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Noonan-like Syndrome with Multiple Giant Cell Lesions in the Jaws: A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case study

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ABSTRACT

Aims: To present a case report of a patient with Noonan syndrome who presented with multiple giant cell lesions in the mandible and describe the management and follow-up of this pathology, discussing the different treatment modalities and our experience.

Presentation of case: We present the case of a 7-year-old boy with Noonan phenotype and genetic SOS1 mutation who presented with bilateral giant cell lesions of the mandible. He underwent curettage and steroid injection, presenting with recurrence in the follow-up. Corticosteroid injections were decided given the small size of the lesion with good results. However, 2 years later, he presented with a new recurrence that required a new curettage. He is now free of recurrence, with satisfactory bone regeneration and occlusion.

Discussion: Giant cell lesions are frequently found in Noonan syndrome patients. They are usually multiple and indolent but can show an aggressive behaviour.

Different treatment modalities have been described in the management of giant cell lesions. Curettage is the most frequently used. Nonetheless, reports of high recurrence with this technique have been made in the literature and several authors have applied more aggressive surgical resections, with the high morbidity it entails.

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Moreover, several adjunctive treatments have also been described, such as corticosteroid injections, interpheron alpha-2a, calcitonin, etc. with variable and unclear results.
Conclusion: We believe the combination of corticosteroids and surgical curettage is an adequate treatment since it can lower recurrence rates and minimizes severity and morbidity while preserving the dentition and mandibular morphology.

Keywords: Noonan syndrome; giant cell lesions; giant cell tumours.

1. INTRODUCTION

Noonan syndrome is a relatively common genetic syndrome occurring in an estimated 1 in 1,000–2,500 live births [1]. It is an autosomal-dominant disorder of which both familial and sporadic cases have been described, showing a broad phenotypic variability. Mutations in the Ras/mitogen-activated protein kinase (*RAS/MAPK*) pathway, which regulates cell growth, differentiation, senescence, and death, have been identified in Noonan syndrome [2].

These mutations (*PTPN11, SOS1, RAF1, RIT, KRAS, NRAS, BRAF, MAP2K1, and LZTR1*) account for most cases with clinical diagnosis of Noonan syndrome [3]. The most frequent mutation found in Noonan syndrome is the mutation of the *PTPN11* gene, located on chromosome 12q24.1 [3].

Patients with Noonan syndrome can present with a wide spectrum of phenotypes and features, including facial dysmorphism, short stature, developmental delay and congenital heart disease. Patients are also at increased risk of developing haematological abnormalities, such as bruising, bleeding and malignancies [4]. The diagnosis is based on clinical suspicion and must be confirmed with genetic testing.

Giant cell tumours, also known as giant cell lesions or granulomas, are considered benign tumours that frequently occur in the mandible and/or maxilla. These can present as slowly growing lesions or, on the contrary, can show an aggressive and expansile behaviour[4]. Histologically, giant cell tumours show groups of multinucleated giant cells and an abundant stroma of mononucleated cells within fibrous connective tissue. These lesions are microscopically and macroscopically similar to cherubism and brown tumours of hyperparathyroidism [5].

These giant cell lesions are frequently found in Noonan syndrome patients. Michael Cohen and Robert Gorlin published a review from 1974 to 1989 of 15 where they coined the name Noonan-like/multiple giant cell lesion syndrome to describe those patients who presented with Noonan syndrome features along with giant cell lesions of bones, joints, and/or soft tissues [6]. Nowadays, this syndrome is considered a variant of the classical Noonan syndrome, rather than a distinct entity.

In this case report we present the case of a 7-year-old boy who present with multiple giant cell lesions in the mandible, associated to a Noonan syndrome phenotype. We describe the evolution and management of this pathology.

2. CASE REPORT

We present the case of 8-year-old male patient who presented with a progressive mandibular swelling in 2014 at the Department of Oral and Maxillofacial Surgery in Hospital La Paz, Madrid, and was diagnosed with Noonan syndrome. The pregnancy underwent controlled with no adverse events. The first genetic evaluation showed a male new-born with short length, dysmorphic features with hypertelorism and palpebral ptosis, low and rotated ears, pectus excavatum and broad and short neck with *pterigion colli*. He was diagnosed of pulmonary stenosis at 4 months of age and cryptorchidism that did not require surgical intervention. He presented with palpebral ptosis that was operated at 3 and 6 years of age. He was evaluated and followed by the endochrinologist, showing both height and weight in the lower limit of normal values and was diagnosed with a language delay and attention deficit hyperactivity disorder (ADHD). He was diagnosed with vitamin D defficiency, so DELTIUS 10.000 U/mL 4 drops a day was decided for 6 months.

At 7 years of age, he presented at our department with progressive swelling of both sides of the mandible at the angle region. On clinical evaluation, a soft bilateral swelling at both mandibular angles was observed. No signs of infection were present. On intraoral examination, this swelling comprised gingiva on the vestibular region over the mandibular angle. No ulceration

nor other lesions were observed. No teeth mobility was present.

Radiographic evaluation showed radiolucent symmetrical lesions located at both mandibular angles, and CT evaluation was performed (Fig. 1). The CT showed expansile lytic lesions located at both angles, symmetrical in appearance and size, multiloculated with cortical thinning of buccal and lingual cortex. Given the previous phenotype of the patient, the suspicion of Noonan syndrome and giant cell lesions was established. Hyperparathrioidism was ruled out on laboratory tests, with normal PTHi values (PTHi 46 pg/mL).

Surgical intervention was decided under general anaesthesia. Through and intraoral bilateral approach dissection and curettage of both lesions was performed. Integrity of lingual cortex was checked and 1ml of triamcinolone acetonide (trigon depot ® 40mg/ml, Brystol Myers Squibb) was injected in the surgical field. The histopathological analysis confirmed the diagnosis of giant cell tumour, showing multiple giant cells scattered through a cellular fibrous stroma and hemosiderin laden macrophages.

The patient underwent genetic testing for Noonan syndrome by gene sequence analysis of *PTPN11, SOS1, KRAS* and *RAF1* genes. He tested positive for *SOS1* gene mutation (*p.Thr266Lys*). Both parents tested negative for such mutation. He was evaluated by the endocrinologist and hyperparathyroidism was discarded.

Two years later, he presented with swelling in the left mandible and a new CT was performed. The CT showed new radiolucent lesions measuring 22x11x15cm located in the left mandibular body and two small lesions at located in the right body of the mandible and left mandibular ramus, measuring 7x4x7mm and 10x9x7mm, respectively.

Corticosteroid injection was decided and infiltrated in both sides of the mandible in all lesions, injecting a total of 2ml of triamcinolone acetonide (trigon depot ® 40mg/ml). The infiltration was repeated at 3 and 6 months. Radiographic evaluation showed good bone regeneration with no residual lesions. (Fig. 2).

Radiographic follow-up was performed, and no relapse was observed, with good evolution and no adverse effects. Two years later, the orthopantomography showed new radiolucent lesions at both mandibular bodies (Fig. 3). CT evaluation was performed (Fig. 4). CT showed 2 lytic lesions located at the most anterior region of both mandibular bodies, expansile and multilobulated, measuring 22x10x14mm and 23x9x15mm, respectively, with cortical thinning and no periosteal reaction or soft tissue involvement.

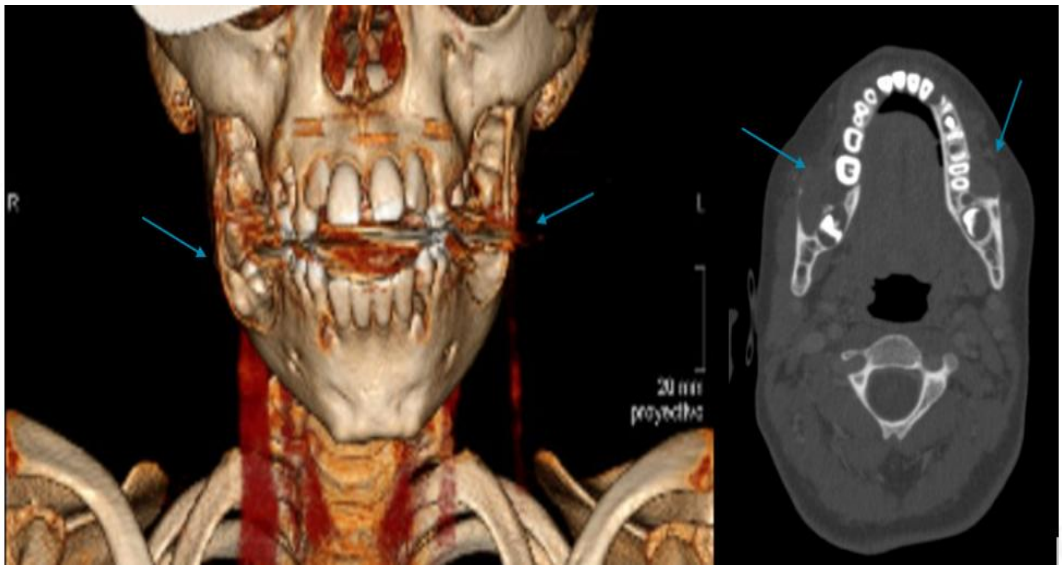

Fig. 1. Preoperative CT in the first operation. Expansile and multiloculated lesions at both mandibular angle are seen, with cortical destruction

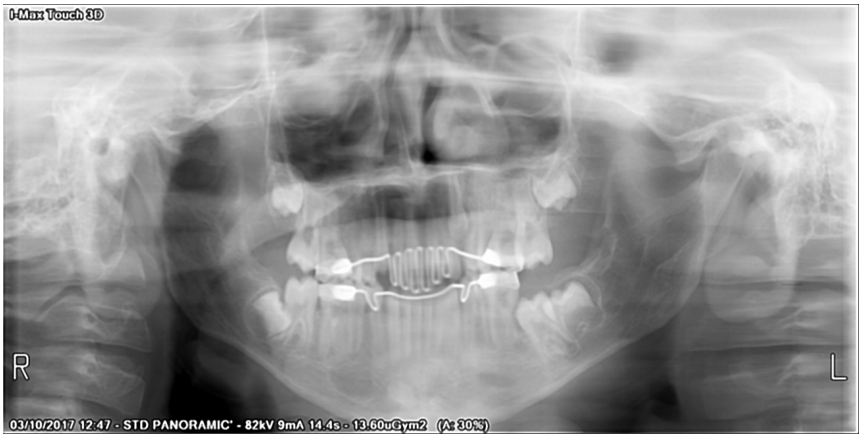

Fig. 2. Orthopantomography after 3 corticosteroid injections in the second recurrence. Trabeculae and bone regeneration is observed at both mandibular bodies and ramus

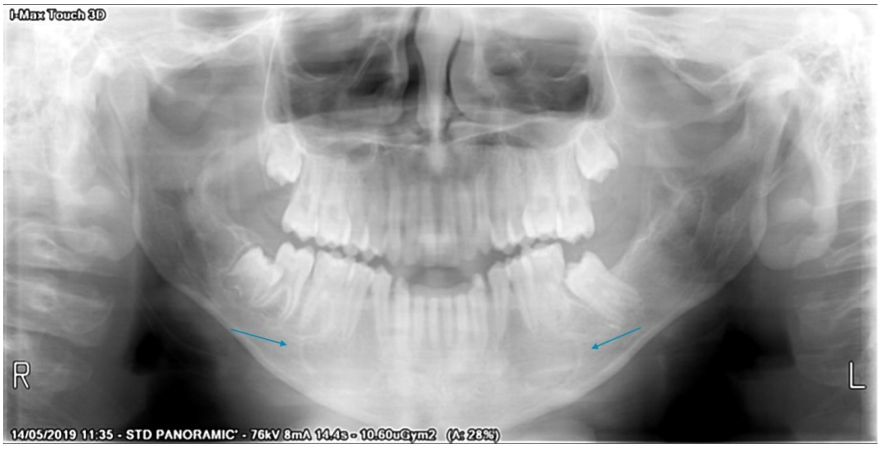

Fig. 3. Orthopantomography at 5 years follow up showing new lesions in both mandibular body and bony expansion

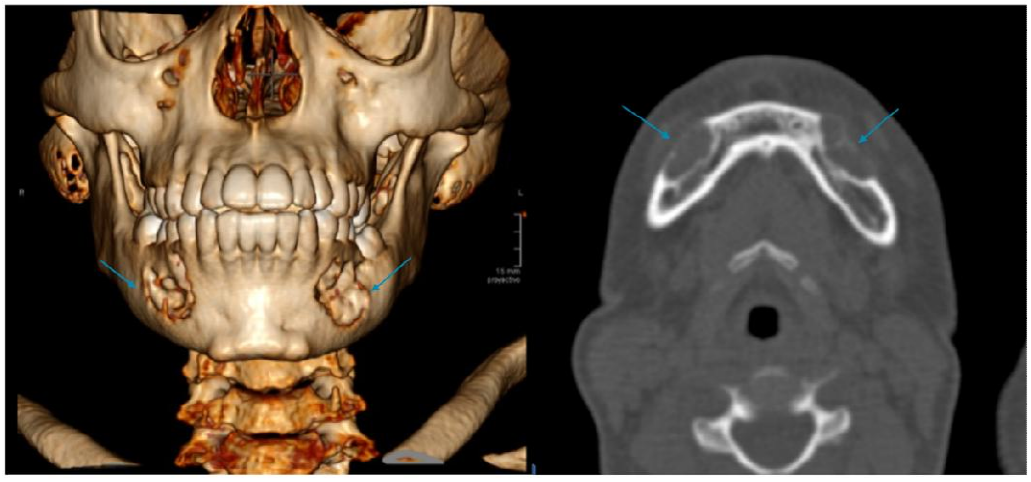

Fig. 4. Preoperative CT showing giant cell lesions at both mandibular bodies.

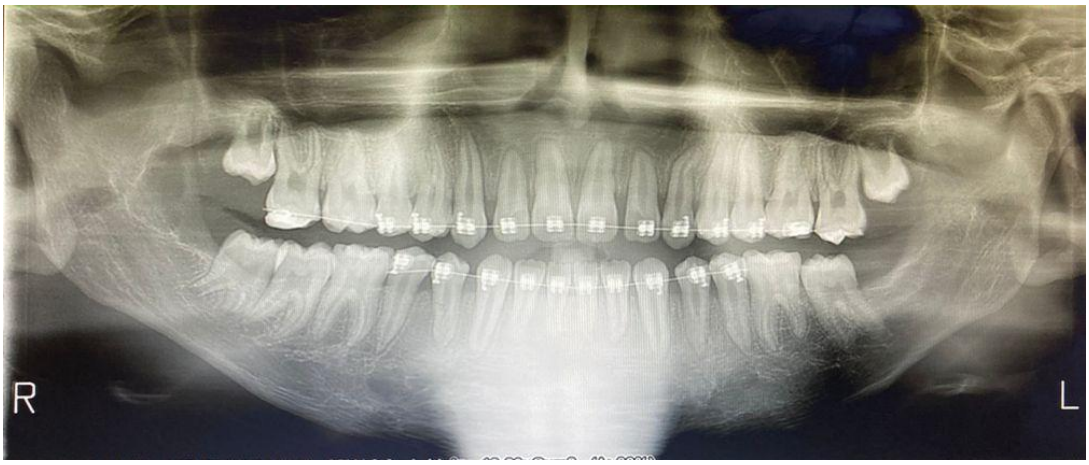

Fig. 5. Postoperative orthopantomography at 6 years follow up, bone regeneration and trabeculae formation are observed

Surgical intervention was decided. A bilateral intraoral approach was performed and profound curettage and enucleation of both lesions with preservation of structures like nerves or teeth was performed, with posterior instillation of triamcinolone acetonide (trigon depot ® 40mg/ml) tumour curettage of the mandibular lesion was performed. The biopsy was consistent with a diagnosis of giant cell tumour.

Postoperative evaluation and follow at 7 years after the first surgery showed satisfactory bone regeneration (Fig. 5) with no residual lesions and currently the patient has had no recurrence of the lesions and shows adequate occlusion and facial symmetry with no sensory disturbance.

The patient underwent orthodontic treatment that was first initiated 5 months after the first surgery and a transpalatine arch maintainer was applied when finished (3 years after the first surgery), as seen in Fig. 2. Nonetheless, new orthodontic treatment was applied again 2 years later given the impaction of the third right inferior molar and still active.

3. DISCUSSION

In 1991 [6], Cohen and Gorlin described the Noonan like /Multiple Giant Cell Lesions syndrome, in which the Noonan syndrome phenotype is associated to multiple giant cell tumours. This syndrome is nowadays considered a variant of the Noonan syndrome spectrum, rather than a distinct entity.

The Noonan like /Multiple Giant Cell Lesions syndrome was found to be associated to *PTPN11* and *SOS1* gene mutations [4]. These mutations ultimately lead to overactivation of the *RAS-MAPK* signalling pathway. Giant cell tumours may also be seen in other *RASopathies*, such as neurofibromatosis type I, cherubism, cardiofaciocutaneous syndrome, Costello syndrome and LEOPARD, which is now known as Noonan syndrome with multiple lentigines syndrome [4]. Mutations in *SH3BP2* are associated to cherubism. Giant cell lesions in cherubism tend to resolve spontaneously, whereas those observed in Noonan like /Multiple Giant Cell Lesions syndrome can have aggressive signs and symptoms [2].

Therefore, when on diagnosing a giant cell lesion of the jaws a broad differential diagnosis should be kept in mind. In Noonan like /Multiple Giant Cell Lesions syndrome giant-cell lesions occur sporadically but are histologically identical with non–syndrome-linked giant cell granulomas7. Hyperparathyroidism must also be routinely discarded, since these tumours can mimic the brown tumour found in hyperparathyroidism cases.

Most frequently, giant cell lesions present as a painless, slowly growing swelling of the jaw. Pain and sensory disturbances are usually rare. Teeth displacement can also be present and lead to malocclusion.

Regarding radiological evaluation, findings are diverse. Giant cell lesions may appear as small unilocular radiolucent lesions or, on the contrary, as large aggressive multilocular lesions with teeth displacement, root resorption and cortical thinning or, even, perforation [7].

Some authors [8,9] have historically differentiated between aggressive and nonaggressive lesions, based on signs and symptoms and radiological features. Aggressive lesions are characterized by one or more of the following features: pain, paraesthesia, root resorption, rapid growth, cortical perforation, and a high recurrence rate after surgical curettage [7].

In giant cell tumours the histopathological examination shows a highly cellular fibroblastic stroma with multinucleated giant cells. It has been stipulated that these giant multinucleated cells are osteoclast-like and are formed secondarily to the expression of *RANKL*.

At present, surgical curettage and enucleation is the “gold standard” in the management of giant cell lesions. It has been stipulated in the literature that this technique may not be enough and lead to high rates of recurrence. Nevertheless, surgical resection may lead to disfigurement, loss of teeth/tooth germs, damage to surrounding structures, and may cause sensory nerve deficit [10], especially in bigger mandibular lesions. Surgical decompression is not indicated in this type of lesions due to its solid morphology and the absence of a cystic cavity.

In several studies the results of surgical therapy have been evaluated and recurrence rates ranging from 11% to 49% have been reported [11]. Recurrences in patients with aggressive lesions are even more frequent. Chuong [8], for instance, reported a recurrence rate of 72% in aggressive lesions.

Thus, several alternative treatments have been proposed in the literature to overcome the recurrence rates associated to curettage and minimize the sequalae of wide surgical resection, including corticosteroid injections, calcitonin, imatinib, osteoprotegerin and interferon alpha-2a, showing overall variable efficacy and unclear results. In 2002, Kaban [12] reported a set of cases with giant cell lesions successfully treated with interferon alpha-2a. However, he did not obtain complete resolution, most probably because interferon has no direct effect over the proliferating tumour cells.

In a study of 18 patients with aggressive giant cell lesions by Bataianeh et al. [13] who underwent surgical resection with 0.5-cm margins of healthy tissue, only 1 patient (6%) presented with recurrence. Such an aggressive surgical therapy, despite effective, resulted inevitably in loss of teeth and tooth germs and sensory disturbances in the inferior alveolar nerve.

In this case report, we present the case of a 7-year-old boy who presented with multiple giant cell lesions in the mandible and tested positive for the *SOS1* mutation, establishing the diagnosis of Noonan like syndrome. Curettage of the lesions was performed, with adequate bone regeneration. However, the patient presented with relapse two years after this first surgery, and the lesions were treated with corticosteroid injections given the reduced size of them. Two years later, he presented with a new relapse of these giant cell lesions at both mandibular bodies, and a new curettage and several corticosteroid injections were decided (3 in total), with adequate bone regeneration whilst preserving structures such as teeth and the inferior alveolar nerve. It is important to highlight the importance of teeth mobility and root resorption, which was not present in our case, and all teeth were preserved, given the conservative approach that was decided. Furthermore, the patient underwent simultaneous orthodontic to treatment for alignment and proper occlusion.

Radiographic evaluation showed adequate mandibular morphology and symmetry at 6 years follow up. Despite the patient presented relapse, we believe this is an adequate approach since a more aggressive surgery would have resulted in loss of teeth and tooth germs as well as the need for bone reconstruction and the consequent loss of sensory function and morbidity associated to such an aggressive surgery.

4. CONCLUSION

Giant cell lesions can be found in the presence of a Noonan phenotype, which is known as Noonan like syndrome. These patients usually present with multiple symmetrical lesions in the jaws.

The management of these lesions remains difficult and controversial for oral and maxillofacial surgeons. These tumours may be locally aggressive and show recurrence. Curettage and enucleation is currently the most frequently applied treatment since surgical resection can be very aggressive and provoke high. Thus, teeth and tooth germs can be preserved. It is advisable to associate other local therapies, such as corticosteroids, to minimize recurrence.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline patients consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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