

UNILATERAL GIANT CELL LESION OF THE JAW IN NOONAN SYNDROME

M. Eyselbergs^{1,2}, F. Vanhoenacker^{1,2,3}, J. Hintjens⁴, M. Dom⁴, K. Devriendt⁵, H. Van Dijck⁶

Noonan syndrome (NS) is an etiologically heterogeneous disorder caused by mutations in the RAS-MAPK signaling pathway. Noonan-Like/Multiple Giant Cell Lesion (NL/MGCL) syndrome is initially described as the occurrence of multiple gnathic giant cell lesions in patients with phenotypic features of NS. Nowadays, NS/MGCL syndrome is considered a variant of the NS spectrum rather than a distinct entity. We report the case of a 14-year-old female patient carrying a *SOS1* mutation with a unilateral giant cell lesion of the right mandible. Cross-sectional imaging such as CT and MRI are not specific for the diagnosis of oral giant cell lesions. Nonetheless, intralesional scattered foci of low SI on T2-WI, corresponding to hemosiderin deposits due to hemorrhage, can help the radiologist in narrowing down the differential diagnosis of gnathic lesions in patients with NS.

Key-word: Jaws.

Case report

A 14-year-old girl was referred to the department of Oral and Maxillofacial Surgery because of a radiolucent lesion in the right mandible seen on a routine panoramic photograph (Fig. 1). Her past medical history was relevant for congenital pulmonary stenosis, which was successfully treated endovascularly at the age of 2. The diagnosis of Noonan syndrome (NS) was suspected clinically during childhood because of dysmorphic features (Fig. 2), including ocular hypertelorism, posteriorly angulated low-set ears and mildly downslanting palpebral fissures. In addition, short stature, short neck, widely spaced nipples and abnormal chest morphology with superior pectus carinatum and inferior excavatum were present. She experienced minor learning disabilities. Further genetic investigations revealed a point mutation in exon 10 of the *SOS1* gene (c.1654A > G resulting in p.R552G), that confirmed the clinical diagnosis.

Additional dental Computed Tomography (CT) imaging revealed a multiloculated, expansile lesion in the right mandible with cortical thinning of the buccal and lingual cortex (Fig. 3). Tooth resorption was absent. For further lesion characterization, magnetic resonance imaging (MRI) was performed (Fig. 4). The lesion was iso- to slightly hypointense to muscle tissue on T1-weighted images (WI) and showed intermediate



Fig. 1. — Panoramic radiograph revealed a unilateral well defined radiolucent lesion in the right mandibular ramus (arrow).

signal intensity (SI) compared to fat with intralesional foci of low SI on T2-WI. The intralesional low SI foci raised suspicion for hemosiderin deposits and therefore favored the diagnosis of a giant cell lesion. Vivid enhancement was seen on T1-WI after intravenous gadolinium chelate administration. Laboratory analysis was normal. Enucleation of the lesion was performed under general anesthesia. Histopathological 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 (Fig. 5).



Fig. 2. — Clinical features of the patient at 14-years of age: note the ocular hypertelorism, the mildly downslanting palpebral fissures and short neck.

From: 1. Department of Radiology, AZ Sint Maarten Duffel-Mechelen, Duffel, Belgium, 2. Department of Radiology, Antwerp University Hospital, Edegem, Belgium, 3. Faculty of Medicine and Health sciences, Ghent University, Ghent, Belgium, 4. Department of Oral and Maxillofacial Surgery, AZ Sint Maarten, Duffel-Mechelen, Duffel, Belgium, 5. Centre for Human Genetics, University Hospitals Leuven, Leuven, Belgium, 6. Department of Surgical Pathology, AZ Sint Maarten Duffel-Mechelen, Duffel, Belgium. *Address for correspondence:* Dr F. Vanhoenacker, M.D., Ph.D., Rooienberg 25, 2570 Duffel, Belgium. E-mail: filip.vanhoenacker@telenet.be

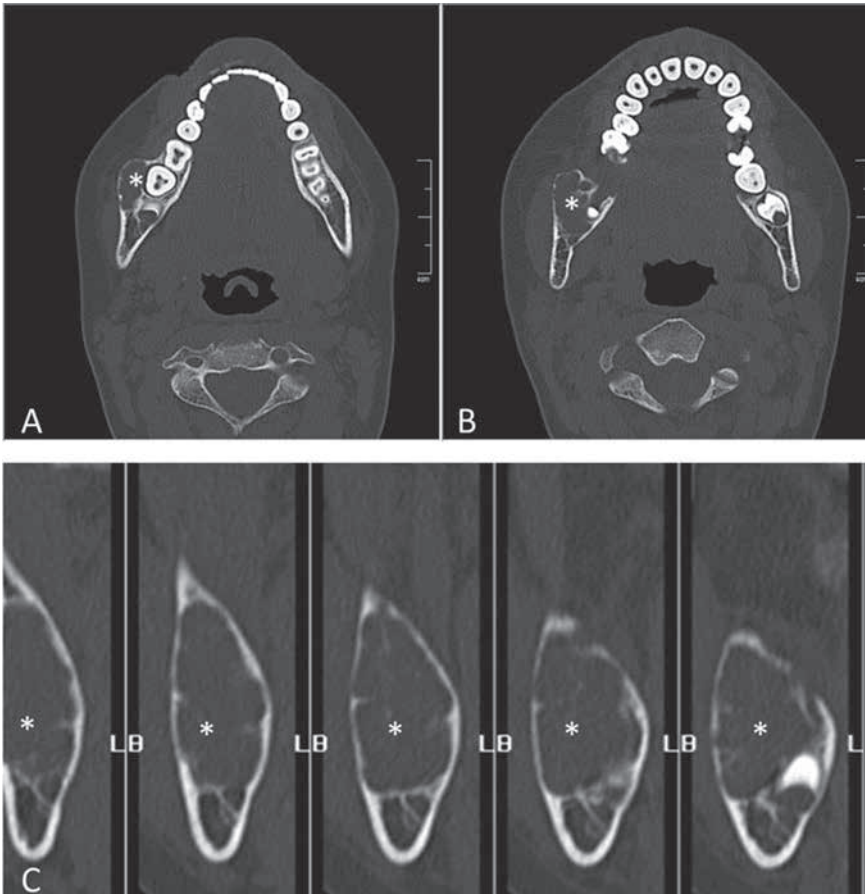


Fig. 3. — Dental Computed Tomography (A and B, axial reformatted and C, parasagittal reformatted slices) shows an expansile and multiloculated lesion in the right mandibular ramus (asterisk).

Discussion

NS is a autosomal dominant disorder with complete penetrance but wide phenotypic variability and an estimated prevalence of approximately 1 out of every 1000-2500 births (1). Although first reported by Kobylinski in 1883 it was not before 1968 that Jacqueline Noonan – a pediatric cardiologist – published her findings concerning the association of pulmonary stenosis in patients with characteristic facial features and chest deformities (2).

The most striking craniofacial characteristics of NS include a broad based webbed neck, posteriorly angulated ears, (mild) ptosis, ocular hypertelorism and downward slanting palpebral fissures. Specific oral findings in patients with NS comprise a deeply grooved philtrum, a high arched palate, micrognathia, dental anomalies with associated malocclusion, delayed tooth eruption, bifid uvula, articulation difficulties and – although rare – cleft palate (Table I) (1, 3-5). These features however change throughout life and are partly responsible for the phenotypic variability (1, 5, 6). Since its large phenotypic variability, mild cases are clinically easily overlooked. These patients are also predisposed for bleeding diathesis, lymphatic dysplasias, cryptorchidism and, although rare, hematological malignancies (1).

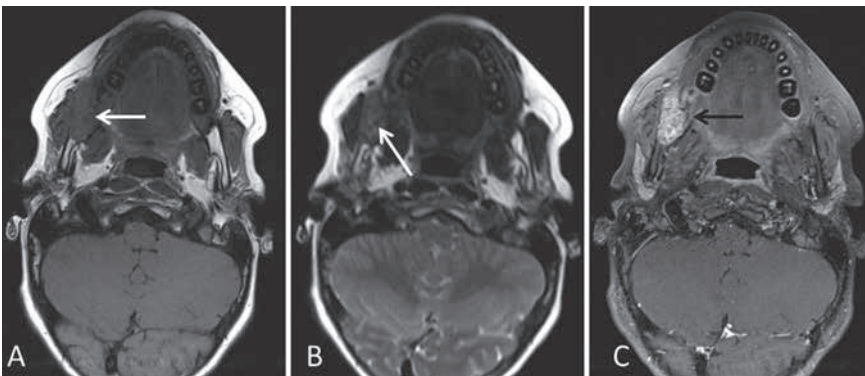


Fig. 4. — MRI of the mandible (A, T1-WI; B, T2-WI and C, T1-WI after intravenous administration of gadolinium chelate). The lesion is iso- to slightly hypointense to muscle on T1- (white arrow) and heterogeneously hypo-intense on T2-WI with foci of low SI (white arrow). Vivid enhancement is seen after contrast administration (black arrow).

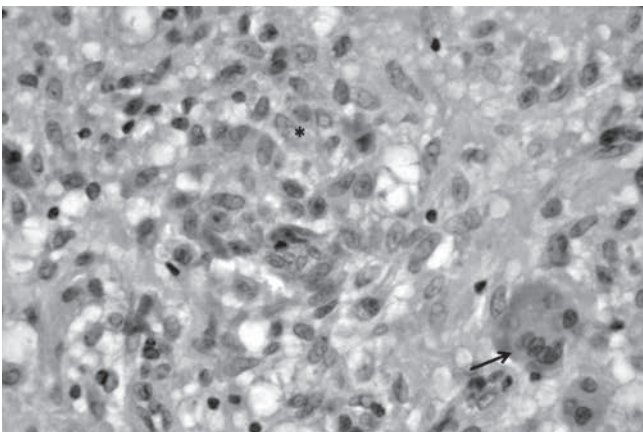


Fig. 5. — Photomicrograph showing giant cells (arrow) in a background of fibrous tissue interspersed with some hemosiderin laden macrophages (asterisk) (magnification: 400x, H and E stain).

Table I. — Summary of the most frequent oral manifestations in Noonan syndrome other than giant cell lesions (1, 3, 4).

High arched palate
Micrognathia
Dental anomalies with associated malocclusion
Delayed tooth eruption
Articulation difficulties
Bifid uvula
Cleft palate

The genetic heterogeneity is reflected by the occurrence of mutations in different genes, including *PTPN11*, *SOS1*, *KRAS*, *RAF1*, *BRAF*, *SHOC2* and *MEK1*, resulting in hyperactivation of the RAS-MAPK transduction pathway (7).

Our patient present with many of the classical features of NS such as short stature, short webbed neck, chest shape with superior pectus excavatum and inferior pectus carinatum, typical craniofacial dysmorphisms and congenital pulmonary stenosis, fulfilling the diagnostic criteria such as described by Tullu (Table II) (8). In addition, she presented with a unilateral giant cell lesion posterior in the right mandible. The association between NS and the presence of bilateral gnathic giant cell lesions has been extensively described in the international literature (1, 3, 4, 6, 9-11) and therefore has been named Noonan-like/Multiple Giant Cell Lesion syndrome (NL/MGCL). Most case reports and series comprising NL/MGCL syndrome report bilateral gnathic involvement although unilateral lesions are also possible. Also, the continuing evolving knowledge of molecular genetic testing has suggested that NL/MGCL syndrome is a variant of the NS spectrum rather than a distinct entity. In

our opinion, the presence of a unilateral giant cell lesion in our patient with genetically confirmed NS adds weight to this assumption. However, it is beyond the scope of this brief case report to review the whole literature concerning this association in detail. Moreover, our goal is to try elucidating the difficult differential diagnosis of gnathic giant cell lesions combining a thorough clinical examination, specific laboratory tests, genetic analysis and specific emphasis on imaging.

Gnathic lesions can be acquired or genetic and give rise to an extensive differential diagnosis (12). The central giant cell granuloma (CGCG) is a relatively frequent condition predominantly occurring in children and young adults. This benign lesion appears before the age of 30, occurs predominantly in females and is seen twice as much in the mandibular region compared to its maxillary counterpart (12, 13). Multiple and multifocal giant cell lesions are more rare and need to raise the suspicion for brown tumors due to hyperparathyroidism with overproduction of parathyroid hormone (6). Multifocal gnathic giant cell lesions also can occur in cherubism, a rare autosomal dominant disorder characterized by radiolucent lesions causing charac-

teristic facial swelling. Mutation analysis of the *SH3BP2* gene is diagnostic (14).

Imaging features of giant cell lesions are not pathognomonic since other (aggressive) lesions can have a similar appearance. CT mostly shows an expansive lesion with remodeling of the adjacent bone, lytic bony destruction and often with multilocular aspect due to intralesional mineralization. MR findings of giant cell lesions reported in the literature are scarce. Nonetheless, MRI can add more diagnostic certainty in gnathic lesion characterization. Giant cell lesions are mostly hypointense compared to normal muscle tissue on T1- and T2-WI. Intralesional low SI foci can be seen on T2-WI that correspond with hemosiderin deposits in response to intraosseous hemorrhage (12) and suggest the presence of a giant cell lesion. Also, vivid enhancement is seen after intravenous gadolinium chelate administration. A more cystic multiloculated appearance has been reported as well (15-18).

Multiple treatment options exist for giant cell lesions such as surgical curettage and use of calcitonin and interferon although no specific therapeutic option has been described for NS patients so far (19). Clinical and radiological follow up is essential since enucleation and curettage implies a recurrence risk (4).

Conclusion

Although imaging of giant cell lesions of the jaw is not specific, MRI may be useful in the differential diagnosis of gnathic lesions. The intralesional low SI foci on T2-WI suggestive of hemosiderin deposits should raise suspicion of a giant cell lesion especially in the specific clinical context of NS.

Table II. — Major diagnostic features of Noonan syndrome according to Tullu (8).

<i>General feature:</i> short stature
<i>Neurological features:</i> mild mental retardation
<i>Craniofacial features:</i> epicanthic folds, ptosis, hypertelorism, downward slanting palpebral fissures, deeply grooved philtrum with high wide peaks of vermilion border of upper lip, moderate retrognathia, high arched palate, low nasal bridge, low set posteriorly angulated ears with thickened helix and/or abnormal auricles, short webbed neck, excess nuchal skin with low posterior hair-line
<i>Thoracic features:</i> pectus carinatum and/or excavatum
<i>Skeletal features:</i> cubitus valgus, vertebral anomalies
<i>Cardiac features:</i> pulmonary valve stenosis, asymmetrical septal hypertrophy, atrial septal defects, patent ductus arteriosus, branch pulmonary artery stenosis, left axis deviation
<i>Skin features:</i> café-au-lait spots, lentigines, pigment nevi
<i>Genital features:</i> cryptorchidism, small penis

Acknowledgment

The authors would like to thank the parents of the patient for their permission in allowing us to use the photograph of their daughter.

References

- Romano A.A., Allanson J.E., Dahlgren J., Gelb B.D., Hall B., Pierpont M.E., Roberts A.E., Robinson W., Takemoto C.M., Noonan J.A.: Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics*, 2010, 126: 746-759.
- Noonan J.A.: Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease. *Am J Dis Child*, 1968, 116: 373-380.
- Lee S.M., Cooper J.C.: Noonan syndrome with giant cell lesions. *Int J Paediatr Dent*, 2005, 15: 140-145.
- Wolvius E.B., de Lange J., Smeets E.E., van der Wal K.G., van den Akker H.P.: Noonan-like/multiple giant cell lesion syndrome: report of a case and review of the literature. *J Oral Maxillofac Surg*, 2006, 64: 1289-1292.
- Roberts A.E., Allanson J.E., Tartaglia M., Gelb B.D.: Noonan syndrome. *Lancet*, 2013, 381: 333-342.
- Bufalino A., Carrera M., Carlos R., Coletta R.D.: Giant cell lesions in Noonan syndrome: case report and review of the literature. *Head Neck Pathol*, 2010, 4: 174-177.
- Tartaglia M., Zampino G., Gelb B.D.: Noonan syndrome: clinical aspects and molecular pathogenesis. *Mol Syndromol*, 2010, 1: 2-26.
- Tullu M.S., Muranjan M.N., Kantharia V.C., Parmar R.C., Sahu D.R., Bavdekar S.B., Bharucha B.A.: Neurofibromatosis-Noonan syndrome or LEOPARD Syndrome? A clinical dilemma. *J Postgrad Med*, 2000, 46: 98-100.
- Lee J.S., Tartaglia M., Gelb B.D., Fridrich K., Sachs S., Stratakis C.A., Muenke M., Robey P.G., Collins M.T., Slavotinek A.: Phenotypic and genotypic characterisation of Noonan-like/multiple giant cell lesion syndrome. *J Med Genet*, 2005, 42: e11.
- Cohen M.M., Jr., Gorlin R.J.: Noonan-like/multiple giant cell lesion syndrome. *Am J Med Genet*, 1991, 40: 159-166.
- Karbach J., Coerdts W., Wagner W., Bartsch O.: Case report: Noonan syndrome with multiple giant cell lesions and review of the literature. *Am J Med Genet A*, 2012, 158A: 2283-2289.
- Bernaerts A., Vanhoenacker F.M., Hintjens J., Chapelle K., Salgado R., De Foer B., De Schepper A.M.: Tumors and tumor-like lesions of the jaw: radiolucent lesions. *JBR-BTR*, 2006, 89: 81-90.
- Orhan E., Erol S., Deren O., Sevin A., Ekici O., Erdogan B.: Idiopathic bilateral central giant cell reparative granuloma of jaws: a case report and literature review. *Int J Pediatr Otorhinolaryngol*, 2010, 74: 547-552.
- Reichenberger E.J., Levine M.A., Olsen B.R., Papadaki M.E., Lietman S.A.: The role of SH3BP2 in the pathophysiology of cherubism. *Orphanet J Rare Dis*, 2012, 7 Suppl 1: S5.
- Mohammed T.L., Brummett D.P., Hahn F.J., Sharma P.: Intracranial giant cell reparative granuloma arising from the temporal lobe area: MR findings. *AJNR Am J Neuroradiol*, 2001, 22: 873-875.
- Nemoto Y., Inoue Y., Tashiro T., Mochizuki T., Katsuyama J., Hakuba A., Onoyama Y.: Central giant cell granuloma of the temporal bone. *AJNR Am J Neuroradiol*, 1995, 16: 982-985.
- Reis C., Lopes J.M., Carneiro E., Vilarinho A., Portugal R., Duarte F., Fonseca J.: Temporal giant cell reparative granuloma: a reappraisal of pathology and imaging features. *AJNR Am J Neuroradiol*, 2006, 27: 1660-1662.
- Sharma R.R., Verma A., Pawar S.J., Dev E., Devadas R.V., Shiv V.K., Musa M.M.: Pediatric giant cell granuloma of the temporal bone: a case report and brief review of the literature. *J Clin Neurosci*, 2002, 9: 459-462.
- de Lange J., van den Akker H.P., van den Berg H.: Central giant cell granuloma of the jaw: a review of the literature with emphasis on therapy options. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2007, 104: 603-615.