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BRIEF REPORT

Noonan syndrome with multiple Giant cell lesions, management and treatment with surgery and interferon alpha-2a therapy: Case report

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Abstract

We report the case of a 14-year-old girl that was referred to the maxillo facial surgery unit at age 11 years because she exhibited swelling in the right side of her maxilla and right mandible. After a conservative surgery, she started with interferon alpha-2a to avoid recurrence. She has remained in treatment with successful results during her follow up. Considerable reduction of both maxilla and mandible lesions and bone fill have been documented. In addition, her clinical history and phenotype were suggestive of Noonan syndrome. She has short stature, broad and short neck; hypertelorism (increased distance between the eyes); downslanting palpebral fissures; sparse eyebrows and eyelashes; posteriorly rotated ears with fleshy lobes; follicular keratosis over the face, and developmental delay. Her karyotype was 46, XX. Molecular analysis of RAS/MAPK pathway genes showed a *SOS1* amino acid substitution of arginine to lysine at position 552 (p.R552K). This case presents the infrequent condition of Noonan syndrome with multiple giant cell lesions (NS/MGCL) that would be the first patient as far as we know treated with surgery and interferon alpha-2a for her giant cell lesions.

KEYWORDS

interferon alpha-2a, maxilla and mandible lesions, Noonan syndrome with multiple giant cell lesions; SOS1 variant, RAS/MAPK pathway

1 | INTRODUCTION

In 1968, Jacqueline Noonan described 19 patients (12 males and seven females) with Turner-like physical features, hypertelorism, pulmonary stenosis and no evidence of a chromosome abnormality (Noonan, 1968). Subsequent research described a new syndrome currently known as Noonan Syndrome (NS, MIM 163950). The cardinal features of NS are (a) distinctive dysmorphic facial features with hypertelorism, ptosis and low-set ears; (b) congenital heart defect such as pulmonary stenosis (20%–50%) and/or hypertrophic cardiomyopathy (20%–30%); (c) postnatal growth retardation with final adult height approaching the lower limit of normal. Other findings can include broad or webbed neck; chest deformity (superior pectus carinatum and inferior pectus excavatum); bleeding diathesis, ectodermal anomalies; lymphatic dysplasia and cryptorchidism in males. Finally, up to one fourth of affected individuals have mild intellectual disability (Allanson & Roberts, 2019; van der Burgt, 2007). Noonan syndrome is an autosomal dominant disorder, genetically heterogeneous, with variable

expression and an estimated prevalence of 1 in 1,000–2,500 live births (Nora, Nora, Sinha, Spangler, & Lubs, 1974; Roberts, Allanson, Tartaglia, & Gelb, 2013).

Dominant activating germline mutations in genes encoding components or regulators of the RAS - mitogen activated protein kinase (MAPK) signaling pathway (*PTPN11*, *SOS1*, *RAF1*, *RIT*, *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, and *LZTR1*) account for most cases with clinical diagnosis of NS (Allanson & Roberts, 2019). This pathway is essential for the regulation of various cellular processes such as proliferation, survival, differentiation and migration (Atay & Skotheim, 2017; Simanshu, Nissley, & McCormick, 2017).

Michael Cohen and Robert Gorlin in a review of 15 cases published from 1974 to 1989 coined the name Noonan-like/multiple giant cell lesion syndrome to describe patients with NS features who in addition presented with giant cell lesions of bones, joints, and/or soft tissues (Cohen Jr. & Gorlin, 1991). From a genotype–phenotype correlation published by Tartaglia and coworkers in 2002 it was established that the entity described by Cohen and Gorlin is actually a phenotypic variation within the NS spectrum that received the name of Noonan syndrome with multiple giant cell lesions (NS/MGCL) (Tartaglia et al., 2002).Pathogenic variants in three genes have been found in this condition: in *PTPN11* (Beneteau et al., 2009; Bufalino, Carrera, Carlos, & Coletta, 2010; Carapito et al., 2014; Jafarov, Ferimazova, & Reichenberger, 2005; Karbach et al., 2012; Lee et al., 2005; Sinnott & Patel, 2018; Tartaglia et al., 2002; Wolvius, de Lange, Smeets, van der Wal, & van den Akker, 2006); in *SOS1* (Beneteau et al., 2009; Eyselbergs et al., 2014; Hanna, Parfait, Talaat, Vidaud, & Elsedfy, 2009; Neumann et al., 2009) and *RAF1* (Denayer et al., 2010).

We report a 14-year-old patient with a phenotype compatible with Noonan syndrome that in her teens developed two large giant cell lesions one in her right maxilla and the other in her right mandible. Her molecular study showed a *SOS1* pathogenic variant not associated previously with this phenotypic variant of Noonan syndrome. In addition, we describe management of these lesions with a combination of enuclation and curettage surgery, and the use of interferon alpha-2a as a therapeutic measure to avoid recurrence. The patient has had a favorable evolution during her follow up.

2 | CASE SUMMARY

This 14-year-old girl is the only child of her non-consanguineous parents. There is no family history of congenital anomalies; both of them have had children with other couples. Her mother was 31 years old at the time of her pregnancy and the proband's father was 55 years old. She was born after an uneventful pregnancy by cesarean section at 38 weeks of gestation, because previous cesarean in her mother. Her neonatal parameters were birth weight 3,360 g; birth length 46 cm and CC 35 cm, being adequate for gestational age. In the neonatal period, she underwent study due to a "heart murmur". She required nasogastric tube feeding during her first 3 weeks of life because she had poor suction that inhibited breast or bottle-feeding. The first genetic evaluation in this period, showed a female newborn with short length; dysmorphic features with hypertelorism, bulbous nose, rotated ears with short helix, short and broad neck with pterigion colli (webbed neck), shield chest with low set nipples, and no edema in her hands or feet. She had poliosis (patches of white or gray hair), a sign that was shared with her father and some of her half-paternal brothers, that has disappeared during her follow up.

Karyotyping ruled out Turner syndrome, being 46, XX. The echocardiogram showed mild mitral and tricuspid insufficiency. At age 11, she was referred to the maxillo facial unit at Dr. Luis Calvo Mackenna Hospital, because of swelling in the right side of her maxilla and mandible with loss of the normal anatomy that started about a year before (Figure 1a,b). Computed tomography scan imaging (Figure 2a,d) showed a multiloculated, expansile lesion in the right mandible with cortical thinning of the buccal and lingual cortex. It also showed a big expansile lesion at the right side of maxilla with a extensive swelling and large displacement of teeth. They were asymptomatic lesions without pain or sensitive disturbances, although she experienced pain at palpation. The biopsy was consistent with a diagnosis of giant cell tumor. Histopathologic analysis showed the presence of multiple giant cells scattered through a cellular fibrous stroma interspersed with some hemosiderin laden macrophages confirming the diagnosis of a giant cell lesion.

For giant cell lesion resolution the patient was treated according to the protocol reported by Kaban and coworkers (Kaban et al., 2002). Liver function test and hematologic blood counts were done before surgery and were normal. Her first surgery was done in January 2018, and tumor curettage of the maxilla lesion was performed, with preservation of structures like nerves or teeth. During this procedure, the patient had abundant bleeding so it was decided to postpone the mandibular surgery for a second time. Seventy-two hours after surgery she started receiving a subcutaneous injection of 3 million units/m^2 daily of interferon alpha-2a. Eight months later mandibular surgery was performed, during the interferon treatment, where it was found that the mandible lesion

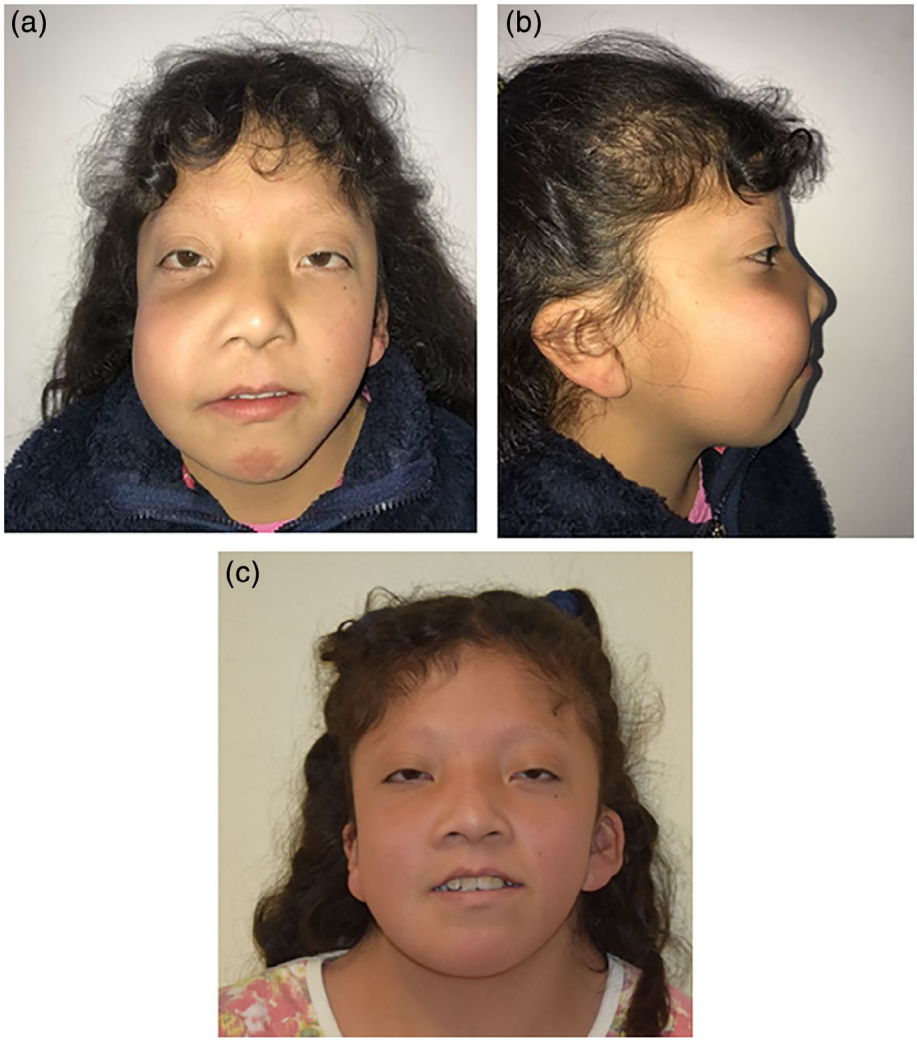

FIGURE 1 (a and b) Frontal and lateral view of patient at 11y 9mo old before surgery and interferon alpha-2a treatment. Note sparse and curly hair, hypertelorism, scarce eyebrows and eyelashes; downslanting and droopy eyelids, low and posteriorly set ears. Asymmetry of face with extensive swelling of her maxilla and mandible. (c) Frontal view during treatment

showed considerable reduction and the surgery proceeded with no complications (Figure 1c). Both lesions had considerable bone fill (Figure 3a,b). Laboratory, clinical and image evaluation during the 23 months follow up has shown no evidence of adverse effects and demonstrates good results in terms of generation of new bone formation in both lesions. The patient is still receiving interferon alpha-2a treatment and she will complete 18 months, as suggested in the protocol (Kaban et al., 2002). This treatment has been sometimes discontinued due to administrative problems. At December 2019 she underwent surgery for a residual lesion of the mandible.

A genetic reevaluation was performed at 11 years 9 months old at the request of maxillo facial team. Her morphometric parameters were height: 122 cm (−4 SDS); weight: 26 kg (−5.65 SDS); BMI: 17.5 (−0.15 SDS) and CC: 51 cm (−2.53 SDS). She presented curly hair with low posterior hairline; scarce eyebrows and eyelashes; downslanting and droopy eyelids and prominent eyes; low and wide nasal bridge; low set, dysplastic and posteriorly angulated ears; nevus on her face; poor quality of tooth enamel; short, wide, and webbed neck (Figure 1c); shield chest with low set nipples, and cubitus valgus (an abnormally great angle of the extended forearm from the body). Abnormal position of both second toes, overlapping the first ones, was detected. She had mild developmental delay and attended a regular school where scholastic performance was considered middle to low compared to her classmates. She has had delayed puberty, and there were no secondary sex characteristics.

No pathogenic variants were found in the *PTPN11*, *RAF1* and *KRAS* genes. However, one missense substitution was documented in the *SOS1* gene.

3 | GENETIC TESTING

The Pediatric Scientific Ethics Committee of *Servicio de Salud Metropolitano Oriente Santiago*, Chile approved this report, as well as the informed consent for DNA

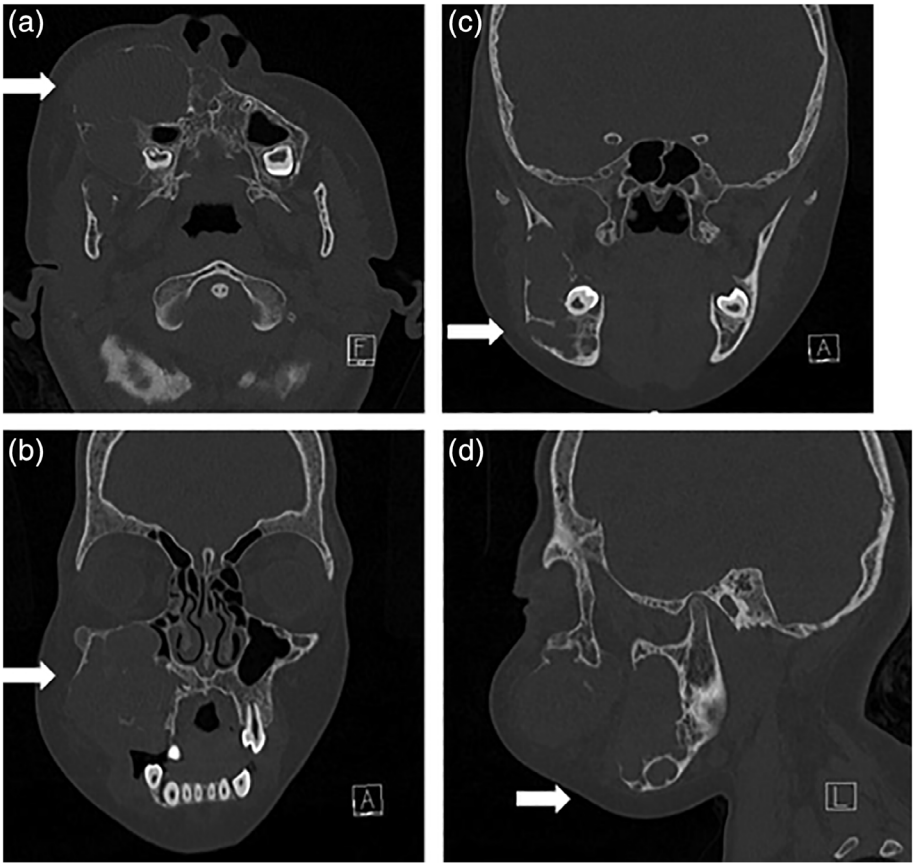

FIGURE 2 (a–d) Pre-surgery computed tomography scan revealed bilateral multilocular expansive lesions (white arrows) with loss of the normal anatomy of the maxilar and mandible

extraction and clinical pictures. Informed written consents were obtained from patient's mother and patient for the genetic analyses and clinical photographs.

Variants in *PTPN11*, *SOS1*, *KRAS* and *RAF1* genes were screened by High Resolution Melting (HRM) analysis. Briefly, exons frequently associated with NS were amplified with specific primers (Rodríguez et al., 2018). The PCR conditions were ×1 HOT FirePol® Eva Green® HRM Mix (Solis BioDyne, Estonia) or ×1 SensiFAST HRM Mix (Bioline, UK), 0.25–1 μM each oligonucleotide and 15 ng genomic DNA in a total volume of 10 ul. The annealing temperatures for the amplification of the different exons were described previously (Rodríguez et al., 2018). Amplification and melting curve analysis were performed in an Eco Real-Time PCR System (Illumina, San Diego, CA) and those exons with abnormal profiles relative to control samples (at least three) were sequenced bi-directionally in an ABI3730XL sequence analyzer (Applied Biosystems, Foster City, CA). This analysis revealed a heterozygous guanine to adenine change at position 1,655 (c.1655 G>A) in the *SOS1* gene according to NCBI reference sequence NM_005633.3. It affects codon 552 (AGG>AAG), leading to an arginine to lysine amino acid substitution (p.R552K) (Figure S1).

4 | DISCUSSION

We describe a patient with Noonan syndrome with multiple giant cell lesions due to a pathogenic variant in *SOS1* gene. Up to date there are 23 patients molecularly diagnosed with NS/MGCL (Beneteau et al., 2009; Bufalino et al., 2010; Carapito et al., 2014; Denayer et al., 2010; Eyselbergs et al., 2014; Hanna et al., 2009; Jafarov et al., 2005; Karbach et al., 2012; Lee et al., 2005; Neumann et al., 2009; Sinnott & Patel, 2018; Tartaglia et al., 2002; Wolvius et al., 2006). Thirteen of them present a pathogenic variant in *PTPN11* gene, nine in *SOS1* gene and one in *RAF1* gene; which partially agree with the distribution of pathogenic variants associated with isolated Noonan syndrome (El Bouchikhi et al., 2016). Pathogenic variants in the *SOS1* gene reported in NS/MGCL concentrate in exon 10; which codes for a pleckstrin homology domain (PHD) and a helical linker segment that connects the PHD domain to a RAS exchange motif (REM). Most *SOS1* pathogenic variants associated with isolated Noonan syndrome have also been reported in these domains (Tartaglia et al., 2007; Lee et al., 2011; Lepri et al., 2011). It supports the concept that the clinical picture of our patient and others described in the literature correspond to a variant of

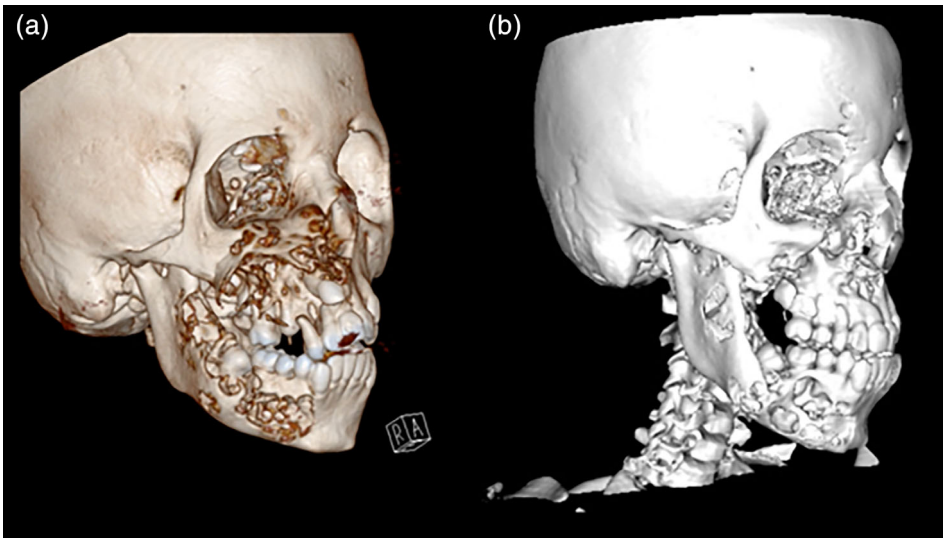

FIGURE 3 (a and b) 3D computed tomography scan reconstruction (a) shows the extended lesions in maxillary and mandible with great bone destruction; (b) 1 year follow up after surgery and during interferon alpha-2a treatment shows new bone formation in both lesions

Noonan syndrome and not a separate syndrome (Tartaglia et al., 2002). Within the nine pathogenic variants of the *SOS1* gene found in patients with NS/MGCL, those that affect residue p.R552 were reported in four patients: p.R552T, p.R552S (Beneteau et al., 2009; Neumann et al., 2009) and p.R552G (Eyselbergs et al., 2014) (Table S1). The substitution found in our patient affects the same residue but generates a codon for lysine (p.R552K); this change has been reported only in isolated Noonan syndrome up to now.

The cause for this particular variant within the Noonan syndrome spectrum is unknown. A possible explanation could be different allelic expressions of *SOS1* as was suggested by Moncini and coworkers (Moncini et al., 2015) from the studies of three family members with the same *SOS1* pathogenic variant (c.755T>C, p.I252T) and variable phenotype. This different allelic expression might be the consequence of epigenetic regulation of *SOS1*. Evidence that support differential *SOS1* methylation was provided by an epigenome wide association study where a specific *SOS1* methylation variant was associated with fat mass index (kg/m^2) in preschool children (Rzehak et al., 2017). An epigenome association with the phenotype of a cohort of patients that shares a specific *SOS1* variant will contribute to clarify this hypothesis.

A recent research by Gomes applied next-generation sequencing technology to determine the somatic genetic variant signature of sporadic giant cell lesions of the jaw (GCLJ) in 58 biopsy samples (Gomes et al., 2018). Somatic heterozygous variants of *TRPV4* (polymodal Ca^{2+} permeable channel that regulate osteoclast differentiation and activity) (Masuyama et al., 2008), *KRAS*, and *FGFR1* (FGF receptor with tyrosine quinase activity) genes where detected in 72% of GCLJ analyzed. It is known that TRPV4/Ca^{2+} influx, FGFR1 and KRAS converge on activating MAPK signaling pathway (Chen et al., 2013; 2016; Rosen, Ginty, Weber, & Greenberg, 1994; Dhillon, Hagan, Rath, & Kolch, 2007; Porta et al., 2017). It is noteworthy that all samples show hyperactivation of RAS/MAPK pathway in the mononuclear cells but not in the multinucleated giant cells. Authors propose a "landscaping effect" where mutated cells (10–35%) induce abnormal accumulation of non-mutated cells that form the lesion mass (Gomes et al., 2018). A search for *TRPV4*, *FGFR1* and *KRAS* somatic variants in GCLJ biopsies of patients with NS/MGCL could shed light on the co-existence of germline/somatic RAS/MAPK variants to explain the etiology for NS/MGCL.

The management of giant cell lesions remains a difficult problem for oral and maxillofacial surgeons. These lesions rarely metastasize, but are often locally aggressive and have a high recurrence rate. The traditional treatment of giant cell lesions has been surgical excision. Extensive surgical therapy may lead to loss of teeth/tooth germs, damage to surrounding structures, and may cause sensory nerve deficit (Pogrel, 2012). In addition, recurrence rates following surgery range from 11 to 49% (Eisenbud, Stern, Rothberg, & Sachs, 1988; Kruse-Losler et al., 2006; Rawashdeh, Bataineh, & Al-Khateeb, 2006; Whitaker & Waldron, 1993). A number of alternatives to surgery have been proposed, including intra-lesional corticosteroids (Comert, Turanli, & Ulu, 2006; Dolanmaz, Esen, Mihmanlı, & Işık, 2016; Flanagan et al., 1988; Kermer, Millesi, & Watzke, 1994) and systemic calcitonin

(Harris, 1993; O'Regan, Gibb, & Odell, 2001; Pogrel, Regezi, Harris, & Goldring, 1999). Nevertheless, the effectiveness of these treatments, particularly in relation to aggressive lesions, is unclear.

It was proposed that giant cell lesions are proliferative vascular lesions that should respond to antiangiogenic therapy (Kaban et al., 1999). In the early 1980s, interferon alpha-2a was found to inhibit angiogenesis (Sidky & Borden, 1987). It was demonstrated that interferon alpha-2a suppresses the production of basic fibroblast growth factors (bFGF) which are involved in neo-angiogenesis (de Lange, van der Akker, van der Berg, Richel, & Gortzak, 2006). In 2002, it was reported a set of cases with giant cell lesions successfully treated with interferon alpha-2a (Kaban et al., 2002). Nevertheless, total resolution was not obtained, probably because interferon has no direct effect over the proliferating tumor cells. It has been proposed that aggressive lesions should be enucleated and adjuvant therapy with interferon alpha-2a should be started post-operatively (Baker, Parikh, Rhodes, Abu-Ghosh, & Shad, 2008; Kaban et al., 2002; O'Connell & Kearns, 2013). It is noteworthy that interferon alpha-2a inhibits the production of bFGF, a ligand of FGFR1 (Chen et al., 2019), where somatic variants have been detected in giant cell lesion biopsy.

The evolution observed in our patient agrees with those described previously, where longer follow-up periods have been reported (O'Connell & Kearns, 2013:144 and 81 months; Baker et al., 2008:60 months; Kaban et al., 2002:12–72 months). Nevertheless, our patient represents a more complex therapeutic challenge since the giant cell lesions were present in the maxillary and the mandible with an extensive destruction of tissues and the girl has a Noonan syndrome background, which demands a closer follow-up.

Here we report a 14-year-old patient with a phenotype compatible with Noonan syndrome with multiple giant cell lesions due to a *SOS1* pathogenic variant not associated previously with this phenotypic variant of Noonan syndrome. In addition, we describe the first NS/MGCL patient published as far we are aware, treated with surgery and interferon alpha-2a, using a standardized treatment protocol. This combination of treatments resulted in generation of new bone in both lesions, recovery of a symmetric facial appearance in our patient without any adverse effects up to date.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

https://uchile.cl/u92726

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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