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CASE REPORT

Extensive mandibular multiloculation in a patient with Nevoid Basal Cell Carcinoma Syndrome: Case Report

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Abstract:

Gorlin Goltz Syndrome, or Nevoid Basal Cell Carcinoma Syndrome, is an autosomal dominant genetic disease characterized especially by the manifestation of basal cell carcinomas in the skin and keratocysts in the jaws. Additionally, patients may present with several other manifestations, such as bifid ribs, hypertelorism and calcification of the falx cerebri. The diagnosis has physicians and dentists as protagonists in the investigation and involves a good anamnesis associated with a detailed physical examination, imaging, anatomical and histopathological exams and, if possible, the identification of the PTCH1 gene, which covers approximately 85% of patients. The present study aims to present an up-to-date integrative literary review of the Gorlin Goltz Syndrome, highlighting the care and management of the case of a syndromic patient treated at a stomatology clinic, carrying a series of major and minor findings of the disease.

Keywords: Basal Cell Nevus Syndrome; Carcinoma, Basal Cell; Odontogenic Cysts; Medulloblastoma.

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INTRODUCTION

Gorlin Goltz syndrome or Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant hereditary condition, with high penetrance, variable expressivity, and a wide range of developmental abnormalities and predispositions to postnatal tumors[1-3]. It was first mentioned in 1894 by Jarish and White, who highlighted the various basal cell carcinomas identified, and later detailed by Gorlin and Goltz in 1960, who established in more detail the varied phenotypic expressions that characterize the disease[4,5]. The syndrome arises from the mutation of the PTCH1 gene, mapped on chromosome 9q22.3-q31, and involved in the sonic hedhehog (SHH) molecular pathway, directly involved in the action of embryonic cells in determining the correct development of the embryo, in tissue repair and in carcinogenesis[2-4,6,7].

Multiple basal cell carcinomas usually appear between 20 and 30 years of age, in areas most exposed to ultraviolet radiation in the head and neck of syndromic patients. Odontogenic keratocysts of the maxillary bones are the second most frequent clinical manifestation and occur preferentially in the first and second decades of life. It is originated from the dental lamina of odontogenesis and can present multiple imaging patterns, of varying dimensions, in gnathic bones[2,8]. The presence of two major findings, or one major and two minor findings, completes the diagnosis of NBCCS. Major criteria include: 2 or more basal cell carcinomas in individuals under 20 years of age; odontogenic keratocysts in patients under 20 years of age confirmed in histopathological studies; three or more palmoplantar depressions; bilamellar calcification of the falx cerebri; fused or markedly expanded bifid rib; first-degree relative with the aforementioned syndrome and meduloblastoma[1,9]. Minor criteria include macrocephaly, congenital malformation (such as cleft lip or palate, prominent face, Sprengel deformity, and syndactyly), radiographic abnormalities (such as vertebral abnormalities, shaping defects of the hands and feet, and ovarian fibroma) and ocular abnormalities (strabismus, hypertelorism, congenital cataract, glaucoma)[1,5,10,11].

The treatment of NBCCS is interdisciplinary and individualized for the particularities of each individual affected by the disease 9. The role of the dermatologist involves the approach of basal cell carcinomas, with surgical excisions and photodynamic therapy with 5-aminolevulinic acid, always minding the importance of the anatomical and histopathological examination for the investigation of malignancies, in addition to the appropriate preventive guidelines[5,12]. The role of the dentist involves the treatment of keratocysts, with the chosen treatment method depending on the size, location and extent of the lesion, as well as on its primary or recurrent presentation[13,14]. It is possible that the treatment chosen is a simple enucleation followed by curettage and/or ostectomy for smaller lesions, or prior marsupialization and the use of Carnoy's solution for larger lesions[9].

The present study reports a case of extensive mandibular multiloculation in a patient with NBCCS, as well as an integrative literature review of the updated objective of the NBCCS, highlighting the management of the patient treated at a stomatology clinic.

CASE REPORT

A 22-year-old female attended the stomatology clinic accompanied by her mother who reported the presence of a mandibular lesion identified approximately two months ago, found by chance due to a routine clinical imaging control carried out as a result of previous comorbidities. According to the mother's report, the patient presented cognitive limitations since the early stages of childhood. Thus, the anamnesis was entirely conducted through direct dialogue with the mother, who reported the daughter's absence of painful symptoms and the history that doctors would have reported the probable existence of a hereditary disease whose diagnosis the mother did not remember.

In this first consultation, multislice computed tomography images were brought by the mother, which showed an insufflating osteolytic lesion, in the left mandibular region, measuring 3.8 x 2.7 cm, containing a tooth inside, in addition to a right occipital craniotomy and calcifications in the basal ganglia. Another tomographic reconstruction also showed a hypodense and well-delimited lesion associated with an upper molar. The mother also reported a history of two neoplasms during her daughter's childhood, one bilateral ovarian ossifying fibroma-type tumor and the other a medulloblastoma, culminating in therapeutic success in both surgical interventions. In addition, the mother reported the existence of numerous small surgical interventions to excise skin lesions throughout the patient's body.

During the physical examination, it was possible to observe her short stature (1.40 m in height), numerous hyperpigmented papules and nodules in the regions of the face, neck and back (Figure 1A), a posterior cervical scar compatible with the incision to remove the medulloblastoma (Figure 1B) and punctated palmar depressions

Figure 1. Records of the patient at different times of clinical follow-up highlighting the numerous skin lesions suggestive of basal cell carcinomas. Figure 1B highlights the scar resulting from the removal of medulloblastoma in adolescence and 1C the patient's right hand with punctate palmar depressions.

(Figure 1C). The intraoral examination allowed the identification of numerous missing teeth (Figures 2A and 2B) and a slight bulge in the mandibular body on the left side (Figure 2C).

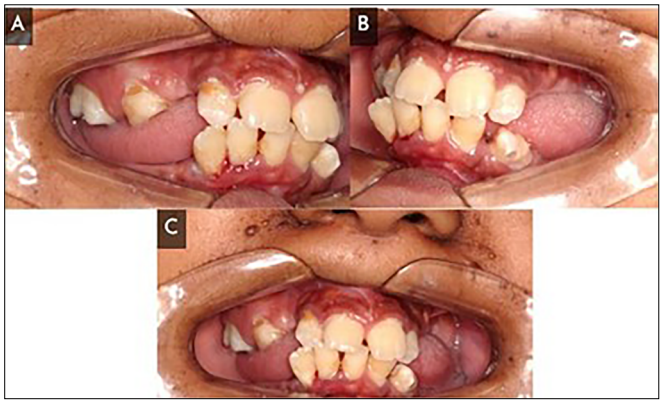

Figure 2. Intraoral physical examination allowed the identification of several missing teeth and a slight bulging of the left mandibular ridge.

In order to perform an adequate evaluation of the lesion, a panoramic radiography was requested (Figure 3A). The image allowed the identification of a well-defined, multilocular radiolucent lesion in the left mandible, measuring approximately 5 cm in its largest diameter, extending from the coronoid process / mandibular notch to the region of the lower left second premolar. The lesion caused expansion and thinning of the inferior border of the mandible. The lower left second premolar was inside the lesion, dislocated, positioned close to the mandibular angle. In the same radiography, it could be observed another radiolucent area in the periapical region of the upper right first molar, which apparently caused an elevation of the adjacent maxillary sinus floor. In addition, the only teeth present were elements 16, 55, 12, 11, 21, 23, 35 (inside the lesion), 34, 32, 31, 41 and 42. The previously

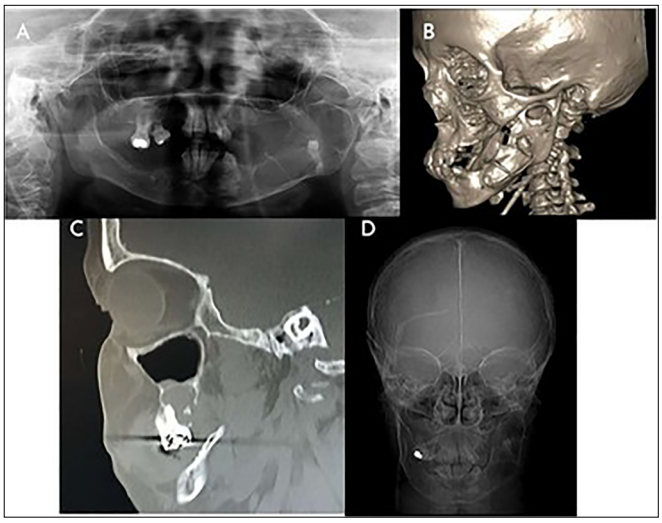

Figure 3. Panoramic X-ray suggesting extensive mandibular lesion (A). Three-dimensional reconstruction and lesional multiloculation (B). Sagittal section showing a well-defined lesion near tooth 16 (C). Posteroanterior X-ray showing the presence of calcification of the falx cerebri (D).

performed computed tomography allowed visualization of the multilocular nature of the mandibular lesion, as well as the three-dimensional visualization of a lesion associated with element 16 (Figures 3B and 3C). Subsequently, a posteroanterior radiograph of the head was also acquired (Figure 3D), which allowed the visualization of calcification of the falx cerebri.

Following the investigative process of the gnathic lesions, aspiration and incisional biopsies of the maxillary and mandibular lesions were performed, both of which were positive for yellowish liquid contents with whitish granules suggestive of keratin. Histopathological analysis of the material obtained from both lesions revealed lesions of cystic architecture, lined by stratified squamous, parakeratotic, thin epithelium, with palisaded basal cells with hyperchromatic nuclei. The capsule consisted in non-inflamed connective tissue, with a flat interface and eventually detached from the overlying epithelium. Such findings were considered conclusive for the diagnosis of odontogenic keratocyst (Figures 4A and 4B). In view of all the findings in the physical examination, with special emphasis on five major criteria (basal cell carcinomas, keratocysts, palmar depressions, calcification of the falx cerebri and medulloblastoma) and one minor (ovarian fibroma), the diagnosis of NBCCS was confirmed. The mother denied similar clinical findings in any other family member, including the patient's two sisters on the mother's side, which ruled out the major criterion relating to first-degree relatives with the same diagnosis.

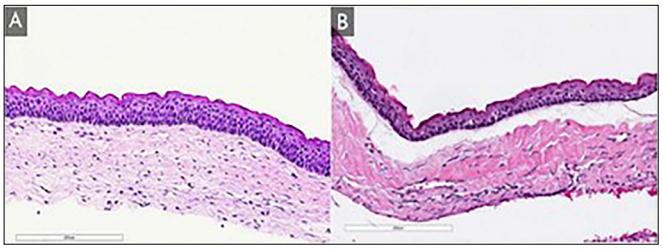

Figure 4. Representative histopathological appearance of the lesions, showing a thin epithelial lining, with a parakeratinized and corrugated surface, with a flat interface with the fibrous capsule, with occasional detachment (B). Such findings are characteristic of an odontogenic keratocyst. Staining: hematoxylin and eosin.

The patient was followed up with several medical specialties due to the various syndromic alterations, including dermatology due to the numerous basal cell carcinomas. In order to treat the intraosseous lesions, the patient underwent decompression of the extensive mandibular lesion, followed by home care with irrigation twice a day with 0.12% chlorhexidine digluconate, in addition to complete enucleation of the maxillary lesion. Monthly follow-up appointments were held, with panoramic radiographs repeated every three months. Approximately one year after the initial consultation, there was new bone formation next to the mandibular lesion and complete bone repair in the region of the superior enucleated cyst (Figure 5). Then, the residual lesions were enucleated, as altogether with the extraction the teeth 35, 16 and 55 due to periodontal status (Figure 6). The patient had an excellent postoperative recovery and has been attending quarterly clinical follow-ups. Clinical and radiographic exams were performed on the sixth follow-up (Figure 7) and the patient was also referred for prosthetic rehabilitation of the edentulous areas. It is also worth noting that probable basal cell carcinomas should be progressively and periodically excised by the dermatology team at the same institution.

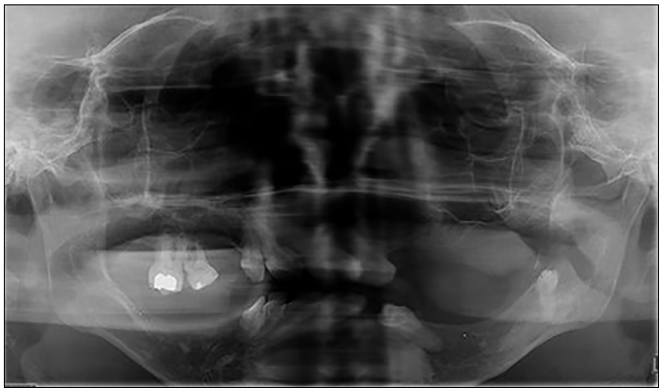

Figure 5. Panoramic radiography of follow-up of approximately one year suggesting satisfactory new bone formation of the lesion after marsupialization.

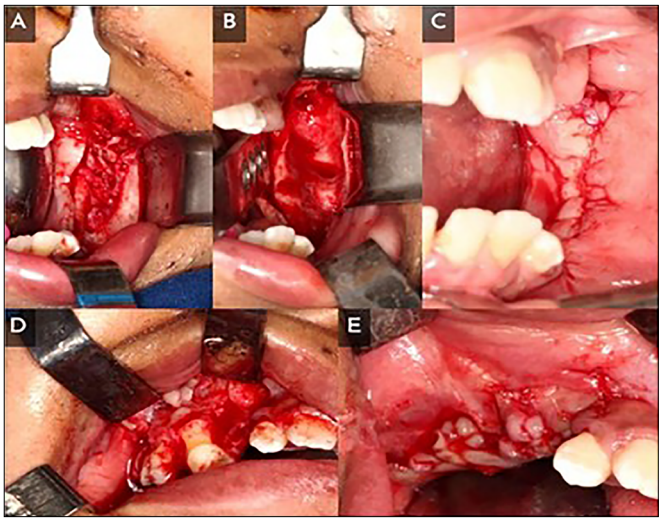

Figure 6. Final Surgery Records. Exposure of the marsupialized mandibular lesion(A). Enucleated lesion curetted and without the associated tooth (B). Completed suture (C). Teeth 16 and 55 before extractions (D). Suture in the maxillary surgical bed (E).

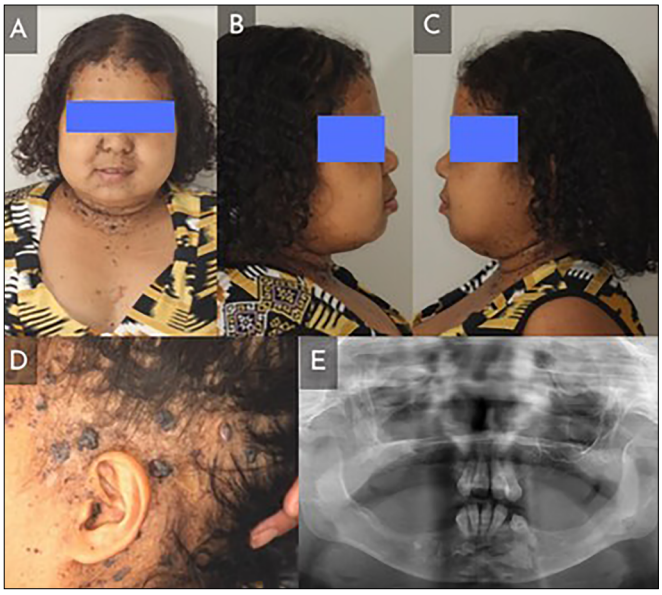

Figure 7. 1.5-year follow-up of the patient's initial care. Figures A, B and C with frontal and lateral registers of the patient. Figure D showing several probable basal cell carcinomas requiring dermatological evaluation. Panoramic X-ray showing excellent new bone formation and patient awaiting prosthetic rehabilitation (E).

DISCUSSION

Gorlin-Goltz syndrome or nevoid basal cell carcinoma syndrome (NBCCS) is characterized as an autosomal dominant hereditary condition with high penetrance and varied prevalence of approximately 1 in every 60,000 inhabitants worldwide[2,4]. Genetic mutations are well described in the literature, determining a range of clinical manifestations in affected patients. Particularly,

alterations in the germline of the PTCH1 tumor suppressor genes, locus 9q22.32 of chromosome 9, are well associated with the etiopathogenesis of the disease in the vast majority of cases[1,15]. Multiple basal cell carcinomas in the skin and keratocysts in the gnathic bones, in addition to the disease affecting first-degree relatives, are some of the main characteristics of the syndrome[16]. However, many other findings are described in patients, depending on the moment and intensity of the genetic mutation, such as calcifications of the falx cerebri, bifid ribs, hypertelorism, medulloblastomas, ovarian fibromas, palmoplantar depressions, diverse genetic alterations, and congenital malformations[5,17].

The genetic study, especially related to mutations in the PTCH1 gene, associated with the various possible clinical manifestations, consist of the findings that allow the conclusive diagnosis of NBCCS. Given the possible inaccessibility of genetic evaluation, especially in public services, sometimes the syndrome is defined through the clinical presentations 6,15. In the present study, the patient attended the stomatology clinic with hundreds of basal cell carcinomas throughout her body, in addition to several other lesions, such as two keratocysts diagnosed and excised in the stomatology outpatient clinic, palmar depressions, calcification of the cerebral scythe, in addition to the history of surgical treatments for medulloblastoma in childhood and ovarian fibromas, therefore consisting of five major and one minor criteria found, sufficient findings for the diagnostic conclusion of NBCCS. Short stature and impaired cognitive ability also drew attention. It is worth mentioning that in the family investigation, other family members with syndromic manifestations were not identified, including the research with the two sisters on the mother's side. We emphasize that further investigation of the patient is in order, at an opportune moment, to verify other skeletal alterations that may also be present.

The treatment directed to patients with NBCCS is extremely challenging and complex, since it depends on the magnitude of the related gene alterations and the concomitant amount of clinical manifestations that will involve different therapies for those affected by the syndrome. Basal cell carcinomas are frequently present and requires the care and periodic interventions of dermatologists, including the possibility of malignancy of these skin lesions 17. Odontogenic keratocysts also account for extremely common findings and, as they occur exclusively in the gnathic bones, dentists are the professionals responsible for the treatment and follow-up of these lesions 18. Many other possible clinical conditions can occur in patients and, when necessary, resolving, or palliative therapeutic interventions should also occur. In the present report, the patient attended the stomatology service with a mandibular lesion compatible with an odontogenic keratocyst, which required marsupialization prior to final enucleation and curettage, given the large extent of the lesion. In the diagnostic investigation, another keratocyst was identified and treated in the maxilla. The patient also arrived at the stomatology clinic under concomitant treatment with a team of dermatologists, with a history of several excisions of basal cell skin carcinomas and with hundreds of lesions still present. In the anamnesis, previous treatments of ovarian fibromas and a medulloblastoma were also evidenced, important manifestations that required other medical specialties, such as gynecologists and neurosurgeons, exemplifying the interdisciplinary character necessary for the management of this disease 15.

NBCCS is a disease of absolute relevance for the dental surgeon, considering the enormous incidence of maxillary keratocysts as commonly present clinical manifestations in affected individuals. Thus, it is imperative that the dentist minimally understand the etiology of the disease, its manifestations and necessary management, so that they can act interdisciplinary in favor of adequate guidelines for the health and quality of life of patients. Our patient presented after many dental procedures (fillings and extractions), but the diagnosis of her gnathic lesions was clearly delayed. There was risk of further complications such as pathological fracture, infection, and insidious development of intraosseous malignancy. Knowledge of main syndromic features and proper imaging investigation could accelerate clinical suspicion 19. The presented report also shows how much cooperative and interdisciplinary approach is fundamental in the treatment of NBCCS, since, over the years, the patient underwent the care of many specialists, such as dermatologists, dentists, neurosurgeons, and gynecologists 11,12. Specifically in relation to the syndrome's dental issues, it is worth mentioning the routine need to perform decompressions for the treatment of large keratocystic lesions that may be present 14. The syndromic young woman in this report presented an extensive mandibular lesion that underwent initial decompression, and another one in the maxilla, enucleated and curetted directly, both of which resulted in satisfactory outcomes. It is also worth emphasizing to patients and family, especially when there is loss of

cognitive capacity of the patient, as was the case in this case, how necessary is the periodic follow-up of these individuals, given the high rate of recurrence associated with this cyst of odontogenic development 6.

CONCLUSION

Gorlin Goltz Syndrome is a complex disease that requires a cohesive and proactive interdisciplinarity during the management of affected individuals. In this context, this work can conclude that the dentist has a crucial importance in the well-being of patients, since odontogenic keratocysts are frequently present lesions that require an assertive and effective approach in favor of improving the quality of life of affected individuals.

REFERENCES

1. Medeiros L, Ferreira JC. Síndrome de Gorlin-Goltz: revisão bibliográfica a propósito de um caso clínico. Rev Port Estomatol Cir Maxilofac [Internet]. 2006; [cited 2022 Sep 07]; 47(1):25-32. Available from: https://www.spemd.pt/imagens/anexo_270.pdf
2. Freitas DA, Veloso DA, Santos ALD, Freitas VA. Maxillary odontogenic keratocyst: a clinical case report. Rev Gaúch Odontol [Internet]. 2015; [cited 2022 Sep 07]; 64(4):484-8. Available from: https://www.scielo.br/j/rgo/a/m87tzPq3jQJLvCkJK8DFNDH/abstract/?lang=en
3. Russo F, Liso FG, Santi F, Provvidenziale L, Taddeucci P, Rubegni P. Gor-lin goltz syndrome: beware of melanoma. Dermatol Pract Concept [Inter-net]. 2022 Jan; [cited 2022 Sep 07]; e2022038. Available from: https://dpcj.org/index.php/dpc/article/view/1715
4. Kiwilsza M, Sporniak-Tutak K. Gorlin-Goltzsyndrome – a medical condition requiring a multidisciplinary approach. Med Sci Monit [Internet]. 2012; [cited 2022 Sep 07]; 18(9):145-53. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3560657
5. Ribeiro PL, Souza Filho JB, Abreu KD, Brezinscki MS, Pignaton CC. Syn-drome in question: Gorlin-Goltz syndrome. An Bras Dermatol [Internet]. 2016 Jul; [cited 2022 Sep 07]; 91(4):1-3. Available from: https://www.scielo.br/j/abd/a/Z8dm5zb9M888zW4sNVqpbzh/abstract/?lang=en#
6. Vieira EC, Abbade LPF, Marques SA, Marques MEA, Stolf HO. Síndrome de Gorlin. Diagn Tratamento [Internet]. 2012; [cited 2022 Sep 07]; 17(3):110-4. Available from: http://files.bvs.br/upload/S/1413-9979/2012/v17n3/a3115.pdf
7. Uribe-Valencia MA, Jurado-Delgado J, Velásquez-Tafur LM, Cárdenas-Cardona LF. Gorlin-Goltz syndrome in an older black adult. Case Report. Rev Fac Med [Internet]. 2021 Jul; [cited 2022 Sep 02]; 69(2):1-6. Available from: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0120-00112021000200500
8. Davalos CP, Vélez JU, Estévez ADM. Sindrome de Gorlin: a proposito de un caso. Rev Haban Cienc Méd [Internet]. 2008 Mar; [cited 2022 Sep 07]; (7)1:1-12. Available from: http://scielo.sld.cu/scielo.php?pid=S1729-519X2008000100011&script=sci_arttext&tlng=en
9. Bomfin LE, Vivas APM, Rocha AC, Achatz MIW, Pinto CAL, Alves FA. Keratocystic odontogenic tumor related to nevoid basal cell carcinoma syndrome: clinic pathological study. Braz J Oral Sci [Internet]. 2013 Mar; [cited 2022 Sep 02]; 12(1):23-29. Available from: https://www.scielo.br/j/bjos/a/vzcqJkPkZsShCBxqBnCVDmK
10. Onodera S, Nakamura Y, Azuma T. Gorlin syndrome: recent advances in genetic testing and molecular and cellular biological research. Int J Mol Sci [Internet]. 2020 Oct; [cited 2022 Sep 08]; 21(20):1-17. Available from: https://www.mdpi.com/1422-0067/21/20/7559
11. Neville BW, Damm DD, Allen CM, Bouquot JE. Patologia oral e maxilofaci-al. 3th ed. Rio de Janeiro: Elsevier; 2009.
12. Rosón-Gómez S, González-García R, Naval-Gías L, Sastre-Pérez J, Mu-ñoz-Guerra MF, Díaz-González FJ. Síndrome de Gorlin-Goltz: serie de 7 casos. Rev Esp Cir Oral Maxilofac [Internet]. 2009 Sep/Oct; [cited 2022 Sep 9]; 31(5):309-15. Available from: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1130-05582009000500002&lang=pt
13. Carbia SG, Marrero M, Glorio R, Etchart C, La Forgia M. Síndrome del carcinoma basocelularnevoide (síndrome de Gorlin). Dermatol Argent [In-ternet]. 2009 May; [cited 2022 Sep 09]; 15(3):1-4. Available from: https://dermatolarg.org.ar/index.php/dermatolarg/article/view/279
14. Stolz ASB, Oliveira MO, Ferreira F, Uggeri CM. Proservação pós-operatória de paciente com Síndrome de Gorlin-Goltz - relato de caso. RSBO [Internet]. 2010 Jun; [cited 2022 Sep 09]; 7(2):226-30. Available from: http://revodonto.bvsalud.org/scielo.php?pid=S1984-56852010000200015&script=sci_abstract
15. Moyano D, Gondos L, Peirano E, Bermeo J, Sáez E. Síndrome de Gorlin-Goltz: una presentación atípica. Rev Otorrinolaringol Cir Cabeza Cuello [Internet]. 2016; [cited 2022 Sep 07]; 76(1):1-5. Available from: https://www.scielo.cl/scielo.php?pid=S0718-48162016000100013&script=sci_arttext&tlng=en
16. Kato C, Fujii K, Arai Y, Hatsuse H, Nagao K, Takayama Y, et al. Nevoid ba-sal cell carcinoma syndrome caused by splicingmutations in the PTCH1 gene. Fam Cancer [Internet]. 2017 Aug; [cited 2022 Sep 09]; 16(1):131-8. Available from: https://link.springer.com/article/10.1007/s10689-016-9924-2
17. Rodríguez RG, Cossío PI, Parejo PR, Carranza ET, García AGP, Castro DS. Síndrome de Gorlin-Goltz: manejo del carcinoma baso celular facial. Rev Esp Cir Oral Maxilofac [Internet]. 2013 Jan/Mar; [cited 2022 Sep 09]; 35(1):1-8. Available from: https://pesquisa.bvsalud.org/portal/resource/pt/ibc-109780
18. Nilius M, Kohlhase J, Lorenzen J, Lauer G, Schulz MC. Multidisciplinary oral rehabilitation of an adolescent suffering from juvenile Gorlin-Goltz syn-drome – a case report. Head Face Med [Internet]. 2019 Feb; [cited 2022 Sep 09]; 15(1):1-5. Available from: https://head-face-med.biomedcentral.com/articles/10.1186/s13005-019-0189-5
19. Lazaridou MN, Dimitrakopoulos I, Tilaveridis I, Iliopoulos C, Heva A. Basal cell carcinoma arising in association with a maxillary keratocyst in a patient with Gorlin-Goltz syndrome. Report of a case. Oral Maxillofac Surg. 2012 Mar;16(1):127-31. DOI: https://doi.org/10.1007/s10006-011-0270-0