Bilateral Central Giant Cell Granulomas of the Mandible in An Eight Year-Old Girl with Noonan Syndrome (Noonan-Like/Multiple Giant Cell Lesions Syndrome)

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Abstract

A number of conditions can present with lesions that histologically are indistinguishable from the central giant cell granuloma (CGCG) of bone, including brown tumors of hyperparathyroidism, cherubism, and, less commonly, a number of inherited syndromes.

We report a case of an eight-year girl who presented with bilateral CGCGs of the posterior mandible. Characteristic facial features, reported increased post-operative bleeding and history of pulmonary stenosis led us to suspect a diagnosis of Noonan syndrome. A medical geneticist confirmed this on further evaluation.

This case report will discuss the salient features of this diagnosis.

Case Presentation

An eight-year-old girl (Fig. 1) was referred for evaluation after routine panoramic radiographic evaluation revealed well-defined bilateral multilocular radiolucencies of the posterior mandible associated with the developing third molars (Fig. 2). Each lesion measured more than 2.5 cm in greatest dimension. Also noted was displacement of the prematurely developing right and left mandibular third molar teeth. On axial computed tomographic examination, no cortical expansion was evident (Fig. 3). There was no history of prior trauma or surgery to the mandible.

The patient was the product of a full-term uncomplicated pregnancy. At 10 days of age an atrial septal defect and pulmonic stenosis were detected. Her family history was unremarkable, with no record of jaw abnormalities or atypical facies among other family members.

On physical examination she was at the 5th percentile for weight, 10% for height and 50th percentile for head circumference. She had thick kinky hair and several pigmented nevi. She had brilliant blue eyes with slight ptosis of the left eye. The palpebral fissures were not downslanting. Her ears were low set and small with thickened helices bilaterally (Fig.1). The nose had a bulbous tip. Pectus excavatum was present. Her neck was not webbed. A systolic murmur was present at the right upper sternal border. The rest of her extra-oral examination was unremarkable, and no facial asymmetry or bony expansion was noted.

A clinical and radiographic differential diagnosis was formulated (Table 1), and after excluding a vascular process via needle aspiration, incisional biopsies of the radiolucent lesions were performed. The patient's mother reported "prolonged bleeding" during the

immediate post-operative period. However, it was not significant enough to require additional intervention.

Discussion

Histopathologic examination of both lesions (Fig. 4) revealed a proliferation of giant cells in a fibrovascular connective tissue background, consistent with a giant cell granuloma. Based on the histopathology, the differential diagnosis was revised to include only lesions with a histology compatible with CGCG, as shown in Table 2.

Central giant cell granuloma (CGCG) is a benign lesion of bone of variably aggressive nature that was first described by Jaffe[1]. As defined by the World Health Organization, CGCG is a central lesion of bone with aggregates of multinucleated giant cells in a background of cellular fibrous connective tissue that contains multiple foci of hemorrhage with or without trabeculae of reactive bone.

Initially termed "giant cell reparative granuloma", these lesions are no longer believed to represent a reparative process[2]. Various hypotheses have been proposed to explain their pathogenesis, including the possibility that these are related to intraosseous hemorrhage following trauma, develop in association with other pre-existing bone lesions (e.g. fibrous dysplasia), are of neoplastic nature or represent an idiopathic reactive process.

The peak incidence of CGCG is in the second decade, with most cases appearing between the ages of 10 and 25 years. It is more common in females. The radiographic appearance of CGCG is not pathognomonic. Usually, a radiolucent lesion, which can be either unilocular (usually lesions less than 6 cm) or multilocular, is noted on routine radiographic examination. The borders are generally well defined. While it is frequently reported that lesions of CGCGs are usually located anterior to the mandibular first molar and often cross the

midline[3], a recent review of 80 cases suggested that there is an equal predilection for the posterior mandible[4]. CGCGs can displace teeth and developing tooth follicles, but rarely cause tooth resorption.

Most reported cases of multiple concurrent CGCGs are associated with some form of congenital syndrome or systemic disease, hence the possibility that these radiolucent lesions simply represented bilateral central giant cell granulomas was considered unlikely.

"Brown tumors" of hyperparathyroidism are the result of excessive parathyroid hormone secretion. This can occur either primarily, due to hyperplasia or neoplasia of the parathyroid glands, or secondarily in association with renal osteodystrophy[5]. Hypercalcemia, hypophosphatemia and elevated parathyroid hormone blood levels characterize hyperparathyroidism. Radiographic findings are also characteristic. Besides multiple lytic lesions of bone, intraorally there is a loss of the lamina dura adjacent to the roots of the teeth and an altered trabecular pattern in the tooth bearing areas of the jaws. In our patient, an endocrine workup was unremarkable, effectively excluding this condition.

Cherubism, an autosomal dominantly inherited condition with variable expressivity, is characterized by multiquadrant radiolucent lesions of the jaws.

Clinically, cherubism is first noted between ages 1 and 4 years and is more common in males. There is usually a family history of similarly affected family members. It most commonly manifests as a progressive and symmetrical enlargement of the mandible and/or the maxilla. Mandibular swelling produces plump cheeks and maxillary enlargement causes

retraction of the lower eyelids and elevation of the pupils upward, resulting in an "angel-like" appearance reminiscent of the cherubs depicted in Renaissance art.

Dental findings include marked displacement of developing second and third molars as well as premature exfoliation of primary teeth. Marked cervical lymphadenopathy is common. Regression is often seen following puberty[6]. Currently cherubism is believed to be caused by a gain-of-function mutation in the gene coding a c-Abl-tyrosine kinase-binding protein (SH3BP2) located on the short arm of chromosome 4[7].

A number of congenital syndromes have been reported to be associated with giant cell lesions of the jaws, including Noonan syndrome[8], neurofibromatosis type-1[9] and Ramon syndrome (gingival fibromatosis, hypertrichosis, epilepsy, mental and somatic retardation and cherubism-like lesions)[10]. "Noonan-like syndrome, cherubism, and polyarticular pigmented villonodular synovitis" is a congenital syndrome that includes additional findings of multiple lesions of pigmented villonodular synovitis affecting multiple bones, commonly the knees and ankles.

It has been suggested[8] that some of these entities represent different levels of expression of a contiguous gene syndrome, resulting from defects or deletions of two or more genes that map near each other on the same region of a chromosome. Each defective or deleted gene is responsible for the overall characteristics of the syndrome. Thus, the overall phenotype seen would depend on the number and function of the specific genes affected.

Noonan syndrome, one of the most common multiple congenital anomaly syndromes, occurs in approximately one out of every 1000 to 2500 live births[11]. Noonan syndrome is also known as "Turner-like syndrome", "male Turner syndrome", "female pseudo-Turner

syndrome", "Turner phenotype with normal karyotype", "Bonnevie-Ullrich syndrome" and "pterygium colli syndrome".

Noonan syndrome was initially described in 1963 by Jacqueline Noonan[12], a pediatric cardiologist. She had noticed that a number of her patients with cardiac anomalies (most commonly pulmonary stenosis and atrial and ventricular septal defects) were also of short stature and had atypical facies. Characteristic facial features include a broad or webbed neck, low set and posteriorly angulated ears, ptosis, hypertelorism, and downward slanting eyes. These manifestations tend to become less pronounced with increasing age. Since the initial discovery of this syndrome, a number of other associated features have been described (Table 3)[11].

Similar to cherubism, Noonan syndrome is an autosomal dominantly inherited syndrome with variable expressivity. Cases can also occur sporadically; presumably the result of a spontaneous mutation. Tartaglia et al[13] reported that in slightly over 50% of 22 unrelated individuals tested, Noonan syndrome phenotype was associated with missense mutations in the gene PTPN11, which encodes the non-receptor tyrosine phosphatase protein SHP-2 located on the long arm of chromosome 12. This protein is involved in a number of signal transduction pathways that regulate several developmental pathways, including cardiac semilunar valve development[14]. Recently, the same PTPN11 gene mutation was identified in two siblings in a family inheriting Noonan-like/ multiple giant cell lesions syndrome[15].

Diagnosis is usually based on clinical criteria. Since many affected individuals have mild manifestations, many cases go undiagnosed. Prenatally, an association with fetal edema and cystic hygroma has been reported. Molecular genetic testing of the PTPN11 gene is now

clinically available, with mutations being identified in about 50% of patients. PTPN11 genetic testing was not available when this patient was initially evaluated.

Based on our patient's clinical and radiographic presentation and histologic findings, our working diagnosis was that these giant cell lesions were a manifestation of Noonan syndrome. Molecular testing has been offered to the family, but to date they have opted not to undergo testing.

Review of the Literature

Cohen and Gorlin[8] published the first review detailing the association of central giant cell granuloma-like lesions of the jaws with Noonan syndrome in 1991. They reviewed previously published clinical and pathologic findings of 13 patients and included one patient that they had been following since 1974. Of the 14 total cases described, 7 also had polyarticular lesions of pigmented villonodular synovitis, which would place these cases under the spectrum of "Noonan-like syndrome, cherubism, and polyarticular pigmented villonodular synovitis". Cohen and Gorlin believed that both of these types of giant cell lesions have a common pathogenesis.

To date, excluding the 7 cases described by Cohen and Gorlin that also presented with polyarticular pigmented villonodular synovitis, fewer than 15 cases of Noonan-like/multiple giant cell lesion syndrome have been reported in the English language literature (Table 4).

Significance and Management

There are a number of potentially significant medical concerns that clinicians should be aware of prior to performing any surgical procedure on a patient with suspected Noonan

syndrome (Table 5). These risks include a high prevalence of congenital heart disease (as in our patient), bleeding diatheses (decreased coagulation factors XI and II, von Willebrand disease, thrombocytopenia, abnormal platelet function and stem cell dysfunction), an association with malignant hyperthermia and the potential of developing a life-threatening chylothorax.

To rule out an occult bleeding diathesis, preliminary hematologic evaluation should include a complete blood count and differential, prothrombin time, partial thromboplastin time, and possibly measurement of factor XI levels.

As the reported incidence of Noonan syndrome-associated giant cell lesions of the jaws is low, little is known of its natural history or what treatment approaches are most effective. Current treatment modalities have largely been extrapolated from published reports of the management of either conventional CGCGs of the jaws or cherubism.

CGCGs of the jaws, especially smaller lesions, are commonly treated by surgical curettage. Aggressive lesions are occasionally treated by en bloc surgical resection. However, this approach can be disfiguring. Recent approaches for the treatment of large or multiple lesions have included weekly intralesional corticosteroid injection[16,17], daily subcutaneous[18] or intra-nasal[19] administration of calcitonin and the use of interferon alpha-2a[20]. The principal disadvantage to these approaches is the necessity of continuing treatment over a prolonged period of time.

Based on the apparent clinical and histologic similarity between patients with Noonan syndrome-associated giant cell lesions of the jaws and cherubism, the few reported cases that describe the management of these lesions have based treatment on the assumption that their

behavior and clinical course is also similar. Consequently, management has generally involved long term follow-up, with the assumption that these lesions will stabilize or regress during puberty. Treatment is reserved for patients with functional or cosmetic impairment.

Our plan is to follow this patient on a biannual basis. Presently, she has no functional or cosmetic impairment and is asymptomatic.

Conclusion

Even though our patient was eight years old at the time of presentation and had a history of pulmonary stenosis, her Noonan syndrome had gone undiagnosed until she presented with bilateral giant cell lesions of the mandible. This case underscores the importance of formulating a thorough differential diagnosis of giant cell lesions of the jaws. The histologic findings must be interpreted in light of the radiographic and clinical findings to arrive at a correct diagnosis.

As in our patient, children with Noonan syndrome are predisposed to having a wide array of health problems (including congenital heart disease, bleeding diatheses, malignant hyperthermia, lymphangiomatosis), making it essential that all practitioners involved in caring for these patients be aware of their special needs prior to performing any surgical procedure.

Figure 1: Clinical Photograph. The patient's ears were low set and small with thickened helices bilaterally.

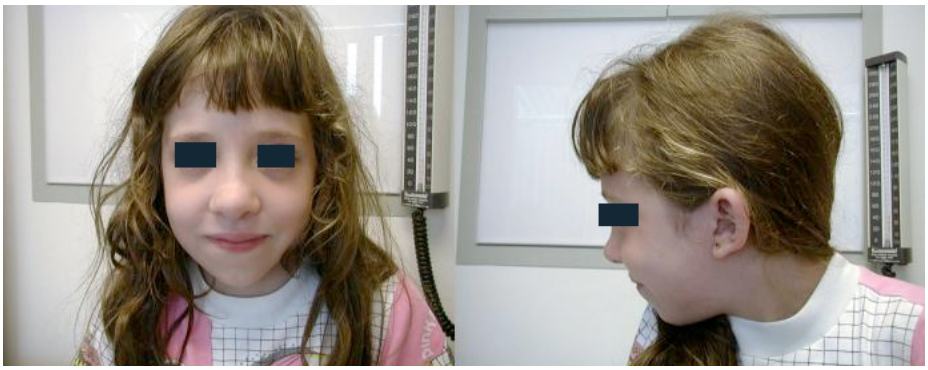

Figure 2: Panoramic Radiograph. Note bilateral multilocular radiolucencies of the posterior mandible and anterior displacement of the prematurely developing mandibular third molar teeth.

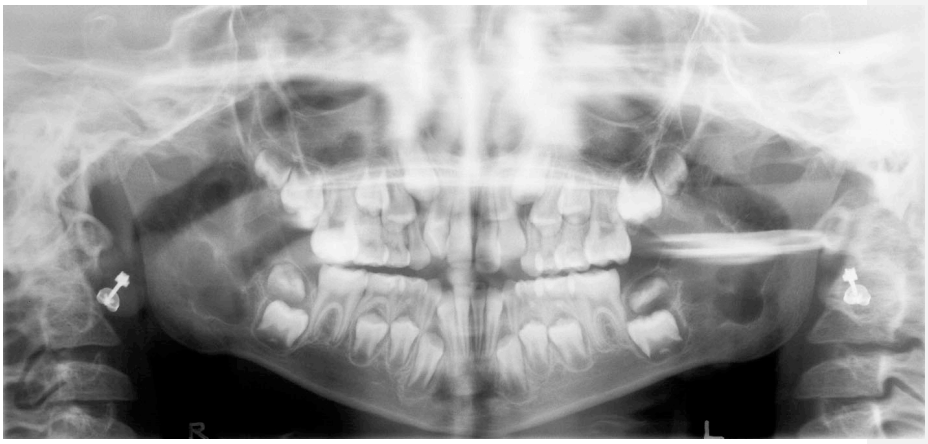

Figure 3: Axial CT Scan. Note lack of significant cortical expansion.

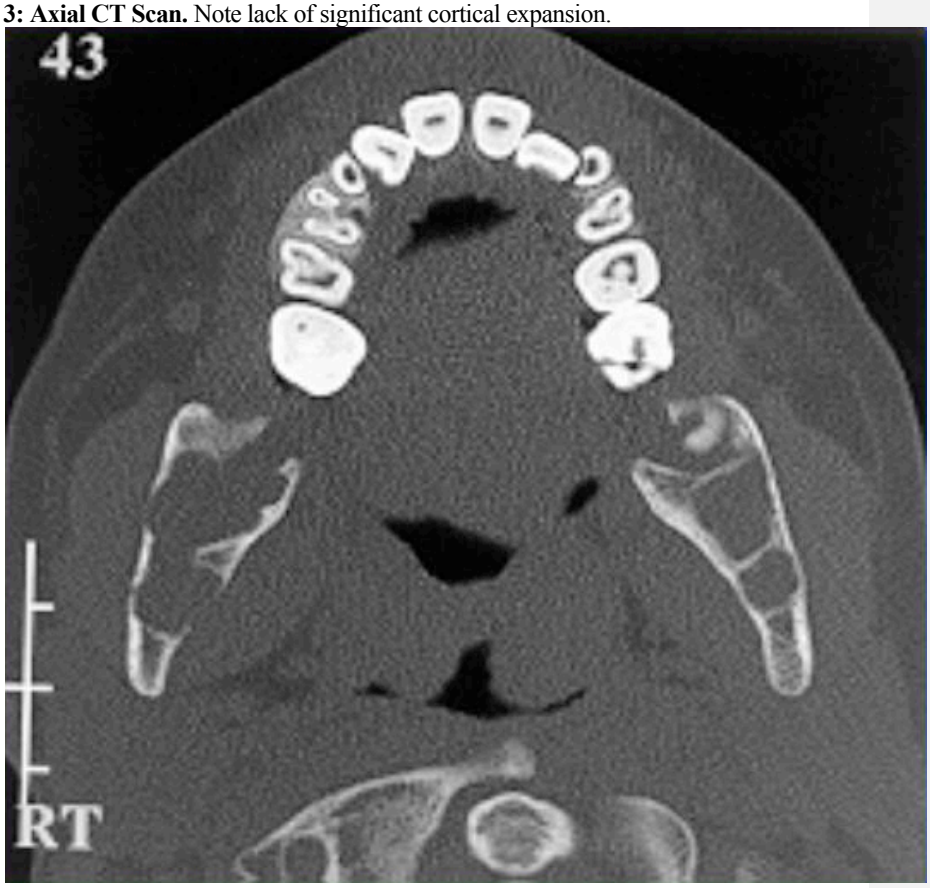

Figure 4: High Power View of Histology. Numerous osteoclast-like giant cells in a background of spindle-shaped fibroblasts (Hematoxylin and eosin, original magnification 40x).

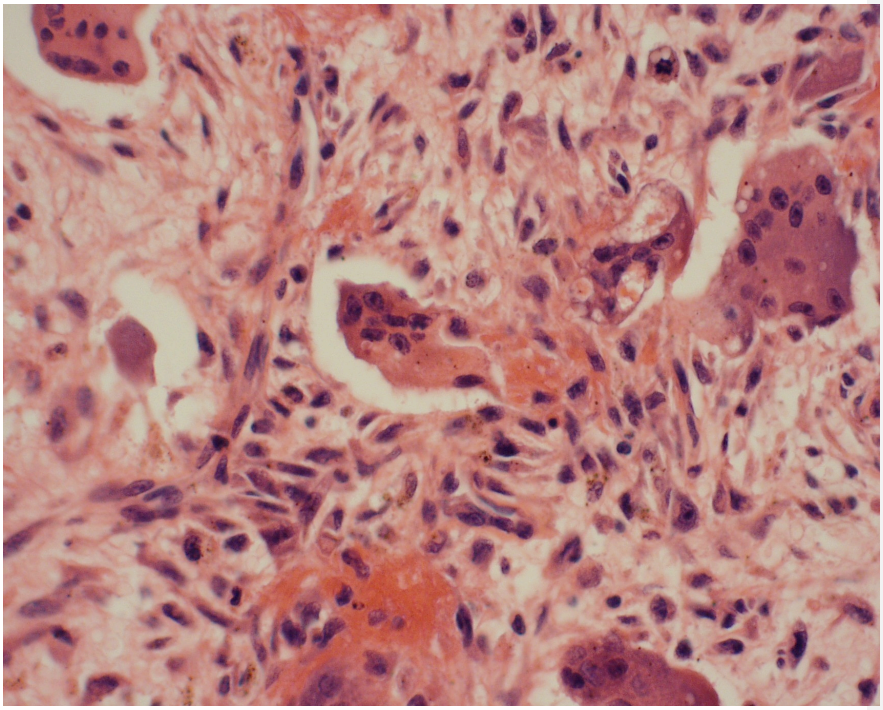

Table 1: Initial Clinical and Radiographic Differential Diagnosis
•Multiple odontogenic keratocysts (e.g. associated with nevoid basal cell carcinoma syndrome) •Central giant cell granuloma (CGCG), bilateral •Cherubism •Syndromes associated with CGCGs (e.g. Noonan syndrome, neurofibromatosis type 1) •Multiple dentigerous cysts •Brown tumors of hyperparathyroidism •Langerhans' cell histiocytosis

Table 2: Bilaterally Occurring Central Giant Cell Lesions Of The Jaws

- •Central giant cell granuloma, bilateral
- •"Brown tumor" of hyperparathyroidism
- •Cherubism
- •Noonan-like / multiple giant cell lesion syndrome
- •Noonan-like syndrome, cherubism, and polyarticular pigmented villonodular synovitis
- •Neurofibromatosis type 1
- •Ramon syndrome (cherubism, gingival fibromatosis, epilepsy, mental deficiency, hypertrichosis, and stunted growth)

Note: Histologically and radiographically, all of these conditions are essentially indistinguishable[21]. Clinical-radiological-pathologic correlation is required to arrive at the final diagnosis.

Table 3: Clinical Features of Noonan Syndrome

- Congenital heart defects (pulmonary stenosis, hypertrophic cardiomyopathy, ASD, VSD)
- Short stature
- Broad or webbed neck
- Low set, posteriorly angulated ears
- Ptosis, hypertelorism, downward slanting eyes
- Coarse +/- curly hair
- Pectus excavatum (depressed sternum)
- High arched palate
- Cherubism-like multiple giant cell lesions
- Cryptorchidism
- Conductive hearing loss
- Hypoplasia of lymphatics: potentially leading to chylothorax
- Bleeding diatheses: decreased factors XI and II, von Willebrand disease, thrombocytopenia, abnormal platelet function[22]
- Learning disabilities
- Tendency to develop keloids following surgery
- Association with multiple subcutaneous granular cell tumors[23]

Table 4: Published Reports of Noonan Syndrome/Central Giant Cell Granuloma-Like Lesions of the Jaws

Authors	Year	Number of Patients
Chuong et al[24]	1986	2
Dunlap et al[25]	1989	4
Cohen and Gorlin[26]	1991	1
Levine et al[27]	1991	1
Betts et al[28]	1993	1
Addante and Breen[29]	1996	1
Ucar et al[30]	1998	1
Bertola et al[31]	2001	2

Table 5: Surgical Risks in Patients with Noonan Syndrome
•Congenital heart disease •Bleeding diatheses. Presurgical hematology work-up recommended •Lymphangiomatosis of the pleura, lungs and chest wall; potentially leading to life-threatening chylothorax[32] •Association with malignant hyperthermia (King syndrome)

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