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A Unique Case of Aggressive Central Giant Cell Granuloma in a 10-Year-Old Boy With 16p13.11 Microdeletion Syndrome

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Abstract

Central giant cell granuloma (CGCG) is a rare disease characterized by sporadic, benign, intraosseous mandibular lesions of unknown etiology. Histologically, these lesions are indistinguishable from brown tumors of hyperparathyroidism and cherubism, and occasionally have been associated with different syndromes raising a question for genetic etiology. The CGCG has varied presentation ranging from nonaggressive and indolent to aggressive, destructive, and recurrent, often posing diagnostic and therapeutic challenges. Herein, we present the first case of a 10-year-old boy with CGCG and 16p13.11 microdeletion syndrome, highlight the diagnostic challenges inherent to this heterogeneous disorder, and discuss the genetics and treatment approaches of these complex lesions.

Keywords

pediatrics, central giant cell granuloma, brown tumor, treatment, surgery

Introduction

Central giant cell granuloma (CGCG) is a rare disease characterized by sporadic, non-neoplastic intraosseous lesions of unknown etiology. Histologically, lesions present with proliferation of granulation tissue containing multinucleated giant cells embedded in a fibrous stroma.[1,2] The CGCG accounts for approximately 10% of all benign tumors of the jaws affecting the mandible and maxilla in patients aged 10 to 25 years.[3,4] The CGCG has a heterogeneous presentation ranging from asymptomatic, slow-growing lesions to more aggressive, rapidly growing lesions with cortical expansion, thinning, and perforations requiring medical and surgical treatment depending on the lesion variation.[5]

The CGCG lesions radiographically and histologically are similar to brown tumors of primary hyperparathyroidism, aneurysmal bone cysts, and cherubism, thereby occasionally presenting a diagnostic challenge. The pathogenesis of CGCG remains unknown, though it has been proposed to occasionally be due to a reactive process occurring secondary to trauma, resulting in intraosseous hemorrhage and giant cells.[6] Recent evidence has suggested that CGCGs are derived from osteoclastic origin, and the spindle-like stromal cells recruit monocytes promoting their fusion into giant cells.[7,8]

In addition, CGCGs have been shown to be associated with several genetic syndromes. Noonan syndrome involving multiple genes such as *PTPN11* and *SOS1* that regulate the Ras/mitogen-activated protein kinase (RAS/MAPK) pathway,[9-12] neurofibromatosis 1 caused by pathogenic variants in *NF1*, and cherubism due to variants in *SH3BP2* have been described to present with CGCG,[13-16] implying a potential genetic etiology.

Chromosome 16p13.11 microdeletion syndrome is a rare copy number variation syndrome with a wide spectrum of

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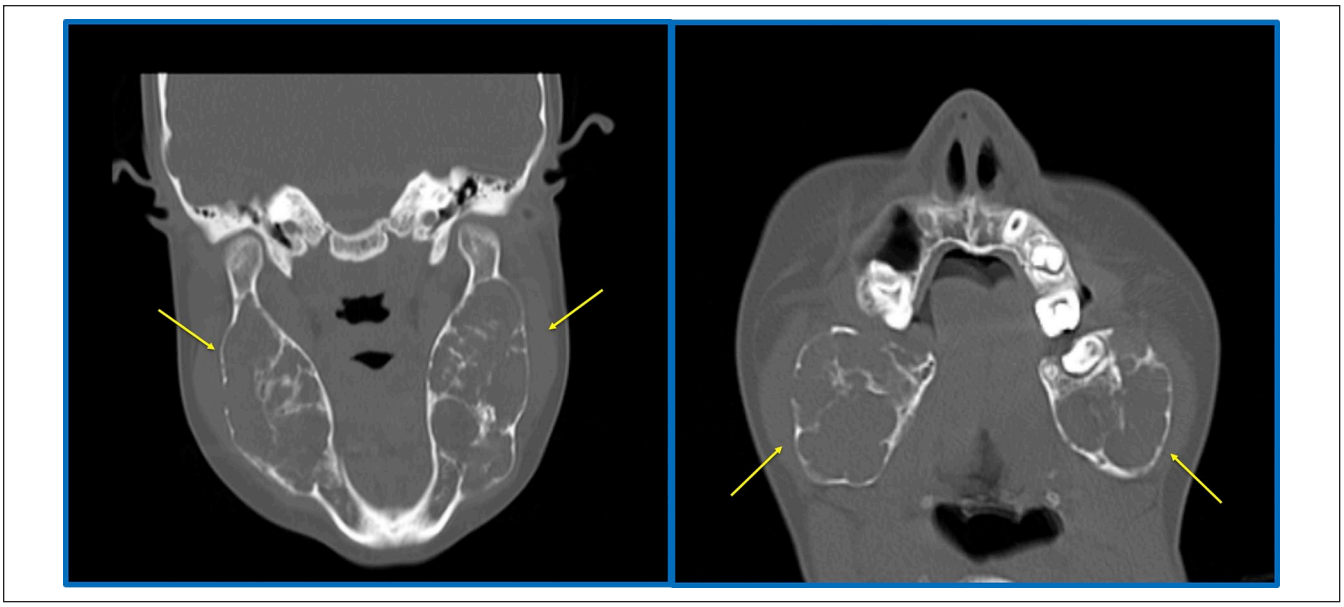

Figure 1. Initial computed tomographic (CT) imaging of the head in a 10-year-old boy. Multiple cystic lytic lesions were noted in the right and left ramus (yellow arrows).

presentations. It has predominantly been associated with neurocognitive disorders, epilepsy, autism, schizophrenia, and behavioral abnormalities.[17,18] To our knowledge, bone lesions have not been previously described with the syndrome. Herein, we present the first case of a pediatric patient with 16p13.11 microdeletion syndrome and bilateral aggressive CGCG lesions of the mandible and discuss the treatment and surgical approach to these lesions.

Case Presentation

A 10-year-old boy with a history of autism, pulmonary stenosis, and dental caries was admitted to the hospital for biopsy of lytic lesions of the jaw with a history of progressive painless facial swelling more than 10 months. As part of routine evaluation, he was found to have an elevated parathyroid hormone level (iPTH); endocrinology was consulted for concerns for brown tumor of hyperparathyroidism. On examination, he had facial dysmorphism with microcephaly, hypertelorism, down-slanting palpebral fissures, and low-set protuberant ears. He had poor dentition with bilateral swelling of mandibular regions without any rashes, thyromegaly, or palpable thyroid nodules. Family history was negative for thyroid or parathyroid diseases.

Computed tomographic (CT) imaging of the head revealed large lesions in the right ramus body, and multiple radiolucencies and cystic-like lesions in the left ramus (Figure 1). Initial biochemical testing showed elevated iPTH of 113 pg/mL reference range (7.5-53.5), normal total calcium level 9.4 mg/dL (8.8-10.8), and slightly low phosphorus 4 mg/dL (4.5-5.5), normal albumin 5.2 g/dL (3.8-5.4), vitamin 25-OH level 30 ng/mL (30-100), vitamin 1,25-OH level 44 pg/mL (30-83), and alkaline phosphatase 280 U/L (184-415).

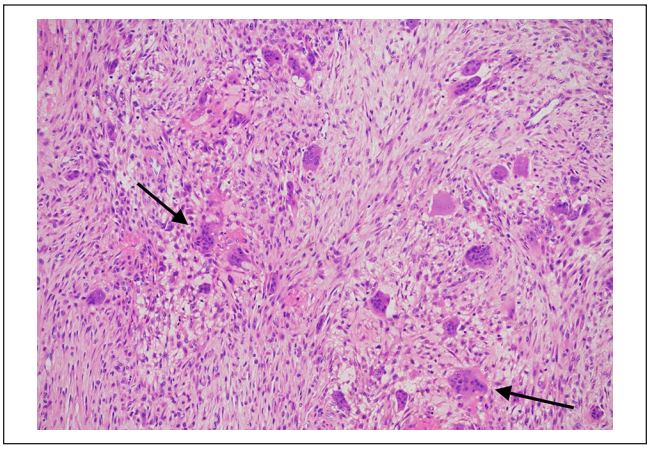

Figure 2. Histological pathology of the resected lesions in a 10-year-old boy. Histopathology of tissue from surgical enucleation shows several multinucleated giant cells with proliferation of benign spindle cells (black arrows).

He underwent an enucleation with peripheral ostectomy of the right mandibular intrabony tumor (6.5 cm × 4.3 cm × 1.7 cm) with inferior alveolar nerve decompression, cryoprecipitate application on the resection bed, and right buccal fat flap by craniofacial surgeons. An impending subcondylar pathologic fracture was identified intra-operatively; thus, the decision was made to address the contralateral side at a later date to avoid further weakening the mandible while awaiting final diagnosis. Histopathology revealed benign spindle cells and giant cell proliferation of the bone consistent with brown tumor of hyperparathyroidism, CGCG, or cherubism (Figure 2). A skeletal survey was performed to evaluate for

other possible lesions revealing only an expansile lucent appearance of the mandible, and no other lesions. Repeat laboratory testing showed normalized iPTH of 20 pg/mL and normal total calcium 10.5 mg/dL and phosphorus 4.6 mg/dL, ruling out hyperparathyroidism. Four months later, the patient underwent enucleation with peripheral ostectomy of the left mandibular intraosseous tumors (4.5 cm × 4.1 cm × 1.0 cm and 3.6 cm × 2.8 cm × 0.9 cm, fresh and frozen segments, based on pathology) with inferior alveolar nerve decompression, 3 branch decompression of the left mental nerve, cryoprecipitate application, and left buccal fat flap. Similarly, a left-sided impending subcondylar pathologic fracture was identified intra-operatively, extending from the sigmoid notch to the mental nerve branches. Given concern for mandibular integrity in the setting of a large defect, closed reduction of the mandible with intermaxillary fixation wiring was performed. The patient tolerated the procedure well, and deep hardware removal of the maxilla and mandible was performed on postoperative day 17. Histopathology again revealed benign spindle cells and giant cell proliferation of the bone, and with hyperparathyroidism ruled out, these lesions were consistent with CGCGs.

Tissue molecular testing of the lesions was negative for clinically established somatic mutations in oncogenes. However, genetic testing of the blood with single-nucleotide polymorphism microarray revealed a pathogenic 1.5 Mb heterozygous deletion in 16p13.11, as well as a duplication of Xq21.1, a variant of unknown significance. Deletions in the region of chromosome 16p13.11 have been associated with autism, epilepsy, developmental delay, microcephaly, facial dysmorphism, behavioral problems, and cleft lip and have been termed 16p13.11 microdeletion syndrome.[17,19] There are 11 genes in the deleted region of 16p13.11 in our patient (*NOMO1, NPIPA1, PDXDC1, NTAN1, RRN3, KIAA0430, NDE1, ABCC1, ABCC6, MYH1*, and *MARF1*), none of which have yet to be implicated in CGCG. *NDE1* and *NTAN1* have been proposed as candidate genes related to the syndrome's neurological and behavioral features.[19,20]

Repeat CT imaging of the head 2 months postoperatively revealed postresection changes with expansile multifocal lytic lesions within the bilateral mandible and maxilla. The patient was referred to oncology for consideration of denosumab treatment of the remaining CGCG lesions that were unresectable by surgery. However, his parents opted for monitoring at that time. Repeat CT scan 5 months postoperatively showed stable, expansile multifocal lytic lesions, at which time the patient had remained asymptomatic.

Discussion

The CGCG lesions were first described in 1953 by Jaffe[6] as giant cell reparative granuloma, and later defined by the World Health Organization as an intraosseous lesion consisting of fibrous tissue with hemorrhage and osteoclastic-like giant cells and reactive bone formation.[21] Its clinical presentation can occasionally be a diagnostic conundrum as CGCG is histopathologically indistinguishable from brown tumor of hyperparathyroidism and cherubism. However, laboratory findings of hyperparathyroidism and location of osteolytic lesions can help to differentiate between brown tumors and CGCG. Significant elevations in PTH level (200-3000 pg/mL) have been reported in patients with hyperparathyroidism presenting with brown tumors, with high-circulating PTH leading to increased osteoclastic bone resorption and the development of osteopenia and multiple circumscribed lytic lesions.[22] Osteolytic lesions of hyperparathyroidism are usually found in the clavicle, ribs, pelvis and facial bones.[23] This is in contrast to CGCG lesions which are found in the mandible and maxilla, with normal PTH levels. Our patient had a mild transient elevation in PTH to 113 pg/mL, and a normal Ca level, possibly secondary to intra-operative stress with catecholamine surge leading to a transiently elevated iPTH.[24]

The CGCG lesions have been described in patients with various syndromes including Noonan, cardio-facio-cutaneous (CFCS), LEOPARD, neurofibromatosis type 1, and cherub ism.[9-11,13-16] Noonan and CFCS syndromes are genetically heterogeneous disorders involving *PTPN11, SOS1, RAF1, KRAS* and *BRAF, MEK1, MEK2, KRAS* genes, respectively.[11] Neurofibromatosis type 1 is caused by pathogenic variants in *NF1*, which encodes for neurofibromin, a tumor suppressor protein.[11,25,26] These genes are involved in the RAS/MAPK pathway.[9-12] Dysregulation and activation of RAS/MAPK pathway have been postulated to be a common mechanism contributing to the development of CGCG in these syndromes.[11] It has also been proposed that pathogenic variants in *NF1* may cause a decrease in type 1 collagen expression, which alters bone formation leading to intraosseous defects.[26,27] Cherubism is caused by pathogenic variants of *SH3BP2* gene on chromosome 4p16.3, which, along with the activation of the receptor activator of nuclear factor kappa B (RANK), has been shown to contribute to increased osteoclastogenesis potentially leading to the development of CGCG.[16,28]

The CGCGs have not been previously described in association with 16p13.11 microdeletion syndrome. There are at least 11 genes within the deleted region, of which 6 (*NDE1, MARF1, ABCC1, ABCC6, MYH11, NTAN1*) have known function, and some have been associated with neurological findings including epilepsy and intellectual disability.[20,29] 16p13.11 microdeletion syndrome presents with a significant phenotypic variability and incomplete penetrance,[19,20] thus, it is plausible that some unidentified genes within the region may play a role in the pathogenesis of giant cell granulomas. The RAS/MAPK signaling pathway has been identified as an important underlying mechanism in the development of CGCG; as such, it is attractive to speculate of a potential gene in the microdeletion region involved in the pathway and pathogenesis of CGCG. Further genetic studies are necessary to determine whether the genes in 16p13.11 microdeletion syndrome may interact with this pathway or potentially express yet unidentified tumor

suppressor genes allowing for the development of CGCG. It is important to expand our genetic understanding to further elucidate the pathogenesis of syndromic and sporadic CGCG.

The CGCG lesions regardless of the cause are often subcategorized into brown tumors, nonaggressive giant cell lesions, and aggressive giant cell lesions to reflect graded treatment approaches and recurrence rates. Aggressive lesions may be characterized by (1) rapid growth, (2) size greater than 5 cm, (3) tooth displacement or loosening, (4) radiographic evidence of tooth displacement or root resorption, (5) radiographic evidence of cortical bone perforation or thinning, and (6) recurrence. The CGCG lesion is considered aggressive if it has 3 of the 6 aforementioned findings, is greater than 5 cm, or is recurrent.[30] Brown tumors of hyperparathyroidism tend to regress upon treatment of the endocrine derangement. Nonaggressive lesions are treated with enucleation or curettage given low recurrence rate.[30,31] Aggressive lesions carry a high recurrence rate, reported in 15% to 49% of cases, and thus, typically require a complex, multistep approach involving en bloc resection with 1-cm margins followed by adjunct cryotherapy, peripheral ostectomy, use of Carnoy's solution, intralesional steroid injections, calcitonin, or embolization, and are often supplemented with adjuvant denosumab or bisphosphonate treatments postoperatively.[30,32-34] Denosumab has recently emerged as a potential adjuvant therapy to treat CGCG through inhibiting the activation of osteoclasts.[29,35] RANK is expressed in the giant cells of CGCG and mononuclear stromal cells express RANK ligand which leads to osteoclast activation.[36] Denosumab is a monoclonal antibody against RANKL which acts to block osteolytic activation. One longitudinal study of 5 patients with large giant cell tumor of the jaw, treated with denosumab for 25 to 49 months, showed curative treatment response.[27] A second case series of 4 pediatric patients also showed improvement both clinically and radiographically with denosumab treatment.[36] However, close monitoring is needed for hypocalcemia during treatment and rebound hypercalcemia post discontinuation.[36]

Our patient underwent staged bilateral enucleations with peripheral osteotomy to mitigate impending subcondylar pathologic fractures, deter nerve damage, and provide a histopathologic diagnosis. Enucleation, rather than en bloc resection, was performed to avoid the morbidity of a large resection requiring complex reconstruction; preserve critical structures, such as the inferior alveolar nerve, teeth, and inferior border of the mandible; allow time for final diagnosis before more aggressive intervention; and allow for initiation of adjuvant therapy with denosumab or bisphosphonate. Six-week postoperative head CT revealed remaining expansile lytic lesions, reinforcing the role for adjuvant medical therapy. The family has chosen to monitor and deferred initiation of denosumab or bisphosphonate therapy. The patient remained asymptomatic with stable lesions on recent imaging.

The diagnosis and management of CGCG requires an interdisciplinary team including genetics, oral surgery, endocrinology, and oncology. Early recognition is important to prevent complications of aggressive lesions including disfigurement, perforations, nerve impingement, teeth displacement, and root resorption. Genetic testing can help distinguish between different causes of CGCG including potential syndromic cases. Surgical resection has been the mainstay of therapy, with a high recurrence rate, which further highlights the need for necessity to investigate pathogenesis of these lesions, and the safety and efficacy of nonsurgical therapies.

Conclusions

To our knowledge, this is the first pediatric case of 16p13.11 microdeletion syndrome presenting with CGCG lesions. Our case highlights the diagnostic and surgical challenges inherent in this heterogeneous disorder, potentially adding to the phenotypic variability of the syndrome, and raises the questions of the potential mechanistic role of the affected genes. The mainstay treatment of CGCG is surgical intervention, although emerging medical therapy is a consideration in cases where lesions are aggressive, recurrent, or inoperable. Treatment of CGCG requires an interdisciplinary team and early recognition helps prevent complications from aggressive lesions.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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