

## Familial case of Gorlin-Goltz syndrome associated with craniosynostosis

Ravi Prakash Sasankoti  
Mohan <sup>1\*</sup>  
Akanksha Gupta <sup>1</sup>  
Nagaraju Kamarthi <sup>1</sup>  
Sangeeta Malik <sup>1</sup>

### Abstract:

Gorlin-Goltz Syndrome is inherited as an autosomal dominant disorder and occurs due to mutations in the PTCH1 (Patched 1) gene. It is characterized by multiple keratocystic odontogenic tumors, multiple basal cell carcinomas, skeletal, ophthalmic, neurological abnormalities and facial dysmorphism. Craniosynostosis is the premature fusion of calvarial bones leading to an abnormal head shape. In addition to all the classical features, presence of craniosynostosis in one of our cases was an interesting finding which has never been reported previously in Gorlin-Goltz syndrome. Giant congenital melanocytic nevus was also present making the case more unique.

**Keywords:** Basal Cell Nevus Syndrome; Odontogenic Tumors; Nevus, Pigmented; Cranial Sutures.

<sup>1</sup> Subharti Dental College .

**Correspondence to:**

Ravi Prakash Sasankoti Mohan.  
Subharti Dental College  
Swami Vivekanand Subharti University  
Subhartipuram, NH-58, Delhi-Haridwar Bypass  
Road, Meerut-250005.  
E-mail: sasan\_ravi@rediffmail.com

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## INTRODUCTION

Gorlin-Goltz syndrome or nevoid basal cell carcinoma syndrome (NBCCS) was first recognized in 1894 by Jarisch and White. Genetic studies have suggested that markers such as PTCH1, PTCH2, and SUFU are responsible for this syndrome and is transmitted in an autosomal dominant manner with high penetrance and variable expressivity<sup>1</sup>.

Different clinical features were delineated by Dr. Robert Gorlin and Dr. Robert Goltz in 1960 in their study on “multiple naevoid basal cell epithelioma, jaw cysts and bifid rib syndrome”<sup>2</sup>. Evans et al. gave a criteria in 1993<sup>3</sup> to establish the diagnosis of Gorlin-Goltz syndrome and was modified by Kimonis et al. in 2004<sup>4,5</sup>. The presence of two major and one minor or one major and three minor criteria are necessary to establish diagnosis (Table 1). Craniosynostosis is the premature fusion of calvarial bones leading to an abnormal head shape. Although craniosynostosis has been reported in more than 180 different syndromes<sup>6</sup> yet our case report is the first one to report its association with Gorlin-Goltz syndrome making it unique. Giant congenital melanocytic nevus (GCMN) is also reported for the first time in this syndrome.

## CASE REPORT

A five year old male patient came to our department with the chief complain of cavities in all his teeth. His medical history and previous records unveiled that he went through a surgery for scaphocephaly when he was one year old. Strip craniectomy was done at the level of frontoparietal region with bifrontal release and reconstruction. Extraoral examination revealed increased occipitofrontal circumference of the skull,

frontal bossing, hypertelorism and broad nasal bridge (Figure 1A). There were multiple flesh coloured papules resembling nevi lateral to the nose on right and left side (Figure 1A) and multiple melanotic nevi were present in the neck region (Figure 1B).

Multiple palmer pits (Figure 1C) and syndactyly of second and third toe on both right and left sides were evident (Figure 1D). Hyperpigmented macule resembling giant congenital melanocytic nevus (GCMN) with hypertrichosis was present involving thumb of left hand (Figure 1E). Intraoral examination did not reveal any abnormality other than multiple carious teeth. His clinical features suggested the possibility of Gorlin-Goltz syndrome and thus, he was subjected to radiographic investigation.

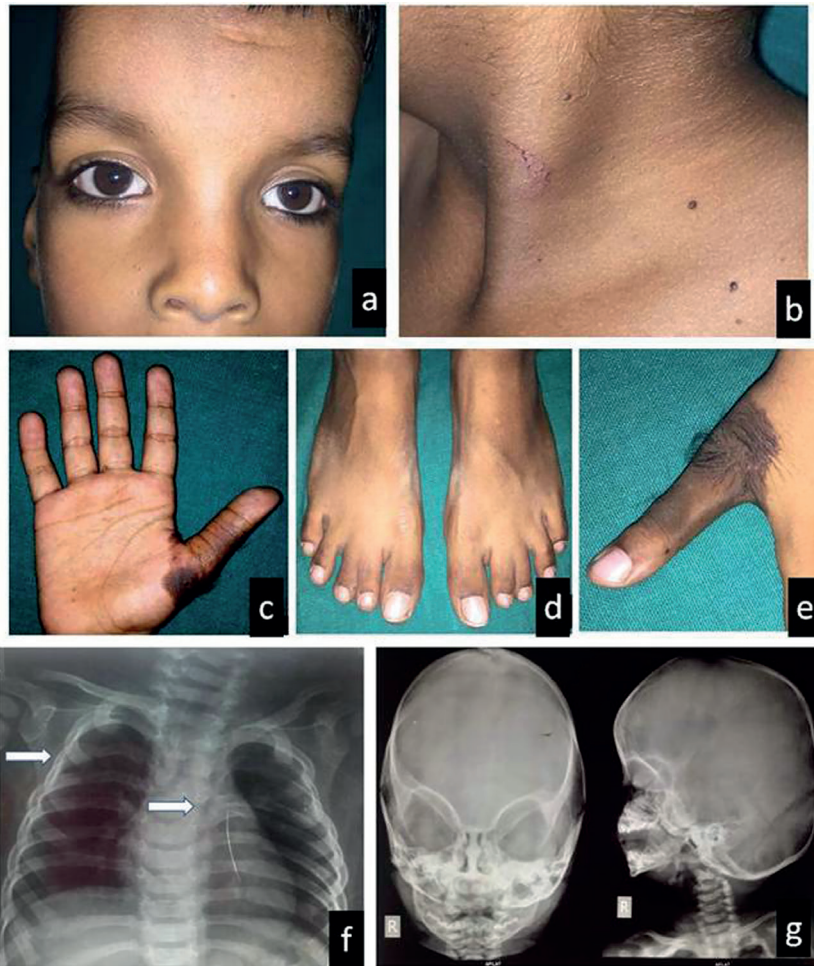
His previous and present chest X-rays revealed the presence of bifid ribs, slight Sprengel deformity and scoliosis (Figure 1F). There was no sign of any cyst or tumor in the orthopantomograph (OPG). Skull radiographs which were taken when he was six months old unveiled premature ossification of the sutures (Figure 1G). His clinical and radiographic features pointed towards the diagnosis of Gorlin-Goltz syndrome with craniosynostosis and GCMN.

Patient’s mother who had accompanied him was also examined for the presence of the signs and symptoms of Gorlin-Goltz syndrome.

His mother was thirty-two year old. On general and extraoral examination we found that she had multiple melanotic and flesh coloured papules on the face (Figure 2A) which according to her developed when she was thirteen or fourteen years old and a melanotic papule resembling a nevi was present on the dorsal aspect of the hand. She had frontal bossing, broad nasal bridge, hypertelorism and strabismus (Figure 2A).

**Table 1.** Enumerating major and minor criteria for the diagnosis of Gorlin-Goltz syndrome.

Major Criteria	Minor Criteria
Multiple basal cell carcinomas or one occurring under the age of 20 years.	Macrocephaly (adjusted for height)
Histologically proven OKCs of the jaws.	Congenital malformation: Cleft lip or cleft palate, frontal bossing, coarse face moderate or severe hypertelorism
Palmar or plantar pits (three or more)	Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
Bilamellar calcifications of the falx cerebri	Radiological abnormalities: Bulging of sella turcica, vertebral anomalies such as hemi vertebrae, fusion or elongation of vertebral bodies, modeling defects of the hands and feet, or flame-shaped hands or feet
Bifid, fused, or markedly splayed ribs	Ovarian fibroma
First degree relative with nevoid basal cell carcinoma syndrome	Medulloblastoma



**Figure 1.** A. Showing frontal bossing, hypertelorism, broad nasal bridge and multiple flesh coloured papules resembling nevi lateral to the nose on right and left side; B. showing multiple melanotic nevi in the neck region; C. showing multiple palmer pits and GCMN involving the thumb; D. showing syndactyly of second and third toe on both right and left sides; E. showing hyperpigmented macule resembling GCMN with hypertrichosis involving the thumb; F. Chest X-ray done at the age of one year revealed the presence of bifid ribs, slight Sprengel deformity and scoliosis; G. Skull radiographs taken when patient's son was six months old revealing premature ossification of the sutures.

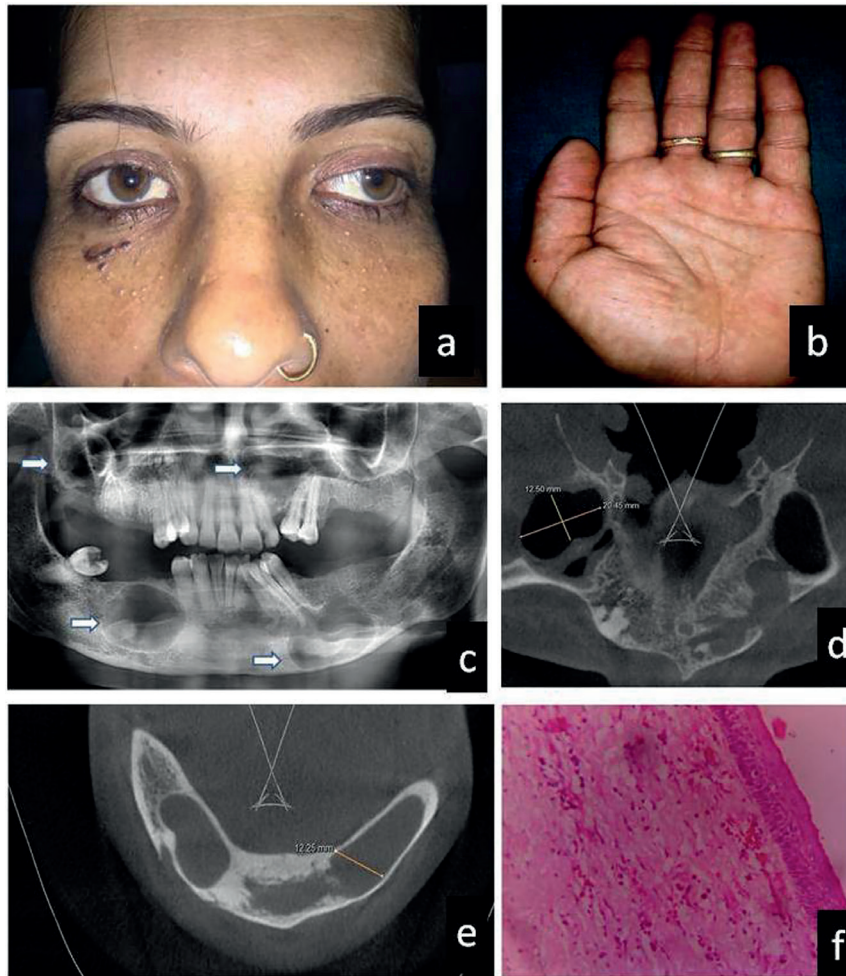
Multiple palmer pits were evident (Figure 2B). Intraoral examination revealed partially edentulous maxillary and mandibular arch. There were multiple missing teeth with malocclusion. She was subjected to radiographic investigation. OPG revealed well-defined radiolucent lesions in all the four quadrants (Figure 2C). Cone beam computed tomography (CBCT) was done for more details of the lesions (Figure 2D, 2E).

Radiographic diagnosis of multiple odontogenic keratocyst was made which was confirmed by histopathology (Figure 2F). There were no other skeletal deformities. All the clinical and radiographic features pointed towards the diagnosis of Gorlin-Goltz syndrome.

Patient was kept on follow-up because of the possibility of development of cysts in the jaws and skin changes such as growth, ulceration or haemorrhage of basal cell nevi. Patient was advised to get the neurological examination done in every six months and his mother was referred to the department of oral and maxillofacial surgery for surgical management of the cysts of the jaws.

## DISCUSSION

Each offspring of an individual with Gorlin-Goltz syndrome has a 50% chance of inheriting the PTCH1 or SUFU pathogenic variant<sup>1</sup>. Our patient inherited this syndrome from his mother. Patient fulfilled four major



**Figure 2.** A. Showing multiple melanotic and flesh coloured papules, frontal bossing, broad nasal bridge, hypertelorism and strabismus in the patient; B. Showing evidence of multiple palmer pits; C. OPG revealed that first lesion was present in right maxillary third molar region. Second lesion extended from left maxillary lateral incisor to second premolar region displacing the root of 22 mesially, roots of 24 and 25 distally and had approached the maxillary sinus. Third radiolucency was present in left mandibular premolar and molar region displacing the crowns of 33 and 34 mesially and roots distally. Fourth radiolucency was present in right mandibular premolar and molar region; D. Axial section of CBCT showing radiolucency in the right maxillary third molar region and left maxillary region extending from left maxillary lateral incisor to second premolar region; E. showing radiolucency in left and right mandibular premolar and molar region; F. The H & E section showing cystic capsule lined by parakeratinized stratified squamous epithelium of 6-10 cell layer thickness showing corrugated surface and basal cell layer composed of cuboidal to tall columnar cells showing palisading pattern of hyperchromatic nuclei suggestive of odontogenic keratocyst.

criteria i.e. presence of multiple basal cell carcinomas, palmer pits, bifid ribs and first degree relative with NBCC, with five minor criteria i.e. macrocephaly, frontal bossing, hypertelorism, Sprengel deformity and syndactyly of digits. He also presented with GCMN with hairy patch on the thumb. Its incidence is estimated in less than 1:20,000 newborns<sup>7</sup>.

It is estimated that for patients with GCMN, the lifetime risk for developing melanoma is between 5 and

10%. Although one of the complications of GCMN is neurocutaneous melanosis, a rare syndrome and several alterations on skin and other organs have been described in association with GCMN<sup>7</sup> yet it has not been reported to be associated with any other syndrome in the literature. Patient not only fulfilled the criteria necessary for the diagnosis of this syndrome but also presented with craniosynostosis which has never been reported before in NBCC to the best of our knowledge.



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Craniosynostosis can be associated with many complications affecting sensory, respiratory and neurological function so it is important to recognize and treat it. The three major objectives of elective surgical management of craniosynostosis include correction of skull deformity, prevention of its progression and reduction of the future risk of raised intracranial pressure (ICP). Patient went through the surgery for craniosynostosis at the age of one year. Patients with craniosynostosis should be followed-up throughout childhood to monitor for symptoms of raised ICP, such as headaches or change in behaviour<sup>8</sup>.

There was presence of three major criteria i.e. presence of multiple basal cell carcinomas on face, histologically proven odontogenic keratocysts and multiple palmer pits with two minor criteria, i.e. hypertelorism and frontal bossing in patient's mother.

In conclusion it is important to make an early diagnosis of Gorlin-Goltz syndrome as it can lead to serious complications. Relatives of NBCCS patients should always be examined for the signs and symptoms of this syndrome. Craniosynostosis which can affect sensory, respiratory and neurological function was also present in our patient. This was the first case in which craniosynostosis was found associated with Gorlin-

Goltz syndrome. Presence of GCMN also added to the uniqueness. More case reports are required to consider craniosynostosis and GCMN as a consistent finding in this syndrome.

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