Central Giant Cell Granuloma in a Patient with Neurofibromatosis Type 1: A Case Report

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Abstract
Background: We encountered a rare case of central giant cell granuloma (CGCG) in association with neurofibromatosis type 1 in a middle-aged Asian woman. Most reported cases involve isolated central giant cell granuloma or neurofibromatosis type 1 (NF1), and concurrence of these two entities is very rare.

Methods: We report a case of concurrent central giant cell granuloma with neurofibromatosis type 1. Thorough clinical and radiological examinations were performed.

Result: After diagnosis of possible concurrent central giant cell granuloma with neurofibromatosis, surgical excision with curettage was performed. Based on histopathological and clinico-radiological findings, the final diagnosis was central giant cell granuloma with neurofibromatosis type 1. Follow-up at 1 year did not show any recurrence.

Conclusion: We review the proposed mechanisms underlying the apparent association between CGCG of the jaws and neurofibromatosis 1. This case could represent either a coincidental association or a true genetic linkage; the mechanism in the present case appears most likely related to NF1-related osseous dysplasia.

Introduction
Neurofibromatosis 1 (NF1) is a relatively common (1 in 3500 newborns) autosomal-dominant inherited genetic disorder, caused by a spectrum of mutations affecting the neurofibromatosis (Nf1) gene. This gene is located at 17q11.2, spanning more than 350kbp and comprising 60 exons (1). The skeletal system is frequently affected in NF1, with bony abnormalities present in 50–70% of patients. Severe scoliosis, congenital bowing and thinning of long cortical bones, focal bone gigantism, and osseous dysplasia of the lambdoid suture and fibrocystic lesions of the long bones are the major skeletal complications. Macrocranium, micro-cephaly and sphenoid wing dysplasia are well-recognised features of NF1 (2). Oral and panoramic radiographic examinations have placed the frequency of oral manifestations at 70% or even 90%. The most common oral lesions are neurofibromas, enlarged fungiform papillae, intrabony cystic lesions, and branched mandibular canals, and enlarged mandibular foramen and canals. (2). A diagnosis of NF1 can be reached based on clinical diagnostic criteria originally established by the 1987 National Institutes of Health Neurofibromatosis Consensus Development Conference (3) (Table 1).

Table 1. Diagnostic criteria for Neurofibromatosis 1

- Six or more café-au-lait macules > 5mm in greatest diameter in prepubertal individuals and >15mm in greatest diameter in postpubertal individuals.
- Two or more neurofibromas of any type or one plexiform neurofibroma.
- Freckling in the axillary or inguinal region.
- Optic glioma.
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis.
- A first-degree relative (parent, sibling, or offspring) with NF1 according to the above criteria.

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At least two of the above clinical criteria are needed to diagnose NF1.

We report a case of central giant cell granuloma (CGCG) of the mandible in a female patient with familial NF1 with clinical, radiographic and pathological findings.

**Case Report**

A 50-year-old female patient reported to the outpatient with a 2-month history of swelling in the anterior mandible. She had been diagnosed with NF1 at 5 years old, along with her siblings (3 brothers). She displayed multiple café-au-lait macules over the entire body and arms, cutaneous and subcutaneous nodules over the arms and trunk and sebaceous cyst on the scalp. Intra-oral examination revealed a solitary, sessile growth in the mandible, extending from the lower right central incisor up to the lower left second premolar region crossing the midline, measuring about $4 \times 2$ cm in size. The surface over the lesion was lobulated (Fig. 1a, b). Panoramic radiography showed a multilocular radiolucency extending from the lower right central incisor to the lower left second molar. Resorption of the root of the lower right lateral incisor was evident (Fig.2). Axial computed tomography (CT) showed an osteolytic lesion in the anterior mandible extending to the left posterior mandible, with bucco-lingual expansion of cortical plates (Fig.3a, b). Incisional biopsy of the lesion revealed aggregates of multinucleated giant cells and areas of fibrosis, consistent with CGCG (Fig.4). Serum parathyroid hormone and calcium levels were within normal limits. Surgical excision with marginal osteotomy was performed under general anaesthesia. The excised specimen comprised grey-brown friable material (Fig. 5). Histological examination of the resected specimen was consistent with that of CGCG (Fig. 6). At the 1-year follow-up, no evidence of recurrence was noted (Fig. 7).

**Discussion**

CGCG was first described by Jaffe in 1953 as a giant cell reparative granuloma of the jaw bones. CGCG is defined by the World Health Organization as an intraosseous lesion consisting of cellular fibrous tissue containing multiple haemorrhagic foci, aggregations of multinucleated giant cells and occasionally trabaculae of woven bone. This uncommon, non-neoplastic bone lesion accounts for less than 7% of all benign jaw lesions. Clinically, CGCG occurs more commonly in young adults, with a slight predilection for...
female patients (4). Whitaker and Bouquot (5) investigated the correlation between hormonal influence and female predominance, and their findings suggested that factors other than ovarian hormones, oestrogen and progesterone are responsible for the development of CGCG.

According to Austin et al. (6), CGCG involves the mandible more frequently than the maxilla, with no predilection for any specific site in the jaw. In most cases, the lesion presents as a painless, slow-growing swelling of the jaw. Pain and sensory disturbances are rare, but displacement of the teeth occurs frequently and can lead to malocclusion. Radiographically, CGCG usually appears as a radiolucent lesion, and can be uni- or multilocular. Root resorption can sometimes be seen and characterizes the potential for the lesion to be benign locally aggressive (7).

CGCG may mimic a variety of other lesions, such as cysts, odontogenic tumours, fibro-osseous lesions, vascular malformations and even malignancies (8). Radiographically, CGCG should be differentially diagnosed with other entities containing giant cells, such as giant cell tumour (9), cherubism (10), brown tumour of hyperparathyroidism (11, 12) and aneurismal bone cyst (11, 13).

Giant cell tumour (GCT) is an aggressive, frequently recurrent entity with a predilection for long bones and rarely occurring in the jaws (13). Radiologically, GCT usually presents with an aggressive, eccentric, lytic lesion.
centred on the metaphysis and extending to the subchondral bone with expansile remodelling, but lacking internal mineralisation (13). Soft tissue involvement is usually found in GCT.

Cherubism appears microscopically indistinguishable from CGCG, except when a fairly characteristic condensation of perivascular collagen is evident (12). Clinico-pathological correlations provide helpful clues to distinguishing cherubism from CGCG (10, 12). CGCG mainly affects patients between 10 and 30 years old and is typically found unilaterally in the frontal region of mandible, whereas symmetrical lesions are found in cherubism (14). An analysis of the SH3BP2 gene in patients with aggressive CGCG did not show any mutations, indicating that cherubism is indeed a distinct entity (15). Hyckel et al. (16) confirmed the hypothesis that cherubism originates from a genetic alteration in this gene.

Multifocal giant cell lesions usually appear in cases of hyperparathyroidism and are known as “brown tumours”. In cases of bilateral or multifocal giant cell granulomas, hyperparathyroidism must be considered among the differential diagnoses (4).

Aneurismal bone cysts appear as trabeculated osteolytic lesions, associated with cortical thinning and displaying a “blow out” appearance. The definitive diagnosis of CGCG should be confirmed by histopathology (11, 13).

Concerning intra-osseous neurofibroma, the tumour appears as a well-circumscribed or poorly demarcated radiolucent lesion, usually involving the mandibular canal (17). However, the present case showed no presence of a circumscribed radiolucency expanding the mandibular canal as described by other authors (17, 18).

Surgery remains the most frequent treatment for CGCG (8, 19). Surgical curettage is suitable for the treatment of jaw CGCGs that lack aggressive signs (8), as seen in the present case. Simple curettage of clinico-radiographically aggressive lesions appears inadequate (8) and resection has been suggested to be the surgical treatment method of choice for the removal of aggressive CGCGs and recurrent lesions (8, 19, 20). Recently, non-aggressive treatment methods such as systemic daily application of calcitonin (19), intralesional injections of corticosteroids (21) and subcutaneous injections of alpha-interferon (22) have been applied. Treatment strategies such as using imatinib to directly target the activity of osteoclasts has also been reported (23).

Recurrences are not uncommon, with an estimated 5-year disease-free success rate of 75% following conventional surgical therapy. Chuong et al. (24) and Ficarra et al. (25) reported a 72% recurrence rate for aggressive lesions, compared to 3% for non-aggressive lesions.

In the literature, multiple CGCGs have been reported with syndromes such as cherubism, Noonan syndrome, NF1 and systemic disease like hyperparathyroidism and fibrous dysplasia. Orhan et al. (26) reported a case of idiopathic bilateral central giant cell granuloma of the jaws.

Kerl et al. (27) first reported an association between NF1 and multiple CGCGs of the jaws. An association between CGCG and neurofibromatosis without hyperparathyroid disease was reported by Van Damme and Mooren in 1994 (28), Ardekian et al. in 1999 (4), Ruggeri et al. in 1999 (2), de

Fig. 6 Aggregates of multinucleated giant cells (black arrow) in fibrous stroma and areas of haemorrhage (yellow arrow). (Magnification 40 ×).

Fig. 7 Postoperative clinical photograph of the patient.
Lange and Van Den Akker in 2005 (29), Edwards et al. in 2006 (1) and Chrcanovic et al. in 2011 (30). The apparent association between NF1 and increased incidence of CGCG of the jaws could represent a coincidental association, a genetic linkage, or an underlying susceptibility to the development of CGCG-like lesions in quantitatively abnormal bone (1). A Dutch study reviewing all histologically confirmed cases of CGCG of the jaws in Holland over a 5-year period reported an incidence of 0.00011% in the 83 cases of CGCG identified, with 2 patients showing NF1 and 1 patient with NF1 with a Noonan-like phenotype (29).

Alternatively, the association between NF1 and CGCG could represent a true genetic linkage, resulting from defects or deletions of two or more genes that map near each other on the same chromosomal region. Arguing against a genetic linkage is the apparent lack of a specific genetic basis for CGCG (1).

The increased incidence of CGCG of the jaws in patients with NF1 most likely represents an inherent susceptibility to intraosseous trauma or haemorrhage in bone previously altered by underlying osseous dysplasia. This qualitatively abnormal bone would be more susceptible to developing CGCG-like lesions in response to as-yet unidentified factors such as excessive mechanical stress or vascular fragility (1).

Although little is known about the underlying basis for the development of dysplastic bone in NF1, several possible mechanisms have been proposed. These include a direct pressure effect from adjacent excessive soft tissue on developing or remodelling bone, altered function of the Nf1 gene product (neurofibromin), or loss of function of genes coded for either within or contiguous to the deleted position of the Nf1 gene (31).

Yu et al. (32) demonstrated that Nf1+/− (haploinsufficient) mice had normal bone mass but a tendency toward decreased bone homeostasis compared to wild type. However, Nf1 haploinsufficiency alone was not sufficient to cause bone lesions, suggesting that other events (e.g., loss of remaining Nf1 allele, loss of additional gene or adverse change in the microenvironment) are required prior to the development of pathological changes in bone.

Abdel-Wanis and Kawahara (33) proposed several mechanisms by which decreased neurofibromin function could result in altered bone formation. Under normal conditions, ras activation negatively regulates type 1 collagen synthesis, as the organic constituent of bone. In Nf1 mutations, increased ras activity would be expected to result in a decrease in type 1 collagen gene expression. The resultant collagen-deficient bone would have a decreased ability to respond to functional demands, and would thus be more prone to the development of intraosseous defects.

**Conclusion**

The presence of CGCG of the jaw in patients with NF1 could represent a coincidental association or genetic linkage, but is most likely related to NF1-mediated osseous dysplasia. Compared to normal bone, Nf1-haplosufficient bone in a patient with NF1 may be less able to remodel in response to as-yet unidentified stimuli, and consequently may be more susceptible to the development of CGCG-like lesions.

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