Loss of Heterozygosity in Tumor Cells of a Recurrent Mandibular Giant Cell Granuloma in Neurofibromatosis Type 1

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Abstract. Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited disease affecting about 1:3000 humans. Neurofibromas are benign soft tissue tumors. Giant cell granuloma (GCG) is a benign tumor-like lesion that is preferentially located in the jaws. GCG can develop in NF1 patients. A 7-year-old female NF1 patient was successfully treated for a recurrent GCG of the right mandibular premolar region. The serum levels of calcium and phosphate, alkaline phosphatase and parathormone were within the normal range. Genetic analysis of the tumor sample (GCG) and blood using 7 microsatellite markers revealed LOH of the NF1 gene in both sources. Inactivation of the NF1 gene may thus contribute to the development of GCG.

Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited disease affecting about 1 in 3000 humans (1). Neurofibromas are benign soft tissue tumors. These tumors are the hallmark of the disease (2). NF1 is a disease with a high predisposition for the development of cancer (3). Plexiform neurofibroma can give rise to cancer, in particular malignant peripheral nerve sheath tumors (4). There is also an increased risk for children with NF1 to develop cancer of non-neurogenic origin (5).

Neurofibromas are composed of different cell types, e.g. Schwann cells, fibroblasts and mast cells. The neurofibromatosis 1 gene, NF1, is located on chromosome 17q11.2. This gene encodes for a protein called neurofibromin, a protein with tumor-suppressor function (6). Loss of heterozygosity (LOH) of the NF1 gene was identified in Schwann cells from cutaneous and plexiform neurofibroma, but not in fibroblasts (7). Numerous skeletal lesions can occur in NF1, e.g. scoliosis or pseudarthrosis (1). Indeed, some alterations of the skeleton are pathognomonic for NF1, being included in the NIH (USA) revised diagnostic criteria on NF1 (2, 8).

Giant cell granuloma (GCG) is a rare and benign tumor-like lesion that is preferentially located in the jaws (9 - 12). The origin of GCG is unknown. Despite the histological similarity of GCG it is unlikely that all GCG have the same etiology. GCG can develop in the course of different kinds of hyperparathyroidism (9, 13 - 15).

One skeletal finding associated with NF1 is GCG in bones (1, 16). GCG were also found in the jaws of NF1 patients (16-25). A genetic link between GCG and NF1 is presently not well established. Recently it was shown that a mutation of the NF1 gene occured in leukocytes of a NF1 patient with GCG (24). We were able to investigate a patient with NF1 who developed a GCG and to compare the genetic alterations identified in the same patient.

Case Report

A 7-year-old female patient was submitted to our outpatient clinic for diagnosis and treatment of a recurrent GCG of the right premolar region of the mandible. The patient fulfilled the diagnostic criteria for NF1 (1, 2, 26). The first surgical treatment (curettage) had been carried out 3 months before. Some weeks before admission, the patient had again noticed a growing oral mass in the surgically treated mandibular region. Oral inspection revealed a protruding, painless mass in the premolar region. Furthermore, the comparisons of teeth emergence between both mandibular sides showed that the premolars of the right were more deeply retained in the bone than those on the left. On the other hand, the permanent incisors of the right mandibular side had already completely emerged, whereas tooth 71 (numerical code of teeth...
according to the Fédération Dentaire Internationale) was still in place. Further, a supernumerary incisor was depicted on the radiographs, distal to the right lateral inferior incisor and adjacent to the tumor region (Figure 1).

Orthopantomogram and occlusal view showed a radiolucent area superior to the developing premolars of the right side and an initial deviation of the forming dental root from the length axis of the crown.

The morphological aspect of the upper frontal teeth suggested that the central deciduous incisors were still in place. The emergence of the completely developed permanent central incisors was inhibited by the predecessors.

The serum levels for parathormone, alkaline phosphatase, calcium and phosphate were within the normal range.

Intraorally, a superficial vestibular incision of the mucosa exposed the bluish, highly vulnerable solid tumor that had penetrated through the cortical layer. The tumor was macroscopically completely removed from the bone and tooth surfaces. Excavation of the tumor was followed by uneventful healing after wound closure by primary intention.

An orthopantomogram 3 months after surgery depicted the rapid eruption of the retained and displaced mandibular right first premolar after tumor removal and the acceleration of tooth emergence, compared to the contra-lateral premolars. Treatment proved to be successful in terms of rapid eruption of the depressed premolar. No local recurrence was observed over the 2-year follow-up. At that time, the dentition was complete in the surgically treated area.

Immediately after tumor removal representative sections were sent under sterile conditions to the laboratory for genetic analysis. Bone biopsies from the mandible adjacent to the tumor border were also harvested for histological investigation.

Histology. Microscopically, the resection specimens consisted of connective tissues comprising a spindle-cell lesion. This lesion showed invasion of the adjacent alveolar bone. Multiple isolated multinucleated giant cells were found in the gel-like tumor scratched from the teeth and bone and also in the excised lamellar bone adjacent to the lesion. The lesion showed no signs of malignancy and was diagnosed as a giant cell granuloma (Figure 2).

Genetics. Loss of heterozygosity (LOH) of the NF1 gene region on 17q was examined using seven micro-satellite markers within or flanking the NF1 gene (19). As shown in Figure 3, partial NF1-LOH was found in the GCG.

Discussion

This study reveals a genetic alteration of the NF1 gene in a giant cell granuloma (GCG) of a neurofibromatosis type 1 patient. Krammer et al. (24) also investigated an NF1 patient, an 11-year-old girl, who had a mandibular GCG. However, in that study the identification of a novel NF1 mutation was restricted to the blood sample.
Figure 2. Recurrent giant cell granuloma of the mandible in an NF1 female, HE staining.

Figure 3. LOH in giant cell granuloma of the mandible (arrow indicates LOH in GCG). The same LOH was found in a plexiform neurofibroma of the same patient (not shown).
GCG of the jaws is rare. The entity is poorly described. In a population-based study covering the Dutch population over a period of 5 years, the incidence of GCG was calculated as 0.00011% (20). The clinical features of GCG may vary considerably. A more aggressive growth can be found with paresthesia, pain or root resorption in contrast to the non-aggressive type with asymptomatic swellings of the cheek or jaws. A concomitant syndrome was found in the Dutch epidemiological study in 5 of 83 evaluated patients, 3 of them being diagnosed as NF1 patients (3.6%, (20)).

GCG of the jaws in NF1 were reported by Kerl and Schroll (23), van Damme and Mooren (15), Ardekian et al. (17) and Friedrich et al. (21). In these case reports, recurrent GCG were located bilaterally and were found either inside the bone or were located peripheral to the jaws. In none of these four case reports was an alteration of calcium metabolism noted. A bilateral, recurrent (central) GCG of jaws without hyperparathyroidism is very rare (12, 27).

Brannin and Christensen (28) described siblings with GCG affecting the mandible bilaterally. Both had no dental germ of one second lower molar, left or right side each.

Calderon et al. (18) described a neurofibroma and GCG of the mandible. Goetsch (22) described an NF-patient with local recurrence of GCG in the region of a retained premolar of the right side of the maxilla. This unilateral finding is similar to the findings of the current report of a tumor that developed in the lower jaw. Ruggieri et al. (16) found a unilateral GCG and further giant cell tumor of the lower extremity in an NF1 patient in the absence of hyperparathyroidism.

Daly et al. (13) described a female with neurofibromatosis and recurrent, multiple GCG in both jaws, who, during the follow-up period, developed a mild hyperparathyroidism caused by an adenoma of the parathyroid gland. However, no other part of the skeleton developed a GCG.

De Lange et al. (20) described a 31-year-old female with 4 GCG in both jaws and a 17-year-old male with unilocular lesion in the midline region of the maxilla. The third patient also had features of a Noonan-like phenotype and was described elsewhere in detail (15).

Conclusion

GCG can be found in NF1 patients. This study reveals a genetic alteration of the NF1 gene in a giant cell granuloma (GCG) of a neurofibromatosis type 1 patient. The results suggest a possible activation/involvement of the NF1 gene in the development of GCG. The current investigation is, to the knowledge of the authors, the first report on a genetic link between GCG and NF1.

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References


