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| A novel PTCH1 gene mutation in a pediatric patient associated multiple keratocystic odontogenic tumors of the jaws and Gorlin–Goltz syndrome | | | |
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| [Gozde Ozcan](http://www.ijpmonline.org/searchresult.asp?search=&author=Gozde+Ozcan&journal=Y&but_search=Search&entries=10&pg=1&s=0)**1,**[Burhan Balta](http://www.ijpmonline.org/searchresult.asp?search=&author=Burhan+Balta&journal=Y&but_search=Search&entries=10&pg=1&s=0)**2,**[Ahmet Ercan Sekerci](http://www.ijpmonline.org/searchresult.asp?search=&author=Ahmet+Ercan+Sekerci&journal=Y&but_search=Search&entries=10&pg=1&s=0)**1,**[Osman A Etoz](http://www.ijpmonline.org/searchresult.asp?search=&author=Osman+A+Etoz&journal=Y&but_search=Search&entries=10&pg=1&s=0)**3,**[Claudia Martinuzzi](http://www.ijpmonline.org/searchresult.asp?search=&author=Claudia+Martinuzzi&journal=Y&but_search=Search&entries=10&pg=1&s=0)**4,**[Ozlem Kara](http://www.ijpmonline.org/searchresult.asp?search=&author=Ozlem+Kara&journal=Y&but_search=Search&entries=10&pg=1&s=0" \t "_blank)**5,**[Lorenza Pastorino](http://www.ijpmonline.org/searchresult.asp?search=&author=Lorenza+Pastorino&journal=Y&but_search=Search&entries=10&pg=1&s=0)**4,**[Fatma Kocoglu](http://www.ijpmonline.org/searchresult.asp?search=&author=Fatma+Kocoglu&journal=Y&but_search=Search&entries=10&pg=1&s=0" \t "_blank)**1,**[Omer Ulker](http://www.ijpmonline.org/searchresult.asp?search=&author=Omer+Ulker&journal=Y&but_search=Search&entries=10&pg=1&s=0)**1,**[Murat Erdogan](http://www.ijpmonline.org/searchresult.asp?search=&author=Murat+Erdogan&journal=Y&but_search=Search&entries=10&pg=1&s=0)**2** 1 Department of Oral and Maxillofacial Radiology, Faculty of Dentistry, Erciyes University, Kayseri, Turkey 2 Department of Medical Genetics, Kayseri Education and Research Hospital, Kayseri, Turkey 3 Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Erciyes University, Kayseri, Turkey 4 Genetics of Rare Cancers, IRCCS Azienda Ospedaliera Universitaria San Martino, IST Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy 5 Department of Pathology, Faculty of Medicine, Erciyes University, Kayseri, Turkey | | | |
| **http://www.ijpmonline.org/images/aboutbul.gif****Abstract** | |  |  |

Gorlin–Goltz syndrome (GGS) is an uncommon autosomal dominant inherited disorder which comprises the triad of basal cell carcinomas (BCCs), odontogenic keratocysts, and musculoskeletal malformations. Besides this triad, neurological, ophthalmic, endocrine, and genital manifestations are known to be variable. It is occasionally associated with aggressive BCC and internal malignancies. This report documents a case of GGS with a novel mutation in the PTCH1 gene in an 11-year-old child. The clinical, radiographic, histopathologic and molecular findings of this condition, and treatment are described, and a review of GGS was carried out.

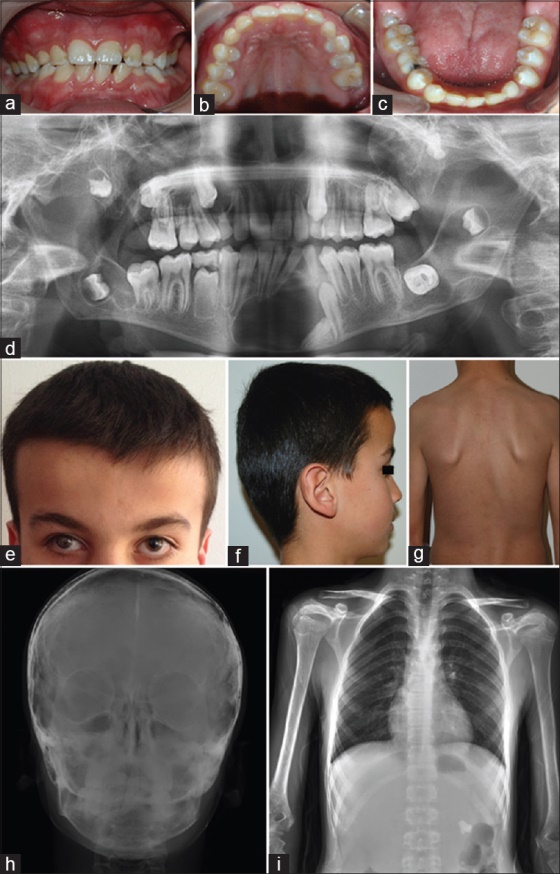
**Keywords: Gorlin–Goltz syndrome, nevoid basal cell nevus syndrome, odontogenic keratocyst, pediatric, PTCH1 gene**

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| **http://www.ijpmonline.org/images/aboutbul.gif  Introduction** |  | [Top](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan#top) |

Gorlin–Goltz syndrome (GGS) is inherited as an autosomal dominant trait with variable expressivity ranging from oral lesions to skeletal deformities.[[1]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref1) The prevalence of GGS has been estimated to be 1:60,000 individuals.[[2]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref2) It appears in all ethnic groups, but most often in whites;[[3]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref3) it has a 3:1 male/female gender predilection.[[4]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref4) The common manifestations in this syndrome include multiple basal cell carcinomas (BCCs), odontogenic keratocysts (OKCs) of the jaw, congenital skeletal anomalies, palmar pits, and intracranial ectopic calcifications of the falx cerebri. More than 100 less common features have been identified.[[5]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref5) The molecular origin of the syndrome could be attributed to the loss of the human patched gene (PTCH1 gene) on chromosome 9q22.3–q31, which is a tumor suppressor gene.[[6]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref6)  
  
Despite the number of cases reported in the literature, the understanding of the complete form of GGS is not as yet conclusive. The present report and review attempt to highlight the salient features of an unusual case of multiple keratocysts in association with GGS with its management.

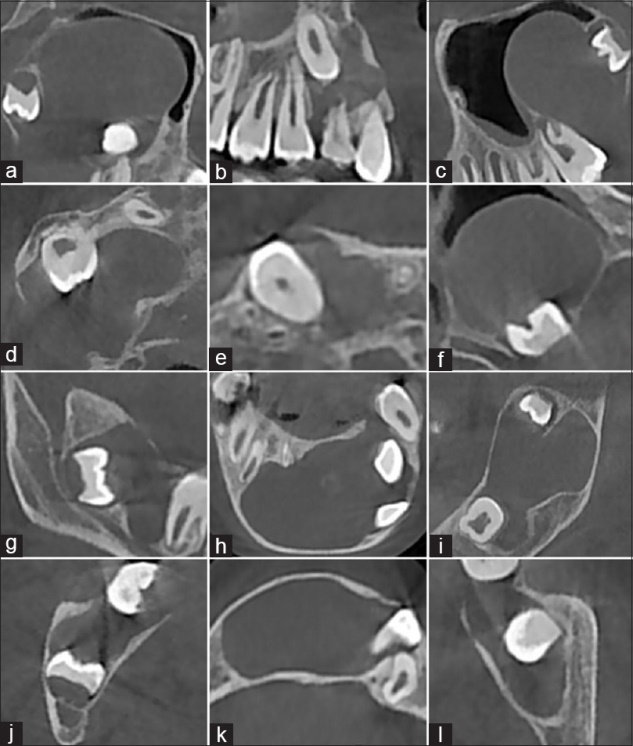
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| **Case Report** |  | [Top](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan#top) |

An 11-year-old boy was referred to our department with a chief complaint of swelling in the anterior region of the mandible of 2 weeks duration. Intraoral examination revealed displaced lower incisor teeth and swelling in the upper right canine region [[Figure 1]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f1.jpg)a, [[Figure 1]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f1.jpg)b,[[Figure 1]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f1.jpg)c. The panoramic radiograph revealed three cystic lesions in each jaw. They were associated with an impacted right second molar, right canine, and left third molar in the maxilla. The lesions were located in the mandible and were related with an impacted left canine and lateral, left second and third molar and right third molar [[Figure 1]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f1.jpg)d.



**Figure 1: (a-c) The intraoral images of the patient revealed normal appearance except displacement of lower incisors and swelling in the maxillary right canine area. (d) Panoramic radiograph of the patient showed three cystic lesions on each jaw. (e-g) The clinical examination revealed congenital cataract of the right eye, frontal bossing, hypertelorism, and relative macrocephaly. (h) The posteroanterior radiograph indicates calcification of falx cerebri. (i) The chest radiograph showed thoracic scoliosis**

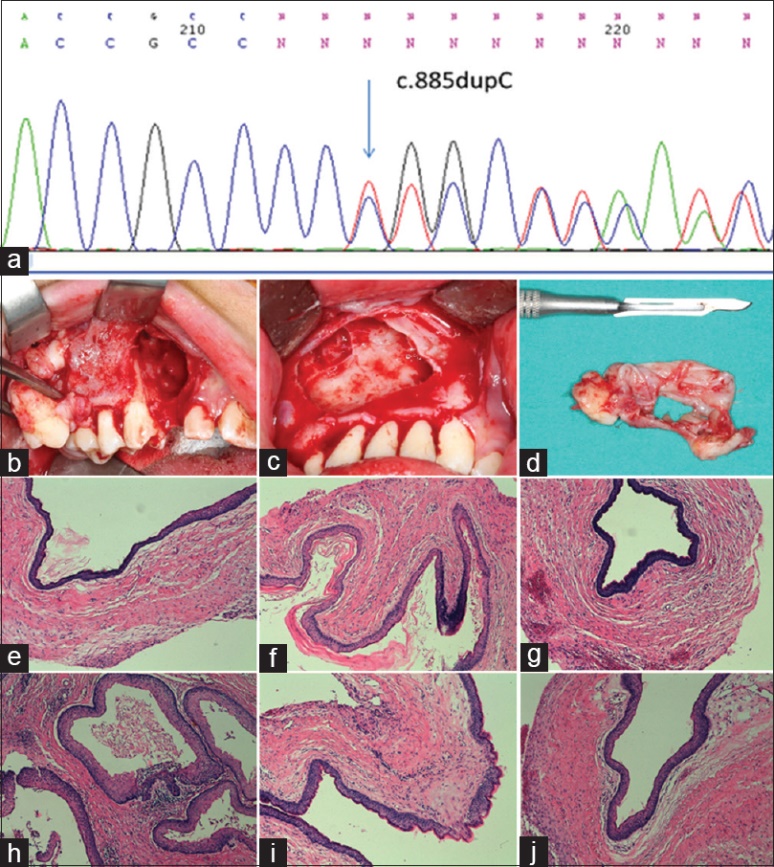
On clinical examination, there was no extra-oral asymmetry or swelling; however, the patient was noted to have frontal bossing, relative macrocephaly, hypertelorism, and congenital cataract of the right eye [[Figure 1]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f1.jpg)e, [[Figure 1]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f1.jpg)f, [[Figure 1]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f1.jpg)g. Further examination revealed that the child was unable to bend both the thumbs. Palmar pits and terra firma-forme dermatosis was observed in the dermatological examination. The patient's mother was not examined, but she had undergone three operations because of BCC.  
  
The skull radiograph demonstrated calcification of the falx cerebri [[Figure 1]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f1.jpg)h. X-rays of the full spine and rib examination did not show rib or vertebra abnormality but revealed a thoracic scoliosis curve with Cobb of 13°, from T5 to T10. The total thoracic kyphosis was 47° [[Figure 1]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f1.jpg)i. Surgery was not recommended to the patient.  
  
To avoid unnecessary exploration of this defect before the beginning of the treatment phase and to reveal the exact location definition of the pathologic features, a cone-beam computed tomography (NewTom 5G, QR, Verona, Italy) scan was requested to confirm the entity. Multiplanar sections confirmed the lesions [[Figure 2]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f2.jpg).



**Figure 2: The cone-beam computed tomography images of maxillary lesions were arranged from the right lesion to the left one at sagittal (a-c) and axial (d-f) aspects. The cone-beam computed tomography images of mandibular lesions are arranged from the right lesion to the left one at sagittal (g-i) and axial (j-l) aspects**

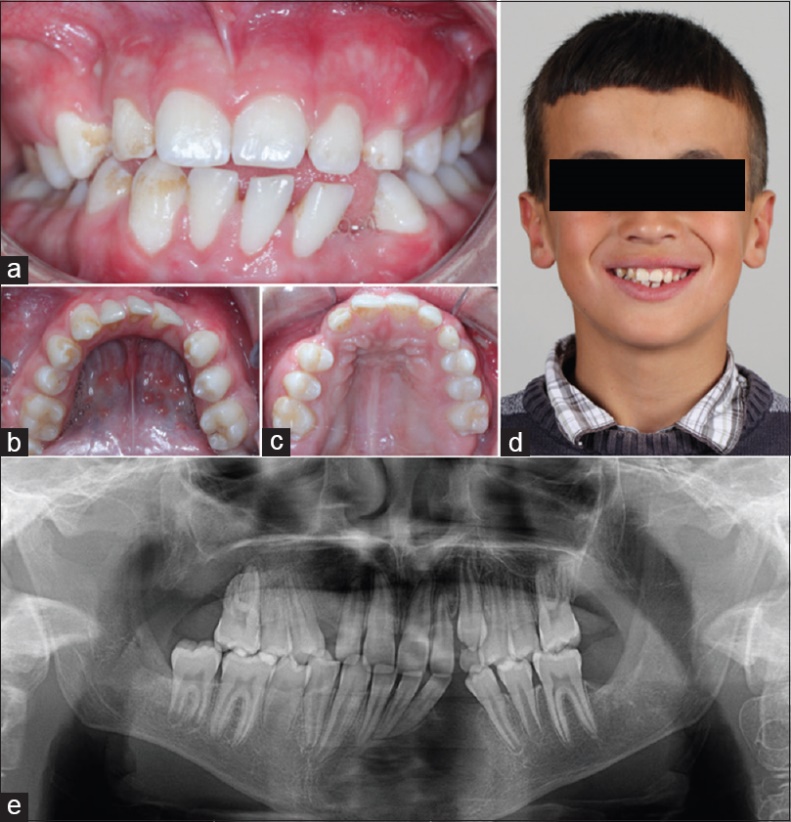
Owing to the presence of multiple cysts such as lesions in the jaw, GGS was suspected, and further investigations were carried out. Molecular analysis, performed as previously described,[[7]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref7) revealed a novel germline mutation in exon 6 of the PTCH1 gene, c. 885insC. This is a frameshift mutation determining a stop codon after 23 amino acids [[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)a. On the basis of clinical and molecular findings, diagnosis of GGS was made.

**Figure 3: (a) Molecular analysis revealed a novel germline mutation in exon 6 of the PTCH1 gene, c.885insC. (b and c) The intraoperative images of the right maxillary canine associated lesion. (d) The image of enucleated lesion with impacted permanent canine and erupted primary canine. The histopathologic examination of enucleated lesions from the right to left and maxillary to mandibular (H and E, ×100). (e) The typical folded cyst lining with thin squamous epithelia. (f) Focal hemorrhage focuses in the wall and parakeratinization on the surface. (g) The inflammatory infiltrate consisting chiefly of lymphocytes in collagen fibers. (h) The satellite cysts in the wall. (i) Odontogenic keratocyst showing a characteristic thin squamous epithelial lining with a distinct palisaded basal layer. (j) The folded cyst lining with thin squamous epithelia**



DNA was extracted with the MagCore extractor system H16 with a MagCore Genomic DNA Large Volume Whole Blood Kit (RBC Bioscience Corp., Taiwan). We designed pairs of primers to amplify the complete coding region and intron-exon boundaries of PTCH1 and SUFU. A detailed list of the primers designed is available on request. The polymerase chain reaction (PCR) mix contained, 40 ng DNA, 25 pmol primer, 200 μM deoxynucleotide triphosphate (dNTP), and 1.5 U hot start Taq PCR (Qiagen, Germany). The cycling conditions were as follows, 15 min activation at 95°C followed by 35 cycles of 95°C for 40 s, 60°C for 30 s, 72°C for 50 s, and 10 min at 72°C for the final extension. After PCRs, the amplicons were treated with the Illustra ExoProStar ™ (GE Healthcare Life Sciences) to degrade unincorporated PCR primers and dNTPs, and 20–40 ng amounts of template were sequenced in forward and reverse orientations using the BigDye Terminator v3.1 Cycle Sequencing Kit (Life Technologies) and analyzed on a 3130XL Genetic Analyzer (Life Technologies) according to the manufacturer's protocol.  
  
Sequence numbering follows the recommendations indicated by the Human Genome Variation Society. The PTCH1 complementary DNA (cDNA) sequence from GenBank (ref. sequence NM\_000264.3) and SUFU cDNA (ref. sequence NM\_016169.3) were used as a reference sequence, where the A of the automatic tank gauge translation initiation start site represents nucleotide +1.  
  
Multiplex ligation-dependent probe amplification (MLPA) was performed to identify large deletions and duplications for both genes. The MLPA PTCH1 kit P067 and SUFU Kit P301 were obtained from MRC-Holland and analyses were performed according to the manufacturer's protocol (Amsterdam, The Netherlands).[[8]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref8)  
  
The patient was then referred to the Department of Oral and Maxillofacial Surgery for surgical planning. The cyst enucleation was done under general anesthesia via intraoral approach. After the cystic lesions were enucleated, large areas of bone loss were seen and the displaced impacted permanent teeth (maxillary right second and third molars and canine, left second and third molars; mandibular right third molar, left lateral, canine, second and third molars) and primary teeth with physiological root resorptions (upper canines and lower left canine and right second molar) were visible on the floor of the cystic cavity [[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)b, [[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)c, [[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)d.  
  
Excisional biopsy of the oral lesions was performed, and histopathological examination demonstrated a well-developed basal layer of palisaded columnar cells with polarized hyperchromatic nuclei. Multiple satellite and daughter cysts were seen in the connective tissue wall[[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)e, [[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)f, [[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)g, [[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)h, [[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)i, [[Figure 3]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f3.jpg)j. This condition confirmed the diagnosis of OKC.  
  
Under regular follow-up, intraoral and radiological examinations were performed 6 months later. These examinations showed that the healing process of the operated areas and psychological status of the patient were quite good [[Figure 4]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f4.jpg)a, [[Figure 4]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f4.jpg)b, [[Figure 4]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f4.jpg)c, [[Figure 4]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f4.jpg)d, [[Figure 4]](http://www.ijpmonline.org/viewimage.asp?img=IndianJPatholMicrobiol_2016_59_3_335_188148_f4.jpg)e. The patient is currently being called in every 6 months for checkups in case of primary or recurrent lesions.

**Figure 4: (a-c) The postoperative intraoral images of the patient after 6 months. (d) The extraoral image of patient under follow-up period. (e) The panoramic radiograph showed right healing process of operation areas 6 months later**



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| **Discussion** |  | [Top](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan#top) |

The oral and dental anomalies of GGS were described by Premalatha *et al*.[[9]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref9) they include agenesis, oligodontia, hypodontia, microdontia, dysplasia and enamel fragility, enamel defects, delayed eruption, irregular teeth spacing, prognathism, and malocclusion. In addition to these dental anomalies, hard and soft tissue anomalies of the oral region were identified and showed that high-arched palate, cleft lip and/or palate, hypertrophy of the gums and papillomas of the tongue, gums, buccal mucosa, and palate may occur in patients with GGS. In the current case, malocclusion and delayed eruption due to the presence of keratocystic odontogenic tumors (KCOTs) were observed.  
  
KCOTs are the most consistent and representative signs of this syndrome.[[10]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref10) Less than 10% of patients with multiple KCOTs have other features of GGS; however, it has been suggested that multiple KCOTs alone can be confirmation of this syndrome.[[11]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref11) KCOT is an epithelial developmental tumor of the jaw whose most significant manifestation, is its potential for locally infiltrative growth pattern causing bone destruction, and its propensity to multiplicity, particularly when associated with GGS.[[12]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref12)  
  
Histologically, KCOTs in GGS, unlike sporadic KCOTs, show a greater epithelial proliferation and presence of mitoses, and also inflammatory infiltration and larger para-keratinization of the stromal component.[[13]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref13) Woolgar *et al*.[[14]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref14) also found remarkable differences between syndrome KCOTs and sporadic KCOTs. GGS-associated KCOTs were identified to have significantly increased solid islands of epithelial proliferation, odontogenic rests within the capsule, presence of daughter cysts, and mitotic figures in the epithelial lining of the main cavity. These differences explain why GGS-related KCOTs show a higher recurrence rate than those seen in patients without GGS.[[15]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref15)  
  
GGS is an autosomal dominant disease caused by mutations in the PTCH1, PTCH2, and SUFU genes. So far, 329 mutations have been identified in the PTCH1 gene. We identified a novel insertion mutation in the PTCH1 gene. An early diagnosis of GGS, good genetic counseling and a thorough assessment of clinical and radiological findings are of great importance for the treatment of this hereditary disorder. Because of the several systems being clinically affected, these patients should be monitored and diagnosed by a multidisciplinary approach.[[16]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref16) To make an early diagnosis, the high determination rate of PTCH1 mutations in GGS patients allows molecular examinations to become a valuable tool, especially in the case of the atypical phenotype and for yet unaffected family individuals.[[17]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan" \l "ref17) It may also provide the opportunity to decrease the severity of the long-term sequelae of GGS which include malignancies and maxillofacial destructions and deformations.[[2]](http://www.ijpmonline.org/article.asp?issn=0377-4929;year=2016;volume=59;issue=3;spage=335;epage=338;aulast=Ozcan#ref2)  
  
**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.  
  
**Acknowledgments**  
  
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**Financial support and sponsorship**  
  
Nil.  
  
**Conflicts of interest**  
  
There are no conflicts of interest.

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