Cherubism: A Case Report

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Abstract Cherubism is a benign, self-limiting fibro-osseous lesion characterized by bilateral symmetric painless expansion of jaw which is more prominent in mandible than in maxilla. Males are commonly affected (2:1) and with greater severity. It becomes noticeable in early childhood and gradually regresses after puberty. Although cherubism is considered as a familial/inherited disease but many sporadic cases have been reported in literature with no familial history. Osteoblastic and osteoclastic remodeling replaces normal bone by excessive amount of fibrovascular tissue containing multinucleated giant cells. Here, we present a case report of cherubism in a 10 year old boy describing the clinical, histological, biochemical and radiographic features.

Keywords Cherubism · Giant cell lesion

Introduction

Cherubism [1] is an inherited disorder that is transmitted as an autosomal dominant trait, but sporadic cases have also been documented. It was first described by Jones [2] in 1933 characterized by bilateral painless expansion of mandible. It may appear as early as 1 year and involutes mostly after

puberty. Maxilla is less commonly involved. In extreme cases, entire mandible and maxilla are involved resulting in marked facial disfigurement. The term cherubism arose from plump cheeked little angels (cherubs) [3]. Marked involvement of maxilla can result in stretching of the skin of upper face to expose the sclera below the iris of eye resulting in an eye-upturned-to-heaven appearance. Radiographically, the lesion presents as multilocular lytic defects and dislocated tooth. Histologically, perivascular cuffing [4] is specific for the diagnosis. Differential diagnosis [5] includes giant cell granuloma, brown tumor of hyperparathyroidism, ossifying fibroma, fibrous dysplasia. Treatment of cherubism is not standardized. Few cases have responded well to curettage, some cases have shown increased growth after surgical intervention. In other cases, lesions tend to stabilize or even regress after puberty. Radiotherapy is contraindicated due to possible retardation of jaw growth, osteoradionecrosis and increased induction of malignancy.

Case Report

A 10 year old male patient was referred from a private dental clinic with a complaint of progressive swelling of right cheek since 3 years (Fig. 1). It was associated with pain and there was no extra oral secondary skin changes. There was discrepancy in normal teeth eruption pattern. Based on clinical findings, our provisional diagnosis was cherubism, giant cell granuloma, and brown tumor of hyperparathyroidism.

Panoramic radiograph was taken which revealed multifocal lytic lesion of jaw involving bilateral posterior body of mandible, angle and rami extending towards coronoid process sparing condyle which was more extensive on right side (Fig. 2). The lesion caused impaction of 46 and 47

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Fig. 1 Pre-op profile of patient

appeared as floating tooth syndrome. Primary treatment like enucleation and curettage of lesion in region of 46 and 47 was done at private dental clinic. Surgical removal of impacted 46 and 47 were carried out along with extraction of 45.

Patient was referred for plain CT scan of mandible which revealed evidence of multiple expansile multiloculated radiolucent lesion bilaterally anterior 2/3rd ramus, extending up to parasymphysial region and posterolateral wall of antrum in right side of maxilla with cortical break and displacement of teeth. The patient was then referred to dental college, Mysore. No history of similar disease was noted in any of the siblings or in parents of affected child. On clinical examination, the child had firm swelling of bilateral cheeks, more prominent on right side which was seen to involve body, angle and ramus. There was local tenderness with pus discharge intraorally from the surgical wound opening in the region of missing 45, 46 and 47 (Fig. 3). Patient was referred for repeat CT with thin axial and coronal section and multiplanar images were reconstructed and three dimensional images were obtained.

Fig. 2 Panoramic radiograph showing multiloculated osteolytic lesions involving the jaw

CT confirmed the presence of multiloculated expansile lytic lesions involving body and rami of the mandible on both the sides—more extensive on the right side (Figs. 4, 5). Similar smaller lesions were seen on the posterior aspect of maxillary sinus. The lesions also showed multiple cortical breakthroughs in the mandible. The lab tests of the patient and results obtained are given below:

	Observed value	Normal value
Alkaline phosphatase	663.31 U/L	108–306 U/L
Acid phosphatase	5.7 K.A. units	1–5 K.A. units
Serum calcium	9.5 mg/dL	9–11 mg/dL
Parathyroid hormone level	35.3 pg/mL	15–65 pg/mL

There are no blood markers for cherubism. No unusual biochemical findings have been reported in patients with cherubism. The most useful biochemical investigations [6] are calcium, parathyroid hormone (PTH) and alkaline phosphatase level which were within normal range and serve to differentiate it from hyperparathyroidism in which all of them are elevated. However, elevated alkaline phosphatase level was observed in this case which indicates bone formation.

An incisional biopsy and curettage of lesion done bilaterally under general anesthesia, because total removal could result in pathological fracture, and bismuth iodoform paraffin paste packed in the surgical defect. Sections stained with hematoxylin-eosin showed proliferating loose fibrous connective tissue composed of fibroblasts along with scattered aggregates of small multinucleated giant cells (Fig. 6). The giant cells were thinly disseminated

Fig. 3 Surgical wound opening with pus discharge (arrow)

Figs. 4, 5 CT scan showing multiple expansile and osteolytic lesions involving the jaw bilaterally

throughout the fibrous tissues. Stroma showed areas of hemorrhage. Perivascular eosinophilic cuffing is the pathognomonic feature [7] which is seen around the small blood vessels (Fig. 7).

The diagnosis of cherubism is strongly suggested by correlating the clinical, histological, radiographic features and lab tests result with that of literature.

Discussion

Cherubism [8] is characterized by typical painless, relatively symmetric expansile lesion resulting in gross deformity of jaw. It is a rare genetically inherited fibro-osseous lesion of the jaw as an autosomal inherited trait. The gene for cherubism was mapped to chromosome 4P16.3 [9]. The clinically conspicuous disturbance in osteogenesis and possible relation to tooth development, as well as the location of the gene in an interval between

Fig. 7 High magnification showing typical perivascular cuffing

Fig. 6 Low magnification showing multinucleated giant cells scattered within highly vascular fibrous stroma

D4S127 and the telomere of 4p, led to the hypothesis that the genes *FGFR3* and *MSX1*, located in this area, are causative for this disease. Finally, in a larger study, found mutations in the gene for the SH3-binding protein *SH3BP2*, which is located within the critical area in 12 out of 15 families with cherubism. *SH3BP2*-dependent signal transduction seems to be involved especially in the regulation of elevated osteoclastic and osteoblastic activities during dentition. There is an influence of *SH3BP2* on the regulation of the receptor for PTH and PTH related protein (PTHrP): *SH3BP2* interacts with the chaperone protein 14-3-3, which recently was described as a regulatory protein of the type I PTH/PTHrP receptor. Current investigations suggest that the PTHrP–PTHrP receptor interaction is of fundamental importance for the spatio-temporal organisation of bone cells and their osteoclastic function in normal development of the tooth germ and the surrounding alveolar bone, as well as in the dentition.

Sporadic cases do occur and are assumed to represent spontaneous mutation or incomplete penetrance. Cases of

cherubism associated with other disorders such as fragile X syndrome, gingival fibromatosis with psychomotor retardation, neurofibromatosis type 1, and craniosynostosis have been published in the literature [10–12]. Cherubism has also been reported to be associated with Ramon syndrome [13] and Jaffe–Campanacci syndrome [10]. Ramon syndrome is extremely rare with only eight cases reported in the literature and presents with mental retardation, short stature, gingival fibromatosis and epilepsy [13, 14]. Jaffe–Campanacci syndrome [15], which includes non-ossifying fibromas that can be localized in long bones and/or jaw bones, mental retardation, café au lait spots, hypogonadism, ocular and cardiovascular anomalies is also rare [16]. However, to our knowledge only eccentric or unilateral mandibular or maxillary lesions have been described in the literature for Jaffe–Campanacci syndrome [17, 18]. Few cases of cherubism have been described as associated with Noonan's syndrome [17], a lesion in the humerus, gingival fibromatosis, mental retardation, orbital involvement and obstructive sleep apnea. Abnormality in the configuration of dental arch or dental eruption, premature exfoliation of deciduous or permanent teeth, transposition, rotation, resorption of roots and malformation are frequently seen [19]. The radiographic feature i.e. diffuse multilocular radiolucencies were replaced by irregular patchy sclerosis with progressive calcification. CT is best method for demonstrating expansile lesion.

The grading system for classification of cherubism is based on location and severity of fibro-osseous expansion [20]. Fordyce in 1976, described the following grades of this disorder:

Grade I The fibro-osseous expansion of the mandible tends to be bilateral and symmetrical. It is primarily in the rami of the mandible.

Grade II The ramus and body of the mandible is involved, resulting in the congenital absence of the third and occasionally the second mandibular molar teeth. In this group the tuberosity region of the maxillae are affected.

Grade III The lesion affects the mandible and the maxillae in their entirety and may result in considerable facial deformity.

Based on the above classification, our case comes under grade II.

Hitomi et al. [8] reported a case of a 15 year old boy with a complaint of bilateral expansion of cheeks. There were obvious areas of expansion from mandibular ramus to angle which were more marked on the right side. On palpation it was a hard bony expansion on buccal areas on both sides of the mandible. Radiographs revealed extensive involvement of both jaws. Bilateral multilocular radiolucent lesions were found extending from the ascending rami to body of mandible excluding condyle. Both the maxillary tuberosities were affected. CT revealed replacement of

Fig. 8 Profile of patient four months post-op

affected bone of jaw by a soft tissue density and disruption of cortexes more marked on buccal side. Laboratory studies showed an elevated alkaline phosphatase level of 611 IU/L. Results of other laboratory tests were within normal limits. Biopsy specimens were composed of fibrous connective tissue containing multinucleated giant cells. Lesion was diagnosed as grade II cherubism.

In our case, after surgical intervention patient's profile improved. We can appreciate the change in patient's post-op profile (Fig. 8) showing facial symmetry. Post-op panoramic radiograph (Fig. 9) and CT scan (Figs. 10, 11) also show evidence of bone formation and resolution of osteolytic lesion.

Being a self limiting disease, treatment is mainly for esthetic needs and for unerupted teeth. Curettage alone or in combination with surgical contouring has been considered the treatment of choice for aggressive lesions [21]. Pharmacological intervention in form of calcitonin has been suggested but clinical evidence in literature to endorse its application in cherubism is still lacking. Calcitonin has been shown to cause inhibition of bone resorption caused by multinucleated giant cells.

Fig. 9 Four months post-op panoramic radiograph showing evidence of bone formation

Figs. 10, 11 Post op CT scan showing evidence of bone formation

Conclusion

According to [22] WHO classification cherubism belongs to a group of non-neoplastic bone lesions affecting only jaws. Symptoms and signs depend on the severity of the condition. It ranges from no clinically or radiologically detectable features to grossly deformed mandible and maxilla with respiratory embarrassment, impaired vision and hearing. Patients seek medical attention mainly for esthetic and functional concerns. Since the lesion undergoes regression, the surgical intervention is usually delayed until puberty. However, in patients with functional, cosmetic problems or emotional disturbances [23], surgical intervention consisting of debulking of lesions with surgical recontouring can be considered.

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