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Central giant cell lesions with an unusual behavior in patient with Noonan syndrome: A case report with 8-year follow-up

Lesões Centrais de Células Gigantes com comportamento incomum em paciente com Síndrome de Noonan: Um relato de caso com 8 anos de acompanhamento

Lesiones centrales de células gigantes con comportamiento inusual en un paciente con síndrome de Noonan: reporte de un caso con 8 años de seguimiento

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Abstract
This study describes a patient with Noonan syndrome affected by multiple Central Giant Cell Lesions (CGCL) in jaws. The lesions presented an unusual behavior since there was no regression size after puberty. The syndrome was diagnosed by collecting clinical information, represented by ocular hypertelorism, low insertion of ears, pulmonary stenosis, cryptorchidism, cardiac abnormalities, short stature, multiple CGCL in the jaws, and blood analysis that found a mutation of the *PTPN11* gene. The treatment consisted of systemic calcitonin for a period of 14 months and three surgical procedures at distinct moments. The patient is currently with 20 years and in the eighth-year of follow-up. Although he presented an improvement in deformity, radiological findings showed remodeling without resolution of mandibular injuries, making it clear that injuries will did not always regress after puberty and not confirm previously publications in the literature. We therefore advocate a larger time of follow-up before patient discharge in these cases.
Keywords: Giant cell granuloma; Noonan syndrome; Multimodal treatment; Calcitonin.

Resumo
Este trabalho descreve um relato de caso de paciente com síndrome de Noonan afetado por múltiplas Lesões Centrais de Células Gigantes (LCCG) nos maxilares. As lesões apresentaram um comportamento incomum desde que não houve regressão do tamanho após a puberdade. A síndrome foi diagnóstica por coleta de dados clínicos, representados

por hipertelorismo ocular, baixa inserção das orelhas, estenose pulmonar, criptorquidismo, anormalidades cardíacas, baixa estatura, múltiplas LCCG nos maxilares e análise sanguínea que encontrou uma mutação do gene *PTPN11*. O tratamento consistiu no uso de calcitonina sistêmica por um período de 14 meses e três procedimentos cirúrgicos em momentos distintos. O paciente está atualmente com 20 anos de idade e no oitavo ano de acompanhamento. Embora ele tenha apresentado uma melhora na deformidade, achados radiológicos mostraram remodelamento sem resolução das lesões mandibulares, deixando claro que as lesões não regridem sempre após a puberdade e não confirmam as publicações anteriores na literatura. Desta forma, nós defendemos um grande período de acompanhamento antes da alta destes pacientes.
Palavras-chave: Granuloma de células gigantes; Síndrome de Noonan; Terapia combinada; Calcitonina.

Resumen
Este artículo describe un caso clínico de un paciente con síndrome de Noonan afectado por múltiplas lesiones centrales de células gigantes (LCCG) en los maxilares. Las lesiones exhibieron un comportamiento inusual ya que no hubo regresión de tamaño después de la pubertad. El síndrome se diagnosticó mediante la recolección de datos clínicos, incluyendo hipertelorismo ocular, inserción baja del oído, estenosis pulmonar, criptorquidia, anomalías cardíacas, baja estatura, múltiples LCCG en los maxilares y hallazgo de una mutación del gen *PTPN11*. El tratamiento consistió en calcitonina sistémica por un período de 14 meses y tres procedimientos quirúrgicos en diferentes momentos. Actualmente el paciente tiene 20 años y se encuentra en el octavo año de procervación. Aunque se observó mejora de la deformidad, los hallazgos radiológicos exhibieron remodelación sin resolución de las lesiones mandibulares, dejando claro que, al contrario de lo que prevalece en la literatura, las lesiones no siempre sufren regresión después de la pubertad. Por lo tanto, abogamos por un largo período de procervación antes de que estos pacientes sean dados de alta.
Palabras clave: Granuloma de células gigantes; Síndrome de Noonan; Tratamiento multimodal; Calcitonina.

1. Introduction

CGCL of jaws are usually unifocal, and the occurrence of multifocal lesions is extremely rare and usually associated with systemic diseases or syndromes (Edwards et al., 2005; Moghadam, Lotfi, Moghadam, 2013; Sandhya et al., 2016). Noonan syndrome, first described by Noonan and Ehmkel in 1963, is a dominant autosomal disorder derived from mutation in the *PTPN11* gene, responsible for the control of cell growth, differentiation, migration and apoptosis (Noonan & Ehmke, 1963; Feng, 1999).

Patients with this syndrome have phenotypic features such as multiple CGCL, short stature, learning difficulties, hypertelorism, prominent ears, cryptorchidism and cardio-pulmonary alterations (Cohen & Gorlin, 1991). The difficulty in diagnosis may be due to incomplete investigation. Differential diagnosis should cover cherubism and hyperparathyroidism secondary to chronic renal failure (Cohen & Gorlin, 1991; Ferretti & Muthray, 2011; Aditya & Aditya, 2016). Histologically, CGCL are indistinguishable in such cases, thus requiring imaging, clinical, laboratory and genetic assessment to define mutation in order to establish definitive diagnosis. The presence of lesions in syndromic cases represent a challenge in treatment, since they affect both jaws bilaterally, expansively and in large areas, often requiring a combination of therapies for manage lesions and prevent recurrences (Jerkins et al., 2016; Chrcanovic, Gomes, Gomez, 2018; Chrcanovic et al., 2019). Usually, it is seen stagnation of lesions and even regression after the pubertal period (Noonan & Ehmke, 1963; Cohen & Gorlin, 1991).

The case described covers the whole story, from diagnosis up to clinical and surgical procedures in a patient with Noonan syndrome with large CGCL in both jaws that did not stabilize their expansion after the end of pubertal growth.

2. Methodology

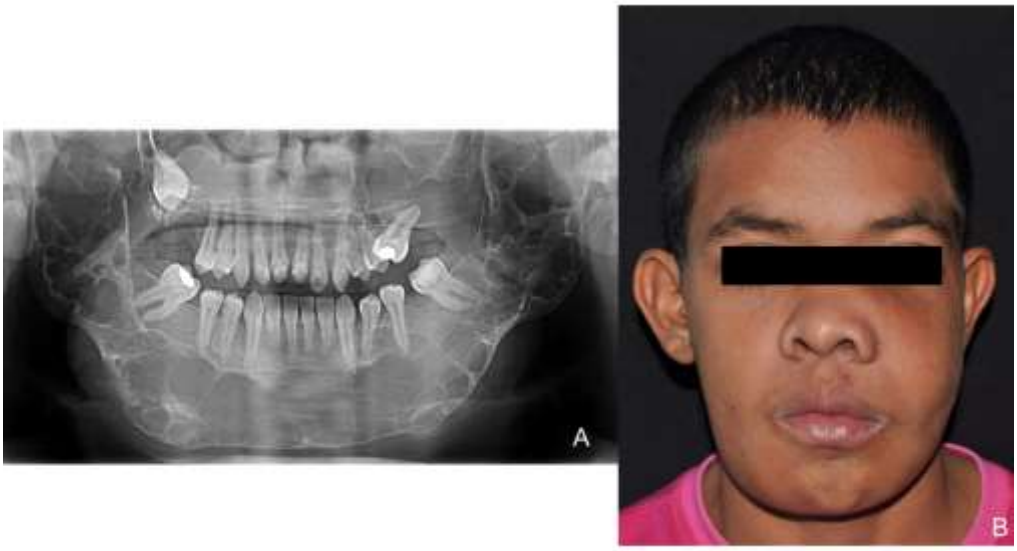
This work is a study of case, descriptive and qualitative. According to Pereira, Shitsuka, Parreira & Shitsuka (2018), this type of study refers to a description of a specific subject, detailing it in an effective way that can highlight its nuances and qualify its relevance. This article details the case of a patient with a long-term follow-up of giant cell lesions associated with Noonan syndrome. Regarding ethical aspects, information was provided to the patient through the Informed Consent Form

(ICF) and the procedures and scientific divulgation was authorized by signing this document.

3. Case report

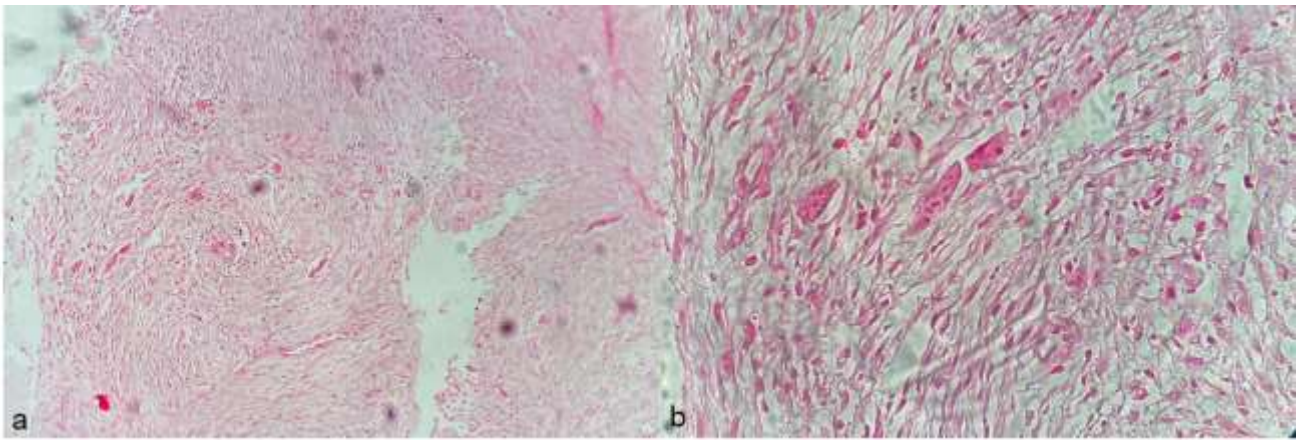
A 12-year-old male patient, was referred to treat lesions in the jaw that were causing facial asymmetry with expansive lesions as seen in the panoramic radiography (Figure 1a, b). During initial consultation, the patient had a genetic report of Gorlin Goltz Syndrome, thus alterations that would prove the genetic report were researched with no positive findings. Incisional biopsies in the 4 quadrants of the jaws revealed only the presence of CGCL, the diagnosis of the Gorlin Goltz syndrome was ruled out and other syndromes were researched (Figure 2 a, b).

Figure 1. Initial clinical and radiographic aspect. (A) Multiple radiolucent lesions in the jaws. (B) facial asymmetry.



Note the multiple radiolucent and multilocular lesions in the whole mandible and maxilla bilaterally with cortical expansion causing facial asymmetry.
Source: Authors.

Figure 2. Histologic findings of the CGCL.

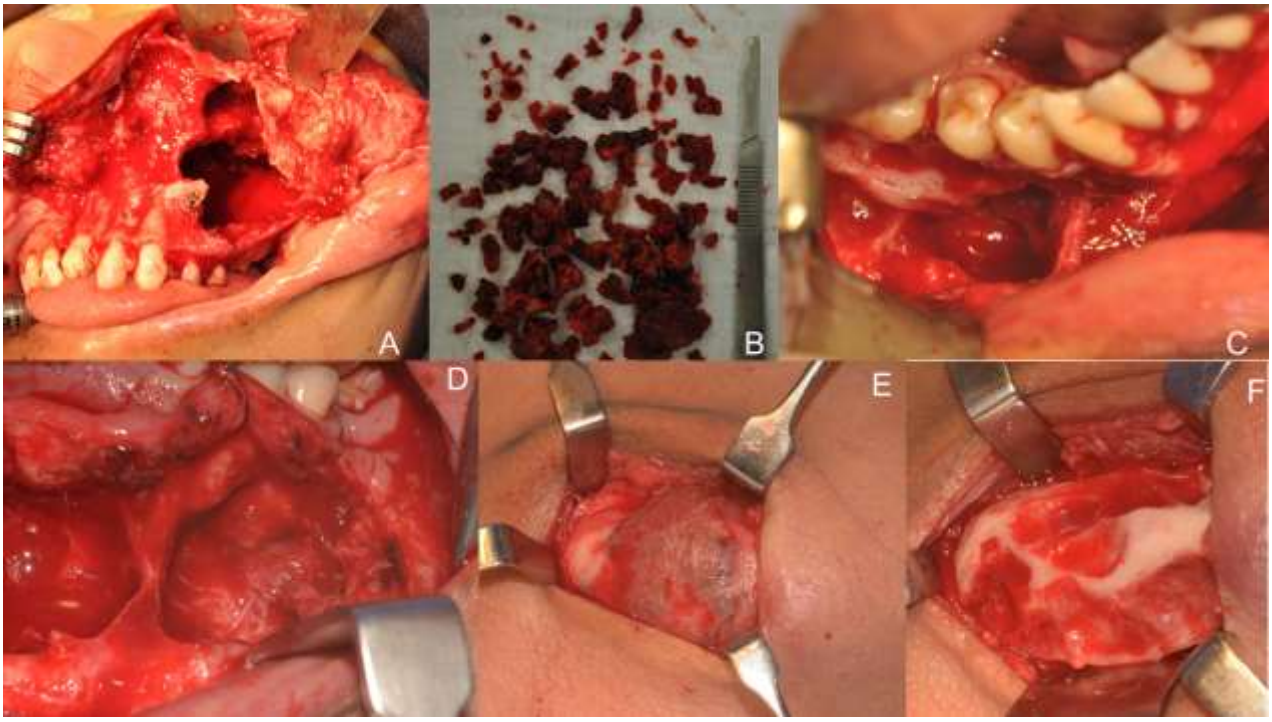


(a) Haematoxylin and eosin (H&E)-stained section of the lesions showing fragment of stroma with dense fibrous connective tissue, regions of hemorrhagic leakage and multinucleated giant cells (10x). (b) In detail, an agglomeration of multinucleated giant cells of eosinophilic cytoplasm in the middle of the conjunctive stroma (40x).
Source: Authors.

Cherubism, Ramon Syndrome, Jaffe Companacci Syndrome and Noonan syndrome were considered, in addition to verifying the parathyroid hormone levels. Blood tests for parathyroid hormone dosage presented normal values; therefore, brown hyperparathyroidism tumor was also ruled out. Cherubism characteristics such as multiple lesions in the jaw, increased bilateral mandibular volume, sharp exposure of eye sclera due to bone expansion from the growth of lesions were present, but other features such as ocular hypertelorism, low insertion of ears with posterior angulation, cardiopulmonary alterations, cryptorchidism, short stature and learning difficulties made the Noonan syndrome the most likely diagnosis. To confirm the diagnosis, the genetic material was investigated through blood analysis and a mutation in the *PTPN11* gene was found.

Due to their multiplicity and extent, the lesions were treated in combination with surgical curettage and systemic therapy with calcitonin in the form of nasal spray with daily dosages of 200 IU for 14 months. The first surgery consisted of curettage of the lesions in the left maxillary bone by Weber-Ferguson approach (Figure 3a, b). The second procedure consisted of a mandibular bilateral curettage, through a intra oral approach, performed 2 years later (Figure c, d). The third surgical procedure was carried out 6 years after the first surgery and was performed through a combined intra and extra oral approaches to the mandibular body and base with curettage and osteoplasty (Figure 3e, f).

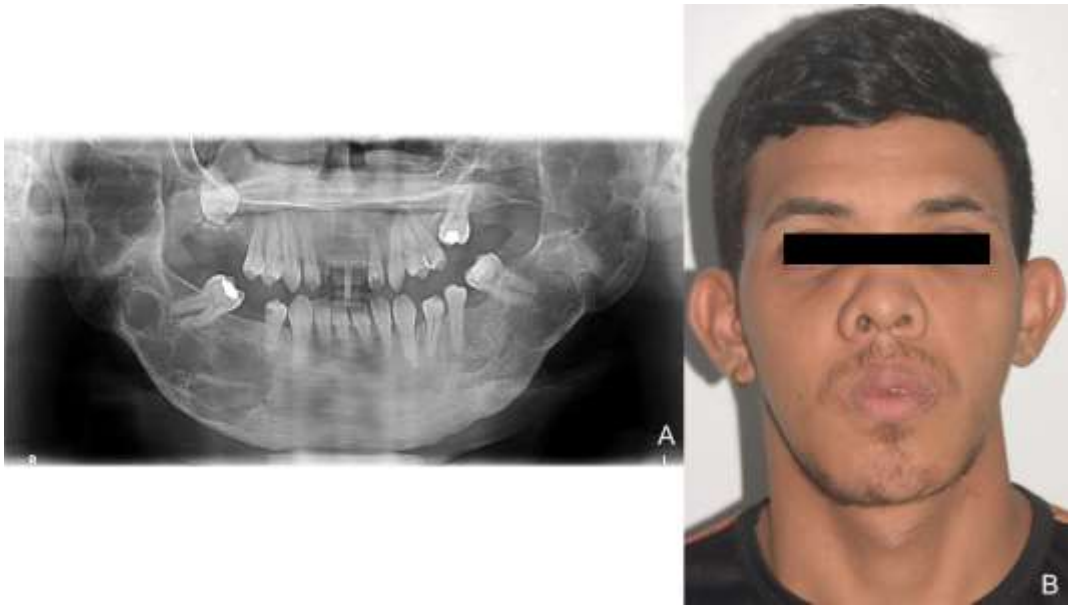
Figure 3 Surgical procedures to treat expanding lesions.



(A and B) Curettage of the maxillary lesions by Weber-Ferguson approach. (C and D) Mandibular bilateral curettage. (E and F) Extra oral access to the mandible with curettage and osteoplasty.
Source: Authors.

Currently the patient is in the eighth year of follow-up since the first surgical procedure and, though he reached puberty, the lesions did not stop expanding (Figure 4a, b). This behavior turns this in an unusual case and clinical visits are scheduled every six months.

Figure 4. Patient in the eighth year of follow-up.



(A) Radiographic aspect showing no total regression of the lesions. (B) Clinical appearance with acceptable aesthetic.
Source: Authors.

4. Discussion

CGCL is a rare intraosseous lesion, which represents less than 7% of all benign lesions of gnathic bones; which highlights the importance of such report. The clinical behavior can vary from painless growth of slow progression and low recurrence to a symptomatic condition that causes bone destruction and tooth displacement (Losler et al., 2006; Ferretti & Muthray, 2011).

Noonan syndrome, an autosomal dominant disease caused by a mutation on the *PTPN11* gene, has an estimated incidence of 1: 1500 live births. It should be considered during diagnosis when typical facial features are present such as ocular hypertelorism, triangular face, palpebral ptosis, broad nasal filter, shallow nose base, anteverted nostrils and short columella, low implantation and incomplete rotation of the ears, with thickening of the ear helix, micrognathia and short or webbed neck. Cardiac defects can also be found, in particular, pulmonary valve stenosis and hypertrophic cardiomyopathy (Noonan & Ehmke, 1963; Cohen & Gorlin, 1991; Jamieson et al., 1994; Bertola et al., 2006).

CGCL has conventionally been treated by surgical approach, ranging from simple curettage to radical resection. These lesions can also be treated by injections of corticosteroids, calcitonin, and interferon alpha-2 (Lange, Akker, Berg, 2007; Ferretti & Muthray, 2011). In this case, it was opted for the combination of therapies. Surgical therapy due to functional and esthetic impairment, requiring an immediate approach and conservative therapy with systemic calcitonin in order to allow stabilization or regression of lesions until the period of patient's growth is finished (Jerkins et al., 2016).

Though there is little scientific documentation on the behavior of CGCL in patients with Noonan syndrome, it is expected that with the completion of the patient's growth, lesions regress substantially. Therefore, radical surgery should be avoided until the completion of facial growth of these patients (Lange, Akker, Berg, 2007). In this case, the pattern previously thought true did not confirm and the patient still has a case of developing central giant cell lesions in adult life. We therefore advocate a larger time of follow-up before patient discharge in these cases.

5. Final Considerations

For being a rare clinical condition, Noonan syndrome is poorly documented in literature. Its investigation should be

thorough and correlated with clinical examination, radiological and histopathological data, as well as genetic evaluation for mutations in specific genes. Importantly, the patient must have a multidisciplinary approach from diagnosis to therapy. Surgical approaches for CGCL control associated with drug therapies such as the use of calcitonin should be considered, especially in extensive cases of great aggressiveness, as in this case, and the long-term monitoring of these patients is essential. This case also highlights an unusual behavior in Noonan syndrome, since lesion expansion did not cease after the patient reached adulthood, and this brings out the importance of follow-up evaluations.

We hope that future studies can better explain the pathogenetic of central giant cell lesions related to Noonan syndrome and that the advent of new treatment modalities with less morbidity and increasingly effectiveness may emerge.

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