Gorlin-Goltz Syndrome and Neoplasms: A Case Study

Nilza N F Lopes * / Eliana M. Caran ** / Maria Lucia Lee *** /
Nasjla Saba Silva **** / André Caroli Rocha***** / Carla R D Macedo ******

Gorlin syndrome is a rare autosomal dominant disorder exhibiting high penetrance and variable expressivity. It is characterized by facial dysmorphism, skeletal anomalies, multiple basal cell carcinomas, odontogenic keratocysts (OKC), palmar and plantar pits, bifid ribs, vertebral anomalies and a variety of other malformations. Various neoplasms, such as medulloblastomas, meningiomas, ovarian and cardiac fibromas are also found in this syndrome. ***Objective:*** *To describe a twelve-year-old patient with Gorlin-Goltz syndrome, with basal cell carcinomas and promyelocytic leukemia developed after receiving craniospinal radiation for a medulloblastoma. Bifid ribs as well as mandibular and maxillar OKC were also diagnosed.* ***Conclusion:*** *The patient with Gorlin-Goltz syndrome should receive close follow-up for early detection of malformations and malignant neoplasias.*

Keywords: *Gorlin syndrome, odontogenic keratocysts, basal cell carcinoma, medulloblastoma, acute myeloid leukemia*
J Clin Pediatr Dent 35(2): 203–206, 2010

INTRODUCTION

Gorlin-Goltz syndrome is an infrequent multisystemic disease that is inherited in a dominant autosomal way, with a high level of penetrance and variable expressiveness.[1,2] The gene responsible for this syndrome was mapped to the long arm of chromosome 9 at band q22.3-q31.[3,4,5,6]

The diagnosis of the Gorlin-Goltz syndrome is characterized by early cutaneous basal cell carcinoma, plantar or palmar pits, calcification of the falx cerebri, multiple odontogenic keratocysts (OKC), macrocephaly, cleft lip or palate, hypertelorism and skeletal anomalies (bifid ribs, splayed ribs, syndactyly of digits and vertebral anomalies) and a variety of other malformations.[6,7,8,9] Various low-frequency neoplasms, such as medulloblastomas, meningiomas, ovarian and cardiac fibromas also accompany this syndrome.[9,10,11] This manuscript presents a patient with Gorlin-Goltz syndrome who developed multiple cutaneous basal cell carcinomas (BCC) and acute myeloid leukemia, odontogenic keratocysts in the mandibular and maxillary bones after having had a medulloblastoma and post-operative craniospinal radiation. The diagnosis and management are discussed.

* Nilza N F Lopes, DDS, MSc, PhD, Pediatric Oncology Institute – GRAACC, Medical School of São Paulo, Federal University of São Paulo, SP, Brazil
** Eliana M Caran, MD, PhD, Pediatric Oncologist. Pediatric Oncology Institute – GRAACC, Medical School of São Paulo, Federal University of São Paulo, SP, Brazil
*** Maria Lucia Lee3 MD, Pediatric Hematologist. Pediatric Oncology Institute – GRAACC, Medical School of São Paulo, Federal University of São Paulo, SP, Brazil.
**** Nasjla Saba Silva, MD, Pediatric Oncologist. Pediatric Oncology Institute – GRAACC, Medical School of São Paulo, Federal University of São Paulo, SP, Brazil
***** André Caroli Rocha, DDS, MSc, Oral and Maxillo-Facial Surgeon at the Hospital das Clínicas of São Paulo State University.
****** Carla R D Macedo, MD, MSc, Pediatric Oncologist. Pediatric Oncology Institute – GRAACC, Medical School of São Paulo, Federal University of São Paulo, SP, Brazil

Send all correspondence to: Nilza Nelly Fontana Lopes, Rua Padre Priuli n11 –Bairro do Limão, São Paulo SP, Brazil, 02559-020

Phone/Fax: 55 11 3858 8234

E-mail: nnflopes@terra.com.br

CASE REPORT

A two-year-old Caucasian boy had resection of a brain stem medulloblastoma and was treated with radiation: 5.400cGy to the cranium and 2.400cGy to the spinal canal.

During a follow-up examination at age 5, cutaneous basal cell carcinomas (BCC) on the trunk, in the region of the craniospinal irradiation were detected. He underwent surgical excision of BCC and at age 10 the BCC relapsed. It was at this time that suspicion of Gorlin-Goltz syndrome arose and the clinical diagnosis was confirmed according to Kimonis *et al* [14] with 2 major criteria and 1 minor criterion: Multiple BCC, bifid ribs (Figure 1) and medulloblastoma. To receive early detection and treatment of new tumors, the patient was referred to the Pediatric Oncology Institute –GRAACC/UNIFESP.

At the time of admission, the twelve-year-old patient had moderate gingival swelling, epistaxis, fatigue, pallor, petechiae, fever and lymphodenopathy. The diagnosis of leukemia was made based on peripheral blood data: Hb 7g/dl, WBCs count 25.000/µl, platelet count at 20.000/µl

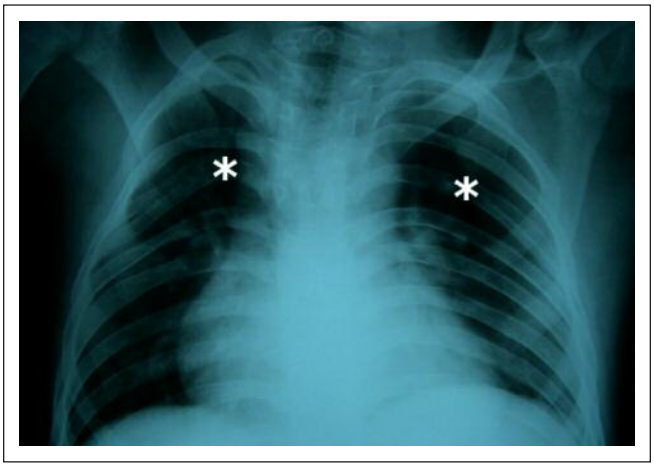

Figure 1. Chest radiograph demonstrates bifid ribs (asterisks)

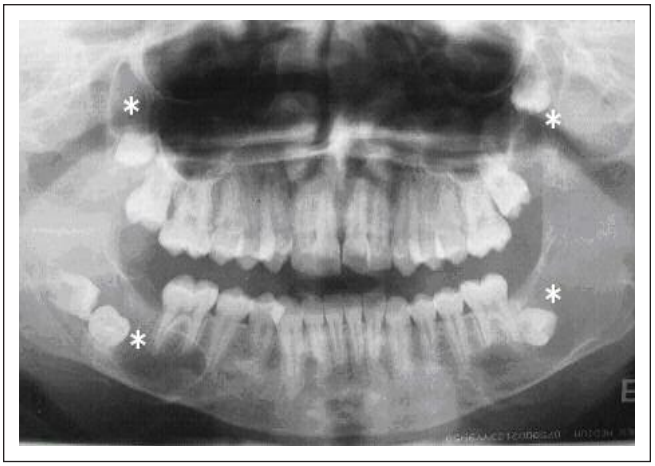

Figure 2. Radiograph shows keratocysts in mandible and maxilla (asterisks)

and the peripheral blood smear containing 30% myelocytic blasts; and bone marrow aspirate confirmed AML-promyelocytic. After cytogenetic analysis of chromosomal translocation t(15;17), the morphologic diagnosis of promyelocytic leukemia (AML-M3) was confirmed. Initially the patient was treated with trans-retinoic acid (ATRA) for forty-five days followed by a high-dose chemotherapy according to the LMAIO-I protocol. Maintenance-therapy of methotrexate, 6 mercaptopurine and ATRA continued for two years. At the end of treatment, remission of leukemia was achieved.

During a follow-up examination at the age of 15, an increase in volume in the maxillary region was noted. The panoramic radiograph revealed several radiolucent images suggestive of keratocysts (Figure 2). A biopsy was performed confirming the diagnosis of odontogenic keratocysts in both, the mandibular and maxillary bones. The patient was submitted for curettage under general anesthesia with complete removal of the lesions, which required extractions of the left and right mandibular molars as well as the second and third left and right maxillary molars. The keratocysts were completely removed with surgical enucleation and curettage. Post-operatively, bone repaired as expected (Figure 3).

Two years after completion of the leukemia treatment, the disease relapsed (AML-M3) and treatment was reinitiated with chemotherapy and arsenic acid. However, the leukemia progressed and as a result, the patient died.

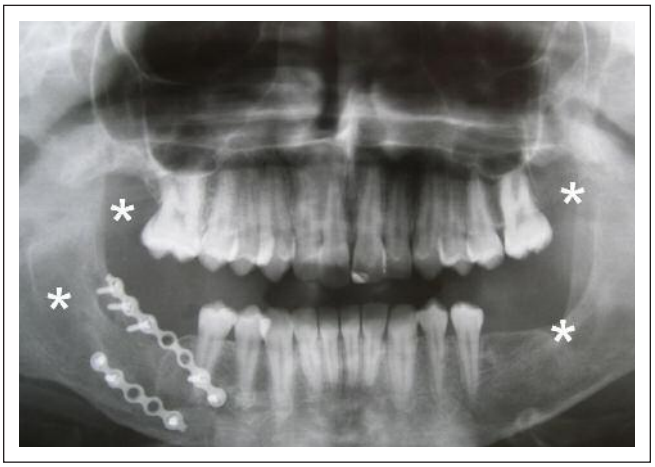

Figure 3. Panoramic radiograph after two years of surgical, bone repair. (asterisks).

DISCUSSION

Although the Gorlin-Goltz syndrome is distinctive when fully expressed, many of its physical findings are absent in early childhood. Several developmental anomalies accumulate with age so the median time of diagnosis occurs in the second or third decade of life. This variation makes definitive diagnosis in childhood difficult in many patients.[13] According to Kimonis *et al*[14] 2 major or 1 major and 2 minor criteria should be present for the diagnosis (Table 1). The most important criteria to make a diagnosis for this syndrome are the presence of pigmented basocellular carcinomas, odontogenic keratocysts, palmar and/or plantar pits and ectopic calcifications of the falx cerebri. However, more than 100 minor features have been described. The more relevant are the following: cardiac or ovarian fibroma, macroencephaly, bifid ribs, cyphoscoliosis, cleft palate, medulloblastoma, alterations in the sella tucica, mandibular prognathia, lateral displacement of the inner canthus, frontal and biparietal bossing, imperfect segmentation of the cervical vertebrae, linfomesenteric cysts that tend to calcify, meningiomas, fibrosarcoma, rhabdomyosarcoma, strabism, ocular hypertelorism, congenital blindness, spina bifida occulta, pectum excavatum, short fourth metacarpal, low-pitched voice in women, renal anomalies and hypogonadism in men .[14,15]

Probably the most important reason for recognizing Gorlin-Goltz syndrome is that, like other cancer syndromes, patients may develop multiple neoplasms at an early age.[13] Despite its occurrence generally before two years of age, patients with Gorlin-Goltz syndrome-associated medulloblastoma tend to present a better prognosis than patients who suffer exclusively from medulloblastoma.[12,13,16,17]

Table 1. Diagnosis criteria for Gorlin-Goltz syndrome according to Kimonis *et al* [14]: 2 major or 1 major and 2 minor

Major Criteria	Minor Criteria
More than 2 BCC or 1 under age 20 years	Macrocephaly determined after adjustment for height
Odontogenic Keratocysts of the jaw proven by histology	Congenital malformations: cleft lip or palate, frontal bossing, moderate or severe hypertelorism, blindness, amaurosis
3 or more palmar or plantar pits	Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
Bilamellar calcification of the falx cerebri	Medulloblastoma or ovarian fibroma
Bifid, fused or markedly splayed ribs	Radiologic abnormalities: bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet
First degree relative with Gorlin-Goltz syndrome.	Glaucoma, Cataract

*BCC- Basal cell carcinoma

In the case reported, the development of medulloblastoma occurred at an early age (two-year-old). In the general population, this brain tumor appears at the age of 7 or 8. Approximately 10% of the patients with medulloblastoma who are younger than 2 years have Gorlin-Goltz syndrome.[13,17] The early occurrence of medulloblastoma could be associated with tumor suppressor gene loss. [4,18]

The biochemical basis for Gorlin-Goltz syndrome provides some insight into the potential molecular mechanism for the proclivity to develop second tumors. The tumor suppressor gene called *Pached* (PTCH) has been mapped to chromosome 9q22.3 and identified as the cause of Gorlin-Goltz syndrome. The gene codifies a transmembrane glucoprotein which can be found in the *Hedgehog* signaling pathway[9,11,15]. In patients with Gorlin-Goltz syndrome, one allele produces a non-functional protein leaving the cell sensitive to a "second hit" that would disrupt the other allele and render the cell resistant to sonic hedgehog-mediated regulation of the cell cycle. Radiation could probably provide the mutagenic force necessary to cause this second hit and allow for unregulated cell growth and tumor formation. [11]

Although craniospinal irradiation is a mainstay of treatment for medulloblastoma, it should be acknowledged that patients with Gorlin-Goltz syndrome might develop second neoplasmas at a much higher frequency than the general population. While reviewing the literature, Dickerman [21] refers to nonmalignant and malignant late effects caused by chemotherapy and radiotherapy. According to the author, skin cancer is probably the result of decreased immuno-surveillance secondary to radiation and chemotherapy, when sun exposure occurs. Malignant melanoma and non-melanotic skin cancer represent 10 to 20% of second malignancies after therapy, with an associated increased risk of developing skin cancer over time.[21] The median age of onset of BCC in Gorlin-Goltz syndrome is 25 years of age in contrast to 61 years of age in the general population.[14] The number of BCC can range from only a few to hundreds. They most frequently involve the face as well as unexposed areas such as the back and the chest.[14] In this case the occurrence of BCC is possibly a result of an ionizing radiation induced complication. Similar cases of BCC have been reported after radiotherapy for brain tumors.[22]

El Demellawy *et al* reported an unusual case of BCC and synchronous precursor B Acute Lymphoblastic Leukemia (ALL) in the absence of any prior history of radiotherapy or immune deficiency.[23] However, ALL associated with metachronous but not synchronous BCC has been reported.[24-26] Such cases occurred in children who received radiotherapy as part of the treatment protocol of ALL and as possible consequence of BCC. To the best of our knowledge, no cases of Gorlin-Goltz syndrome with an associated AML-M3 and synchronous BCC in children have been reported in the English language literature. Could the occurrence of AML in this case have been caused by the radiation therapy that the patient received at age two? Clinical evidence suggests that young children with Gorlin-Goltz syndrome and medulloblastoma are best treated without standard radiation therapy.[13] Further clinical studies and discussions are warranted in this area.

The OKC were detected accidentally, since they present intramedullary growth and are commonly diagnosed when they reach large proportions, sometimes in association with an unerupted tooth.[27] The most common site is the molar-ramus region (44%) followed by the incisor-canine region (18%) in the mandible.[10] The majority of maxillary cysts occur in the incisor-canine (15%) and molar-tuberosity (13%) regions.[10] In this case report, odontogenic keratocysts occurred in both mandibular and maxillary bones. None of the cysts were found to have undergone malignant transformation and bone healing was evidenced. Patient follow-up continued for one year after surgery, as the recurrence rate is high and new cysts could still develop.[28]

CONCLUSION

Through the analysis of this case and the review of the literature, it can be inferred that patients presenting Gorlin-Goltz syndrome should receive close follow-up for early detection of malformations and malignant neoplasias. They may require multidisciplinary consultation.

REFERENCES

1. Bonifas JM, Bare JW, Kerschmann RI, Master SP, Epstein EH Jr. Parenteral origin of chromosome 9q22.3-q3 lost in basal cell carcinomas from basal cell nevus syndrome patients. Hum Mol Genet, 3: 447–448, 1994.
2. 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, 130: 669–674, 1999.
3. Farndon PA. Complications of the nevoid basal cell carcinoma syndrome: results of a population based study. J Med Genet, 30: 460–4, 1993.

4. Gailani,MR, Bale SJ, Leffell DJ, DiGiovanna JJ,Peck GL, Poliak S, *et al*. Developmental defects in Gorlin syndrome related to a putative tumor suppressor gene on chromosome 9. Cell, 69: 111–117, 1992.
5. Schofield DM, West DC, Antony DC, Marshal R and Sklar J. Correlation of loss the heterozygosity at chromosome 9q with histological subtype in medulloblastomas. Am J Pathol, 146: 472–480, 1995.
6. Kansal A, Brueton L, Lahiri A, Lester R. Hypoplastic thumb in Gorlin´s syndrome. J Plast Reconstr Aesthet Surg, 60(4): 4410–2, 2007.
7. Shanley S, Rarcliffe 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, 50: 282–290, 1994.
8. Tabuchi K; Okubo H. Takahashi K; Uemaetomari I; Shimoyamada H, Nakayama Y, et al. Nevoid basal cell carcinoma syndrome: report of an aggressive case with ethoid sinus invasion. Auris Nasus Laryns, 30: 421–3, 2003.
9. Scanlan D, Radio ST, Nelson M, Zhou M, Streblow R, Prasad V *et al.* Loss of the PTCH1 gene locus in cardiac fibroma. Cardiovascular Pathol, 17: 93–97, 2008.
10. 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, 55: 34–40, 1999.
11. Pribila JT, Ronan SM, Trobe JD. Multiple intracranial meningiomas causing papilledema and visual loss in a patient with nevoid basal cell carcinoma syndrome. J Neuro Ophthalmol, 28: 41–46, 2008.
12. O´Malley S, Weitman D, Olding M and Sekhar L Multiple neoplasms following craniospinal irradiation for medulloblastoma in a patient with nevoid basal cell carcinoma syndrome. J Neurosurg, 86: 286–288, 1997.
13. Walter AW. Gorlin Syndrome. Publish on line www.emedicine.com/ped/topic 890.htm, 2006.
14. Kimonis VE, Goldstein AM, Pastakia B, Yang ML, Kase R,Di Giovanna JJ e*t al.* Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet, 69: 299–308, 1997.
15. Ortega Garcia de Amezaga A, Garcia Arregui O, Zepeda Nunõ S, Acha Sagredo A, Aguirre Urizar JM. Gorlin-Goltz syndrome: clinicopathologic aspects. Med Oral Patol Oral Cir Bucal, Jun 1;13(6): E338–43, 2008.
16. Howell JB, Lamar Byrd D, McClendon JL and Anderson DE. Identification and treatment of jaw cysts in the nevoid basal cell carcinoma syndrome. J Oral Surg, 25: 129–138, 1967.
17. Blaney SM, Kun Le ,Hunter J,Rorke-Adams LB, *et al*. In Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology Philadelphia, Ed 5^{a} PA: Lippincott-Raven, 786–864, 2006.
18. Albrecht S, Goodman C, Rajagopolan S, Levy M, Cech DA, Cooley LD. Malignant meningioma in Gorlin´s syndrome: cytogenetic and p53 gene analysis. J Neurosurg, 81: 466, 1994.
19. Compton JG, Goldstein AM, Turner M *et al*. Fine mapping of the locus for nevoid basal cell carcinoma syndrome on chromosome 9q. J Invest Dermatol, 103: 178–181, 2004.
20. Villavicencio EH, Walterhouse DO, Iannaccone PM. The sonic hedgehog-patched-glia pathway in human development and disease. Am J Hum Genet, 67: 1047–1054, 2000.
21. Dickerman JD. The late effects of childhood cancer therapy. Pediatrics, 119: 554–568, 2007.
22. Dinehart S, Anthony JL, Pollack SV. Basal cell carcinoma in young patients after irradiation for childhood malignancy. Medical and Pediatric Oncology, 19: 508–510, 1991.
23. Demellawy DE, Sur M, Ross C, DeNardi F, Alowam S. Composite multifocal basal cell carcinoma and precursor B Acute Lymphoblastic Leukemia. Diagn Pathol, 2: 32–35, 2007.
24. Gracia-Silva J, Velasco-Benito JA, Pena-Penadad C, *et al*. Basal cell carcinoma in a girl after cobalt irradiation to the cranium from acute lymphoblastic leukemia. Pediatric Dermatology, 13: 54–57, 1996.
25. Youshihara T, Ikuta H, Hibi S, *et al*. Second cutaneous neoplasms after acute lymphoblastic leukemia in childhood. International J Hematol, 59: 67–71, 1993.
26. Whitmore SE, Greer KE. Multiple neck papules ina a child with acute lymphoblastic leukemia. Archives of Dermatology, 126: 102–105, 1990.
27. Chiang ML, Huang WH. Odontogenic keratocyst clinically mimicking an eruption cyst: report of a case. J Oral Pathol Med, 33(6): 373–5, 2004.
28. Gorlin RJ. Nevoid basal cell carcinoma syndrome. Dermatol Clin, 13: 113–125, 1995.