

Histopathological and Radiographic Analysis of Dental Follicle of Impacted Teeth Using Modified Gallego's Stain

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ABSTRACT

Introduction: In the WHO classification of odontogenic tumours, hard tissue formation has been considered as a sub-classification however, this parameter has not been much explored in dental follicle in literature. Epithelial-mesenchymal interactions play an important role in odontogenesis and its associated pathologies; therefore research on dental follicle should also include mesenchymal components along with epithelial components. Additionally, special stains to identify the nature of such depositions in dental follicle have been less explored. Modified Gallego's stain is such an example which has not been tried in odontogenic lesions which makes this study unique.

Aim: Aim of this study was to study histopathological variations in dental follicle, the nature of calcification and depositions using Modified Gallego's stain and to correlate histological features of dental follicle with pericoronal width radiographically.

Materials and Methods: A prospective histological study of the dental follicles of 50 impacted teeth was carried out

to microscopically evaluate the dental follicular tissues for pathological changes, and to correlate it with pericoronal radiolucency. Impacted teeth with pericoronal radiographic width less than 3mm were included in the study and symptomatic teeth were excluded. Further Modified Gallego stain was used to differentiate the nature of hard tissue formation in dental follicle tissues.

Results: Dental follicle histologically showed pathological changes resembling dentigerous cyst, ameloblastoma, odontogenic fibroma (Simple and WHO Type), clear cell odontogenic tumour, neurofibroma, neurilemmoma and mucoepidermoid carcinoma.

Conclusion: The dental follicle surrounding an impacted tooth has the potential to differentiate into a wide variety of tissue types, and thus shows the potential for cyst and tumour development which was observed in this study in most of the specimens with normal follicular width radiographically.

Keywords: Benign neoplasms, Dental follicle, Odontogenic tumours, Odontogenic cysts, Oral pathology, Pathologies, Radiographic width

INTRODUCTION

The primitive dental sac, or dental follicle, which originates from odontogenic ectomesenchyme, is part of the tooth germ and is physiologically involved in the formation of cementum, periodontal ligament, and alveolar bone. This fibrous connective tissue usually contains odontogenic cell rests, which could be the source of any pathology like ameloblastoma, ameloblastic fibroma etc., It radiographically appears as thin pericoronal radiolucency, considered normal by some authors when within 3mm of thickness and by others when it is within 2.5mm of thickness [1].

Reports in the literature discuss the prevalence of various cyst and tumour development associated with the asymptomatic follicle of impacted tooth [2]. Dental follicle may show various histopathological changes during tooth development which may sometimes lead to the development of odontogenic tumours and cysts.

Foci of calcification are seen as a normal finding in the stroma of dental follicles [2]. In the WHO classification of odontogenic tumours, the hard tissue formation has been considered as a sub-classification; however, this parameter has not been much explored in earlier studies on dental follicle. Epithelial-mesenchymal interactions play an important role in odontogenesis and its associated pathologies and therefore in the studies of dental follicle, along with epithelial component emphasis should be laid on mesenchyme as well.

Therefore, this study was conducted to analyse the pathologic changes occurring in dental follicle with radiographic pericoronal radiolucency of less than 3mm. Unlike previous studies, the present study evaluated dental follicular tissues for the presence of pathological changes associated with both epithelial and mesenchymal components using H&E and Modified Gallego's stain which is a differential stain for mineralized components.

AIM

Thus, the aim of this study was to evaluate the histopathological variations in dental follicle, the nature of calcification and depositions using Modified Gallego's stain and to correlate histological features of dental follicle with pericoronal width radiographically.

MATERIALS AND METHODS

This case control study was conducted on dental follicles associated with freshly extracted impacted teeth submitted during July 2013 to December 2013.

Patients attending Oral Surgery Department (OPD) of D.Y.PATIL, School of Dentistry, Nerul, Navi Mumbai indicated for extractions of third molar impactions who usually do not have major surgical procedures and complications were randomly included in the study. The discarded extracted impacted teeth along with the dental follicle were collected and preserved in fixative. Therefore ethical clearance was not considered for this study. Additionally

patients' identity was also not revealed. Total 50 dental follicles of impacted teeth were included in this study.

Patients requiring removal of mandibular or maxillary completely impacted teeth of all types having sufficient dental follicle tissue were enrolled in the study. Following the extraction of third molar, the pericoronal tissue was carefully curetted, sent for histopathological analysis. Sections of developing tooth germs and decalcified teeth from archives were selected as control group [Table/Fig-1].

Patients showing radiographic width >3mm and impacted teeth with established pathosis were excluded from the study.

The panoramic radiographs of every case was examined for the presence of pericoronal radiolucency suggestive of a dental follicle. "Kodak Dental Imaging Software- 6.12.26.0- Measuring tool" was used to measure pericoronal space from mesial, distal and occlusal surfaces, and the largest width was recorded [Table/ Fig-2].

Microscopic examination of epithelial and mesenchymal components of all the dental follicular specimens was performed under light microscopy. The type of epithelium (reduced enamel epithelium,

stratified squamous epithelium, ameloblastomatous epithelium), connective tissue, presence and nature of calcification, presence and activity of odontogenic cell rests and additional features like giant cells, clear cells, adipose cells, neoplastic transformation etc., were assessed at 4X, 10X, and 40X magnification.

During microscopic evaluation of the tissues using H&E stain, dental follicles which were lined by a few layers of stratified squamous epithelium were considered as cystic as reported by Timuçin Baykul T et al., because dentigerous cyst is usually lined by reduced enamel epithelium [3].

The nature of calcifications present in the connective tissue of dental follicle which may be formed during pathological alterations was determined by using Modified Gallego's stain as being cementum like when stained red, dentinoid/bone like when stained green in colour.

Staining procedure for Modified Gallego's Stain [2]

1. Deparaffinized in two changes of xylene.
2. Stained in haematoxylin 8-12min.
3. Rinsed in distilled water.
4. Sensitized in mordant (Ferric chloride solution in 100ml of water) for 2 minutes.
5. Rinsed in distilled water.
6. Stained with carbol fuschin diluted in acetic acid for 5 minutes.
7. Rinsed in distilled water.
8. Sensitize in mordant for 1-2 minutes.
9. Stain with aniline blue saturated with picric acid.
10. Rinsed in distilled water.
11. Mounted in DPX.

Observations were tabulated and percentage was obtained.

Data was tabulated statistically and associations between the attributes were tested using Pearson chi-square test. Descriptive data that included mean and percentages were calculated for each group. Categorical data were analysed by using Chi-square test. For all the tests, a p-value of 0.05 or less was considered for statistical significance.

Extensive literature search was done to retrieve similar studies published in the literature using keywords such as dental follicle, odontogenic fibroma, pathology, alterations, radiographic width, Modified Gallego's stain, dentigerous cyst, ameloblastoma, impacted teeth, mesenchymal pathologies.

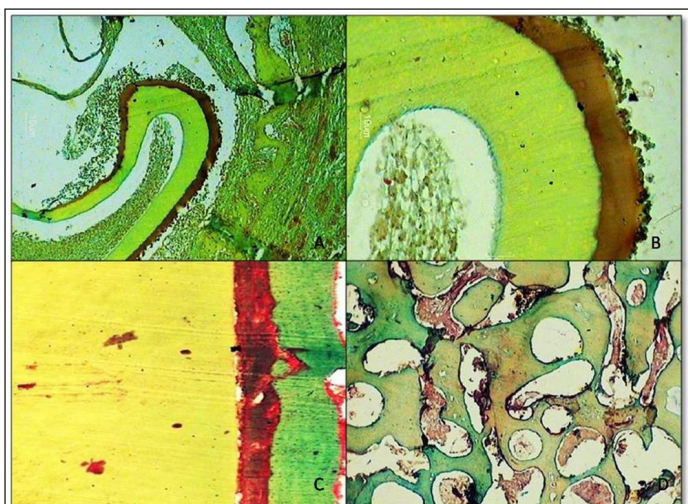
RESULTS

The age of the subjects varied from 16 to 43 years, and out of 50 subjects, 27 were male and 23 female.

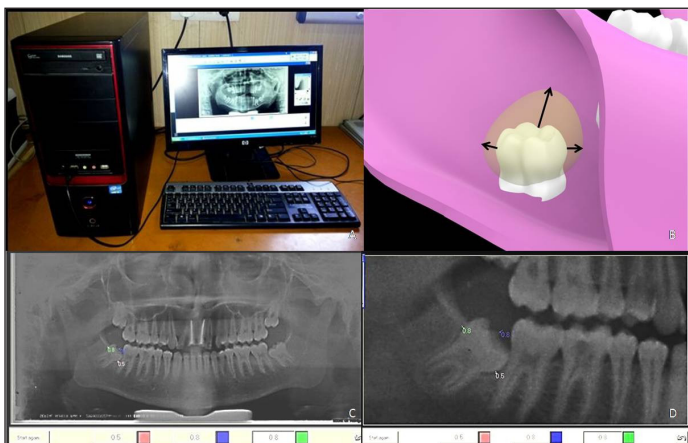
Of the 50 cases evaluated, it was found that as the age increased the reduced enamel epithelial lining of the dental follicle showed transformation into stratified squamous epithelial lining and this is considered to be a cystic change. Statistical analysis with Chi-square test showed statistically insignificant correlation between age group and inflammation with a p-value of 0.8437 [Table/Fig-3].

In this study as the grade of inflammation changed from mild to severe, there was corresponding cystic transformation in the epithelial lining [Table/Fig-4]. As the width of the pericoronal radiolucency increased, the rate of calcifications also increased and the type of calcification was further confirmed with Modified Gallego's stain [Table/Fig-5].

The epithelial lining showed variations [Table/Fig-6]. Few cases showed complete absence of epithelial lining. The connective tissue stroma of dental follicles showed changes resembling 11 different neoplastic lesions such as Mucous Cell Differentiation in odontogenic



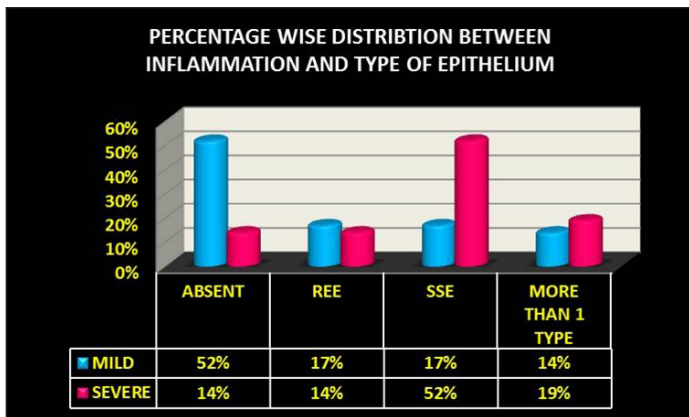
[Table/Fig-1]: Photomicrograph shows: (a) Tooth germ showing pre dentine in green colour (Modified Gallego's stain 10X); (b)-higher magnification [40X]; (c) Decalcified section of tooth (L.S) showing red coloured cementum, (Modified Gallego's stain, 10X) Ground section of bone showing green colour [40X].



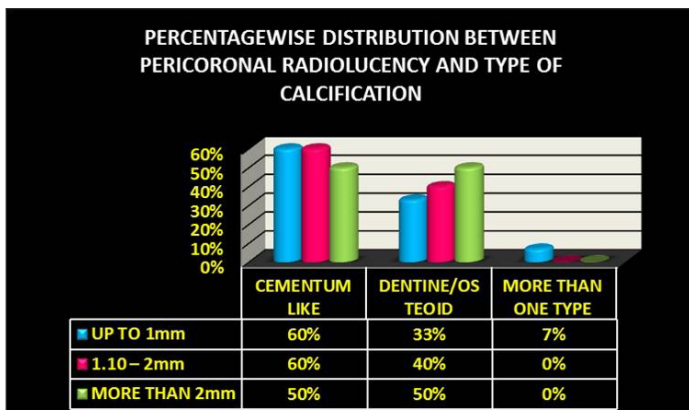
[Table/Fig-2]: (a) Photomicrograph shows Kodak Dental Imaging Software; (b) Schematic 3D representation of measurement of dental follicle; (c) Measurement of Radiographic width of dental follicle using Kodak software; (d) Measurement of mesial, distal and occlusal pericoronal width of dental follicle (Zoomed view).

Age Group	Inflammation		p-value
	Mild	Severe	
16-24 Years	19 (55.9%)	15 (44.1%)	0.8437 (NS)
25-33 Years	9 (64.3%)	5 (35.7%)	
34-43 Years	1 (50%)	1 (50%)	
TOTAL	29 (58%)	21 (42%)	

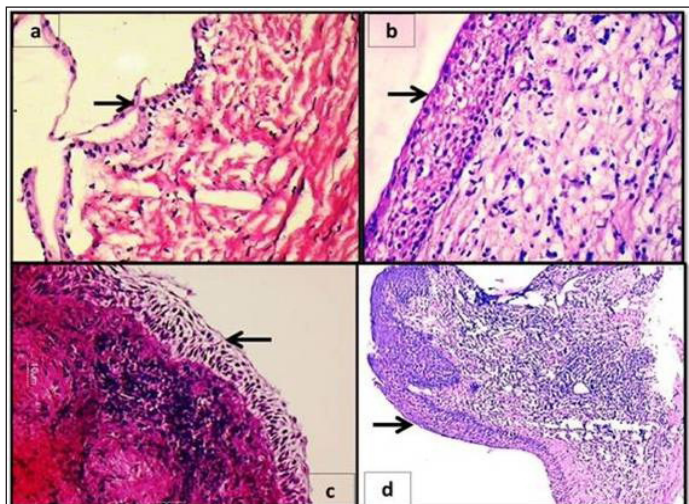
[Table/Fig-3]: Correlation between age and inflammation.



[Table/Fig-4]: Graph shows correlation between inflammation and type of epithelium. There was a statistically significant correlation between grade of inflammation and cystic changes with a p-value of 0.029 (p-value <0.05).



[Table/Fig-5]: Graph shows correlation between width of pericoronal radiolucency and type of calcification.

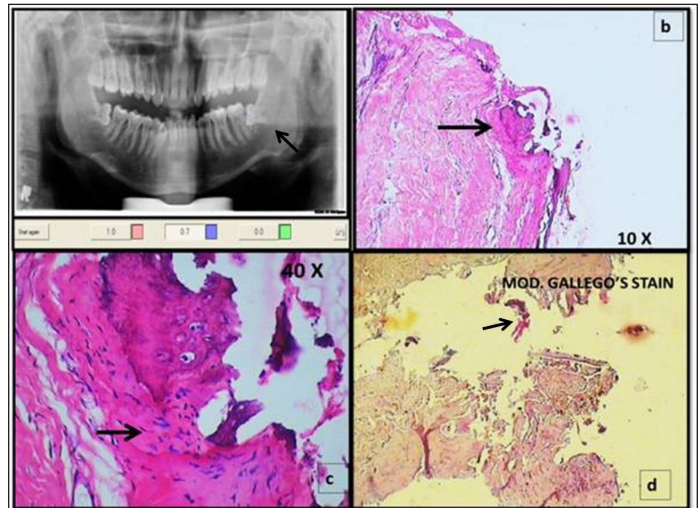


[Table/Fig-6]: a- Dental follicle showing reduced enamel epithelial lining and loose connective tissue stroma (H&E stain,10x). b- dental follicle showing stratified squamous epithelium (resembling dentigerous cyst) and dense connective tissue stroma (H&E stain,10x). c- dental follicle showing epithelial lining with vickers and gorlin criteria (H&E stain,10x). d- dental follicle showing odontogenic Reduced enamel epithelial lining transforming into stratified squamous epithelium in areas of intense inflammation. (H&E Stain, 10X).

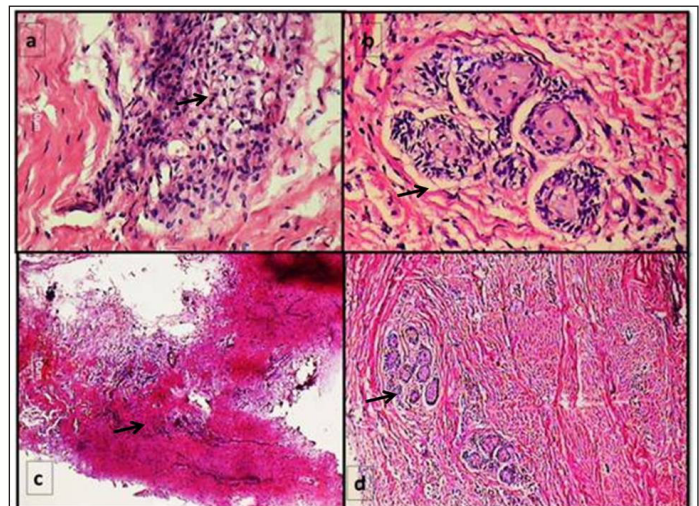
islands, unicystic ameloblastoma, acanthomatous ameloblastoma, follicular ameloblastoma, desmoplastic ameloblastoma, clear cell odontogenic tumour, odontogenic fibroma (simple type), odontogenic fibroma (who type), neurofibroma, neurilemmoma and mucoepidermoid carcinoma, thus, accentuating the pluripotent nature of dental follicle and also emphasizing its ability to show pathologic changes histologically in the absence of clinical or radiographic pathology [Table/Fig-7-12].

DISCUSSION

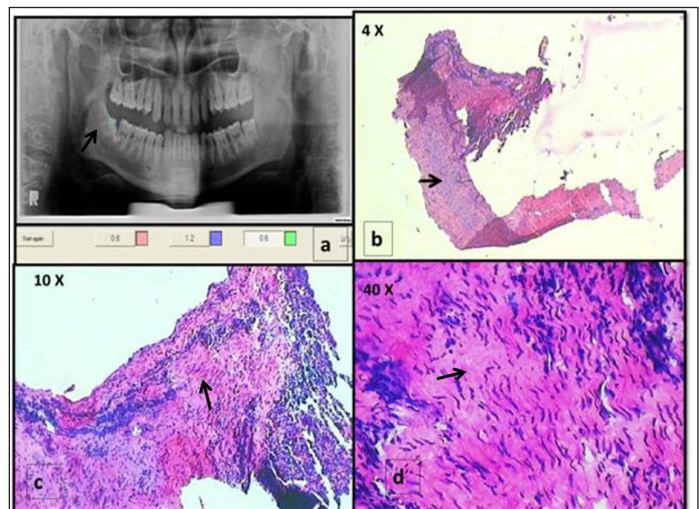
The dental follicle is characterized as being the remnant of tissues that participate in the odontogenesis and remained circumadjacent



[Table/Fig-7]: photomicrograph shows-a-OPG showing greatest radiographic width of 1.0 mm impacted lower right third molar in a patient with Odontogenic fibroma like changes. b,c- Dental follicle showing focal areas of cellular stroma with basophilic depositions resembling Odontogenic Fibroma 10X and 40X respectively. (H&E). d- Dental follicle showing red colored cementum like depositions resembling Odontogenic Fibroma (WHO Type) with modified gallego's stain.

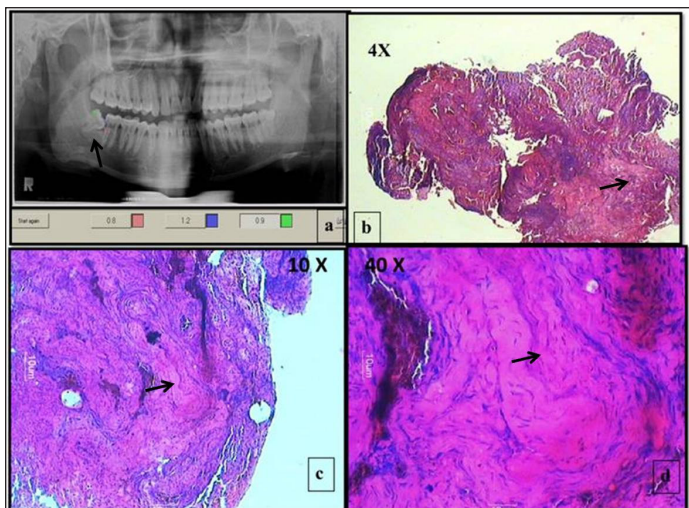


[Table/Fig-8]: Photomicrograph shows-Odontogenic islands in dental follicle showing mucous cell differentiation [40X]; b-Dental follicle showing odontogenic islands with acanthomatous ameloblastoma like changes [40X]. c,d- Dental follicle showing odontogenic islands in the connective tissue with follicular Ameloblastoma like changes [4X] and [10X] respectively.

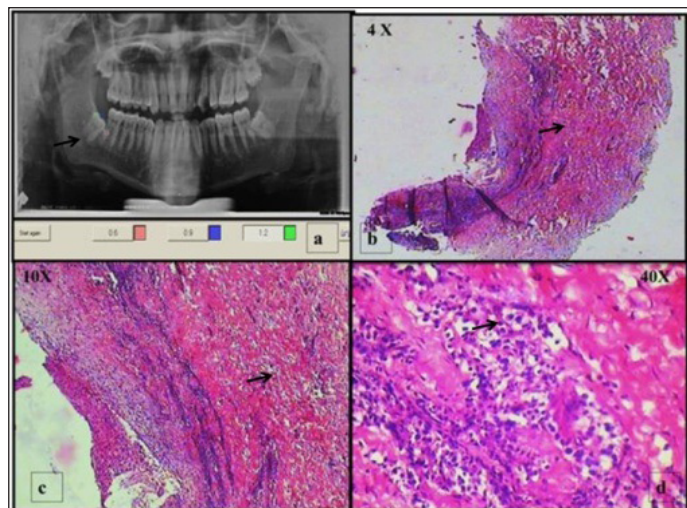


[Table/Fig-9]: photomicrograph shows-OPG showing greatest radiographic width of 1.2 mm in impacted lower right third molar in patient with Neurofibroma like changes. (b-d) Dental follicle showing cells with wavy nuclei resembling neurofibroma [4X],[10X] and [40X] respectively.

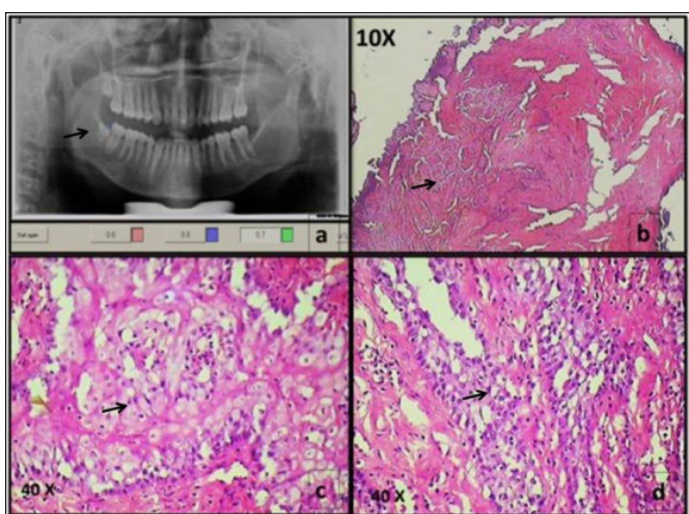
to the crown of a tooth which has not yet erupted normally to be seen clinically [4].



[Table/Fig-10]: a. Photomicrograph shows-OPG of patient showing maximum radiographic width of 1.2 mm in patient with neurilemma like change. (b-d)- Dental follicle showing schwann cells with wavy nuclei and Verocay bodies resembling neurilemma.[4X], [10X] and [40X] respectively.



[Table/Fig-12]: a. Photomicrograph shows OPG showing greatest radiographic width of 1.2mm impacted lower right third molar in a patient with mucoepidermoid carcinoma like changes (b-d) Dental follicle showing mucous cells, epidermoid cells and clear cells resembling mucoepidermoid carcinoma. [4X],[10X] and [40X] respectively.



[Table/Fig-11]: a. photomicrograph shows OPG showing greatest radiographic width of 0.8 mm in impacted lower right third molar in patient, showing histological features resembling Clear Cell odontogenic tumour. (b-d) Dental follicle showing biphasic cells with both vesicular nuclei and hyperchromatic nuclei along with clear cells resembling Clear cell odontogenic tumour. [4X],[10X]and [40X] respectively.

In the present study, 38% of the follicular specimen's associated with impacted teeth were devoid of epithelial lining and were characterized by presence of only connective tissue layer. The probable reason for absence of epithelium appears to be that the follicle was separated from its associated tooth and as the lining epithelium was derived from enamel organ type, most of it remained attached to the enamel of the tooth and consequently was not seen in the microscopic section of the dental follicle [5].

A 62% of cases showed presence of epithelium 16% of cases in the present study showed reduced enamel epithelial lining.

According to Saravana [6], if odontogenic epithelial lining of the dental follicle, changes from reduced enamel epithelium to stratified epithelium, it is indicative of dentigerous like changes. In this study, 32% cases demonstrated stratified squamous epithelium which was indicative of cystic transformation of the dental follicle. We found 3 cases which demonstrated all the classical Vicker's & Gorlin features suggestive of ameloblastoma like changes. It has been reported that natural progression of reduced enamel epithelium to squamous epithelium overlying impacted teeth with increased age of the patient leads to an increased incidence of dentigerous cysts [7].

Another interesting observation made was the presence of ameloblastomatous epithelium in association with reduced enamel epithelium in one case and stratified squamous epithelium in the

other [Table/Fig-6b,d]. This is in favour of two out of the three theories of pathogenesis of ameloblastoma postulated by Lieder et al., which states that ameloblastoma develops from luminal and mural proliferations of existing odontogenic cyst [8].

One of the case, exhibiting the presence of reduced enamel epithelium and ameloblastomatous epithelium suggested that the retained dental follicle of an asymptomatic impacted tooth has the potential to transform into a unicystic ameloblastoma.

The two cases lined by stratified squamous epithelium resembling dentigerous cyst like changes along with ameloblastomatous epithelium, was suggestive of the fact that the relatively harmless pericoronal follicle could transform into dentigerous cyst and could further progress into unicystic ameloblastoma.

In the present study, 52% cases with severe inflammation showed cystic changes. It is postulated by Khorasani M et al., that inflammation may act as a stimulator on the lining epithelium of the dental follicle and may result in its change from normal cuboidal or columnar form to a squamous type, which is more resistant to external stresses [9].

The mesenchymal component showed increased incidence of calcifications as the pericoronal width increased. The calcifications are a part of the mesenchyme and therefore seen as an increased radiolucent width radiographically. Since the calcifications were dentinoid and cementoid like depositions, under Gallego's stains, therefore they were not fully mineralized to appear radiopaque radiographically [Table/Fig-7].

In the WHO classification of odontogenic tumours, hard tissue formation has been considered as a sub-classification [10]. However, studies on hard tissue formation and on the nature of calcification in dental follicle of impacted teeth have so far not been documented in dental literature. Calcifications are a part of the mesenchymal tissue and hence its presence in the follicle needs to be emphasized along with the epithelial component.

Modified Gallego's, stain is a variant of Lille's stain that uses basic reagents hematoxylin, carbol fuschin and aniline blue [2]. The advantage of this stain is that it differentially stains the hard tissues seen in tooth, dental follicle and other pathological lesions and gives a clearer understanding of the histological picture of the hard tissue deposits in oral lesions. Under Modified Gallego's stain, dentine and bone appears green. Whereas, cementum like deposition appears red in colour [Table/Fig-1]. Few cases in the present study showed calcifications which were present close to the epithelium (epithelial- connective tissue interface) whereas maximum calcifications were seen deep in the stroma. The

presence of calcification closer to the epithelium can suggest an inductive activity.

Modified Gallego's stain not only used in soft and decalcified tissue but can also be used in ground sections. We could confirm that 38% of dental follicle showed cementum like depositions, 24% showed dentinoid/osteoid depositions and 2% showed a mixture of more than one type of calcification. Enamel like depositions were not found in the present study.

Small areas of focal odontodysplasia and ossification are commonly found in the follicular tissue. Calcifications were found in 54 out of the 130 dental follicles examined by Duane E. Cutright (1976). Forty-two cases contained areas of focal odontodysplasia; 17 contained osteoid or bone, and seven contained material resembling dentin and cementum. Some cases contained all three types [11].

Few cases in our study showed the presence of dentinoid with tubule formation. The possible pathogenesis could be the inductive changes between tall columnar ameloblasts like cells of the epithelial lining and mesenchymal cells, leading to calcium deposits. Metaplasia can be regarded as another probable explanation for the presence of the cementum, bone and dentinoid calcifications [12].

The dental follicle that surrounds the developing tooth germ contains progenitor cells for the development of the periodontium. These progenitor (stem) cells have been shown to differentiate into osteocytes, adipocytes and chondrocytes [13].

In the present study emphasis was also given on the lesions arising from the ectomesenchyme and therefore the connective tissue stroma was classified as either predominantly cellular which had mature interlacing collagen fibers with plump fibroblasts which are uniform and placed equidistant from each other (resembling the stroma of odontogenic fibroma) or fibro cellular which had fewer inconspicuous fibroblasts.

A 22% cases in the present study showed odontogenic fibroma like features in the stroma of dental follicle. No similar findings have been reported in dental literature. Extensive literature search have been done using key words dental follicle, odontogenic fibroma, pathology, alterations.

Out of total 11 cases of odontogenic fibroma, eight were of the WHO type showing calcification whereas three cases were of Simple type which showed only cellular stroma with or without odontogenic cell rests. The incidence of WHO type of odontogenic fibroma was more compared to the simple type.

In the study done by Jim Kin et al., scattered epithelial rests were present in 79% of follicles and features of ameloblast differentiation characterized by tall columnar cells with nuclear polarization, stellate reticulum type tissue, nuclear and cytoplasmic pleomorphism, or mitotic activity were not observed [14].

However, in the current study, the odontogenic cell rests differentiated to show features of mucous cell differentiation, acanthomatous, desmoplastic and also follicular ameloblastoma.

Present study also showed other pathologies in the connective tissue stroma of dental follicles. One case showed areas with proliferation of delicate spindle shaped cells with thin wavy nuclei, interspersed with intertwining connective tissue fibrils which histologically resembled neurofibroma [Table/Fig-9].

Another case on histological examination showed Antoni Type A tissues with Verocay bodies in some areas and were characteristic of neurilemmoma [Table/Fig-10].

The stem cells of a dental follicle have the potential to differentiate into osteogenic, adipogenic and neurogenic cells which were demonstrated in vitro studies [15]. The same mechanism could be possible for the appearance of neurofibroma like and neurilemmoma like features in the follicular tissues.

One specimen in the current study showed a biphasic pattern characterized by nests of clear cells intermixed with smaller islands of polygonal cells with eosinophilic cytoplasm resembling clear cell odontogenic tumour [Table/Fig-11]. The odontogenic islands in the follicle being pluripotent in nature maybe the source of clear cells in this case.

One case in the present study showed stratified squamous (dentigerous cyst like) epithelial lining which was proliferating into the connective tissue in the form of sheet of neoplastic cells composed of mucous cells which had abundant pale foamy cytoplasm and epidermoid cells which were polygonal in shape and had prominent intercellular bridges and resembled mucoepidermoid carcinoma [Table/Fig-12].

Aberrant salivary gland neoplasms that arise within the jaws as primary central bony lesions are rare and make up 2–3% of all mucoepidermoid carcinomas [16].

Speculation abounds regarding its pathogenesis and four possible origins have been described. Entrapment of retro molar mucous glands within the mandible, which subsequently undergo neoplastic transformation; developmentally included embryonic remnants of the submaxillary gland within the mandible; neoplastic transformation of the mucous secreting cells commonly found in the pluripotent cells seen in the epithelial lining of dentigerous cysts associated with impacted third molars; and neoplastic transformation and invasion from the lining of the maxillary sinus.

This case in the current study goes in favour of the hypothesis of origin of intraosseous Mucoepidermoid carcinoma from the lining of dentigerous cyst [17].

Mesgarzadeh AH et al., also conducted similar study on dental follicles in 2008 to investigate abnormalities associated with radiographically normal follicular tissue of third molar impactions. In their study of large sample size the prevalence of dentigerous cyst, ameloblastoma, actinomycosis like changes and chronic non specific infection were observed. In contrast, the present study, it additionally included the evaluation of mesenchymal component of dental follicle using gallego stain and found pathological changes in the form of odontogenic fibroma and neurilemmoma, neurofibroma etc., like changes in addition to epithelial alterations [18].

It can be concluded that the dental follicle surrounding an impacted tooth has the potential to differentiate into a wide variety of lesions especially cyst and tumour. Various studies in the literature have evaluated the epithelial alterations in dental follicle without giving importance to mesenchymal components which is one of the category in WHO classification of odontogenic tumours. Therefore, this study evaluated both the components. Additionally, this study also evaluated the type of calcifications present in dental follicle using Modified Gallego's stain making this study unique.

The advantage of this stain is that it can be used not only in soft tissues and decalcified tissues but also in ground sections.

One disturbing finding from this study was that many of the specimens with radiographically normal follicular radiolucency (less than 3mm) had developed pathological entities. In the current study, wide arrays of pathological changes including non odontogenic lesions were observed. Although dentigerous cysts constituted the majority of the observed pathological changes, odontogenic fibroma was the second most frequently observed pathological change. Ameloblastoma, neural tumours, clear cell odontogenic tumour, and mucoepidermoid carcinoma comprised the rest of the pathological changes detected in the study. However, the data describing different changes in follicular tissue around impacted teeth is very limited as many surgeons discard the follicular tissue after extraction rather than submitting it for histopathological evaluation, thus losing a potential source of odontogenic pathosis arising from it. It is generally believed in the dental community

that the absence of an abnormal radiolucency indicates a healthy dental follicle. Findings from this study contradict this belief.

CONCLUSION

Within the limits of the study population and method, the findings of the present study show that radiographic analysis may not be a reliable technique for the evaluation of dental follicle as it give 2D imaging. CBCT could be used as an adjunct to measure radiographic width of dental follicle. Additionally the immunohistochemical makers could be used to confirm the nature of diagnosis.

This study would surely help clinicians to reduce the rate of occurrence of odontogenic pathologies if the dental follicle tissues are routinely examined by pathologists associated with each impaction. It will also benefit the patient to undergo regular follow up if such pathologies detected at an early stage.

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