CASE REPORT

Giant cell lesion of the jaw as a presenting feature of Noonan syndrome

Bridget P Sinnott,¹ Maya Patel²¹Department of Endocrinology, Augusta University, Augusta, Georgia, USA²Augusta University Medical College of Georgia, Augusta, Georgia, USACorrespondence to
Dr Bridget P Sinnott,
bsinnott@augusta.edu

Accepted 27 April 2018

SUMMARY

This is a case of a 20-year-old woman who presented with a left jaw mass which was resected and found to be a giant cell granuloma of the mandible. Her history and physical examination were suggestive for Noonan syndrome which was confirmed with genetic testing and the finding of a *PTPN11* gene mutation which has rarely been associated with giant cell lesions of the jaw. Given her particular genetic mutation and the presence of a giant cell lesion, we present a case of Noonan-like/multiple giant cell lesion syndrome.

BACKGROUND

Noonan syndrome is an autosomal-dominant syndrome with a prevalence of 1 in 1000–2500.¹ This syndrome results from dysregulation of the RAS-MAPK signalling cascade which is an important signal transduction pathway involved in cell differentiation, proliferation, survival and metabolism.² Patients with this mutation can present with features including facial dysmorphism, developmental delay, short stature, learning difficulties and congenital heart disease. Patients are also at increased risk of developing haematological abnormalities, such as bruising, bleeding and malignancies.^{3,4} A broad differential should be kept in mind following the diagnosis of giant cell lesions of the jaw as these lesions may be associated with other syndromes, such as Noonan-like/multiple giant cell lesion (NL/MGCL) syndrome or they could be the initial presentation of an underlying medical condition such as primary hyperparathyroidism. The following is a case report of NL/MGCL syndrome which was diagnosed after she presented with a giant cell lesion of the jaw.

CASE PRESENTATION

A 20-year-old woman presented to the oral maxillo-facial surgery clinic for a left jaw mass. The patient stated that in the past, she had multiple cysts and tumours removed from her jaw, with the first being diagnosed at the age of 15 years. They had been painless and did not cause significant dental dislocation or tooth loss. A panoramic radiograph showed multityc lesions of the left mandible. She underwent enucleation and curettage of the mandibular mass. Pathology was remarkable for central giant cell granuloma with some concern for a Brown's tumour. She was subsequently referred to the endocrine clinic for evaluation of possible primary hyperparathyroidism, given its association with brown tumours of the bone.

Her medical history included a cardiac murmur related to mild pulmonic valve stenosis which was diagnosed as an infant. She underwent a balloon pulmonic valvuloplasty at age 3 years. She had delayed puberty with her menarche at age 18. She currently has 'hormone pellets' in place and has had some breakthrough bleeding. She had a history of life-long easy bruising. She underwent extraction of her wisdom teeth as well as seven baby teeth as a child. Her family history was unremarkable, specifically there was no history on Noonan syndrome or congenital anomalies. She works at an outreach programme for job placement.

On physical examination, the patient had short stature at 5'2" (her mother and father were 5'6" and 6'0", respectively) and a body mass index of 19. She has an inverted triangle-shaped face with a wide forehead which tapered to a pointed chin (see figure 1). She had blue irises and micrognathia, but did not have any palpable mandibular or maxillary masses or tenderness. On intraoral inspection, she had normal dentition and a high arched palate. She had a low posterior hair line, posteriorly rotated ears but no webbing of the neck (see figure 2). She had prominent pectus carinatum. She had ecchymosis on her upper and lower extremities but no evidence of any hyperpigmented lesions. She had cubitus valgus bilaterally (see figure 3). No heart murmurs were audible. She had myopia requiring corrective lenses.

During workup, the patient was noted to be vitamin D replete, with a normal serum calcium and parathyroid hormone levels. Based on the clinical history and physical examination findings, the patient underwent genetic testing for Noonan syndrome and related disorders by gene sequence analysis of *PTPN11*, *SOS1*, *KRAS* and *RAF1* genes.

OUTCOME AND FOLLOW-UP

The patient was heterozygous for the p.N308D pathogenic mutation located on exon 8 of the *PTPN11* (protein tyrosine phosphatase, non-receptor type 11) gene. This genetic alteration was initially reported in three families and one sporadic proband with Noonan syndrome⁵ and in one case with NL/MGCL.⁶

Following the diagnosis of Noonan syndrome, the patient had X-rays taken of her spine which showed incomplete fusion of the posterior elements of S1. Her sternum X-ray showed an anterior deformity of the body of the sternum (pectus carinatum) (see figure 4). Ultrasound of retroperitoneal structures showed normal kidneys without hydronephrosis or

To cite: Sinnott BP, Patel M. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-224115

Figure 1 Frontal view of patient with Noonan-like/multiple giant cell lesions syndrome showing an inverted triangle-shaped face.

other abnormalities. She had a normal complete blood count, prothrombin time and activated partial thromboplastin time. Her ECG revealed normal sinus rhythm with right axis deviation. Her cardiac echo revealed mild pulmonary valve stenosis with mild pulmonic valve regurgitation; there was trace mitral regurgitation. The right and left ventricular sizes were normal, with normal wall thickness and wall motion. She follows with a

Figure 2 Lateral view of patient with Noonan-like/multiple giant cell lesions syndrome showing a low posterior hair line and posteriorly rotated ears.

Figure 3 Frontal image of the upper extremities of a patient with Noonan-like/multiple giant cell lesions syndrome showing prominent bilateral cubitus valgus.

cardiologist yearly. She had a normal hearing examination and wears glasses for myopia.

DISCUSSION

Noonan syndrome is an autosomal-dominant disorder in which 45% of familial and sporadic cases are caused by missense, gain of function mutations in the *PTPN11* gene on chromosome 12q24.1.⁷ Our patient's mutation was felt to be sporadic given her lack of family history for Noonan syndrome. Noonan syndrome was originally described in 1963 and has broad phenotypic variability.⁸ Features of this syndromic mutation include short stature, facial dysmorphism, right sided congenital heart defects most commonly pulmonic stenosis, intellectual disability, webbed neck, sternal abnormalities, abnormal skin pigmentation and coagulation defects.² Patients with the *PTPN11* gene mutation have a 3.5 times increased risk of developing a cancer compared with the general population,⁹ necessitating long-term follow-up. Additionally, patients with the *PTPN11* gene mutation have a higher prevalence of pulmonic stenosis compared with Noonan patients with other mutations.¹⁰ It is important to establish a diagnosis of Noonan given the need for long-term follow-up for haematological malignancies, congenital heart disease and multiple other medical and developmental complications.⁴

The patient in this case presented with many of the features associated with Noonan syndrome and genetic testing confirmed a p.N308D pathogenic mutation in the *PTPN11* gene. Her initial

Figure 4 Lateral view of the sternum showing a prominent anterior bowing deformity of the body of the sternum, known as pectus carinatum.

presentation was a left mandibular mass which was confirmed to be a giant cell tumour and is a recognised feature of her particular mutation⁶ and of Noonan syndrome.¹¹ Giant cell tumours, also known as giant cell lesions or granulomas, are rare but benign conditions that most frequently occur in the mandible and/or maxilla. The incidence usually peaks in the second decade and occurs more frequently in women compared with men.¹² There is a wide spectrum of clinical activity from slow growing indolent lesions to aggressive expansile lesions.¹² These tumours typically respond well to surgical curettage. Histologically, they consist of multinucleated giant cells within fibrous connective tissue with abundant stroma of mononucleated cells.¹³ These giant cell tumours are microscopically and macroscopically similar to cherubism and brown tumours of hyperparathyroidism.¹³ To establish the correct diagnosis, one needs to evaluate clinical, laboratory and radiologic data of the patient.

In 1991, Cohen and Gorlin initially described the syndrome, NL/MGCL syndrome, in which the Noonan syndrome phenotype was associated with MGCLs.¹⁴ NL/MGCL syndrome is currently considered a variant of the Noonan syndrome spectrum rather than a distinct entity.^{7,15} Subsequently, NL/MGCL cases were found to be associated with *PTPN11* and *SOS1* gene mutations.^{6,15,16} These mutations lead to dysregulation and overactivation of the RAS-MAPK signalling pathway. Giant cell granulomas can also be seen in other RASopathies including neurofibromatosis type I, cardiofaciocutaneous syndrome, Costello syndrome and LEOPARD, which is now known as Noonan syndrome with multiple lentiginos syndrome.¹⁷

In summary, MGCLs are rare but can be a feature of syndromes that occur from dysregulation of the RAS-MAPK signalling pathway. The incidence of MGCL in Noonan syndrome is not known. The diagnosis of Noonan syndrome is primarily based on clinical suspicion and confirmed with genetic testing. Our case is unique in that the diagnosis of a mandibular giant cell lesion preceded the discovery of Noonan syndrome. Diagnosis of MGCL should alert the physician to other clinical syndromes or associated medical disorders.

Learning points

- ▶ Noonan syndrome is a common, often unrecognised disorder with a prevalence of 1 in 1000–2500. The diagnosis may be delayed until adulthood.
- ▶ A diagnosis of Noonan syndrome is primarily based on a clinical suspicion followed by performance of a gene sequence analysis of the *PTPN11*, *SOS1*, *KRAS* and *RAF1* genes, which have been linked to Noonan syndrome.
- ▶ Noonan syndrome is the second most common syndromic cause of congenital heart disease after trisomy 21, with pulmonary stenosis being the most common abnormality.
- ▶ Multiple giant cell tumours of the jaw may be a presenting feature of Noonan syndrome and is referred to as Noonan-like/multiple giant cell lesion syndrome, which is part of the Noonan syndrome spectrum.
- ▶ The following syndromes may overlap and share phenotypic features with Noonan syndrome and include cardiofaciocutaneous syndrome, Turner syndrome, Costello syndrome, LEOPARD syndrome and Aarskog syndrome.

Contributors BPS initially saw and evaluated the patient and confirmed her suspicion of a diagnosis of Noonan syndrome with genetic testing. MP drafted the case report with discussion and BPS critically revised the content and finally approved the case report for submission. Both authors are accountable for the content of the case report and are willing to address any questions regarding its content.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Tartaglia M, Zampino G, Gelb BD. Noonan syndrome: clinical aspects and molecular pathogenesis. *Mol Syndromol* 2010;1:2–26.
- 2 Roberts AE, Allanson JE, Tartaglia M, et al. Noonan syndrome. *Lancet* 2013;381:333–42.
- 3 Kratz CP, Rapisuwon S, Reed H, et al. Cancer in Noonan, Costello, cardiofaciocutaneous and LEOPARD syndromes. *Am J Med Genet C Semin Med Genet* 2011;157C:83–9.
- 4 Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics* 2010;126:746–59.
- 5 Tartaglia M, Mehler EL, Goldberg R, et al. Mutations in *PTPN11*, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 2001;29:465–8.
- 6 Beneteau C, Cavé H, Moncla A, et al. *SOS1* and *PTPN11* mutations in five cases of Noonan syndrome with multiple giant cell lesions. *Eur J Hum Genet* 2009;17:1216–21.
- 7 Lee JS, Tartaglia M, Gelb BD, et al. Phenotypic and genotypic characterisation of Noonan-like/multiple giant cell lesion syndrome. *J Med Genet* 2005;42:e11.
- 8 Noonan JA, Ehmke DA. Associated noncardiac malformations in children with congenital heart disease. *Midwest Soc Pediatr Res* 1963;63:468–70.
- 9 Jongmans MC, van der Burgt I, Hoogerbrugge PM, et al. Cancer risk in patients with Noonan syndrome carrying a *PTPN11* mutation. *Eur J Hum Genet* 2011;19:870–4.

- 10 Tartaglia M, Kalidas K, Shaw A, *et al.* *PTPN11* mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. *Am J Hum Genet* 2002;70:1555–63.
- 11 Mallineni SK, Yung Yiu CK, King NM. Oral manifestations of Noonan syndrome: review of the literature and a report of four cases. *Rom J Morphol Embryol* 2014;55:1503–9.
- 12 de Lange J, van den Akker HP, Klip H. Incidence and disease-free survival after surgical therapy of central giant cell granulomas of the jaw in The Netherlands: 1990-1995. *Head Neck* 2004;26:792–795.
- 13 Lee SM, Cooper JC. Noonan syndrome with giant cell lesions. *Int J Paediatr Dent* 2005;15:140–5.
- 14 Cohen MM, Gorlin RJ. Noonan-like/multiple giant cell lesion syndrome. *Am J Med Genet* 1991;40:159–66.
- 15 Bertola DR, Kim CA, Pereira AC, *et al.* Are Noonan syndrome and Noonan-like/multiple giant cell lesion syndrome distinct entities? *Am J Med Genet* 2001;98:230–4.
- 16 Neumann TE, Allanson J, Kavamura I, *et al.* Multiple giant cell lesions in patients with Noonan syndrome and cardio-facio-cutaneous syndrome. *Eur J Hum Genet* 2009;17:420–5.
- 17 Wolvius EB, de Lange J, Smeets EE, *et al.* Noonan-like/multiple giant cell lesion syndrome: report of a case and review of the literature. *J Oral Maxillofac Surg* 2006;64:1289–92.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow