis for this different biologic behaviour among JTrOF, PsOF and OF is challenging to describe. According to the literature recurrence rate of JTrOF is about 20% while that of PsOF ranges from 30-56%.[7] Various biomarkers such as oncogenes CDK4, MDM2, p53 and α-SMA have been investigated to predict biological behaviour of these lesions for precise treatment planning.[3]

CDK4 is an enzyme that mediates cell cycle progression in G1 to S phase preparing the cell to initiate DNA synthesis.[1]

pHH3 is a nuclear core protein of DNA chromatin that plays a crucial role in chromosome condensation and cell cycle progression during mitosis and meiosis. Both CDK4 and pHH3 are proliferative markers, playing important role to predict biologic behaviour.[3]

The study included the clinicopathological diagnosed 3 cases of JTrOF, 2 cases of PsOF and 5 cases of conventional OF for analysis. Immunohistochemical (IHC) analysis for expression of CDK4 and pHH3 was performed to uncover the basic mechanism involved in pathogenesis and potential for local invasiveness.

2. Materials and Methods

In this study, 3 formalin fixed paraffin embedded tissue block of JTrOF, 2 blocks of PsOF and 5 blocks of conventional OF were collected from the archives of the department of oral pathology and microbiology. Clinical information including age, gender and lesion location was retrieved for each case. Immunohistochemistry for CDK4 and pHH3 expression was performed. For CDK4, smooth muscle served as the internal control and skin as the external control. For pHH3 squmaous epithelium was used as internal control and lymph node as external control.

IHC Scoring (CDK4 and pHH3) method

IHC expression was evaluated based on the percentage of positive cells and the intensity of the staining. The scoring criteria was as follows:

Percentage of positive cells: + (0-5% positive cells), ++ (6-25% positive cells), +++ (26-50% positive cells) and ++++ (51-100% positive cells). The Intensity of staining was weak (W), moderate (M), strong (S). Data analysis was performed using the SPSS software Package. Statistical analysis was conducted using one way ANOVA with post hoc turkey HSD test. Significance was established at P value of <0.01.[1]

3. Results

Demographic and clinical data of JTrOF, PsOF and conventional OF cases were evaluated. JTrOF and PsOF were more frequently noted in maxilla as compared to the mandible. The mean age of five cases of OF was 37.23 yrs. (Table 4 , Graph 1)

Imaging examination revealed that all lesions appeared as mixed areas of lucency and opacity with well-defined borders, associated with tooth displacement and bony expansion. (Figure 4)

Microscopically, there were 3 cases of juvenile trabecular ossifying fibroma 2 cases of psammamatoid and 5 cases of conventional OF exhibits typical histological features. Histopathologic examination of conventional OF revealed fibrocellular stroma with foci of calcification presenting in globular and spherical pattern with prominent osteoblastic rimming. JTrOF characterized by a hypercellular stroma which composed of spindle cells, with minimal collagen production and long slender strands of osteoid. The immature bone trabeculae show no sign of maturation and are typically devoid of osteoblastic rimming. The lesions are sharply demarcated from their surroundings, either by a fibrous capsule or by a rim of the pre-existing bone. PsOF exhibits multiple irregulars and spherical psammamatoid basophilic bodies characterized by concentric pattern of lamination embedded in cellular fibroblastic stroma. (Figures 1, 2 and 3)

3.1. Immunohistochemical analysis

Immunohistochemical expression of CDK4 enzyme revealed that diffuse and strong expression was found in PsOF compared to JTrOF,. In contrast, five cases of conventional OF showed weak and focal positivity. The staining intensity of pHH3 immunohistochemical marker was very weak and focal in both the variants of OF and negative in conventional OF. (Tables 1, 2 and 3) (Graphs 2, 3 and 4)

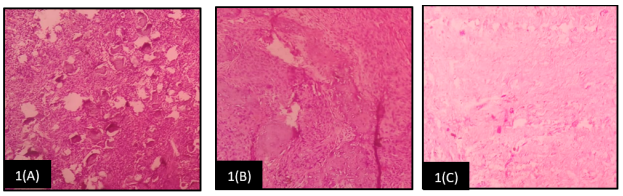


Figure 1: Photomicrograph (1A, 1B and 1C) showing H & E stained sections ofPsOF, JTrOF and OF respectively.

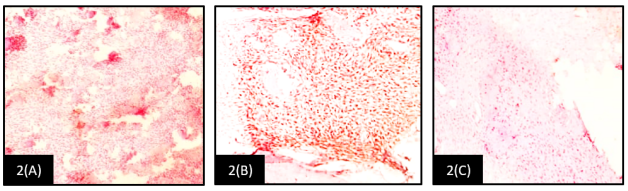


Figure 2: Photomicrograph (2A, 2B and 2C) showing Phh3 stained sections ofPsOF, JTrOF and OF respectively showing strong, moderate and weak staining intensity respectively.

Table 1: Age wise distribution of mean integrated score of CDK4 and pHH3 in Variants of OF

Age	OF (n=5)		JTrOF (n=3)		PsOF (n=2)	
	CDK4 Mean ± SD	Phh3 Mean ± SD	CDK4 Mean ± SD	Phh3 Mean ± SD	CDK4 Mean ± SD	Phh3 Mean ± SD
< 20 (n=5)	0	0	1.8 ± 1.41	0.4 ± 0.54	2.9 ± 1.41	1.4 ± 0.04
20 – 39 (n=3)	3.5 ± 0.7	0	0	0	0	0
>40 (n=2)	6 ± 2	0.67 ± 1.15	0	0	0	0

Table 2: Gender wise distribution of mean integrated score of CDK4 and pHH3 in variants ofOF

	Male (n = 3)		Female (n = 7)	
	CDK4 Mean ± SD	Phh3 Mean ± SD	CDK4 Mean ± SD	Phh3 Mean ± SD
JTrOF (n=3)	0	0	2.75 ± 1.21	1.5 ± 1
PsOF (n=2)	3 ± 1.1	0 ± 0.2	1.9 ± 0.98	1.4 ± 0.67
OF (n=5)	0.3 ± 0.7	2 ± 0.7	2 ± 1.8	0.5 ± 0.57

Table 3: Mean integrated score of CDK4 and pHH3 among JTrOF, PsOF and OF

Group	Mean integrated score		
	CDK4 Mean ± SD	Phh3 Mean ± SD	P value
JTrOF (n=3)	3.4 ± 1.3	1.8 ± 0.9	0.001*
PsOF (n=2)	4.2 ± 2.1	2.6 ± 1.09	0.015*
OF (n=5)	2 ± 1.41	0.4 ± 0.54	0.05*

Table 4: Mean age of JTrOF, PsOF and OF

	JTrOF	PsOF	Conventional OF
Mean Age	16.33 years (13-21 years)	19.5 years (15-24 years)	37.23 years
M:F Ratio	1:2	Females	

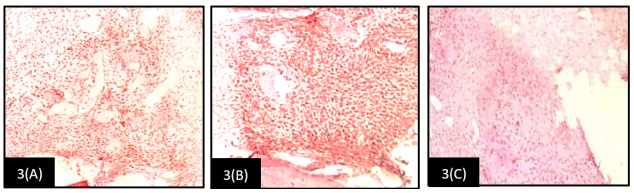
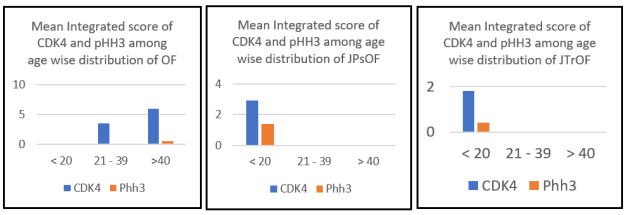
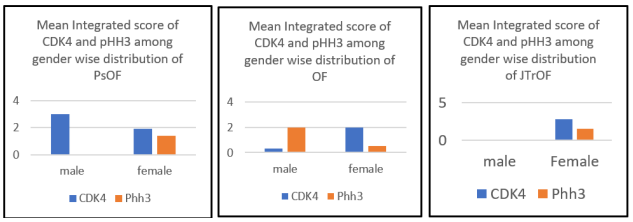


Figure 3: Photomicrograph (3A, 3B and 3C) showing CDK4 stained sections of PsOF, JTrOF and OF respectively showing strong, moderate and weak staining intensity respectively.

Graph 1: Age wise and gender wise distribution in variants of OF.



Graph 2: Age wise distribution of Mean Integrated score ofCDK4 and pHH3 in Variants of OF.



Graph 3: Gender wise distribution of Mean Integrated score of CDK4 and pHH3 in variants of OF.

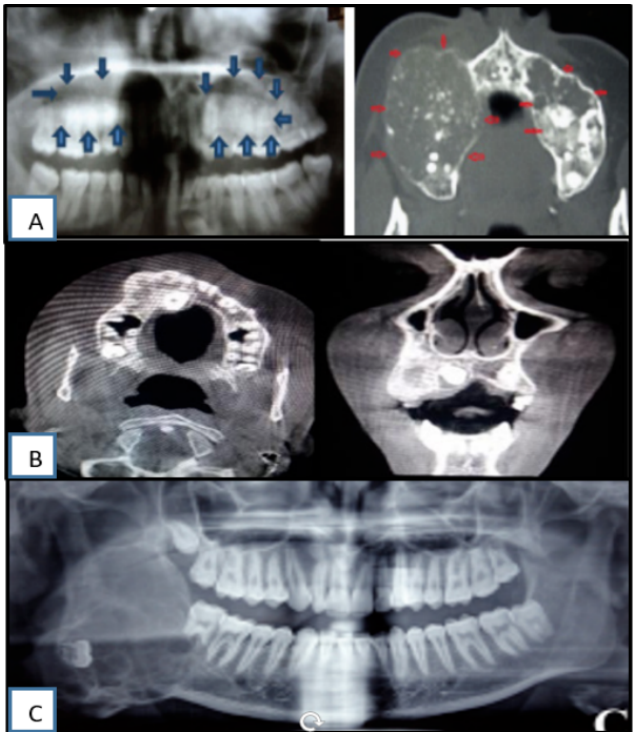
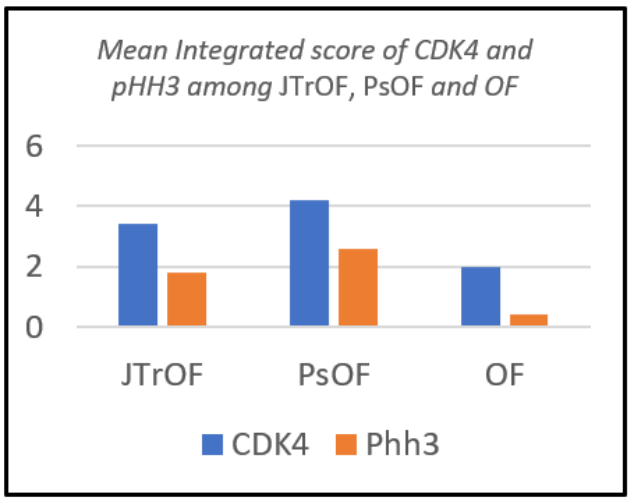


Figure 4: Variation in radiographic finding of Ossifying Fibroma **A)** juvenilepsammomatoid ossifying fibroma: Bilateral Mixed radiopacity with multiple ossifications body maxillary region. **B)** juvenile trabecular ossifying fibroma: Expanded and thin cortical outlines with easy separation from adjacent cortical bone. **C)** Ossifying fibroma: Multilocular radiolucency involving left ramus with distal root resorption 47.



Graph 4: Mean integrated score of CDK4 and pHH3 among JTrOF, PsOF and OF.

4. Discussion

The spectrum of fibro-osseous lesions includes a variety of developmental, reactive / dysplastic lesions, and neoplastic entities.[4,8] According to the 2022 WHO classification of head and neck tumors, JTrOF and PsOF are two histopathological variants of OF characterized by rapid growth, high potential of local invasiveness and a tendency to recur, which are included in fibro-osseous lesions.[4,9] The diagnosis of JTrOF and PsOF requires clinicopathological correlation and biologic behavioural analysis.[4,10] The molecular pathogenesis of ossifying fibroma and its subtypes remains unclear. Some studies detected mutations in CDC73 (HRPT2) in patients with hyperparathyroidism-jaw tumour (HPT-JT) syndrome.[1,10]

According to the literature, OF is a rare benign fibroosseous lesion characterized by an osteoclastic nature with rapid and aggressive growth, mostly observed in the third and fourth decades of life.[4,10,11]

The term "JOF" was first used by Johnson in 1952 when he was describing aggressive forms of ossifying fibroma as it occurred in the craniofacial bones of children. JOF has been classified as a distinct disease due to its local aggressive behaviour and its tendency to occur predominantly in children and adolescents.[3]

Slootweg et al. classified JOF into two distinct groups, the JOF-WHO type and JOF-PO (psammoma-like ossicles) type, based on the difference in the age of occurrence; the mean age of JOF-WHO type is 11.8 years and that of JOF-PO is 22.6 years. El-Mofty[6] (2005) categorized JOF into two trabecular JOF (TrJOF) and psammomatoid JOF (PsJOF), based on histologic criteria. However, the two categories also have a distinct predilection for specific age-groups: the average age of occurrence of TrJOF is $8\frac{1}{2}$ –12 years, whereas that of PsJOF is 16–33 years.[6]

The term 'juvenile' was removed from the terminology in 2022, as psammamatoid variant (16–32 yrs) has wide age distribution. The PsOF form is more frequently reported compared to the trabecular type.[1] In current study, the average age of TrJOF and PsOFs was 16.33 and 19.5, respectively.

According to Bhuyan L et al. (2017),PsJOF is reported more frequently and in larger case series than TrJOF. In a comprehensive review of the literature, the total number of cases of PsOF reported exceeded those of JTrOF by a ratio of more than 4 : 1 (230 vs. 55). Both the types showed predilection for males. In the present study, male:female ratio was reported as 1:4 which is in concordance with the literature.[9,12]

Approximately 75% of PsOFs develop in the orbit, paranasal sinuses,[13] and calvaria, whereas only about 25% of all cases involve the maxilla or mandible.[6] In the present study, both cases of PsOFs were involved in maxilla. Conversely, JTrOF is predominantly a gnathic lesion affecting the jaws, with a predilection for maxilla.

The size of these lesions varies from 0.5 cm to 10 cm. In the present study two cases were in maxillary anterior region and in one case was observed in body of mandible.

Microscopically, PsOFs exhibits Psammomatoid-type spherical ossicle structures, termed as psammoma-like bodies, derived from a Greek word 'psammos' meaning 'sand'. Ultra structurally, these psammoma-like bodies in PsJOF were found to possess a dark rim of crystals, from which small spicules and needle-like crystalloids project toward the periphery. Psammoma-like bodies are the hallmark of this neoplasm.[13] JTrOF is a well-demarcated but unencapsulated tumor with a tendency to infiltrate adjacent bone.[9] Microscopically, JTrOF exhibits variable amounts of fibrous tissue proliferation and calcifications, a hypercellular stroma of small uniform stellate and spindle-shaped fibroblast-like-cells with scant collagen, multinucleated giant cells, as well as scattered mitotic figures. The trabecular form is characterized by osteoid developing from fibrous stroma as long, slender strands.[9,12]

Multiple sites of origin have also been reported and these tumors behave aggressively.[14] The pathogenesis for these jaw lesions are related to the developmental disturbances in the basal generative mechanism.[3] The presence of non-random chromosomal breakpoints at Xq26 and 2q33 resulting in (x, 2) translocation has been reported by Sawyer JR in 1995.[13,15]

5. Conclusion

PsOF and JTrOF are fibro-osseous lesion that occur rarely and behave aggressively show aggressive local invasion into adjacent structures, causing difficulty in removing the lesion "in toto," resulting in a high recurrence rate. Early correct diagnosis and proper treatment modalities are necessary. If left untreated, the extension of the lesion into nasal, orbital, and cranial cavities is common. Pre-treatment biopsy and CT scan are necessary for proper diagnosis and treatment planning of the lesion. Due to the high recurrence rate, long-term follow-up is essential.

6. Ethical Approval

Ethical approval has been granted by institutional ethical committee for this study.

7. Source of Funding

None.

8. Conflict of Interest

None.

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