INTRODUCTION

Diagnosis and management of Neviod basal cell carcinoma syndrome (NBCCS) with concomitant occurrence of odontogenic keratocysts (OKC) in this syndrome has always been a matter of debate in the literature since ages. OKCs may be presented as the first sign of NBCCS and can be well-identified in patients younger than 10 years of age.\(^{[1-3]}\) OKCs usually arise somewhat earlier and have more recurrence rate in patients who have NBCCS than non-syndromic patients. NBCCS is caused by mutation in patched tumor suppressor gene (PTCH) 1 gene and is transmitted as an autosomal dominant trait with complete penetrance and variable expressivity.\(^{[4]}\) However in NBCC patients there is continued development of new and recurring cysts until about age 30, when the rate of development tends to decrease. Most non-NBCCS keratocysts are isolated lesions whereas in NBCCS the keratocysts are commonly multiple, from 1 to 30, and the average number is 5 with the most common site in mandible being the molar-ramus region followed by the incisor–canine region. In maxilla, the most common location is incisor-canine followed by molar tuberosity regions [Table 1].\(^{[3,5]}\)

Despite the fact that it is known to be a familial and an autosomal dominant syndrome, the exact pathogenesis is not understood. The syndrome usually exhibits extremely high penetrance and unpredictable expressivity.\(^{[3]}\) Furthermore, the genetic abnormality underlying Basal Cell Carcinoma Nevus Syndrome (BCCNS) is caused by mutations in the PTCH gene and by down regulation of the sonic hedgehog signaling pathway. The PTCH gene acts as a tumor suppressor gene, and has been mapped to the long arm of chromosome 9 q22.3-q31 in a 12-cM interval between the microsatellite marker loci D9S12.1...
and D9S109. Loss of function of the gene induces abnormal growth and development of normal tissues, which leads to the syndrome. This article is an endeavor to potentially attract the researcher’s attention to this routinely obscured field with special emphasis on innovative modern techniques at the molecular level to best diagnose NBCCS cases with their early detection.

### Potential recurrence of keratocyst; the literature viewpoint

Basal cell carcinoma (BCC) in this disorder has been found in 50-75% of patients, and they most often appear between puberty and 35 years of age. However, the number of lesions varies from a few to several thousand and ranges in size from 1 mm to 30 mm in diameter. Pits of palms and soles are distinct features of this syndrome, and these lesions are 2-3 mm in diameter and 1-3 mm in depth. Diagnosis of BCNS can be made when two of the five major criteria, or one major and two minor criteria are present. Major criteria of this syndrome include the following: (1) multiple (two or more) basal cell carcinomas 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, marked syndactyly of the digits, and scoliosis; (2) congenital malformation, including cleft lip or palate, macrocephaly, hypertelorism, and frontal bossing; (3) medulloblastoma in young children; and (4) cardiac or ovarian fibroma. BCNS must be distinguished from rare disorders, such as linear unilateral neviod BCCs, Bazex syndrome, and Rombo syndrome. Bazex syndrome is an X-linked dominant syndrome, characterized by multiple BCCs of the face, hypohidrosis, hypotrichosis, and follicular atroderma of the extremities. Rombo syndrome is a dominantly inherited disorder with multiple BCCs, hypotrichosis, vermiculate atrophoderma, milia, trichoepitheliomas, and peripheral cyanosis.

Recurrence of OKC in NBCCS is well-documented to be due to the familial inheritance that require immediate detection in families with critical genetic counseling, retained satellite cysts during enucleation or retained neural cell islands, or portions of lining left behind, proliferations of basal cells of the oral mucosa called as basal cell hamartias. As clinical diagnosis always relies on a criterion which may lead to delayed diagnosis of NBCCS, gene mutation analysis should be used in suspicious cases to substantiate the diagnosis. In addition, the antenatal diagnosis is also feasible by means of ultrasound scans and analysis of deoxyribonucleic acid extracted from fatal cells obtained by amniocentesis. Eventually, it is worth stating the major differential diagnosis that includes Bazex syndrome, trichoepithelioma papulosum multiplex and Torre’s syndrome.

OKCs associated with NBCCS have found to be immune-positive for P 53 protein and over expression of cyclin D1 with various degrees of staining intensity while non-syndromic OKCs have mostly been found to be negative for P 53 and cyclin D1. This type of immune expression could be considered as a hallmark of a mutated cellular phenotype, thus leading to the aggressive clinical behavior showing recurrence as there is deregulation of the expression of cyclin D1 and P 53, involved in a check point control of cellular proliferation. Management requires a multidisciplinary approach involving surgical removal, laser ablation, photo dynamic therapy and topical chemotherapy.

Management requires a multidisciplinary approach. Keratocysts are treated by surgical removal. Surgery for NBBCs is indicated when the number of lesions is limited; other treatments include laser ablation, photodynamic therapy and topical chemotherapy. Radiotherapy should be avoided. Vitamin An analogs may play a preventive role against development of new NBCCs. Life expectancy in NBCCS is not significantly altered, but morbidity from complications can be substantial. Regular follow-up by a multi-specialist team (dermatologist, neurologist and odontologist) should be offered. Patients with NBCCS should strictly avoid an excessive sun exposure. OKC has a particular tendency to recur after surgical treatment. Pindborg and Hansen 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 have a familial tendency, and early family detection and genetic counseling
are critical.\textsuperscript{[14]} These cysts arise earlier in patients with NBCCS than in those who are unaffected by the syndrome. OKC associated with NBCCS have occasionally been reported to transform into aggressive neoplasms such as ameloblastomas and squamous cell carcinoma. The cyst lining seen in the NBCCS-related OKC is classically parakeratinized and does not appear to be associated with the orthokeratinized variant of the OKC.\textsuperscript{[15]} The cystic nature of OKC has long been debated, with some investigators classifying the OKC as a benign tumor. In recent years, the World Health Organization has recommended that the term “keratocystic odontogenic tumor” replace the term “OKC,” as it better reflects the neoplastic nature of the lesion.\textsuperscript{[16]}

In a study conducted by Hansen, a recurrence rate of 52% in a series of 52 cases followed for a period of at least 6 months had been shown although Browne and Miller reported that there was a very similar rate of recurrence following removal of OKCs with satellite cysts and those without satellite cysts. Afterward, these observations were confirmed by the studies done by Vedtofte and Praetorius.\textsuperscript{[17,18]} In addition, 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.\textsuperscript{[19]} 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; however, the highest frequency of recurrences occurred in patients treated by cystostomy.\textsuperscript{[20]} another systematic review of 256 patients showed significantly higher recurrence rates for the 14 of 17 patients in the 41-50 year age group. Their overall recurrence rate was 58.3% in an average follow-up period of 29 months. Conversely, a total of 11.7% of patients with recurrences had reported with multiple recurrences during follow-up periods.\textsuperscript{[21]}

In the recent literature, the substantial discrepancy in recurrence rate reported by different workers may be ascribed partly to the unpredictability in the follow-up period. Browne et al. were among those researchers who reported that the recurrence rate increased with extension of the follow-up period to 5 years or more. In addition, it was found that of 75 keratocysts with follow-up times ranging from 5 to 17 years (mean 8.3), 32 (43%) recurred.\textsuperscript{[18]} The collective recurrence rate of the 67 annually examined cysts increased from 3% after the 1\textsuperscript{st} year following the operation to 37% after the 3\textsuperscript{rd} year. After that, no new recurrences were noted. They further observed that recurrences were quite 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 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.\textsuperscript{[18,22,24]}

Goldstein et al. in 1994 have found strong evidence for linkage between 9q22.3 and 9q31 markers and an NBCC locus in eight NBCC pedigrees, and they had localized the NBCC locus to a 10-cM region distal to D9S196 and confined the localization proximal to D9S109. They finally proposed the following order for the NBCCS markers; D9S119-D9S12-D9S197-D9S196-(NBCC, D9S180-D9S173, ALDOB; Aldolase Dehydrogenase B)-D9S109-D9S127-(D9S553, D9S29).\textsuperscript{[25]}

There are a number of possible explanations have been documented in the literature 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. In case the enucleation procedures are incomplete, some instances of recurrence may be new cysts arising from retained satellite microcysts or retained mural cell islands. Moreover, the OKC linings mucosas 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 and constitute the origin of a recurrence. The recurrences were exceptionally infrequent if the cyst was enucleated in one piece but occurred in over half of the cases when the cyst was removed in several pieces. Nevertheless, an endeavor to save vital adjacent teeth during the procedure may lead to incomplete eradication and therefore to future recurrence of the lesion.\textsuperscript{[26]}

Conclusion and future perspective

NBCCS is a genetic complex of the abnormalities transmitted as an autosomal dominant trait. Apart from the various characteristic features of NBCCS including cutaneous and skeletal abnormalities, most distinguished and characteristic cutaneous manifestation is nevoid basal cell carcinoma. It is imperative to note that the dental professional may be the first to come across and identify this syndrome when the multiple cyst like radiolucencies are discovered on routine radiographs of the jaws. Therefore, for the correct follow-up and management of the case, the patient must be referred to a clinical geneticist for counseling. The family persons of patients with NBCCS have to be thoroughly examined for the genetic basis as it is inherited as an autosomal dominant disorder. Some accustomed guidelines for the follow-up period include the following: Neurological examination twice yearly, cerebral magnetic resonance imaging once in a year for 1-7 years of age, orthopantomogram every
12-18 months starting at the age of 8 years, yearly skin examination and cardiologic examination according to the signs and symptoms. Conversely, there is a significant lack of scientific literature that could authenticate the exact etiology and frequent recurrent of OKC in NBCCS. However, we look forward to have some long term clinical studies with detailed molecular and gene analysis that could precisely establish some reliable clinical guidelines in this regards.

REFERENCES


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