ejpmr, 2021,8(4), 654-660

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ODONTOGENIC KERATOCYST: A SYSTEMIC REVIEW

Devangi Dwivedi*

MDS (Oral and Maxillofacial Pathology and Microbiology) Assistant Professor, Babu Banarasi Das College of Dental Sciences, Lucknow, UP.

***Corresponding Author: Dr. Devangi Dwivedi**

MDS (Oral and Maxillofacial Pathology and Microbiology) Assistant Professor, Babu Banarasi Das College of Dental Sciences, Lucknow, UP.

Article Received on 15/02/2021 **Article Revised on 07/03/2021** **Article Accepted on 27/03/2021**

ABSTRACT

The odontogenic keratocyst is a common odontogenic cyst which accounts for 10% of all oral cysts. Odontogenic keratocysts are believed to arise from remnants of the dental lamina and have a distinctive histopathologic appearance. They are known to be locally aggressive and have a high recurrence rate, thus requiring close long term follow up. Odontogenic keratocysts are one component of the basal cell nevus syndrome and all patients with odontogenic keratocysts should be evaluated for this syndrome. This paper reviews odontogenic keratocysts covering all its aspects.

KEYWORDS: Oral cyst, Locally aggressive, High recurrence rate.

INTRODUCTION

First described by Philipsen in 1956, the odontogenic keratocyst is now designated by the World Health Organization as a 'keratocystic odontogenic tumor (KCOT)' and is defined " a benign uni or multicystic, intraosseous tumor of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior". WHO recommends the term keratocystic odontogenic tumor as it better reflects its neoplastic nature.[1]

The odontogenic keratocyst is a distinctive form of developmental odontogenic cyst that deserves special consideration because of its specific histopathologiic features and clinical behavior. This cyst is derived from the remnants of dental lamina, with a biological behavior similar to a benign neoplasm, with a distinctive lining of six to ten cells in thickness, and that exhibits a basal cell layer of palisaded cells and a surface of corrugated parakeratinization.[2]

Studies indicate that a significant number of OKC's show clonal loss of heterozygosity of common tumor suppressor genes. The finding of clonal deletion mutations of genomic DNA in these cysts support the hypothesis that they are neoplastic rather than developmental in origin. The odontogenic keratocyst is regarded as a distinctive entity because of its characteristic histology, proliferation kinetics and behavior. Therefore, although keratinization may be present in many other types of cysts, the specific histologic pattern of the odontogenic keratocyst separates it from all others.[3]

Etiopathogenesis

It is generally agreed that OKCs develop from dental lamina remnants in the mandible and maxilla. However, it has also been suggested that this cyst is originated from the extension of basal cells of the overlying oral epithelium. Factors that may contribute to the pathogenesis of this cyst include a high proliferation rate, overexpression of the antiapoptotic protein Bcl-2 and several growth factors. Studies on NBCCS and sporadic OKCs have provided evidence of a two – hit genetic mechanism at two or more chromosome loci on chromosome 9q22.3, leading to overexpression of several proteins, including cyclin D1 and p53. Central to the development of OKCs are mutations of the PTCH gene mapped to chromosome 9q22.3-q31. The defective gene associated with NBCCs was found to be homologous to the Drosophila (fruit fly) patched (PTCH) gene. The protein product of the PTCH gene (a tumor-suppressor gene) is a component of the Hedgehog-signaling pathway and is essential for the development during embryogenesis and cell signaling in the adult. The PTCH gene product normally represses the activity of the so-called Sonic Hedge Hog (SHH) protein and other signaling proteins, such as smoothened protein. If the PTCH gene is nonfunctional, overexpression of SHH and/or smoothened proteins occurs, leading to increased cell proliferation. Mutations of the PTCH gene are involved in the development of human syndromic basal cell carcinoma and are present in a proportion of sporadic basal cell carcinomas, providing further evidence of the crucial role of PTCH as a tumor suppressor in human keratinocytes.[4]

PTCH mutations are also found in OKCs in NBCCS patients and probably in many OKCs that occur sporadically. Thus, the currently proposed change in terminology from OKC to KCOT reflects the concept that these are cystic tumors and not developmental cysts. These cysts have a greater potential to undergo malignant change than the other types of cysts.[5]

Clinical features

Odontogenic keratocysts may be found in patients who range in age from infancy to old age, but about 60% of all cases are diagnosed in people between 10 and 40 years of age. There is a slight male predilection.[6] The mandible is involved in 60% to 80% of cases, with a marked tendency to involve the posterior body and ascending ramus. It may be superimposed over the apices of tooth roots or adjacent to the crowns of impacted teeth.[7]

Small odontogenic keratocysts are usually asymptomatic and discovered only during the course of a radiographic examination. Larger odontogenic keratocysts may be associated with pain, swelling or drainage, aggressive growth and invasion of adjacent structures. Some extremely large cysts, however, may cause no symptoms.[7]

There are two varieties of this cyst, orthokeratinized and parakeratinized. Orthokeratinized odontogenic cyst is a relatively uncommon developmental cyst comprising about 10% of cases that had been previously coded as odontogenic keratocysts. Wright termed orthokeratinized as variant of OKC which showed little clinical aggressiveness. On the clinical basis orthokeratinized odontogenic cyst occur predominantly in young adults and show a 2:1 male to female ratio. The lesion occurs twice as frequently in the mandible than the maxilla. The size can vary from less than 1cm to large lesions greater than 7 cm in diameter. Histologically the cyst lining is composed of stratified squamous epithelium, which shows an orthokeratotic surface of varying thickness. Keratohyaline granules may be prominent in the superficial epithelial layer subjacent to the orthokeratin. The epithelial lining may be relatively thin, and a prominent palisaded basal layer, characteristic of the odontogenic keratocyst is not present.[8]

Parakeratinized odontogenic cyst is clinically more aggressive in nature. It is found in patients who range between 10 and 50 years of age. The males are more commonly affected. Histologically the cyst lining is composed of stratified squamous epithelium, which shows an parakeratotic surface of varying thickness. The epithelial lining may be relatively thick, and a prominent palisaded basal layer is present. It is associated with nevoid basal cell carcinoma syndrome (NBCCS). The prevelance of NBCCs is estimated to be about 1 in 60,000.[9]

Nevoid basal cell carcinoma syndrome (gorlin syndrome)

This syndrome, first described by Binkley and Johnson in 1951, has been thoroughly reviewed by Gorlin and his coworkers. A hereditary condition, it is transmitted as an autosomal dominant trait, with high penetrance and variable expressivety. It is caused by mutations in patched (PTCH), a tumor suppressor gene that has been mapped to chromosome 9q22.3-q31.[10,11]

Clinical features of gorlin syndrome[12]

50% or greater frequency

- Multiple basal cell carcinomas
- Odontogenic keratocysts
- Epidermal cysts of the skin
- Palmar / plantar pits
- Calcified falxcerebri
- Enlarged head circumference
- Rib anomalies (splayed, fused, partially missing, bifid)
- Mild ocular hypertelorism
- Spina bifida occulta of cervical or thoracic vertebrae

15% to 49% frequency

- Calcified ovarian fibromas
- Short fourth metacarpals
- Kyphoscoliosis or other vertebral anomalies
- Pectus excavatum or carinatum
- Strabismus (exotropia)

Less than 15% frequency (But not random)

- Medulloblastoma
- Meningioma
- Lymphomesenteric cysts
- Cardiac fibroma
- Fetal rhabdomyoma
- Marfanoid build
- Cleft lip and/ or palate
- Hypogonadism
- Mental retardation

Radiographical features

Radiographically, the cysts in patients with nevoid basal cell carcinoma syndrome do not differ significantly from isolated keratocysts. The cysts in patients with this syndrome are often associated with the crowns of unerupted teeth; on radiographs they may mimic dentigerous cysts.[13]

Histopathologic features

The cysts in the nevoid basal cell carcinoma syndrome histopathologically are invariably odontogenic keratocysts. The keratocysts in patients with this syndrome tend to have more satellite cysts, solid islands of epithelial proliferation, and odontogenic epithelial rests within the fibrous capsule than do isolated keratocysts. Foci of calcification also appear to be more common. These features, however, are not diagnostic for nevoid basal cell carcinoma syndrome because they may

be seen in isolated keratocysts. Odontogenic keratocysts associated with this syndrome have been shown to demonstrate overexpression of p53 and cyclin D1 (bcl-1) oncoproteins when compared with nonsyndrome keratocysts.[14]

Tha basal cell tumors of the skin cannot be distinguished from ordinary basal cell carcinomas. They exhibit a wide spectrum of histopathologic findings, from superficial basal cell lesions to aggressive, noduloulcerative basal cell carcinomas.[15]

Treatment and Prognosis

Several cases of ameloblastoma have developed in cysts of this syndrome, thus emphasizing the importance of surgical removal of the cysts and their histologic examination. Whenever a diagnosis of odontogenic keratocyst is received by the dentist, he must be certain to rule out the presence of this syndrome because of the many associated problems which these patients ultimately will face.[16]

Radiographic features

Radiographically, most OKC's are unilocular, presenting a well – defined peripheral rim. Scalloping of the border is also a frequent finding and this represents variations in the growth pattern of the cyst. Multilocular radiolucent OKC is also observed, generally representing a central cavity having satellite cysts and may exhibit the presence of cholesterol granulomas. When it is multilocular and especially if located in the third mandibular molar area, it may be confused radiographically with an ameloblastoma. Occasionally OKC may mimic a dentigerous cyst and contain the crown of a retained tooth within its lumen. The final diagnosis of any cystic cavity within the jaw bones will be achieved only after biopsy of the surgical specimen. Multilocularity (20 %) is often present and tends to be seen more frequently in larger lesions. Most lesions, however, are unilocular, with as many as 40% noted adjacent to the crown of an unerupted tooth (dentigerous cyst position). Approximately 30% of maxillary and 50% of mandibular lesion produce buccal expansion.[17,18]

Some cysts appear to surround the crown of an unerupted tooth. Such cysts may be "envelopmental" in nature or, if the reduced enamel epithelium of the follicle of an unerupted tooth fuses with the cyst, there may be a true dentigerous relationship. Occasionally a lateral periodontal cyst develops on the lateral aspect of a root.[19]

Mandibular lingual enlargement is occasionally seen. Proximity to the roots of adjacent normal teeth sometimes causes resorption of these roots, although displacement is more common. Sometimes these cysts displace the neurovascular bundle.[20]

They demonstrate a well – defined unilocular or multilocular radiolucency with smooth and often corticated margins which may simulate that of a dentigerous, radicular, residual or a lateral periodontal cyst. Root resorption is seldom a feature. In older individuals, keratocysts of anterior midline can mimic nasopalatine duct cyst.[20]

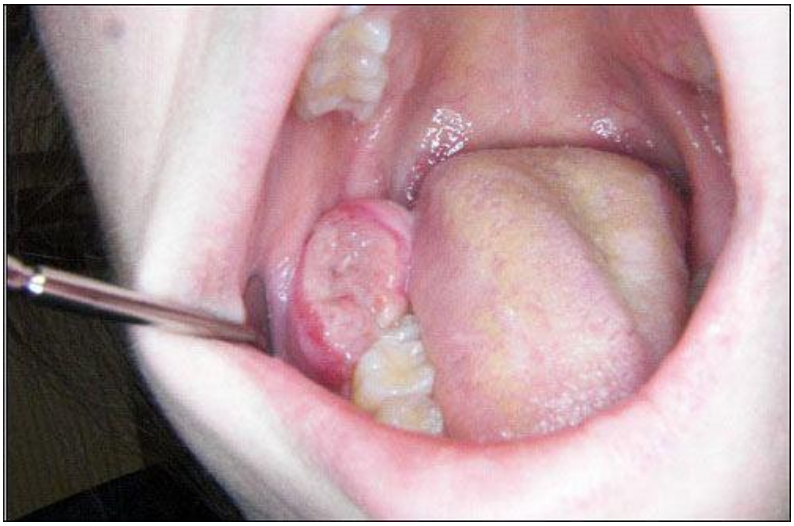

Fig. 1: Odontogenic keratocyst in the mandibular third region.

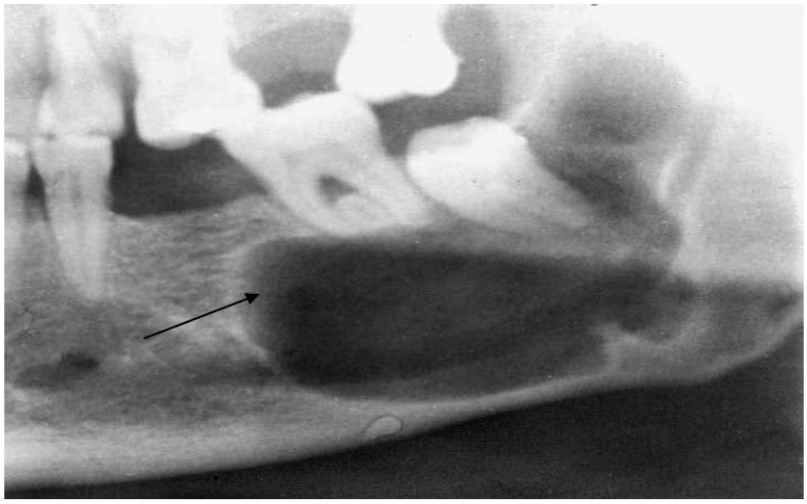

Fig. 2: Radiograph of an odontogenic keratocyst with scalloped margins.

Histological features

Histologically, these cysts are formed with a stratified squamous epithelium that produces orthokeratin (10%), parakeratin (83%), or both types of keratin (7%). No rete ridges are present; therefore, OKC grows in a neoplastic fashion and not in response to internal pressure. In the presence of an intense inflammation process, the adjacent epithelium loses its keratinized surface, may thicken and develop rete processes or may ulcerate.OKC may show intercellular edema at places in the spinous layer.[4]

The odontogenic keratocyst wall is usually rather thin unless there has been superimposed inflammation. The lining epithelium is highly characteristic, and is composed of [4]

- A parakeratinzed surface which is typically corrugated, rippled or wrinkled.
- A remarkable uniformity of thickness of the epithelium, usually ranging from 6 to 10 cells thick.
- A prominent palisaded, polarized basal layer of cells often described as having a 'picket fence' or 'tombstone' appearance.

The connective tissue wall often shows small islands of epithelium similar to the lining epithelium; some of these islands may be small cysts. In at least some cases, the apparent islands of epithelium and small satellite or 'daughter' cysts actually represent the ends of folds of the lining epithelium of the main cystic cavity which have been cut in cross section; the linings of these cysts are very commonly folded. Although rare, hard tissue deposits, namely dystrophic calcifications and cartilage, have been reported to occur in the connective tissue wall of the odontogenic keratocyst.[19]

The lumen of the keratocyst may be filled with a thin straw colored fluid or with a thicker creamy material. Sometimes the lumen contains a great deal keratin, while at other times it has little. Cholesterol, as well as hyaline bodies at the sites of inflammation, may also be present. The electrophoretic measurement of fluid from these cysts has been reported by Toller to show that it contains a very low content of soluble protein compared with the patient's own serum.[18]

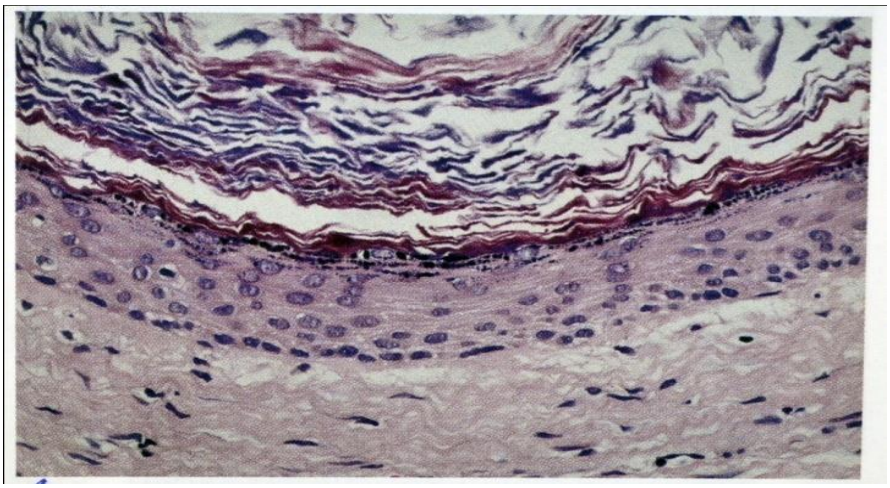

Fig. 3: Parakeratinized Cyst.

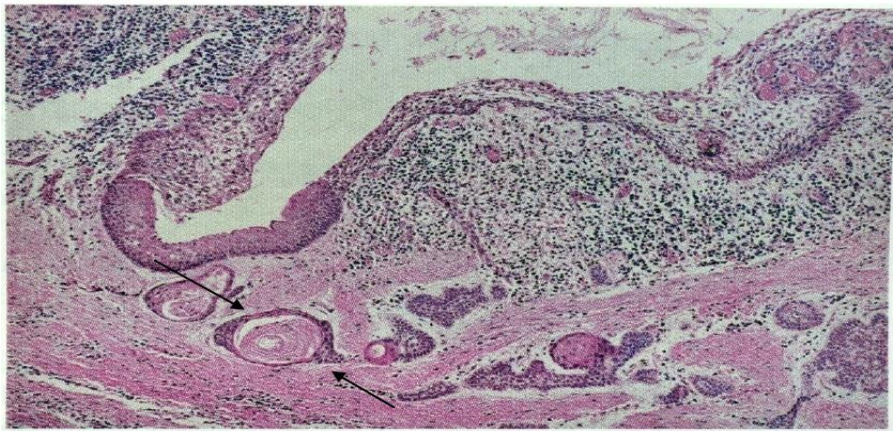

Fig. 4: Odontogenic keratocyst cyst showing daughter or satellite cysts.

Malignant transformation of odontogenic keratocyst

The possibility that the epithelium lining the cavity of an odontogenic cyst may occasionally undergo malignant change has been recognized for a number of years, but it is difficult to establish that such an event has actually occurred. The presence in the jaws of a cystic epithelial-lined cavity and a contiguous carcinoma is open to a number of interpretations. Ward and Cohen have pointed out at least three possible explanations[17]

1. That a pre existing cyst has become secondarily involved in a carcinoma of unrelated organ, arising either from an adjacent epithelial structure or as a metastasis from a distant primary tumor.
2. That the lesion was a carcinoma from the outset, a part of which has undergone cystic change, and
3. That the initial lesion was a cyst and that malignant change has subsequently taken place in its epithelial lining. There have been numerous reports of malignant change believed to have arisen in the epithelial lining of odontogenic cysts.

It has been suggested that odontogenic keratocysts have a greater potential to undergo malignant change than the other types of odontogenic cyst.[23]

The variant of OKC that produces only orthokeratin acts somewhat differently than other OKCs. These almost always are found in a dentigerous association, usually around the mandibular third molar, and they are much less aggressive. They do not have a hyperchromatic basal layer; in fact, the basal layer is flattened. Finally, the highly characteristic nature of the parakeratinized lining epithelium and its relationship to the high recurrence rate have been emphasized by a report dealing with orthokeratinized odontogenic cysts and their recurrence rate.[17]

Wright investigated 59 cases of orthokeratinized odontogenic cysts which showed a predilection for occurrence in males, most commonly in the second to fifth decades of life. These cysts were located predominantly in the posterior mandible, where they most typically appeared as dentigerous cysts. The thin, uniform lining epithelium was covered with orthokeratin and showed a prominent granular layer. Follow-up of 24 of these patients revealed only one case of recurrence. This difference in biologic behavior would further underscore the necessity for very strict application of the definition of the term odontogenic keratocyst in diagnosis of the lesion.[1]

Diagnosis

Diagnosis of OKC is based on various methods such as Conventional radiographic examination (panoramic and intraoral periapical radiographs are usually adequate to determine the location and estimate the size of a KCOT), CT scan, MRI, Biopsy followed by Microscopic findings. Fine Needle Aspiration Cytology (FNAC) also plays a vital role in the chairside diagnosis of OKC. The different methods of lab diagnosis are.[1]

A. Examining the cyst fluid

Toller (1970) considered that estimation of the soluble protein level in aspirated cyst fluid might be a valuable aid in the diagnosis of OKCs. He showed that fluids from keratinizing cysts had soluble protein levels below 3.5 g per 100ml, whereas the values for non – keratinizing cysts were in the range. 5.0-11.0 g per 100 ml, with a mean of 7.1 g per 100 ml. Electrophoratic studies corroborated the finding that a protein level of less than 4.0 g per 100 ml indicated a diagnosis of OKC.

B. Keratocyst antigen

Kusela et al (1982) demonstrated an antigen in the fluid of OKCs that was not present in the fluids of other cyst types nor in plasma or saliva. A double-antibody fluorescence technique localized the antigen to the epithelial cells of the OKC and they called it keratocystantigen (KCA)

C. Lactoferrin in keratocyst fluids

Douglas and Craig used a competitive enzyme-linked immunosorbent assay (ELISA) to measure the concentration of lactoferrin in fluids from OKCs, dentigerous and radicular cysts. OKC fluids contained significantly higher concentrations of lactoferrin than fluids from the other two cyst types.

D. Elafin

Elafin, also known as skin-derived antileucoproteinase inhibitor, is an epithelial specific, cationic elastase inhibitor that has been studied in OKC epithelium.

E. Enzyme histochemistry

Magnusson demonstrated a high level of leucineaminopeptidase activity in the fibrous capsule of OKCs. This is an enzyme that has been implicated in the invasiveness of malignant tumours.

F. Immunohistochemistry

Epithelial cell markers based on antigen-antibody reactions can be used for diagnosing OKCs. Some examples are-

1. CK19 expressed in suprabasal cells and some basal cells
2. CK16 expressed strongly in suprabasal layers.
3. P53 expressed only in OKCs.
4. CK17 strong reactivity in all layers.
5. Ki-67 positive cells are present in the suprabasal layer of OKC.
6. p63 expression in superficial layers
7. IPO-38 in superficial layers.
8. Bcl-1 expressed in basal layers

Differential diagnosis

When cysts are associated with teeth, several entities might be considered, such as dentigerous cyst, ameloblastoma, odontogenic myxoma, adenomatoid odontogenic tumor and ameloblastic fibroma. Radiolucent, non odontogenic tumors, such as central giant cell granuloma, traumatic bone cyst, and aneurysmal bone cyst, might be included in a differential diagnosis of this entity in young patients.[9]

Treatment

Although the presence of an odontogenic keratocyst may be suspected on clinical or radiographic grounds, histologic confirmation is required for the diagnosis. Consequently, most odontogenic keratocysts are treated similarly to other odontogenic cysts, that is, by enucleation and curettage. Complete removal of the cyst in one piece is often difficult because of the thin, friable nature of the cyst wall. In contrast often tend to recur after treatment. Whether this is due to fragements of the original cyst that was not removed at the time of the operation or a 'new' cyst that has developed from dental lamina rests in the general area of the original cyst cannot be determined with certainty.[4]

Many surgeons recommend peripheral ostectomy of the bony cavity with a bone bur to reduce the frequency of recurrence. Others advocate chemical cauterization of the bone cavity with Carnoy's solution after cyst removal. Intraluminal injection of Carnoy's solution also has been used to free the cyst from the bony wall, thereby allowing easier removal with a lower reccurence rate.[16]

After cystotomy and incisional biopsy, some surgeons have treated large odontogenic keratocysts by insertion of a polythene drainage tube. This treatment protocol for OKC based on decompression offers a conservative and effective option with low morbidity and similar recurrence rates to those reported in the literature.[11]

Recurrences

The rate of recurrence of OKCs quoted in the literature varies from 6 to 60%. Recurrence rates have been lower in recent years as the risk is more fully appreciated and therefore more appropriate treatment is applied. The reasons for the high rate of recurrence are unclear but probably include the following:[2]

1. The thin, friable, fibrous capsule and the tendency for the epithelium to separate from the fibrous wall makes removal of the cyst difficult. In addition, the large size of the cyst and the scalloped margin which extends into the cancellous bone adds to the technical difficulty of complete enucleation.
2. A tendency towards multiplicity and the presence of daughter cysts.
3. Some believe that the OKCs has an intrinsic growth potential and behaves like a 'hollow benign neoplasm', as suggested by its 'infiltrative pattern of growth'.
4. In some individuals there may be a genetic propensity to form cysts from residues of the dental lamina.
5. Actual biological qualities of the cyst epithelium, such as an increased mitotic index and production of bone-resorbing factors, may be associated with recurrence.

CONCLUSION

Other than the tendency for recurrences, the overall prognosis for most odontogenic keratocysts is good. Ocasionally, a locally aggressive odontogenic keratocyst cannot be controlled without local resection and bone grafting. In extremely rare instances, keratocysts have been seen to extend up into the skull base region.[4]

A few examples of carcinoma arising in an odontogenic keratocyst have been reported. Patients with odontogenic keratocysts should be evaluated for manifestations of the nevoid basal cell carcinoma syndrome, particularly if the patient is in the first or second decade of life or if multiple keratocysts are identified.[8]

PCNA, Ki-67, p53 protein and IPO-38 antigen have in common that they are all expressed in actively proliferating cells, particularly in neoplasms. The evidence provided by laboratory studies on the expression of these substances is that, in general, they are expressed more strongly in OKC's than in other odontogenic cysts and particularly so in the OKCCs associated with the NBCCS. Furthermore, the evidence of mutation of the NBCCS gene PTCH in OKCs of patients with the syndrome, and at least some sporadic OKCs, has made an important contribution to the understanding of these cysts, and has provided supportive evidence that the OKC is a benign neoplasm.[1]

REFERENCES

1. Madras J, Lapointe H. Keratocystic odontogenic Tumour: Reclassification of the odontogenic

keratocyst from cyst to tumour. JCDA, 2008; 74(2): 165.
2. Waldron C. A. Odontogenic cysts and tumors. Oral and maxillofacial pathology. Neville B.W, Damm D. D , Allen C.M, Bouquot J.E. Saunder's, Philadelphia, 2002; 581-642.
3. Regezi, Sciubba, Jordan. Cysts of the jaws and neck. Oral pathology: Clinical pathologic correlations. Elsevier, New Delhi, India, 2014; 6: 246-259.
4. Brownie R.M. Malignant change in the epithelium lining odontogenic cysts. J of O Pathol, 1972; 29(5): 1200-1207.
5. Regezi J. Odontogenic cysts, odontogenic tumors, fibro osseous and giant cell lesions of the jaws. Med Pathol 2002; 15(3): 331-341.
6. Dong Q, Shuian P, Shasun L, Junli T. Orthokeratinizedodontogenic cysts. A clinicopathologic study of 61 cases.
7. Arch Pathol Med, 2010; 134(5): 271-275.
8. Gowley T.E, Kaugars G. E, Gunsolley J. C. Odontogenickeratocyst: a clinical and histologic comparison of the parakeratin and orthokeratin variants. J Oral Maxillofac Surg, 1992; 5(1): 22-26.14.
9. Dominguez F.V, Keszler A. Comparative study of keratocysts, associated and non associated with nevoid basal cell carcinoma syndrome. J of Oral Pathol, 1988; 17(3): 39-42.
10. Lorenzo L. Nevoid basal cell carcinoma syndrome (Gorlin syndrome) Orphanet journal of rare diseases, 2008; 3(1): 32.
11. Robert J. Nevoid basal cell carcinoma (Gorlin) syndrome. Genet Med, 1987; 1139(7): 66-98.
12. Altini M. The follicular primordial cyst (odontogenic keratocyst). Int.J. Oral Surg, 1982; 11(4): 175-182.
13. Cawson R, Eveson J W. Cysts and cyst like lesions of the jaw In oral pathology and diagnosis-Colour atlas with integrated text. Gower Medical Publishing, London, New York, 1987; 3: 5.3-5.4
14. Haring J.L, Van D. Odontogenic keratocysts: a clinical, radiographic and histopathologic study. Oral Surg, Oral Med and Oral Pathol, 1988; 66(7): 145-53.
15. Khan M.T, Khan A. Odontogenic keratocysts: a clinical and radiographic study. Pakistan Oral and Dental Journal, 2010; 30(1): 25-29.
16. Gupta V, Sengupta S. Odontogenic keratocyst: A peripheral variant. Nigerian Journal of Clinical Practice, 2011; 14(4): 69-73.
17. Ahlfors E, Larson A, Sjogren S. The Odontogenic keratocyst: A benign cystic tumor? J Oral and Maxillofac Surg, 1984; 42(1): 10-19.
18. Kok H, Chong H. Odontogenic keratocyst with dentinoid formation. Oral Surg, Oral Med, Oral Pathol, 2003; 95(5): 601-606.
19. Gowley T.E, Kaugaus G.E. Odontogenic keratocysts: A clinical and histologic comparison of the parakeratin and orthokeratin variants. J. Oral Maxillofac Surg, 2006; 64(3): 379-383.
20. Maurette P.E, Jorge S, Moraes M. Conservative Treatment Protocol of Odontogenic keratocyst: A preliminary study.
21. J Oral Maxillofac Surg, 1992; 50: 22-26.
22. Chuong R, Donoff R.B, Gurelnick W. The Odontogenic keratocyst. J. Oral Maxillofac Surg, 1982; 40(6): 797-810.