Cherubism

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Abstract Cherubism is one of the very few genetically determined disorders that affect only jaw bones. A typical form of cherubism in an 11 years old girl with features of bilateral swelling of the cheeks and soap bubble radiographic appearance on the maxilla and the mandible was presented. Multiple members of the first and second degree relatives were also affected. The clinical presentation of the case, differential diagnosis and treatment modalities were discussed.

Keywords Cherubism · Giant cell granuloma · Bilateral facial swelling · Maxilla · Mandible

Case Report

History

An 11 years old girl presented with painless bilateral enlargement on the lower portion of the face (Fig. 1). The jaw enlargement was first noticed within the first year of life and showed progressive swelling since then. There was no pain or paresthesia related to the lesion. She was otherwise healthy. Family history revealed that her 33 year-old mother, 27 year-old aunt and two uncles (21 and 24 years of age) had swelling on their face during childhood which regressed partially through adulthood.

The two siblings aged 5.5 and 7 years, had no such clinical or radiographic presentation.

Clinical Examination

Intraorally, bilateral, bony hard swelling of the posterior mandible and maxilla surfaced by unremarkable mucosa was evident (Fig. 2). The swelling in the anterior sulcus of mandible was soft on palpation. The patient had malocclusion with rotated and displaced incisors in the mandible. Bilateral submandibular nodes were palpable however no cervical lymph node enlargement was noted. No orbital manifestations or functional deficits were seen.

Radiographic Features

Panoramic radiograph showed that the entire body, ramus and angle of the mandible except condylar region had multilocular radiolucent lesions imparting a soap bubble appearance. She had missing mandibular second and third molars bilaterally. The two canine teeth and an incisor were impacted and surrounded by a cystic-appearing lesion. Severe resorption of the roots of the anterior teeth was noticed. The anterior part of the maxilla seemed unaffected but maxillary molar region and the tuberosity area were involved bilaterally. Although the canines were in their path of eruption there was no space for their full eruption in the alveolar arch. Second molars were present but misplaced (Fig. 3). PET CT images which show the distribution and metabolism of fluoro-deoxy glucose, demonstrated actively growing sites located at the maxilla and mandible bilaterally (Fig. 4). Lytic-sclerotic hypermetabolic lesions were detected at the posterior wall of the maxillary sinus and anterior maxilla (SUV max: 9.57); and at the ramus and symphysis in the mandible (SUV max: 10.38).

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Fig. 1 Right oblique view of the patient showing considerable bulging of both cheeks. Submandibular lymph enlargement can also be seen

Fig. 2 Intraoral view of the patient showing malocclusion and malposition of the dentition together with bilateral obliteration of the vestibule sulcus due to sessile swellings

Diagnosis and Management

In the light of the family history together with the radiographic and clinical presentation, a clinical diagnosis of familial cherubism was established. The results of the

Fig. 3 Panoramic radiograph of the patient is showing multilocular radiolucent lesions covering the entire body, ramus and angle of the mandible except condylar region. Note impacted and displaced teeth within the lesions

Fig. 4 PET images of the patient superimposed on the coronal CT images revealing both maxillary and mandibular involvement. Note lytic hypermetabolic lesions at the posterior wall of the maxillary sinus, anterior maxilla, ramus regions

laboratory tests showed increased level of alkaline phosphatase (181 U/L, normal range 30–120). No biopsy was taken because of the characteristic presentation of the disorder. The treatment plan was daily administration of 100 IU calcitonin in the form of nasal spray (Miacalcic, Novartis AG, Switzerland). On the follow up at 6 months, no regression of the lesion was observed. The medical therapy was planned for further 6 months however; the drug was withdrawn from the market due to possible association of nasal calcitonin treatment with malignancy. Therefore, medical therapy had to be ceased. Partial excision of the lesion on the anterior mandible together with endodontic treatment of teeth 21, 23, 24 and 25 was performed under local anesthesia to inhibit root resorption. The specimen was sent to pathology and the hematoxylin and eosin stained sections showed a large number of spindle-shaped fibroblasts and numerous osteoclast-like

Fig. 5 Microscopic view of the samples showing spindle-shaped fibroblasts and numerous osteoclast-like multinucleated giant cells (hematoxylin and eosin stain, $\times 200$)

multinucleated giant cells (Fig. 5) which confirmed the clinical diagnosis of cherubism. The parents were informed about the natural course of the disorder during the growth period and the family was scheduled for regular follow-up.

Discussion

Cherubism is inherited in an autosomal dominant manner and may affect multiple members of a family. It is characterized by bilateral, symmetrical multilocular bone resorptions filled with fibrous tissue in the mandible and/or maxilla. Fibrous dysplastic tissue masses can expand the cortical bone and lead to swelling of the cheeks. In severe cases where dysplastic expansile masses in the maxilla bulges into the orbital floor, the sclera below the iris with upward tilting of the eyes is visible. The face of the affected individual resembles the “cherubs” of Renaissance paintings with chubby cheeks and ‘looking-up-to-heaven’ eye appearance hence the name cherubism [1, 2].

The disorder exhibits a typical clinical course in most cases. The first signs of the disorder appear around 2–7 years of age, with bone resorption and fibrous expansion continuing until puberty. This follows a stable period of 2–4 years, with spontaneous partial or total regression following thereafter [1–3]. However, aggressive forms of the disorder even after cessation of the growth and development have been reported [4].

Most of the cases show bilateral involvement, the mandible appearing to be affected more so than the maxilla. When both jaws are affected the fibrous lesions usually present initially in the mandible with secondary involvement of the maxilla [3]. Lesions in patients with the progressive form of cherubism result in extensive bone

resorption and leave only a fenestrated shell of cortical bone.

Associated dental anomalies include missing teeth especially the mandibular second and third molars. Misaligned erupted teeth as well as numerous unerupted teeth displaced within the lesion are notable [5]. Radiographic images reveal multilocular radiolucent lesions which give a soap bubble appearance that is seen bilaterally, with severe cases affecting virtually the entire jaw. Condyles are usually intact, which is another typical feature of the disorder.

The histology of the lesions in cherubism is not diagnostic and can mimic central giant cell granuloma with multinucleated osteoclast-like giant cells within vascular fibrous connective tissue stroma. Although perivascular eosinophilic cuffing reported as a specific finding of cherubism to differentiate the lesions from giant cell granuloma by some authors, this characteristic may not present in all lesions [1]. Therefore, definitive diagnosis is made on the basis of radiographic and clinical presentation [5]. Other fibro-osseous lesions containing multinucleated giant osteoclast-like cells such as brown tumor of hyperparathyroidism and aneurysmal bone cysts may be included in the differential diagnosis. Brown tumor associated with hyperparathyroidism can be distinguished from cherubism by laboratory studies exhibiting elevated levels of serum calcium and parathyroid hormone [6]. Aneurysmal bone cyst may also exhibit giant cells microscopically, but its main feature is a cavity that consists of hemorrhagic and blood-filled cavernous spaces separated by fibrous septa. However, the solid type is encountered in a few cases characterized by a dense stroma, few blood vessels and caverns [7]. All the above-mentioned lesions hardly ever present in symmetrical-bilateral fashion, do not show the typical ‘cherubic’ look, and do not have a tendency to regress after puberty.

Mutations in the *SH3BP2* gene located on chromosome 4p16.3 have been identified in cherubism and genetic analysis of this gene has been recommended in cases of the disorder [5]. Mutation analysis of *SH3BP2* may be useful to confirm the diagnosis especially in mild, atypical or sporadic cases. However no mutation detected in *SH3BP2* protein does not necessarily exclude the diagnosis. Prescott et al. [8] examined 24 individuals affected by cherubism and reported that a mutation in exon 9 of *SH3BP2* were detected in all 22 familial cases but was negative in two sporadic cases. No evidence of non-penetrance was found as all individuals who did not harbor their family’s mutation were clinically unaffected [8]. Mutation analysis is also important to distinguish multiple giant cell lesions seen in some syndromes, most notably Noonan syndrome as mutations of the *SOS1* gene and *PTPN11* gene in patients with Noonan syndrome are distinct from cherubism [9].

Management of cherubism classically involves following patients for the stabilization or regression of the disorder and providing cosmetic surgical correction by means of osseous contouring when necessary (mostly after regression of disease activity). Removal of impacted teeth or curettage of the lesions in areas showing fibrous alterations may also be carried out. Successful treatment outcome was obtained with long term (1–2 years) administration of calcitonin [10, 11]. However, the European Medicines Agency's Committee for Medicinal Products for Human Use has recommended that calcitonin-containing medicines should only be used for short term treatment, because of evidence that long term use of these medicines is associated with an increased risk of cancer. Apart from calcitonin, other medical approaches like intralesional steroid injections and subcutaneous administration of α -interferon have been advocated for central giant cell granuloma. In addition, anti-osteolytic agent, imatinib was suggested as a promising option for the treatment of central giant cell granuloma [12]. Although cherubism is a distinct entity from central giant cell granuloma, these treatment modalities may be effective in regression/resolution of osteolytic lesions and recontouring of the face in cherubism.

Conflict of interest The corresponding author states that there are no conflicts of interest.

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