



GORLIN-GOLTZ SYNDROME WITH *SITUS INVERSUS*: a rare case report

Síndrome de Gorlin-Goltz com situs inversus: relato de um caso raro

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Abstract

OBJECTIVE: To review the literature and present a case of Gorlin's syndrome with *situs inversus*. **RESULTS AND DISCUSSION:** Together with the major features, a great number of processes considered as minor features have also been described in the Gorlin's syndrome. The latter includes numerous skeletal, dermatology related and neurological anomalies among others. In the present clinical case many criteria allowed a diagnosis of Gorlin's syndrome, but for the first time this unique finding of *situs inversus* is seen with this syndrome. **CONCLUSION:** However, further research is needed to confirm the association between *situs inversus* and Gorlin's syndrome.

Keywords: Gorlin-Goltz syndrome. *Situs inversus*. Odontogenic keratocyst.

Resumo

OBJETIVO: Revisar a literatura e apresentar um caso de síndrome de Gorlin com *situs inversus*. **RESULTADOS E DISCUSSÃO:** Conjuntamente com os aspectos principais, um grande número de processos considerados menores têm sido descritos na síndrome de Gorlin. Entre outras, numerosas anomalias esqueléticas, dermatológicas e neurológicas têm sido relatadas. No presente caso clínico, muitos critérios permitiram o diagnóstico da síndrome de Gorlin, porém, pela primeira vez relata-se a ocorrência deste achado único, o *situs inversus*. **CONCLUSÃO:** Entretanto, pesquisas adicionais são necessárias para confirmar a associação entre *situs inversus* e síndrome de Gorlin.

Palavras-chave: Síndrome de Gorlin-Goltz. *Situs inversus*. Queratocisto odontogênico (OKC).

INTRODUCTION

Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant disorder with a high degree of penetrance and a variable expressivity characterized by several development defects and a predisposition to cancer (1-5). The nevoid basal cell carcinoma syndrome prevalence has been variously estimated from 1 in 57 000 (6) to 1 in 164 000 (7), but there is now general agreement that the prevalence is about 1 per 60 000 (8). NBCCS probably arises in all, ethnic groups but most reports have been of whites. Males and females are equally affected. The clinical features of NBCCS arise in the first, second or third decade (9, 10). This syndrome has received several names throughout the times such as "basal cell nevus syndrome" (11, 12), "nevoid basal cell carcinomas syndrome" (8, 13-18) or the most complex name of "multiple basal epithelioma, jaw cysts and bifid rib syndrome" (19). The nevoid basal cell carcinoma syndrome (NBCCS) was first reported by Jarish in 1894 (20) who described a patient with multiple basal cell carcinomas, scoliosis and learning disability. Howell and Caro (21) were the first to associate the basal cell nevus with other cutaneous disorders and anomalies, while Gorlin and Goltz (1) defined the condition as a **syndrome** comprising the principal triad of multiple basal cell nevi, jaw keratocysts, and skeletal anomalies (21). This triad was later modified by Rayner et al (22), who established that for giving the diagnosis at least cysts had to appear in combination with calcification of the falx cerebri or palmar and plantar pits. A spectrum of other neurological, ophthalmic, endocrine, and genital manifestations (1, 23, 24) are now known to be variably associated with this triad (25, 26). Indeed almost 60% of patients with NBCCS have not known affected family members, 35 to 50% of these representing new mutations (27). The causative gene of NBCCS is on chromosome 9q (22.3-q31) and has no apparent Heterogeneity (4, 28). This defect also occurs in relevant sporadic tumours such as basal cell carcinoma, medulloblastoma and trichoepithelioma (27, 28). The genetic mechanisms that underlie NBCCS have received considerable attention in recent years. The principal causative mutations occur in the human equivalent of the Patched (PTCH) gene, this functioning as a tumour suppressor gene as well as having other roles (6, 29, 30).

Diagnostic guidelines include familial history, oral care, skin examinations, chest, skull, and panoramic radiographs, maxillofacial computerized tomography, brain magnetic resonance imaging, and pelvic ultrasonography in women (31, 32).

The diagnostic criteria for nevoid basal cell carcinoma was put forth by Evans and colleague and modified by Kimonis et al. in 1997. According to them, diagnosis of Gorlin syndrome can be established when two major or one major and two minor criteria as described below are present (33). The following diagnostic criteria for nevoid basal cell carcinoma syndrome (NBCCS) was taken from Evans et al. (34).

Major criteria

- More than two basal cell carcinomas (BCCs), one BCC in patients younger than 30 years of age or more than 10 basal cell naevi;
- Any odontogenic keratocyst (proven by histology) or polyostotic bone cyst;
- Three or more palmar or planter pits;
- Ectopic calcification in patients younger than 20 years of age (lamellar or early falx cerebri calcification) and a positive family history of NBCCS.

Minor criteria

- Congenital skeletal anomaly (e.g. bifid, splayed, fused or missing rib, or bifid, wedged or fused vertebra);
- Occipital-frontal circumference greater than the ninetyseventh percentile, with frontal bossing;
- Cardiac or ovarian fibromas;
- Medulloblastoma;
- Lymphomesenteric cysts;
- Congenital malformation, such as cleft lip/palate, polydactylism or eye anomaly (e.g. cataract, coloboma or microphthalmos).

The following diagnostic criteria for nevoid basal cell carcinoma syndrome (NBCCS) was taken from Kimonis et al. (10).

Major criteria

- More than two basal cell carcinomas (BCCs) or one BCC in patients younger than 20 years of age;
- Odontogenic keratocysts of the jaw (proven by histological analysis);
- Three or more palmar or plantar pits;
- Bilamellar calcification of the falx cerebri;
- Bifid, fused or markedly splayed ribs;
- A first-degree relative with NBCCS.

Minor criteria

- Macrocephaly;
- Congenital malformations (e.g. cleft lip or palate, frontal bossing, coarse facies, and moderate or severe hypertelorism);
- Other skeletal abnormalities (e.g. Sprengel deformity, marked pectus deformity and marked syndactyly of the digits);
- Radiological abnormalities (e.g. bridging of the sella turcica, vertebral anomalies, modelling defects of the hands and feet, or flame-shaped lucencies of the hands and the feet);
- Ovarian fibroma or medulloblastom.

Other diagnostic findings in adults with the Nevoid basal cell carcinoma reported by Gorlin and his colleagues (35) and their incidence of occurrences are:

a) Skeletal anomalies (18, 35)

1. Bifid ribs, splayed/ fused ribs, absent/ rudimentary ribs (60-75%)- may be bilateral and several ribs may be affected;
2. Scoliosis - seen in 30- 40% of the patients;
3. Hemivertebrae;
4. Flame - Shaped lucencies of hand/ feet;
5. Polydactyly;
6. Syndactyly;
7. Shortened 4th metacarpal.

b) Craniofacial anomalies (18, 35)

1. Frontal bossing (25%) - Increased size of calvaria (occipitofrontal circumference 60 cms. or > in adults);
2. Brachycephaly;
3. Macrocephaly (40%);
4. Coarse face (50%);
5. Calcification of the falxes (37-79%);
6. Tentorium cerebelli calcification;
7. Bridged *sella turcica*;
8. Heavy fused eyebrows;
9. Broadened nasal root;
- 10 Low positioning of *occiput*;
11. Congenital blindness due to corneal opacity;
12. Congenital or precocious cataract or glaucoma;
13. Coloboma of iris, choroids or optic nerve;
14. Convergent or divergent strabismus and nystagmus.

c) Neurological anomalies (18, 35)

1. agenesis / dysgenesis of corpus callosum;
2. congenital hydrocephalus;
3. mental retardation;
4. medulloblastoma (3-5%) – developing in the first two years of life. About 20% of them cause death during infancy;
5. meningioma (1% or <);
6. schizoid personality.

d) Oropharyngeal anomalies (2, 7)

Oral abnormalities are of fundamental importance mainly in childhood and adolescence and are important signs for diagnosis. They are:

1. Cleft lip/ palate (4%);
2. High arched palate or prominent ridges (40%);
3. Odontogenic Keratocysts – (75%);
4. Malocclusions;
5. Dental ectopic position;
6. Impacted teeth and / or agenesis.

e) Skin anomalies

1) **Basal cell carcinoma** – These are major dermatological components seen in 50-97% of the people with the syndrome (36). Suspicion for Gorlin's syndrome should be high if basal cell carcinomas are detected in pediatric age range. Basal cell carcinomas are also seen at puberty or 3rd decade of life (35). After puberty they can become aggressive and locally invasive (18, 35). Tumor may vary from flesh coloured papules to ulcerating plaques. They often appear on sun exposed skin.

2) **Palmar and/or plantar pits** are present in about 65% of the patients. They are asymmetrical, ranging from 2-3mm in diameter & 1-3 mm in depth. These pits usually develop late in the second decade but could be seen in patients as young as 5 years of age. They are caused by partial or complete absence of dense keratin in sharply defined areas. They become more evident when patient's hands or feet are placed in warm water for several minutes. Basal cell carcinomas may arise from these pits (35). Multiple palmar pits became evident when we placed our patient's hands in warm water (35-40).

f) Anomalies of the Reproductive system (18, 35)

1. uterine and ovarian fibromas (15%);
2. calcified ovarian cysts;
3. supernumerary nipple;
4. hypogonadism and cryptorchidism.

g) Cardiac anomalies (18, 35)

Cardiac fibromas (3%) - The occurrence of findings associated with the syndrome varies from person to person and is important in diagnosis and formulating a treatment plan.

CASE REPORT

A 16-years-old male patient visited the Department of Oral Medicine & Radiology, Government Dental College & Research

Institute, Bangalore, India, with a chief complaint of swelling (Figures 1 and 2) on right lower one-third of face since 1 month. He gave a history of slowly progressing swelling, initially the size of a peanut, which gradually increased to attain the present size.

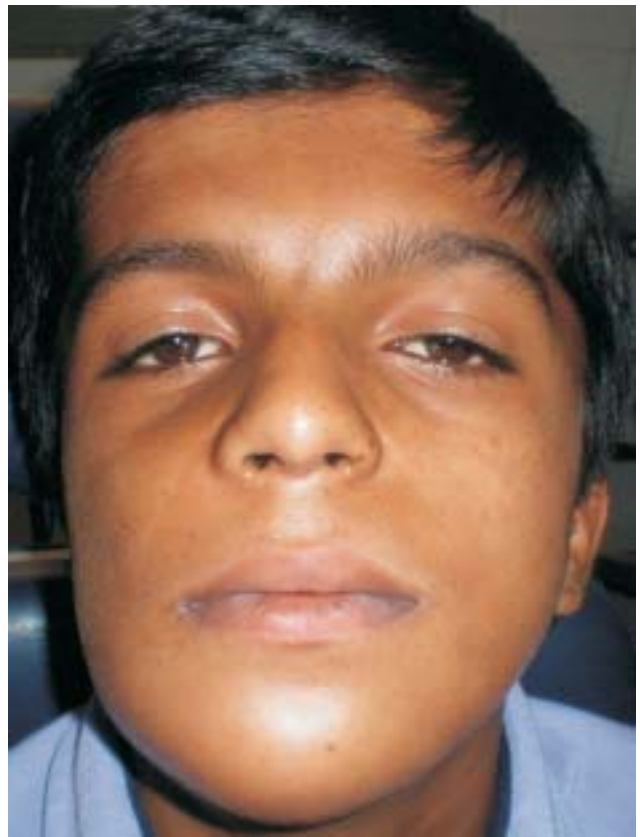


FIGURE 1 - Frontal aspect of the patient



FIGURE 2 - Sub-mental view of the patient

On general physical examination, the patient was moderately built and nourished, presenting with normal gait and satisfactory vital signs. There were multiple palmer pits (Figure 3) measuring 0.2 -0.3mm in diameter and brownish black in color present on the palms of both his hands.



FIGURE 3 - Multiple palmer pits

The dorsum of the patient revealed presence of the Sprengel deformity. The approximately 3 x 7 cm facial swelling was extended superiorly from right corner of mouth to 1 cm inferiorly beyond the lower border of the mandible, medially from left para-symphysis region to distally half of the body of the mandible (Figures 1 and 2). The swelling was hard in consistency and tender on palpation. Intraoral examination revealed missing right and left mandibular canine, while in the maxilla the right canine was missing and the left maxillary canine was in erupting phase, with rotated left maxillary premolars. Intraoral swelling was present in relation to 42 and 44, extending from mesial aspect of 42 to distal aspect of 44, with obliteration of right lower buccal vestibule. The swelling was hard in consistency and tender on palpation. There was a pus exudation from the gingival sulcus of 42 and 44 during palpation (Figures 4 and 5).



FIGURE 4 - Intraoral swelling, mandible, region 42 and 44



FIGURE 5 - Maxillary aspect

Based on the history and clinical findings, a provisional diagnosis of infected dentigerous cyst in relation to 43 was given and a differential diagnosis of odontogenic keratocysts considered. The patient was subjected to the following radiographic examination:

Mandibular occlusal radiograph (Figure 6) revealed a well defined radiolucent lesion with a sclerotic border extending from periapical region of lower anteriors encroaching the lower border of the mandible in relation to 33 and 43.



FIGURE 6 - Radiolucent region with sclerotic borders

Orthopantomograph revealed multiple unilocular well defined radiolucencies with sclerotic border in maxilla and mandible (Figure 7).



FIGURE 7 - Extensive radiolucent area in the mental region. A canine is inside the lesion

The presence of multiple cysts in the jaws, in association with unerupted teeth, raised a suspicion of Gorlin-Goltz's syndrome. For that patient was further evaluated. A postero-anterior view of the skull revealed an impacted 28, with a well defined cystic lesion at the level of the left infra-orbital margin and an impacted 38 with cystic lesion in the left ramus.

Lateral skull view revealed bridging of the *sella turcica* (Figure 8).



FIGURE 8 - Profile image presenting with bridging of the *sella turcica*

Postero-anterior (Figure 9) chest radiograph revealed a bifid 3rd rib in the right side and an unusual finding of dextrocardia.



FIGURE 9 - Bifid third rib in the right side. Dextrocardia

Computed tomographic images showed multiple cystic lesions in maxilla (Figure 10) and mandible (Figure 11).



FIGURE 10 - CT, axial cut, multiple cystic lesions in maxilla

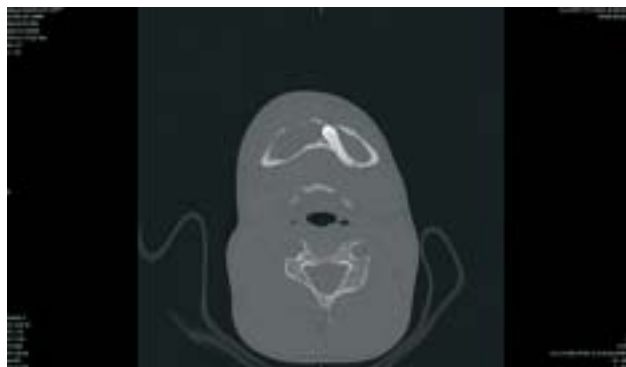


FIGURE 11 - CT, axial cut, extensive cystic lesion with a canine inside

CT images of the brain showed areas of hyper-densities suggestive of *falx cerebri* (Figure 12) and *tentorial cerebelli* (Figure 13) calcification.

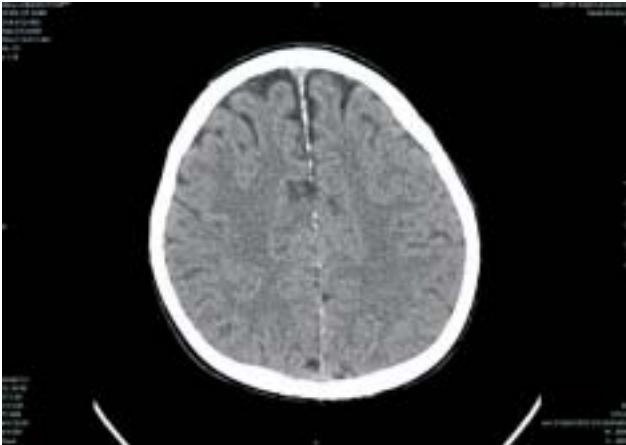


FIGURE 12 - Image suggestive of *falx cerebri*



FIGURE 13 - Suggestion of *Tentorial cerebelli* calcification

CT images of spine revealed bifid spine in relation to C₆ C₇ T₁ (Figure 14).

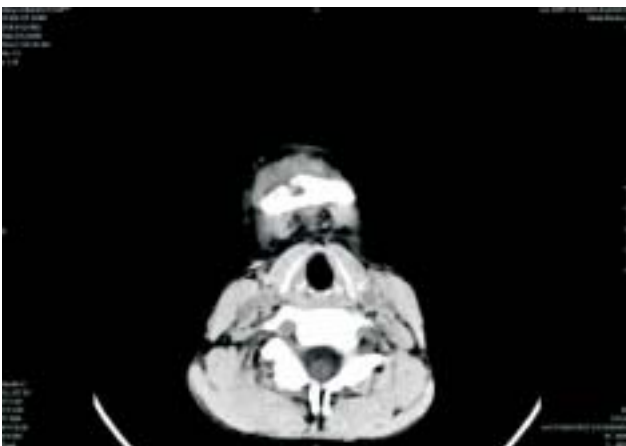


FIGURE 14 - Bifid spine, cervical and thoracic

Ultrasonographic images showed presence of spleen in right hypochondrium (Figure 15) and liver in, the left hypochondrium (Figure 16) with transposition on great vessels (Figure 17).



FIGURE 15 - Spleen in right hypochondrium



FIGURE 16 - Left hypocondrium



FIGURE 17 - Image of transposition on great vessels

A tissue specimen was taken for microscopic examination, which revealed a stratified squamous parakeratinised epithelium with palisading pattern of basal cells (Figure 18), suggestive of odontogenic keratocyst.

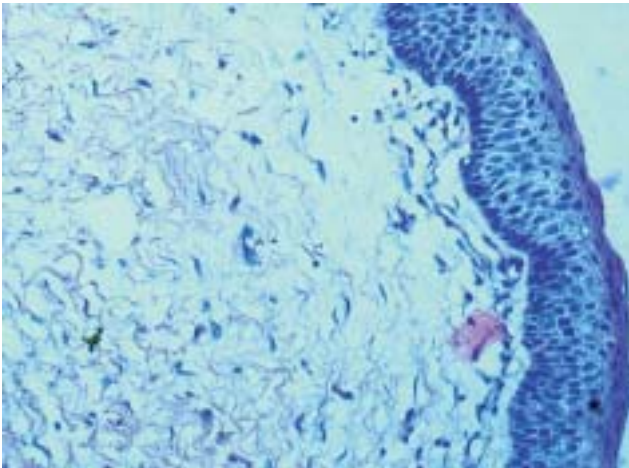


FIGURE 18 - Stratified squamous parakeratinised epithelium presenting a palisading pattern of basal cells (HE 40 X)

Since the patient fulfilled the three major criteria for multiple odontogenic keratocysts, palmer pits and *falx cerebri* and *tentorial cerebelli* calcification, with three minor criteria of bifid rib, *spina bifida* and sprengele deformity, the final diagnosis was given as Gorlin Goltz syndrome with *situs inversus*.

CONCLUSION

In the present clinical case many criteria allowed a diagnosis of Gorlin syndrome, but for the first time this unique finding of *situs inversus* is seen with this syndrome. However, this does not represent that there is an association between Gorlin's syndrome and *situs inversus*. Further research is needed to confirm this finding.

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