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**CASE STUDY**

# CHERUBISM: REPORT OF A RARE PATHOLOGY

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**ABSTRACT**

Cherubism is a skeletal dysplasia characterized by bilaterally symmetric fibro-osseous lesions limited to the mandible and maxilla. Affected children appear normal at birth. Swelling of the jaws usually appears between 2 and 7 years of age, after which, lesions proliferate and increase in size until puberty. The lesions subsequently begin to regress, fill with bone and remodel until age 30, when they are frequently not detectable. Cherubism is due to autosomal dominant mutations in the SH3BP2 gene on chromosome 4p16.3. The lesions seen in Cherubism are painless and more or less symmetrical. Frequently, Cherubism is accompanied by dental arch and tooth eruption abnormalities with rare extra gnathic skeletal involvement. The rounded face, due to jaw hypertrophy and upward gaze with exposure of the sclera below the pupil gives a reminder of cherubs depicted in Renaissance paintings. This paper reports a case of non-familial cherubism with its clinical, radiological, histopathological features along with treatment aspects.



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## INTRODUCTION

Cherubism is non-neoplastic, autosomal dominant inherited disorder of jaw bones characterized by bilateral, painless enlargements that are mostly symmetrical. Enlargements are as a result of replacement of bone with fibrous tissue. (Silva *et al*., 2011; Peñarrocha *et al*., 2006) Familial fibrous dysplasia was the synonym given to this fibro-osseous entity. (Lima *et al*., 2010) Clinically the age of onset of this disease lies around 2-4 years. Clinically lesion progress and show varied manifestations within first 2 years and may regress or progress slowly from age of 7 to puberty. (Silva *et al*., 2011; Lima *et al*., 2010) Cherubism presents as an autosomal dominant trait with 100% rate of penetrance in males and 50–70% rate of penetrance in females. (Kandakure *et al*., 2012) Mandible is more commonly involved than maxilla or both may be involved. (Teixeira *et al*., 2004) As the enlargements are bilaterally symmetrical which leads to rounded face and swollen cheeks accompanied by upward-looking eyes, this gives a impression of a cherub angel. (Teixeira *et al*., 2004; Mehrotra *et al*., 2011) Molecular pathogenesis revealed mutations in the gene encoding SH3 - binding protein 2 (SH3BP2 gene on chromosome 4p16.3 between D4S127 and 4p telomere) and possible degradation of the Msx-1 gene which is involved in the regulation of mesenchymal interaction during craniofacial morphogenesis. (Lima *et al*., 2010; Teixeira *et al*., 2004)

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Here in this paper a non familial inheritance case of cherubism is discussed.

### Case report

A 4 year old boy presented with painless swelling over middle and lower third region of face bilaterally since 2 years. There was no history of trauma, fever, toothache, pus discharge and restricted mouth opening. There was no significant family history present. All the vital signs were within the normal limits. Both sclera were prominent and conjunctiva was visible. On extraoral examination and palpation (Fig.1) bilaterally diffuse swelling was present over cheeks which are soft, non-tender and non-fluctuant in nature. No anaesthesia or paresthesia was present. Bilateally submandibular lymph nodes were palpable, enlarged, non-tender and mobile. Intraoral examination and palpation (Fig.2) revealed a V shaped diffuse swelling present on the entire palatal region with midline demarcation and appeared to be a cleft palate. Obliteration of buccal vestibule was noted which extended till distal end of 53, 64. Swelling was soft, non-tender and non-fluctuant in nature. Mouth opening was adequate, occlusion was normal. Overlying mucosa was normal in colour. Based on clinical findings, a provisional diagnosis of multiple dentigerous cysts was given. The patient was advised for radiographic investigations. Intraoral anterior occlusal radiograph (Fig.3) was taken which revealed fused intermaxillary suture ruling out cleft palate. Orthopanatmograph (OPG) (Fig.4) revealed bilateral soft tissue expansile swelling with normal muscular components with no abnormal calcifications present.

**Table 1. Values of different bio-chemical investigations done**

| S.No. | Bio-chemical Investigation done | Test Values | Normal Range |
|---|---|---|---|
| 1. | Serum parathormone | 46 pg/mL | 10-65 pg/mL |
| 2. | Serum calcitonin | 8 ng/L | <12 ng/L |
| 3. | Serum calcium | 9.6 mg/dL | 8.5 – 10.2 mg/dL |
| 4. | Serum alkaline phosphatase | 268 U/L | 149-369 U/L |
| 5. | Serum acid phosphatase | 1.2 ng/mL | ≤2 ng/mL |

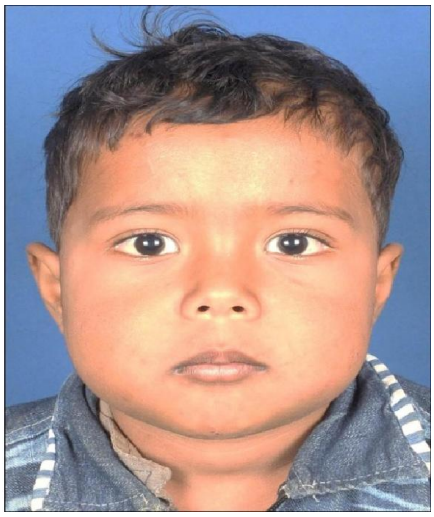

**Fig.1. Bilateral diffuse swelling was present over cheeks**

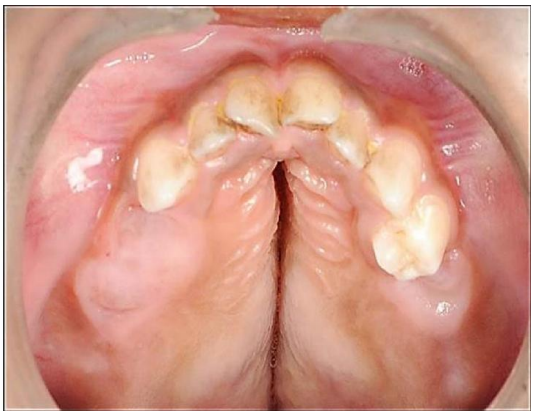

**Fig.2. V-shaped palate and diffuse swelling present on the entire palatal region with midline demarcation with obliteration of buccal vestibule appeared to be a cleft palate**

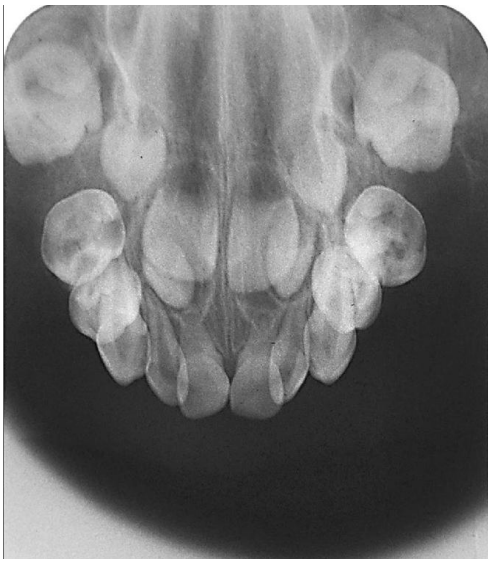

**Fig.3. Intraoral anterior occlusal radiograph revealed fused intermaxillary suture ruling out cleft palate**

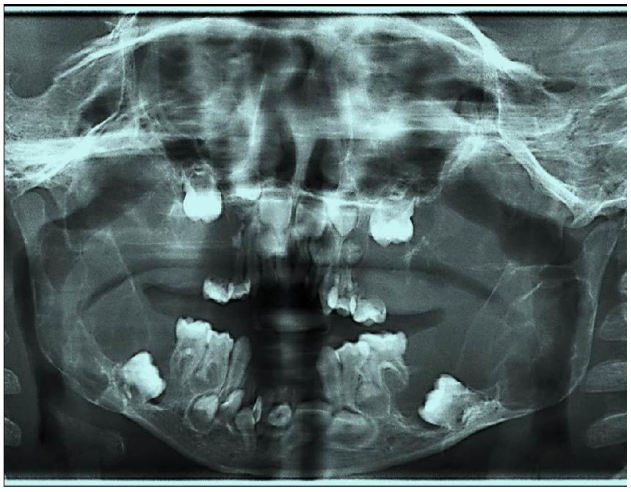

**Fig.4. Orthopantomogram (OPG) revealed bilateral soft tissue expansile swelling giving ground glass and floating tooth appearance**

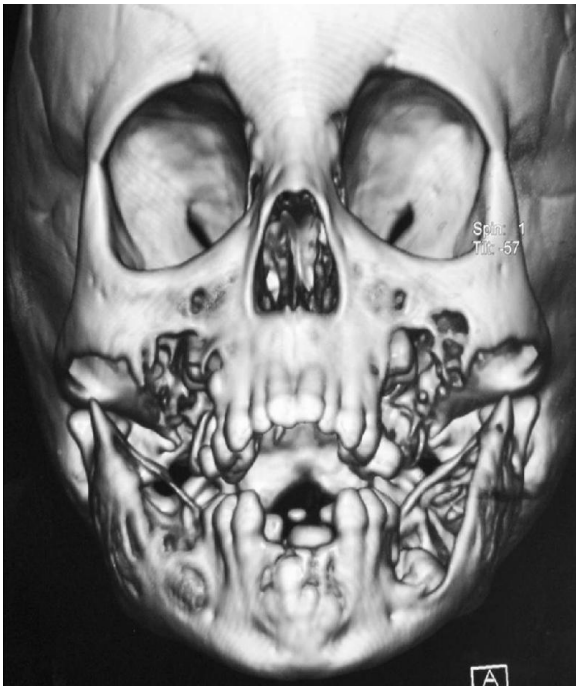

**Fig.5. 3D reconstruction radiograph revealed multiple radiolucent expansile lesions involving ramus, part of body of mandible, maxillary sinus**

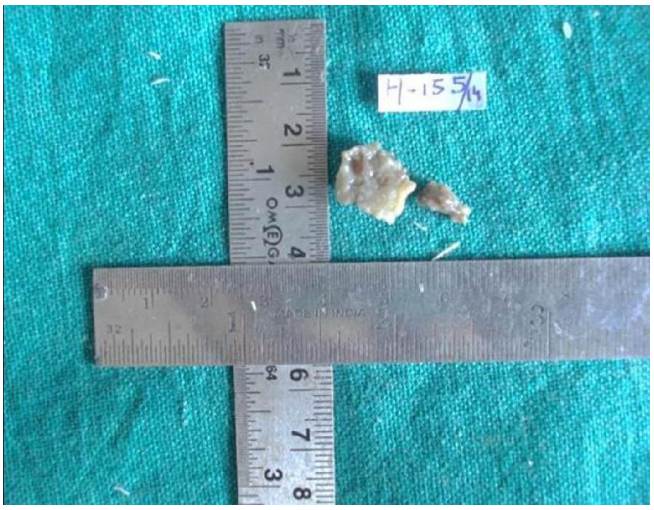

**Fig.6. Grossing of specimens showed soft tissue masses, creamish brown in colour, measuring approximately (i) about 1.5×1.5×0.5 cm (ii) about 0.7 ×0.4×0.4 cm**

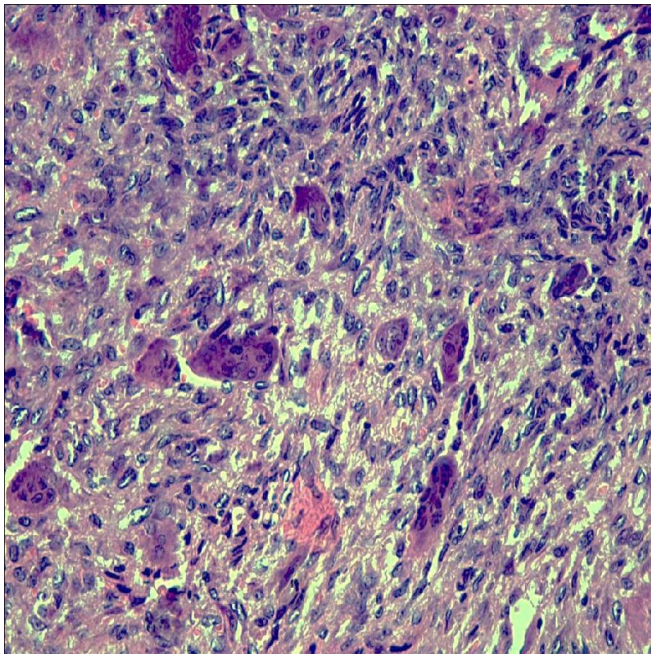

**Fig.7. H & E stained (40X photomicrograph) connective tissue stroma revealed multinucleated (10-15) osteoclasts type giant cells intermixed with fibroblasts showing pleomorphism and presence of few or no inflammatory cells**

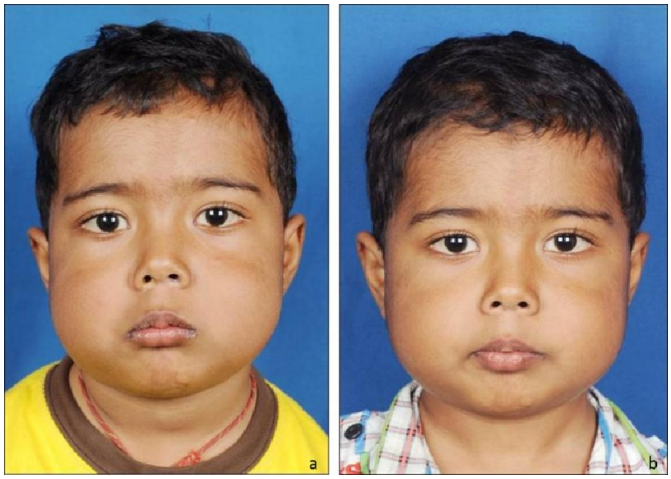

**Fig.8. Follow-up clinical images after drug therapy revealed decrease in prominence of swellings bilaterally. Fig.8a follow up after 1 month; Fig.8b follow-up after three months**

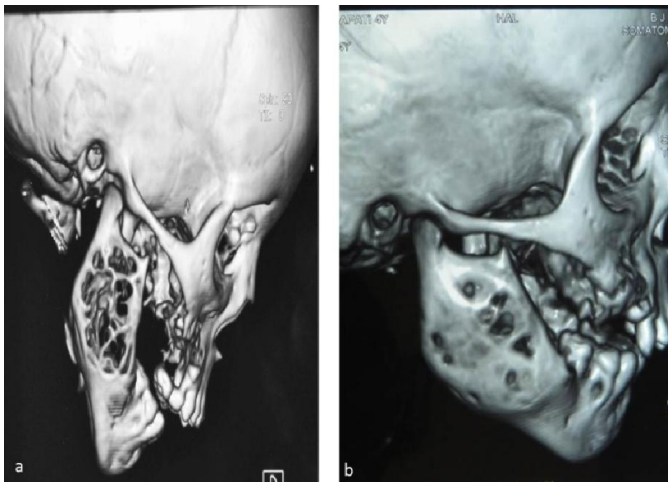

**Fig.9. Follow-up radiological findings after drug therapy revealed improvement in bone formation. Fig.9a follow up after 1 month; Fig.9b follow-up after three months**

3D reconstruction images (Fig.5) revealed multiple radiolucent expansile lesions involving ramus of mandible, some part of body of mandible, maxillary sinus and with presence of few interseptations however no breach of cortex was seen. Biochemical investigations like serum parathormone, serum calcitonin, serum calcium, serum alkaline phosphatase and serum acid phosphatase (Table 1) were carried out to further rule out any systemic pathology, but all those findings were normal. Biopsy was advised to ascertain the nature of pathology. All preoperative investigations were made and a medical fitness report was obtained from physician. Incisional biopsy was taken from body of the mandible under general anaesthesia. The biopsy specimens (Fig.6) obtained was soft in consistency, creamish brown in colour, measuring approximately (i) about 1.5×1.5×0.5 cm (ii) about 0.7 ×0.4×0.4 cm. Incisional biopsy specimens were fixed, processed and stained with Haematoxylin and Eosin (H & E) and examined under light microscope. Histopathological examination (Fig.7) revealed numerous multinucleated osteoclasts type giant cells in the fibrocellular connective tissue stroma with surrounding fibroblasts, no inflammatory cells were seen and few dilated blood vessels were evident. Correlating clinical, radiological, biochemical and histopathological findings final diagnosis of non-familial type Cherubism was made. Based on the diagnosis, the patient was treated with calcitonin in the form of intranasal spray and intralesional corticosteroids triamcinolone acetonamide for 6 months was given. Patient was benefitted from this treatment as shown in the follow-up clinical (Fig.8) and radiological (Fig.9) findings.

## DISCUSSION

Cherubism was first described by Jones who presented four cases of same family origin. (Mehrotra *et al*., 2011) Cherubism is a hereditary lesion which has features of painless, repeatedly symmetrical, enlargement of the jaws due to replacement of bone with fibrous tissue. (Lima *et al*., 2010) It usually presents as bilateral swellings but cases with unilateral involvement have also been reported. Clinically, affected children are normal at birth and are without any evidence of disease till 14 months to 3 years of age. Symmetric enlargement of the jaw begins after this age, and progresses till 12-15 years of age. At puberty, the lesion begins to regress and remodelling of the jaw continues up to the third decade of life by which time the abnormality usually becomes indiscernible. (Lakshmi *et al*., 2011) Cherubism is a genetic disease; in which mutation occurs in the SH3BP2 gene with a marked variability in clinical expression. Cherubism affects males and females with equal frequency and has been reported in patients of all racial and ethnic background. It was initially characterized as exclusively familial; however, intermittent cases have been also reported. The latter or some cases develop without family histories of the disorder. These presumably represent examples of spontaneous mutation. (Wagel *et al*., 2012) In the present case there was absence of any family history and we anticipate this as a case of non-familial cherubism. Mutations in Sh3bp2 gene causes cherubism, which is characterized by inflammation and bone loss in the jaw. Sh3bp2 is a multi-domain scaffolding protein with a pleckstrin-homology domain (PH), a proline-rich domain (Pro), and a Src-homology 2 domain (SH2). Most of the known cherubism mutations (CM) lie in a stretching region between the Pro and the SH2 domains. (Novack and Faccio, 2007) Swelling of the jaws in cherubism typically first appear between age of 2 to 7 years, after which it proliferates and increase in size until puberty. (Papadaki *et al*., 2012) The

enlarged cervical lymph nodes which contribute to fullness of face in cherubism are usually large, mobile, discrete and non-tender in nature. (Wagel *et al*., 2012) The jaw lesions begin at the angle of mandible and extend into ramus and body with or without involvement of maxilla. Involvement of maxillary ridge gives rise to a "V" shaped palate and orbital encroachment leading to an "eyes to heaven appearance". (Lakshmi *et al*., 2011) All these findings were significant in the present case. As cherubism usually does not affect osseous metabolism; the bone markers are generally within the normal limits in relation to age. (Wagel *et al*., 2012) Biochemical investigations like, serum parathormone, serum calcitonin, serum calcium, serum alkaline phosphatase and serum acid phosphatase done in the present case were within the normal limits.

In 1992, Marck and Kudryk proposed a grading system (Reddy *et al*., 2012) for cherubism depending on the location of the lesions.

**Grade 1:** Involvement of bilateral mandibular molar regions and ascending rami, mandible body, or mentis.
**Grade 2:** Involvement of bilateral maxillary tuberosities (in addition to grade 1 lesions) and diffuse mandibular involvement.
**Grade 3:** Massive involvement of the entire maxilla and mandible, except the condyles.
**Grade 4:** Involvement of both jaws, including the condyles. According to Ramon and Engelberg grade 4 lesions not only push the orbital floor upward but also penetrate it.

According to the above classification system the present case could possibly be classified as grade 3 variant of cherubism. Cherubism being a self-limiting disease which regresses on its own as the age advances, so treatment is given based on cosmetic and functional needs (Gnepp, 2002) and in some cases liposuction has been proposed to reduce the mass of the lesion. (Dubin and Jackson, 1990) Cherubism in mild stage i.e without facial disfigurement, dental and ocular involvement is managed with long-term observation without any treatment, as it regresses on its own after puberty. Surgical treatment is required in conditions where aesthetic or functional concerns arise due to nasal blockage, eye protusion or facial disfigurement which is treated in the form of partial resection, contour resection, curettage or combination of above, but treatment should always be done after puberty when cherubism lesions are in inactive stage. (Papadaki *et al*., 2012) Calcitonin has been used successfully for long-term treatment of giant cell granuloma which contains osteoclasts type of giant cells similar to cherubism. (Silva *et al*., 2011) In 1994, Terry and Jacoway have seen very positive results when treated with calcitonin. In the present case case calcitonin as intranasal spray was used based on Terry and Jacoway protocol. (Kurtz *et al*., 2001) As tumour necrosis factor-α(TNF-α) is found to be major pathogenic factor in cherubism, intralesional corticosteroid is an attractive option, particularly for children and young adults because corticosteroids reduce tumour necrosis factor-α(TNF-α) activity. (Lima *et al*., 2010) intralesional corticosteroids were given in the present case, which showed positive results. Being a fact that osteoclastic hyper response can be seen in cherubism, tacrolimus an immunosuppressive drug inhibit osteoclast formation by targeting the NFAT/calcineurin pathway. Calcineurin is required for the genesis of bone-resorbing osteoclasts. (Mark S. McMahon, 2009; Kadlub *et al*., 2015) Radiotherapy in contraindicated in cherubism due to risk of osteoradionecrosis, malignancy and growth disturbance. (Wagel *et al*., 2012) Kaban *et al*. in 1999 has reported surgical intervention in combination of interferon therapy for aggressive giant cell lesions and syndrome associated with it. (Papadaki *et al*., 2012)

**Conclusion**

A pre-schooler child with plump face is always attractive to parents and people, but it should alarm for any excessive bulging or fullness of the cheeks which can be ruled out with radiographic investigations. As a general rule of differential growth of body, lymphoid tissue grows to its peak in the age group of 3-10 years and the enlarged cervical lymph nodes contributes to fullness of the face in cherubism. In the present case the diagnosis of cherubism was made on the basis of patient age, family history, clinical examination, radiographic findings, biochemical analysis and histopathological findings. Hence keeping in view of literature, careful monitoring and evaluations helps in diagnosing these non pariel pathologies.

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