Archives of Clinical & Experimental Surgery

Case Report
Arch Clin Exp Surg 2015;4:49-53
doi:10.5455/aces.20140108034044

Gorlin syndrome: Importance of clinical signs and danger of delayed diagnosis - A case report with eight years follow-up

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ABSTRACT

Nevoid basal cell carcinoma (NBCCS) or Gorlin-Goltz syndrome (GS) is a multidisciplinary problem, the early diagnosis of which allows secondary prophylaxis that follows an appropriate regimen to delay progression of the syndrome. The aim of this study was to present a case of delayed diagnosis of GS in a young patient who received multidisciplinary treatment 5 years after onset. The patient presented for evaluation with painless swelling of the left maxilla. Histological examination confirmed the diagnosis of a keratocyst odontogenic tumor (KOT) that was enucleated. On presentation, the patient's symptoms and clinical signs were not related to complications of GS, and the possibility of GS was initially rejected, as he did not have a family history of the syndrome. Four years after the first surgery to remove the lesion, the patient came to our clinic with a brown, pigmented lesion. Computed tomography revealed ectopic lamellar calcification of the falx cerebri, which was the conclusive factor for the diagnosis of GS. It is important that clinicians recognize the clinical signs of GS, which mainly manifests itself as multiple basal cell carcinomas in the skin.

Key words: *Basal cell nevus syndrome, Gorlin syndrome, keratocyst odontogenic tumor*

Introduction

Nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin-Goltz syndrome (GS) is an autosomal dominant disorder characterized by multiple basal cell carcinomas (BCCs), epidermal cysts of the skin, keratocyst odontogenic tumors (KOTs) of the jaw, palmar and plantar pits, calcified dural folds, and various stigmata of maldevelopment [1,2]. In 1960, Gorlin-Goltz described the association between NBCSS and cutaneous disorders as a syndrome comprised of multiple BCCs, KOTs, and bifid ribs. A spectrum of other neurologic, ophthalmic, endocrine, and genital manifestations are known to be variably associated with this triad [3].

It is estimated that NBCCS occurs in approximately 1 in 60,000 people, with males and females being equally affected [4]. The clinical characteristics can be detected during the first three decades of life, with 90% of patients 40 years of age exhibiting BCC. The pathogenesis of GS is attributed to mutations of Patched, which is a tumor suppressor gene located on

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Received / Accepted : *September 15, 2013 / January 08, 2014*

chromosome 9q22.3-q31. Tumor suppressor genes are recessive oncogenes whose homozygous inactivation is required for their carcinogenic expression. However, when only one allele is modified, the individual is predisposed to cancer [5]. The etiology is autosomal dominant with approximately 35-50% of new mutations. Despite the hereditary characteristics of the syndrome, almost 60% of patients have no known affected family members. Therefore, the absence of family history does not exclude the diagnosis of GS [1,6].

Here, we present a case of delayed GS diagnosis in which the patient received multidisciplinary treatment 4 years after onset. The goal of this study was to discuss and emphasize the importance of establishing a diagnosis as soon as possible to prevent fatal consequences, especially from multiple skin cancers and other tumors associated with the syndrome.

Case Report

A 26-year-old white male presented himself for evaluation at the Department of Oral Diagnosis and Surgery with painless swelling of the left maxilla (Figure 1). Oral examination showed poor occlusion, an unerupted left canine and an oral cavity fistula that communicated to the maxillary sinus in the upper third molar region. A panoramic radiograph showed a unilocular radiolucent lesion located in the left maxillary sinuses involving the third molar with possible association of the maxillary sinus. A permanent unerupted canine was detected in the orbit region on the right side. On the left maxillary side, there was another lesion still in early development.

Under general anesthesia, an incisional biopsy of several lesions was taken. The histological findings were a characteristic band-like lining of stratified squamous epithelium 5 to 8 cells thick, with a flat epithelium-connective interface, and flattened luminal parakeratotic cells that were wavy or corrugated in appearance. Histological examination confirmed the diagnosis of KOT. The cysts were enucleated (Figure 2), and careful curettage with application of Carnoy's solution was performed. The patient reported the presence of pigmented skin lesions that were diagnosed as carcinomas, but no correlation with GS was made at this time. The patient was asked to return to monitor the lesion. Four years after the first surgery to remove the lesion, the patient came to our clinic with a brown, pigmented lesion in the palate between the right first molar and second premolar.

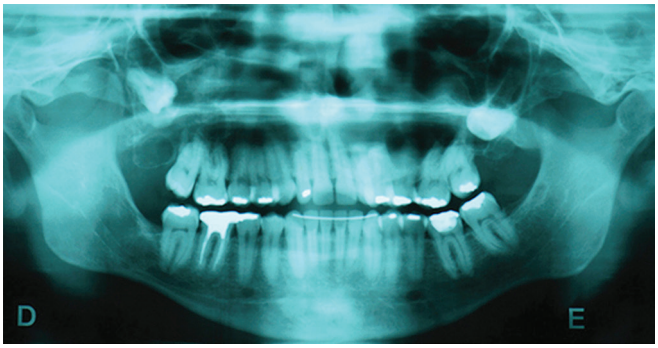

Figure 1. Swelling and communication buccal sinus in the left maxilla.

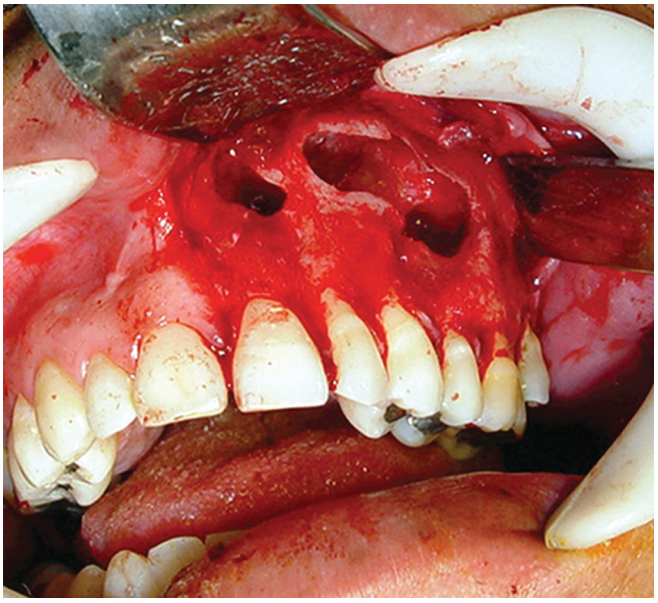

Figure 2. Enucleation of KOT.

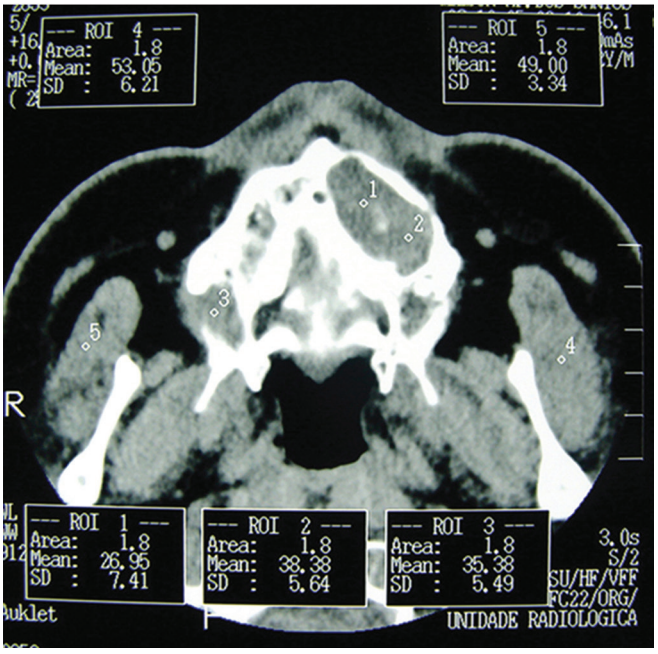

Figure 3. CT axial imaging showing maxillary expansion.

Subsequently, the patient was examined by maxillofacial computerized tomography (CT). Axial CT images of the maxilla confirmed the multilocular and bilateral aspects of the lesions. The lesions caused the large expansion of the left maxillary sinus toward the lateral and anterior walls (Figure 3). Evaluation of the CT images revealed ectopic lamellar calcification of the falx cerebri (Figure 4) and was the conclusive factor in the diagnosis of GS. On presentation, the patient's symptoms and clinical signs were not related to complications of GS and the possibility of GS was initially rejected, as he did not have a family history of the syndrome.

Laboratory exams revealed no alteration of renal function (urea, creatinine) and alkaline phosphatase. The patient was examined by a dermatologist and neurologist so that a multidisciplinary decision could be made about his treatment. The patient was again placed under general anesthesia to remove the KOT on the right. The Caldwell Luc procedure was used to enucleate and curette the tumor, and to remove all of the maxillary sinus membrane. After 15 days, the patient was in good general health, without pain or signs of infection and paresthesia in the infra-orbital region. During the 6-month follow-up period, a panoramic x-ray showed bone healing in the region of the angle and the ascending ramus of the maxilla. Eight years after the first surgery, clinical and radiograph images show no recurrence of KOT (Figure 5).

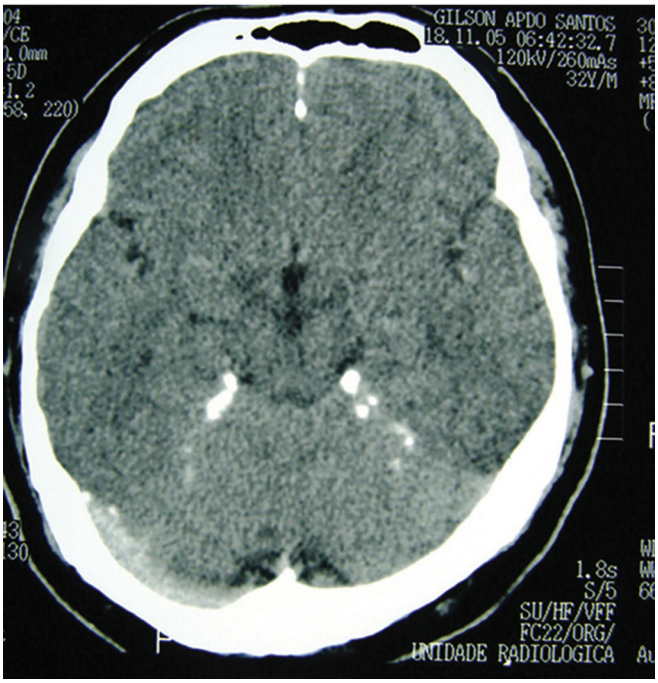

Figure 4. Cranial tomogram showing calcification of the falx cerebri.

Discussion

It is estimated that approximately 1 in 200 patients with one or more BCCs have GS, and the risk increases with decreasing age of BCC diagnosis. Similarly, 1 in 5 patients under the age of 20 with BCC diagnosis have GS [7]. In GS, BCC usually manifests itself clinically between puberty and 35 years of age, and mainly involves the thoracic and cervical-facial, as seen in this case study [6]. Their sizes vary from 1-10 mm and tumors may be the first signs observed in the syndrome [1]. Despite the fact that NBCCS is rare, isolated BCC is the most common malignancy of the skin.

KOTs are the second most common characteristic associated with NBCCS, with an incidence of 7-10% among all developing oral cysts, and an occurrence of 66-92% in these patients. Onset is generally between the second and third decade of life and is 3 times more frequent in the mandible than in the maxilla. Some authors suggest that about half of these tumors are reported in patients with GS [8].

Many of the clinical signs of GS can be diagnosed during childhood, and some of these patients receive a succession of treatments for isolated lesions that are classically related to this syndrome without the syn-

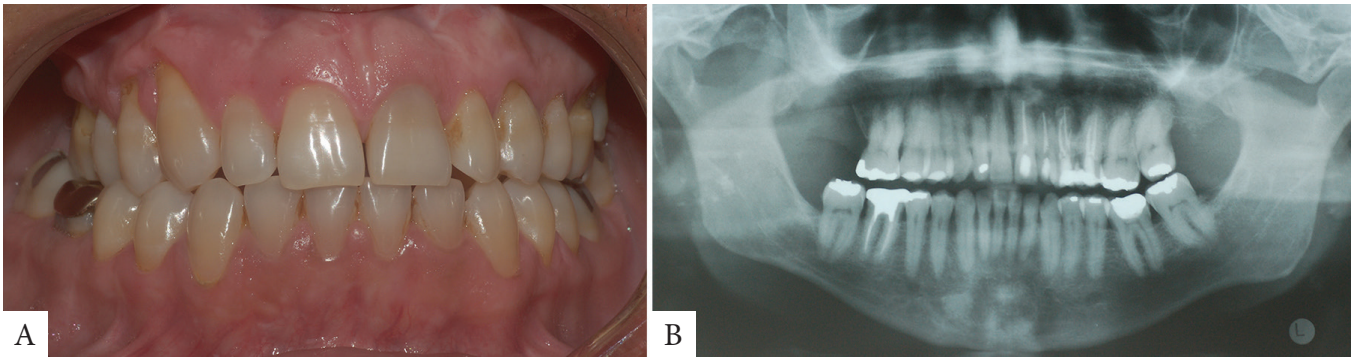

Figure 5. Clinical **(A)** and radiographic **(B)** images showing no recurrence of KOT.

drome being suspected. Commonly, KOT is the first observable characteristic, which directs the patient to seek professional care before the final diagnosis is made [9]. However, in this study, the KOTs were determined to be an isolated case and were not diagnosed as GS. Lam et al. (2009) performed a retrospective study reviewing the occurrence of KOT in patients with GS, and their results suggested that evaluations and monitoring should be done early and frequently in these patients [10].

This case illustrates three important characteristics of GS: the presence of KOT in the jaw, BCCs throughout the body, and intracranial calcification. However, because 50-60% of patients have affected family members [1,3], and this patient had no family history, the diagnosis of GS was delayed. The diagnosis of a familial cancer syndrome may influence the clinical management of a patient. The failure to detect a cancer predisposition syndrome could lead to serious consequences for a patient or their family, such as severe, late treatment toxicity or delayed diagnosis of malignancy for which early screening may have been possible [11]. Although GS has the highest life expectancy among all tumor predisposing syndromes, 19% of deaths appeared to be related to this syndrome [12]. In our case, the clinician did not correlate the patient's physical characteristics with the multiple KOTs of the oral cavity. For this reason, examinations, such as CT of the head, were not requested to assist in the diagnosis.

Asymptomatic lamellar calcification of the falx develops in 85% of patients, and may be present by the second decade of life. Signs and symptoms are usually observed in patients older than 8 years of age [2]. Due to the high mutation rate of the gene responsible for development of the disease, diagnosis relies on family history and clinical and imaging examinations. These examinations include panoramic radiography, which evaluates the presence of KOTs, and CT and magnetic resonance imaging, which verify calcifications in the dura mater seen in 65-92% of patients [13,14]. Treatment is multidisciplinary because the different systems affected by the syndrome require a team of specialists for successful management. In 2010, Visioli et al. described the case of a patient with multiple tumors, who was not diagnosed with NBCCS keratocysts, resulting in the development of an investigational protocol. The simple protocol proposed by the authors for use in GS carriers has made it possible for these patients to receive treatment and have better prognoses, particularly in the early detection of other conditions inherent to GS. Thus, radical and mutilating treatments can be avoided, and a better quality of life may be offered. The protocol is based on a series of tests applied to all patients with KOT [15].

Although benign, KOT grows aggressively by extending into adjacent bone areas, and has a high rate of recurrence, which is reported to be between 5-62 % [16]. For this reason, KOT is often treated aggressively by surgery and closely monitored post-operatively. Marsupialization or decompression of the KOT, followed by secondary enucleation, are frequently used procedures. However, in our case, marsupialization was not necessary because removal was possible without damaging adjacent structures and risking bone fracture.

BCCs should be investigated jointly by a dermatologist and a plastic surgeon, and any procedures should be done in partnership to minimize the risk of incorrect biopsies or biopsies that cause esthetic or functional damage to the patient [15]. Likewise, as part of the multidisciplinary investigation, neurologists are responsible for investigating intracranial tumors, which are lesions that can lead to death. Soufir et al. (2010) suggested that patients harboring the full complement of NBCCS criteria should, as a priority, be screened for PTCH mutations by sequencing, followed by a deletion analysis if no mutation is detected. According to the authors, the finding of a PTCH mutation confirms the clinical diagnosis of NBCCS, therefore validating the clinical and radiological diagnostic criteria of this syndrome [17].

GS is a rare autosomal dominant disorder with a predisposition for developing into cancer. The dentist may be the first professional to assist the patient with oral lesions. According to Pandeshwar et al. (2012), the appropriate evaluation and characterization of clinical features are essential for correct diagnosis and management [18]. Thus, it is important that physicians recognize the clinical signs that help in the diagnosis of the syndrome, which is mainly the presence of multiple BCCs in the skin. The presence of lesions in the body can be conclusive for the definitive diagnosis.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

The authors extend a sincere thanks to Mrs. Kim Kubitza for editing the English language of this manuscript.

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