CASE REPORT

Gorlin-Goltz syndrome: Case report and literature review

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ABSTRACT

Gorlin-Goltz syndrome (GGS) is an infrequent multisystemic disease with an autosomal dominant trait, with complete penetrance and variable expressivity, though sporadic cases have been described. This article includes a case report and an extensive review of the GGS with regard to its history, incidence, etiology, features, investigations, diagnostic criteria, keratocystic odontogenic tumor and treatment modalities.

Key words: Gorlin-Goltz syndrome, keratocystic odontogenic tumor, odontogenic keratocyst

INTRODUCTION

Gorlin-Goltz syndrome (GGS) is an infrequent multisystemic disease with an autosomal dominant trait, with complete penetrance and variable expressivity, though sporadic cases have been described.[1-8] Its clinical features arise in the first, second or third decade of life, affecting multiple organ systems which include skeletal, eye, skin, reproductive and neural system, although all the features are rarely observed in a single patient.[9]

This syndrome has been termed with several names such as, basal cell nevus syndrome, GGS, nevoid basal cell carcinoma syndrome (NBCCS), multiple basal cell carcinoma (BCC) syndrome, multiple basalioma syndrome, jaw cyst basal cell tumor skeletal anomalies syndrome, jaw cyst bifid rib basal cell nevus syndrome, nevoid basalioma, odontogenic keratocysts skeletal anomalies syndrome and fifth phacomatosis.[10,11]

This article describes a case of GGS in a 15-year-old male patient. It also provides literature review of GGS.

CASE REPORT

A male patient aged 15 years reported to the Department of Oral and Maxillofacial Pathology with a chief complaint of swelling in the right side of the upper and lower jaws. It had started as a small swelling that increased in size over 10 months. On examination, the swellings were found to be firm and slightly tender.

An orthopantomograph [Figure 1] revealed multiple radiolucent lesions on both sides of the maxilla and the right side of the mandible. Impacted teeth were present on both sides of the maxilla and on the right side of the mandible that were displaced by the enlarging cysts [Figures 1 and 2]. He also had hypertelorism and synophyrs [Figure 3]. Computed tomography (CT) scan of the brain did not reveal calcification of the falx cerebri [Figures 4 and 5]. Skin lesions like basal cell nevus or keratosis were absent. However, a chest radiograph showed the presence of a bifid rib on the right side [Figure 6]. The presence of multiple cysts in the jaws and extra oral features raised suspicion of GGS. Routine biochemical and hematological evaluations were carried out and the patient was hospitalized. Under all aseptic precautions, general anesthesia was administered. Local anesthesia with adrenaline was injected and flaps were raised intraorally in all quadrants one after the other. A surgical window was needed only in the third quadrant to reach the cyst. No vital structures were seen near the lesions. A slow speed straight hand piece (E-type Nosecone; NSK) with tungsten carbide burs (tapering fissure and flame shaped) and a surgical curette

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were used with saline irrigation for enucleating the cysts. Curettage was done using a curette and a round bur. The remnants of the cysts were removed using chemical cautery with Carnoy's solution (2.5%) for 3 min without chloroform followed by irrigation with saline. The cysts were enucleated from all four quadrants followed by extraction of impacted teeth 17, 18, 28, 38 and 48. The tissues removed were put in separate bottles containing formalin and the corresponding quadrant number was noted. As bone regeneration in children is faster, bone grafts were not used. The enucleated tissues were sent for histopathological evaluation. All three lesions were sectioned and studied using hematoxylin and eosin stains. The sections showed a cystic lining of corrugated parakeratinized stratified squamous epithelium consisting of 6–10 layers of uniform thickness. The basal layer showed palisading nuclei and tombstone appearance [Figure 7]. Epithelial connective tissue separation was seen [Figure 8]. The underlying

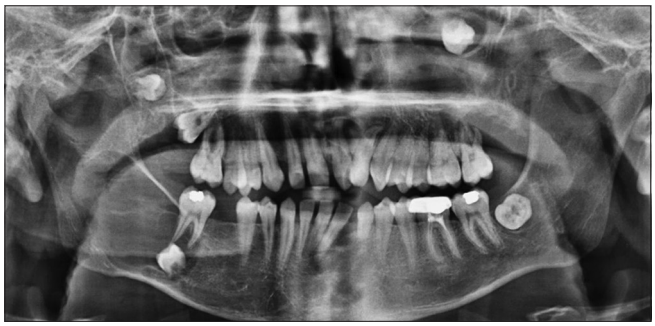

Figure 1: Orthopantomograph revealing ectopic teeth present on both sides of the maxilla and on the right side of the mandible, displaced by cysts

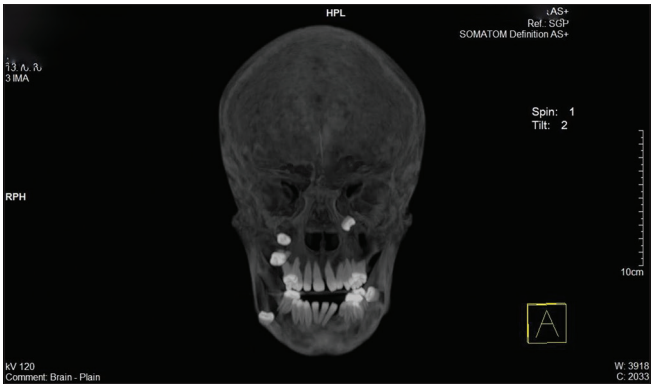

Figure 2: Computerized tomography scan revealing ectopic teeth present on both sides of the maxilla and on the right side of the mandible, displaced by cysts

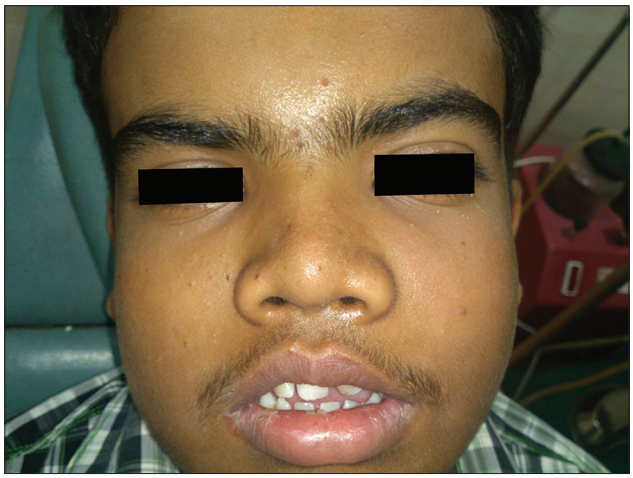

Figure 3: Extra-oral clinical image shows hypertelorism and synophyrs

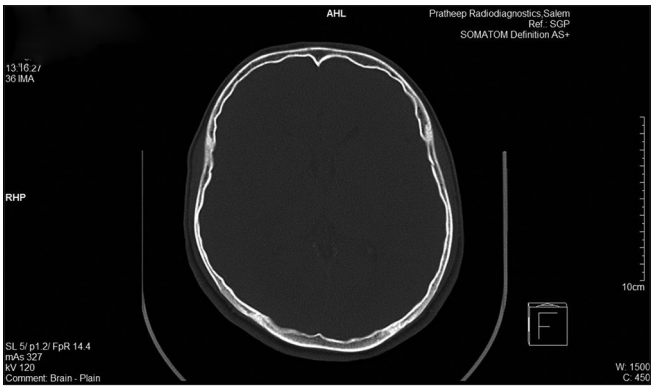

Figure 4: Computed tomography scan of the skull showing absence of calcification of the falx cerebri

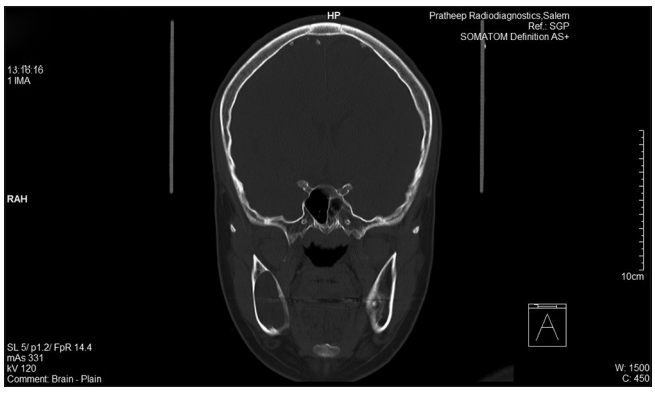

Figure 5: Computed tomography scan of the skull showing an oval radiolucent lesion in the right mandibular ramus

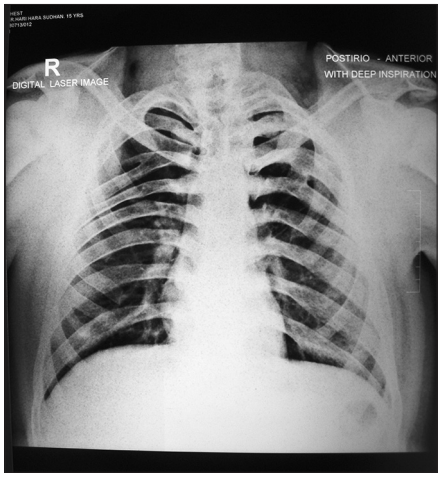

Figure 6: Chest radiograph showing the presence of a bifid rib on the right side

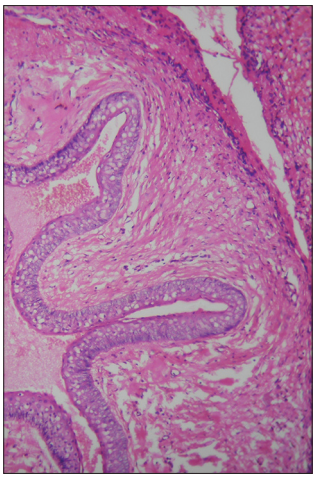

Figure 7: Photomicrograph showing a cystic lumen lined by corrugated, parakeratinised stratified squamous epithelium of 6-8 cell thickness. The epithelium is thrown into folds, with basal palisading nuclei and tomb-stone appearance. The underlying connective tissue shows blood vessels and inflammatory cells (H&E stain, x100)

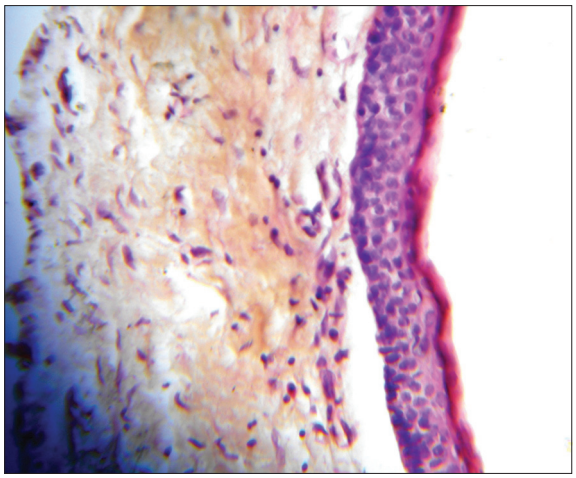

Figure 8: Photomicrograph showing cystic lumen lined by parakeratinised stratified squamous epithelium of 6 to 8 layer thickness showing epithelial connective tissue separation. The underlying connective tissue contains blood vessels and inflammatory cells (H&E stain, x400)

connective tissue showed odontogenic epithelial islands, blood vessels and inflammatory cells. All three lesions were diagnosed as odontogenic keratocysts. The presence of two major signs (bifid rib and multiple odontogenic keratocysts) and one minor sign (hypertelorism) confirmed that our patient was a case of GGS. The patient is being followed up at 3-month intervals and no recurrence has been noted.

DISCUSSION

The presence of two major signs (bifid rib and multiple odontogenic keratocysts) and one minor sign (hypertelorism) helped us make a diagnosis of GGS in the patient. A literature review of GGS is as follows:

History

The first report of the syndrome was made in 1894 by Jarisch and White in a patient with multiple BCCs, scoliosis and learning disability.[12,13] In 1939, Straith described a case with multiple basocellular carcinomas and cysts.[14] Binkley and Johnson in 1951 and Howell and Caro in 1959 observed a relationship between basal cell epitheliomas and developmental malformations.[15,16] Gross in 1953 presented a case with additional signs such as synostosis of the first left rib and bilateral bifurcation of the 6th ribs.[17]

In 1960, Robert James Gorlin and William Goltz discovered the classical triad (multiple basocellular epitheliomas, keratocysts in the jaws and bifid ribs) that established the diagnosis of this syndrome.[18] Later this triad was modified by Rayner *et al*., who established that cysts had to appear isimultaneously, either with calcifications of the falx cerebri, or with palmar and plantar pits, in order to arrive at a diagnosis.[19] The association of palmar and plantar pits with the syndrome was first described by Bettley and Ward.[20,21]

Incidence

In the general population, the incidence of GGS is estimated at 1 in 50,000–150,000.[22,23] Farndon *et al*. reported a minimum prevalence of 1 in 57,000 people.[24] However, a prevalence from 1/57,000 to 1/256,000, with a male to female ratio of 1:1 has also been described.[2,25,26] Shanley *et al*. in Australia and Muzio *et al*. in Italy estimated the prevalence as 1/64,000 and 256,000, respectively.[27,28] Evans *et al*. reported a prevalence rate of 1/560,000 in the United Kingdom.[29] The syndrome occurs with equal frequency in both sexes, but most reports have been in whites.[9,30] It has both a sporadic and a familial incidence.[24] Although detected in very young children, they are commonly expressed between the ages of 17 years and 35 years.[31] New mutations are seen in 35% to 50% of cases.[32] Nine variants of mutations have been reported in patients with GGS.[33]

Etiology

Mutations of the human patched gene (PTCH1 gene), which is part of the hedgehog – signaling pathway, is the molecular basis of the syndrome.[10,34,35] This gene was first isolated in 1996 as the human homologue of the Drosophila segment polarity PTCH1 gene, mapped to the long arm of chromosome 9q22.3–q31 with no apparent heterogeneity, in Australia and in the USA.[2,28,30,32,36-40] This gene plays a role in tumor suppression, embryonic structuring and cellular cycle. Mutations in this gene results in loss of control of several genes known to play a role in organogenesis, carcinogenesis and odontogenesis thus resulting in the development of GGS.[10,41-43] Pruvost-Balland *et al*. carried out a clinical and genetic study in 22 patients with GGS. PTCH 1 mutations were identified in 13 patients, out of which, six were familial cases, three were sporadic and in four patients, it was not possible to conclude if they were familial.[38]

Features

Clinical manifestations of the syndrome can be grouped into the following nine categories.[9,18]

- Cutaneous anomalies - Basal cell nevus/carcinoma (50–97%), other benign dermal cysts and tumors (21%), palmar/plantar pitting (90%), palmar and plantar keratosis and dermal calcinosis
- Dental anomalies - Multiple odontogenic keratocysts (75–100%), maxillary hypoplasia, mandibular prognathism, high arched palate or prominent palatine ridges (40%), cleft lip/palate (4%), impacted teeth and/or agenesis (3%), ectopic teeth and malocclusion
- Craniofacial anomalies - Calcification of falx (37–79%), tentorium cerebellum calcification (3%), bridged sella turcica (21%), macrocephaly (40%), brachycephaly, frontal bossing (25%), parietal and temporal bossing and coarse face (50%)
- Skeletal anomalies - Polydactyly (3%), syndactyly, scoliosis (15%), hemivertebrae or other vertebral defects, flame-shaped lucencies of hand/feet, spina bifida (3%), osteoporosis (3%), cervical/bifurcated/fused/splayed/absent/rudimentary ribs (26%), brachymetacarpalism and shortened fourth metacarpal (12%)
- Cardiac - Cardiac fibroma (3%)
- Ophthalmic anomalies - Hypertelorism (40%), dystopia canthorum, congenital blindness (15%), internal strabismus (15%), congenital amaurosis, exotropia, glaucoma (3%), ptosis and coloboma (3%)
- Neurological anomalies - Mental retardation (6%), dural calcification, bridging of sella, agenesis of corpus callosum, congenital hydrocephalus (3%), medulloblastoma (3–5%), agenesis/disgenesis of corpus callosum, meningioma (1% or less) and schizoid personality
- Sexual anomalies - Hypogonadism (3%), uterine and ovarian fibromas (15%), calcified ovarian cysts (3%) and supernumerary nipple
- Laboratory findings - Increased serum uric acid level (3%), increased levels of alkaline phosphate and cyclic adenosine monophosphate.

Investigations

Muzio had suggested the following investigation protocol.[44]

- Family history - Past medical and dental history
- Clinical examinations - Oral, skin, central nervous system, head circumference, interpupillar distance, eyes, genitourinary system, cardiovascular system, respiratory system and skeletal system
- Genetic testing
- Radiographs - Chest, anteroposterior and lateral skull, panoramic radiograph, cervical and thoracic spine (anteroposterior and lateral), hands (for pseudocysts), pelvic (female), ovarian ultrasound (female) for ovarian fibroma and echocardiogram (children) for cardiac fibroma.

However, confirmation is by ultrasound and DNA analysis.[34]

Diagnosis

Diagnosis of NBCCS may be difficult because of the variability of expressivity and because of different ages of onset for the different traits of this disorder.[31] Early diagnosis of GGS is crucial for the affected children and their families, considering the risk of developing malignancies such as medulloblastoma and aggressive skin cancers.[45] A negative family history could hamper the early clinical recognition of patients with GGS. However, it may be diagnosed during early childhood if the clinician is well aware of clinical signs of the disease.[7] The diagnostic criteria for GGS was put forth by Evans *et al*. in 1991 [Table 1] and modified by Kimonis *et al*. in 1997 [Table 2].[26,29] According to Kimonis, diagnosis can be established only when two major, or one major and two minor criteria are present.[26]

Keratocystic odontogenic tumor and its treatment

Odontogenic keratocysts linked with GGS are now termed as "keratocystic odontogenic tumor" (KCOT).[46] These are a constant feature present in about 75% of cases with GGS.[36] KCOT are often the first sign of GGS in 78% of cases.[28,47] They develop during the first decade of life, usually after 7 years and peak during the second and third decade.[4,19,32,47,48] Their occurrence is approximately a decade earlier than that of odontogenic keratocysts not associated with the syndrome.[28,49-51] The male to female ratio is 1:0.62 for conventional odontogenic keratocysts and 1:1 for KCOT.[52-54]

Table 1: Diagnostic criteria by Evans *et al.* in 1991

Major criteria
More than 2 BCCs, one BCC in patients younger than 30 years of age or more than 10 basal cell nevi
Any odontogenic keratocyst (proven by histology) or polyostotic bone cyst
Three or more palmar or plantar pits
Ectopic calcification in patients younger than 20 years of age (lamellar or early falx cerebri calcification)
A positive family history of NBCC
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 ninety-seventh percentile, with frontal bossing
Cardiac or ovarian fibromas
Medulloblastoma
Lymphomesenteric cysts
Congenital malformations such as cleft lip/palate, polydactylism or eye anomaly (e.g., cataract, coloboma or microphthalmos)

BCCs: Basal cell carcinomas, NBCC: Nevoid basal cell carcinoma

Table 2: Diagnostic criteria by Kimonis *et al.* in 1997

Major criteria
More than 2 BCCs or one BCC in patients younger than 20 years of age
Odontogenic keratocysts of the jaw (proven by histologic 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 faces 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, modeling defects of the hands and feet, or flame-shaped lucencies of the hands and the feet)
Ovarian fibroma or medulloblastoma

BCCs: Basal cell carcinomas, NBCCs: Nevoid basal cell carcinomas

KCOT have a greater predilection for the mandible (69%) than the maxilla (31%).[28,53-55] In the mandible, 43% of KCOT occur in the molar-ramus region, followed by 18% in the incisor-canine region and 7% in the premolar region. In the maxilla, 14% occur in the incisor-canine region, followed by 12% in the molar tuberosity region and 3% in the premolar region.[54]

Their high mitotic index and increase in proliferating cell nuclear antigen suggests the greater proliferative potential of the epithelial lining leading to cyst expansion.[48,56] Heparanase is an endo-d-glucuronidase enzyme that specifically cleaves heparan sulfate and its increased level in tumors promotes invasion, angiogenesis and metastasis. Katase *et al*. suggested that heparanase expression may be correlated with the neoplastic properties of KCOT.[57]

In young patients, the cysts may be associated with unerupted teeth and cause tooth displacement and root resorption. They are asymptomatic unless secondarily infected and rarely cause pathological fractures. Ameloblastoma and squamous cell carcinoma have risen from these cysts.[49] On the orthopantomograph, KCOT may show a unilocular or multilocular pattern and the cystic spaces may have smooth or scalloped border.[44,49] Multiple odontogenic keratocysts may be confirmatory of the syndrome.[32] Histologically, in comparison to conventional odontogenic keratocysts, syndromic KCOT show more number of satellite cysts, solid islands of epithelial proliferation, intramural epithelial remnants, odontogenic rests within the capsule, increased parakeratinization and mitotic figures in the epithelium.[53,58-60] Moreover, syndromic KCOT have shorter epithelial height and smaller nuclei when compared with solitary odontogenic keratocysts.[59] Immunohistochemical analysis has shown that cytokeratins CK17 and CK19 are overexpressed in odontogneic keratocysts.[61]

CT has been employed in estimating the size of the cysts.[11,49] There are two methods of treating odontogenic keratocysts: Conservative or aggressive. In the conservative method, simple enucleation with or without curettage and marsupialization are suggested. Aggressive methods include peripheral ostectomy, chemical curettage with Carnoy's solution and resection.[3,9,50,62-64] Application of Carnoy's solution into the cyst cavity for 3 min after enucleation results in a lower rate of recurrence (0–2.5%) without any damage to the inferior alveolar nerve.[65,66] Moreover, the use of Carnoy's solution following cyst enucleation (applied over areas where the cyst was attached to the mucosa) and cryosurgery (because liquid nitrogen devitalizes bone, while leaving the inorganic framework untouched) is advised to destroy epithelial remnants and dental lamina within the osseous margin and thus, prevent recurrences.[67,68] Cryosurgery using liquid nitrogen is indicated in the large complex mandibular lesions if there is a risk of damage to vital structures with conventional treatment methods.[68]

Consideration is given to *en-bloc* resection of odontogenic keratocysts in the following situations: (1) When cysts recur despite previous enucleation with an adjunctive procedure. (2) When cysts recur despite previous marsupializationandenucleation with an adjunctive procedure. (3) In cases of multilocular (multilobular) aggressive intraosseous cysts. (4) In cases of multiple nonsyndromic and syndromic cysts. (5) Cysts exhibiting aggressive clinical behavior that should require resection as the initial surgical treatment.[69] In children, conservative management is considered, because an aggressive operation can affect tooth eruption and development of the involved jaw.[70]

Although benign, the recurrence rate after excision of KCOT is high, ranging from 12% to 62.5% and multiple recurrences do occur.[13,24,26,71-73] Recurrence rates of 82% and 61% for KCOT and solitary odontogenic keratocysts, respectively, has also been reported.[59] Due to the recurrence of odontogenic keratocysts, jaw deformities may result from multiple surgeries.[35] An annual dental panoramic radiograph is usually suggested between the ages of 8 and 40 years to aid in monitoring the recurrence or development of new KCOT.[24,74] A recurring cyst can be a new cyst that originates from epithelial residue or a microcyst left behind in the overlying mucosa.[47,75] It is believed that the aggressive behavior and high rate of recurrence of KCOT are due to a higher rate of proliferation of the epithelial lining.[48]

CONCLUSION

The presence of two major signs (bifid rib and multiple odontogenic keratocysts) and one minor sign (hypertelorism) confirmed that our patient was a case of GGS. It is important to make an early diagnosis of GGS, as the case presents malignant predisposition and hence can be managed appropriately. Health specialists like pediatricians, dentists, maxillofacial

surgeons, dermatologists, etc., must have good knowledge of the features of GGS so that the patient can be treated early and further monitored.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Casaroto AR, Loures DC, Moreschi E, Veltrini VC, Trento CL, Gottardo VD, *et al.* Early diagnosis of Gorlin-Goltz syndrome: Case report. Head Face Med 2011;7:2.
2. Yordanova I, Gospodinov D, Kirov V, Pavlova V, Radoslavova G. A familial case of gorlin-goltz syndrome. J IMAB 2007;13:59-63.
3. Stoelinga PJ, Peters JH, van de Staak WJ, Cohen MM Jr. Some new findings in the basal-cell nevus syndrome. Oral Surg Oral Med Oral Pathol 1973;36:686-92.
4. Totten JR. The multiple nevoid basal cell carcinoma syndrome. Report of its occurrence in four generations of a family. Cancer 1980;46:1456-62.
5. Gu XM, Zhao HS, Sun LS, Li TJ. PTCH mutations in sporadic and Gorlin-syndrome-related odontogenic keratocysts. J Dent Res 2006;85:859-63.
6. R Yang X, Pfeiffer RM, Goldstein AM. Influence of glutathione-S-transferase (GSTM1, GSTP1, GSTT1) and cytochrome p450 (CYP1A1, CYP2D6) polymorphisms on numbers of basal cell carcinomas (BCCs) in families with the naevoid basal cell carcinoma syndrome. J Med Genet 2006;43:e16.
7. Veenstra-Knol HE, Scheewe JH, van der Vlist GJ, van Doorn ME, Ausems MG. Early recognition of basal cell naevus syndrome. Eur J Pediatr 2005;164:126-30.
8. Sabbia T, Bovone S, Camera A, Gambini C, Balbi P. Gorlin-Goltz syndrome with odontogenic keratosis. Report on a patient followed for 10 years. Minerva Stomatol 1994;43:359-63.
9. Manfredi M, Vescovi P, Bonanini M, Porter S. Nevoid basal cell carcinoma syndrome: A review of the literature. Int J Oral Maxillofac Surg 2004;33:117-24.
10. Acocella A, Sacco R, Bertolai R, Sacco N. Genetic and clinicopathologic aspects of Gorlin-Goltz syndrome (NBCCS): Presentation of two case reports and literature review. Minerva Stomatol 2009;58:43-53.
11. Mamatha GP, Reddy S, Rao BB, Mujib A Gorlin syndrome. A case report. Indian J Dent Res 2001;12:248-52.
12. Jarisch W. On Doctrine of skin tumors. Archiv of Dermatology and Syphilis. 1894;28:163-222.
13. White JC. Multiple benign cystic ephiteliomata. J Cutan Dis 1894;12:477-81.
14. Straith FE. Hereditary epidermoid cyst of the jaws. Am J Orthod Oral Surg 1939;25:673-7.
15. Binkley GW, Johnson HH Jr. Epithelioma adenoides cysticum; basal cell nevi, agenesis of the corpus callosum and dental cysts; a clinical and autopsy study. AMA Arch Derm Syphilol 1951;63:73-84.
16. Howell JB, Caro MR. The basal-cell nevus: Its relationship to multiple cutaneous cancers and associated anomalies of development. AMA Arch Derm 1959;79:67-77.
17. Gross PP. Epithelioma adenoides cysticum with follicular cysts of maxilla and mandible. J Oral Surg (Chic) 1953;11:160-5.
18. Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. N Engl J Med 1960;262:908-12.
19. Rayner CR, Towers JF, Wilson JS. What is Gorlin's syndrome? The diagnosis and management of the basal cell naevus syndrome, based on a study of thirty-seven patients. Br J Plast Surg 1977;30:62-7.
20. Bettley FR. Two cases of multiple naevoid basal cell epitheliomata? porokeratosis of Mantoux. Br J Dermatol 1953;65:219-21.
21. Ward WH. Naevoid basal celled carcinoma associated with a dyskeratosis of the palms and soles. A new entity. Aust J Dermatol 1960;5:204-8.
22. Patil K, Mahima VG, Gupta B. Gorlin syndrome: A case report. J Indian Soc Pedod Prev Dent 2005;23:198-203.
23. Deepa MS, Paul R, Balan A. Gorlin-Goltz syndrome. A review. J Indian Assoc Oral Med Radiol 2003;15:203-9.
24. Farndon PA, Del Mastro RG, Evans DG, Kilpatrick MW. Location of gene for Gorlin syndrome. Lancet 1992;339:581-2.
25. Evans DG, Ladusans EJ, Rimmer S, Burnell LD, Thakker N, Farndon PA. Complications of the naevoid basal cell carcinoma syndrome: Results of a population based study. J Med Genet 1993;30:460-4.
26. Kimonis VE, Goldstein AM, Pastakia B, Yang ML, Kase R, DiGiovanna JJ, *et al.* Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet 1997;69:299-308.
27. Shanley S, Ratcliffe J, Hockey A, Haan E, Oley C, Ravine D, *et al.* Nevoid basal cell carcinoma syndrome: Review of 118 affected individuals. Am J Med Genet 1994;50:282-90.
28. Lo Muzio L, Nocini PF, Savoia A, Consolo U, Procaccini M, Zelante L, *et al.* Nevoid basal cell carcinoma syndrome. Clinical findings in 37 Italian affected individuals. Clin Genet 1999;55:34-40.
29. Evans DG, Sims DG, Donnai D. Family implications of neonatal Gorlin's syndrome. Arch Dis Child 1991;66:1162-3.
30. Cohen MM Jr. Nevoid basal cell carcinoma syndrome: Molecular biology and new hypotheses. Int J Oral Maxillofac Surg 1999;28:216-23.
31. Ramaglia L, Morgese F, Pighetti M, Saviano R. Odontogenic keratocyst and uterus bicornis in nevoid basal cell carcinoma syndrome: Case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:217-9.
32. Lo Muzio L, Nocini P, Bucci P, Pannone G, Consolo U, Procaccini M. Early diagnosis of nevoid basal cell carcinoma syndrome. J Am Dent Assoc 1999;130:669-74.
33. Pastorino L, Cusano R, Nasti S, Faravelli F, Forzano F, Baldo C, *et al.* Molecular characterization of Italian nevoid basal cell carcinoma syndrome patients. Hum Mutat 2005;25:322-3.

34. Kalogeropoulou C, Zampakis P, Kazantzi S, Kraniotis P, Mastronikolis NS. Gorlin-Goltz syndrome: Incidental finding on routine CT scan following car accident. Cases J 2009;2:9087.
35. Lench NJ, Telford EA, High AS, Markham AF, Wicking C, Wainwright BJ. Characterisation of human patched germ line mutations in naevoid basal cell carcinoma syndrome. Hum Genet 1997;100:497-502.
36. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. 2nd ed. New Delhi: Elsevier; 2002. p. 598-601.
37. Gorlin RJ. Nevoid basal cell carcinoma (Gorlin) syndrome. Genet Med 2004;6:530-9.
38. Pruvost-Balland C, Gorry P, Boutet N, Magnaldo T, Mamelle G, Margulis A, *et al.* Clinical and genetic study in 22 patients with basal cell nevus syndrome. Ann Dermatol Venereol 2006;133:117-23.
39. Ljubenovi M, Ljubenovi D, Bini I, Jovanovi D, Stanojevi M. Gorlin-Goltz syndrome. Acta Dermatovenerol Alp Pannonica Adriat 2007;16:166-9.
40. Hahn H, Wicking C, Zaphiropoulous PG, Gailani MR, Shanley S, Chidambaram A, *et al.* Mutations of the human homolog of *Drosophila* patched in the nevoid basal cell carcinoma syndrome. Cell 1996;85:841-51.
41. Donatsky O, Hjørting-Hansen E. Recurrence of the odontogenic keratocyst in 13 patients with the nevoid basal cell carcinoma syndrome. A 6-year follow-up. Int J Oral Surg 1980;9:173-9.
42. Dowling PA, Fleming P, Saunders ID, Gorlin RJ, Napier SS. Odontogenic keratocysts in a 5-year-old: Initial manifestations of nevoid basal cell carcinoma syndrome. Pediatr Dent 2000;22:53-5.
43. Soekarman D, Fryns JP, Casaer P, Van Den Berghe H. Increased head circumference and facial cleft as presenting signs of the nevoid basal-cell carcinoma syndrome. Genet Couns 1991;2:157-62.
44. Lo Muzio L. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). Orphanet J Rare Dis 2008;3:32.
45. Kim HM, Lee CH, Kim SK, Sung TJ. Basal cell nevus syndrome (Gorlin Syndrome) confirmed by PTCH mutations and deletions. Korean J Pediatr 2007;50:8.
46. Shear M. The aggressive nature of odontogenic keratocyst. Is it a benign cystic neoplasm? Part 3. Immunocytochemistry of cytokeratin and other epithelial cell markers. Oral Oncol 2002;38:407-15.
47. Yeo JF, Loh FC. Multiple odontogenic keratocysts of the jaws. Case report. Aust Dent J 1989;34:503-6.
48. el Murtadi A, Grehan D, Toner M, McCartan BE. Proliferating cell nuclear antigen staining in syndrome and nonsyndrome odontogenic keratocysts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81:217-20.
49. Gorlin RJ. Nevoid basal cell carcinoma syndrome. Medicine. Vol. 66. Baltimore: Williams and Wilkins Co.; 1977. p. 97-113.
50. Myoung H, Hong SP, Hong SD, Lee JI, Lim CY, Choung PH, *et al.* Odontogenic keratocyst: Review of 256 cases for recurrence and clinicopathologic parameters. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:328-33.
51. Shah J, Thakkar S. Basal cell nevus syndrome – A case report. IAOMR 2001;12:386-90.
52. Tong AR, Fitzpatrick TB. Neoplasms of the skin. In: Holland II, Frei II, Bast RC Jr, Kufe DW, Morton DL, Weichselbaum RR, editors. Cancer Medicine. 3rd ed. Hamilton (ON): BC Decker;1993. p. 1782-3.
53. Woolgar JA, Rippin JW, Browne RM. The odontogenic keratocyst and its occurrence in the nevoid basal cell carcinoma syndrome. Oral Surg Oral Med Oral Pathol 1987;64:727-30.
54. Maroto MR, Porras JL, Saez RS, de los Rios MH, Gonzalez LB. The role of the orthodontist in the diagnosis of Gorlin's syndrome. Am J Orthod Dentofacial Orthop 1999;115:89-98.
55. Yesudian D, Krishnan SG, Jayaraman M, Janaki VR, Yesudian P. Atypical gorlin's syndrome. Indian J Dermatol Venereol Leprol 1995;61:314-6.
56. Woolgar JA, Rippin JW, Browne RM. A comparative study of the clinical and histological features of recurrent and non-recurrent odontogenic keratocysts. J Oral Pathol 1987;16:124-8.
57. Katase N, Nagatsuka H, Tsujigiwa H, Gunduz M, Tamamura R, Pwint HP, *et al.* Analysis of the neoplastic nature and biological potential of sporadic and nevoid basal cell carcinoma syndrome-associated keratocystic odontogenic tumor. J Oral Pathol Med 2007;36:550-4.
58. Lo Muzio L, Staibano S, Pannone G, Bucci P, Nocini PF, Bucci E, *et al.* Expression of cell cycle and apoptosis-related proteins in sporadic odontogenic keratocysts and odontogenic keratocysts associated with the nevoid basal cell carcinoma syndrome. J Dent Res 1999;78:1345-53.
59. Dominguez FV, Keszler A. Comparative study of keratocysts, associated and non-associated with nevoid basal cell carcinoma syndrome. J Oral Pathol 1988;17:39-42.
60. Todd R, August M. Molecular approaches to the diagnosis of sporadic and nevoid basal cell carcinoma syndrome-associated odontogenic keratocysts. Oral Maxillofac Surg Clin North Am 2003;15:447-61.
61. Stoll C, Stollenwerk C, Riediger D, Mittermayer C, Alfer J. Cytokeratin expression patterns for distinction of odontogenic keratocysts from dentigerous and radicular cysts. J Oral Pathol Med 2005;34:558-64.
62. Woolgar JA, Rippin JW, Browne RM. A comparative histological study of odontogenic keratocysts in basal cell naevus syndrome and control patients. J Oral Pathol 1987;16:75-80.
63. Kolokythas A, Fernandes RP, Pazoki A, Ord RA. Odontogenic keratocyst: To decompress or not to decompress? A comparative study of decompression and enucleation versus resection/peripheral ostectomy. J Oral Maxillofac Surg 2007;65:640-4.
64. Kuroyanagi N, Sakuma H, Miyabe S, Machida J, Kaetsu A, Yokoi M, *et al.* Prognostic factors for keratocystic odontogenic tumor (odontogenic keratocyst): Analysis of clinico-pathologic and immunohistochemical findings in cysts treated by enucleation. J Oral Pathol Med 2009;38:386-92.
65. Voorsmit RA, Stoelinga PJ, van Haelst UJ. The management of keratocysts. J Maxillofac Surg 1981;9:228-36.
66. Stoelinga PJ. The treatment of odontogenic keratocysts by excision of the overlying, attached mucosa, enucleation, and treatment of the bony defect with carnoy solution. J Oral Maxillofac Surg 2005;63:1662-6.
67. Schmidt BL. The use of liquid nitrogen cryotherapy in the management of the odontogenic keratocyst. Oral Maxillofac Surg Clin North Am 2003;15:393-405.
68. Schmidt BL, Pogrel MA. The use of enucleation and liquid nitrogen cryotherapy in the management of odontogenic keratocysts. J Oral Maxillofac Surg 2001;59:720-5.
69. Tolstunov L, Treasure T. Surgical treatment algorithm for odontogenic keratocyst: Combined treatment of odontogenic keratocyst and mandibular defect with marsupialization, enucleation, iliac crest bone graft, and dental implants. J Oral Maxillofac Surg 2008;66:1025-36.

70. Hyun HK, Hong SD, Kim JW. Recurrent keratocystic odontogenic tumor in the mandible: A case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:e7-10.
71. Oikarinen VJ. Keratocyst recurrences at intervals of more than 10 years: Case reports. Br J Oral Maxillofac Surg 1990;28:47-9.
72. Blanas N, Freund B, Schwartz M, Furst IM. Systematic review of the treatment and prognosis of the odontogenic keratocyst. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:553-8.
73. Mustaciuolo VW, Brahney CP, Aria AA. Recurrent keratocysts in basal cell nevus syndrome: Review of the literature and report of a case. J Oral Maxillofac Surg 1989;47:870-3.
74. Kopera D, Cerroni L, Fink-Puches R, Kerl H. Different treatment modalities for the management of a patient with the nevoid basal cell carcinoma syndrome. J Am Acad Dermatol 1996;34:937-9.
75. Stoelinga PJ. Excision of the overlying, attached mucosa, in conjunction with cyst enucleation and treatment of the bony defect with carnoy solution. Oral Maxillofac Surg Clin North Am 2003;15:407-14.