Case Report

An enigma of Gorlin–Goltz syndrome: Two cases reported in mother and daughter

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Abstract

Gorlin–Goltz syndrome (GGS) also known as the nevoid basal cell carcinoma syndrome or the nevus–Bifid rib syndrome is an inherited autosomal dominant syndrome. It is caused by genetic alteration produced by a mutation in the "patched" tumor suppressor gene. This rare syndrome is characterized by basal cell carcinoma of skin, multiple odontogenic keratocyst and bifid ribs along with other features such as hypertelorism, sex organ abnormalities, palmar and/or plantar pits and calcification of falx cerebri. Early detection and treatment are essential for patients suffering from this syndrome. Only a few cases of this syndrome with familial background have been reported from India. In this study, we present a rare case of GGS in a mother and her daughter. The purpose of this study is to discuss the role of a dentist in early detection and the need for a multidisciplinary approach for the treatment of this syndrome.

Keywords: Gorlin–Goltz syndrome, nevoid basal cell carcinoma syndrome, odontogenic keratocyst

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INTRODUCTION

The Gorlin–Goltz syndrome (GGS), typically characterized by a classical triad comprising multiple basocellular epitheliomas and keratocysts in the jaws and bifid ribs, was first thoroughly reviewed by Gorlin and Goltz.[1] This triad was later modified by Rayner in 1977 who established that for giving the diagnosis cysts had to appear at least in combination with calcification of the falx cerebri or palmar and plantar pits.[2] Pathogenesis of this syndrome has been attributed to mutation of the PTCH1 gene, which is mapped to chromosome 9q22.3.[3] Six major and more than 100 minor criteria for diagnosis have been described.[3,4] According to Evans *et al.*'s finding, two major or one major and two minor criteria are essential to establish a diagnosis.[5]

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Albeit some cases of the GGS have been reported, GGS with familial history has rarely been reported from India. Here, we present two cases of GGS in a 42-year-old woman and in her 18-year-old daughter diagnosed on the basis of 4 and 5 major and 2 and 3 minor criteria, respectively. From 1977 to present, a total of 53 patients in 39 case reports have been reported from India. According to our best knowledge, this is the first case of GGS in a mother and her daughter to be reported from India.

CASE REPORTS

Case report 1

An 18-year-old girl reported to our department with a chief complaint of swelling in the left side of the face

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[Figure 1a]. Initially, the swelling was small and gradually attained its present size over 1 year time. There was no history of pain, and dental history was irrelevant. Medical history revealed that she had cleft lip, which was repaired during infancy. The patient had no deleterious habits. Extraoral examination showed that the swelling was 6 cm × 5 cm in size, extending anteroposteriorly from the corner of the mouth to the tragus of the ear and supero-inferiorly from the lower border of the mandible to the zygomatic buttress of the affected side. The swelling was soft-to-firm, nontender and nonfluctuant on palpation. Intraoral examination showed mild vestibular swelling on the left side. On local examination, we found a soft-to-hard palpable swelling on the right side of her back adjacent to the midline [Figure 1b] and palmar pits in both hands. Sprengel's deformity was absent [Figure 1c].

Orthopantomogram revealed missing 18 and 28, impacted 38 and 48, rotated 22, a single supernumerary tooth between 22 and 23 and the presence of multiple well defined unilocular radiolucencies with a radiopaque border in the left and right side of the maxilla and mandible [Figure 2a]. A differential diagnosis of odontogenic keratocyst (OKC), ameloblastoma, dentigerous cyst and aneurysmal bone cyst was made.

A dirty creamy white viscous suspension was found in aspiration, which was suggestive of OKC. Hence, we made a provisional diagnosis of OKC.

Axial and coronal computerized tomography (CT) with three-dimensional (3D) reconstruction was done to know the exact location and extent of the lessons [Figure 2b]. Noncontrast CT report said that expansive soft tissue attenuation content was present in the left maxillary antrum with an unerupted tooth and the antral wall (anteroinferior aspect) was eroded with extension into premaxillary soft tissue. Another cystic lesson was present with soft tissue content in the posterior wall of the right maxillary antrum with extension to retro maxillary fat pad. A lytic lesson also noted in both mandibular condyles with soft tissue component.

Incisional biopsy from both mandible and maxilla showed parakeratinized stratified squamous epithelium with no rete ridges, which confirmed the diagnosis of OKC. These findings insinuated toward GGS and we started looking for other features. Chest radiograph (anteroposterior [AP] view) revealed bifid ribs [Figure 2d] and skull radiograph (AP view) revealed calcification of falx cerebri [Figure 2c]. Ultrasound examination of the abdomen concluded that both ovaries were mildly enlarged (RO: 4.0 cm × 2.5 cm, LO: 4.9 cm × 2.0 cm) with multiple subcentrimetric cysts. All these above-mentioned findings together confirmed the case as GGS.

Cyst enucleation followed by curettage of the lesion was chosen as the treatment modality. The maxillary cysts were enucleated along with the antral linings on both sides and 16 was extracted [Figure 3a]. Whitehead's varnish pack was given bilaterally, which was gradually removed after the 4th postoperative day. In case of mandibular lesions,

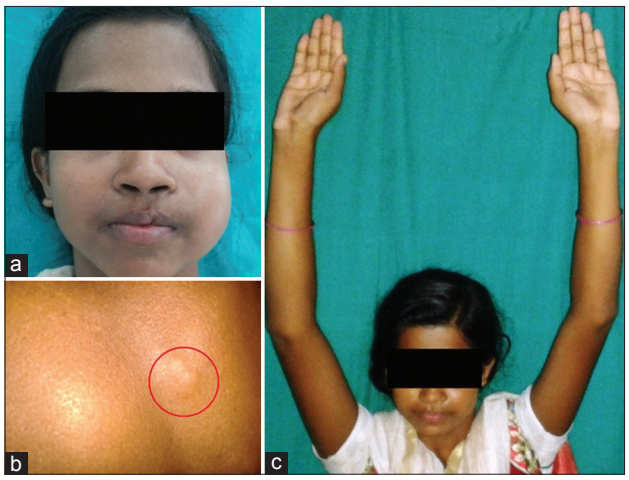

Figure 1: (a) Patient profile showing facial asymmetry and the cleft lip scar. (b) Palpable swelling on the on the back close to midline. (c) Sprengel's deformity not evident

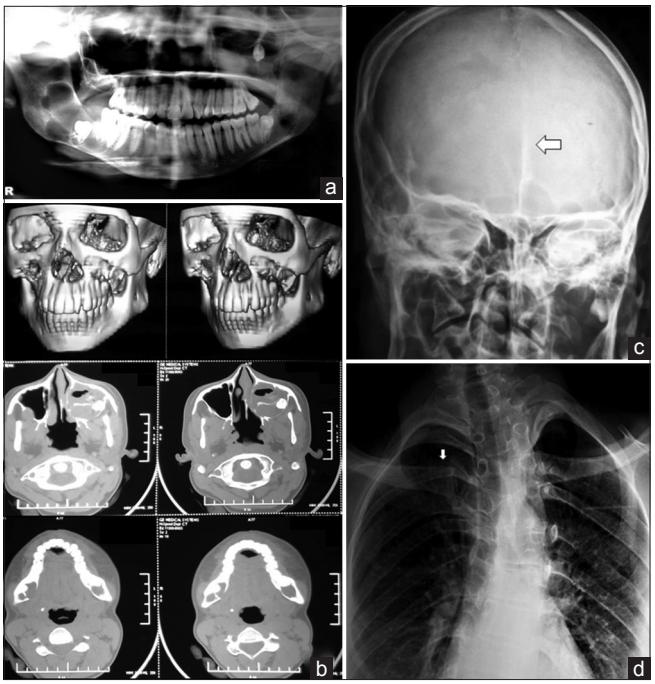

Figure 2: (a) Orthopantomogram showing multiple cystic radiolucencies. (b) Computerized tomography with three-dimensional reconstruction showing extent of the lesions. (c) Radiograph of skull showing calcification of falx cerebri. (d) Chest radiograph showing bifid ribs

enucleation of cysts was done along with the extraction of 37, 38 and 47, 48 teeth. Scraping of the bony cavity was done with surgical bur and curette, which was followed by chemical cauterization by Carnoy's solution [Figure 3b]. Four specimens were sent for histologic evaluation [Figure 3c].

Histologic evaluation consolidated our diagnosis by showing a parakeratinized surface which was typically corrugated and wrinkled. A uniformly thick epithelium (6–10 cells) was seen, which was prominently palisaded. Basal cell layer was polarized, giving the characteristic "picket fence" or "tombstone" appearance [Figure 4a and b]. Postoperative follow-up at every 6 months interval showed a smooth and uneventful recovery [Figure 5].

Considering the familial aspect of the syndrome, the family members of the patient were advised to undergo thorough physical and radiological examination.

Case report 2

After a thorough examination, the mother of the patient of "Case Report 1" started showing signs of GGS. Extraoral examination showed mild swelling, unlike her daughter, on the right side of the face [Figure 6a]. Left submandibular and mental lymph nodes were tender and palpable. Intraoral examination revealed the presence of a single ill-defined, mild-firm, immobile, nontender, mucosa colored swelling in the right buccal mucosa extending from the gingivobuccal sulcus of 45 area till the retromolar region, measuring approximately 2 cm × 3 cm in size with missing 45, 46, 47 and 48 and root stumps of 16, 21, 22, 27, 28, 36, 37 and 38. On local and general examination, a soft palpable swelling on the right side of her back adjacent to the midline [Figure 6b] and palmar pits in both hands was found same as in her daughter. Sprengel's deformity was also absent as in her daughter [Figure 6c].

Radiographic examination showed multiple unilocular well-defined radiolucencies with radiopaque borders on both side of the mandible and a single large well-defined radiolucency bordered by radiopacity was found in the anterior maxilla [Figure 7a]. Chest radiograph (AP view) revealed bifid ribs same as her daughter [Figure 8a].

For a better understanding of the extent and location of the lesions, axial and coronal contrast-enhanced CT (CECT) with 3D reconstruction was done. In CECT, multiple lytic well-defined lesions were seen bilaterally in the mandible (involving ramus bilaterally and right body) and midline

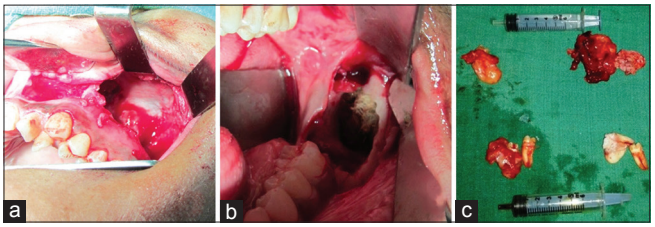

Figure 3: (a) Excision of the left maxillary lesion. (b) Packing of the defect by Carnoy's solution postenuleaction of the left mandibular lesion. (c) Excised specimens with extracted teeth

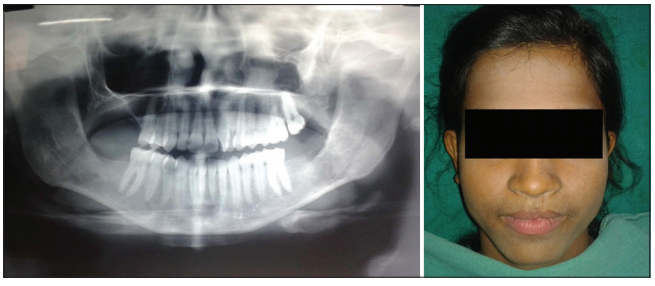

Figure 5: Postoperative follow-up showing satisfactory healing and no recurrence

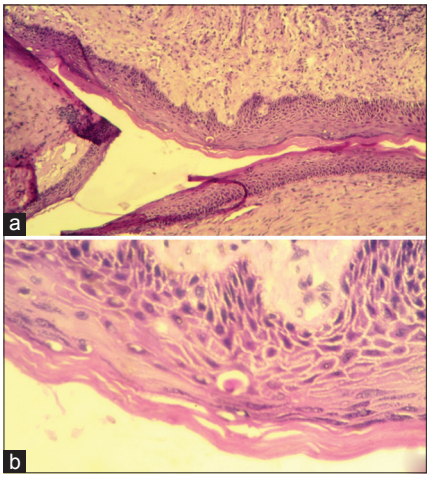

Figure 4: (a) Histopathology (10%) showing cyst lumen filled with keratin flex and (b) Histopathology (×40) showing 8–10 cell layer thick epithelium

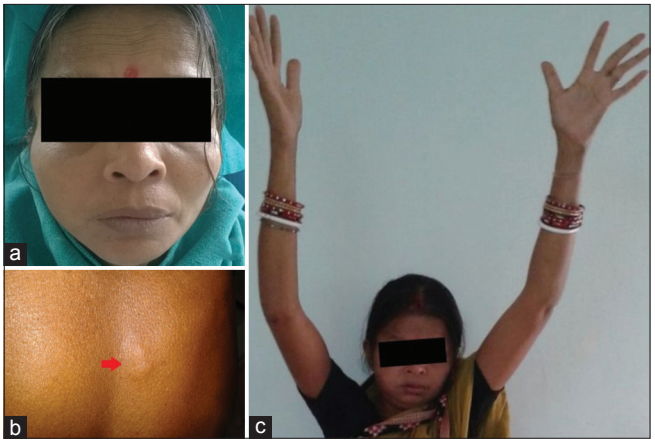

Figure 6: (a) Patient profile showing mild facial asymmetry on the right side. (b) Solitary palpable swelling on the back close to the midline. (c) Sprengel's deformity not evident

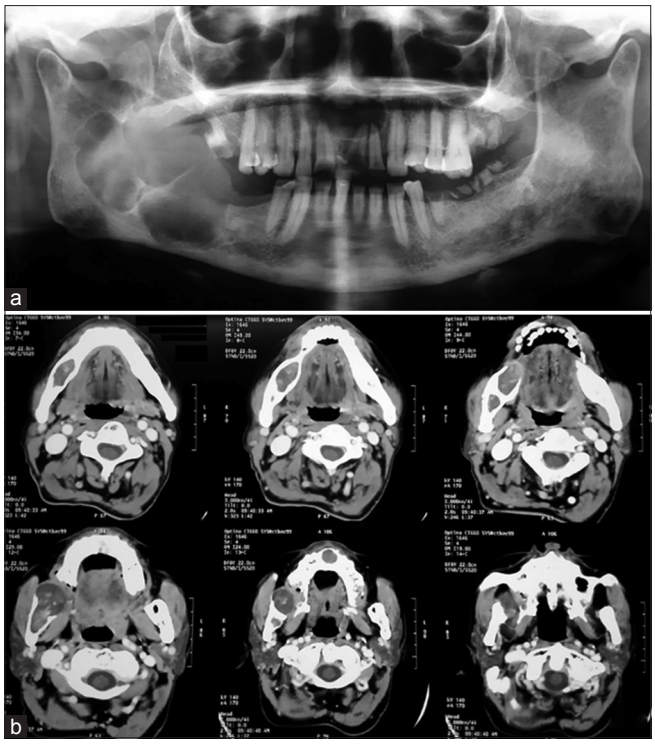

Figure 7: (a) Orthopantomogram showing multiple radiolucencies. (b) Computerized tomography showing location and extent of the lesions

maxilla with scattered calcification foci. Cortical thinning with erosion was also seen [Figure 7b]. Right frontal lobe of the brain showed a homogeneously enhancing hyperdense lesion in convexity region with few internal calcification foci and mild perilesional edema, which was suggestive of meningioma in frontal lobe [Figure 8b], but that is yet to be proven by histopathological examination.

Aspiration report showed white cheesy pus-like material containing mature squamous cells along with a good number of cyst macrophages, polymorphs and cholesterol crystals in a granular neurotic background, which was suggestive of OKC, but biopsy was needed for confirmation.

Ultrasound examination of the abdomen revealed no abnormalities which were contradictory to her daughter.

Based on all these findings, we came to a diagnosis of GGS and made a treatment plan same as her daughter. The cysts were enucleated followed by application of Carnoy's solution and Whitehead's varnish. Furthermore, the root stumps were extracted.

Histologic examination of the excised lesions showed cyst lumen filled with keratin flecks and was covered with a cystic lining of corrugated parakeratinized stratified squamous epithelium, 6–10 cells thick. The lining showed a palisaded row of basal cells with reverse basal polarity

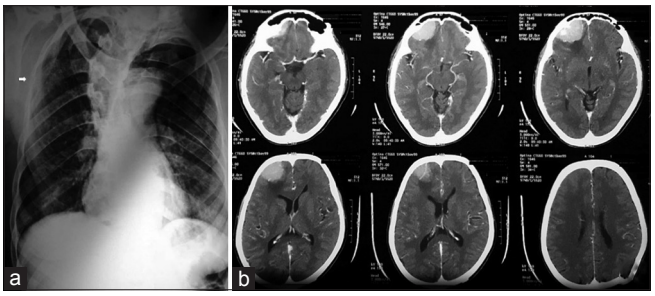

Figure 8: (a) Chest radiograph showing bifid ribs. (b) Computerized tomography showing meningioma

and a flat epithelium connective tissue junction. The cystic wall showed fibrocellular connective tissue stroma with scattered inflammatory cells [Figure 9a and b]. Postoperative follow-up at every 6-month interval showed a smooth and uneventful recovery.

DISCUSSION

Jarish and Whitein first reported this syndrome in 1894. It was first described by Binkley and Johnson in 1951, and Gorlin and Goltz in 1960 first established a classical triad of multiple basal cell carcinomas (BCCs), multiple keratocysts of jaws and bifid ribs as characteristics of nevoid BCC syndrome.

The syndrome is very complex and includes a variety of possible abnormalities such as:[1,6]

a. Cutaneous anomalies: BCCs, benign dermal cysts and tumors, palmoplantar keratoses and dermal calcinosis
b. Dental and osseous anomalies: Multiple OKC, mandibular prognathism, rib anomalies (often bifid), vertebral anomalies, brachymetacarpalism and kyphoscoliosis
c. Ophthalmological anomalies: Hypertelorism, wide nasal bridge, dystopia and strabismus
d. Neurological anomalies: Mental retardation, dural calcification, congenital hydrocephalus, agenesis of corpus callosum and medulloblastomas
e. Sexual abnormalities: Hypogonadism in males and ovarian tumors in females.

The estimated prevalence varies from 1 in 57,000 to 1 in 256,000, with a male-to-female ratio of 1:1.1.

Mutation in tumor suppressor gene PTCH1 situated in the long arm of chromosome 9 (q22.3- q31) is the most accepted cause of this syndrome. A transmembrane glycoprotein which is an antagonist to members of the Hedgehog family is encoded by this mutated PTCH1 gene. Multiple embryonic structures and cell proliferation are controlled by these intercellular signaling molecules.

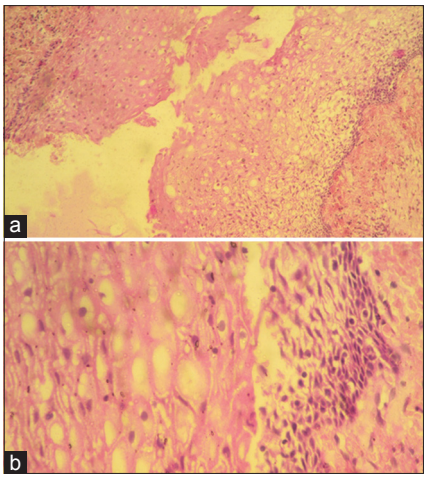

Figure 9: (a) Histopathology (×10) showing cyst lumen filled with keratin flex. (b) Histopathology (×40) showing thinned epithelium and inflammatory cells

A two-hit mechanism of tumor suppresser gene was suggested by Knudson, where first hit is a germline mutation in PTCH1 gene which results in the characteristic developmental abnormalities associated with Gorlin syndrome. The second hit is a somatic inactivating mutation or deletion causing loss of heterozygosity and subsequently results in BCC.[7] As the syndrome is a hereditary condition with a 50% chance of inheritance in offspring of affected patients, it is common among family members, but to our best knowledge, this is the first report of this syndrome in mother and her daughter[Figure 10] to be reported from India. Genetic screening and counseling of patients and family members are important to screen for familial predisposition of this syndrome.[8] The genetic mapping of individuals would help in early diagnosis and management of suspected disease, thus decreasing the severity of abnormalities.

Diagnosis is based on the most frequent and specific features of the syndrome as given by Evans *et al.* in 1993.[5] and later modified by Kimonis *et al.*[9] in 1997. To establish a diagnosis of the GGS, two major or one major and two minor criteria must be present [Table 1]. Although a molecular diagnostic test has been described by Pastorino *et al.*,[10] we were unable to perform it due to lack of infrastructure.

Yordanova *et al.*[11] in 2007 reported a case of familial GGS in a 29-year-old woman and her 50-year-old mother from Pleven, Bulgaria. Gupta *et al.*[12] in their study of six cases described that the frequency of clinical and radiological features of GGS in Indian patients differs from other ethnic groups. Hegde and Shetty[13] in 2012 presented a rare event of GGS occurring in a 39-year-old male and his

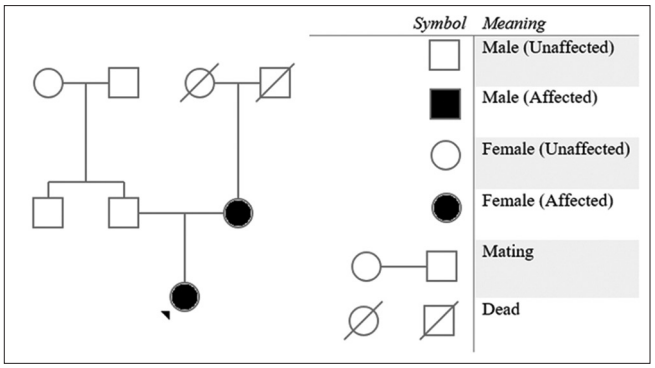

Figure 10: Pedigree chart of the affected family shows the mode of inheritance of Gorlin–Goltz syndrome

Table 1: Major and minor criteria to diagnose Gorlin-Goltz syndrome

Major criteria	Minor criteria
Multiple BCC or one occurring under the age of 20 years	Macrocephaly (adjusted for height)
Histologically proven OKCs of the jaws	Congenital malformation: Cleft lip or palate, frontal bossing, coarse face, moderate or severe hypertelorism
Palmar or plantar pits (three or more)	Other skeletal abnormalities: Sprengel's deformity, marked pectus deformity, marked syndactyly of the digits
Bilamellar calcification of the falx cerebri	Radiologic abnormalities (e.g., bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet, flame-shaped lucencies of the hands and the feet)
Bifid, fused or markedly splayed ribs	Ovarian fibroma (not applicable if patient is male)
First-degree relative with NBCCS	Medulloblastoma

OKC: Odontogenic keratocyst, NBCCS: Nevoid BCC syndrome, BCC: Basal cell carcinoma

8-year-old daughter from Mangalore, India. Nikam *et al.*[14] in 2013 reported a familial GGS case of a father and son from Maharashtra, India. Anchlia *et al.*[4] in 2015 detailed an unusual occurrence of GGS in twin brothers from Gujarat, India. Ours is the first case of GGS in a mother and her daughter to be reported from India, diagnosis of which was done on the basis of major and minor criteria detailed in Table 2.

Although multiple OKCs can occur as a part of some rare dermatological syndromes, such as Bazex syndrome or Torre's syndrome, our patients had no features suggestive of these syndromes.[15] BCC is a disorder of white individuals, especially those with very fair skin and it is rare in dark-skinned individuals.[16] Both of our patients were dark skinned and this melanin pigmentation could have prevented BCC in these patients.

Hard tissue deposits, namely dystrophic calcifications, cartilage and dentinoid, are rare findings in

Table 2: Comparison of the features of the patients

Criteria	Case report 1	Case report 2
Major criteria		
Multiple BCC	Absent	Absent
OKC	Multiple OKCs in both maxilla and mandible	Multiple OKCs in mandible and one single in maxilla
Palmar or plantar pits	Palmer pits present	Palmer pits present
Calcification of the falx cerebri	Present	Absent
Bifid, fused or markedly splayed ribs	Bifid ribs	Bifid ribs
First-degree relative with NBCCS	Daughter of the second patient	Mother of the first patient
Minor criteria		
Macrocephaly	Absent	Absent
Congenital malformation	Bifid ribs, cleft lip	Bifid ribs
Other skeletal abnormalities	None	None
Radiologic abnormalities	Bifid ribs	Bifid ribs, meningioma in frontal lobe
Ovarian fibroma	Ovaries were mildly enlarged with multiple sub centrimetric cysts	Absent
Medulloblastoma	Absent	Absent

OKC: Odontogenic keratocyst, NBCCS: Nevoid BCC syndrome, BCC: Basal cell carcinoma

OKC.[17] According to Brown, the prevalence of dystrophic calcifications in primary OKC is 16.9% and in syndromic OKC is 33.3%.[18] These are usually caused by degeneration as a result of necrobiosis or a foreign-body reaction. In addition, injured tissue of any kind is predisposed to dystrophic calcification.[19] In our case, the type of calcification is most likely to be dystrophic as it is the predominant type in syndromic OKCs. Although it was not confirmed, calcification was not evident in our histologic slides.

Katase *et al*. analyzed the neoplastic nature and biological potential of sporadic and GGS associated OKC.[20] Heparanase, which is an endo-D-glucuronidase enzyme, specifically cleaves heparan sulfate. Its increased level in tumors promotes invasion, angiogenesis and metastasis. In the study, all odontogenic cysts have shown positive immunoreaction for the heparanase protein in various intensities. Interestingly, intense gene and protein expressions have been observed in the OKC associated with GGS, as compared to the sporadic ones and the dentigerous cyst. Their results imply that heparanase expression may be correlated with the neoplastic properties of OKC, particularly in GGS-associated cases.[3]

The GGS consists of a farrago of findings in and outside the head and neck region. Clinical and radiological examination in young patients is essential for early diagnosis. In its clinical management and follow-up, the oral pathologist, maxillofacial surgeon and several other medical specialists are involved. For diagnosis, management and follow-up of patients with the GGS, an interdisciplinary cooperation is mandatory. Fortunately, in our case, except for the OKC, no serious or life-threatening complications of the multisystem anomalies were found. However, a long-term follow-up for the entire life is mandatory for both the patients. The patients were informed about the high risk of recurrence of the OKC and were advised a carefully review by the different specialty doctors once in every 6 months.

CONCLUSION

It is essential that patients with OKC, especially if multiple, be evaluated medically to rule out the possibility of the GGS because of the many associated problems which these patients will ultimately face. The GGS is an autosomal dominant disorder, so follow-up of other family members is also warranted for early detection of BCC and GGS. The aim of this study is to draw attention to the fact that OKC is the major presenting manifestation of this syndrome and the valuable role of the dental team for early detection and treatment of this rare syndrome along with the evaluation of any possible familial inheritance.

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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