Case Report - Surgical Pathology

The syndromic multiple odontogenic keratocyst in siblings: A familial study

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ABSTRACT

Purpose: Our aim is to demonstrate the importance of postoperative assessment and highlight the need for a lifetime follow-up of the patient and the siblings in cases of Nevoid Basal Cell Carcinoma Syndrome (NBCCS). **Materials and Methods**: Three siblings out of which two were of syndromic multiple odontogenic keratocysts, with multiple basal cell nevae were followed-up for manifestations of NBCCS from year 2001 till date. Two of the patients were treated for multiple bilateral odontogenic keratocysts (OKCs). Familial occurrence of the syndromic multiple odontogenic keratocysts was studied. **Result:** Although NBCCS is associated with multiple OKCs, it does not imply that a patient should have more than one cyst at a given point in time, rather it refers to the lifetime history of the patient. Early diagnosis will often make it possible to use conservative therapies rather than complex treatments. **Conclusion:** Recognition of the syndrome permits early treatment in other but possibly asymptomatic relatives. Close attention of the family and past medical history and physical examination will alert the clinician to its presence, allowing for appropriate genetic counseling and serial screening for the development of malignancies and other complications besides OKCs.

Keywords: Basal Cell Nevus syndrome, familial study, odontogenic kertocystic tumor, syndromic multiple keratocysts

INTRODUCTION

Nevoid Basal Cell Carcinoma Syndrome (NBCCS) is an autosomal dominant condition that can cause unusual facial appearances and a predisposition for basal cell carcinomas, a malignant type of skin cancer. The prevalence is reported to be 1 case per 56,000–164,000[1,2] population with a male predilection of 3:1.[3] A recent work in molecular genetics has shown NBCCS to be caused by mutations in the PTCH (Patched) gene found on chromosome arm 9q22.3, 9q31, and 1p32.[4,5]

NBCCS, Basal cell nevus syndrome (BCC), (Gorlin's syndrome, or McKusick Mendelian Inheritance in Man 109400) was first described by Jarisch and White in 1894.[6] He used the term epithelioma adenoids cysticum for this combination.[5] Later in the year 1960, Gorlin–Goltz established the association of basal cell epithelioma, jaw cyst and bifid ribs, a combination which is now frequently known as Gorlin–Goltz syndrome as well as NBCCS.[7] This syndrome is known to express a high degree of penetrance, variable expressivity and is characterized by several developmental defects.[8] The characteristics may include basal cell carcinomas, multiple Odontogenic Keratocysts (OKCs), palmar and/or plantar pits, and ectopic calcifications of falx cerebri. These features are considered major diagnostic criteria. More than 100 minor criteria have been described, including cardiac and ovarian fibromas, mild mandibular prognathism, frontal and bilateral bossing, and others.[1,8] Penel[9] reported an association of head and neck angiosarcoma and NBCCS. Although NBCCS is associated with multiple OKCs, it does not imply that a patient should have more than one cyst at a given point in time, rather it refers to the lifetime history of the patient. Single or multiple OKCs in the absence of other features of NBCCS may also be considered an incomplete form of this syndrome.[10]

Despite a number of cases reported in the literature, the understanding of complete form of NBCCS, incomplete form of NBCCS, and cases of isolated OKCs is not yet conclusive. Besides the fact that the signs and symptoms of NBCCS appear as the patient ages, they do not occur concomitantly; these are challenges to the diagnostician.

MATERIALS AND METHODS

We present here, cases of three siblings, two of whom have Gorlin–Goltz syndrome and are on long-term follow-up. These cases are considered pertinent because both the siblings showed bilateral OKCs and also evidence of basal cell carcinoma lesions on the skin. In the present clinical cases it was interesting to speculate on a familial association of NBCCS. Our aim is to demonstrate the importance of post-operative assessment and highlight the need for a lifetime follow-up of the patient and the siblings.

Case 1

In July 2001, a 28-year-old male reported with a chief complaint of pain and swelling of the left lower jaw causing facial asymmetry. The patient reported of similar symptoms on the same side 8 years back. He had visited several dentists over this period of time with a complaint of mobility of teeth on both sides of the jaw and swelling on the left side. He was advised removal of 48, 47, and 38 followed 2 years later by removal of 37, 36, 35, and 34. Since the pain and mobility of the teeth did not subside, the patient reported to us. He did not carry any past histopathological records with him. His past medical history was unremarkable and his general physical examination revealed the presence of skin lesions on the forehead [Figure 1].

Clinical examination of the head and neck region showed left facial swelling along with an expanded buccal and preauricular area leading to facial asymmetry. He denied any neurosensory problem associated with inferior alveolar nerve.

Intraoral examination revealed a firm, hard swelling on the crest and buccal vestibule of left mandibular alveolar ridge, around 5 cm in the anterior–posterior direction and overlying the crest of 36, 37, 38. There was no discharge intraorally. All other hard and soft tissue components of oral cavity appeared normal.

The OPG showed a multilocular radiolucency on the left side in the body of the mandible. One radiolucent lesion was seen extending from the condylar, coronoid processes up to the body of mandible on the same side. There was another smaller radiolucent lesion evident on the distal aspect of 35 [Figure 2].

The computed tomography (CT) scan confirmed that the lesion was multiloculated and expansion of the cortical bones of the inferior and posterior borders on the left side of mandible was evident. Another radiolucency was seen just adjacent to the main lesion. In our opinion, it could have been an extension of the same lesion, which radiographically appeared as "daughter cyst."

On histopathological examination, the diagnosis of OKC was made [Figure 3].

In July 2000, under general anesthesia, hemi-mandibulectomy was performed followed by placement of reconstruction plate. In June 2002, the reconstruction plate was removed and a nonvascularized iliac crest graft was placed. In subsequent visit, impacted 18 was removed along with the cystic lining and its contents under local anesthesia. The lesion was reported to be a dentigerous cyst [Figure 4].

In 2004, the orthopantomograph showed evidence of resorption of graft. Also, it was noticed that the skin lesions on the face and axilla appeared to be enlarging slowly. Dermatological consultation resulted in agreement with diagnosis of Basal Cell Nevous Syndrome. On submission of histopathological specimen, the skin naevi were reported to be basal cell carcinomas [Figure 5]. Chest radiograph did not show any evidence of bifid rib [Figure 6].

In the clinical and radiographic follow-up from 2007 to 2009, the OPG showed increase in the level of resorption of the graft, although the patient did not have any functional or aesthetic problem. In the recent follow-up visits, the BCC lesions have gradually shown an increase in size as well as number [Figure 7].

The patient is scheduled for regular periodic follow-up with dermatology and maxillofacial department.

Case 2

Since the family became knowledgeable about the disease process after the first member was diagnosed and treated, his sibling, a 36-year-old woman reported to us when she noticed swelling on the right side of the jaw, which gradually increased in size. The patient had skin lesions similar to her brother on the forehead and face. The forehead also showed frontal bossing.

OPG revealed a multilocular radiolucency in the region of 36, 37, 38 extending to the ramus of mandible. A similar radiolucency was seen on the left side in association with 46, 47, 48 involving the angle region.

On histopathological examination, it was diagnosed to be a case of bilateral OKCs. Marsupialization followed by enucleation of the cyst was carried out on both the sides [Figure 8].

In 2008 and a year later in 2009, the OPG showed satisfactory healing of the lesion on both the sides [Figure 9]. The case is being followed-up periodically. There is no evidence of recurrence of the lesion. Regular dermatological consultations are being taken for the skin lesions, which seem to be benign at this time.

Case 3

The third sibling does not show evidence of any cystic or skin lesions till date. We plan to follow-up the case so that any evidence of the syndrome can be reported at an early stage for early treatment if required [Figure 10].

DISCUSSION

NBCCS is a syndrome with a wide variety of manifestations ranging from oral lesions to skeletal deformities. It becomes the responsibility of the maxillofacial surgeon to diagnose the

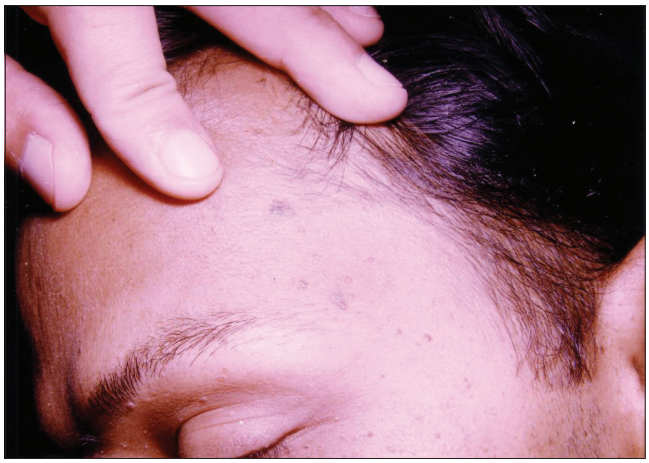

Figure 1: Skin lesions on forehead

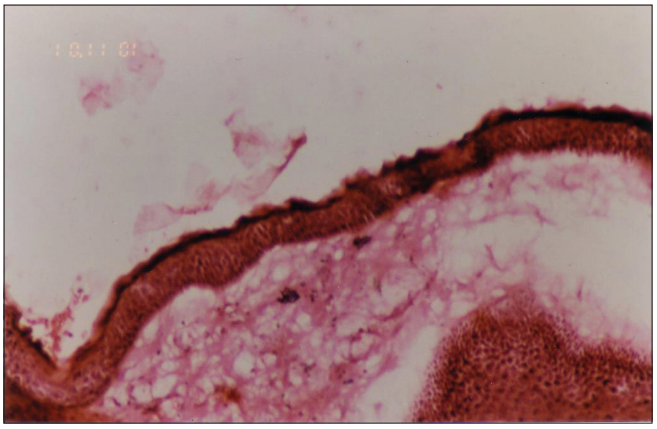

Figure 3: Pictomicrograph showing characteristic lining of odontogenic keratocyst (H and E, 10x)

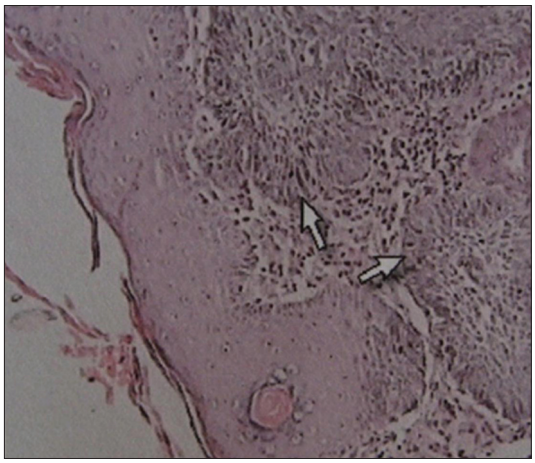

Figure 5: Pictomicrograph showing histopathological picture of basal cell carcinoma (H and E, 40x)

syndrome because very often they are the first health professionals to see the patient for the treatment of OKC. Patients often receive treatment for lesions which are classically related to this syndrome, without the syndrome being suspected.

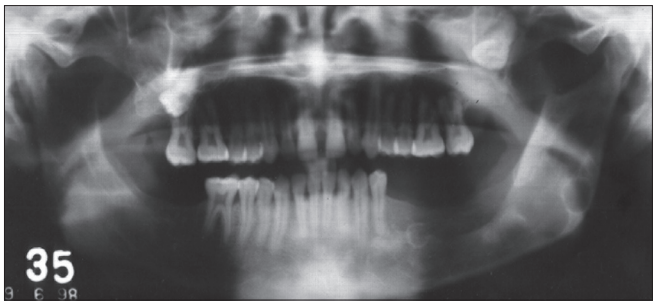

Figure 2: Preoperative panoramic radiograph showing multilocular lesion

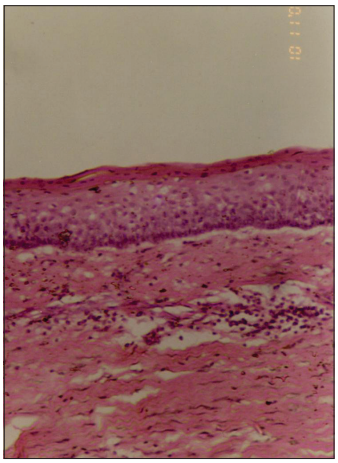

Figure 4: Pictomicrograph of the cystic lining showing characteristic features of dentigerous cyst (H and E, 10x)

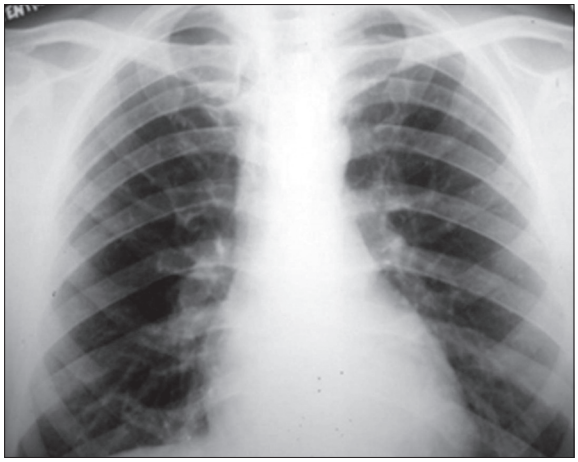

Figure 6: Chest radiograph without evidence of bifid rib

One of the manifestations of NBCCS, BCC, the most common malignancy in humans, has increased to epidemic levels in the UK, Western Europe, and Australia.[7] Although they rarely metastasize, they are capable of significant local tissue destruction and disfigurement. The majority of BCCs arising sporadically are also associated with NBCCS.

A second developmental feature of this autosomal dominant

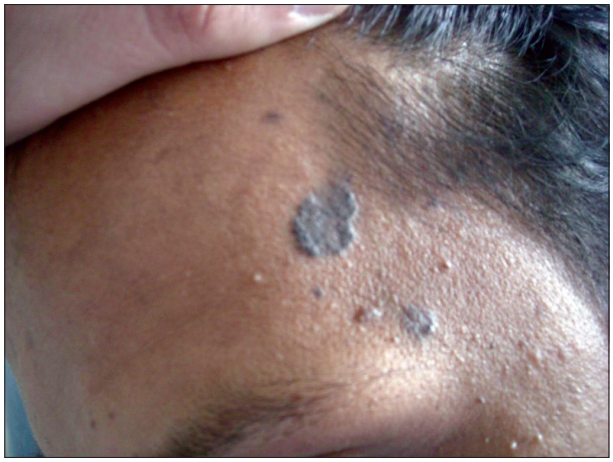

Figure 7: Increase in the size of skin lesion

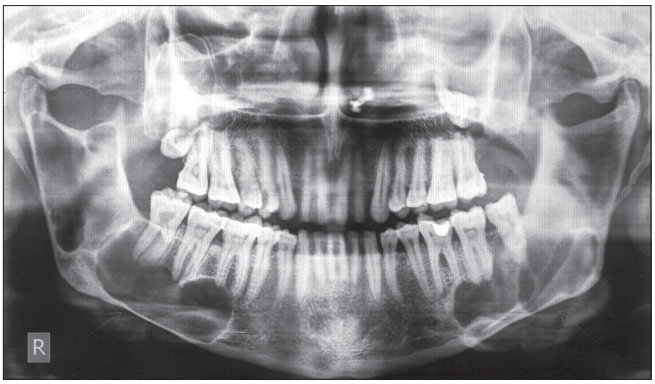

Figure 8: Patient 2: Panoramic radiographs showing multilocular appearance of the lesion

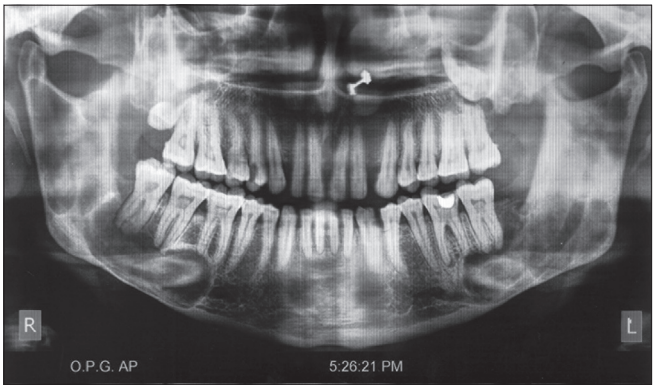

Figure 9: Patient 2: Follow up radiograph after 2 years showing bone healing

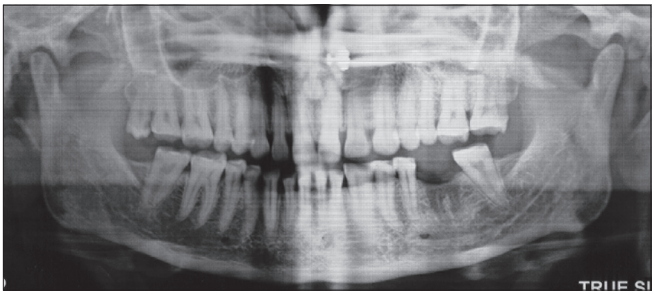

Figure 10: Patient 3: Panoramic radiograph

syndrome is the OKC, which is a common lesion in the jaws. Among patients with BCNS, 65% to 75% have OKCs. These may be bilateral, may involve both jaws and most commonly arise in the lower third molar and maxillary canine regions. They develop continuously, can become very large, and can recur.[11,12] Like BCCs, they can also demonstrate locally destructive behavior and if left untreated, may cause pathological fracture. In patients with BCNS, OKCs are more frequent and recur faster and more commonly, consistent with a more "aggressive" phenotype.[7] This feature, that is, bilateral OKCs is evident in two of our case reports. Also it is well known that dentigerous cysts associated with unerupted teeth occur only in few individuals, whereas unerupted teeth are a common occurrence. This suggests that some people are prone to cystic formation. A genetic predisposition may be a possibility. This also suggests that our first case might have a predisposition for jaw cysts. The OKC shows clinicopathological features of both a cyst and a benign neoplasm.[13] Shear *et al*[14] emphasized that the aggressive behavior and high recurrence rate of OKC suggests a true neoplastic potential. In the year 2005, in WHO classification of odontogenic tumors, the name of the cyst has been changed to "Keratocystic Odontogenic Tumor" owing to its aggressive nature and recurrence rate.

Studies demonstrate that sporadic and syndrome-related OKCs harbor mutations in PTCH.[15] Mutations in the tumor suppressor gene PTCH are identified as the underlying genetic events in NBCCS. It has been proposed that the development of an OKC would follow the "2-hit" hypothesis.[11,14,16] According to this hypothesis, OKCs present in NBCC arise from precursor cells that contain a hereditary "first hit," and the allelic loss represents loss of the normal allele while sporadic OKC might arise from susceptible cells in which two somatic "hits" have occurred. Shear[2] suggested that two cysts from one syndrome patient that occurred on opposite sides of the mandible had the same pattern of allelic loss, suggesting that this genetic mutation occurred at a very early stage of embryogenesis. OKCs associated with NBCCS occur at least a decade earlier than cases of isolated OKCs.

Although testing for PTCH gene is likely to become a gold standard for diagnosis of NBCCS, it is still not widely available and clinicians are left to rely on clinical judgment. In our first case, the diagnosis was established on the basis of the presence of basal cell nevae and multiple odontogenic cysts. Since the patient did not carry any past records with him, there is a possibility that the lesion on the right side of mandible might have regressed during multiple extractions of teeth. Our second case was diagnosed on the basis of multiple OKC, basal cell nevae, and frontal bossing. Nohl *et al*[12] suggest that OKCs associated with syndrome have different histological features with a greater potential for proliferation than lesions not associated with syndrome. In histopathological studies, the deep staining has been shown in palisading basal layer, this represents an epithelial proliferative capacity not found in sporadic cysts where superficial staining is present.

Parakeratinization and satellite cysts common to sporadic cysts are even more common to syndromic counterparts. It has been shown that keratocysts, when associated with NBCCS, show a higher number of satellite rests of tumor and more solid areas of epithelial proliferation and odontogenic epithelial rests within the fibrous capsule than is found in sporadic type.[15,17] However, Figueroa *et al*[18] studied that on the basis of the analysis of the expression of histological markers PCNA, Ki67, and p53, there appears to be no evidence to indicate higher aggressiveness in growth and infiltrative behavior in syndromic KCOT compared with the sporadic type. Therefore, surgical treatment may be approached in the same manner in KCOT sporadic and syndromic with the goal of minimizing recurrence.[19] In our first as well as second case, radiological features were in agreement with van Rensburg *et al*[8] who stated that CT displays aspects of bone morphology not seen in plain films, and demonstrated the importance of the combination of several imaging modalities to improve the diagnosis of NBCCS.

RESULT

The literature contains references to various treatment modalities for OKC,[20,21] for example:

- Simple Curettage
- Enucleation (Intact Shelling With Or Without The Use Of Carnoy's Solution Or Cryotherapy)
- Radical Enucleation
- Marsupialization
- Resection (Marginal or Segmental)

Recently, the hypothesis that suppression of the SHH signaling pathway can be an effective treatment for KCOT has been postulated and possible antagonist candidates are being investigated.[22]

In our first case, because of the size, multilocularity, and extent of the lesion, resection was performed followed by placement of nonvascularized iliac crest graft. Long-term follow-up of the patient revealed resorption of the graft. In light of our current knowledge we feel microvascular graft could have been a better option. These findings emphasize the importance of long-term follow-up as an essential aspect of OKC treatment.

In the second case, diagnosis was made on the basis of the presence of multiple OKCs, basal cell nevae, and frontal bossing. Marsupialization followed by enucleation was the treatment of choice with no recurrence till date. This is in accordance with number of other studies which state that OKCs may resolve completely after marsupialization followed by enucleation.[7] It appears that keratocysts may respond more rapidly to marsupialization than other odontogenic cysts. Immunohistochemical studies show that levels of interleukin-1 (an inflammatory, multifunctional cytokeratine, which plays a crucial role in expansion of OKC) decrease significantly after marsupialization. It also appears that cystic lining is replaced by normal epithelium during this treatment.[21] Overactivity of HH Pathway in OKC lesion and oral mucosa imply that adjacent oral mucosa may be removed along with the cyst during enucleation.[23]

We agree that the presence of NBCCS should be suspected when jaw cysts, particularly if they are multiple or bilateral, are observed in association with one or more of other major or minor characteristics.[1]

Multiple OKCs should not be treated as isolated cases. While planning the treatment all associated characteristics should be taken into consideration. Recognition of the syndrome is important since the jaw cysts by virtue of their continued development in multiple regions of the mandible and maxilla, pose problems in management.[3]

Although patients may have BCC at any site, most tumors are located on sun-exposed areas, especially the head and neck region. This mimics the most common location of sporadic BCC, implying that sun exposure plays a role in the development of these tumors and that sun protection could help decrease the number of tumors in the life time.[24] Also, beginning at the age of 8 years, children with NBCCS should minimally have yearly maxillofacial panoramic radiographic exposures. Likewise, to rule out recurrences, annual panoramic radiographs are recommended for patients who have undergone the ablation of OKC.

Early diagnosis will often make it possible to use conservative therapies rather than complex treatments. Furthermore, it offers patients and their families the chance of discovering the possible hereditary risks of the condition.

Recognition also permits early treatment in other but possibly asymptomatic relatives. Close attention of the family and past medical history and physical examination will alert the clinician to its presence, allowing for appropriate genetic counseling and serial screening for the development of malignancies and other complications besides OKCs.

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