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How the Cystic Neoplasm Turned Back to Cyst Again, OKC – A Comprehensive Review

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Abstract:- The world health organisation has categorised KCOT as an odontogenic keratocyst as of now . Though having the characteristic features of neoplasia and increased capability of proliferation of epithelial layers , disputation on top of the the behaviour and management still persists from centuries. Many prior attempts have been made to classify this cyst from centuries back starting from 1887. In 1971 & 1992 it was under the category of developmental odontogenic cyst in classification proposed by WHO, OKC has been recategorized and given a name as keratocystic odontogenic tumor (KCOT) by the WHO classifications of head and neck tumors in 2005 due to its aggressive behavior, high recurrence rates and specific histological characteristics. But recently WHO classification of Head and Neck pathology (2017) has reclassified the lesion back to cystic entity. The purpose of the article is to discuss this fascinating kind of lesion and to provide a clear cut information regarding the reason for reclassification , its behaviour and new modalities in treatment.

Keywords:- *Odontogenic Keratocyst, Keratocystic Odontogenic Tumour, Who, Aggressive Behaviour, Infiltrative Nature, Reccurence, Ptch Gene.*

I. INTRODUCTION

Parakeratin lined cyst like lesion/tumour of jaw bones was first categorized as OKC by Philpsen in 1956[1,3]. WHO proposed/sentenced a definition for this lesion as " a benign uni-cystic/ multi-cystic intraosseous tumour which traces its origin from odontogenic epithelium i.e., (stratified squamous epithelium) and it has a potential for aggressive nature and infiltrative-type of behavior". (2005)[1]. The nature of odontogenic keratocyst (OKC) either it is a cystic or tumor, is still a continuing topic of debate from past few decades and some researchers have categorized it as a benign tumor of jaw[2]. Recent breakthrough in genetics and molecular level research, i.e. PTCH1 gene mutations along with Hedgehog signalling pathway inclusion, have lead to acquire knowledge of OKC's pathophysiology which provided a clue in arriving potential new treatment modalities [1,7,15]. This article accounts to explains head to toe particulars of OKC with regard from its timeline journey to its future trends.

TIMELINE

- 1876 – Cholesteatoma (Milkulicz)
- 1774 – Dental cyst (John hunter)
- 1945 – primordial cyst (Robinson)
- 1956 – the terminology odontogenic keratocyst was framed by Philipsen
- 1963 – the Researchers Pindborg and his colleague Hansen reported the essential features as cyst
- 1967 – Benign neoplasm (Toller)
- 1984 – True benign type of cystic neoplasm coined by Ahlfors
- 1992 –the same term odontogenic keratocyst has been designated by WHO
- 2005 – keratocystic odontogenic tumour given a definition mentioned earlier
- 2017 – again characterized as Odontogenic keratocyst (WHO) [1,2,9]

II. CLINICAL FEATURES

OKC is the rare and distinctive developmental entity. It includes 6-9 % of all cyst of the jaw, incidence vary from 5-18%. Incidence is common in 2nd to 4th decade of life with male prediliction .Location is mostly seen in higher frequency in mandible as compared to maxilla. Mandible angle – ascending ramus region (69-83%) is the most common location. It present as slow growing swelling either with pain or without pain, discharge, commonly diagnosed during routine radiographic procedures [5,9]. The outgrowth/expansion is very mild in the early stage reason is it has a peculiar characteristic that it grows in antero-posterior direction which even includes medullary space. A substantial number of OKCs are asymptomatic and hence are elicited only by incidental radiographic findings. Lesions occuring in children are often a multiple type odontogenic keratocysts as a component of the naevoid basal cell carcinoma syndrome. However, the multiple cyst occurring are independent of these syndrome. The aspirate from this lesion contains a cheesy material mostly suggestive of keratin. Sometimes, the aspirate may also contain a straw-coloured fluid. [1,2,3,11]

RADIOGRAPHIC VARIANTS (fig1):

1. **Replacemental**
2. **Envelopmental**
3. **Extraneous**

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4. Collateral

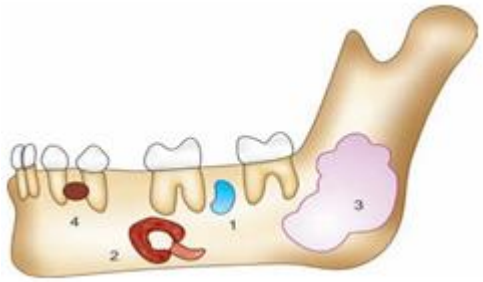


Fig 1: radiographic variants ,Source: www.jaypee.com

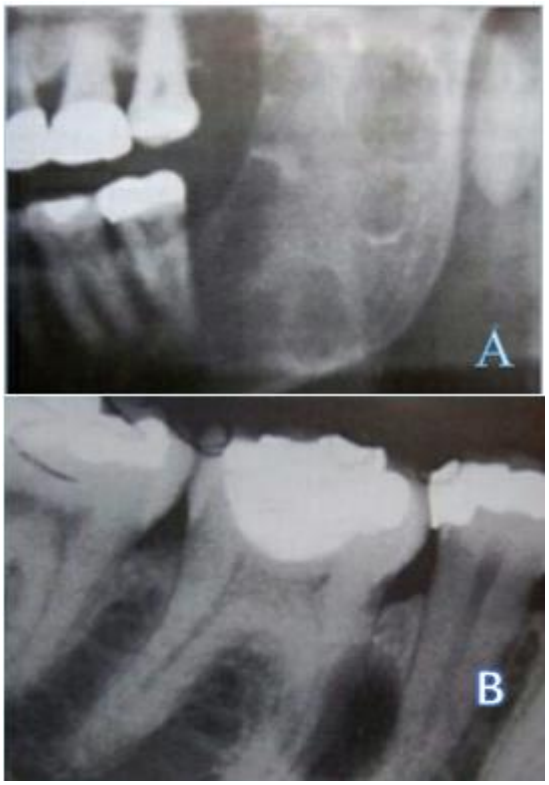
III. RADIOGRAPHIC FEATURES

LOCATION: epicentre is located at higher level to that of mandibular canal

PERIPHERY AND SHAPE: well defined smooth, round or oval shape / scalloped outline, in case of secondarily infected cortical border is lost

INTERNAL STRUCTURE: commonly present as radiolucent lesion , appearence of keratin content does not increase the radio opacity, in some clinical cases curved internal septa might be existing, imparting multilocular radiolucent appearance.

EFFECT ON SURROUNDING TISSUE: buccal and lingual cortical plate expansion, throughout the mandible except coronoid process and upper part of ramus. KCOT occasionally causes the displacement / resorption of teeth. mandibular canal may get displaced inferiorly. In case of maxilla it invaginates and occupies the entire maxillary sinus. [1,5,6]



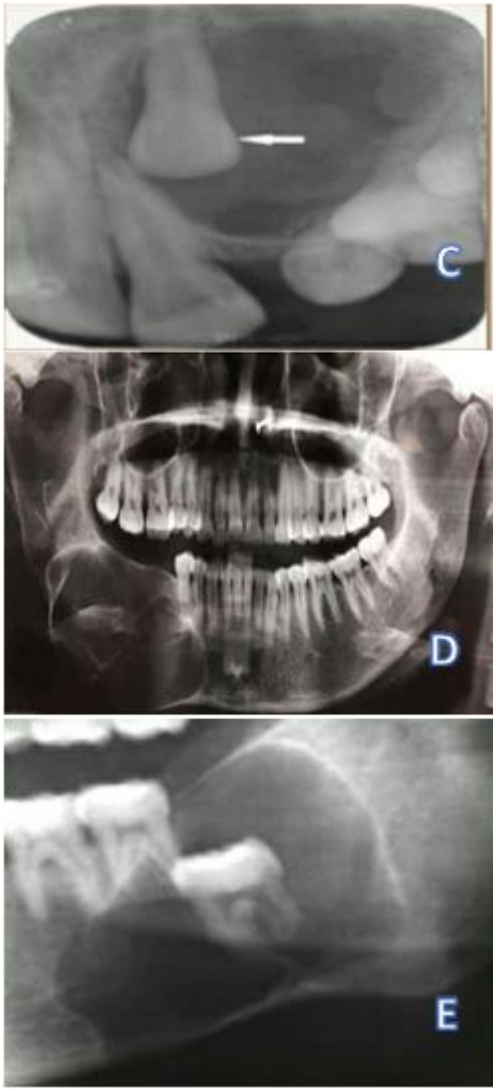


Fig: 2 ; A) EXTRANEOUS VARIANT , B) COLLATERAL VARIANT ,C) REPLACEMENTAL VARIANT, D) OKC GROWTH IN ANTEROPOSTERIOR DIRECTION E) ENVELOPMENTAL VARIANT SOURCE: WWW.RADIOPEDIA.ORG

IV. HISTOLOGY

Thin, uniform thickness lining of stratified squamous epithelium imparting a ribbon –like appearance which consist of 8-10 cell layer thickness.

Absence of rete ridges.
A palisading cuboidal or columnar hyper chromatic basal cell layer arranged in "picket fence or tombstone appearance".

A spinous layer of epithelium is actually thin in which there is a obvious conversion from basal cell layer where epithelium gets separated from basement membrane [1,3]

Key features: Surface keratinisation will be present which shows corrugated and rippled appearance and mostly it is a para-keratinization (i.e., keratinized cells with nuclei)[5]

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Weak epithelial-connective tissue interface

Fibrous connective tissue which is thin present in the cystic wall and free of inflammatory products. The presence of daughter cyst may be evident. [1,9]

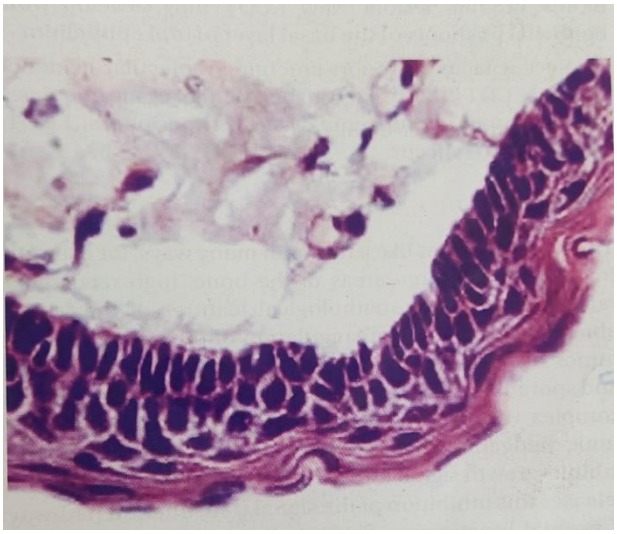

Fig: 3 corrugated , para-keratinized epithelium with tall columnar cells devoid of rete pegs

HISTOLOGIC DIAGNOSTIC CRITERIA – WHO 2001

The lesion is characterized by a thin fibrous capsule and a lining of keratinized stratified squamous epithelium, usually about 5-8 cell layer in thickness and generally without rete ridges[9]

HISTOLOGICAL VARIANTS:

PARAKERATINIZED ODONTOGENIC KERATOCYST	ORTHOKERATINIZED ODONTOGENIC KERATOCYST
Included in classification of tumour by WHO (2005)	Not added in proposed classification of tumours who (2005)
Cells which are keratinised and contain nuclei in palisaded basal layer	Keratinized cells without nuclei, basal layer not palisaded or polarized
Incidence – 86%(associated with NBSCC syndrome)	Incidence – 12%(not associated with syndromes)
More aggressive in nature	Less aggressive when compared to other variant
Recurrence – 47.8%	Recurrence – 2.2%

V. DIFFERENTIAL DIAGNOSIS

HISTOLOGICALLY included differential diagnosis: Myxoma, uni-cystic Ameloblastoma, Central giant cell granuloma. .The key differentiating factor is the presence of daughter cysts in OKC.

RADIOLOGICALLY: Dentigerous cyst ,residual cysts, radicular cyst, Ameloblastoma ,Primordial cyst have been included as differential diagnosis of OKC ,because the Most predominant location is in the mandibular 3rd molar areas and the lesions occur in 3rd-5th decade of life[1,11]

IMAGE INTERPRETATION KEYS TO RULE OUT DIFFERENTIAL DIAGNOSIS

OKC – usually present as unilocular radiolucency contains few number of septations.

DENTIGEROUS CYST-unilocular radiolucency surrounding the crown of impacted tooth and characteristic feature with no septa.

AMELOBLASTOMA: multilocular radiolucency with presence of thick septa is the peculiar feature.

RADICULAR CYSTS -unilocular radiolucency surrounding the apex of a non vital teeth septa might be present or absent .[11]

VI. GENETICS

The KCOT/OKC behaves like a tumour in various directions, for example inclusion of almost large areas of bone, shows a high recurrence , peculiar histopathological characteristics of the condition , abnormal function / loss of regulation of the drosophila segment polarity gene patched (PTCH) - a tumour suppressor gene have been noticed in both NBCCS associated and sporadic KCOT'S etc., normally , PTCH forms a receptor -complex with the oncogene SMO(smoothened) for the sonic hedgehog ligand. PTCH binding to SMO inhibits growth signal transduction pathway. If normal functioning of PTCH is absent, the proliferation stimulation effect of SMO are allowed to predominate. Pathogenesis includes 2-hit mechanism with alleles loss at 9q22. Tumour suppressor gene activation is a mechanism responsible. The first hit type of mechanism involves the process of mutation of one alle which is dominating and has been taken over with no phenotypic effect. The second hit type of mechanism is the loss of other allele and is commonly categorized as a condition called loss of heterozygosity. In KCOT, this lead to abnormally-regulated oncoprotein cyclin d1 and p53 [8,9,15]

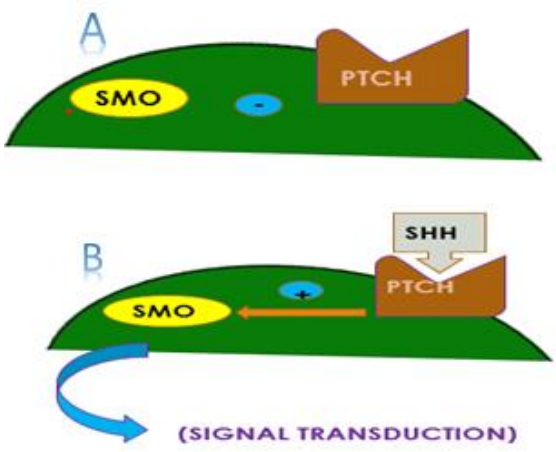

Fig : 4
A- PTCH COMBINES WITH SMO TO FORM RECEPTOR COMPLEX FOR SONIC HEDGEHOG LIGAND, PTCH -SMO RECEPTOR COMPLEX INHIBITS GROWTH SIGNAL TRANSDUCTION
B- SHH RELEASES PTCH FROM SMO,ALLOWING SIGNAL TRANSDUCTION

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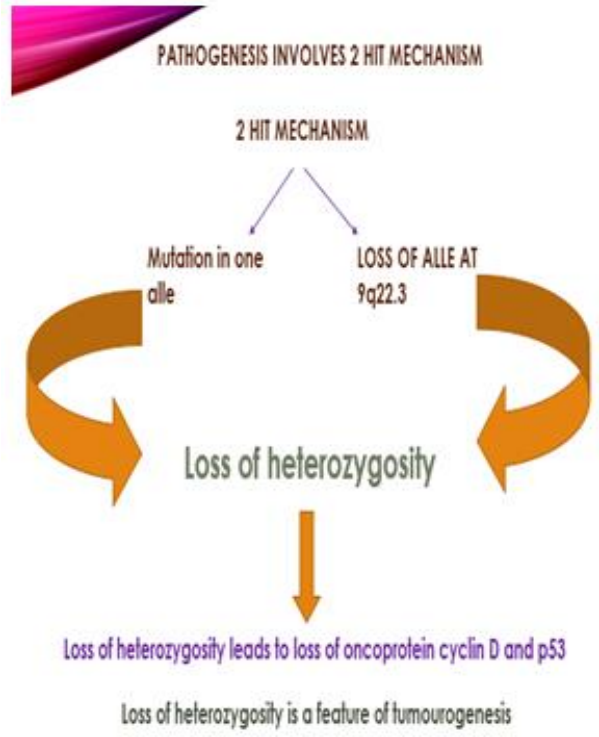

Fig: 5 loss of heterozygosity
Source: Dr. sai charan gallery

VII. ASPIRATION

KCOT/OKC aspiration content is thick , creamy, dirty-white viscous suspension of keratin which has an appearance of pus but without an offensive odour. Smear preparation : we can even prepare a smear from the aspiration content and it should be examined for the presence of keratin cells. Electrophoresis : done to assess the protein content in the aspiration content , IMPRESSION : minimal protein content with maximal albumin to globulin ratio. Total protein will be found below 4g/100ml which differentiates the lesion form other cystic lesion. Cholesterol crystal , keratin squames , hyaluronic acid, ruston bodies heparin and chondroitin sulfate also found in aspirate. Immunofluorescent studies : by kuusela et al demonstrated an antigen in the cystic fluid, which is not present in other cystic lesion nor in plasma or saliva and they named it as keratocyst antigen.

VIII. MANAGEMENT :

ENUCLEATION : This method indicates complete removal of tumour along with its envelope. The recurrence rate is high of about 30-60 % as the fibrous wall comprises of minute satellite cysts which makes it hard to enucleate.(Giuliani et al.,2006).

ENUCLEATION IN COMBINATION WITH CARNOY' SOLUTION: The components of this solution are chloroform 3ml, absolute alcohol 6ml ,glacial acetic acid 1ml and ferric chloride 1gm. Carnoy's solution is the cauterizing solution and it is applied in the cavity after enucleation.

ENUCLEATION FOLLOWING PERIPHERAL OSTECTOMY: A procedure in which powered hand piece and rotary instruments are used to deplete the peripheral bone in cranial and caudal direction followed by iodoform guage filling in the defect.

ENUCLEATION + CARNOY'S SOLUTION + PERIPHERAL OSTECTOMY: After enucleation the cyst should be washed/rinsed with saline and stuffed with guage which is immersed in carnoys solution and should be kept undisturbed for 120 seconds. the cystic lumen is again rinsed with saline after 3 minutes and by this time the cystic walls would have been turned dark brown and fixed. By doing this so complete removal of the remains is achieved .the overlying attached mucosa is excised after the peripheral osteotomy and is finally filled with Vaseline -iodoform guage.

ENUCLEATION + CRYOTHERAPY: The epithelial remnants and the satellite cysts should be killed after enucleation .This is achieved by spraying liquid nitrogen two times for 1 minute regularly done for 5 mins then between the freezes followed by concurrent bone grafting. Liquid nitrogen causes direct damage to the cell from intracellularly to extracellularly by ice crystal formation. It also has the property to leave inorganic osseous framework untouched and devitalize the bone. By leaving the bony matrix untouched the bone acts as framework to form new bone. Bone grafts are to be placed immediately in order to accentuate healing ,decreases the certainty of pathological fracture and as haemostasis agent for minimizing the scar formation.

MARSUPILIZATION(Decompression): In this method, a surgical window measuring about 1 X 1 cm is created and the epithelial lining of the wall is sutured to oral mucosa to alter the cystic cavity into a pouch so that the decompression is achieved. Cavity is then packed with iodoform gauge which is left open till healing. PARTSCH-I involves method of marsupialization and PARTSCH II involves Enucleation + primary closure.

MARSUPIALIZATION IN COMBINATION WITH CYSTECTOMY: Which is also called as Waldron's method. Procedure is conducted in two steps. First step : Marsupialization in combination with Iodoform gauge pack which leads to shrinkage of cavity , Second step is been carried out which includes complete enucleation of entire cyst. This technique is carried out in cases of large cysts and vital structures in vicinity to it. Advantages includes prevention of pathological fractures and quick healing process. Disadvantage is that patient has to undergo two appointments.

RESECTION: Resection is been carried out either segmentally or marginally followed by rehabilitation . [3,4,6,7,8,12]

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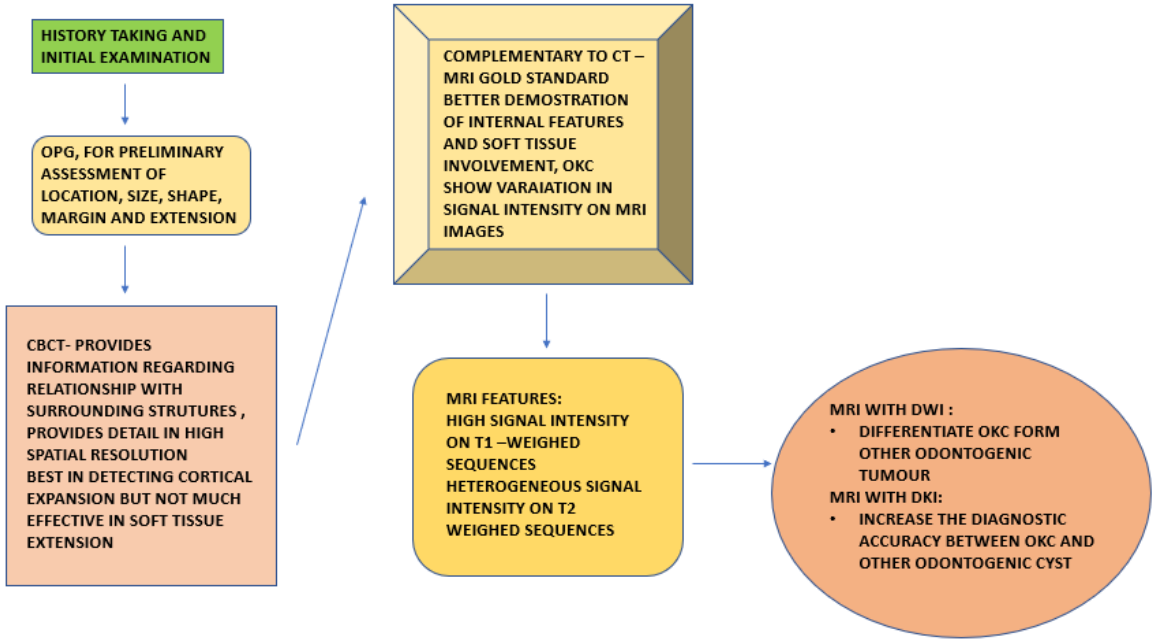
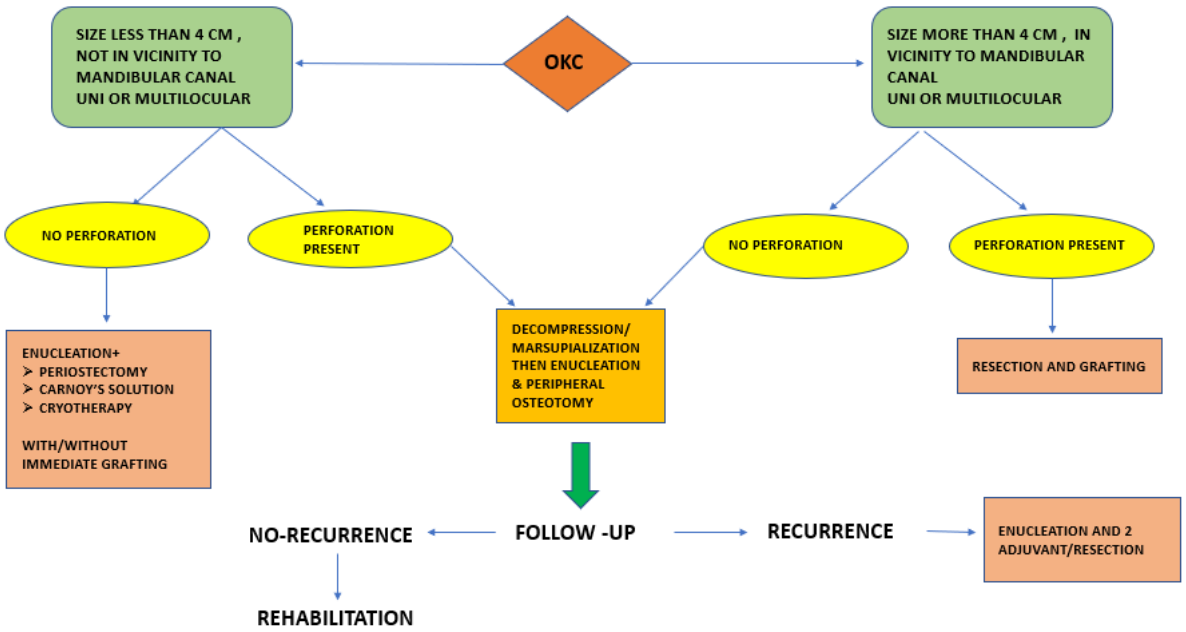
REASON FOR RECURRENCE

- Insufficient excision of cyst's epithelial lining
- fragility of epithelial lining
- 3.Cells in the lining shows high proliferative rate .
- invasion of the basal layers of the epithelium into connective tissue
- Cortical bone perforation.
- Adhesion of lesion to surrounding soft tissue.
- Supra-epithelial and infra-basal epithelial split of the epithelial lining.
- Para-keratinization present in the surface layer
- development of new okc in areas vicinity to previous lesion
- presence of daughter/ satellite cysts [1,5,9]

IX. ROUTE MAP FOR INVESTIGATION



X. TREATMENT PROTOCOL



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XI. DISCUSSION

Redesignation of OKC to KCOT by WHO 2005 , is due to following reason, based on Behaviour, it is locally destructive, aggressive in nature & high recurrence rate 3-6%, When associated with goltz-gorlin syndrome recurrence rate is very high ranging from 25-65% . KCOT grows not by expansion which is osmotic in nature like other odontogenic cysts, it grows by epithelial cell proliferation exhibit infolding of epithelial lining. It has a un-remitting type of growth. Mean mitotic count is 8.0 which is same as that of ameloblastoma. Proportion/ratio of 83 kda mmp9 to 92kda in OKC fluids than greater when compared to cysts. Histopathological findings is basal cell layers of KCOT invaginate the underlying connective tissue and mitotic figures are more commonly found in supra-basal layers of epithelium.

Immunohistochemical studies reveals

- ✓ Higher expression of oxidative enzymes – NADPH2, NADH2, G6PD AND ACID PHOSPATASE, PTHRP.
- ✓ Leucine aminopeptidase-responsible for invasiveness of lesion.
- ✓ P53 staining in supra basal layer- increase the proliferative potential of epithelial cells.
- ✓ Mmp1 – dissemination of cyst to trabecular spaces.
- ✓ Mmp2 – degradation of extracellular layer around the cyst.[1]

In the year 2017 the KCOT was been reclassified as OKC for the following reasons

- ✓ Loss of heterozygosity on 9q22.3 region have been found in other developmental cyst like dentigerous cyst.
- ✓ Mutation of PTCH gene were more in syndromic cases and no detection of PTCH mutation in sporadic cases.
- ✓ No detection of SMO mutation in both syndromic and sporadic cases.
- ✓ PTCH gene mutation is seen in ortho keratinized odontogenic cyst and dentigerous cyst
- ✓ Tumour can either denote a swelling or neoplasm and cannot be used for lesion that has morphological appearance of a cyst [2, 4 ,9,15]

FUTURE TREATMENT MODALITIES PROPOSED BY VARIOUS AUTHORS:

Studies on genetic level have proposed a new techniques of treatment of OKC at a molecular level. This modalities might minimizes or eradicate the need for complex surgical procedures. Taipale et al. - Cyclopamine prevents the generation of the response to the SHH signal. Antagonist of shh signalling factors could effectively treat KCOT was postulated by Zhang et al (2006). It included the method of introducing a varied form of PTCH inhibiting the SMO molecule by synthetic antagonist which suppresses down-stream transcription factors of the shh pathway. Injection of SMO protein intra-lesionally provides a antagonistic effect and has a maximum potential option as a future treatment modality .[5,9,15]

XII. CONCLUSION

The aggressive behaviour of OKC is a cause for an complex treatment modality, and its reclassification by WHO as a cyst should further direct the practitioners in this regard. As research is in progress, treatment will soon become a molecular approach. This might potentially minimize or completely eradicate the need for aggressive surgical procedures to handle these lesions. The journey of OKC had been a controversial and tedious process. The reason for reclassification of KCOT to cyst is still unclear even though the reasons were mentioned. Although there are chances again for this to move back to KCOT due to its aggressiveness and recurrence.

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