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Gorlin Goltz Syndrome – Case Series and Review of Literature.

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Abstract: *The Gorlin-Goltz syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS), is an infrequent multisystemic disease inherited in a dominant autosomal way, which shows a high level of penetrance and variable expressiveness It is characterized by disorders affecting multiple systems including skeletal, cutaneous, ophthalmic, reproductive, and nervous systems.. Gorlin syndrome is associated with germlinemutations in components of the Sonic Hedgehog pathway, including Patched1 (PTCH1) and Suppressor of fused (SUFU). The purpose of this present article is to describe the clinical, radiological, and histopathological findings in three cases of Gorlin Goltz syndrome diagnosed in our department, and to discuss the role of gene mutation analysis and circumstances to avoid in order to prevent primary manifestations.*

Keywords: *Gorlin-Goltz syndrome, Multiple odontogenic keratocysts, Nevoid basal cell carcinoma syndrome*.

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I. Introduction

Gorlin-Goltz syndrome (GGS) is an infrequent, autosomal dominant inherited disorder known as nevoid basal cell carcinoma syndrome (NBCCS) showing high level of penetrance and variable expressiveness. The syndrome was first described by Jarisch and White in 1894, but it was also existed during dynastic Egyptian times.[1,2]Later in 1939 a familiar case was described by Straith in which multiple basocellular carcinomas and cysts appeared.[3]Gross in 1953 presented a case suggesting additional signs such as synostosis of the first left rib and bilateral bifurcation of the 6th ribs.[4] Palmar and planter pits which is associated with the syndrome was first described by Bettley and Ward.[5,6] In 1960 Gorlin-Goltz established a classical triad of basal cell carcinoma, odontogenic keratocyst and bifid ribs, that characterizes the diagnosis of this syndrome. Later this triad was modified by Rayner et al., who established that for giving the diagnosis, at least cysts had to appear in combination with calcification of the falxcerebri or palmar and plantar pits.[7,8] The incidence of the disorder is estimated to be 1 in 50,000- 1, 50,000 in the general population, varying by region with males and females being equally affected.[9]

It is characterized by multiple odontogenic keratocysts (OKCs), multiple basal cell carcinomas (BCC), skeletal, ophthalmic, neurological abnormalities, and facial dysmorphism. Earlier it was believed that GS have germ line mutations in the only susceptibility gene PTCH1 located at chromosome 9q22.3 . But in 2008 Pastrorino et al[10]identified the SUFU germ line splicing mutation in a family that was PTCH1-negative and who had signs and symptoms of GS, including medulloblastoma. As the syndrome is a hereditary condition with a 50% chance of inheritance in offsprings of affected patients, genetic screening and counselling of patients and family members become important to screen for familial predisposition of this syndrome. [1]The genetic mapping of individuals would help in early diagnosis and management of suspected disease, thus decreasing the severity of abnormalities. Antenatal diagnosis for pregnancies at increased risk patients is also possible by ultrasound scan and extraction of DNA from fetal cells by amniocentesis.[1] Also this provides an opportunity for the development of future drugs for treatment or prevention of syndrome in subsequent generations.

The purpose of this present article is to describe the clinical, radiological, and histopathological findings in three cases of Gorlin-Goltz syndrome diagnosed in our department, and to discuss the role of gene mutation analysis and circumstances to avoid in order to prevent primary manifestations.

II. Case Report

Case 1

A 39-year-old female patient presented with complaint of swelling and associated pain in relation to right maxillary posterior region of 6 months duration. The swelling was small which gradually increased in size to the present. There was no history of bleeding and pus discharge. Extra-oral examination revealed mild frontal bossing, hypertelorism and strabismus. Intra-orally there was a palpable firm tender swelling approximately 2 cm × 2 cm in relation to mucobuccal fold opposite 26, 27 regions.

General examination reveals palmar and plantar pits.OPG shows multiple, unilocular radiolucent lesions in relation to bilateral mandibular premolar region, left mandibular ramus region and left maxillary posterior region. Bifid-rib anomaly was evident on chest X-ray.

Case 2

A 17-year-old male presented with a complaint of pain and swelling in the lower left region of the jaw. He had a history of similar episode three months earlier which settled with a course of antibiotics. Extra-oral examination revealed fused eye brows, depressed nasal bridge and hypertelorism. Intraorally fluctuant and tender swelling of size 3 × 3 cm present in relation to 34, 35 regions.

OPG revealed multiple well circumscribed radiolucent lesions, five in number, three in the maxilla and two in the mandible. PA view of skull showing falx and tentorial calcification. Chest x-ray showing fused anterior end of fifth and sixth rib.

Case 3

A 24-year-old female patient presented with a complaint of pain on right side of the face for 2 months with pus discharge from right upper back tooth region. Extra-oral examination revealed mild frontal bossing, fused eye brows, depressed nasal bridge and hypertelorism. Intraorally there was pus discharge from distal gingival sulcus of 17. Intraorally tenderness over the upper mucobuccal sulcus on palpation with irregular bony margins palpable in relation to 15 region.

General examination reveals palmar pits.OPG shows radiolucent lesions with corticated margins involving right ramus extending into condyle, left body angle region of mandible and right maxilla involving maxillary sinus. Lesions are having scalloped margins and multilocular. 48 is displaced posterosuperiorly upto superior aspect of right ramus of mandible.PNS view shows falx calcification. Ovarian fibroma was also present.

In all the three cases hematologic results were within normal limits. Incision biopsy of the lesions in all cases were performed and a diagnosis of odontogenic keratocyst was made. None of the patients have similar family history.

III. Discussion

Nevoid basal cell carcinoma syndrome (NBCCS) is characterized by the development of multiple jaw keratocysts, frequently beginning in the second decade of life, and/or basal cell carcinomas (BCCs) usually from the third decade onward. Approximately 60% of individuals have a recognizable appearance with macrocephaly, frontal bossing and coarse facial features. Most individuals have skeletal anomalies (e.g., bifid ribs, wedge-shaped vertebrae). Ectopic calcification, particularly in the falx, is present in more than 90% of affected individuals by age 20 years. Cardiac and ovarian fibromas occur in approximately 2% and 20% of individuals respectively. Approximately 5% of all children with NBCCS develop medulloblastoma (primitive neuroectodermaltumor), generally the desmoplastic subtype. Peak incidence is at age one to two years. The defects of stomatologic system, including mandibular prognathism, high arched palate, malocclusion, impacted teeth, ameloblastoma, squamous cell carcinoma, and odontogenic myxoma, have also been reported.[1] In certain occasions, a tall height has been associated with the syndrome.[11]Very few cases of NBCCS had been reported previously in Indian literature probably representing underrecognition. The diagnosis of NBCCS is established by the presence of two major criteria or one major criterion and two minor criteria proposed by by Evans *et al.* (1994) which was later modified by Kimonis*et al (2004).* Full diagnostic criteria have been recently outlined by Jones and colleagues (2011).[12]

Major Criteria

- Lamellar (sheet-like) calcification of the falxcerebri
- Odontogenic keratocyst of the jaw histologically;
- Palmar/plantar pits (≥2)
- Multiple basal cell carcinomas (BCCs) (>5 in a lifetime) or a BCC before age 30 years.
- First-degree relative with NBCCS

Minor Criteria

- Childhood medulloblastoma (also called primitive neuroectodermaltumor)

Note: A consensus meeting consisting of US-based experts (with one French participant) has suggested changing medulloblastoma to a major criterion and allowing the diagnosis of NBCCS with only two minor criteria in addition to a major criterion [Bree et al 2011].[13] The concern would be that this would reduce the specificity of diagnostic criteria, as individuals with medulloblastoma undergoing radiotherapy without NBCCS are likely to develop more than one BCC. Confining the medulloblastoma diagnosis to nodular/desmoplastic and disallowing BCCs occurring after radiotherapy as a major criterion may improve sensitivity without losing specificity. These changes have not yet been adopted. A consensus conference on screening recommendations convened by the American Association of Cancer Research did not propose adopting the Bree et al criteria[Foulkes et al 2017].[14]

- Lympho-mesenteric or pleural cysts
- Macrocephaly
- Cleft lip/palate
- Vertebral/rib anomalies such as bifid/splayed/extra ribs or bifid vertebra
- Preaxial or postaxial polydactyly
- Ovarian/cardiac fibromas
- Ocular anomalies (e.g., cataract, developmental defects, and pigmentary changes of the retinal epithelium)

In additionover 100 minor criteria have been reported in the literature for diagnosing Gorlin–Goltz syndrome.

If clinical features are inconclusive identification of a heterozygous germline pathogenic variant in *PTCH1* or *SUFU* on molecular genetic testing establishes the diagnosis. Germline mutations in genes of the sonic hedgehog (SHH)signalling pathway, including Patched1 (PTCH1) and Suppressor of fused (SUFU), are implicated in Gorlin syndrome .Heterozygous germline mutations in PTCH1 have been detected in the majority of individuals with Gorlin syndrome. Less frequently germline mutations in SUFU are observed.[10]

SHH pathway signalling is normally active only during brain development. Derangements of the SHH pathway have also been linked to the pathogenesis of medulloblastoma, with as well as in basal cell carcinomas and selected other malignancies. PTCH 1 is a transmembrane protein receptor that negatively regulates (tumor suppressor) the Hh signalling pathway. SHH binding to PTCH1 results in an alteration in Smo (smoothened) activity; normal PTCH1 represses Smo and, when mutation occurs, it derepresses Smo. De-repression of SMO culminates in the activation of one or more of the GLI transcription factors that regulate the transcription of downstream targets. One of these targets, SUFU encoding the human ortholog of Drosophila suppressor of used, is a negative regulator of SHHsignalling that interacts with all three GLI proteins and mediates their nuclear export in the absence of SHH. So germline mutations in both SUFU and PTCH1 are associated with LOH of the remaining allele in the tumor and activation of the SHH pathway. This activation results in unregulated expression of pathways involved in proliferation and inhibition of apoptosis.[10,15]

In all of our three cases, clinically atleasttwo major criteria andone minor criteria were present. Histopathologically all the lesions were associated with supporting fibrocellular connective tissue wall lined by parakeratinised corrugated stratified squamous epithelium with palisaded polarized basal cells suggesting it to be an OKC (Fig 1.8,2.6,3.1). Hence, the clinical and histopathological features confirmed the diagnosis of Gorlin Goltz syndrome for all the three cases.

The literature reports wide variation in the incidence of OKCs in NBCCS patients ranging from 62% [16] to 100%.[17,18,19] This association has been found to be 100% in our case series. Usually, multiple keratocysts are found in NBCCS ranging from 1 to 30 in number, average being 5.[1] In our case series, all patients had at least two maxillary or mandibular cysts (Fig 2). Molecular genetic testing reported that approximately 90% of individuals with *PTCH1*-related NBCCS develop multiple jaw keratocyst. They can occur as early as age five years, but the peak occurrence is in the teenage years. Jaw cysts rarely occur after age 30 years. Jaw cysts have not been reported in individuals with *SUFU*-related NBCCS.[20] A rare association between ameloblastoma and NBCCS have been reported in six patients.[21]

Palmar-plantar pits usually occur in 35–87% of the syndromic patients and in 80% develop by the age of 15 years and in 85% after the age of 20 years. They are caused by partial or complete absence of dense keratin in sharply defined areas.[22] Pits were found in two of our cases (Fig 1.4, 3.2) . They are usually more commonly found on palms than on soles. They more pronounced when the hands and feet are soaked in warm water for up to ten minutes. Pits may appear as white "punched-out" or pink "pin-prick" lesions.[22]

Ectopic calcifications of falx cerebri have been found in as low as 21.2% to as high as 92% patients in different reports worldwide whereas in our series, they were found in two of our cases(Fig 2.3, 3.2). Bifid, fused, wide, partially missing, or underdeveloped ribs are usually found in 16–58% of NBCCS patients.[16,17]Bifid ribs were found in two of our patients (Fig 1.5,2.2). Scoliosis of spine rarely being reported in Indian literature was also found in one of our patients (Fig 1.6). Also mandibular prognathism is also found in one of our cases.

A recent review of 182 genotyped individuals with NBCCS by Evans et al found that individuals with *PTCH1*-related NBCCS were more likely to be diagnosed earlier (p=0.02), have jaw cysts and have bifid ribs (p=0.003) or any skeletal abnormality (p=0.003), than individuals with no identified pathogenic variant.[23]
Ovarian fibromas occur in approximately 20% of affected females with NBCCS.[24,25] One of our patients show ovarian fibroma unilaterally. Ovarian fibromas occur with both *SUFU* and *PTCH1*-related NBCCS and may be more common in individuals with *SUFU*-related NBCCS. They can become large and calcified; however, malignant transformation is uncommon.

Other features like pigmented nevi (fig 1.2) and strabismus (Fig1.1) were found in one of our cases. Fused eye brows also found in two of our cases. (Fig 3.1, 2.1)

BCCs can occur in early childhood, but in general do not present until the late teens or early adulthood. They occur more frequently with age, although 10% of individuals with NBCCS never develop a BCC. Individuals with type 1 skin (white skin that burns, but never tans, e.g., Celtic skin)and individuals with excessive ultraviolet light exposure seem especially prone to developing large numbers of BCCs.[26] Clinically some affected individuals appear to be particularly radiosensitive, with new BCCs appearing in the field of radiation following radiotherapy. BCCs are more common in individuals with PTCH mutation. None of our patients being reported had BCC.

Children presenting with medulloblastoma need to be assessed for NBCCS, particularly if they are younger than age three years. Based on published data, nearly all medulloblastoma cases have desmoplastic histology and with extensive nodularity.[27,28]Approximately 5% of all individuals with NBCCS develop the childhood brain malignancy medulloblastoma. *SUFU*-related NBCCS is associated with a high risk for medulloblastoma of up to 33% in contrast to the 2% risk in *PTCH1*-related Gorlin syndrome.[20]InterestinglySeventeen individuals with medulloblastoma and germline*SUFU* pathogenic variants reported by Guerrini-Rousseau et al[29] did not meet NBCCS diagnostic criteria. SUFU molecular testing should be considered first in families with medulloblastoma and without jaw keratocyst.[20] Medulloblastoma (MED) has not been found in any Indian patient in contrast to other studies conducted worldwide. It is also not found in any of our cases.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with nevoid basal cell carcinoma syndrome, the following evaluations are recommended if they have not already been completed:

- Baseline measurement of head circumference, preferably plotted on a chart that accounts for height. Evidence of rapid increase in centiles should prompt further investigation to exclude hydrocephalus.
- Physical examination for birth defects of clinical significance (e.g., orofacial clefts, polydactyly)
- X-rays to evaluate for rib and vertebral anomalies and falx calcification
- Ophthalmologic evaluation for evidence of strabismus, cataract, orbital cyst, microphthalmia, and pigmentary changes of the retinal epithelium
- Evaluation by a dentist or orthodontist familiar with NBCCS; jaw x-ray (orthopantomogram) in individuals of age eight years or older to evaluate for jaw keratocysts and other anomalies.
- Skin examination by a dermatologist familiar with NBCCS
- Ultrasound examination of the ovaries to evaluate for ovarian fibromas prior to pregnancy
- Echocardiography in the first year of life to evaluate for cardiac fibromas
- Consultation with a clinical geneticist and/or genetic counsellor

Treatment of Manifestations

- Manifestations should be treated by specialists (e.g., oral surgeon, dermatologist, plastic surgeon, paediatrician, clinical geneticist) experienced with the condition.

Surveillance

- Head circumference should be followed throughout childhood and plotted on appropriate growth charts. Rapid enlargement should prompt evaluation for possible hydrocephalus
- Orthopantomogram is indicated every 12-18 months in individuals older than age eight years to identify jaw keratocysts.[14]
- Awareness of the risk of medulloblastoma in the first years of life is important and may justify developmental assessment and physical examination every six months. No evidence for the efficacy of regular neuroimaging exists; frequent computed tomography scans should be avoided because of risks associated with radiation sensitivity. A consensus meeting has suggested annual head MRI scans until age eight years in affected children [Bree et al 2011], but this would require general anaesthesia for many

children and is probably not now justified in *PTCH1*-related NBCCS with only a 2% risk.[14] However, it may well be justified in infants with *SUFU* pathogenic variants[20]; this has been supported by a consensus statement recommendation to "consider brain MRI every four months through age three years, then brain MRI every six months until the age five years.[14]

- A baseline heart ultrasound examination in infants has been advocated by Foulkes et al. [14]
- Ovarian ultrasound in women at age 18 has been advocated by Foulkes et al[14].
- Skin should be examined at least annually; some physicians recommend skin examination by a professional every three to four months.
- A new treatment strategy based on the understanding and inhibition of the Hedgehog pathway can provide for specific drug treatment of disease in future to suppress tumor growth.

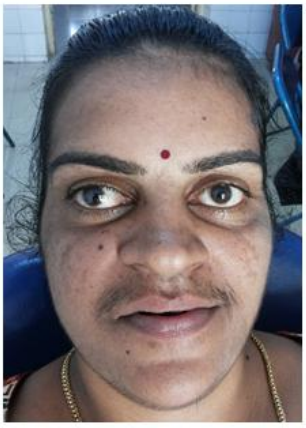
Agents/Circumstances to Avoid

- Use of radiotherapy can lead to the development of thousands of BCCs in the radiation field[30] and therefore should be avoided if there are alternative treatments, especially in childhood. If the treating team believes that no other treatment modality is possible, radiotherapy should be used through as few skin ports as possible.
- Diagnostic x-rays should be used sparingly.
- Individuals with NBCCS should be advised to avoid direct sun exposure as much as possible. Excessive sun exposure increases the likelihood of developing BCCs

IV. Figures

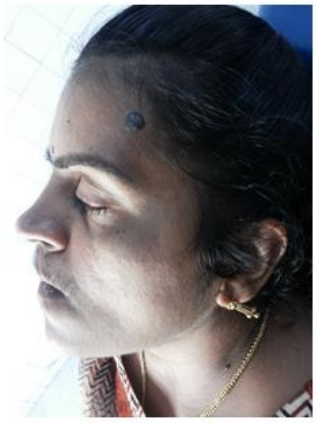
Case 1

Fig 1.1



Patient showing strabismus.

Fig 1.2



Pigmented nevi and prognathic mandible

Fig 1.3

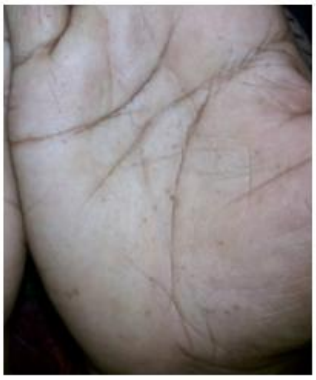
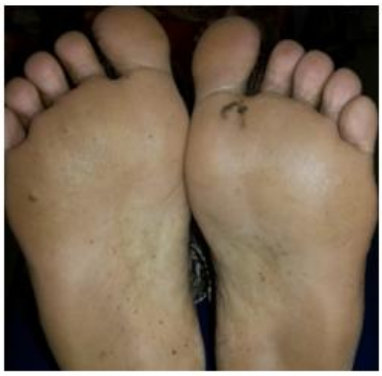
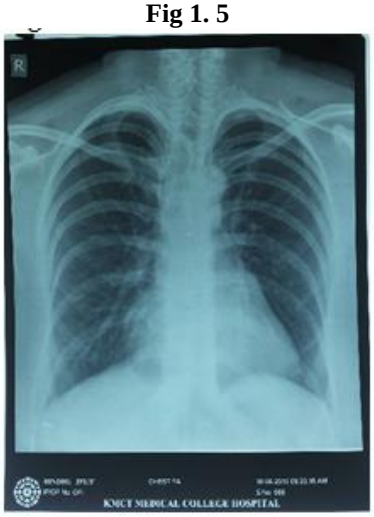


Fig 1.4



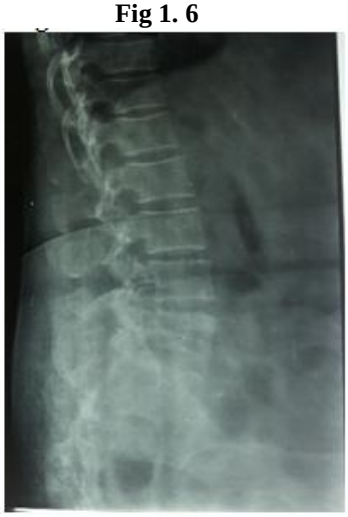
Palmar and Plantar pits

Fig 1. 5



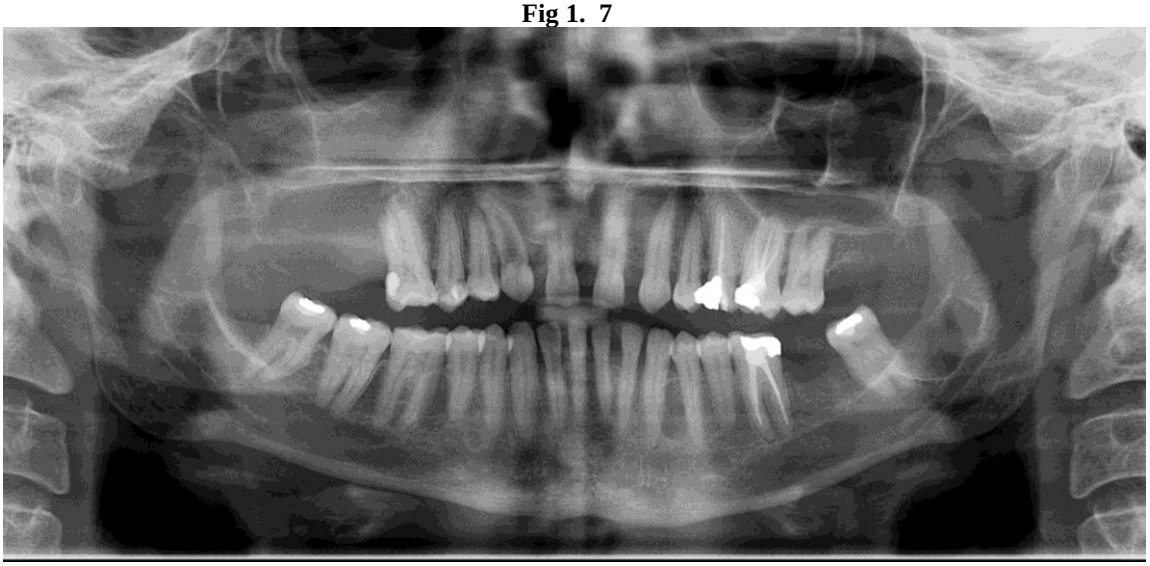
Chest xray showing bifid rib

Fig 1. 6



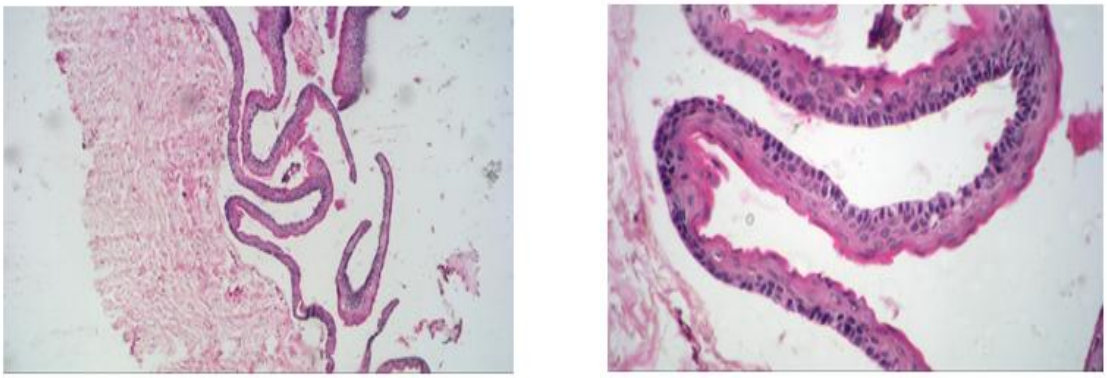
Lumbo sacral AP view shows scoliosis.

Fig 1. 7



OPG showing multiple radiolucency

Fig 1. 8



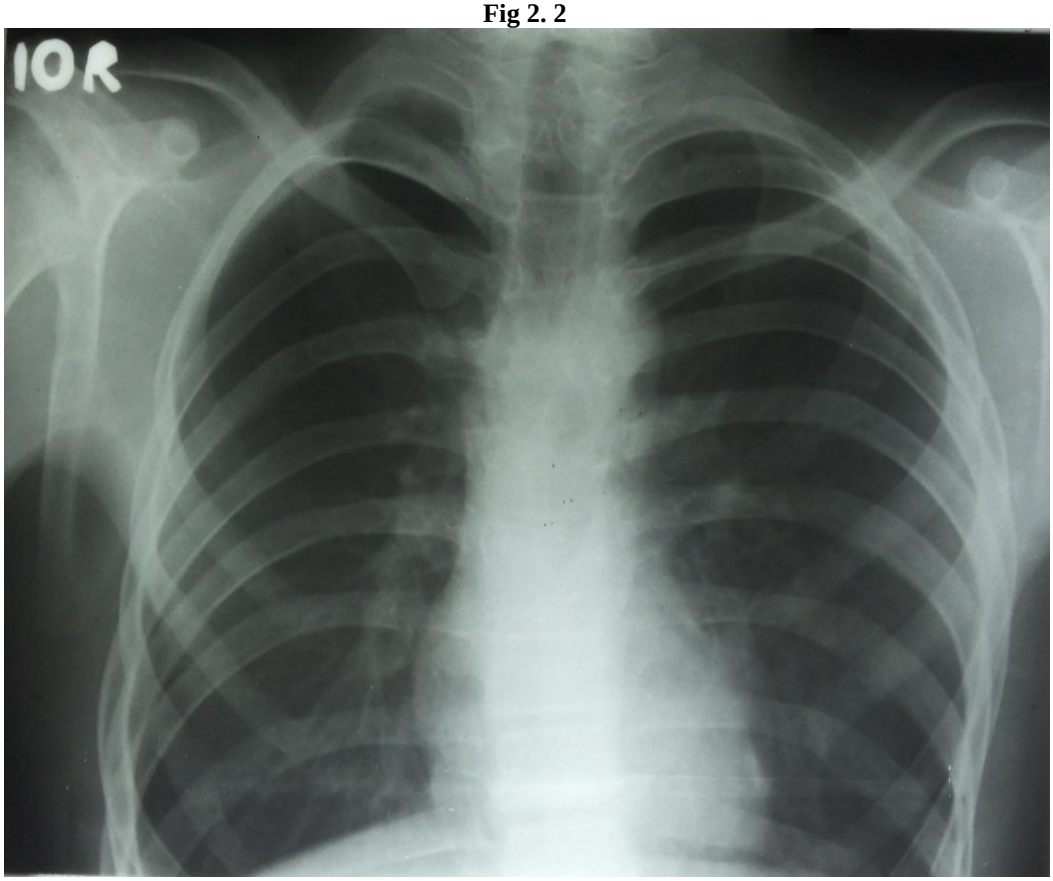
Histopathological examination depicting features of parakeratinized odontogenic keratocyst.

Case 2

Fig 2.1

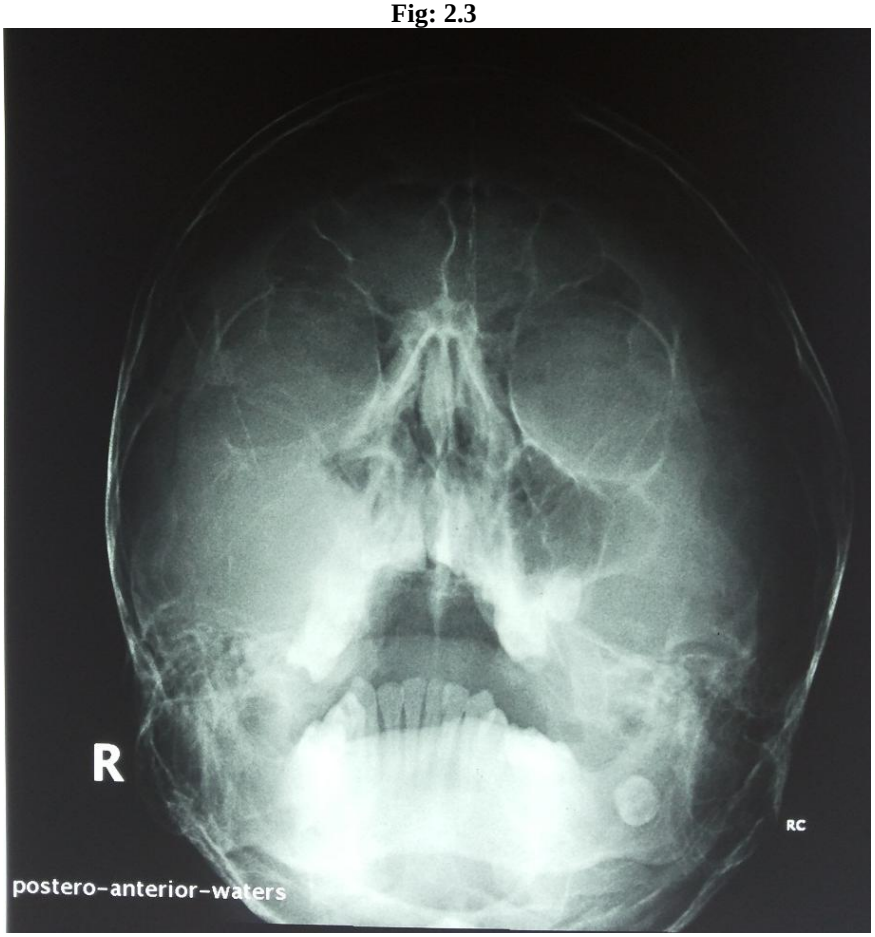
Patient showing fused eye brows and hypertelorism

Fig 2. 2



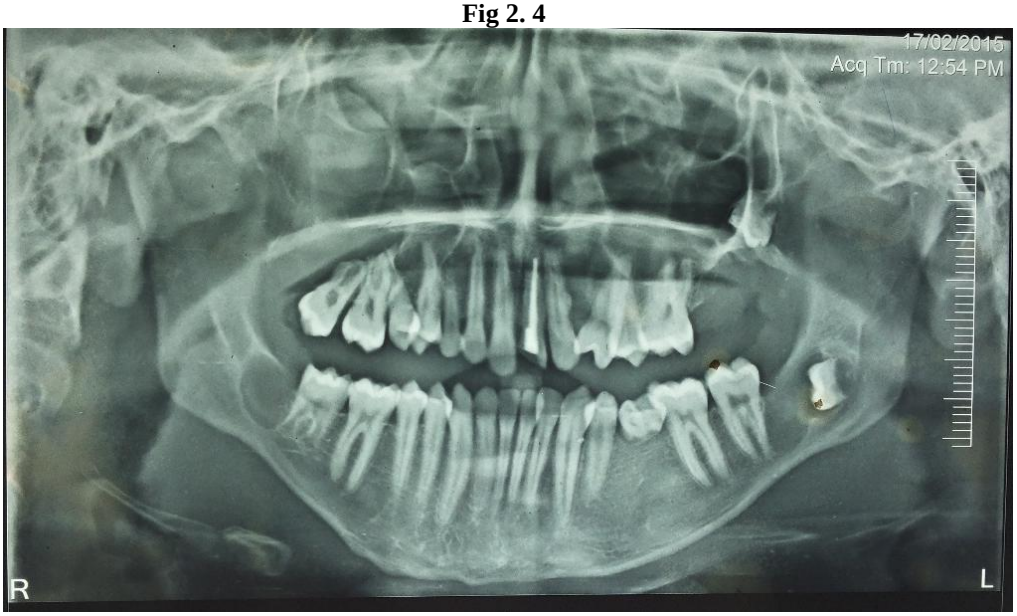
Chest X- ray showing fused anterior end of right fifth and sixth ribs.

Fig: 2.3



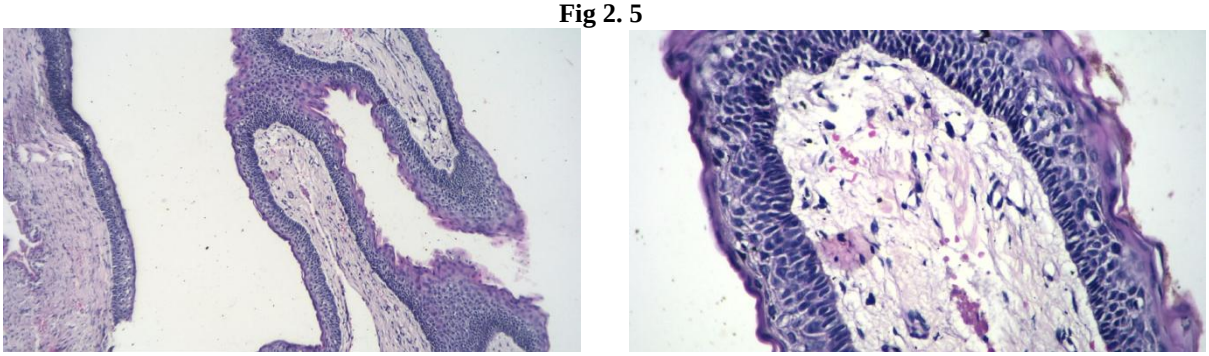
Postero- Anterior -Waters view showing falx and tentorial calcification.

Fig 2. 4



OPG showing multiple radiolucency

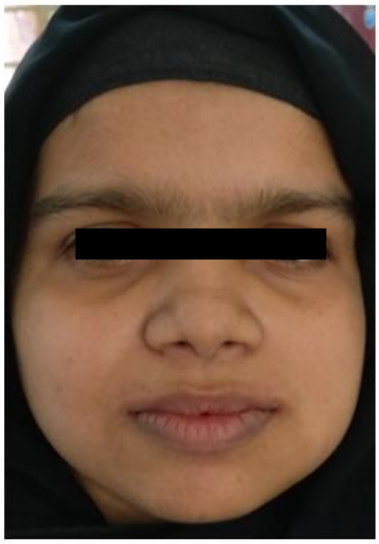
Fig 2. 5



Histopathological examination depicting features of parakeratinized odontogenic keratocyst.

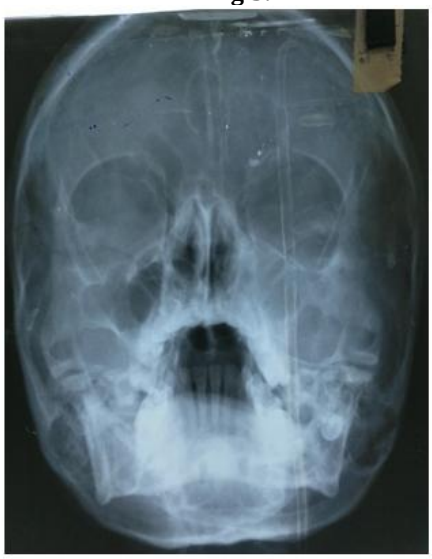
Case 3

Fig 3.1



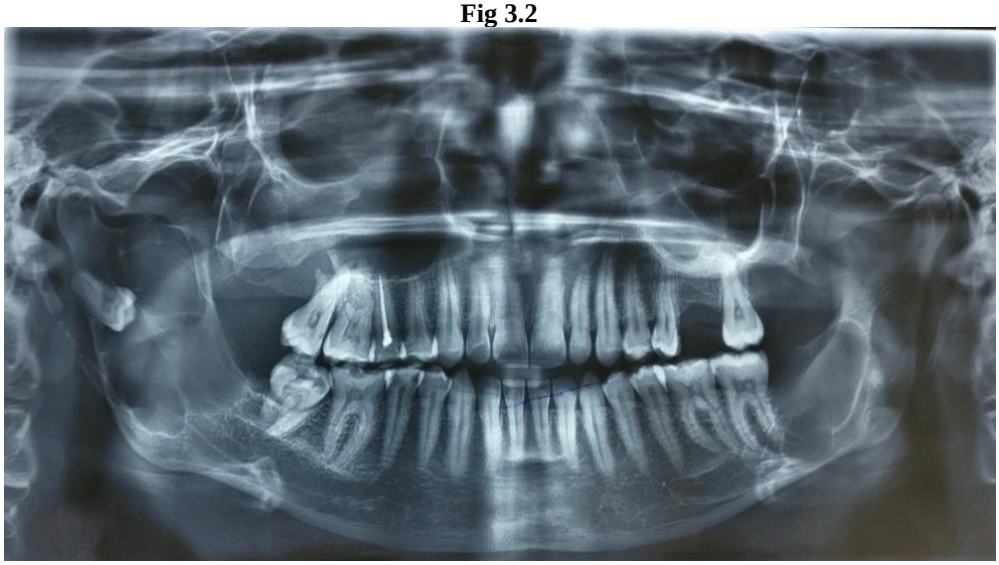
Patient showing fused eye brows.

Fig 3.2



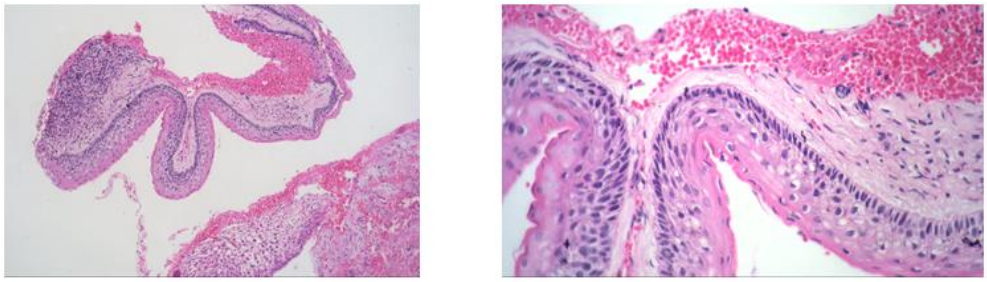
PA view of skull showing falx calcification

Fig 3.2



OPG showing multiple radiolucency

Fig 3. 1



Histopathological examination depicting features of parakeratinized odontogenic keratocyst.

V. Conclusion

Early diagnosis of this syndrome is important for counselling of patients to prevent harmful exposure to UV and ionizing radiations that increase the risk of developing BCC. Regular follow-ups by multispecialists can be offered to prevent substantial morbidity because of complications. Thus, early diagnosis of patients can be used in a preventive multidisciplinary approach to provide a better prognosis. On comparison of our cases of NBCCS

variation in manifestations within the same population can be found probably due to genetic or environmental factors. Further, research on mutation of different genes related to syndrome can provide for gene replacement therapy which can be a boon for these patients.

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