CASE REPORT

Multiple osteolytic lesions of the jaws in a patient with neurofibromatosis type I. A case report and focused literature review

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Abstract

We describe the case of a patient diagnosed with neurofibromatosis type 1 (NF1) where unusually extensive and multiple osteolytic lesions of both jaws consistent with central giant cell granulomas (CGCG) caused massive bone destruction and left her almost “jawless.” The patient was a 58-year-old woman who at the age of 15 years was diagnosed with NF1 and at the age of 53 years underwent radiation therapy for nasal obstruction due to CGCG. The most significant intraoral findings were brown tumors on the maxillary gingiva; bilateral expansion of the hard palate; and a yellow mass on the floor of the mouth. Head and neck examination revealed mandibular asymmetry and features consistent with NF1. Panoramic radiograph and cone beam computed tomography disclosed multiple radiolucent masses. Although the occurrence of multiple CGCG of the jaws in patients with NF1 is rare, early diagnosis, regular follow-up and proper therapeutic intervention may limit the extent of bone destruction.

Clinical relevance

Multiple osteocytic lesions of the jaws in a patient with neurofibromatosis type 1 may represent central giant cell granulomas. Although they are rare, they should be included in the differential diagnosis and managed properly, as they may cause massive destruction of the jawbones.

Introduction

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease or peripheral neurofibromatosis, is the most common form of neurofibromatoses, a heterogeneous group of hereditary syndromes characterised by the development of tumors of the central and peripheral nervous system1. Its incidence is estimated at approximately 1:2000 births per year2 and it is associated with heterozygous inactivating mutations of the NF1 gene, located in chromosome 17q11.21,3. NF1 encodes neurofibromin, a GTPase-activating protein functioning as a negative regulator in the Ras/MAPK signal transduction pathway4,5. Therefore, it belongs to “Rasopathies,” a group of neuro-cardiofaciocutaneous syndromes6 associated with various gain of function mutations in Ras/MAPK pathway, along with Noonan syndrome (NS), LEOPARD syndrome (Lentigines, Electrocardiographic abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of genitalia, Retardation of growth, Deafness), cardiofaciocutaneous syndrome, NS-like syndrome with loose anagen hair and Costello syndrome7.

Although NF1 is typically a neurocutaneous disorder with wide phenotypic variation, other systems, in particular the skeleton, may be involved5.
Patients with NF1 show increased susceptibility to malignancies, mostly malignant peripheral nerve sheath tumors. Diagnosis is based on the recognition of clinical manifestations, as genetic tests do not have clinical utility. Oral manifestations of NF1 are common and include enlarged fungiform papillae and neurofibromas, while various radiologic findings may be detected, including enlarged mandibular foramen, enlarged or branched mandibular canals, increased bone density, concavity of the medial surface of the ramus, pseudoeelongation of condylar neck and deformity of the condylar head, widening of the coronoid notch, intrabony cyst-like lesions, thinning and lateral bowing of the ramus, flat mandibular angle and malposition of teeth.

We describe the case of a patient diagnosed with NF1, presenting multiple and unusually extensive osteolytic lesions of both jaws, consistent with central giant cell granulomas (CGCG), that caused massive bone destruction and left her almost “jawless.” We also, review the English literature for cases of NF1 associated with multiple CGCGs.

**Case Report**

A 58-year-old woman was referred by her dentist for evaluation of multiple tumors on the maxillary gingivae, incidentally noticed during pre-prosthetic evaluation. The patient recalled that the lesions had been present for many years and were “surgically excised, but reappeared several times.” Therefore, she denied further treatment. Her only concern was the significant aesthetic and functional disturbance caused by her dental condition.

Her past medical history revealed that at the age of 15 years she was diagnosed with NF1 confirmed by biopsies of neck tumors. As far as she knew, she was the only member in her family that was diagnosed with this disease. At the age of 53 years she developed nasal obstruction due to obliteration of the nasal cavities by intraosseous lesions, and multiple biopsies were performed from osteolytic maxillary lesions. Microscopic examination of 5 μm thick hematoxylin and eosin stained tissue sections showed numerous multinucleated giant cells on a cellular and vascular connective tissue stroma, presenting haemorrhagic infiltration and hemosiderin depositions. Histochemically, the giant cells were positive for lysozyme and a1-antitrypsine, features consistent with osteoclasts. With this diagnosis of CGCG, radiotherapy (2x5 cycles, x400 kV) was performed with alleviation of her symptoms.

Intraoral examination revealed a fixed prosthetic appliance on the maxilla, while the mandible was edentulous. On the maxilla, two well-defined, brown tumors were seen on the labial attached gingiva and an enlargement on the palatal side (Fig. 1); they were painless and indurated on palpation. The hard palate showed bilateral expansion to the midline covered by normal appearing mucosa, and areas of dark brown pigmentation (Fig. 2). The gingivae were red, swollen and hemorrhagic. The mandibular mucosa showed protrusions and areas of dark brown discoloration, while an indurated, yellow-colored mass extended from the alveolar ridge to the floor of the mouth (Fig. 3). Similar yellow-colored areas were seen on the lower lip mucosa. The rest of the oral mucosa was within normal limit.

Head and neck clinical examination revealed mandibular asymmetry; many skin nodules, consistent with the diagnosis of neurofibromas; freckling in the facial skin (Fig. 4); and lesions consistent with melanocytic nodules or Lisch nodules in both irises (Fig. 5). There were many nodules in the trunk, upper and lower extremities; café-au-lait macules on her back and arms; freckling in the axilla, while she reported similar freckling on the inguinal areas. She also showed slightly down slanting palpebral fissures with high wide peaks of vermilion border of upper lip was noticed, but this could be due to edentulism.

Three panoramic radiographs taken during the 12 year period before presentation, as well as a recent one (Fig. 6), showed expansion and asymmetry of the right mandible; a radiolucency with indiscrete borders that obliterated the right maxillary sinus; and poorly defined, multilocular...
radiolucencies extending from the right mandibular angle to the area of missing second left molar. A comparison of the radiographs showed that the aforementioned lesions had expanded and fused within this period. Cone beam computed tomography images showed large, irregularly shaped, not well-defined and mixed in density masses that occupied the entire maxilla and mandible (Figs. 7, 8, and 9). They had markedly altered the osseous contours of the jaws, causing asymmetry, mostly of the mandible. The residual bone trabeculae gave the impression of a “spider-web” formation (Fig. 9). A mass extended into the right sinus cavity causing destruction of the hard palate and the cortical bone of the alveolar ridge. The mandibular cortices were expanded and thinned, mostly in the anterior and right posterior mandible, where the trabecular bone had almost completely deteriorated, apart from some areas in the posterior-most aspect. The mandibular canals and the mental foramina were not identified and most likely were involved by the lesions.

Regular serologic examinations during the last 5 years for total calcium, ionised calcium, phosphorous, serum alkaline phosphatase activity of parathormone (PTH), urine hydroxyproline and total albumin were within normal limits, ruling out hyperparathyroidism. An abdominal ultrasonography revealed three tumors, measuring 3.1-13.5 cm in the pelvis, consistent with neurofibromas. The patient denied any further investigation, since she was satisfied with her new complete dentures that fulfilled her functional and aesthetic concerns, and was lost to follow-up.

Based on the available data from the medical record, the clinical and radiographic examination,
we conclude that in our patient NF1 coexisted with multiple CGCGs that caused almost complete destruction of both jaws and created the “jawless woman” appearance.

Figure 6 Panoramic radiographs taken at the years (A) 2000, (B) 2006 and (C) 2007, and (D) at presentation, at February 2012, depict the progression of the lesions over time. Notice expansion and asymmetry of the right mandible; radiolucency with indiscrete borders that obliterate the right maxillary sinus; and poorly defined multilocular radiolucencies extending from the right mandibular angle to the area of missing second left molar.

Figure 7 Cone beam computed tomography at presentation. Axial plane of the mandible shows extensive osteolysis and asymmetry.

Figure 8 Cone beam computed tomography at presentation. Axial plane of the maxilla shows extension of a mass into the right sinus cavity.

Discussion

In the case presented herein the patient presented five diagnostic criteria for NF1: multiple nodules on the skin of the head and neck consistent with neurofibromas; multiple nodules on the trunk; café-au-lait spots
on the back; freckling on the auxiliary region; and Lisch nodules in the eyes. In addition, she had multiple osteolytic lesions in both jaws with clinical, radiographic, and, for maxillary lesions microscopic, features consistent with CGCG. The mass occupying the floor of the mouth and adjacent soft tissues was not biopsied, but most probably represented extension of mandibular GCGCs to the soft tissue, through destruction of the cortical plates. Deposition of bilirubin, a catabolic product of hemoglobin, could explain its yellow-colour.

The presence of CGCG of the jaws in patients with NF1 has been documented in 11 cases, none of them presenting phenotypic and/or genetic features of NS or cherubism. The main clinical features of those cases are summarised in Table 1. Nine patients were females and two males, and the median age at diagnosis was 17 years (range 7-51 years). In all cases the diagnosis of NF1 preceded the recognition of jaw lesions. In nine patients there was involvement of the mandible, bilaterally (two cases) or in combination with the maxilla (two cases), while in two patients only the maxilla was affected. One patient had, also, a giant cell lesion in the femur, while in another patient Hashimoto’s thyroiditis and a dysembryoplastic neuroepithelial tumor of the brain were present. Involvement of both jaws, as in our patient, was described in just two cases, both of them considering middle-aged females.

In another three cases NF1 and CGCG coexisted with NS, while multiple CGCG were reported in 29 patients with NS phenotype in the so called “Noonan-like/multiple giant cell lesions”. NS is a multisystem disease whose clinical features show considerable variability and overlap with those of other “Rasopathies”. The most common signs are growth retardation; short stature; a characteristic facial appearance; various congenital heart defects; inconstant cognitive impairment; renal, lymphatic and skeletal malformations; bleeding disorders; and a predisposition for leukaemia or solid tumors. Facial characteristic includes hypertelorism, ptosis, low-set ears and webbed neck. Our patient did not present a history and/or clinical features suggestive of NS, with the exception of slightly down-sllanting palpebral fissures that are not diagnostic of NS.

CGCG of the jaws, cutaneous café-au-lait macules, and non-ossifying fibromas of the long bones have been described in patients without neurofibromas in the so-called Jaffe–Campanacci syndrome. However, recent evidence suggests that many of those patients may represent cases of NF1, as a pathogenic germ-line NF1 gene mutation was found. Multiple giant cell lesions of the jaws are a diagnostic feature of cherubism, an autosomal dominant disease also associated with NF1 or NS. Cherubism was not considered in the differential diagnosis of the present case, as its clinical manifestations usually appear first in early childhood, stabilise after puberty and regress by the third decade. There are, also, cases of hyperparathyroidism involving multiple sites of either the maxilla or the mandible, but in our patient the laboratory findings were not suggestive of hyperparathyroidism. Finally, metachronous multiple CGCG may represent recurrence of or surgical seeding from a primary lesion, or may be due to incomplete excision, but in our case no surgical intervention was performed.

Table 1 Main clinical features of eleven cases of NF1 patients with microscopically documented CGCG of the jaws in the English-language literature

<table>
<thead>
<tr>
<th>Authors</th>
<th>Agea</th>
<th>Genderb</th>
<th>Location</th>
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<tbody>
<tr>
<td>Kaplan et al11</td>
<td>51</td>
<td>F</td>
<td>MANDIBLE</td>
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<tr>
<td>Ardekian et al13</td>
<td>38</td>
<td>F</td>
<td>Mandible bilateral</td>
</tr>
<tr>
<td>Ruggeri et al8</td>
<td>11</td>
<td>F</td>
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<tr>
<td>Krammer et al14</td>
<td>11</td>
<td>F</td>
<td>Maxillary sinus</td>
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<tr>
<td>de Lange and Van den Akker16</td>
<td>31</td>
<td>F</td>
<td>Mandible and maxilla</td>
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<td></td>
<td>17</td>
<td>M</td>
<td>Mandible</td>
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<tr>
<td>Edwards et al15</td>
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<td>Friedrich et al17</td>
<td>14</td>
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aIn years.

bF, female; M, male.
A linkage between “Rasopathies” and CGCG has not been established\(^1\), but a deregulated Ras/MAPK pathway may be involved in the pathogenesis of CGCG\(^2\). Recently, mutations in the \(NF1\) gene were detected in cases of giant cell lesions of the jaws in NF1 patients\(^1\).\(^2\).

Surgical curettage remains the standard management option for CGCG, despite a high recurrence rate\(^16\).\(^28\). En-block resection is indicated in cases with a more aggressive behaviour and a higher recurrence rate\(^28\). Those modalities were successfully applied in most of the cases of CGCG in patients with NF1\(^8\),\(^11\)-\(^15\),\(^17\),\(^18\). Alternative treatments include corticosteroid injections, calcitonin, IFN-\(\alpha\) and other medications, but their value has not been established\(^29\). Radiation therapy may be applied in combination with surgery in anatomic location where surgical management is challenging, like the skull base, with sarcomatous transformation being the main concern\(^29\). In our patient radiation therapy for maxillary lesions obstructing the nasal cavity and the sinuses alleviated the symptoms, but did not eradicate the lesions. It should be noticed that in our case the clinical course, clinical presentation and radiographic findings were not consistent with sarcomatous transformation.

Occurrence of multiple CGCG of the jaws in patients with NF1 is rare, but should be included in the differential diagnosis, as early diagnosis, regular follow-up and proper therapeutic intervention may limit the extent of bone destruction.

**Disclosure**

None.

**References**


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