Nevoid Basal Cell Carcinoma Syndrome Presenting with Neck Pits and Café au Lait Patches

Sathesh Balasundram* / Ferdinand Jesudian Kovilpillai ** / Colin Hopper ***

Background: *A 10- year-old patient presented with a slow growing jaw swelling. The initial general examination did not reveal any significant findings.* ***Method:*** *Conservative enucleation of the cyst confirmed it to be an odontogenic keratocyst. The patient remained asymptomatic for the following 2 years and subsequently presented cystic lesions in jaws with displaced teeth. These cysts were enucleated and were confirmed to be odontogenic keratocysts . The patient has been on regular follow up since then and subsequent scans have shown further occurrence of cysts in the jaws with displacement of the third molars.* ***Results:*** *Clinical examination also revealed macrocephaly, fronto-parietal bossing, pitting on palmar and plantar surfaces, calcification of falx cerebri and splayed ribs, confirming the diagnosis of Nevoid Basal Cell Carcinoma Syndrome. He also presented with a café au lait patch and skin pits on the neck. The family history was negative for features of nevoid basal cell carcinoma syndrome.* ***Conclusion:*** *Nevoid basal cell carcinoma syndrome is a condition that can cause significant morbidity if not detected early. Over the years this syndrome has presented with many other non specific phenotype presentation, of which the current finding may be one of. This calls for meticulous assessment and examination of patients and a standardized protocol in screening and managing these patients that may facilitate a more beneficial outcome for the patient.*
Keywords: *Gorlin Goltz syndrome, nevoid basal cell carcinoma, odontogenic keratocyst*
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INTRODUCTION

The nevoid basal cell carcinoma syndrome (NBCCS) (OMIM #109400) is a rare autosomal dominant disorder with a prevalence of 1 in 57 000 – 164 000.[1] A condition of high penetrance and variable expressivity, this syndrome shows no numerical disparity by sex. Jarish[2] first noted the association of nevoid basal cell carcinoma with skeletal anomalies in a feeble-minded patient who had scoliosis in 1894. That same year, White[3] reported the family history of a patient with multiple basal cell carcinomas that kept appearing throughout life. Subsequently, Nomland[4] described basal cell carcinomas arising from congenital pigmented basal cell nevi because of their similarity to melanocytic nevi in 1932. The association of jaw cysts with multiple basal cell carcinomas of the skin was first noted by Straith[5] in 1939. Howell recognized in 1953 an unusual picture of numerous skin cancers not associated with ultraviolet light, x-rays, arsenic or other known carcinogens, and with Caro[6] described the difference between basal cell carcinoma and epithelioma adenoid cysticum. They noted the similar appearance and clinical behavior of the two conditions, the difficulty in distinguishing them microscopically and their occurrence in patients with developmental defects.[7] In 1960, Gorlin and Goltz[8] defined the condition as a syndrome comprising the principal triad of multiple basal cell nevi, jaw keratocysts, and skeletal anomalies. A spectrum of other neurological, ophthalmic, endocrine and genital manifestations is now known to be variables associated with this triad.[9]

The syndrome occurs in 1 in 200 patients with basal cell carcinomas (BCC) and displays an approximate 40% spontaneous mutation rate.[10] This condition is due to mutations in the *Patched Homolog 1* (PTCH1) gene map locus on chromosome 9q22 or the *Patched Homolog 2* (PTCH2) gene map locus on chromosome 1p34.1. Approximately 70-80% of affected individuals inherit NBCCS from an affected parent, with 20-30% of probands having a de-novo mutation. Mutations are detected in 60-85% of affected individuals by sequencing of PTCH; therefore, clinical examination and radiographs remain important in the diagnosis of NBCCS.[11]

We report the case of a 10 year old male patient

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presenting with multiple recurrence of odontogenic keratocysts. The rarity of this case is evident with the presentation of pits on the surfaces of skin in the neck region and a café au lait patch.

Case Description

A 10 year old male patient, of Asian (Malay) origin, attended the Department of Oral Surgery with a chief complaint of a slow growing jaw swelling of 6 months duration. There was no discharge of any type; neither was there any associated numbness or teeth loosening.

Written informed consent was obtained from the patient and the parents. In the anamnesis of this patient, we confirmed that he had showed weak performance in his studies. He was a child of a non-consanguineous couple. The patient had a history of left maxillary cyst enucleation at the age of 5 years. The histopathology could not be ascertained.

The initial general examination did not reveal any significant findings. Intraorally, the patient had a firm, non-tender swelling over the right body of mandible. The orthopantomograph (OPG) showed cystic lesions in the right body of mandible with displacement of lower right second premolar (tooth 29) towards the lower border of mandible, and in the left posterior maxilla (Figure 1).

Conservative enucleation of the cyst was done under general anesthesia with tooth 29 left *in situ*. There were no complications post-operatively. Histopathological results revealed that the cyst was an odontogenic keratocyst. The patient was placed under a 6 monthly follow up.

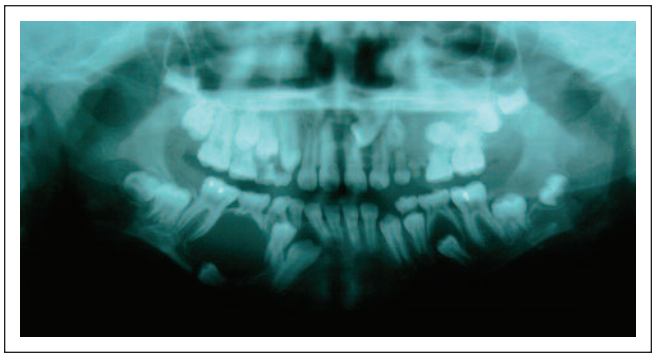

Figure 1. Orthopantomograph of patient showing cystic lesions in the right body of mandible with displacement of lower right second premolar (tooth 29) towards the lower border of mandible and in the left posterior maxilla

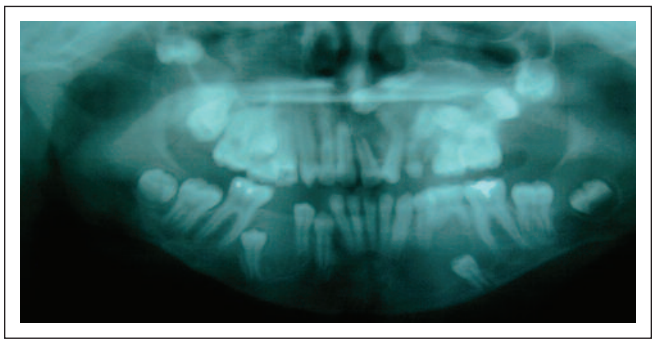

Figure 2. Orthopantomograph of patient showing cystic lesions in the left body of mandible with displacement of lower left second premolar (tooth 20) and in left maxillary tuberosity

The patient remained asymptomatic for the following 2 years and subsequently presented with a mandibular swelling at the age of 12 years. OPG assessment revealed cystic lesions in the left body of mandible with displacement of lower left second premolar (tooth 20) and in the left maxillary tuberosity (Figure 2). Both cysts were enucleated with removal of tooth 20. The histopathology report confirmed that both the cysts were odontogenic keratocysts (OKC). The presence of multiple OKCs at a young age was the catalyst for further investigations.

The patient was referred to the pediatric and the genetic unit for study. The genetic testing revealed heterozygous pathogenic frameshift mutation of the PTCH gene. Sequence analysis of exon 3 of the PTCH gene identified a heterozygous 1bp deletion at nucleotide position 485 (c.485delC). This mutation was predicted to create a down-

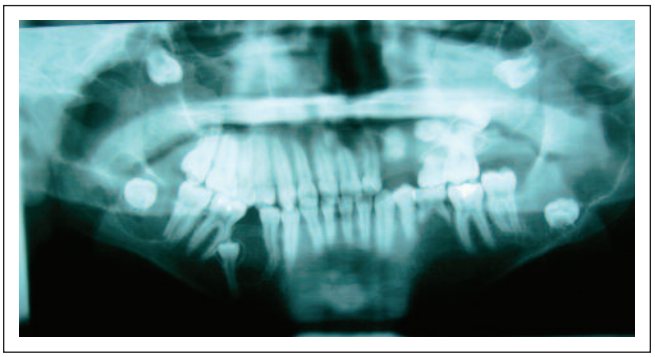

Figure 3. Orthopantomograph of patient showing occurrence of cysts in the left and right angle of mandible and posterior of right maxilla with displacement of the third molars

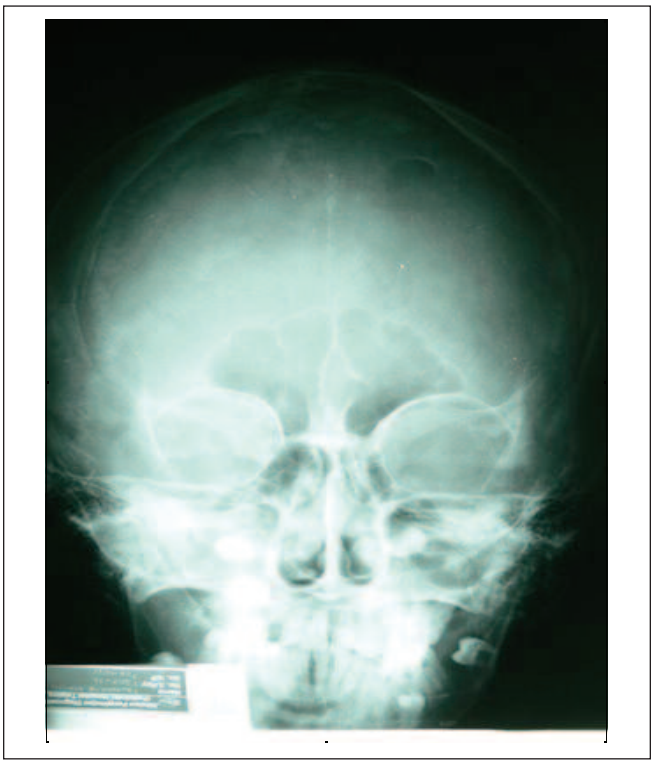

Figure 4. Calcification of falx cerebri

stream stop codon (p.Pro162LeufsX9) and was therefore considered to be pathogenic.

The patient has been on regular follow up since then and has been asked to continue his visits once every 6 months. Subsequent OPG scans have shown occurrence of cysts in left and right angle of mandible and right posterior maxilla with displacement of the third molars (Figure 3).

Further assessment of the patient revealed macrocephaly, fronto-parietal bossing and calcification of falx cerebri (Figure 4). Palmar and plantar pits were also noted (Figure 5). Skin examination revealed a café au lait patch over left leg (Figure 6) and minute nevi over upper arms. Chest x-ray showed splayed ribs. This patient also presented with pits on the surfaces of the skin in the neck region (Figure 7). The family history was negative for features of NBCCS. Both parents were in good health, and both were of average stature. Neither of them had jaw cysts, palmar pits, or basal cell carcinomas.

Our patient has 3 major criteria for NBCCS[12]; odontogenic keratocysts of jaw, palmar and plantar pits and rib anomalies (Table 1). Any 2 of these criteria are deemed sufficient to establish the diagnosis of nevoid basal cell carcinoma syndrome. A new finding of skin pits and café au lait patches in this patient may be another additional feature in patients with NBCCS. Our findings emphasize the importance of careful evaluation and periodic review of the clinical manifestations of NBCCS that appear in young children.

Figure 5. Palmar pits

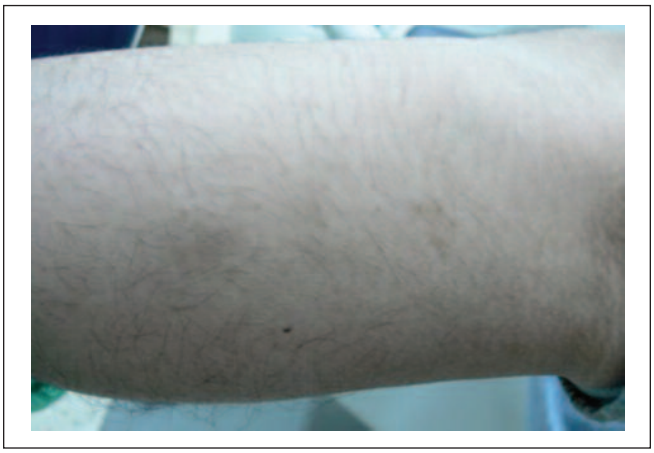

Figure 6.v Café au Lait Patches

Table 1. Major features of Gorlin's syndrome[25,26]

Feature	Frequency(%)
Multiple basal-cell carcinoma	73 -90
Odontogenic keratocysts of jaw	66 -90
Calcified falx cerebri	>85
Characteristic face	70
Palmar and/or plantar pits	65
Rib anomalies	60
Spina bifida occulta of cervical or thoracic vertebrae	60
Epidermoid cysts of skin	>50
Enlarged occipitofrontal circumference	50
Kyphoscoliosis	30-40
Ovarian fibromas	24
Eye abnormalities	7-26
Cleft lip/palate	6
Medulloblastoma	5
Cardiac fibroma	2.5
Postaxial polydactyly (hands and feet)	<5
Lympomesenteric cyst	<5

DISCUSSION

Nevoid basal cell carcinoma syndrome is an autosomal dominant disorder characterized by an increased predisposition to neoplasm as well as a wide variety of developmental defects.[13] There is significant phenotypic variability within and among kindred with respect to malformations. Neither the failure to identify a specific mutation nor the absence of a suggestive family should negate the clinical diagnosis of NBCCS as almost 60% of patients with NBCCS have no known affected family members, 30% to 50% of these representing new mutations.[9] In addition, despite being an autosomal dominant disorder, there is considerable variability in phenotypic expression. Many of the clinical features, especially the congenital malformations such as palmar pits and rib abnormalities, are asymptomatic and may escape attention unless specifically looked for.[14]

Odontogenic Keratocysts in NBCCS

Jaw cysts (odontogenic keratocysts) are a major feature,

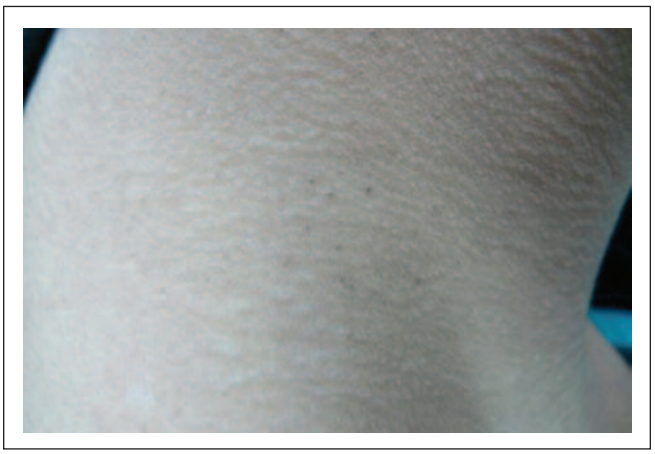

Figure 7. Neck Pits

and are important because they can develop during the first and second decades (82% of patients developed jaw cysts by 20 years in one series), and result in loose teeth or pathological fracture.[15] The odontogenic keratocysts (OKC) can be the first features of the syndrome (usually during the first decade of life) and are typically found as an incidental radiographic findings, for example at orthodontic assessment, although they may also manifest clinically if they became infected or cause symptoms such as swelling or trigeminal neuropathy.[9]

The youngest known affected child was five years. The median age of appearance is about 15 years. This is at least 10 to 20 years earlier than in those without the syndrome. The average number of cysts in nevoid basal cell carcinoma syndrome is 5 but has ranged from 1 to 30.[16] There are differences in the keratocysts between patients unaffected and affected by the syndrome, since in the latter, they frequently occur at an early age, are usually multiple and affect any jaw.[17] Keratocysts of patients affected by NBCCS have a large number of micro-satellite cysts, greater epithelial proliferation and mitosis, as well as a higher level of para-keratinization and inflammatory infiltration of the stroma; all differences which could explain why the keratocysts of patients affected by the syndrome recur more often than those of patients not affected[17]. Recurrent jaw cysts occur in 90% of patients[18].Radiographically, the keratocyst may show a unilocular or multilocular pattern and the cystic spaces may have a smooth or scalloped border[18].

There have been a few reports of an ameloblastoma arising in an OKC. Less commonly, squamous cell carcinoma has arisen in a cyst wall.[16]

The treatment of OKC in patients affected by NBCCS is not different from the one proposed for OKCs in patients not affected by the syndrome. While some authors suggest the OKCs can be managed conservatively,[19] close follow-up is recommended because of the tendency to recur especially with the parakeratinized variant.

Diagnosis in maxilla can be difficult with plain radiographs and justifies the need of CT scans, which could display aspects of morphology not seen in plain films.

Management of OKCs in the maxilla may warrant a midfacial degloving approach with Le Fort 1 downfracture prior to enucleation of the cyst.

In view of the lining being thin and friable, and the possible presence of satellite cysts, a solely surgical approach to the treatment of OKCs of NBCCS patients is unlikely to be successful. As a consequence, adjunctive therapies such as cryotherapy or Carnoy's solution are often indicated. Based on the findings of a series, marsupialization with subsequent enucleation does appear to increase the success rate, although not to a significant degree. This facilitates bone formation adjacent to the cyst walls of the tumor. In this way, the cystic covering tends to become thicker, contributing to its complete removal at the enucleation step.[20]

Basal Cell Carcinomas in NBCCS

All types and sizes of basal cell carcinomas (BCC) are seen, and many of the small ones are indistinguishable from nevi.[7] Clinically, they may vary from flesh-colored papules to ulcerating plaques and may be mistaken for skin tags, nevi, or hemangiomas.[18] In NBCCS syndrome, BCCs usually start to appear at puberty and, by the age of 40 years, up to 90% of patients will develop a BCC.[15] Early exposure to radiation, for example in the treatment of meduloblastoma (Table 2) and excessive sun exposure increases the likelihood of developing BCCs. Notwithstanding this, one obser-

Table 2. Anomalies in Nevoid Basal Cell Carcinoma Syndrome[9]

Skeletal Anomalies
Bifid ribs
Splayed/fused ribs
Cervical ribs
Absent/ rudimentary ribs (26%)
Scoliosis
Hemivertebrae
Flame-shaped lucencies hand/feet
Polydactyly
Syndactyly
Shortened 4th metacarpal
Craniofacial anomalies
Frontal bossing (25%)
Brachycephaly
Macrocephaly(40%)
'Coarse face' (50%)
Calcification of falces (37-79%)
Tentorium cerebellum calcification
Bridged sella turcica
Neurological anomalies
Agenesis/ disgenesis of corpus callosum
Congenital hydrocephalus
Mental retardation
Medulloblastoma (3-5%)
Meningioma(1% or less)
Schizoid personality
Oropharyngeal anomalies
Cleft lip and/or palate (4%)
High-arched palate or prominent palatine ridges (40%)
Odontogenic keratocysts (75%)
Malocclusion(s) (maxillary hypoplasia and mandibular hyperplasia, cleft palate)
Dental ectopic position
Impacted teeth and/or agenesis
Skin anomalies
BCC (50-97%)
Palmar and/or plantar pits (90%)
Sexual anomalies
Uterine and ovarian fibromas (15%)
Calcified ovarian cysts
Supernumerary nipple
Hypogonadism and cryptorchidism
Ophthalmic anomalies
Congenital amaurosis
Exotropia
Hypertelorisms (40%)
Ptosis
Internal strabismus (15%)
Glaucoma
Coloboma
Blindness
Cardiac anomalies
Cardiac fibroma (3%)

vation noted that NBCCS cells harbor normal DNA repair and survival capacities following UV irradiation which better explain that BCC proneness of patients with NBCCS does not solely concern body areas exposed to sunlight and suggest rather that it might be due to cell cycle alterations.[21]

Photodynamic therapy takes advantage of the selective accumulation by tumours of selective accumulation by tumours of systematically administered photosensitizers or of their increased conversion of δ-aminolevulinic acid to the photosensitizing protoporphyrin IX, followed by treatment with high-intensity light. The topical use of aminolevulinic acid (5-ALA) is now established in patients with BCCs. Photodynamic therapy causes the tumor to regress because of oxidative damage, and in contrast to ionizing radiation, does not produce DNA damage; thus, it is less likely than ionizing radiation to cause the development of additional cancers.[22] Whereas early invasive BCCs are conveniently treatable using topically applied photosensitizers (5-ALA or its esters), infiltrative BCCs exceeding 2 mm in tumor thickness require more effective, systemic photosensitization. Appropriate photosensitizers for this indication seem to be mostly Porfimer Sodium of mTHPC (Foscan), and both have been investigated clinically with reasonably high patient numbers. As the former has the downside of a much prolonged, generalized cutaneous photosensitization if compared to the latter, attention in recent years has mostly been drawn to the "second generation" photosensitizer mTHPC.[23]

Other syndromes

Main differential diagnoses in patients with similar clinical presentation of NBCCS include Bazex syndrome, trichoepithelioma papulosum multiplex, Torre's syndrome (Muir-Torre's syndrome)[18] and Beckwith-Wiedemann syndrome.[31]

Non specific phenotypes

Phenotypic features that show variable expression must be influenced by genetic background, epigenetic effects, somatic mutations, or environmental factors.[26] Many anecdotal findings have been reported in association with NBCCS. It remains inconclusive as to whether these findings were nonspecific phenotypes of NBCCS or coincidental observations. These include segmental vitiligo,[27] bilateral hyperplasia of the mandibular coronoid processes,[16,18] nasal dermoid cyst,[28] presence of a single kidney,[29] prognathism,[11] bilateral thumb deformities,[11] von Willebrand type 1 disease,[30] microphthalmia,[24] lung cancer[24] and renal cell carcinoma.[24]

In this particular case, our patient presented with additional features. Although the skin pits and café au lait were asymptomatic, we cannot over exaggerate the fact that this could be an early manifestation of the NBCCS. Notwithstanding this, further evaluation of other patients with NBCCS is necessary to confirm this finding.

Clinical protocol in the examination of patients with NBCCS

We must suspect the syndrome in patients with keratocysts and/or multiple basal cell carcinomas whether associated or not with the other clinical manifestations, in the early stages of life, with the firm objective of making an early clinical-radiographic detection and to be able to establish an early diagnosis of other possible problems or associated malignant neoplasia which could be of major importance.[17] Early diagnosis of NBCCS is crucial to affected children and their families, especially as regards to the risk of developing malignancies, for which specific guidelines for follow-up have been established: neurologic examinations twice yearly, yearly cerebral magnetic resonance imaging between ages 1-7 years, OPGs every 12-18 months starting at the age of 8 years, yearly skin examination, cardiologic examination according to signs and symptoms. Furthermore, targeted strategies need to be implemented for prevention and/or management of UV-radiation therapy-induced BCCs to avoid disfiguring surgical excision.[32]

Rigorous communication between specialties is essential, so that each knows the current treatment being administered, and future plans may be coordinated.[14] It is particularly helpful to follow a specific clinical protocol in the examination of these subjects.

It is recommended to involve families in regular screening. It may be possible to prove whether someone in a family has inherited the condition or not by DNA tests, either by tracking the chromosome 9 containing the faulty gene, or by direct analysis of the mutation causing the disease in a particular family.[18] As a consequence of these highly variable clinical presentations patients potentially affected with NBCCS must be evaluated by several specialists to precisely confirm the diagnosis, detect the likely genetic basis, provide appropriate genetic counseling and manage the various clinical manifestations.[9] Families with NBCCS could be managed by a register system so that regular screening can be assured and the patient kept up to date with recent advances. An interested genetics service would be the best place to run the register and coordinate the screening. Screening can begin during pregnancy with the offer of a fetal anomaly scan to a person with NBCCS or who has an affected partner.[24]

NBCCS is a condition that can cause significant morbidity if not detected early. This calls for meticulous assessment and examination of patients. A standardized protocol in screening and managing these patients may facilitate a more beneficial outcome for the patient.

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