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Multiple giant cell lesions in a patient with Noonan syndrome with multiple lentigines

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ABSTRACT

A patient with Noonan syndrome with multiple lentigines (NSML) and multiple giant cell lesions (MGCL) in mandibles and maxillae is described. A mutation p.Thr468Met in the *PTPN11*-gene was found. This is the second reported NSML patient with MGCL. Our case adds to the assumption that, despite a different molecular pathogenesis and effect on the RAS/MEK pathway, NSML shares the development of MGCL, with other RASopathies.

1. Patient report

1.1. Background of introduction

Noonan syndrome with multiple lentigines (NSML), formerly called LEOPARD syndrome (LS; OMIM 151100) is caused by heterozygous mutations in one of four genes: *PTPN11*, *RAF1*, *BRAF* and *MAP2K1* and shows phenotypic and genotypic overlap with Cardio-Facio-Cutaneous syndrome (CFCS; OMIM 115150) and in particular with the more common Noonan syndrome (NS; OMIM 163950). Mutations p.Tyr279Cys and p.Thr468Met of the *PTPN11* gene are the most frequent mutations (65%) involved in NSML (Aoki et al., 2008). Disorders caused by mutations in one of the genes of the RAS-MAPK pathway, including NS, NSML, CFCS and Costello syndrome (CS; OMIM 218040), are commonly denominated as RASopathies. The RAS-MAPK pathway has a critical role in cell proliferation, motility and death and thereby in regulation of morphology determination, organogenesis and growth. The RAS signaling pathway is frequently altered in a broad spectrum of neoplasms as such. In RASopathies, a carcinogenic potential related to these mutations based on the presence of germline mutations is confirmed by epidemiological findings (Kratz et al., 2011, 2015; Jongmans et al., 2011; Schubbert et al., 2007).

Central giant cell tumor (CGCT), often denominated as central giant cell granuloma (CGCG) or giant cell lesion (GCL), is a rare benign condition with unpredictable variable biologic behavior most frequently occurring in the mandible and/or maxilla. Central giant cell tumors typically demonstrate a peak incidence in the second decade and occur more frequently in the mandible then in the maxilla (Aragao Mdo et al., 2007; de Lange et al., 2004). The pathogenesis is incompletely understood. Probably giant-cells of CGCGs are derived from a subset of mononuclear phagocytes. These mononuclear precursor cells differentiate into mature giant-cells under the influence of RANKL-expressing, proliferating spindle-

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shaped (osteoblast-like) stroma cells. The occurrence of CGCGs in patients with genetic conditions like neurofibromatosis type 1 (OMIM 162200), cherubism (OMIM 118400), and Noonan-like/multiple giant cell lesion syndrome (NL/MGCLS; OMIM 163955) indicates that at least in these patients a genetic etiology plays a role. In most patients the trigger for development of CGCG is however unknown (Schubbert et al., 2007; Aragao Mdo et al., 2007; Auclair et al., 1988; de Lange et al., 2007; Waldron and Shafer, 1966; Jaffe, 1953; Austin et al., 1959; Resnick et al., 2010; Wolvius et al., 2006; Harris, 1993; Cohen and Gorlin, 1991). Currently, no histological, genetic or molecular marker has been validated to predict either biologic behavior or prognosis and discern the "gnathic" CGCT from the giant cell lesions occurring in other locations. Multiplicity of CGCTs is exceptionally rare and closely resembles some of the clinical features of cherubism. Cherubism is a dominantly inherited syndrome with a single symptomatology caused by missense mutations in the SH3 binding protein *SH3BP2* (Ueki et al., 2001). Already in 1986, cherubism-like anomalies in Noonan's syndrome were described (Chuong et al., 1986). Finally, in 1991 the existence of the inheritable NL/MGCLS was recognized and in 2001 this condition was linked with the *PTPN11* gene, which is also involved in NS (Bertola et al., 2001). *SOS1*, *BRAF* and *MEK1* anomalies were reported at later instance (Neumann et al., 2009; Jongmans et al., 2005; Beneteau et al., 2009). Although initially thought to be a separate entity, nowadays it is considered a variant within the NS spectrum.

We observed a patient with NSML and histologically confirmed multiple giant cell lesions (MGCL), which demonstrates for the second time, that MGCL can be found in several syndromes of the RASopathy spectrum.

2. Case history

The patient presented at the age of 9 years with the complaint of a bilateral slowly progressive swelling of the mandible. He was born after an uneventful pregnancy and delivery. Pregnancy had been induced by semen donation of a healthy donor. From mothers side there was no family history of congenital anomalies. In early childhood he had a delayed walking (at 17 months); gross motor skills are still weak. Previous medical history mentioned orchidopexias because of cryptorchidism and an inguinal hernia. At earlier medical care instances a suspicion for NSML had not been raised. At school no deficits were reported. On clinical examination an abundance of lentigines was observed on all parts of his body. Hypertelorism, ptosis, downslant of the palpebral fissures and low-set caudally positioned, posteriorly rotated ears were noted (Fig. 1A–C). There was a non-tender palpable bony mass on the left and right lateral mandibular border. On intra-oral inspection there was a normal dental development with an age appropriate mixed dentition, a normal closed palatal arch and no mucosal lesions. Length was 137 cm (−1.0 SD), weight 29 kg (weight vs length at the age of 10 years −1.0 SD), BMI 15.5 and head circumference 56,8 cm (+1.9SD). Ultrasound of the heart and kidney, ECG, audiological and ophthalmological testing were normal. A facial computed tomography revealed bilateral multiple expanding and confluent osteolytic lesions in the maxilla and especially in the ascending ramus of the mandible with destruction of the osseous cortex and migration of developing tooth buds (Fig. 2). An open bone biopsy was performed demonstrating an intra-osseous solid hemorrhagic mass. Histology showed giant cells dispersed in a highly cellular stroma of mononuclear cells, compatible with CGCT (Fig. 3). Serum calcium, phosphate and PTH levels were normal. Mutational screening for cherubism (exon 9 of the *SH3BP2* gene) was negative. Molecular genetic analysis, as described by Jongmans et al. using a panel of 14 genes involved in the RAS-MAPK pathway, revealed a c.1403C > T (p.Thr468Met) mutation in the *PTPN11*-gene (Jongmans et al., 2005).

There is no consensus on the management of MGCL, especially not in RASopathies and cherubism. Surgical treatment and a wait-and-see policy have been reported (de Lange et al., 2007). An alternative treatment strategy described is pharmacotherapy with calcitonin, based on its ability to inhibit the osteoclast-like multinucleated giant cell (Harris, 1993). Considering the extent of the lesions and the already severe displacement of the developing permanent dentition, this patient was started on daily 100 mg subcutaneous calcitonin. Follow-up of the effect of calcitonin treatment in this patient is pending.s.

3. Discussion

The patient described is the second report of MGCL in NSML. To our knowledge, the patient reported by Sarkozy et al. is the only published case of NSML with MGCL (Neumann et al., 2009). This patient carried a p.Ala461Thr mutation in exon 12 of *PTPN11*, which is not among the most frequent mutations in NSML (Sarkozy et al., 2004), but has also been proven to belong to the class of phosphatase-impaired mutations (Kontaridis et al., 2006). NSML shows large overlap with NS, but discriminating features are the abundant lentigines and the higher frequency of deafness and hypertrophic cardiomyopathy. The predilection to develop MGCL in NS is not correlated with specific mutations in the genes involved (Karbach et al., 2012). Mutations identified in MGCL-patients have also been detected in RASopathy patients without MGCL. Similar to the development of neurofibromas in NSML additional somatic mutations or a genetic modifier might be needed for development of MGCL (Conboy et al., 2016).

In nearly all patients with NSML, the condition is caused by specific mutations in *PTPN11* including the mutation identified in this case report. These mutations involve in the large majority of cases other nucleotides of *SHP2* (encoded by *PTPN11*) in *PTPN11*

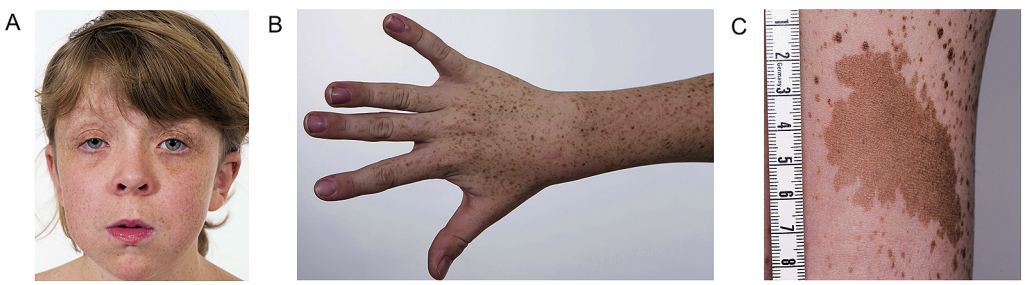

Fig. 1. A,B,C. Nine year-old boy with multiple lentigines, cafè-au-lait spots, hypertelorism, ptosis, downslant of the palpebral fissures and low-set caudally positioned, posteriorly rotated ears.

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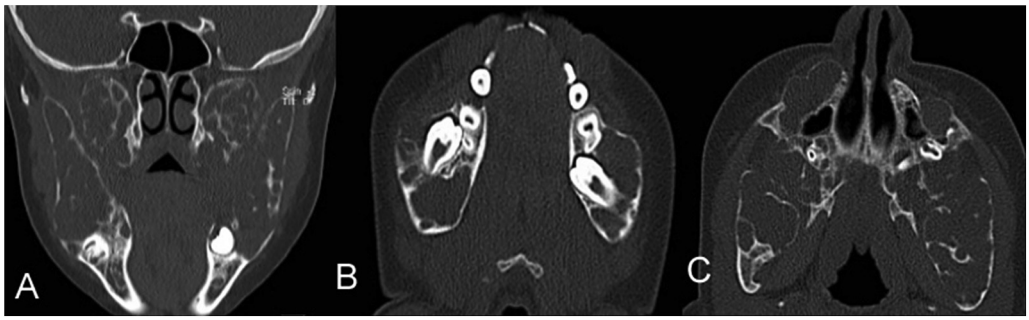

Fig. 2. CT-images: A. coronal image, B. mandible, C. maxilla.

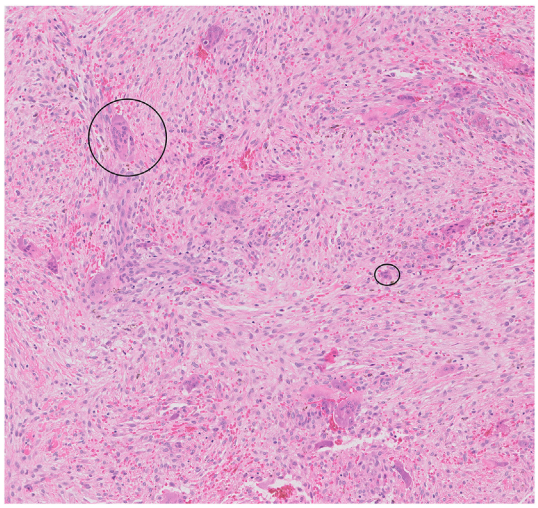

Fig. 3. Pathology specimen showing highly cellular, with multinucleated giant cells in fibroblastic stroma with plump, spindle-shaped cells with a high mitotic rate. Two of the various giant cells are encircled.

than the mutations causing NS (Aoki et al., 2008; Tartaglia et al., 2006). Intriguingly, it is assumed that the functional consequences of mutations associated with either of these disorders are distinct. *PTPN11* mutations involved in NS result in a gain of function of the protein whereas the effect of NSML mutations is still incompletely understood (Kontaridis et al., 2006; Smpokou et al., 2015; Tartaglia et al., 2001). In NSML a disbalance combined dysregulation of RAS/MAPK and PI3K/AKT pathways resulting in hypo- or hyperactivation is assumed (Tajan et al., 2015). The effect however is different from a simple loss-of-function, because such mutations are known to cause a disease called metachondromatosis (Bowen et al., 2011). The large overlap in phenotypic features between NS and NSML, including a shared occurrence of MGCL, a condition based on increased cell proliferation, makes it challenging to understand differences in pathogenesis.

3.1. Tumor formation in NSML

RASopathies have been associated with development of malignancies. A literature search covering the period 1937–2010 revealed 88 malignancies in 1941 cases of NS, CS, CFCS and NSML. Predominantly hematologic malignancies and to a lesser extent solid tumors were reported. Peak incidence was in the pediatric age range. In NSML two cases with acute myeloid leukemia, and single cases of acute lymphoblastic leukemia, neuroblastoma and melanoma were recovered (Kratz et al., 2011). Analysis of data of all German genetic laboratories identified 735 patients with RASopathies (7489.9 person-years of observation). In 12 patients a malignancy was noted vs 1.12 expected, among them only one patient with NSML suffering from acute lymphoblastic leukemia (Kratz et al., 2015). A study on pediatric and adult patients with NS due to a *PTPN11* mutation revealed a 3.5 fold increased risk of cancer compared to the general population (Jongmans et al., 2011). In this study, patients with NSML were excluded. Recently, five patients with NSML and malignant neoplasms were summarized: three cases of leukemia in patients with germline mutations of amino acid residue 279 of *PTPN11* and two patients, both carrying the p.Thr468Met *PTPN11* mutation developed malignant solid tumors; one a medulloblastoma and the other a stage IV neuroblastoma (Smpokou et al., 2015). Due to the low numbers, the exact increase in incidence of malignant tumors specifically for NSML cannot be given.

Benign tumors are poorly recorded in population and disease registries. Therefore, there are no data on the frequency of benign tumors in NS, NSML and other RASopathies. Benign neurogenic tumors have been described in a few patients with NSML (Conboy et al., 2016; Merks et al., 2005); other reported tumors are choristoma of the cornea and granular cell tumors (Choi et al., 2003; Sarkozy et al., 2008; Schrader et al., 2009). As far as we know, Sarkozy et al. reported on the only single case of NSML with MGCL. The mutation found, Ala461Thr in exon 12, which is not the most characteristic mutation in NSML, is different from the mutation noted in our patient (Sarkozy et al., 2004). This earlier reported case on the occurrence of MCGL and NSML can be mere coincidence. Addition of our case, makes it highly unlikely that (despite the differences in the molecular pathogenesis of PTPN11-mutated NS and NSML) both anomalies are not related.

In respect to MGCL development in RASopathies, increased *ERK*-activity induced by RAS activation, as seen in *PTPN11* anomalies, results in upregulation of RANKL. This leads to fusion of mononuclear osteoclasts into multinucleated active osteoclasts triggering the initiation of CGCT development. This is likely regulated by GM-CSF, since RANKL overexpression results in upregulation of GM–CSF–receptor-α and promotes fusion of osteoclasts (Fragale et al., 2004; Miyazaki et al., 2000; Folgueira et al., 1996; Lee et al., 2009; Nakashima and Haneji, 2013; Bauler et al., 2011; Yang et al., 2013). Such an assumption is currently supported by treatment results in CGCT using a monoclonal directed against RANKL. Formerly treatment of solitary CGCT was only surgery, but high recurrence rates was a major drawback for the choice of this treatment (de Lange et al., 2007). Promising developments are reported and were also noted in patients in our center using denosumab, a commercially available monoclonal antibody directed against RANKL (Naidu et al., 2014). Due to reports in preclinical juvenile studies on bone anomalies we are reluctant to use denosumab in children. Mentioned data on treatment options originate

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from patients with monolocular CGCT; as such the effects might not applicable in multiple CGCT as seen in in RASopathies.

Primary conclusion, based on our case and on literature data, is that considering the very low incidence of NSML and the occurrence of both malignant and benign tumors, it is suggestive that MGCL should be considered to be part of the tumor palette shared by NS and NSML.

Conflict of interest

The authors do not have a conflict of interest related to this report.

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