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Management of Odontogenic Keratocysts Tumors Associated with Gorlin-Goltz Syndrome

Literature Review Based on a Case Report

CASE REPORT

Manejo de Queratoquistes Odontogénicos Asociados al Síndrome de Gorlin-Golt

Revisión de la literatura a propósito de un caso

Manejo de Queratocistos Odontogenicos à Síndrome de Gorlin-Goltz

Revisão da Literatura com Base em um Caso Clínico

Abstract

This article aims to describe and discuss, based on current literature, a case of a young patient with Gorlin-Goltz syndrome (GGS), highlighting the therapeutic approach and the challenge posed by the high recurrence rate of odontogenic keratocysts (OKCs) in GGS. We present a 19-year-old patient with GGS and multiple OKCs treated through decompression, enucleation, and cavity treatment with modified Carnoy's solution (MCS). Three years later, the patient returned with recurrent OKCs, and a new approach was taken: enucleation and cavity treatment with MCS for the smaller OKC, while decompression was performed for the larger OKC. Currently, OKC clinical management does not differ between individuals with and without GGS, despite their clinical and molecular differences. Therefore, we highlight the need for a specific treatment for OKCs in GGS patients, which could include Sonic Hedgehog (SHH) pathway inhibitors as adjuvant therapy.

Arturo Javier Henríquez Avendaño[1, 4]
Sebastian Alberto Galleguillos Conejeros [1, 3]
José Tomás Fernández Ibáñez [1,3]
Mauricio Alejandro Lobos Esparza [1,5]
Marcelo Eduardo Mardones Muñoz [1, 2, 3]
Luis Alberto Córdova Jara [1, 2, 3]

CORRESPONDENCE
Arturo Javier Henríquez Avendaño
arturo.henriquezav@gmail.com

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1 Servicio de Cirugía Maxilofacial Hospital San José, Independencia, Santiago, Chile.

2 Universidad de Chile, Facultad de Odontología, Especialista en Cirugía y Traumatología Bucomaxilofacial, Santiago, Chile.

3 Universidad de Chile, Facultad de Odontología, Cirujano Dentista, Santiago, Chile.

4 Universidad Mayor, Facultad de Odontología, Cirujano Dentista, Santiago, Chile.

5 Universidad del Desarrollo, Facultad de Odontología, Cirujano Dentista, Concepción, Chile.

Resumen

El objetivo de este artículo es describir y discutir, con base en la literatura actual, un caso de un paciente joven con síndrome de Gorlin-Goltz (SGG), destacando el enfoque terapéutico y el desafío que representa la alta tasa de recidiva de los queratoquistes odontogénicos (QO) en SGG. Se presenta un paciente de 19 años con SGG y múltiples QO tratados mediante descompresión, enucleación y tratamiento de la cavidad con solución de Carnoy modificada (SCM). Posteriormente, tres años después acude nuevamente por recidiva de QO, optando en esta nueva instancia por la enucleación y tratamiento de la cavidad con SCM del QO de menor tamaño. Mientras que en el QO de mayor tamaño se realizó la descompresión. Actualmente la conducta clínica frente a los QO no varía entre individuos con y sin SGG, pese a sus diferencias clínicas y moleculares. Por lo tanto, destacamos la necesidad de establecer un tratamiento específico para los QO en pacientes con SGG. El cual podría considerar a los fármacos inhibidores de la vía Sonic Hedgehog (SHH) como tratamiento coadyuvante.

Palabras Clave: Síndrome de Gorlin-Goltz, Síndrome de Nevus Basocelular, Queratoquiste Odontogénico, Vismodegib, Sonidegib.

Resumo

O objetivo deste artigo é descrever e discutir, com base na literatura atual, um caso de um paciente jovem com síndrome de Gorlin-Goltz (SGG), destacando a abordagem terapêutica e o desafio representado pela alta taxa de recidiva dos queratocistos odontogênicos (QO) na SGG. Apresentamos um paciente de 19 anos com SGG e múltiplos QOs tratados por meio de descompressão, enucleação e tratamento da cavidade com solução de Carnoy modificada (SCM). Três anos depois, o paciente retornou devido à recidiva de QOs, e uma nova abordagem foi adotada: enucleação e tratamento da cavidade com SCM para o QO de menor tamanho, enquanto a descompressão foi realizada para o QO de maior tamanho. Atualmente, a conduta clínica frente aos QOs não varia entre indivíduos com e sem SGG, apesar das diferenças clínicas e moleculares. Assim, destacamos a necessidade de estabelecer um tratamento específico para os QOs em pacientes com SGG, considerando os fármacos inibidores da via Sonic Hedgehog (SHH) como uma terapia adjuvante.

Palavras-chave: Síndrome de Gorlin-Goltz, Síndrome do Nevo Basocelular, Queratocisto Odontogênico, Vismodegib, Sonidegib.

Introduction

Gorlin-Goltz syndrome (GGS), also known as basal cell nevus syndrome (BCNS), is a rare multisystem disorder with a reported prevalence ranging from 1:30,000 to 1:256,000, depending on geographic region and the studies analyzed.[1,2,3] In 70–80% of cases, it follows an autosomal dominant inheritance pattern, while the remaining 20–30% result from a de novo pathogenic variation. The syndrome is characterized by the early onset of numerous basal cell carcinomas (BCCs) and/or odontogenic keratocysts (OKCs), along with skeletal, ophthalmologic, and neurological abnormalities.[1,2]

The etiology of this syndrome is linked to germline mutations in the human homolog of the Drosophila patched gene (PTCH1) or the suppressor of fused homolog (SUFU) gene, both of which are components of the Sonic Hedgehog (SHH) signaling pathway.[4] When PTCH1 binds to SHH, it allows the expression of genes that regulate cell growth and differentiation. However, a mutated PTCH1 gene cannot bind to SHH, leading to overactivation of this signaling pathway. This, in turn, causes the development of BCCs, OKCs, and a broad spectrum of developmental abnormalities.

The overgrowth observed in GGS evidences the role of PTCH1 as a tumor suppressor gene.[5] Managing this syndrome requires a multidisciplinary approach, typically involving dermatologists, oncologists, geneticists, and maxillofacial surgeons.

OKCs are benign intraosseous lesions of odontogenic origin, characterized by aggressive behavior, including rapid growth, extension into adjacent tissues, soft tissue invasion, and a high recurrence rate.[3,6] They represent the predominant oral manifestation of GGS. Approximately 65% to 100% of patients with GGS develop multiple OKCs throughout their lifetime, with an average age of onset ranging from 15.5 to 17.1 years.[3,7] They present as multiple and are evenly distributed in the maxillary bones, in contrast to non-syndromic OKCs, which are predominantly found in the posterior region of the mandible.[2,8] Current surgical strategies for treating OKCs associated with GGS include decompression or

marsupialization with or without cystectomy/secondary enucleation and with or without peripheral ostectomy, enucleation followed by mechanical curettage/ostectomy with or without topical application of cytotoxic agents ((Carnoy's solution (CS), modified Carnoy's solution (MCS), or 5-fluorouracil (5-FU)), enucleation followed by liquid nitrogen cryotherapy, and en bloc resection with or without mandibular preservation.[2,9,10]

This work aimed to describe and discuss, based on current literature, the case of a young patient with GGS, underscoring the therapeutic approach used and the challenges related to the high recurrence rate of OKCs associated with this syndrome. Likewise, current issues regarding the management of these patients were analyzed, emphasizing the need to explore the potential of emerging treatments, such as SHH pathway inhibitors, in search of better therapeutic outcomes and reduced associated morbidity.

Case report

A 19-year-old male patient with a GGS diagnosis was referred in 2021 from a pediatric hospital for the therapeutic management of maxillary bone OKCs by the Maxillofacial Surgery team at San José Hospital. On clinical examination, he presented with decompression treatment cannulas for multiple OKCs previously diagnosed at the referring hospital. Treatment had started in 2019 and continued until 2021, achieving a size reduction in the OKCs for subsequent surgical management (**Figure 1**).

Under general anesthesia with orotracheal intubation, the cysts were enucleated with peripheral osteotomy, followed by the application of MCS to non-critical surfaces of the surgical sites, away from the orbit. After the procedure, the patient attended follow-up appointments for the first six months but did not return for the following two years.

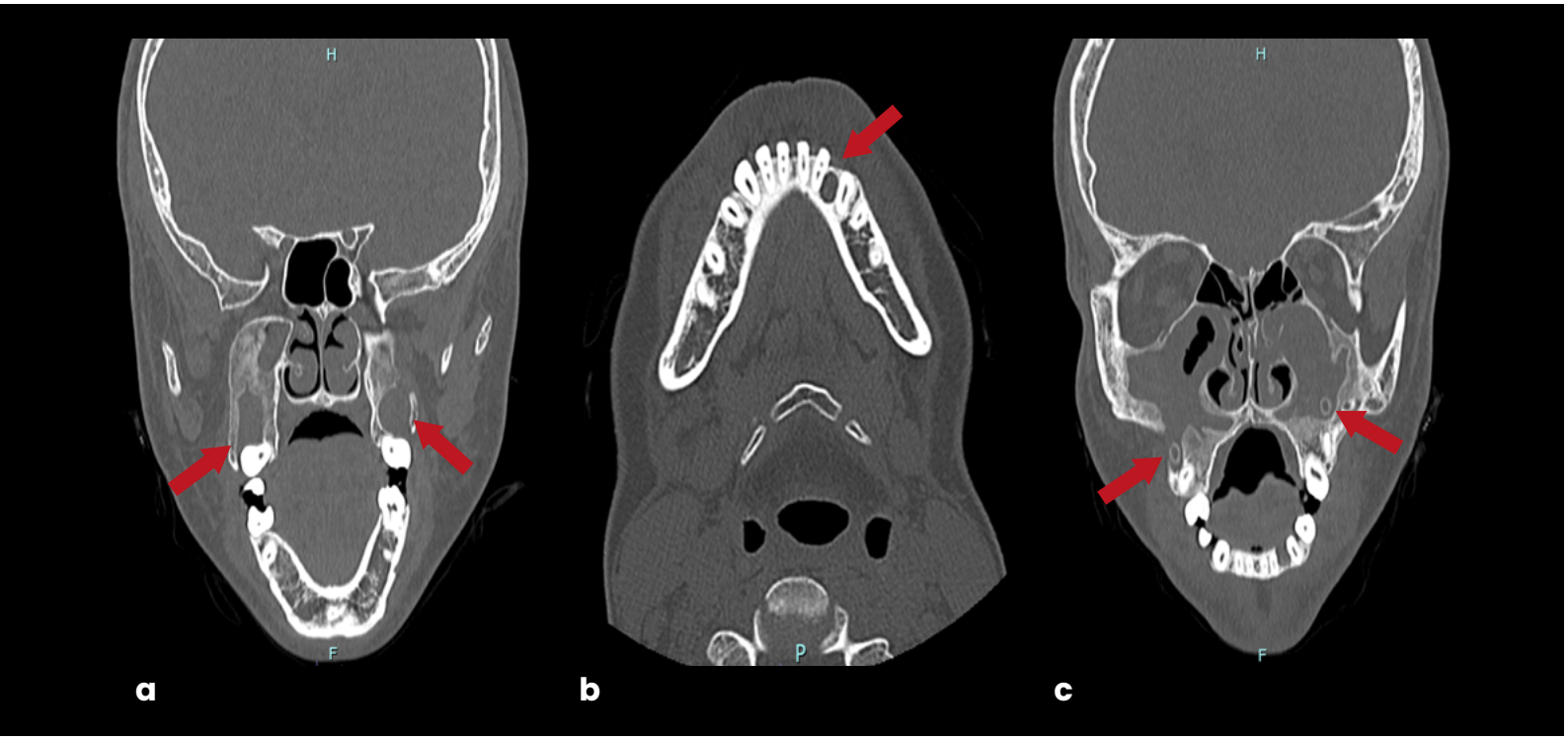

Figure 1 CT scan from 2021 showing three hypodense lesions marked with a red arrow. **(A)** Two bilateral hypodense lesions with a cystic appearance located in relation to both maxillary sinuses. **(B)** Hypodense lesion with a cystic appearance in the left parasymphyseal area. **(C)** Cannulas placed in both maxillary lesions.

The patient presented again in August 2024 due to an episode of left hemifacial volume increase, which was managed in the emergency department of another hospital. Antibiotic treatment and drainage of the purulent content were performed. Maxillofacial computed tomography (CT) revealed three hypodense cystic lesions: one in the left posterior hemimaxillary region, corresponding to the recurrence of an OKC previously treated in 2021,

and two located at both mandibular angles (Figure 2). Biopsy results confirmed the diagnosis of OKCs. Therefore, enucleation with peripheral osteotomy was performed for the smaller mandibular lesions, along with MCS application, and cannulation of the maxillary lesion for decompression followed by enucleation.

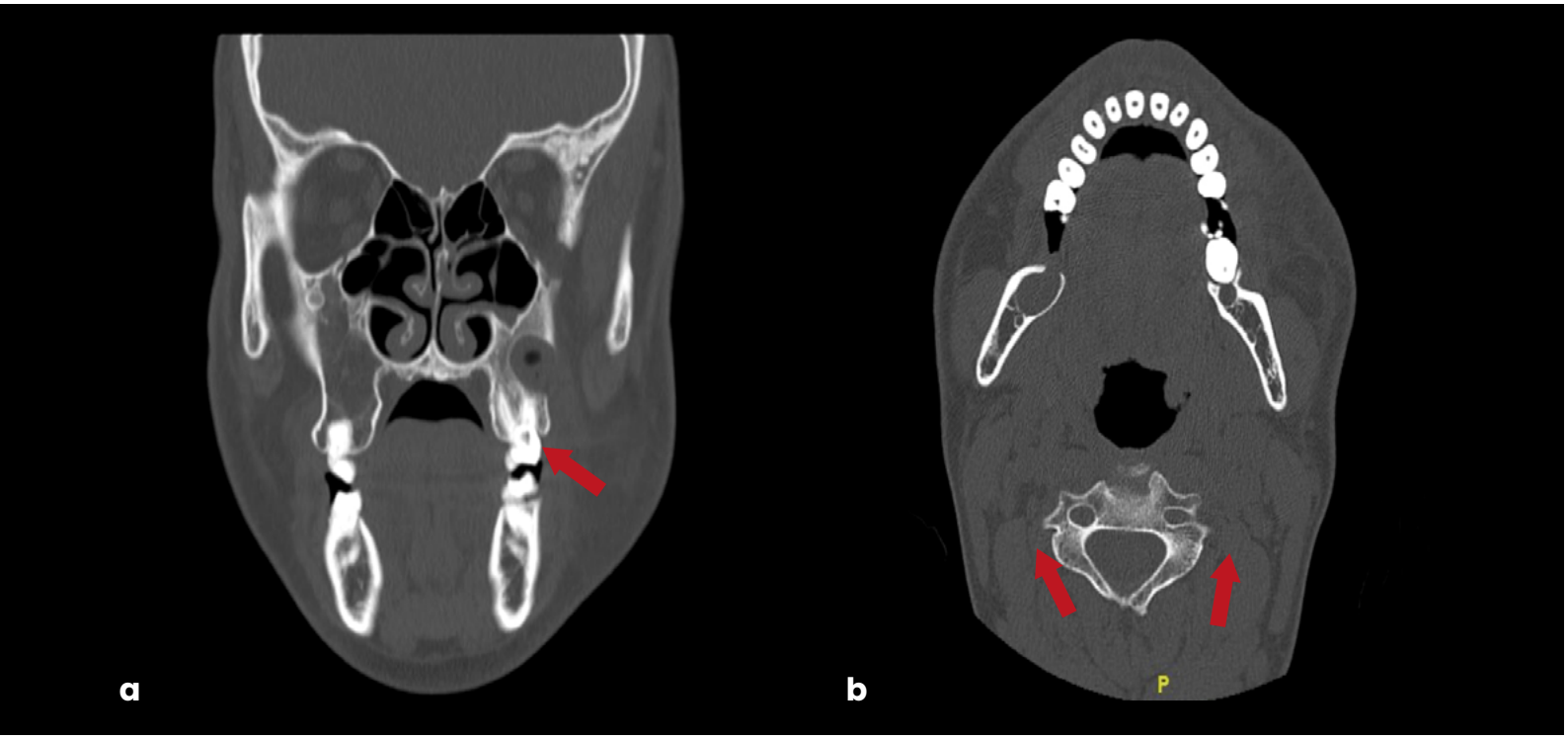

Figure 2 CT scan taken in the Emergency Department showing three hypodense lesions marked with a red arrow. (A) Hypodense cystic lesion in the left maxillary area, superinfected and corresponding to the recurrence of the lesion treated in 2021. (B) Hypodense cystic lesions at both mandibular angles, lesions that were not present in 2021.

Figure 3 Surgical treatment of the lesions.

Under general anesthesia and orotracheal intubation, the following procedures were performed: enucleation of the mandibular lesions, peripheral curettage/osteotomy followed by MCS application for 3 minutes, and placement of a decompressive cannula in the left maxillary lesion. The cannula was kept patent, with daily rinses using 0.12% chlorhexidine until adequate decompression was achieved to allow subsequent enucleation (**Figure 3**). The patient is currently under monthly clinical follow-up and radiological monitoring every 6 months.

Discussion

The gold standard for diagnosing GGS is genetic testing for PTCH1. However, in practice, this can be costly, and diagnostic confirmation through these tests is not necessary in all cases. Clinical findings can strongly support the diagnostic suspicion, with major and minor clinical criteria being considered (**Table 1**). There are three scenarios that can lead to a diagnosis:

(1) one major criterion and molecular confirmation; **(2)** two major criteria; **(3)** one major criterion and two minor criteria.[11]

Genetic testing can be done using a single gene or a multigene panel, including the analysis of the PTCH1 and/or SUFU genes, with PTCH1 showing higher sensitivity.[11] In the reported case, the patient presented with multiple OKCs at an age under 20 years and a first-degree relative with GGS, in this case, his father, thus fulfilling two major criteria.

TABLA 1
Criterios mayores y menores para el diagnóstico de síndrome de Gorlin-Goltz (SGG).[11]

MAJOR CRITERIA	MINOR CRITERIA
Two or more basal cell carcinomas < 20 years	Macrocephaly
Maxillary keratocysts < 20 years	Skeletal malformations and radiographic changes
Palmar or plantar pits	Skeletal malformations and radiographic changes
Early falx cerebri calcification	Ovarian or cardiac fibroma
First-degree relative with GGS	Rib abnormalities and spina bifida
Medulloblastoma, usually desmoplastic	Ocular abnormalities
	Cleft lip and palate

OKCs affect more than 65% of individuals with GGS, leading to significant bone loss and a considerable decrease in quality of life.[12] In non-syndromic individuals, OKCs are usually located in the posterior segment of the body and mandibular ramus, and they can occur throughout life, with an average age of onset of 34.2 ± 17.9 years.[8, 13] In contrast, in the context of GGS, OKCs are evenly distributed in both jaws and are associated with younger patients, with an average onset age between 15.5 and 17.1 years.[3]

The study by Schuch et al. (2020), which analyzed 2497 non-syndromic OKCs, did not find a significant difference between affected males and females, although a slight male predilection was observed, with a ratio of 1.1:1.[8] This finding is consistent with that reported by Titinchi et al. (2012), who noted a male-to-female ratio of 1:0.6.[9] For individuals with GGS, the gender ratio appears to remain balanced. According to the article by Spadari et al. (2022), there is a slight female predilection, with a ratio of 1:1.3.[2] On the other hand, a report by Metha et al. (2014) described a male-to-female ratio of 1:1 in individuals with GGS.[14]

In the case presented in this article, a 19-year-old male patient with GGS experienced a recurrence of an OKC within less than 3 years after surgical treatment, along with the de novo occurrence of two mandibular OKCs. This finding is consistent with that reported by Titinchi et al. (2012), where the overall recurrence rate of OKCs in patients with GGS was significantly higher (50.0%) compared to that of non-syndromic OKCs (29.2%).[9] In contrast, Al-Moraissi et al. (2023) reported an even lower overall recurrence rate in non-syndromic patients, at 17.9%.[10] These variations may depend on the type of treatment used for these patients, as well as the number of lesions they present.

Regarding treatment efficacy and recurrence rates, the systematic review by Winters et al. (2023) reports that complete or partial resection has a recurrence rate of less than 2%, consistent with the 2.3% reported by Al-Moraissi et al. (2023). However, this procedure is associated with considerable morbidity. In contrast, enucleation alone has a recurrence rate between 22.1% and 25%, according to these authors, though it involves less morbidity than resection (10,13). Winters et al. (2023) indicate that enucleation combined with CS and osteotomy reduces the recurrence rate to 11%, while Al-Moraissi et al. (2023) report an even lower rate of 8.8%. However, the use of chloroform in the composition of CS has carcinogenic potential, leading to its restriction. Subsequently, MCS was introduced, offering a comparable composition to CS but without chloroform. According to the systematic review by Al-Moraissi et al. (2023), the use of MCS as an adjuvant in enucleation with peripheral

osteotomy is associated with a recurrence rate of 24.7%.[10,13] More recently, 5-FU has been introduced for topical application due to its antimetabolic effect, which induces cell apoptosis. Systematic reviews by Al-Moraissi et al. (2023) and A.K. Singh et al. (2022) report a 0% recurrence rate when used as adjuvant therapy alongside enucleation and peripheral osteotomy. However, this figure should be interpreted with caution, as the individual studies underlying these reviews have limitations.[10,13,15]

Among the hypothesized causes of OKCs recurrence are several factors, including the tendency for multiplicity, the friability of the lining tissue, and the complexity of complete cyst removal in the root zone of the tooth elements, which often hinders full excision – resulting in fragmented enucleation with the retention of satellite cystic cells, which, given their intrinsic potential for epithelial replication, may lead to OKC recurrence.[2] Additionally, OKCs in the context of GGS can occur either synchronously, meaning they arise simultaneously, or metachronously, meaning they develop at different times. On average, individuals with GGS may develop between 1 and 28 OKCs over their lifetime, with an average of 4 to 6.[7] This high recurrence rate exposes individuals with GGS to multiple reinterventions throughout their lives, leading to considerable morbidity. However, care must be taken not to confuse the development of new OKCs in these patients with the recurrence of previous ones.[9]

Currently, the therapeutic approach to OKCs does not differentiate between individuals with or without GGS, despite their behavioral differences. In this regard, exploring systemic adjuvant treatments that act at the molecular level would be relevant. Taking BCC lesions as a reference, the use of vismodegib and sonidegib—both SHH pathway inhibitors—has been explored. These drugs act at the molecular level to mitigate the clinical manifestations of GGS by compensating for the PTCH-1 gene mutation.[16] Consequently, treatments designed to prevent the occurrence of new BCCs hold promise for future research into the management of OKCs associated with this syndrome.[6]

Both drugs have been approved by the Food and Drug Administration (FDA) for individuals aged 18 years or older with metastatic BCC, locally advanced BCC that recurs after surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.[3,17] However, their use has limitations. In the study by Murgia et al. (2024), the following adverse effects were observed for sonidegib–vismodegib, respectively: dysgeusia (44–58%), fatigue (32–39%), hair loss (49–66%), muscle spasms (54–71%), and weight loss (44–56%).[1]

Current evidence on the impact of drugs such as vismodegib and sonidegib in OKCs remains limited. Booms et al. (2015) reported the efficacy of vismodegib in treating BCCs, and preliminary studies suggest its potential benefit in managing OKCs associated with GGS. Similarly, the multicenter, randomized, double-blind, placebo-controlled phase 2 study by Tang et al. (2016) found that vismodegib effectively reduced the diameter of OKCs by approximately 1.0 cm (95% CI: 0.03–1.94; p=0.02), with no observed increase in the size of pre-existing OKCs or the appearance of new ones during treatment. These findings suggest that vismodegib could serve as a valuable adjunct to surgical therapy. This therapeutic approach may offer a dual advantage, as it not only reduces BCC burden but also decreases the complexity of OKCs surgical resections due to its properties in the context of this syndrome.[12]

While the use of vismodegib and sonidegib is promising, further studies are needed to confirm their safety and efficacy in treating OKCs associated with GGS. Additionally, adverse drug reactions remain the primary reason for treatment discontinuation. In this case, the patient has a long history of OKCs, with a recurrence episode and the emergence of two new cysts. For this reason, it is crucial to consider alternative approaches aimed at achieving long-term resolution, particularly in syndromic patients.

Conclusion

This study not only presents the temporal evolution and surgical management—through decompression, enucleation, peripheral osteotomy, and MCS application—of a patient with OKCs associated with GGS but also underscores the need for a specific treatment approach for these patients, who are prone to recurrence, as demonstrated in this case.

In such cases, systemic adjuvant therapy with SHH pathway inhibitors could be considered alongside surgical treatment. We propose that complementary molecular-level therapies should be integrated into the management of these patients to provide a more comprehensive approach to the syndrome and reduce associated morbidity. However, further research is essential to evaluate new adjuvant therapies for managing OKCs in patients with this syndrome.

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Data Availability

The complete data set supporting this study's results is published within the article itself.

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NAME AND LAST NAME	ACADEMIC COLLABORATION													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Arturo Javier Henríquez Avendaño	x			x		x				x		x		x
Sebastian Alberto Galleguillos Conejeros	x			x		x	x			x		x		x
José Tomás Fernández Íbañez			x			x		x						x
Mauricio Alejandro Lobos Esparza					x	x	x							x
Marcelo Eduardo Mardones Muñoz			x			x			x	x		x	x	x
Luis Alberto Córdova Jara			x			x			x	x		x	x	x

1. Project Administration
2. Funding Acquisition
3. Formal Analysis
4. Conceptualization
5. Data Curation
6. Writing - Review and Editing
7. Research
8. Methodology
9. Resources
10. Writing - Original Draft Preparation
11. Software
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