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Noonan Syndrome with Recurrent Central Giant Cell Granulouma

[1]Majeda Alslimi, [2]Amjad Almalki, [3]Abdulrahman Alissa

[1,2]Prince Sultan Military Medical City, [3]Ministry of Health
[1,2,3]Riyadh, Saudi Arabia

Abstract: **Noonan syndrome (NS) is a common genetic condition with multiple congenital abnormalities, characterized by high incidence of congenital heart disease, facial anomalies, webbed neck, cryptorchidism, behavioural problem, hearing loss and other comorbidities. The cause of this disorder is believed to be mutations of RSA/mitogenactivated protein kinase (MAPK) pathway. Diagnosis can be achieved by the basis of clinical features although it has similarities to patients who have Turner syndrome. A number of cases with features of NS reported with multiple or solitary central giant cell granuloma (CGCG). This report aims to present a case of 14-year-old Saudi patient with NS associated with recurrent CGCG.**

Keywords: **Noonan syndrome, Giant cell granuloma, PTPN11.**

I. INTRODUCTION

Noonan syndrome (NS) is a clinically and genetically heterogeneous condition with multiple congenital abnormalities characterized by congenital heart disease, facial anomalies, chest deformity, short stature, webbed neck and other comorbidities [(1)]. These features were originally reported by Kobylinski in 1883,[(2)] and was documented first in 1963 by Noonan and Ehmke [(3)]. The incidence of NS is estimated to be 1 in 1000 to 1 in 2500 live births and affects both genders [(4)]. The genetic heterogeneity occurs due to mutations in different genes, including PTPN11, SOS1, KRAS, RAF1, BRAF, SHOC2 and MEK1 [(5)]. These mutations result in hyper activation of the RAS-RSA/mitogen activated protein kinase (MAPK) pathway, which is involved in cell cycle differentiation, growth, and senescence [(6)]. Approximately 50% of the cases are a result in the mutation in the protein tyrosine phosphatase non receptor type 11 (PTPN 11) [(7)]. The diagnosis of NS can be achieved clinically, based on facial and musculoskeletal features, additionally molecular genetic testing can provide confirmation in 70% of cases and may have important implications for management [(7)]. Frequently, early diagnosis is important for optimal therapeutic approaches of the patient [(1)]. NS has similarities to patients with Turner syndrome, a chromosomal abnormality in which one X chromosome is absent; 45,X karyotype and can be misdiagnosed because of some common features of theirs such as webbed neck, short stature, low posterior hairline, right side congenital heart disease, epicanthus folds, and various skeletal malformations [(8)]. However, in NS no consistent chromosomal abnormality has been found [(9)]. In Turner syndrome only females are affected, developmental delay is much less frequent, renal anomalies are more common and left-sided heart defects are the rule [(7)]. NS is frequently inherited in an autosomal dominant manner and any person affected has up to a 50% chance of transmitting it to their children [(7)]. There are a number of conditions with significant phenotypic overlap with NS such as LEOPARD, Baraitser-Winter syndrome, Costello syndrome, cardiofaciocutaneous (CFC) syndrome and William's syndrome [(1)]. The most frequent oral findings in patients with NS include central giant cell granuloma, high arched palate, malocclusion, micrognathia, articulation difficulties, delayed tooth eruption, cleft palate and bifid uvula [(1,4,10,11)]. The facial features consist of hypertelorism, epicanthal folds, broad forehead, down-slanting palpebral fissures and posteriorly rotated ears [(1)]. Other features include hearing loss, webbed neck, behavioural conditions, scoliosis, cryptorchidism, increased bleeding tendency, learning difficulties and lymphedema [(1,7,12)].

Central giant cell granuloma (CGCG) is a benign neoplasm occurring mainly in the jaws. It commonly occurs in young adults with a female predominance [13]. They are more common in the mandible than in the maxilla, especially the anterior region [14]. It may be fully asymptomatic and only found accidentally during a radiographic examination [15]. It appears radiographically as multilocular radiolucencies displacing the teeth, root resorption and cortical perforations are also seen [16]. A number of cases with features of NS were reported with multiple or solitary CGCG [10,11,17,18]. Several methods have been used to treat CGCG with various degrees of success such as Intra-lesional steroid injections, calcitonin injections , alpha interferon and cryosurgery [19,20]. This report aims to present a dental and surgical management of a 14-year-old Saudi patient with NS associated with recurrent CGCG.

II. CASE REPORT

A 14-year-old Saudi boy was referred to the Paediatric Dentistry department from Oral and Maxillofacial Surgery (OMFS) department for dental assessment and treatment prior to surgical removal of CGCG. The patient was already diagnosed with Noonan syndrome associated with recurrent central giant cell granuloma. The boy was delivered in good condition at the 8th month of pregnancy via cesaren section. The mother is diabetic, the father has no significant medical findings and the youngest daughter is healthy. He was hospitalized several times and had undergone five operations under general anaesthesia. Two orchiopexy surgeries were performed at the age of 5. Dental rehabilitation, biopsy and conventional surgical enucleation of CGCG were also performed with no complication due to general anaesthesia.

A review of the patient's medical history reveals that he suffers from congenital pulmonary stenosis, hearing loss and learning difficulties (he is attending a special school). Physical examination reveals a relatively short stature (height 143 cm, weight 31 kg), scoliosis (**Fig. 1**), cubitus valgus and abnormal chest morphology. Extra oral examinations shows mild facial asymmetry, palpable and mobile lymph nodes on right side of the face, posteriorly angulated low set ears, mild ptosis, ocular hypertelorism and exophalmos were also noted (**Fig. 2**).

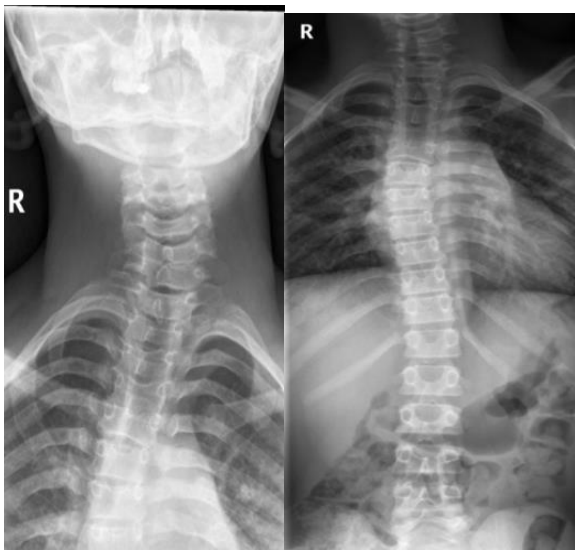

Fig. 1: X-ray of spine shows abnormal lateral curvature of the spine.

Fig. 2: Clinical features of the patient: note the ocular hypertelorism, facial asymmetry, exophalms and mild ptosis.

His facial shape was of an inverted triangle with a relatively large nose and full, incompetent lips. His parents also reported that he has a mouth breathing habit. Intra oral examination showed permanent dentition with carious teeth, generalized plaque induced gingivitis, severe upper crowding, bilateral cross bite, missing teeth #26, #46, #47, #48 and a malaligned tooth #35. Orthopantomography (OPG) showed a unilateral multiocular legion in the posterior right region of the mandible (**Fig. 3**). Computed Tomography (CT) Imaging revealed a multiocular expansile legion with cortical bone thinning of the buccal cortex of the right mandible (**Fig. 4**). Laboratory analysis was normal. The Histopathological analysis showed multinucleated giant cells embedded in fibroblastic stroma, confirming the diagnosis of giant cell lesion (**Fig. 5**).

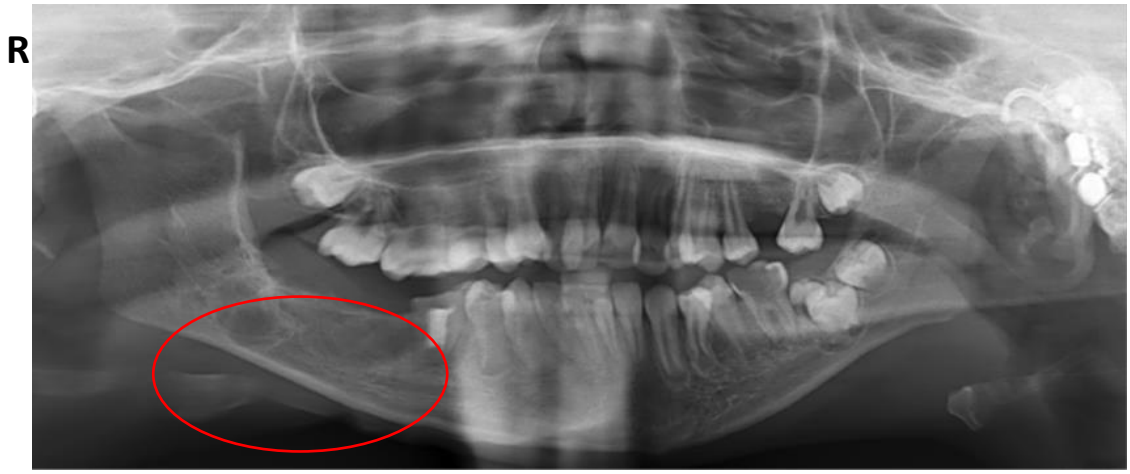

Fig. 3: Orthopantomography (OPG) radiograph revealed a unilateral well defined radiolucent lesion in the right mandibular.

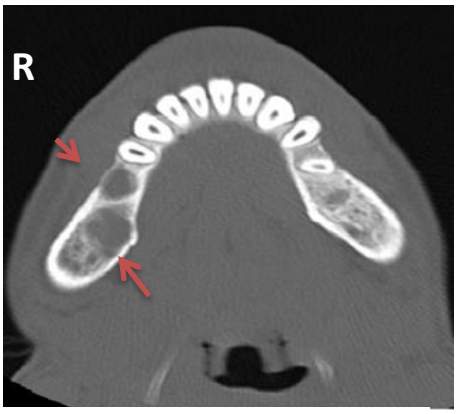

Fig. 4: Computed Tomography (CT) shows an expansile and multiloculated lesion in the right.

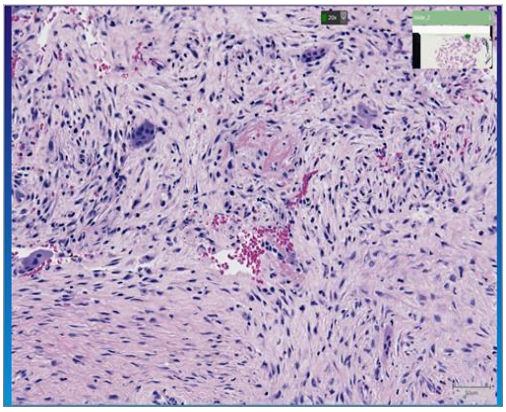

Fig. 5: Pathology specimen shows multinucleated giant cells scattered in fibroblastic stroma.

The patient went through multidisciplinary phases once he was cleared by his physicians. Started with prevention phase which includes prophylaxis, fluoride application, diet monitoring and oral hygiene instructions. The restorative phase contained multiple dental extractions and restorations under general anaesthesia. In the surgical phase the patient underwent surgical enucleation and cryosurgery of the CGCG. The orthodontic and prosthodontics phases will be conducted to achieve the functional and esthetic demand of the patient after the passing of sufficient time to insure no recurrence. Periodontics/Implant might be the future treatment plan option.

III. DISCUSSION

NS is a common genetic disorder that occurs in 1 in 1000 to 2500 live births and affects both genders [(4)]. Our patient displayed most of the clinical features of NS, including congenital pulmonary stenosis, which is estimated to occur in 2/3 patients (50% have pulmonary valvular stenosis and 10% with septal defects),[(21)] hearing loss, learning difficulty, short stature, widely space nipples and scoliosis which is reported in 13% of cases,[(12)] fulfilling the clinical diagnostic criteria proposed by Bhambani et al [(22)].

Central giant cell granuloma is a benign neoplasm which occurs mainly in the jaw [(13)]. A number of NS cases were reported with multiple or solitary CGCG [(10,11,17,18)]. Multiple and multifocal giant cell lesions would point towards brown tumors caused by hyperparathyroidism. Our patient's lab tests displayed normal levels of calcium, phosphate and parathormone [(23)]. A full body radiographic exam showed no other lesions in the body, which rules out brown tumors. Occasionally, when the NS features are mild, CGCG can also be misdiagnosed as cherubism, a bilateral disorder characterized by abnormal bone tissue causing the face to swell. The giant cell lesion from both CGCG and cherubism are histologically identical as both are osteoclastoma. However, genetic testing could be important to distinguish between the two, as each is caused by the mutation of a different gene [(24)]. Conventional management of CGCG is surgical and consists of enucleation and curettage. Despite this, a recurrence rate of 15-20% is often quoted [(19)].Our patient underwent

that treatment two years ago but recurrence occurred after. This time, the surgeons used a combination of surgical enucleation plus curettage and cryosurgery using frozen nitrogen, which was shown to decrease the rate of recurrence of locally aggressive mandibular tumours such as CGCG [20]. The dental treatment is still ongoing as the patient will need extensive prosthodontic and orthodontic procedures in the future.

IV. CONCLUSION

Patients with NS might be difficult to treat in a regular dental chair appointment, most of them have behavioural problems requiring different treatment modalities such as general anaesthesia. For this reason, a prevention program is necessary starting as early as possible in order to avoid the problem that could become difficult to manage. It has been shown that surgical enucleation and cryosurgery decrease the rate of recurrence of locally aggressive mandible tumours such as CGCG [20]. A multidisciplinary team is essential to assist and plan the treatment for dentally complicated cases.

REFERENCES

[1] Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics. 2010; 126: 746-759.

[2] Kobylinski O, Über eine flughautahnliche Ausbreitung amHalse, Arch Anthropol. 1883; 14: 343-348.

[3] Noonan JA, Ehmke DA. Associated noncardiac malformation in children with congenital heart disease. J Pediatr. 1963; 63:468-470.

[4] Mendez HM, Opitz JM. Noonan syndrome: a review. Am J Med Genet. 1985; 21: 493-506.

[5] Tartaglia M., Zampino G., Gelb B.D.: Noonan syndrome: clinical aspects and molecular pathogenesis. Mol Syndromol. 2010; 1: 2-26.

[6] Tidyman WE, Rauen KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev. 2009; 19: 230-236.

[7] Allanson JE, Roberts AE. Noonan syndrome. GeneTests: Reviews. National Center for Biotechnology Information. http://www.ncbi.nlm.nih.gov/books/NBK1124. Accessed May 23, 2013.

[8] Noonan JA. Hypertelorism with Turner pheno‐type. A new syndrome with associated congenital heart disease. Am J Dis Child. 1968; 116: 373‐380.

[9] Judith E Allanson. Noonan Syndrome, Journal Of Medical Genetics. 1987; 24: 9‐13.

[10] Van den Berg H, Schreuder WH, Jongmans M, van Bommel-Slee D, Witsenburg B, de Lange J. Multiple giant cell lesions in a patient with Noonan syndrome with multiple lentigines. Eur J Med Genet. 2016; 59:425-8.

[11] Eyselbergs M, Vanhoenacker F, Hintjens J, Dom M, Devriendt K, Van Dijck H. Unilateral giant cell lesion of the jaw in Noonan syndrome. JBR-BTR. 2014; 97: 90-93.

[12] Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA. The natural history of Noonan syndrome: a long-term follow-up study. Arch Dis Child. 2007; 92: 128-132.

[13] Regezi JJ, Sciubba JJ, Jordan RCK. Oral Pathology Clinicopathological Correlation. (5th ed). Saunders: Elsevier, 2008.

[14] Maxilla Sidhu MS, Parkash H, Sidhu SS. Central giant cell granulomas of jaws: Review of 19 cases. Br J Oral Maxillofac Surg. 1995; 33: 43–6.

[15] Chuong R, Kaban LB, Kozakewich H, Perez-Atayde A. Central giant cell lesions of the jaws: A clinicopathologic study. J Oral Maxillofac Surg. 1986; 44: 708–13.

[16] Kaffe I, Ardekian L, Taicher S, Littner MM, Buchner A. Radiological features of central giant cell granuloma of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996; 81: 720–6.

[17] Lee S.M., Cooper J.C.: Noonan syndrome with giant cell lesions. Int J Paediatr Dent. 2005; 15: 140-145.

[18] 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.

[19] Pogrel AM. The diagnosis and management of giant cell lesions of the jaws. Ann Maxillofac Surg. 2012; 2: 102-6.

[20] Carneiro JT1, Falcão AS2, da Silva Tabosa AK1, Shinohara EH3, de Menezes LM. Management of locally aggressive mandibular tumours using a gas combination cryosurgery. J Craniomaxillofac Surg. 2014; 42: 423-7.

[21] Jamieson CR, van der Burgt I, Brady AF, van ReenM, Elsawi MM, Hol F, Jeffery S, Patton MA,Mariman E. Mapping a gene for Noonansyndrome to the long arm of chromosome 12. NatGenet. 1994; 8: 357-360.

[22] Bhambhani V, Muenke M. Noonan syndrome. Am Fam Physician. 2014; 89: 37-43.

[23] DeLellis RA, Mazzaglia P, Mangray S. Primary hyperparathyroidism: a current perspective. Arch Pathol Lab Med. 2008; 132: 1251–1262.

[24] Jorge AA, Malaquias AC, Arnhold IJ, Mendonca BB. Noonan syndrome and related disorders: a review of clinical features and mutations in genes of the RAS/MAPK pathway. Horm Res. 2009; 71: 185–193.