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Review Article

Possible recurrence of keratocyst in nevoid basal cell carcinoma syndrome: A review of literature

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ABSTRACT

This review will highlight some current areas of difficulty or controversy in diagnosis and treatment of nevoid basal cell carcinoma syndrome (NBCCS). The odontogenic keratocyst (OKC) has significant growth capacity and recurrence potential and is occasionally indicative of the NBCCS. The objective of this study is to clarify the causes of the recurrence of OKC in NBCCS. A literature search was conducted using Medline, accessed via the National Library of Medicine PubMed interface, searching for articles relating to the cause of recurrence of keratocyst in NBCCS written in English. This study has described the previous and the current outcomes of the treatment of OKC (recurrent cause). A protocol was then agreed to search for the possible causes of keratocyst recurrence in NBCCS. The general treatment of other manifestation of NBCCS has excluded from this study. Studies describing cohort, case series and miscellaneous clinical reports were retrieved and evaluated from 2010 to 2012.

Key words: Basal cell carcinomas, keratocyst, nevoid basal cell carcinoma syndrome

INTRODUCTION

Nevoid basal cell carcinoma syndrome (NBCCS), also known as basal cell nevus syndrome, multiple basal cell carcinomas (BCC) syndrome, Gorlin syndrome and Gorlin-Goltz syndrome, is an inherited medical condition involving defects within multiple body systems such as the skin, nervous system, eyes, endocrine system and bones. People with this syndrome are particularly prone to developing a common and usually non-life-threatening form of non-melanoma skin cancers.[1] The absence of major diagnostic criteria such as BCC or palmar or plantar pits in young patients delay the early diagnosis and the correct screening for medulloblastoma, BCC and cardiac fibromas.[1] The odontogenic keratocyst (OKC) has significant growth capacity and recurrence potential and is occasionally indicative of the NBCCS.

The NBCCS is inherited as an autosomal-dominant trait that consists principally of multiple OKC, multiple BCCs, skeletal anomalies and cranial calcifications. Syndrome-associated OKC have the highest recurrence rate and represent approximately 5% of all OKC patients.[2]

The BCCs develop early in life and may number in the tens or hundreds. The most frequently cited skeletal anomaly is bifid rib. Early calcification of falx cerebri is also relatively frequently seen on skull radiograms.[2] This syndrome has been linked to mutations in the PATCHED tumor-suppressor gene that encodes a receptor protein that is a component of the hedgehog (Hh) signaling pathway. Mutations of this gene have been found in syndrome-associated BCCs and OKC.[3-5] Gorlin-Goltz syndrome, also known as basal cell nevus syndrome,

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is an uncommon, autosomal-dominant inherited disorder, which is characterized by numerous BCCs (seen in 50-97% of people with the syndrome), maxillary keratocysts (present in about 75% of patients) and musculoskeletal malformations.

Gorlin and Goltz[6] established the association of multiple basal cell epitheliomas, jaw cysts (which they described as true cysts, having a typical stratified squamous epithelium) and bifid ribs, a combination that is frequently referred to as the "Gorlin-Goltz syndrome, the Gorlin syndrome" or the NBCCS.

Meerkotter and Shear[7] identified the jaw cysts as OKC and numerous clinical and molecular studies have been and continue to be, undertaken on the OKC occurring in patients with the syndrome. The syndrome is inherited as a set of autosomal-dominant characteristics with strong penetrance. It has variable expressivity, including multiple nevoid BCCs, OKC, other congenital skeletal defects, ectopic calcifications, plantar and palmar pits, central nervous system and ocular lesions and fairly typical facial features with frontal bossing and ocular hypertelorism.

It is caused by mutations in the patched tumor suppressor gene (PATCHED gene), a human homologue of the *Drosophila* gene mapped to chromosome 9q21-23.[8] Chromosomal mapping and genetic studies suggest that the underlying basis for this disease is an abnormality in the Hh signaling pathway. The role of this pathway in embryogenesis is well-known. The PATCHED gene product is part of a receptor for the protein called sonic Hh, which is involved in embryonic development.[9]

Diagnosis of NBCCS can be made when two of the five major criteria or one major and two minor criteria are present.[10,11] Major criteria of this syndrome include the following: (1) Multiple (two or more) BCC or one BCC under 30 years or 10 or more basal cell nevi; (2) OKC of the jaw; (3) multiple (three or more) palmar or plantar pits; (4) ectopic calcification, such as lamellar calcification of the falx cerebri; and (5) family history of Gorlin's syndrome. Minor manifestations include the following: (1) Skeletal anomalies, such as bifid, fused rib or vertebrae; (2) congenital malformation, including cleft lip or palate, macrocephaly, hypertelorism and frontal bossing; (3) medulloblastoma in young children; and (4) cardiac or ovarian fibroma.

RECURRENCES OF OKC IN NBCCS

OKC has a particular tendency to recur after surgical treatment. All of studies shown in the literature were case series, case report and miscellaneous studies. Pindborg and Hansen[12] observed no correlation between the size or location of the cyst and its tendency to recur; nor was there any difference in recurrence rate between cases that were treated by extirpation and those treated by fenestration. The increased recurrence of OKC in syndromic patients over non-syndromic patients because of OKC associated with this syndrome has a familial tendency and early family detection and genetic counseling are critical.[13] These cysts arise earlier in patients with NBCCS than in those who are unaffected by the syndrome.[13] OKC associated with NBCCS have occasionally been reported to transform into aggressive neoplasms such as ameloblastomas and squamous cell carcinoma.[14] The cyst lining seen in the NBCSS-related OKC is classically parakeratinized and does not appear to be associated with the orthokeratinized variant of the OKC. The cystic nature of OKC has long been debated, with some investigators classifying the OKC as a benign tumor.[15] In recent years, the WHO has recommended that the term "keratocystic odontogenic tumor" replace the term "OKC", as it better reflects the neoplastic nature of the lesion.[15]

Hansen[16] reported a recurrence rate of 52% in a series of 52 cases followed for a period of at least 6 months. Browne[17] reported a 25% recurrence rate in 85 cysts followed for 6 months or longer. He found that most recurrences occurred in the first 5 years after surgery, but one of his cases recurred 20 years after operation.

Browne and Miller[18] reported that there was a very similar rate of recurrence following removal of OKCs with satellite cysts (23.7%) and those without satellite cysts (24.4%). There was a higher frequency of recurrence of cysts without epithelial residues (28.1%) than with (8.3%), but the difference was not statistically significant. These observations were confirmed by Vedtofte and Praetorius.[19]

A higher recurrence rate of cysts located in the angle or ascending ramus of the mandible was reported in one study, but the size of the cyst did not appear to have an influence.[20]

A total of 33 patients were followed for at least 6 years in a series of 62 patients with OKC and recurrences were found to be related to the operative procedure

employed. The highest frequency of recurrences occurred in patients treated by cystostomy.[21]

A more recent detailed South Korean review of 256 patients showed significantly higher recurrence rates (P = 0.005) for the 14 of 17 patients in the 41-50 year age group; in 30 of 40 patients with cysts in the mandibular molar region (P = 0.001); and in 27 of 37 patients whose cysts had associated daughter cysts (P = 0.03) Myoung *et al*.[22] Their overall recurrence rate was 58.3% in an average follow-up period of 29 months. Nearly, 99% of the cysts were treated by surgical enucleation, 8.6% of them after marsupialization. A total of 11.7% of patients with recurrences had multiple recurrences.

When 24 patients with orthokeratinized OKC were followed for periods of 6 months to 8 years, only one recurrence was found and it occurred 61/2 years postoperatively.[23] This was the first indication that the orthokeratinized cysts may be less aggressive than the more common parakeratinized type, a contention that has been reinforced in other studies and will be referred to later.

The considerable variation in recurrence rate reported by different workers may be ascribed partly to the variability in the follow-up period. Vedtofte and Praetorius,[19] Forssell[20] and Forssell *et al*.[24] have reported that the recurrence rate increased with extension of the follow-up period to 5 years or more. It was found that of 75 keratocysts with follow-up times ranging from 5 to 17 years (mean 8.3), 32 (43%) recurred. The cumulative recurrence rate of the 67 annually examined cysts increased from 3% after the 1st year following the operation to 37% after the 3rd year. Thereafter, no new recurrences were noted. They observed that recurrences were more frequent (63%) with cysts in patients with the NBCCS than with cysts in patients without the syndrome (37%). OKC enucleated in one piece recurred significantly less often (P < 0.01) than cysts enucleated in several pieces and the recurrence rate in cases with a clinically observable infection, a fistula or with a perforated bony wall was higher than when these features were not present. The size of the cyst did not seem to influence its prognosis after surgery, but those whose radiographic appearance was multilocular had a higher recurrence rate than those with a unilocular appearance.

CAUSES OF RECURRENCES

There are several possible reasons why OKC recur so frequently and require meticulous surgical planning and execution. The first of these is related to their tendency to multiplicity in some patients, including the occurrence of satellite cysts, which may be retained during an enucleation procedure. If enucleation procedures are incomplete, some instances of recurrence may be new cysts arising from retained satellite microcysts or retained mural cell islands. Second, OKC linings are very thin and fragile, particularly when the cysts are large and are, therefore, more difficult to enucleate than cysts with thick walls. Portions of the lining may be left behind Fickling[25] and constitute the origin of a recurrence.

Forssell *et al*.[20,24,26] showed that recurrences were extremely infrequent if the cyst was enucleated in one piece, but occurred in over half of cases when the cyst was removed in several pieces. An attempt to save vital adjacent teeth or nerves during the operation may lead to incomplete eradication and hence to recurrence. Likewise, enucleation in one piece may be more difficult with cysts that have scalloped margins and this may explain the higher recurrence rates than with those with a smoother contour.

Toller[27] reported that the epithelial linings of OKCs had intrinsic growth potential and suggested that there was some basis for regarding them as benign neoplasms. Ahlfors *et al*.[28] also proposed that the OKC should be regarded as a benign cystic neoplasm. This was supported by further studies that reported the neoplastic nature of the OKC.[29,30]

Yet another source of the recurrences has been proposed by some authors.[31-34] They have demonstrated convincingly that OKC may also arise from proliferations of the basal cells of the oral mucosa, often referred to as basal cell hamartias, particularly in the third molar region and ascending ramus of the mandible. They have referred to the frequent observation of perforation of the overlying bone and firm adhesion of the cysts to the overlying mucosa and recommended that when the cysts were surgically removed, the overlying mucosa should be excised with them in an attempt to prevent possible recurrence or the formation of new cysts from residual basal cell proliferations. The two theories of origin are not incompatible as both dental lamina and basal cell hamartias have common parentage, the stomodeal ectoderm and both are influenced by ectomesenchyme or residual ectomesenchymal inductive influences.[35] This being the case, it seems reasonable to speculate that mucosal basal cells could be targeted by the same genetic influences as dental lamina.

Voorsmit *et al*.[36] reported that a recurrent OKC may develop in three different ways: By incomplete removal of the original cyst lining; by the retention of daughter cysts, from microcysts or epithelial islands in the wall of the original cyst or by the development of new OKC from epithelial off-shoots of the basal layer of the oral epithelium. Myoung *et al*.[22] reported that OKC had a significantly higher recurrence rate in patients in the fifth decade of life than in patients in the other age groups ($P = 0.005$). Recurrence rates were significantly dependent on the sites of involvement and OKCs in the mandibular molar region had significantly higher recurrence rates than those in other sites ($P = 0.001$). The histopathologic presence of one or more daughter cysts was significantly related to recurrence ($P = 0.03$). Stoelinga *et al*.[34] reported on 82 OKC diagnosed in 80 patients over a 25 year period. The clinical and radiographic data were correlated, which resulted in an accurate picture of the clinical presentation, relationship with teeth and incidence of lingual perforations in mandibular OKC. In 40% of the cysts, no suspicion had arisen before surgery; in 60%, the diagnosis was secured before surgery. Some was treated with the exception of the maxillary OKC, which entailed excision of the attached, overlying mucosa and enucleation of the cyst, after which the defect was treated with Carnoy's solution. The other patients underwent just enucleation of the cysts. For the first 5 years, the patients were seen every year, thereafter, every 2 years if possible. Recurrences (9/82) were mainly found in patients in whom the cyst had just been enucleated. Only three cysts recurred in the group treated according to the above-mentioned protocol. Most recurrences presented within 5 years, but late recurrences did occur even after 25 years.

Emerson *et al*.[37] Partridge and Towers[38] reported that the behavior of OKC so aggressive that they have penetrated cortical bone and involved surrounding soft-tissues. Another reported OKC extended from the maxilla and eventually involved the base of the skull, "behaving rather like a low-grade squamous cell carcinoma" as studied by Jackson *et al*.,[39] whereas others extended from the maxilla into orbit and infratemporal fossa as reported by Chuong *et al*.[40] or into the infratemporal fossa as per Worrall.[41] DeGould and Goldberg[42] described the recurrence of an OKC in a bone graft after partial mandibulectomy and the source of this may well have been the mucosa. Many studies have been carried out on patients with multiple OKC and in patients with the NBCCS in an attempt to find explanations for the recurrences. Payne[43] compared the histological features of recurrent OKC with non-recurrent specimens and those from patients with the syndrome. The presence of inflammation and the type of keratin produced did not seem to be significant. He found bud-like proliferations of the basal cell layer in 5 of 11 recurrent cysts (45%) and four of nine cysts from patients with the syndrome (44%). By comparison, only six of 72 non-recurrent OKC (8%) showed this feature. Satellite microcysts were observed in the cyst walls of 78% of cysts from patients with the syndrome, 18% of the recurrent cysts and 4% of the non-recurrent cysts.

Donatsky and Hjørting-Hansen[44] reported that the jaw cysts removed from patients with NBCCS were clinically, radiologically and histopathologically typical keratocysts with a high occurrence of epithelial islands and/or microcyts in the connective tissue of the capsule. The significantly higher occurrence of proliferative epithelial remnants in the connective tissue of the cyst wall may be an explanation of the high recurrence rate seen in patients with NBCCS and of the recurrence of some solitary keratocysts in patients without any signs or symptoms of NBCCS. In a follow-up period of 2 years, 85% of patients with NBCCS showed recurrence. One-third of these patients did not show any recurrence at the 1 year follow-up. Therefore, a follow-up period of 2 years or more is mandatory in the care of patients with the NBCCS.

Woolgar *et al*.[45] reported that there are histologic differences between OKC occurring in the BCCs syndrome NBCCS and as single lesions in otherwise healthy persons. This study identifies certain differences in age, gender and site between the two groups. The age at removal of the first keratocyst is significantly lower in the syndrome group. On more thorough examination, patients with multiple keratocysts (excluding recurrences) are found to have other features of NBCCS. The term multiple cysts refers to the lifetime history of the patient and does not necessarily imply that more than one cyst is present at any 1 time.

In another study, Woolgar *et al*.[46] have studied the clinical features of 44 recurrent OKC were compared with those of 228 single non-recurrent keratocysts, which had been followed for five or more years. Histological comparisons were made with 44 non-recurrent cysts matched for age, sex and site. There were no significant differences in the age, sex and site between patients with recurrent and non-recurrent cysts. There were no significant

histological differences except for a greater amount of inflammation in the non-recurrent cysts. It is suggested that operative factors have a major influence on the likelihood of recurrence.

Woolgar *et al*.[47] have indicated that 164 OKC from 60 patients with the basal cell nevus syndrome were compared with a similar number of single keratocysts matched for age and site. Significant differences between the two groups were found in the numbers of satellite cysts, solid islands of epithelial proliferation and odontogenic rests within the capsule and in the numbers of mitotic figures in the epithelium lining the main cavity. An index of activity derived from these parameters suggests a greater growth potential in syndrome cysts; in addition, the patterns of association of the features support the theory that the odontogenic rests give rise to satellite cysts.

They found no association to support the theory that satellite cysts arose by basal budding of the epithelium lining the parent cyst from histological point view. Their results did, however, support the view that satellite cysts are formed when islands of proliferating epithelial cells derived from small epithelial rests reach a size where cystic breakdown occurs. They found no evidence that the ameloblastomatoid proliferations develop into true ameloblastomas. They suggested that there was some inherent genetic potential for proliferation of odontogenic epithelium in the syndrome patients.

Dominguez and Keszler[48] reported that keratocysts of the solitary type were histologically and histometrically compared with those associated with the NBCCS. It was observed that parakeratinization, intramural epithelial remnants and satellite cysts were a more frequent finding among NBCCS keratocysts than among solitary keratocysts. Conversely, it was also found that the total nuclear density was greater in non-associated cysts and that the total number of nuclei, the number of basal nuclei and the epithelial height values were also higher in solitary keratocysts. Nevoid BCC-keratocysts and solitary keratocysts are considered to be two morphologically distinct populations of the same entity.

Some authors have referred to the occurrence of multiple OKC in patients without obvious signs of other features of the syndrome or of a familial trend. Brannon[49] reported a frequency of 3% with multiple cysts in his sample, Kinard *et al*.[50] 4%, Ahlfors *et al*.[28] 6%, Voorsmit *et al*.[36] 2% and Stoelinga and Bronkhorst[51] 4.5%. As oral surgeons have become increasingly aware of the need to treat OKC more aggressively than other jaw cysts or by the use of special protocols, it is likely that future studies will show a declining frequency of recurrences.

It is difficult to ignore the possibility that the variability in reported recurrence rates may at least partly be attributable to differences in the surgical techniques used and in the experience of the surgeons. Voorsmit *et al*.[36] reported the results of a follow-up study of two groups of patients treated for OKC. In the first group of 52 cases, the cysts were treated conservatively by careful enucleation of the entire wall. In the second group of 40 cases, the cysts were removed by enucleation along with excision of the mucosa overlying a perforation of the cortical bone, which was determined at operation. Before removal, all cysts in this group were treated with Carnoy's solution. The recurrence rate in their first group was 13.5% in a 1-21 year follow-up while the recurrence rate in their second group was 2.5% in a 1-10 year follow-up.

Furthermore, the current studies show similar results [Table 1] regarding the frequent recurrence of the keratocyst in NBCCS. Furthermore, all of those studies describing cohort, case series and miscellaneous clinical reports. No randomized controlled trials for the treatment of keratocyst in NBCCS were located in the literature.

DISCUSSION

The OKC represent from 65% to 75% of the cases of the NBCCS.[52] These cysts represent a particular entity that has been of interest, mainly due to biological aggressiveness and to the great amount of recurrence.[1,7]

Recently and based on the intrinsic growth potential of its epithelial coating, they have been re-classified and called OKC tumors and they have been included in the odontogenic neoplasias.[7,11,26] The keratocysts have a well-defined scale-like parakeratinized stratified epithelium with an average thickness of 5-8 cells, with a basal layer in which cells present themselves fenced up in a corrugated surface and a connective wall rich in mucopolisacarids, without inflammatory infiltration and with a variable number of microcysts and epithelial islets.[9,50] Its high potential of recurrence is justified by the high mitotic epithelial activity, the frequency of satellite cysts, pieces of epithelium and prolific dental sheet and by the existence of a epithelial coating thicker than in other jaw cysts.[7,10,11]

Table 1: A description of odontogenic keratocyst in nevoid basal cell carcinoma syndrome from clinical view (2010-2012)

Author/s name and publication date	Type of study	Description of NBCCS	Results
Schussel *et al*.[53]	Case series	Twenty-five cases of OKT were diagnosed between the years of 1989 and 2006	56% were females with a mean age of 33 years. 70% occurred in mandibula and all received surgical treatment, associate or not with adjuvant therapy, such as cryotherapy and Carnoy's solution. Recidive was observed in 48% of cases with a mean period of time of 18 months
Ribeiro Junior *et al*.[54]	Case series	Twenty-two OKT treated with Carnoy's solution combined with peripheral months ostectomy were included and the follow-up period varied from 12 to 78 months with a mean of 42.9	Complications included recurrence (4.5%), dehiscence (22.7%), infection (4.5%) and paresthesia (18.2%). Carnoy's solution and peripheral ostectomy appear to provide efficient treatment for OKT. Complications originating from the use of the solution are less frequent and less serious than complications associated with cryotherapy
Leger *et al*.[3]	Case report	A 29-year-old man presented to the dermatology clinic at Bellevue hospital center for evaluation of a lesion on his scalp that had been present for a few years and was enlarging	The patient had a prior history of five BCCs on his scalp, face and upper trunk. The lesion was biopsied and the patient was referred for excision of the lesion on his scalp and an additional lesion on his left eyelid. Past medical history included a meduloblastoma, which was diagnosed in early childhood and treated with radiation therapy
Bartake *et al*.[55]	Case report	OKCs are one of the most frequent features of NBCCS. It is linked with mutation in the PTCH gene. Partial expression of the gene may result in occurrence of only multiple-recurring OKC	Our patient presented with nine cysts with multiple recurrences over a period of 11 years without any other manifestation of the syndrome
Borgonovo *et al*.[56]	Case report	Three young patients affected of (NBCCS or Gorlin-Goltz syndrome) presented large and multiple OKT, which have been treated following a two-stage surgical strategy. Initially, marsupialization was performed and after a mean period of 10 months, contextually to evident reduction in radiological size image, enucleation with peripheral ostectomy was carried out	All the patients showed high collaboration in daily self-irrigation of the stomia with chlorhexidine 0.2% during the period of marsupialization. Definitive surgical intervention led to complete healing and no signs of recurrence have been observed during a 5-year-follow-up
Mello *et al*.[57]	Case report	A total of 64 KCOTs, arising in 46 patients, were evaluated using the following parameters: Association with NBCCS, gender, age at first diagnosis, race, anatomical location, symptoms, radiographic features, history of recurrence, association with teeth and treatment	61 (95.3%) tumors were treated by surgical enucleation followed by bone curettage and the recurrence rate was 13% (*n*=6). This study showed that the KCOTs relapsed within a mean period of 25-36 months
Goldberg *et al*.[58]	Case Report	We report the case of a 55-year-old man with a long-standing history of BCNS. Over a 25-year period, this patient had been treated for many BCCs. He also had multiple large odontogenic keratocysts in the mandible that had previously been treated using surgical, chemotherapeutic and radiation treatment techniques	We report the nearly complete regression of multiple BCNS-associated odontogenic keratocysts following non-surgical treatment with GDC-0449. This novel drug, useful for the treatment of BCC, also appears to be effective for treatment of odontogenic keratocysts
Karagozoglu *et al*.[59]	Case study	Sixty-nine patients treated for a solitary OKT have been followed for the possible development of second KCOTs or other signs indicative of NBCCS. In addition, 11 randomly selected patients of this group were referred for genetic counseling, including identification of germ-line mutations in the PTCH gene	In none of the 69 patients, clinical and radiographic manifestations of second KCOTs and/or other features associated with NBCCS were found during a follow-up period of 49.8 months. In the 11 patients referred for genetic counseling, there were no features indicative of the presence of NBCCS. No mutations in the PTCH gene could be identified
Ba *et al*.[60]	Case report	A retrospective radiographic analysis was performed on 284 cases of KCOT to gain insight into the radiographic characteristics. Expression of Ki-67 in 30 of the 284 cases was detected by the labeled streptavidin-biotin method and evaluated by an image analysis system	The radiographic presentation of KCOT was divided into four types: Unilocular, multilocular, multiple and NBCCS. The expression of Ki-67 in NBCCS was significantly different from the solitary and multiple KCOTs (*P*=0.018, 0.002). In multilocular KCOTs, it was also significantly different from the unilocular and syndrome-associated lesions (*P*=0.000). In contrast, no significant differences were observed between the solitary and multiple lesions (*P*=0.220)

KCOTs: Keratocystic odontogenic tumor, NBCCS: Nevoid basal cell carcinoma syndrome, OKT: Odontogenic keratocyst tumor, BCNS: Basal cell nevus syndrome, OKCs: Odontogenic keratocysts, PTCH: Patched, BCCs: Basal cell carcinomas

The treatment modalities for the keratocysts vary from simple enucleation with curettage, to the enucleation with peripheral osteotomy or to osseous resection in block. This last technique is the most aggressive and it logically follows that the recurrence rate decreases.[61] There are also more conservative options such as the local parietal therapy with Carnoy solution, with cryotherapy or marsupialization of the cysts, or decompression followed by a secondary enucleation.[8] Nevertheless, those methods are not efficient in the long-term and their use is considered to be controversial. It is believed that the nature of the treatment of keratocyst is depending on the following factors: Lesion size, lesion extension, location, possible cortical and soft parts damage, the age and whether it is a primary or recurrent lesion.[8] It is also important to detect if it is an isolated keratocyst or if it is associated with the syndrome, since in the last case, the rate of recurrence is higher as Forssell[20] have suggested the recurrence rate is of 63% in keratocysts associated to the syndrome and of 37% in the isolated ones.[20] Keratocyst is different from other odontogenic cyst. Matsumoto and Ribeiro[62] indicated that immunoreactivity of inducible nitric oxide expression was expressed in several cellular types present in periapical cyst, being positively correlated with the level of inflammation. Therefore, inducible nitric oxide expression plays an important role in the pathogenesis of periapical cysts. Pre-operative diagnosis is important to achieve the optimal treatment planning of cystic lesions of the maxillofacial region.

Matsumoto and Ribeiro[62] reported that the value of fine-needle aspiration biopsy in cystic lesions of the maxillofacial region is found as successful as in the solid lesions.

This study has shown that there is a lack of published evidence regarding the cause of frequent recurrent of OKC that presented in NBCCS. The findings of the study revealed differences in opinion regarding the treatment modalities.

This literature review revealed many papers, which reported the possible causes of the recurrence of keratocyst in nevoid BCC. None of the publications included randomized clinical trials and formal meta-analysis study was not possible. The evidence base was, therefore, determined by comparing case series. Only literature relating to treatment of keratocyst in NBCCS was included.

The limitations of this kind of this study are well-recognized and bias can arise from many sources.[63] In general, literature review offers a number of advantages and disadvantages for data collection, though their limitations must be recognized. The reviews often aim to provide background, identifying relationships between ideas and practice, establishing the context of the topic or problem, rationalizing the significance of the problem, identifying methodologies and techniques that have been used[64] and are designed to collect information from online database (PubMed) as accurately and precisely as possible. Another important limitation is that a review of this kind cannot address the issue of individual case variation. A number of factors determine any treatment selected including lesion size, lesion extension, location, possible cortical and soft parts damage, the age and whether it is a primary or recurrent lesion. This is not surprising as only a limited number of clinical guidelines can be found relating to the management of keratocyst in NBCCS. It would be necessary to identify an expert panel, which was inclusive of other surgical specialties, pathologists and systematic reviewers experienced in formulating guidelines. Additional data would have to be gathered.

As mentioned above, this study has shown that there is a lack of published evidence relating to the cause of recurrence of keratocyst in NBCCS.

Randomized controlled clinical trials could, in theory, be used to address these issues, but are difficult to perform because of likely low accrual rates and the need for prolonged follow-up times to assess clinical outcomes. Inconsistent views revealed by this review, whilst recognizing its limitations, indicate that there may be a need for production of consensus guidelines for the treatment of keratocyst in NBCCS and then it might be the cause of recurrence would be decreased.

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