

NEVOID BASAL CELL CARCINOMA SYNDROME: A CASE REPORT

Oral Pathology

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ABSTRACT

Nevoid basal cell carcinoma syndrome is a rare autosomal dominant disorder with complete penetrance and variable expressivity. This syndrome is characterized by developmental anomalies such as multiple odontogenic keratocyst, skeletal abnormalities and multiple basal cell carcinomas. Considering the rarity of this syndrome, we present a 28 year old female affected by this syndrome. She had multiple odontogenic keratocysts, palmer and plantar pits, skeletal abnormalities such as bifid ribs and spina bifida. The dental clinician may be the first person to encounter and identify this syndrome, when the multiple cysts like radiolucencies are discovered on panoramic view.

KEYWORDS

Basal cell carcinoma, Basal cell nevus syndrome, Gorlin-Goltz syndrome, Gorlin's syndrome, Odontogenic keratocyst.

INTRODUCTION

Nevoid basal cell carcinoma syndrome (NBCSS) also called as 'Gorlin syndrome' or 'Basal cell nevus syndrome (BCNS)' is an autosomal dominant inherited disorder that exhibits high penetrance and variable expressivity.^{[1][2]} This syndrome was first described by Jarish and White in 1894. Gorlin and Goltz in 1960 defined its syndromic nature which consists of multiple basal cell carcinoma, numerous jaw cyst, and skeletal malformations.^[1] This syndrome is caused by mutation in patched (PTCH), the human homologue of the *Drosophila* patched gene, a tumor suppressor gene that has been mapped to chromosome 9q22.3-q31.^{[3][4]} The prevalence of this syndrome is reported to be one case per 56,000 to 164, 000.^[5] About 30-50% patients have no family history.^[6] Here we are presenting a case of NBCSS manifesting with few features of the syndrome.

CASE REPORT

A 28 year old female patient reported with the chief complaint of pain and swelling in the left side of lower jaw for 3 months. Pain was dull, continuous and non-radiating. The growth of the swelling was slow in nature. No relevant medical, family or past dental history was reported. On examination, an ill defined swelling was present in the angle of the mandible, firm in consistency, mild tender on palpation. [Figure: 1] On general examination, numerous tiny blackish pits were evident over her palms and soles [Figure: 2&3].

An Orthopantomogram (OPG) of the patient revealed three well-defined multilocular radiolucencies with sclerotic border, two on each posterior region of mandible and one in right posterior maxilla [Figure:4&5]. The presence of multiple cysts in the jaw and palmer and plantar pits raised a suspicion of Gorlin syndrome and further evaluation with chest and skull radiographs were done, which revealed bifid ribs [Figure:6] and spina bifida [Figure: 7].



Figure 1 Mild swelling in right angle of mandible



Figure 2 Palmer basal pits



Figure 3 Planter basal pits

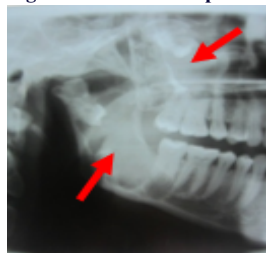


Figure 4 Two well defined radio-lucency associated with impacted third molar in posterior right quadrant



Figure 5 Single well defined radio-lucency associated with impacted third molar in left mandible

The cysts were enucleated under general anesthesia and submitted for histopathological examination. Microscopically, the section was lined by uniform layer of parakeratotic stratified squamous epithelium of six to eight cell thickness. The basal layer is composed of columnar cells with nuclear hyperchromatism and palisading. The epithelium was highly convoluted with surface corrugation. The epithelium connective tissue interface was flat without any rete ridge formation. The underlying connective tissue has well formed fibrous capsule with the absence of satellite cyst. The histopathology of the lesion was suggestive of "keratocystic odontogenic tumor". [Figure:8A&B]. IHC marker PCNA was used which showed suprabasal positive expression. [Figure:9]



Figure 6 Chest radiograph showing bifid fifth right rib



Figure 7 Spina bifida

On the basis of clinical, radiographic and histopathological findings, the patient was diagnosed to present with Nevroid Basal Cell Carcinoma Syndrome.

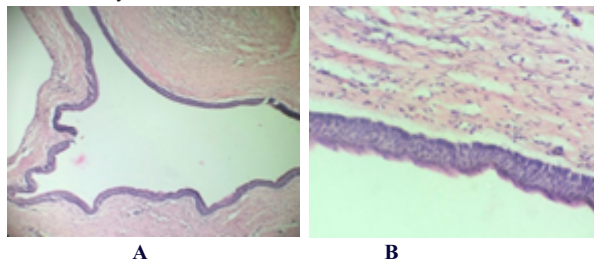


Figure 8 Light Microscopy at 10X (A) and 40X (B) showing palisaded basal layer with flat epithelial connective tissue interface and corrugated parakeratotic surface

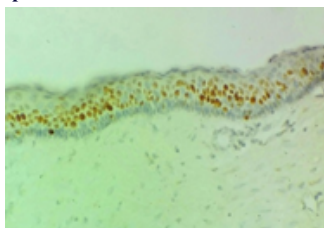


Figure 9 PCNA expression seen predominantly in suprabasal layer and extending almost upto the superficial parakeratin layer

DISCUSSION

Evans *et al* proposed a diagnostic criteria for nevoid basal cell carcinoma syndrome which was further modified by Kimonis *et al* in 1997.^[7] According to them, diagnosis of this syndrome can be established when two major or one major criteria or two minor criteria are present which are enumerated below.^[8]

Major criteria

1. More than two basal cell carcinomas or one basal cell carcinoma before the age of 30 years or more than 10 basal cell nevi.
2. Any odontogenic keratocyst or polyostotic bone cyst.
3. Three or more palmer or plantar pits.
4. Ectopic calcification in patients younger than 20 years of age (lamellar or early falx cerebri calcification).
5. Positive family history of NBCCS.

Minor criteria

1. Congenital skeletal anomaly (e.g. bifid, splayed, fused or missing rib, or bifid wedged or fused vertebra)
2. Occipital-Frontal circumference greater than the ninety-seventh percentile, with frontal bossing
3. Cardiac or ovarian fibromas
4. Medulloblastoma
5. Lymphomesenteric cysts
6. Congenital malformations such as cleft lip/palate, polydactylism or eye anomaly (e.g. cataract, coloboma or microphthalmos).

The genetic defect underlying NBCCS is a germ line mutation in the Sonic Hedgehog receptor *patched* (PTCH) gene. The mutated gene, *Patched*, has been mapped to chromosome band 9q22.3-3. This gene consists of 23 exons and 12 transmembrane-spanning domains coding for two large hydrophilic extracellular loops to which Sonic Hedgehog ligand binding occurs. If a mutation occurs in *Patched*, then the second loop is not formed and Sonic Hedgehog ligand cannot be binded.^[9]

Hedgehog signaling pathway plays a significant role in embryonic patterning and cell fate in many organs.^[10] Aberrant Hedgehog signaling pathway in some cases can lead to certain forms of cancer.

Odontogenic keratocyst is the most consistent and representative sign and develop in more than 90% patient in the first decade.^[11] They are developmental, locally destructive, non-inflammatory oral cysts which can be sporadic or syndrome associated. Woolgar *et al* in 1987 found that there was a significant difference between the syndromic and sporadic keratocysts matched for age and site. They concluded that in syndromic cases maxillary molar area is affected more commonly and it tend to occur at younger age. They also found significant

difference exists histopathologically also. The differences were found in the number of satellite cysts, solid islands of epithelial proliferation and odontogenic rests within the capsule, and in the number of mitotic figures in the epithelium lining the main cavity.^[12]

The odontogenic keratocyst (OKC) is now designated by the World Health Organization (WHO) as a keratocystic odontogenic tumour (KCOT) as it reflects its neoplastic nature.^[13] Katase *et al* analyzed the neoplastic nature and biological potential of sporadic and NBCCS associated KCOT. They showed that the increased level of heparanase which is an endo-d-glucuronidase enzyme that cleaves heparin sulfate is responsible for tumor invasion, angiogenesis and metastasis. In immunohistochemical study for heparanase expression, they observed that KCOT associated with NBCCS has intense positive immunoreactions compared with sporadic KCOT and dentigerous cyst.^{[12][14]}

PCNA (Proliferating Cell Nuclear Antigen) cell proliferate marker, is a nuclear protein essential for nucleic acid metabolism in DNA transcription and repair. It is expressed in high amount in growing cells during cell cycle.^[15] It stains suprabasal cells predominately than the basal cells of OKC lining epithelium as shown in our case.

The palmer or plantar pits appear as shallow depressions which are due to partial or complete absence of the dense keratin in sharply defined area.^[16] They are found on the hands and feet, mainly on the soles and palms, but they can also be demonstrated on the sides, web spaces and dorsum of the fingers and toes. They become more visible after the palms have been held in warm water for about 10 minutes.^[17] Basal cell carcinoma does not seem to arise from these pits.^[18]

Skeletal anomalies are expected in more than 50% Malformations of the rib frequently bifid ribs are proposed as an early diagnostic finding for children with NBCCS.^[19]

Syndromic Basal cell carcinoma tends to occur between puberty and 35 years of age and usually multiple in number. However, it has been shown that this lesion is present in only 50% of patients.^[20] In our case, this feature was absent. However, this case presented with two major and one minor criteria to establish the diagnosis.

CONCLUSION

The nevoid basal cell carcinoma syndrome is an autosomal dominant inherited disease with varying clinical presentation. Several findings other than the diagnostic triad of multiple keratocysts, multiple basal cell carcinoma and skeletal anomalies might occur in these patients and cause severe complications. Interdisciplinary management with regular follow up is mandatory for such patients to prevent from complications.

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